# Asymmetric α-arylation of α-amino acids *via* rearrangement of urea derivatives

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

**2015**

**Rachel Clare Atkinson**

**School of Chemistry**

# Contents

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# Abstract


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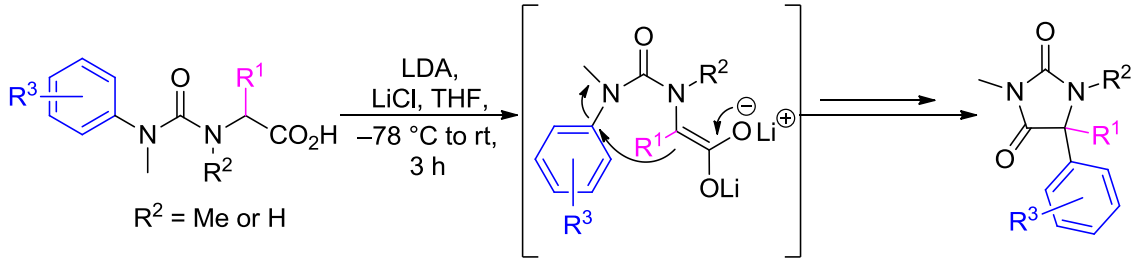
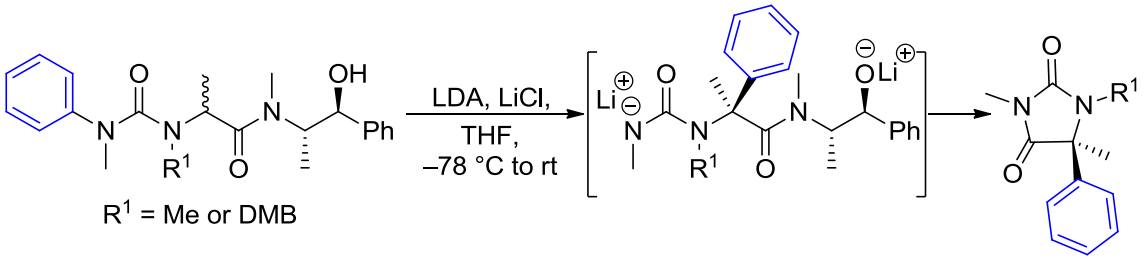
Quaternary amino acids are biologically important and useful building blocks for both natural product and pharmaceutical targets. They can be made from their naturally occurring proteinogenic tertiary counterparts through methods such as alkylation. However, α-arylation of amino acids is challenging with only a small number of methods available, which are far from general and access only a limited substrate scope.

The N to C rearrangement chemistry established in the Clayden group allowed us to develop a transition-metal-free arylation of amino acid enolates. This works by intramolecular delivery of an aromatic ring tethered *via* a urea linkage and has been used to synthesise a variety of protected and unprotected hydantoins, which are derivatives of quaternary amino acids.

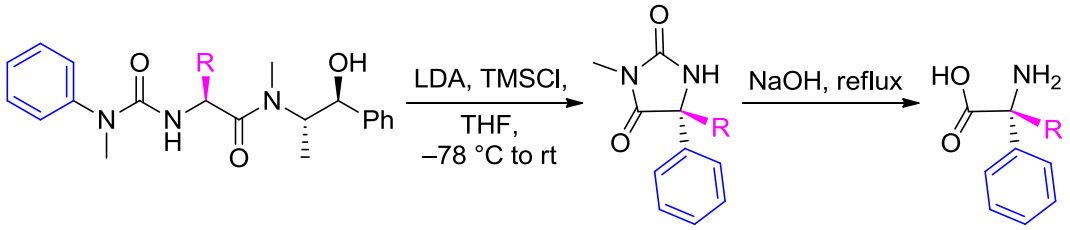



Investigation of the reaction mechanism using *in situ* infra-red spectroscopy (ReactIR) revealed a total of six successive species on the reaction pathway from the starting carboxylic acid to the product hydantoin through analysis of the carbonyl stretching frequencies.

This methodology has also been extended to the challenging asymmetric synthesis of quaternary amino acids. Introduction of pseudoephedrine as a chiral auxiliary to control the stereochemistry of the amino acid enolate arylation leads to enantiomerically enriched hydantoins.




Further development of this asymmetric methodology to allow for hydantoin hydrolysis involved an *in situ* protection. The reaction involved protection, enolisation, arylation, cyclisation and deprotection in one-pot. Hydantoins containing electron-rich aromatic rings were formed selectively and were cleaved into synthetically valuable enantiomerically enriched α-arylated quaternary amino acids.



## Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

## Copyright Statement

## Acknowledgements

Firstly I would like to thank Jonathan for giving me the opportunity to work in his research group. Thank you for your continued support and advice and for always being available when I needed help. I have enjoyed my time working in your group.

I have so many treasured memories from the PhD because of the people that I have worked with. Firstly, Sam, I couldn't have finished my PhD without you, you've been the best friend anyone could ask for, you have been there through the good and bad times and you can always make me laugh. Romy, you have helped me hugely through being a solid friend who has always had time for me and listened, I will never forget our weekend cake outings and San Francisco. Dan, you have been great to work with, I have had a lot of fun, thank you for all your support, I will never forget our wonderful idea about tubing and a pipette column. John, you made my final year in the lab great and it has been good fun working alongside you and chatting about everything. Jenn, I loved the time you spent in our group, your advice was always helpful and I will never forget you were there for me. Bryden and Francis, one of the best year groups, thanks for all the laughs and pep-talks, I knew we would make it in the end. The girls, Cath and Katharina, it has been great getting to know you and I have lots of happy memories. Liam and Matteo, the only remaining postdocs from before I started, thank you for always answering my questions and for all the laughs we have had. Fernando, your help on my project has been valuable and it has been nice getting to know you. Wojceich, for always being understanding and a pleasure to work next to. Romain and Adam for being good students to supervise and friends. Josep and Mike for some memorable times in Revolucion de Cuba on different occasions.

Past group member, Mike Tait, the first person I worked with in our bay, you were great to work alongside, thanks for always trying to be funny. Nicole you were the first person to help me with my project and your help was invaluable, you were also a great friend to me. Edmund, you are fabulous, you always had time for everybody and are one of the nicest people. Daniele and Bea we had some good times, funny you had trouble understanding my accent. Rob and Nadia, part of the original group when I started, you helped me settle in and were lovely people to work with. Gaëlle for all the HPLC and stills fun we had and Phil for being a good friend and a nice person to work with.

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I want to thank my family, Mum, Dad, James, Emily and Matthew for all your support throughout my PhD and life, you are amazing, I couldn't have got this far and wouldn't be the person I am today without all your love and backing. I hope to always make you proud of me.

Finally, the person who I couldn't have done any of this without, James. Thank you for all the help, advice and time you have given me. For the encouragement to never give up and always being by my side. For all your love and care, I thank you for everything, life wouldn't be the same without you.

# Abbreviations

| | |
|---|---|
| Ac | Acetyl |
| $[\alpha]_D$ | Specific rotation |
| aq | Aqueous |
| Ala | Alanine |
| Ar | Aryl |
| br. | Broad |
| BINOL | 1,1'-Bi-2-naphthol |
| Bn | Benzyl |
| Boc | *tert*-Butyloxycarbonyl |
| BSA | *O*,*N*-Bistrimethylsilylacetamide |
| BTMG | *tert*-Butyl-1,1,3,3-tetramethylguanidine |
| Bu | Butyl |
| But | Butyrine |
| Bz | Benzoyl |
| *c* | Concentration |
| ca. | About/around |
| CAN | Cerium ammonium nitrate |
| Cat | Catalyst |
| Cbz | Benzyloxycarbonyl |
| CPME | Cyclopentyl methyl ether |
| Cy | Cyclohexyl |
| d | Doublet |
| δ | Chemical shift |
| DACH | 1,2-Diaminocyclohexane |
| dba | Dibenzylideneacetone |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCC | *N*,*N'*-Dicyclohexylcarbodiimide |
| DCE | 1,2-Dichloroethane |
| DCM | Dichloromethane |
| DDQ | 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone |
| *de* | Diastereomeric excess |
| DFT | Density functional theory |
| DiPA | Diisopropylamine |
| DiPEA | *N*,*N*-Diisopropyl ethylamine |
| DMB | 2,4-Dimethoxybenzyl |

| | |
|---|---|
| DMAP | 4-(Dimethylamino)pyridine |
| DMF | *N*,*N*-Dimethylformamide |
| DMP | 2,6-Dimethylphenol |
| DMPU | 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone |
| DMSO | Dimethylsulfoxide |
| DPPA | Diphenylphosphoryl azide |
| *dr* | Diastereomeric ratio |
| DTBP | Di-*tert*-butyl peroxide |
| $E^+$ | Electrophile |
| EDCi | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| *ee* | Enantiomeric excess |
| eq. | Equivalent |
| *er* | Enantiomeric ratio |
| ESI | Electrospray ionisation |
| Et | Ethyl |
| *et al.* | And others |
| $Et_2O$ | Diethylether |
| EtOAc | Ethylacetate |
| EtOH | Ethanol |
| 9-Fm | 9-Fluorenemethanol |
| Fmoc | Fluorenylmethyloxycarbonyl |
| Gly | Glycine |
| HMPA | Hexamethylphosphoramide |
| HOBt | Hydroxybenzotriazole |
| HPLC | High performance liquid chromatography |
| HRMS | High resolution mass spectrometry |
| Hz | Hertz |
| IPA | Isopropanol |
| *i*Pr | *iso*-Propyl |
| *ir* | Isomeric ratio |
| IR | Infrared |
| *J* | Coupling constant |
| KHMDS | Potassium hexamethyldisilazide |
| LDA | Lithium diisopropylamide |
| LDEA | Lithium diethylamide |
| Leu | Leucine |
| LiHMDS | Lithium hexamethyldisilazide |

| | |
|---|---|
| LiTMP | Lithium tetramethylpiperidide |
| L-Selectride | Lithium tri-*sec*-butylborohydride |
| Lys | Lysine |
| *m* | *Meta* |
| $M^+$ | Metal cation |
| m | Multiplet |
| Me | Methyl |
| MEM | Methoxyethoxymethyl |
| Met | Methionine |
| MHz | Mega Hertz |
| mmol | Millimole |
| mol | Mole |
| MOM | Methoxymethyl |
| mp | Melting point |
| MS | Mass spectrometry, Molecular sieves |
| NaHMDS | Sodium hexamethyldisilazide |
| NMR | Nuclear magnetic resonance |
| NOESY | Nuclear overhauser effect spectroscopy |
| *o* | *Ortho* |
| *p* | *Para* |
| Pet.Ether | Petroleum ether |
| PG | Protecting group |
| Ph | Phenyl |
| Phe | Phenylalanine |
| Piv | Pivaloyl |
| PMB | *para*-Methoxybenzyl |
| PMP | *para*-Methoxyphenyl |
| ppm | Parts per million |
| 4-PPY | 4-Pyrrolidino-pyridine |
| Pro | Proline |
| PTC | Phase transfer catalyst |
| PTSA | *para*-Toluenesulfonic acid |
| PyBOP | Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate |
| q | Quartet |
| $R^1$ | Substituent |
| $R_f$ | Retention factor |
| RBF | Round bottomed flask |

| | |
|---|---|
| Rot | Rotamer |
| rt | Room temperature |
| s | Singlet |
| SARM | Selective androgen receptor modulators |
| sat. | Saturated |
| SET | Single electron transfer |
| SM | Starting material |
| T | Temperature |
| t | Time, Triplet |
| *t* | Tertiary |
| TADDOL | α,α,α,α-Tetraaryl-1,3-dioxolane-4,5-dimethanol |
| TBAF | tetra-*n*-Butylammonium fluoride |
| TBDMS | *tert*-Butyldimethylsilyl |
| TBDPS | *tert*-Butyldiphenylsilyl |
| TBS | *tert*-Butyldimethylsilyl |
| Tf | Triflate |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMG | Tetramethylguanidine |
| TMP | Tetramethylpiperidide |
| TMS | Trimethylsilyl |
| Tolyl | Methylphenyl |
| Trp | Tryptophan |
| Ts | Tosylate |
| Tyr | Tyrosine |
| UV | Ultraviolet |
| Val | Valine |
| *vs.* | Versus |
| X | Halogen |
| $\chi_c$ | Chiral auxiliary |

# Preface

The author graduated from the University of Bath in 2011 with a first class honours MChem(Hons) Chemistry with Industrial Training degree. This included a one year industrial placement working for the pharmaceutical company AstraZeneca in Macclesfield within the process chemistry department. She worked on a drug (Olaparib) for the treatment of breast and ovarian cancer that has now been FDA approved with the trade name Lynparza. Her final year project was undertaken with Dr. Steven Bull entitled 'A retro-aldol based strategy towards the total synthesis of (+)-Cladocroic acid'.

In 2011 the author moved to the University of Manchester and joined Professor Jonathan Clayden's research group. Her work involved N to C rearrangement chemistry developed in the group and her project is based on the asymmetric α-arylation of amino acid enolates detailed in this thesis.

In 2015 the author hopes to train to become a chemistry teacher.

# 1 Introduction

## 1.1 Amino Acids

α-Amino acids have their acidic carboxylic acid and basic amine moieties separated by an α-carbon. This structure is highly important; the twenty natural amino acids present in humans form the building blocks for proteins and act as intermediates in metabolism.[1] The sequence of amino acids and the chemical properties of individual amino acids affect a protein's biological properties.

Amino acids are important in drug synthesis and have uses as chiral and bifunctional catalysts.[1,2] The secondary amino acid proline has frequently been used as an asymmetric organocatalyst in various organic processes such as aldol and Michael addition reactions.[3]

The synthesis of unnatural amino acids has become important for biological studies of proteins and drug progression. In 1998, Schultz *et al.* used molecular modelling to design unnatural amino acids in order to probe various effects such as hydrophobicity of proteins. The effects of packing and side chain conformational entropy on protein stability were investigated by modification of natural amino acids. Two unnatural analogues (**1** and **2**) of leucine (**3**) were synthesised to investigate the factors governing protein stability (Figure 1).[4]

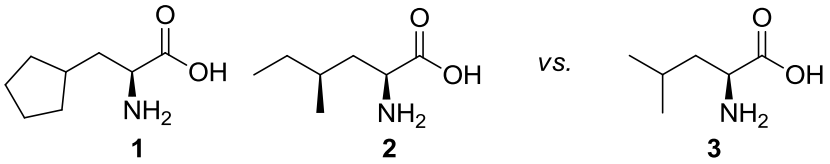


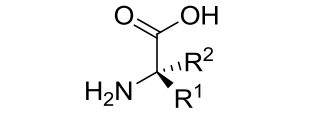

**Figure 1: Investigation of protein stability using unnatural amino acids**

In 2002, Wang *et al.* introduced novel amino acids into proteins in living cells to investigate protein function and if there was enhancement of protein properties.[5] An important area within the study of unnatural amino acids is the synthesis and investigation of the biological properties of α,α-disubstituted amino acids, otherwise termed quaternary amino acids.

## 1.2 Quaternary Amino Acids

Quaternary α-amino acids (Figure 2) have improved metabolic stability compared with tertiary α-amino acids[6] and provide useful building blocks for both natural product and peptide syntheses. The biological function of proteins is highly dependent on the secondary and tertiary structures adopted and it is useful to be able to synthesise peptidic chains with particular conformational properties.[7] One of the biggest challenges within this area is the asymmetric synthesis of quaternary amino acids,[8] as the presence of quaternary centres could alter the conformation of a peptide and

this can provide useful information regarding the bioactive conformation and lead to improved physiological effects.[9,10]



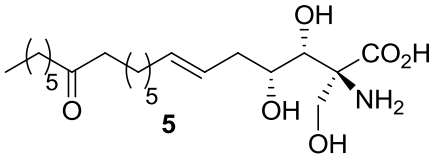

$R^1$, $R^2 \neq H$, if chiral $R^1 \neq R^2$

**4**

**Figure 2: Quaternary amino acid**

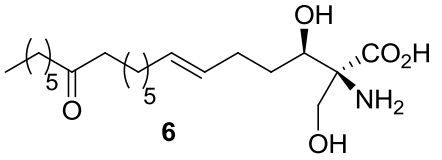
### 1.2.1 Natural Products

Quaternary amino acids feature as residues in several biologically active peptidic metabolites and are important components of, or precursors to, many pharmaceutical and natural product targets. Examples of natural quaternary amino acids include myriocin (**5**),[11,12] mycestericin (**6**)[13] and sphingofungins (**7**, **9**).[6,14-17] These three examples all display antifungal and immunosuppressant properties (Figure 3). Myriocin (**5**) is 10–100 times more potent than cyclosporin A (**8**) as an immunosuppressant drug for the use after kidney, liver and bone marrow transplants.[8,18,19] Cyclosporin A (**8**) is made up solely of tertiary peptide linkages, whereas myricin (**5**) contains a quaternary amino acid centre.



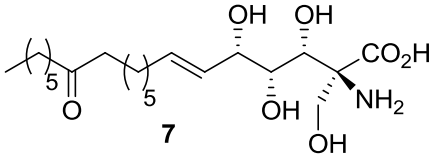

**5**

*Myriocin:* immunosuppressant



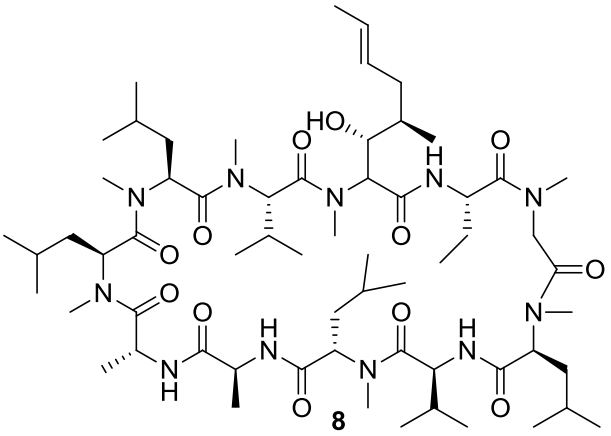

**6**

*Mycestericin E:* immunosuppressant



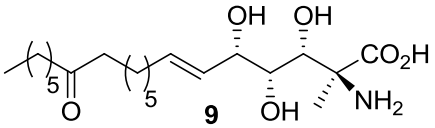

**7**

*Sphingofungin E*: inhibitor in biosynthesis of sphingolipids




**8**

*Cyclosporin A:* immunosuppressant




**9**

*Sphingofungin F*: inhibitor in biosynthesis of sphingolipids

**Figure 3: Natural products containing quaternary amino acids**

Many natural products derived from quaternary amino acids have important uses (Figure 4). (+)-Lactacystin (**10**)[20] exhibits neurotrophic activity, useful for the treatment of diseases associated with the nervous system such as Alzheimer's disease.[21,22] Fumimycin (**11**) is derived from an α-

arylated amino acid and has antibacterial activity against MRSA.[23] Finally, ecteinascidin 743 (**12**),[24,25] also arylated at the α-carbon, has been synthesised by many total syntheses due to its potency as an antitumour agent and its limited availability from natural sources.[26-28]

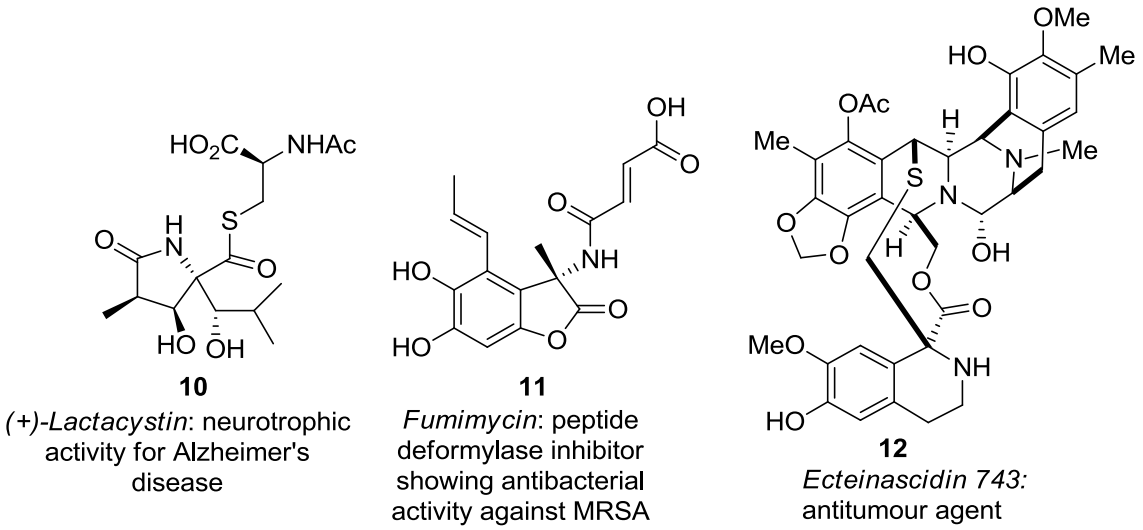



**Figure 4: Natural products derived from quaternary amino acids**

Other important structures also contain quaternary amino acid residues (Figure 5). For example, pseudopeptide platform (**13**) was developed in 2002, to create an enantiomerically pure macrocycle free from racemisation due to its quaternary structure.[29] These platforms are used in supramolecular chemistry, solution-phase combinatorial chemistry and for molecular recognition. Recently, an α,α-disubstituted amino acid based inhibitor of human arginases I and II (**14**) was developed for the treatment of myocardial reperfusion injury, a disorder caused by impaired blood flow due to blockages in the coronary arteries.[30]

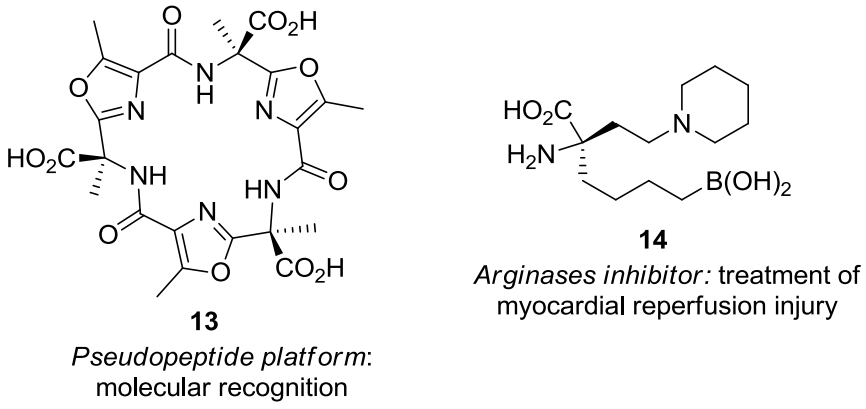
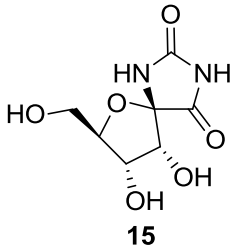



**Figure 5: Other important structures containing quaternary amino acids**

In conclusion, quaternary amino acids and their derivatives are prevalent in a number of important natural products and pharmaceuticals. Many of these display vital assets such as antifungal, anticancer and immunosuppressant properties.

### 1.2.2 Hydantoins

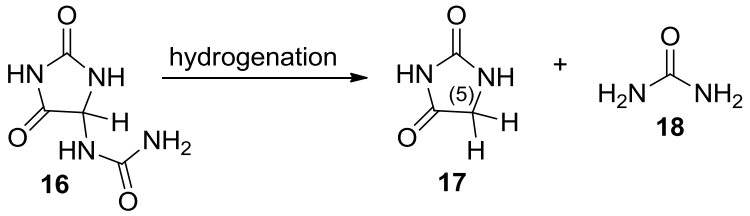
An important class of quaternary amino acid derivatives are hydantoins, heterocyclic compounds that can be hydrolysed to generate quaternary amino acids. Hydantoins have been isolated from various natural sources including trees, sugar beet and wing pigments of butterflies.[31] (+)-Hydantocidin (**15**) is a naturally occurring hydantoin that displays herbicidal and plant growth regulatory activity (Figure 6).[32]




**15**

**Figure 6: (+)-Hydantocidin (15)**

Hydantoin (**17**) is the prototypical hydantoin bearing no substituents at the 5-position. It was the first structure termed 'hydantoin' and discovered in 1861 by Baeyer[33] through hydrogenation of allantoin (**16**) (Scheme 1).




**Scheme 1: Discovery of hydantoin (17)**

The stability of a hydantoin is increased if it is substituted at the 5-position or protected on the nitrogen atoms.[34,35] 5,5-Substituted hydantoins are important medicinally, initially used as hypnotics and for treating chorea, they are now commonly used for the treatment of epilepsy. One of the first hydantoins used for its psycho-activity was nirvanol (**19**) in 1916. However, the toxic side effects of **19** led to the discovery of phenytoin (**20**) in 1939, this antiepileptic drug is listed on the World Health Organisation's List of Essential Medicines. Protection of one nitrogen atom with a methyl group reduces toxicity but can decrease anticonvulsant activity. This is exemplified with mephenytoin (**21**) that was reported to have similar efficacy to phenytoin (**20**) but lower toxicity.[31] Mephenytoin (**21**) was marketed as Mesantoin by Novartis as an antiepileptic. In 1996, nilutamide (**22**), protected on one nitrogen atom with an aromatic group, was FDA approved for the therapy of metastatic prostate cancer (Figure 7).[32]

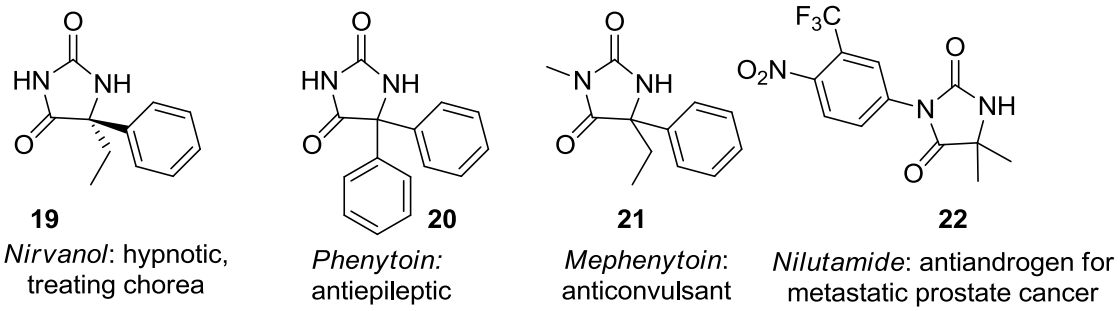
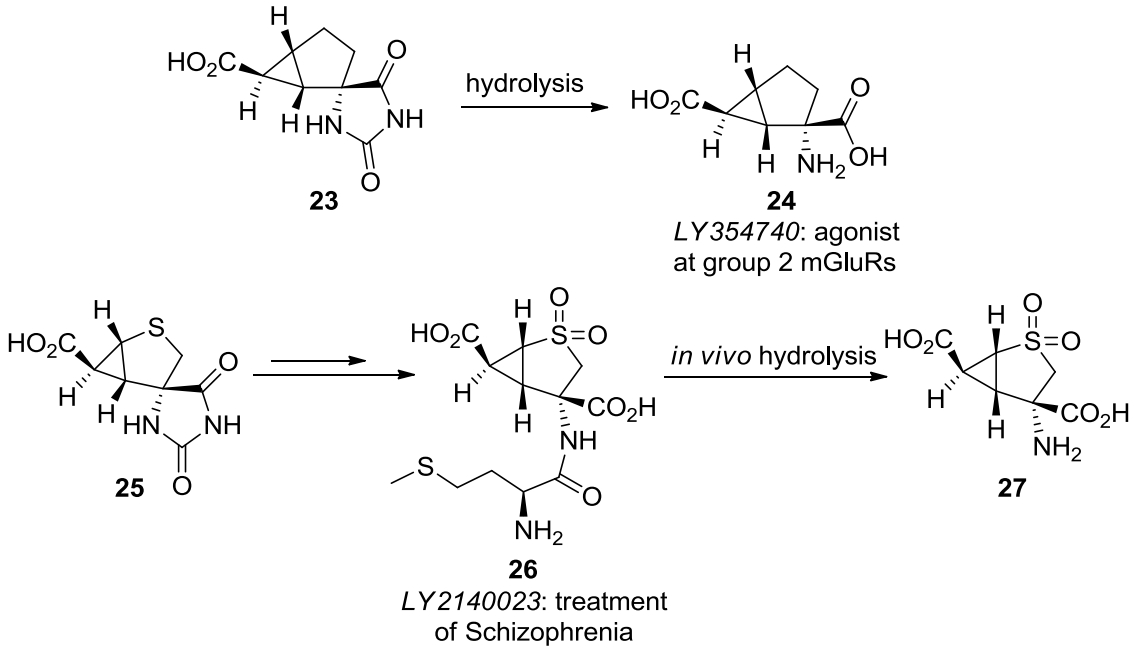



**Figure 7: Medicinally important 5,5-substituted hydantoins**

In the last 20 years, hydantoins have been abundant in the pharmaceutical industry. In 1997, Eli Lilly reported the preparation of LY354740 (**24**) a potent agonist at group 2 metabotropic glutamate receptors (mGluRs), which was synthesised through alkaline hydrolysis of hydantoin **23**.[36] In 2011, Eli Lilly published clinical candidate drug LY2140023 (**26**) bearing structural similarity to **24**, for the treatment of schizophrenia, which was synthesised from hydantoin **25** (Scheme 2).[37]




**Scheme 2: Hydantoins in the pharmaceutical industry**

Boehringer Ingelheim Pharmaceuticals reported a novel class of hydantoins that have potential as therapeutic agents in autoimmune diseases (**28a-c**) (Figure 8).[38] Furthermore, Galapagos Biotech reported the synthesis of hydantoin **29** containing a similar aryl nitrogen protecting group to **28a-c**. Hydantoin **29** showed anabolic activity on muscle with good bioavailability and pharmacokinetic properties and was investigated in phase I clinical trials (Figure 8).[39]

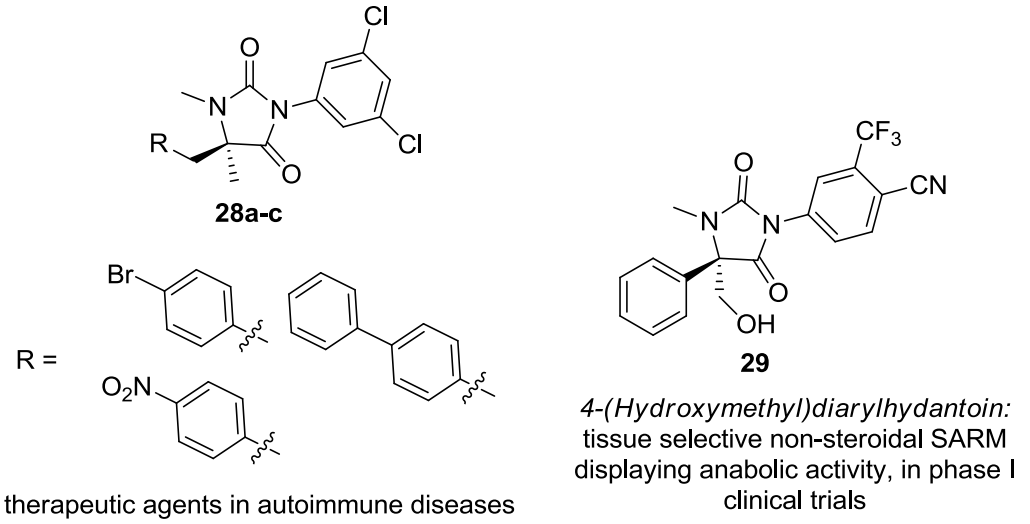
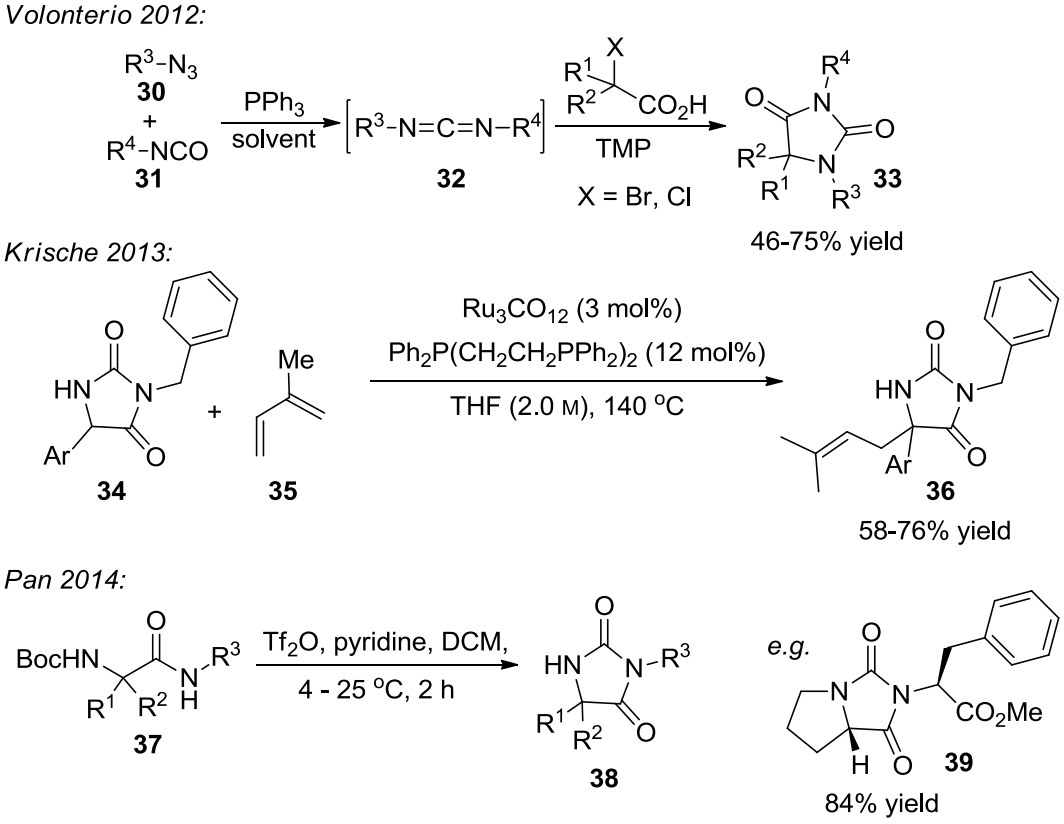



**Figure 8: Hydantoins with interesting biological properties**

In 2012, Volonterio *et al.*[40] reported a one-pot, three-component sequential procedure for the synthesis of hydantoins and spiro-hydantoins. In 2013, Krische *et al.*[41] used ruthenium catalysis for the α-allylation of hydantoins generating 5,5-substituted structures **36**. Most recently, Pan *et al.*[42] reported the synthesis of substituted hydantoins using a $Tf_2O$-mediated dual activation of dipeptides (Scheme 3).




**Scheme 3: Recent methods for the synthesis of hydantoins**

In conclusion, hydantoins are important structural motifs found in a range of natural products and have been exploited medicinally in drug structures. Despite their discovery over 150 years ago, methods for their synthesis are still being developed for uses as diverse as textile printing, polymerisation catalysis and in resins and plastics technology.[31]

## 1.3 Synthesis of Quaternary Amino Acids

The remainder of this chapter discusses some of the more important asymmetric methodologies for the synthesis of quaternary amino acids. The approaches for the asymmetric synthesis of quaternary amino acids have been grouped into alkylation and arylation methods. There are numerous methods available for the asymmetric α-alkylation of amino acids, but very few for α-arylation and currently these methods access only a limited substrate scope and are far from general.

For α-alkylation there are two disconnection approaches. Firstly, synthesis from tertiary amino acids (and their derivatives), which can be further defined based on asymmetric induction. For example, methods that use the configuration of the starting material alone to direct the asymmetry of the quaternary amino acid (chiral memory) and procedures that use external sources such as chiral catalysts or chiral auxiliaries to generate asymmetric quaternary centres. Secondly, the quaternary products may be achieved from alternative starting materials to tertiary amino acids with the major area being the Strecker synthesis but this approach will not be discussed further in this report.

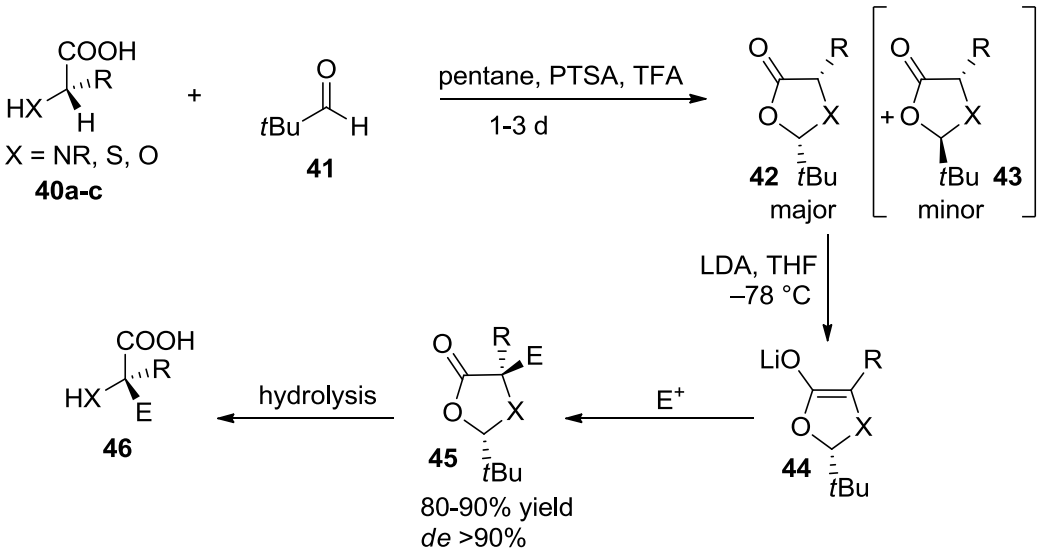
## 1.4 α-Alkylation

### 1.4.1 Self-Regeneration of Stereocentres

One of the classic methods within the field of stereoselective synthesis of α,α-disubstituted amino acids is the Self-Regeneration of Stereocentres (SRS), an area pioneered by Dieter Seebach and co-workers. The general principle involves starting from an α-tertiary amino acid and synthesising a chiral heterocyclic intermediate, for example an oxazolidinone or an imidazolidinone. This is necessary as one of the major challenges in making quaternary amino acids is the retention of the stereochemistry as the reaction goes *via* a planar enolate intermediate. These heterocyclic intermediates can be deprotonated to form an enolate, which can be stereoselectively alkylated due to the two diastereotopic faces of the enolate (Scheme 4).[8]

In 1981, Seebach and Naef described the first results relating to diastereoselective reactions of chiral enolates from α-heterosubstituted carboxylic acids (Scheme 4).[43] The initial reaction was the condensation of heterosubstituted carboxylic acid **40** and aldehyde **41** under acid catalysed conditions with azeotropic removal of water to form heterocycles **42** and **43**. The heterocycles were formed as a mixture of *syn* and *anti* products, which were then separated. The *syn*-heterocycle **42**

was deprotonated with LDA at the α-position forming chiral enolate **44** that underwent diastereoselective reactions with electrophiles such as alkyl halides, aldehydes or ketones. Finally, hydrolytic cleavage of the heterocycle afforded α-quaternary acids (**46**).




**Scheme 4: First example of Self-Regeneration of Stereocentres**

The asymmetry of this reaction was introduced by a temporary chiral centre, which itself was induced from the configuration of the starting material, hence the term 'self-regeneration'. The *syn* form of heterocycle **42** predominates, as both the *t*Bu and R group occupy pseudo-equatorial positions on the 5-membered ring. The electrophile then adds *anti* to the bulky *t*Bu group that is blocking the bottom face (Figure 9).

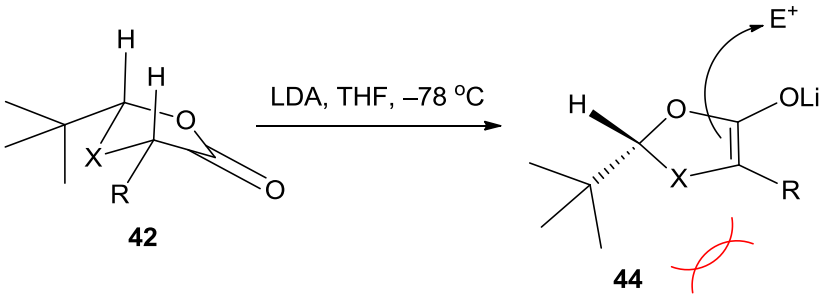
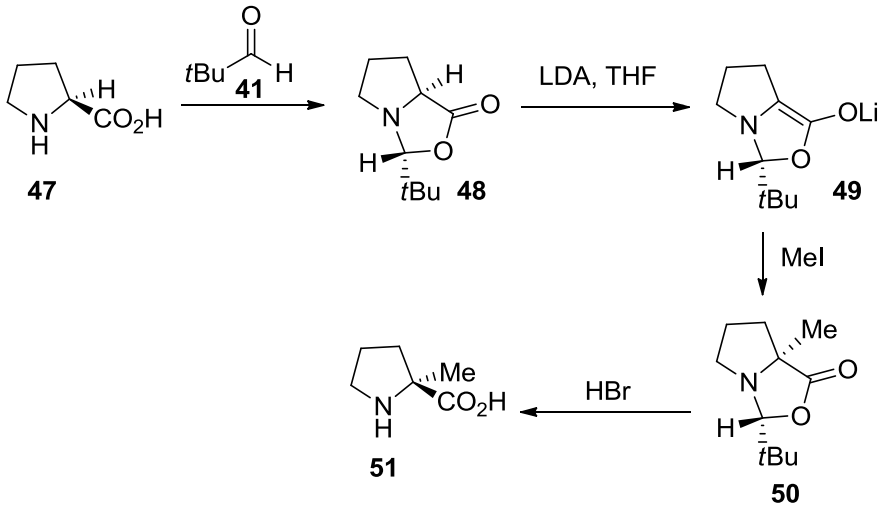



**Figure 9: *Syn* form predominates and electrophile adds *anti* to *t*Bu**

This methodology has been extended to the α-alkylation of α-tertiary amino acids, in 1983 proline was substituted at the α-position with retention of configuration *via* an oxazolidinone intermediate (Scheme 5).[44] The α-stereocentre in proline (**47**) induces selective generation of the new centre in **48**. Upon formation of enolate **49**, the original stereocentre is destroyed and the electrophile adds to the enolate with asymmetric induction controlled by the new stereocentre created in **48**. This method is synthetically useful as there is minimal loss of enantiomeric purity in the transformation and enantiopure products can be obtained from readily available and cheap α-amino acids. In this

example, the *t*Bu group lies on the *exo* face in the equatorial position due to the constrained bicyclic system and the *t*Bu group is *anti* to the α-substituent in **48**.




**Scheme 5: α-Alkylation of proline**

Different electrophiles were added to proline derivative **48** including alkyl halides, carbonyl compounds, and Michael acceptors. The configuration of the product was rationalised through consideration of structures **52** and **53** in Figure 10, which show the product from addition of benzaldehyde.[44] Overall there was retention of configuration after electrophilic addition. In the proposed transition state **53**, the OH and the carbonyl oxygen are close in space as they are coordinated by a lithium atom (Figure 10).[44] Other amino acids such as serine[45] and cysteine[46] have also undergone this Self-Regeneration of Stereocentres procedure to form quaternary amino acids *via* an oxazolidine type intermediate.

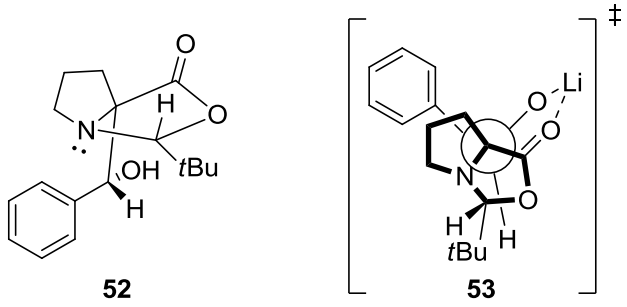
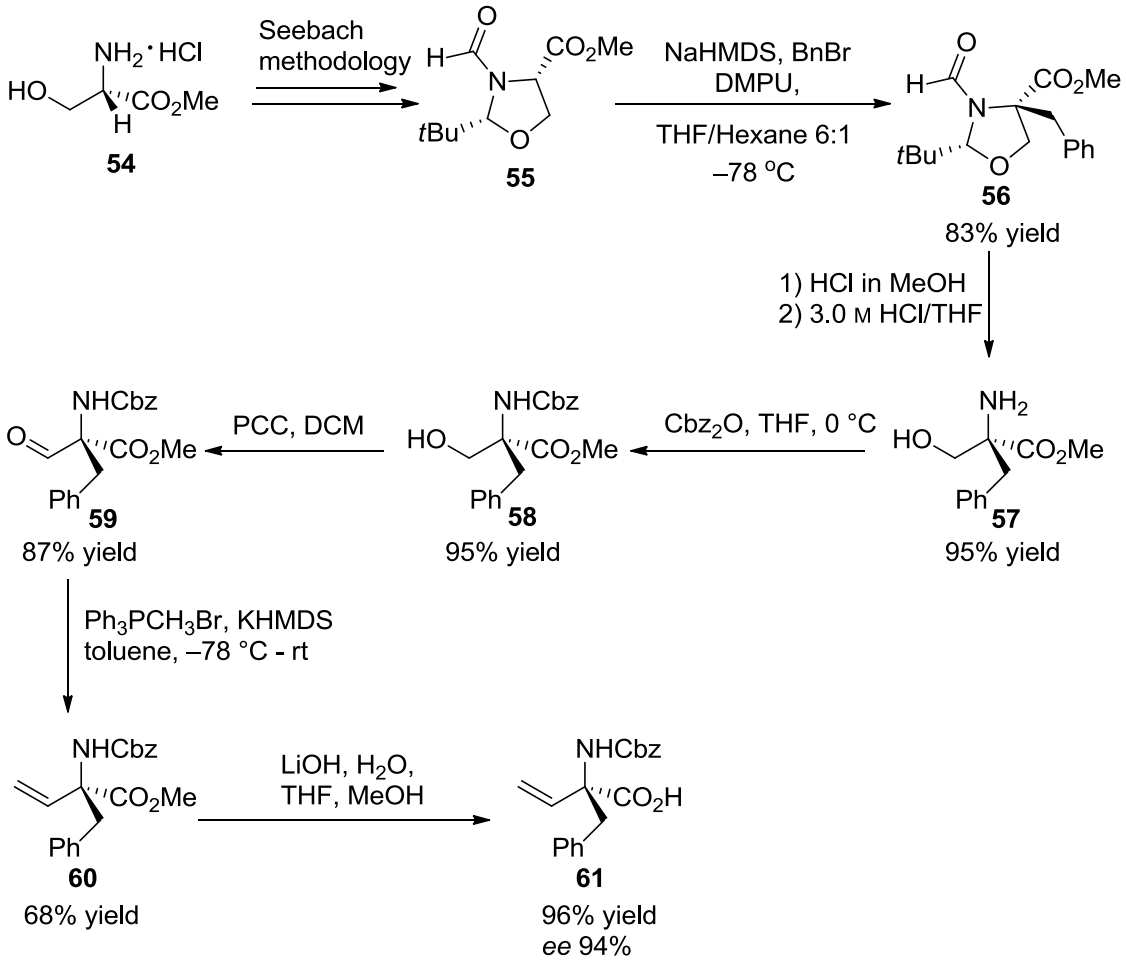



**Figure 10: Determination of the configuration of the product**

Seebach's method[47] of forming a temporary stereocentre that controls the α-addition has been used more recently to form α-vinyl-α-alkyl amino acids. The synthesis of (*S*)-*N*-CBz-α-vinyl phenylalanine (**61**) has been achieved *via* alkylation of an enolate generated from an oxazolidine.[48] The key step in the synthesis was the Wittig reaction of enantioenriched (*S*)-*N*-CBz-α-alkyl amino ester **59**, which was made using the stereoselective alkylation. To improve the yields of the reaction

the alkylation conditions were changed from LDA and HMPA to milder base NaHMDS and DMPU in a mixed solvent system (Scheme 6).



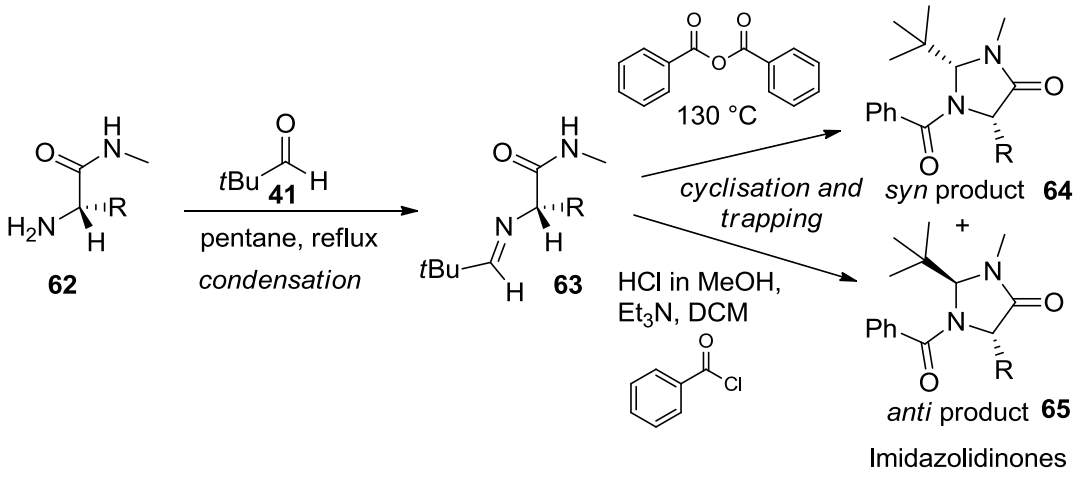

**Scheme 6: Formation of (*S*)-Cbz-α-vinyl-alkyl amino acids**

Vinyl groups in the α-position of an amino acid are useful as they have important biological features and can induce large conformational changes when incorporated in peptides. This motif is also important in enzymatic inhibitors and can increase a peptides' resistance to proteolysis.[48]

Nishi *et al*. also used Seebach's methodology with L-serine-methyl ester to generate an oxazolidine that was converted into a number of α,α-disubstituted α-amino alcohols, which are significant components of novel immunomodulators.[49] For the procedure to be carried out on a multi-kilogram scale the conditions had to be modified with *t*BuOK added *via* inverse addition with tetraglyme as an additive and temperatures maintained between –13 and –20 °C to give the product in 90% yield and a *de* > 99%.

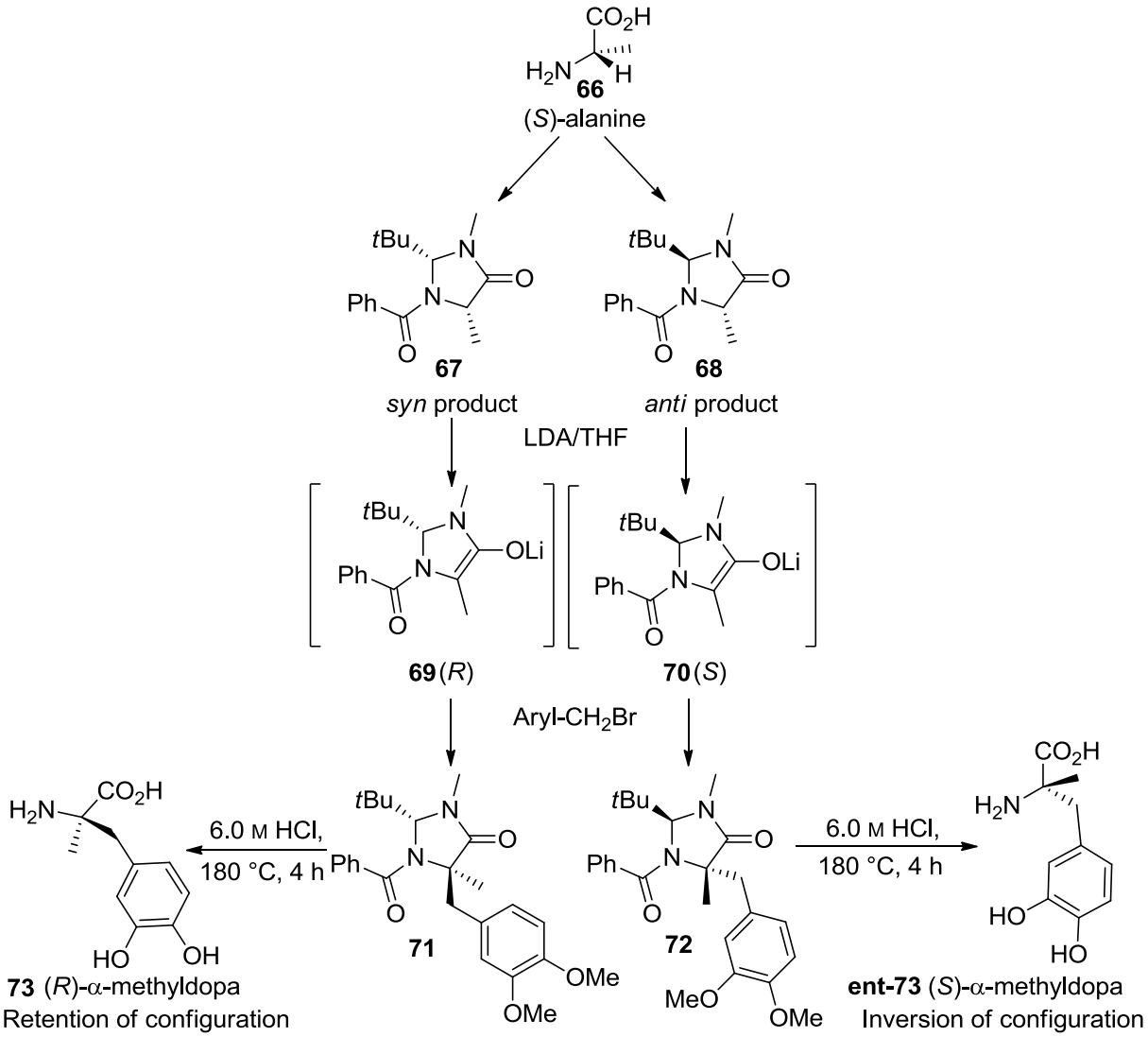
Seebach *et al.* showed that it was possible to prepare imidazolidinones of (*S*)-alanine, (*S*)-phenylalanine, (*R*)-phenylglycine, (*S*)-methionine and (*S*)-valine.[50] Amino acid esters were

converted into *N*-methylamides (**62**), which were first condensed with pivalaldehyde (**41**) to give **63**, before being cyclised and trapped to give *syn* and *anti* imidazolidinones (**64** and **65**) (Scheme 7).



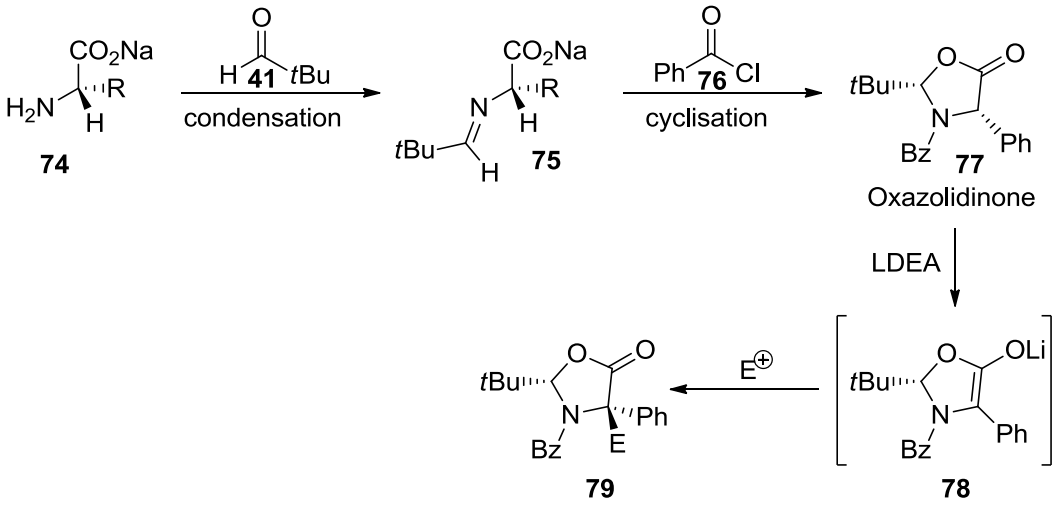

**Scheme 7: Formation of imidazolidinone intermediates**

Imidazolidinones can be deprotonated to form enolate intermediates that can undergo the Self-Regeneration of Stereocentres chemistry. Seebach *et al.* synthesised (*R*) and (*S*)-α-methyldopa (**73** and **ent-73**) from (*S*)-alanine (**66**). (*S*)-Methyldopa is an example of a biologically active α-branched-α-amino acid that displays hypotensive activity. It is also found as a residue in some physiologically active oligopeptides.[51] (*S*)-Alanine (**66**) was converted into *syn* and *anti* imidazolidinones **67** and **68** by the procedure described above (Scheme 7) and the corresponding enolates **69** and **70** were formed by deprotonation with LDA. Alkylation with 3,4-dimethoxybenzylbromide forms 5,5-disubstituted imidazolidinones **71** and **72**, which could be separated and the methyldopa products (**73** and **ent-73**) were obtained through ring-cleavage using HCl. The alkylation occurred from the opposite face to the *t*Bu group, resulting in overall retention of configuration through the *syn* isomer and inversion *via* the *anti* isomer (Scheme 8).[51]




**Scheme 8: Synthesis of (*R*) and (*S*)-α-methyldopa from (*S*)-alanine**

Seebach *et al.* subsequently found that it was possible to generate oxazolidinone intermediates **77** (Scheme 9) directly from the sodium salts of amino acids *via* condensation with pivalaldehyde (**41**) and then cyclisation using benzoyl chloride (**76**) at room temperature.[52] In this case the *syn* isomer was the major product formed.



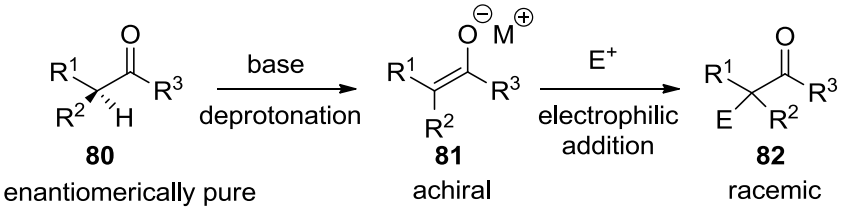

**Scheme 9: Formation of an oxazolidinone intermediate**

To form enolate **78** from the oxazolidinones LDEA ($LiNEt_2$) was required as a base as LDA gave low yields. Hydrolysis of the oxazolidinones was possible using 6.0 M HCl at room temperature in the presence of $FeCl_3/SiO_2$. These are milder hydrolysis conditions than the methodology previously described that required reflux in 6.0 M HCl, making this method more useful.

In summary, starting from α-tertiary amino acids, a chiral heterocyclic intermediate can be synthesised that can be deprotonated to form a chiral enolate, which is stereoselectively alkylated as the two faces of the enolate are diastereotopic. The chirality of the α-position is destroyed in the formation of a planar enolate intermediate but a temporary asymmetric centre, which itself was induced from the configuration of the starting material, leads to enantiomerically enriched products.

### 1.4.2 Chiral Memory

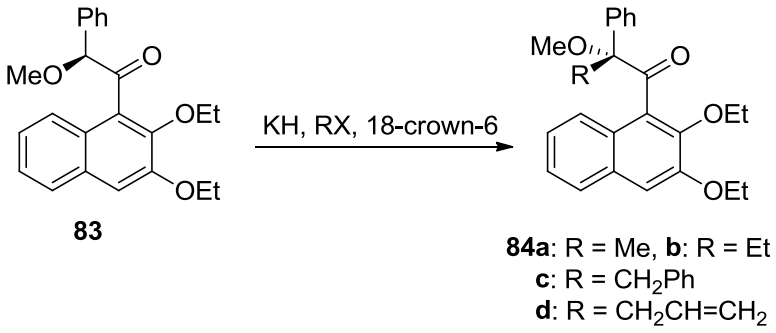
Kawabata and co-workers have pioneered an area of enolate chemistry termed 'Chiral Memory.' This is similar to Seebach's 'Self-Regeneration of Stereocentres (SRS)' approach, as it addresses the issue of amino acid enolates 'remembering' the initial configuration of the starting amino acid. The configuration of the starting material is lost upon deprotonation and formation of a planar enolate prior to alkylation. Their initial communication in 1991 challenged the accepted view of the time that upon formation of an enolate the chiral information is lost and therefore that any addition products generated would be racemic in the absence of an external chiral influence (Scheme 10).[53]




**Scheme 10: Loss of chirality upon enolate formation**

Initial experiments (Table 1) showed that in the absence of an external chiral source the product formed from the alkylation of enolate **85** was non-racemic (Figure 11). The size of the electrophile did not affect the degree of asymmetric induction, suggesting the enolate was responsible for the observed selectivity. It was concluded that the chirality of the α-stereocentre is preserved as axial chirality in the intermediate enolate, leading to the formation of non-racemic products.[53]

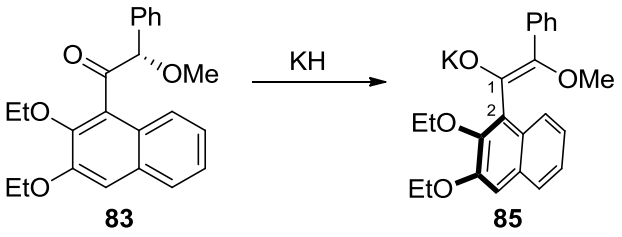
**Table 1: Initial results disproving the achirality of enolate intermediates**




| Entry | RX | Product | Yield (%) | *ee* (%) |
|---|---|---|---|---|
| 1 | MeI | **84a** | 48 | 66 |
| 2 | EtI | **84b** | 27 | 65 |
| 3 | $PhCH_2Br$ | **84c** | 31 | 67 |
| 4 | $CH_2=CHCH_2Br$ | **84d** | 36 | 48 |

In 1998, Kawabata *et al.* published a further explanation of the observed 'chiral memory' effect. It is not only necessary to consider organic molecules in three dimensions, but also to consider the fourth dimension of time. Through consideration of time, an enolate is not always achiral and the chirality of the starting material can be preserved in the reactive enolate intermediate for a 'limited time.' They suggest that this is similar to an equilibrium between two enantiomeric forms that under normal conditions are indistinguishable but can be differentiated by lowering the temperature or having geometric constraints. This idea was proven using a bulky naphthyl substituent in the starting material, which introduced a geometrical constraint (**83**, Table 1). The enolate adopted a specific structure that maintained the original configuration at low temperature but racemised with

an increase in temperature leading to loss of chirality.[54] For example, the chirality of **83** is transferred to the bond between C1 and C2 in **85** upon enolate formation, leading to an axial chiral enolate (Figure 11).

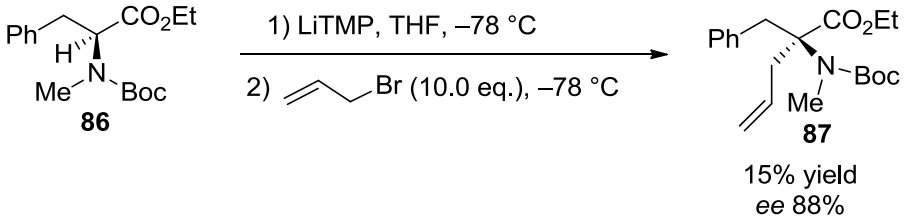



**83** **85**

**Figure 11: Transfer of chirality to axial chirality about the $C_1$-$C_2$ bond[53]**

α-Methylation of substrates with alkoxycarbonyl protecting groups such as Boc gave good levels of asymmetric induction. For *N*-Boc-phenylalanine ethyl ester in THF at –78 °C using LiTMP or LDA the alkylation occurred with retention of configuration (Scheme 11), yet with KHMDS inversion was observed. In addition the number of equivalents of base affected the asymmetric induction with more base decreasing the efficiency. Therefore chiral memory was possible with varying levels of asymmetric induction observed depending on the conditions[55] and the protecting groups on the nitrogen.

The greatest *ee* of 88% was found for the phenylalanine derivative **86** using allyl bromide, although the yield was only 15% (Scheme 11).[56] Investigation of phenylalanine derivatives showed the overall optimum conditions for high yield (88%) and *ee* (84%) used Boc and MOM nitrogen protecting groups and KHMDS as a base.[54]

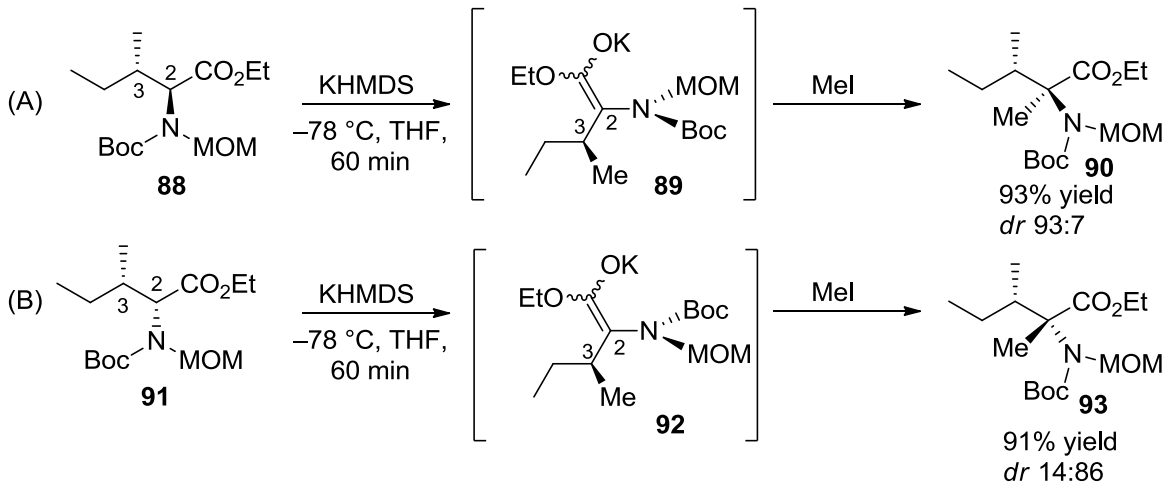



**86** **87**

15% yield
*ee* 88%

**Scheme 11: Formation of α,α disubstituted amino acid derivatives using chiral memory**

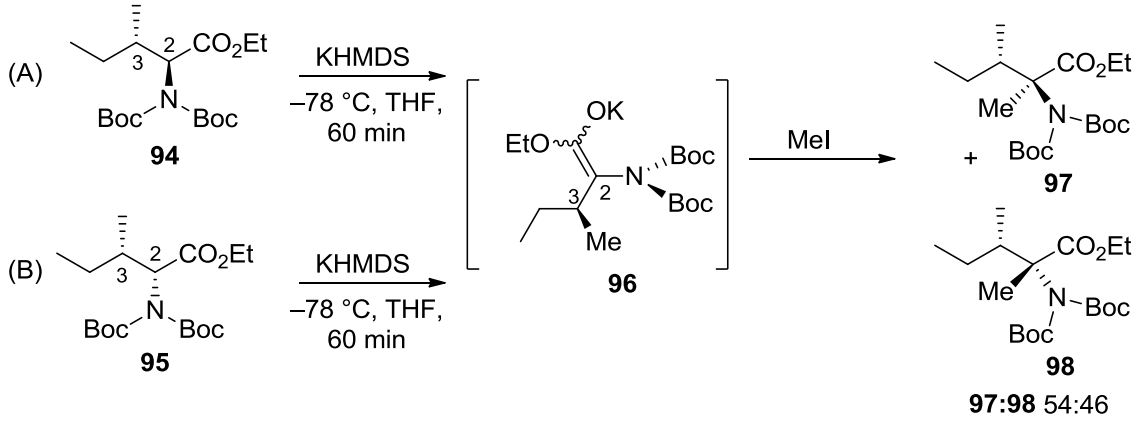
The optimal conditions were applied to the α-alkylation of isoleucine **88** and allo-isoleucine **91** to form amino acid derivatives **90** and **93** with α-quaternary centres (Scheme 12).[57]




**Scheme 12: α-Alkylation of isoleucine and allo-isoleucine**

Kawabata *et al.* showed that the chirality of the product was controlled solely by the axial chirality of the enolate intermediate and that other stereocentres in the molecule had little influence. The example in Scheme 12 showed the central chirality at C2 is preserved during the reaction because of the restricted rotation of the C2-N bond due to the nitrogen protecting groups.[57] If the chirality was lost upon formation of the enolate the same diastereomeric ratio for the products of reactions (A) and (B) would have been observed. However, they were considerably different (*dr* 93:7 *vs dr* 14:86) proving that two distinct diastereomeric enolate intermediates had been formed.

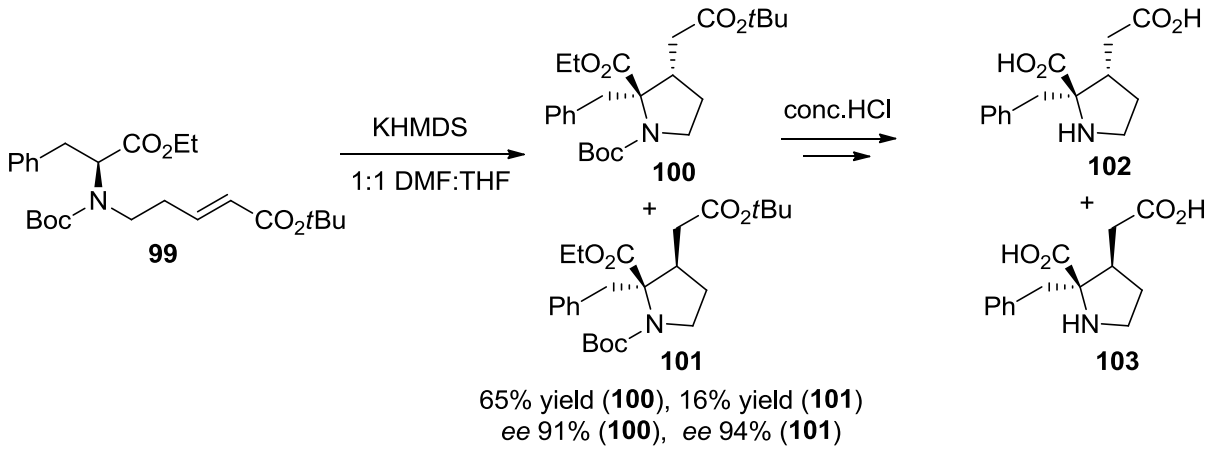
The fact that the stereocentre at C3 had little influence over the stereochemistry in the product was further proved when the nitrogen was protected with two Boc groups (Scheme 13). In this case, both diastereomers of the starting material **94** and **95** formed the same enolate intermediate **96** and gave the product **97** and **98** in the same diastereomeric ratio[58]




**Scheme 13: Proof that the C3 substituent had little control over the stereochemistry of the product**

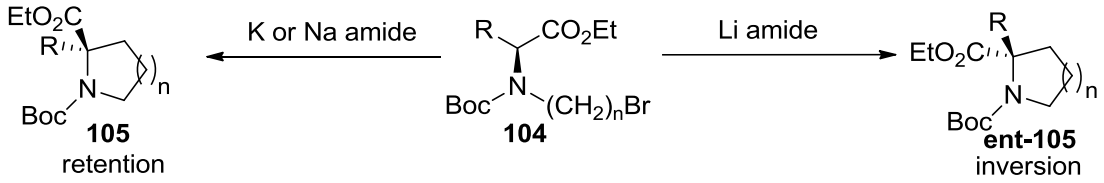
This methodology was applied to the synthesis of cyclic amino acids with quaternary centres[59] using a stereoselective intramolecular conjugate addition controlled by an axial chiral enolate.

Pyrrolidine, piperidine, and tetrahydroisoquinoline derivatives containing adjacent quaternary and tertiary stereocentres were synthesised in high *ee* using KHMDS in 1:1 DMF:THF. These multi-substituted nitrogen heterocycles are common motifs in drug discovery and have been used in the synthesis of natural products (Scheme 14).[60]




**Scheme 14: Formation of nitrogen heterocycles using chiral memory**

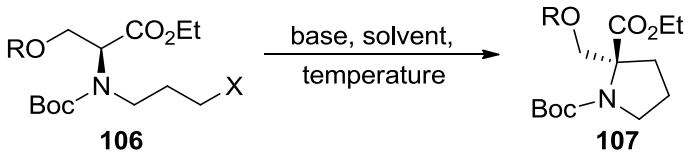
In 2006, Kawabata *et al.* reported the ability to access either enantiomer of nitrogen heterocycles from L-α-amino acids (**105** and **ent-105**) by simply changing the base used for the alkylation. Potassium and sodium amides in DMF at –60 °C gave product **105** with retention of the configuration, whereas lithium amides in THF or toluene up to 0 °C gave inversion product **ent-105** (Scheme 15). For four and five membered rings enantiomeric enrichment of >95% were observed using KHMDS and >80% *ee* was obtained with LiTMP.[61]




**Scheme 15: Through changing the base the opposite enantiomer can be obtained**

It was assumed low temperatures were crucial to achieving a reasonable *ee* in the asymmetric reaction because the half-life of the enolates with the MOM and Boc protected nitrogen at –78 °C was around 22 h, yet at 20 °C it was <0.1 s. However, intramolecular reactions (as in Scheme 15) of the chiral enolates could be carried out at 20 °C in DMSO (1% water) with powdered KOH rather than under anhydrous and low temperature conditions. Four and five membered cyclisations showed greater selectivity under these conditions and generate a highly reactive axial chiral enolate that cyclises rapidly before racemisation. The more reactive the intermediate, the faster the cyclisation and the higher the *ee*.[62] This was extended to the asymmetric cyclisation of serine derivatives, with CsOH as the preferred base (Table 2).[63]

**Table 2: Asymmetric cyclisation at ambient temperature with KOH/CsOH vs KHMDS at low temperature**

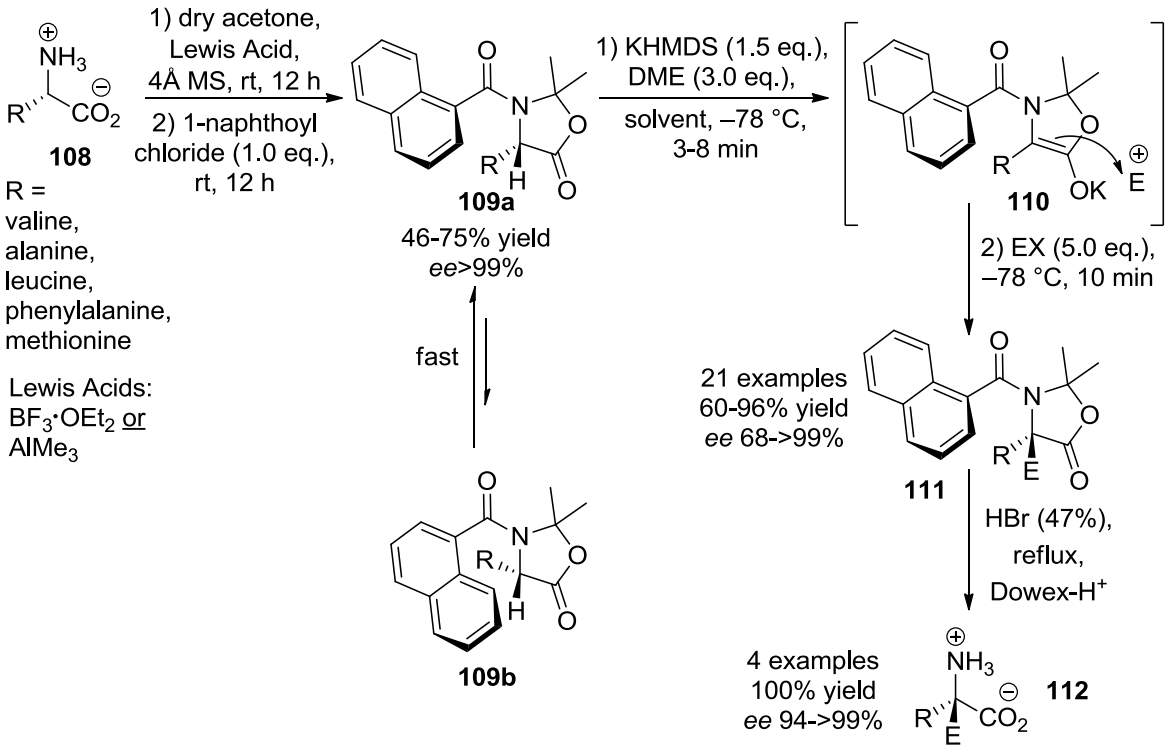



106 107

| Entry | R | X | Base (eq) | Solvent | Temp (°C) | Time (min) | Yield (%) | *ee* (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | Bn | Br | KHMDS (1.5) | THF | –78 | 30 | 96 | 34 |
| 2 | Bn | Br | KOH (3.0) | DMSO | 20 | 60 | 97 | 75 |
| 3 | *t*Bu | I | CsOH (1.5) | DMSO | 20 | 60 | 77 | 94 |

In summary, Kawabata *et al.* have shown a metastable axial-chiral enolate intermediate could be generated. Through modification of the reaction conditions and careful choice of the nitrogen protecting group it is possible to perform asymmetric additions to these enolates to obtain enantioenriched quaternary amino acid derivatives. The products are produced in a high *ee* without the need for an external chiral source as the memory of the configuration of the starting material generates the enantiomeric purity in the product.

In 2009, Kouklovsky *et al.*[64] synthesised a variety of α,α-disubstituted quaternary amino acids in excellent yields and *ee*. Oxazolidinones (**109**) were prepared from amino acids using dry acetone followed by 1-naphthoyl chloride. In this case the stereoselectivity is controlled by the formation of an axial chiral intermediate from the aromatic nitrogen substituent. Prior to deprotonation Ar-C=O bond rotation is fast with conversion occurring between **109a** and **109b**. However, there is preferential deprotonation of conformer **109a** as the ring proton is less sterically hindered. Once the enolate has formed rotation about the Ar-C=O bond is slow, leading to memory of the chirality and alkylation with global retention (**111**) on the opposite face to the naphthyl ring. Finally some examples were converted into quaternary amino acids **112** by heating at reflux with HBr (Scheme 16).



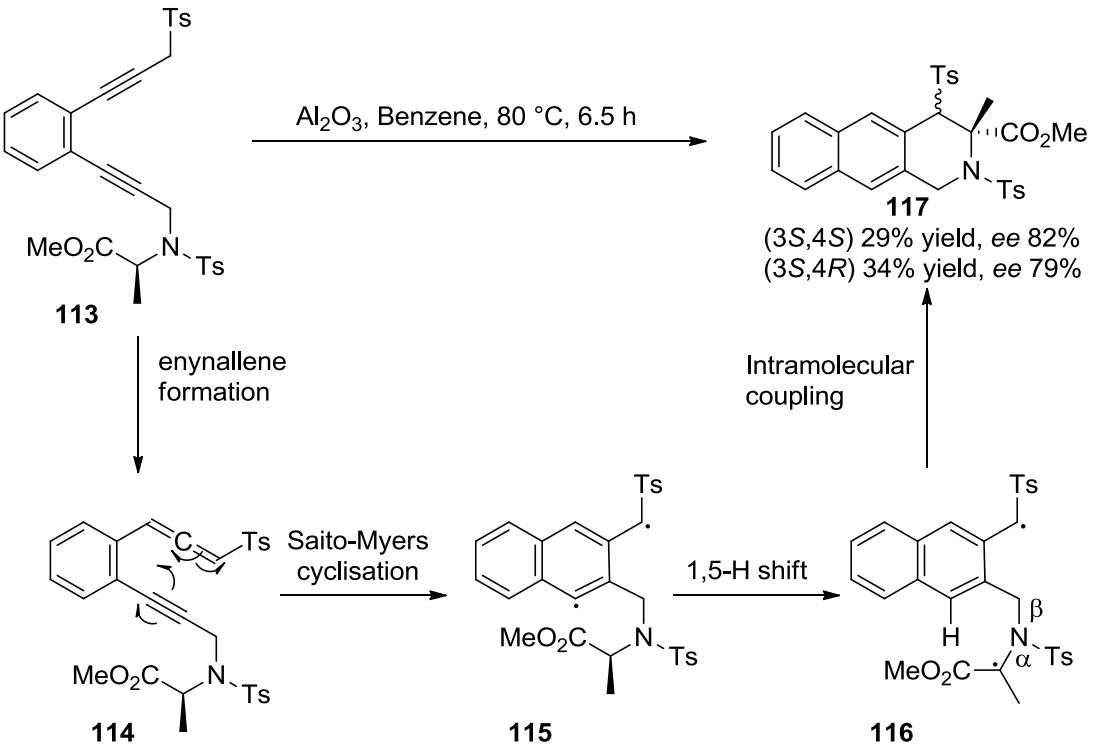

**Scheme 16: Synthesis of α,α-disubstituted quaternary amino acids using oxazolidinones with memory of chirality**

In 2014, this methodology was applied to an aldol reaction using an aldehyde as the electrophile to synthesise enantiopure β-hydroxy quaternary α-amino acids. Cleavage of the oxazolidinones was achieved with 6.0 M HCl in a sealed tube at 125 °C for 24 h.[65] Clayden *et al.* have also used Kouklovsky's method to synthesise 2-aminoisobutyric acid (Aib) with one of the methyl groups $^{13}C$ labelled this was achieved through retentive alkylation of a L-alanine derived intermediate with $^{13}C$ labelled methyl iodide.[66]

In 2012, the use of chiral memory was exemplified further when it was applied to an asymmetric aldol reaction, generating chiral oxazolidinones.[67] These can be converted into β-hydroxy quaternary α-amino acids[64] that are important in natural products. In 2013, memory of chirality was applied to the synthesis of biologically active alkaloid manzacidin A, through an asymmetric intermolecular conjugate addition reaction.[68]

Other groups have also used a memory of chirality approach to synthesise quaternary amino acids. Nechab and Bertrand *et al.* showed the chirality of the starting material was preserved in an intermediate during a cascade rearrangement to generate a quaternary stereogenic centre (Scheme 17). This is one of the few examples known of the reactive intermediate being a radical rather than an enolate.[69] Intermediate **116** is planar but due to the high rotation barrier about the α-C-N bond memory of the initial conformation occurs and is replicated during the intramolecular coupling.

Racemisation through rotation about the β-bond is suppressed by controlling the steric bulk of the substituents on the nitrogen. To improve the diastereoselectivity of the reaction, an electron withdrawing tosyl group was introduced at the allene terminus. In 2012, this method was used to form related six and seven membered rings containing quaternary stereocentres.[70]




**Scheme 17: Memory of chirality with a radical intermediate**

## 1.4.3 External Chiral Influences

In contrast to Seebach and Kawabata's methodology in which the chirality is induced from the configuration of the starting material and 'remembered' in the reaction, alternative approaches use external chiral sources such as catalysts or auxiliaries to control the stereochemistry.

### 1.4.3.1 Catalysts

#### 1.4.3.1.1 Transition Metal Catalysis

Trost *et al*. showed that it was possible to use chiral palladium catalysts to control the asymmetric allylic alkylation of azlactones (Scheme 18(a)).[71] Similar methodology was also applied to the reaction of azlactones with alkoxyallenes.[72] The asymmetric allylation proceeded *via* a π-allyl complex of the transition metal, followed by nucleophilic attack of the enolate generated from the azlactone by basic deprotonation. The transition state structure is proposed to exist as in Figure 12, favoured as it minimises steric interactions. However, the asymmetric configuration of the final product depends on the ligand, π-allyl species and the nucleophile used.

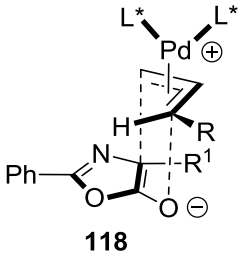
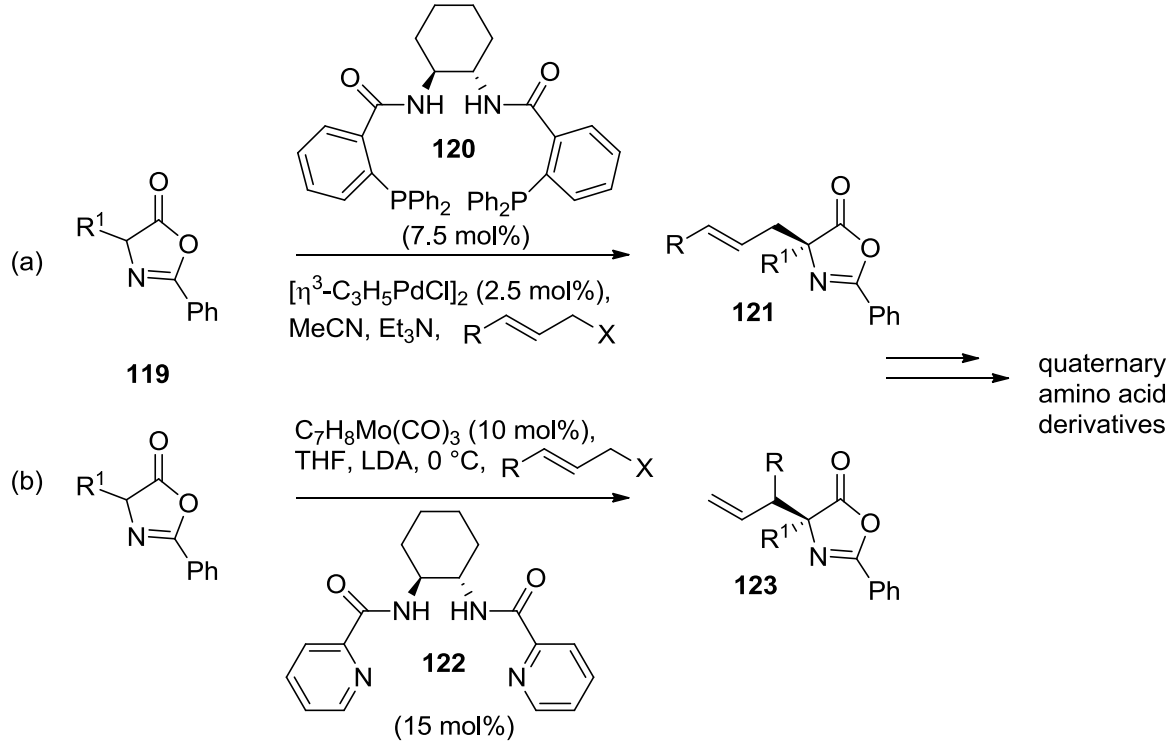



**Figure 12: Proposed transition structure for palladium catalysed reactions**

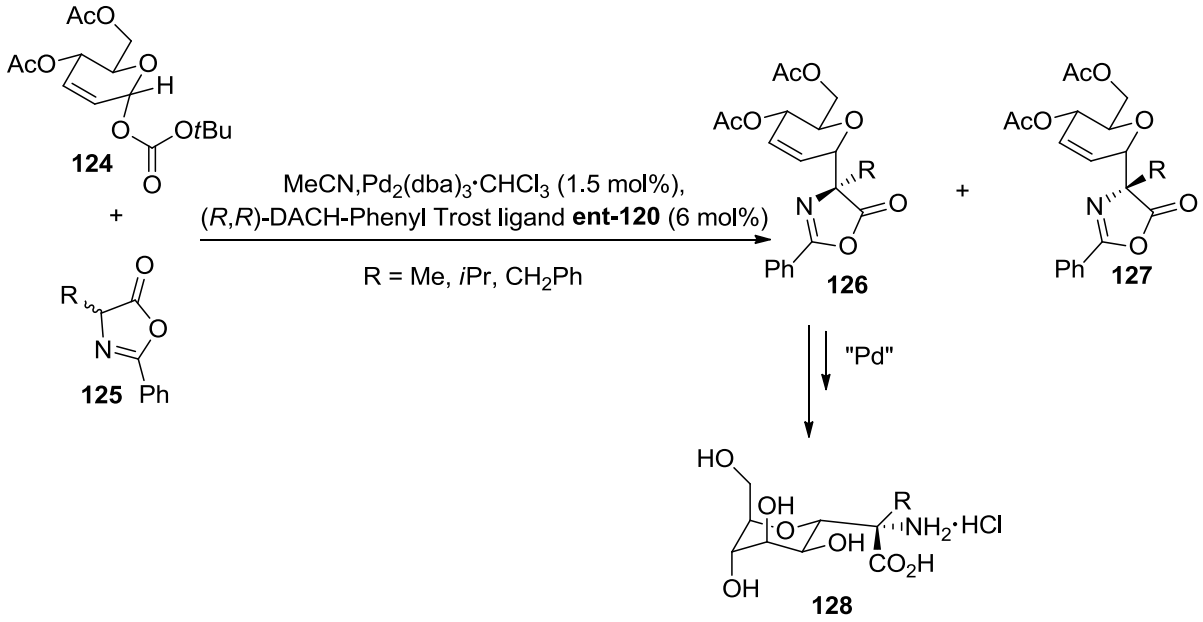
It was possible to obtain different regioisomers of product **121** by changing from a palladium to a molybdenum based catalyst.[73] Using the chiral molybdenum catalyst with ligand **122** it was possible to preferentially form the branched isomer **123** over the linear isomer **121** with *ee* >90% (Scheme 18(b)).




**Scheme 18: Asymmetric allylic alkylation reactions of azlactones to form amino acid precursors**

Recently, others have shown allylic alkylation of glycal-derived π-allyl Pd (II) intermediates as a key step in the stereoselective synthesis of α-D-C-mannosyl-(*S*)-amino acids (**128**) (Table 3).[74] Azlactones of alanine, phenylalanine and valine underwent asymmetric alkylation controlled using a chiral ligand with a palladium catalyst. The optimum conditions for the formation of the alkylated azlactone (**126**) are shown in Table 3, all of which gave excellent levels of diastereoselectivity.[74]

**Table 3: Yield and *dr* for the formation of alkylated azlactones:**

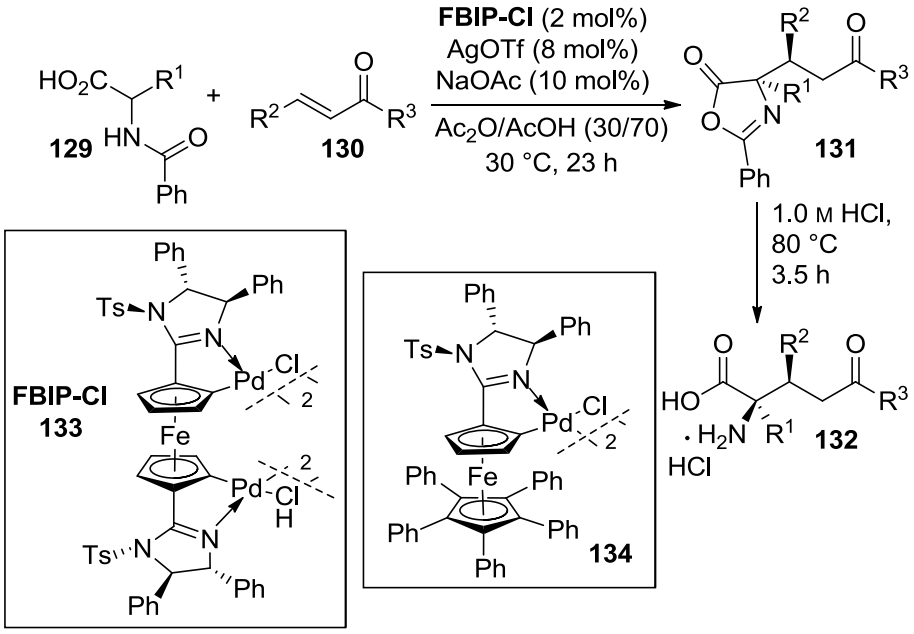



| Entry | R | Time (min) | Yield (%) | *dr*(126:127) |
|---|---|---|---|---|
| 1 | $CH_3$ | 42 | 82 | 99:1 |
| 2 | *i*Pr | 60 | 84 | 99:1 |
| 3 | $CH_2Ph$ | 42 | 81 | 99:1 |

Finally, Trost *et al.* extended the palladium-catalysed methodology to asymmetric benzylation of azlactones, using benzylic phosphates as electrophiles, which gave the products in excellent yields and *ee*.[75,76] In 2014, Jiang *et al.* carried out Brønsted acid accelerated asymmetric allylations using similar conditions to Trost, but there was no need for a base and allylic alcohols could be used directly. The reaction proceeded with a palladium complex using Trost's ligand in the presence of benzoic acid and was successful on a gram scale.[77]

Peters *et al.* have developed an approach that combines a bispalladacycle of ferrocene **133** with a Brønsted acid and base to carry out 1,4-Michael additions involving azlactones.[78,79] The azlactone **131** was generated *in situ* using an anhydride. It is proposed that activation of the azlactone for enolisation occurs through bidentate coordination to both palladium atoms of the catalyst **133**. The Brønsted base (NaOAc) carries out the deprotonation to form the enolate with one face blocked by the ferrocene, resulting in addition of the enone from the opposite face, which is itself activated by the Brønsted acid (AcOH). The products are obtained with excellent *ee* and can be converted into quaternary amino acids through hydrolysis with 1.0 M HCl at 80 °C for 3.5 h (Scheme 19).

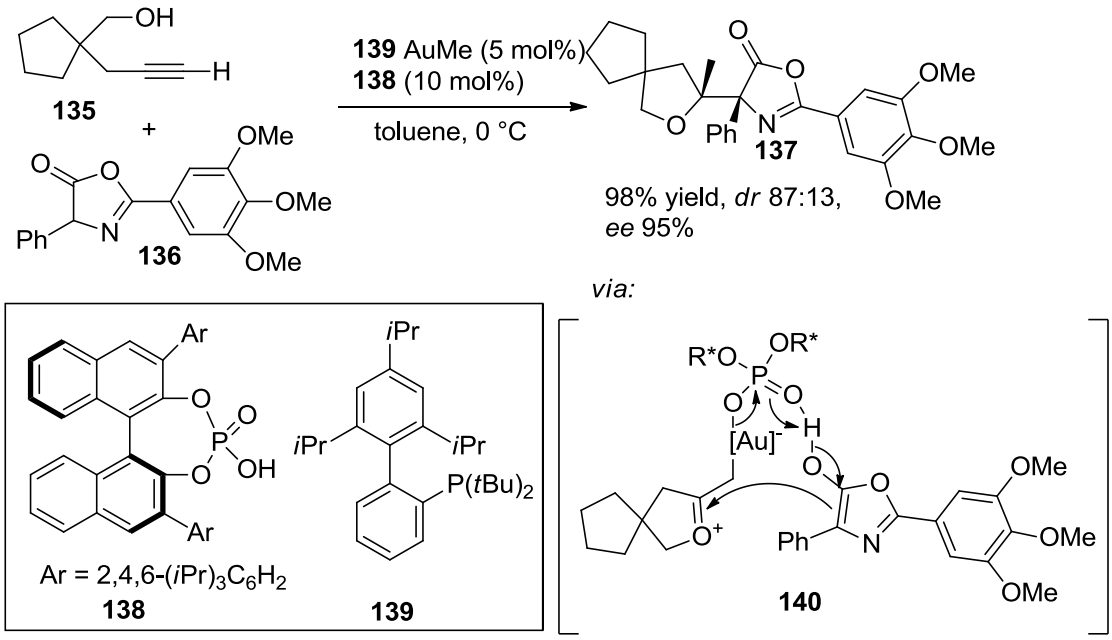
Monopalladocycle catalyst **134** was also shown to be a viable alternative for these transformations.[80]




**Scheme 19: Synthesis of quaternary amino acids through 1,4-Michael addition to an azlactone**

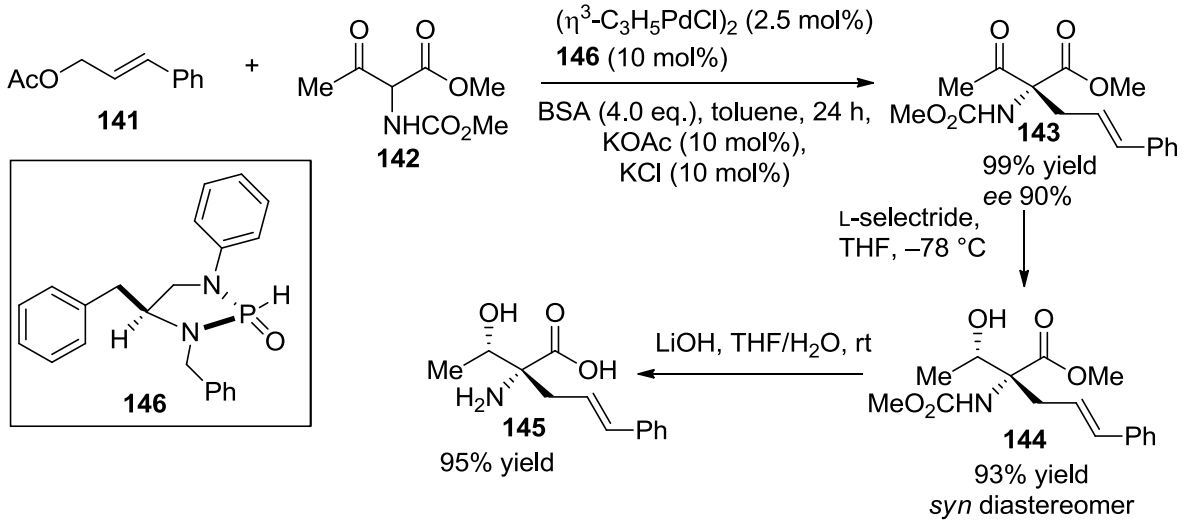
Bispalladocycle **133** was also applied to the synthesis of succinimides using a 1,4-addition followed by a Nef reaction[81] and synthesis of spirocyclic azlactones through a double Michael addition.[82]

Other metals have been successful in the asymmetric synthesis of α-quaternary amino acids. Chiral gold phosphates and phosphoric acids have been used for the synthesis of conformationally restricted α-quaternary amino acid precursors. The reaction involved an asymmetric cyclisation of alkynol **135** followed by addition to azlactone **136**. The scope of substrates was large, generating products with high enantioselectivity, an example of which is shown in Scheme 20.[83] The proposed transition state is shown in **140**. Firstly, an enol ether is formed through intramolecular hydroalkoxylation with the gold catalyst. Then, a chiral oxonium intermediate is generated through coordination of the enol double bond with the gold catalyst that is also coordinated with the chiral phosphoric acid. The phosphoric acid interacts with the azlactone through hydrogen bonding and directs the enolate addition reaction onto the enone.



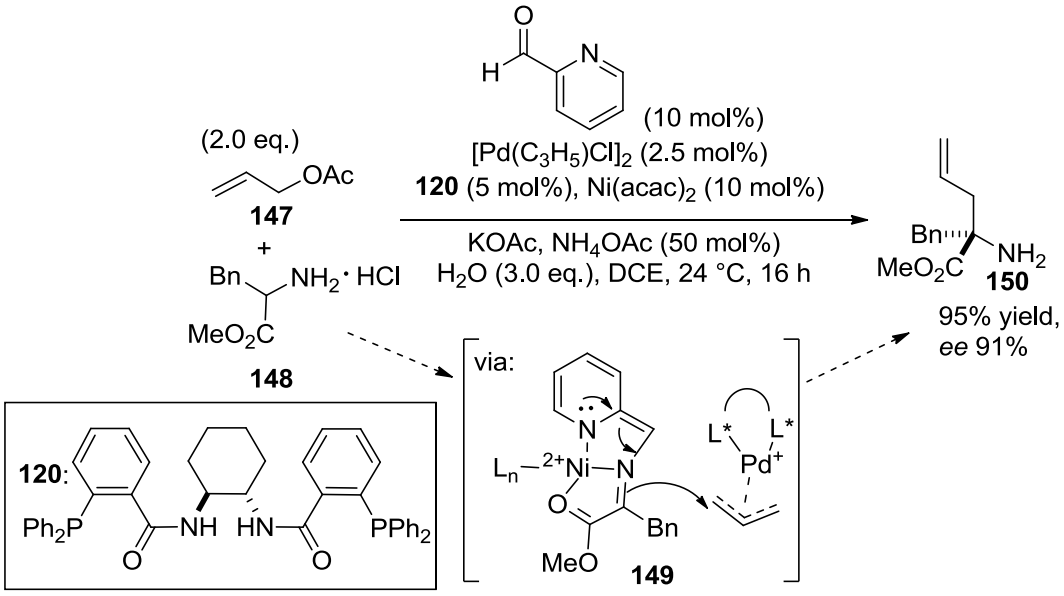

**Scheme 20: Synthesis of conformationally restricted precursors to amino acids**

Asymmetric alkylation using transition metal catalysis has been demonstrated for alternative substrates to azlactones. Hamada *et al.* reported a palladium-catalysed asymmetric allylation of a tertiary amino acid derivatives **142**. Good enantioselectivity was obtained and **144** was hydrolysed under mild conditions into the corresponding quaternary amino acid **145** (Scheme 21).[84]




**Scheme 21: Formation of quaternary amino acids from β-keto esters through palladium catalysis**

Recently, Aron *et al.* described a catalytic α-allylation from unprotected amino acid esters. The reaction proceeds *via* a palladium π-allyl complex and enantioselectivity is achieved using a chiral ligand. They reported that through the addition of nickel (II) salts and picolinaldehyde reactivity at the α-carbon could be induced rather than the free NH (Scheme 22).[85]



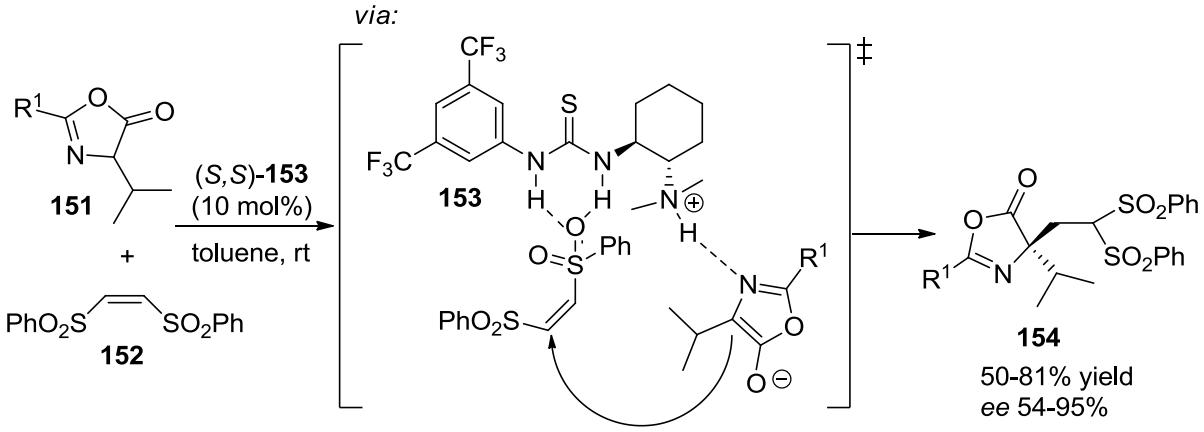

**Scheme 22: α-Allylation from unprotected amino acid esters**

The mechanism is thought to initially form an aldimine through reaction of the amino group of **148** with picolinaldehyde and association of the Ni(II) species at the amino ester carbonyl and the pyridine nitrogen. Deprotonation occurs at the α-carbon and intermediate **149** reacts with the palladium π-allyl species, finally the palladium species decomplexes and quaternary amino acid product **150** is released.

#### 1.4.3.1.2 Organocatalysis

There are also many examples in the literature of methods involving chiral organocatalysts to induce asymmetry in reactions forming quaternary amino acids and their derivatives. Some of the more recent examples are given below.

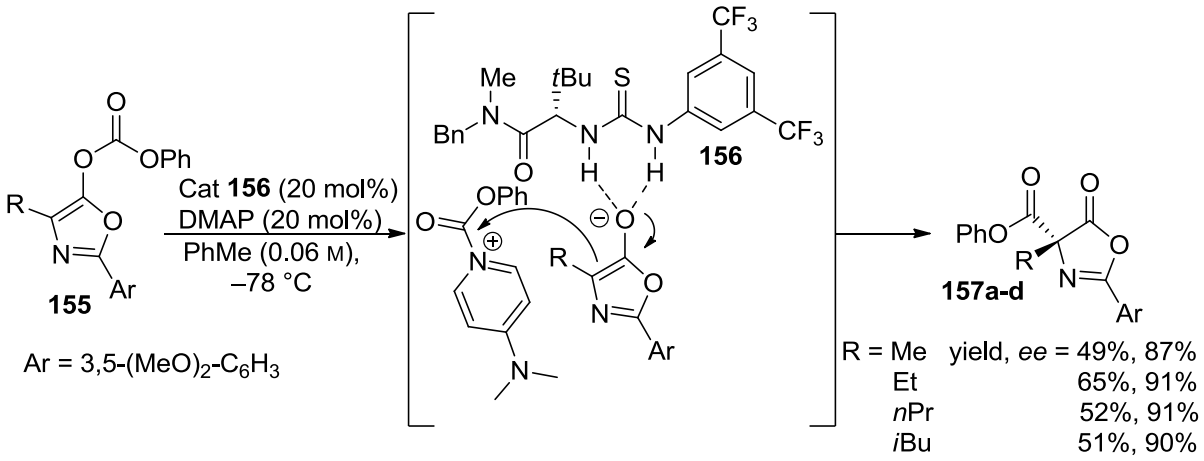
Rios and Moyano *et al.* reported the asymmetric organocatalytic Michael addition reaction of azlactones to 1,2-bis(phenylsulfonyl)ethane (**152**). The Michael addition of racemic azlactones (**151**) proceeded with good enantioselectivity using Takemoto's chiral bifunctional thiourea catalyst (Cat **153**) to control the stereochemistry and this was followed by a 1,2-sulfone rearrangement to generate **154** in moderate to good *ee* (Scheme 23).[86]




**Scheme 23: Organocatalytic Michael addition reaction to form quaternary amino acid precursors**

The selectivity is obtained due to the bifunctional nature of catalyst **153** activating both azlactone **151** and vinyl sulfone **152**. The tertiary amine functionality deprotonates azlactone **151** forming the reactive enolate and the thiourea activates vinyl sulfone **152** through hydrogen bonding.

Seidel *et al.* made use of a chiral thiourea organocatalyst **156** for a Steglich rearrangement resulting in a highly stereoselective O to C acyl transfer forming enantioenriched azlactone products (**157a-d**) (Scheme 24). A dual catalytic approach used DMAP as an achiral nucleophilic acyl transfer catalyst and chiral anion-binding thiourea catalyst **156** to provide stereocontrol.[87]

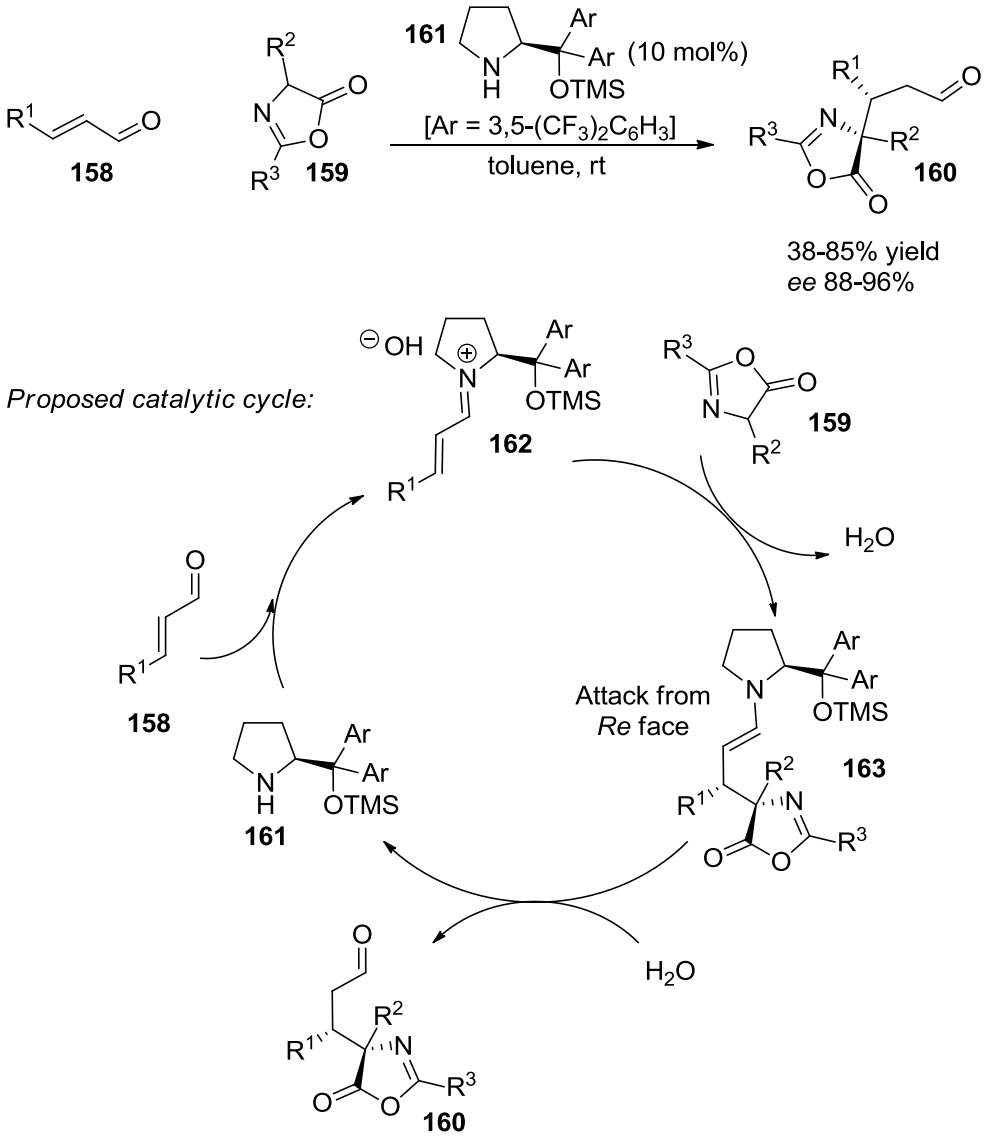



**Scheme 24: Steglich rearrangement by dual catalytic approach**

After acyl transfer, the oxyanion of **155** binds to the thiourea functionality of the catalyst and the *t*Bu group of the catalyst controls the facial selectivity of the acylation leading to enantioenriched products.

In 2008, Jørgensen *et al.* demonstrated racemic azlactones could undergo Michael additions with α,β-unsaturated aldehydes in the presence of diarylprolinol silyl ether organocatalyst **161** to generate products with two new contiguous stereocentres in good *dr* and excellent *ee* across a wide

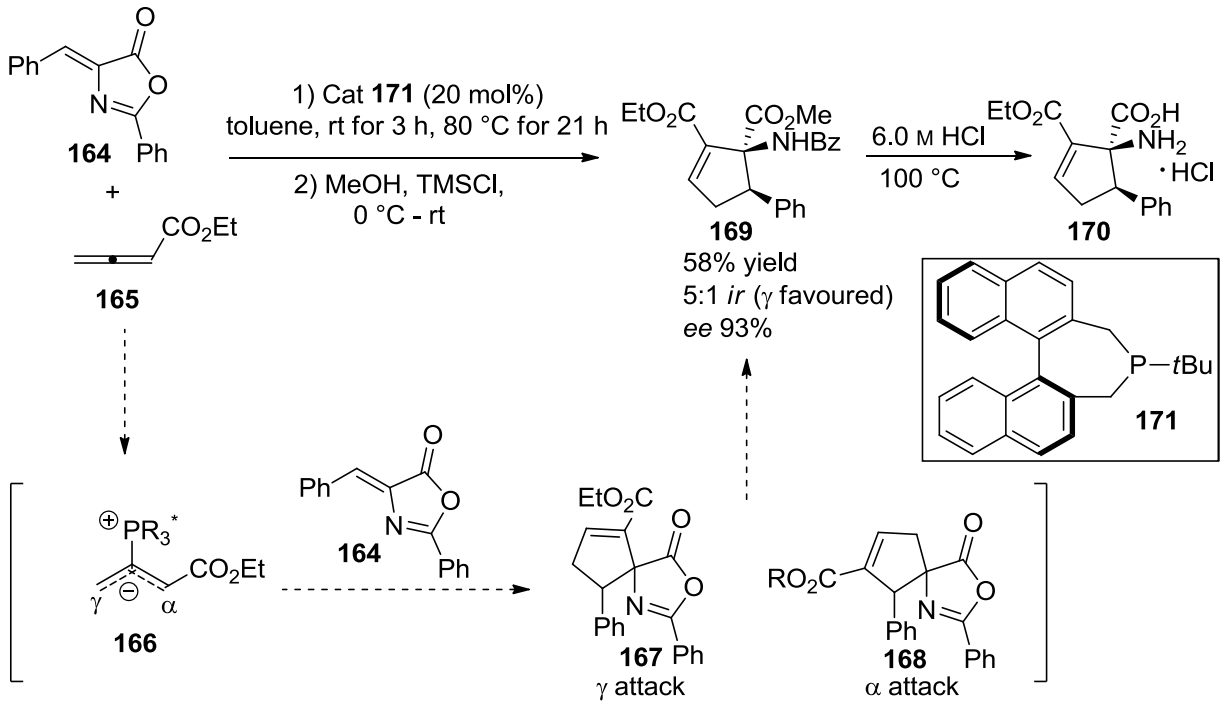
substrate scope (Scheme 25).[88] The proposed catalytic cycle begins with formation of iminium species **162** through reaction of electrophile **158** with catalyst **161**. The catalyst then controls the facial selectivity of the addition of the azlactone enolate and is released through hydrolysis.[88] The stereocentre is formed through *Re*-face attack of the azlactone enolate on planar iminium **162**. This face is favoured due to the steric bulk of the substituent α to the nitrogen on the pyrrolidine ring blocking the *Si* face.




**Scheme 25: Diarylprolinol silyl ether organocatalyzed Michael addition**

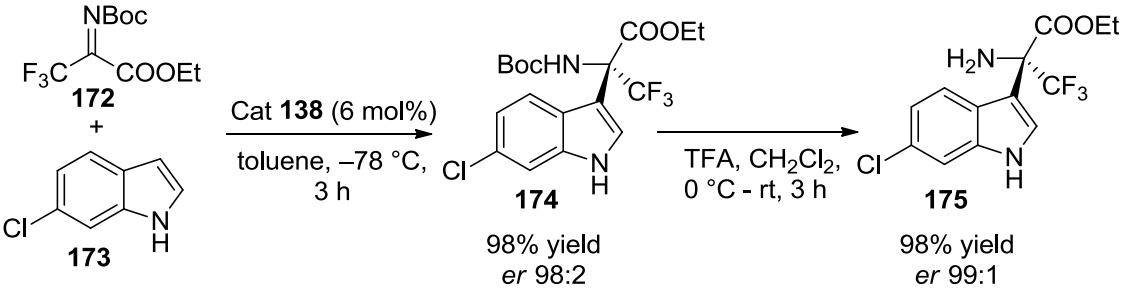
Jørgensen *et al.* have also shown phosphine **171** catalyses a [3+2]-cycloaddition reaction of allene **165** and an olefinic azlactone **164**. The one-pot cycloaddition and methanolysis ring-opening process generated *N*-protected quaternary amino esters **169** that were converted into cyclic amino acids bearing a quaternary centre **170** (Scheme 26).[89,90] There are two isomers that can be formed based on the orientation of the allene in the cycloaddition (γ and α product). Products **169** are

formed in a 5:1 isomeric ratio (*ir*) with the γ product favoured. It is proposed phosphine catalyst **171** coordinates to the allene controlling the facial selectivity of the cycloaddition reaction (**166**).




**Scheme 26: [3+2]-cycloaddition and azlactone ring-opening controlled by a chiral phosphine catalyst**

Chiral phosphoric acids (**138**, Scheme 20) have been used to catalyse aldol reactions of azlactones and vinyl ethers to generate β-hydroxy-α-amino acids.[91] Catalyst **138** has also featured in a highly enantioselective Friedel-Crafts reaction of indole derivatives to produce α-amino ester **175** containing a $CF_3$ group (Scheme 27).[92]

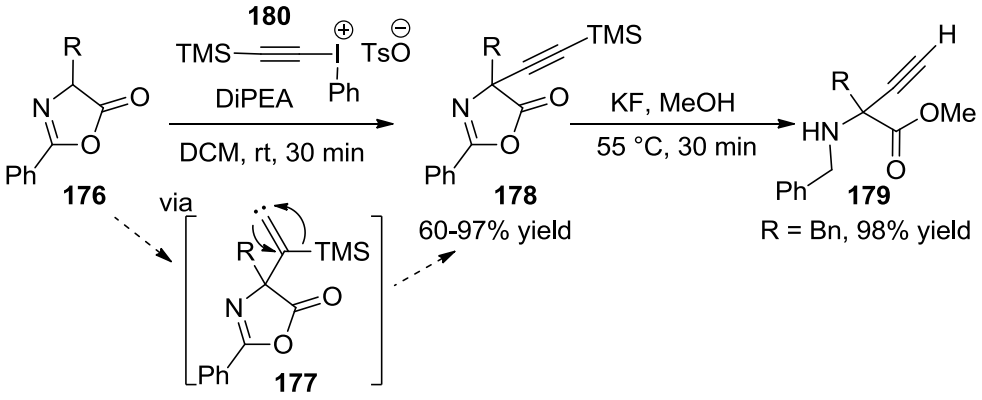



**Scheme 27: Asymmetric Friedel-Crafts reaction controlled by a chiral phosphoric acid**

The NH of indole **173** was essential to the stereocontrol induced by hydrogen bonding to catalyst **138** as using *N*-methyl indoles gave racemic product. The reaction worked well for 5-halogenated indoles but for methyl substituted indoles longer reaction times were required.[92]

In 2014, one of the first examples of direct alkynylation of azlactones was reported. Using alkynyliodonium salt **180** as the electrophile a variety of alkynylated azlactones **178** were prepared

in moderate to excellent yields and these could be converted into quaternary amino acid derivatives **179** (Scheme 28). The alkynyl group in the product could be converted into alkenes, subjected to Sonogashira couplings and reacted with azides to form triazoles.[93]




**Scheme 28: Alkynlation of azlactones**

The iodonium salt **180** is a stable non-toxic alkyne transfer reagent and the mechanism is proposed to proceed *via* vinylidene carbene **177**, which decomposes into **178** through a [1,2]-migration. Ester **179** was formed in a one-pot ring-opening esterification procedure using KF and MeOH.

Alongside the examples given, there have been many more asymmetric reactions using chiral organocatalysts including asymmetric Diels Alder reactions,[94] aza-Mannich reactions,[95] and O to C acyl transfer reactions using N-heterocyclic carbenes.[96]

#### 1.4.3.1.3 Phase Transfer Catalysis

Phase transfer catalysts are heterogeneous catalysts that facilitate the movement of a reactant from the aqueous phase into the organic phase for a reaction to take place. The catalysts are ionic species that form a Lewis acid-Lewis base pair with one of the reactants, transferring it across the phase-boundary. Figure 13 shows a tertiary amino acid derivative **181** that is deprotonated at the interface to generate enolate **182**. The exchange of the potassium counter-ion for the chiral ionic phase transfer catalyst results in movement of the reactive species into the organic phase. The alkylation takes place in this phase and the selectivity is determined by the chiral counter-ion that provides an asymmetric environment for the reaction.

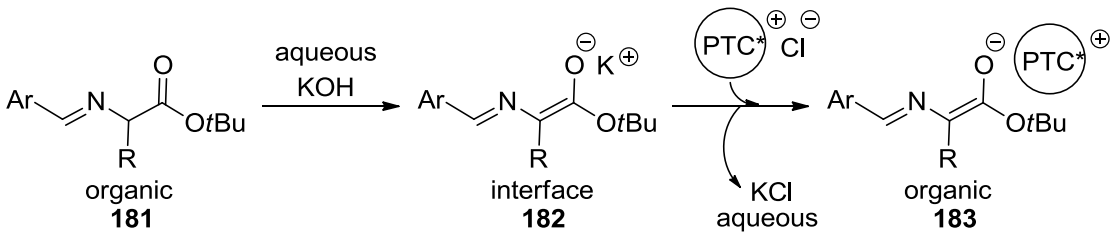
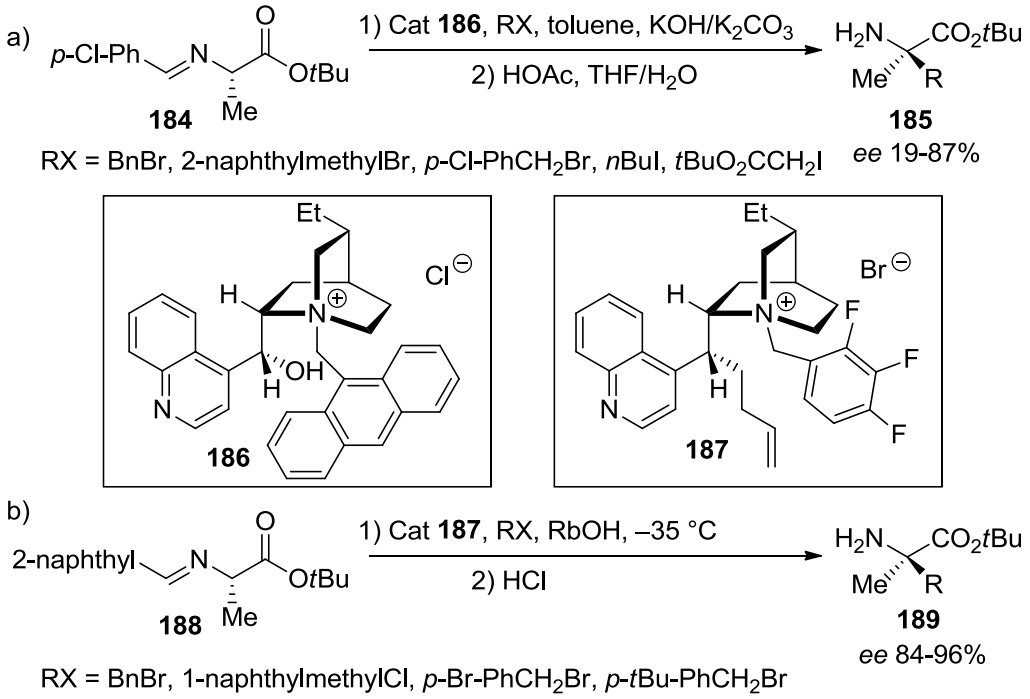



**Figure 13: Phase transfer catalysed reaction**

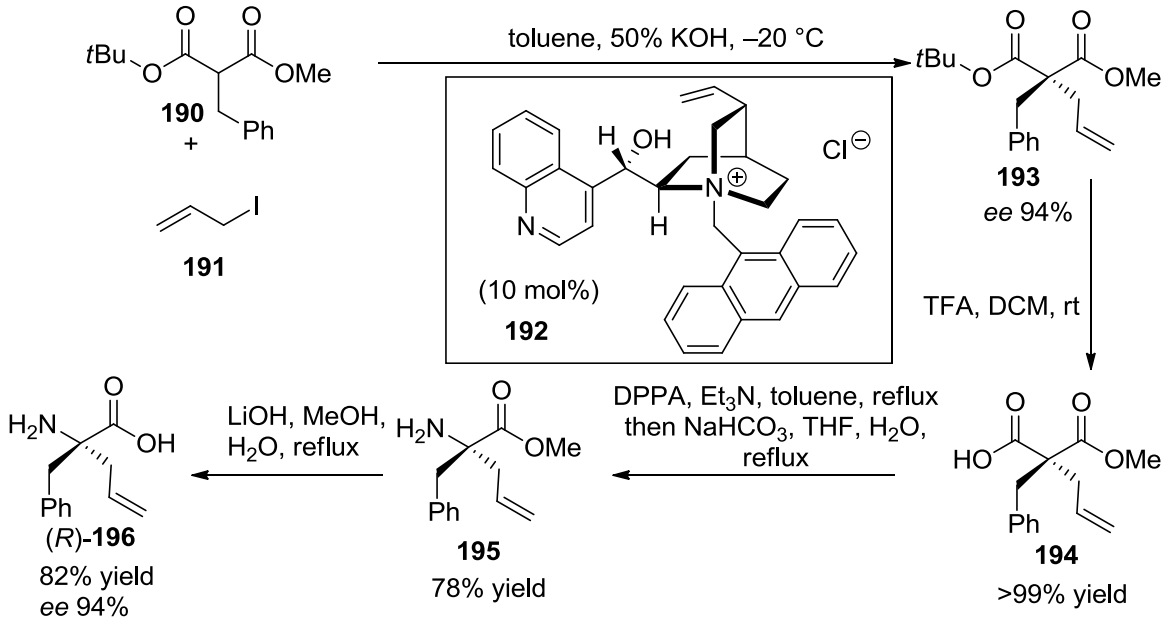
The reaction procedures are often straightforward, require mild conditions, are inexpensive and use reagents that are environmentally friendly,[97] making phase transfer catalysis (PTC)[8] an attractive methodology.

The most common phase transfer catalysts are ammonium salts derived from *cinchona* alkaloids **186** and **187**.[8] These were initially developed and used by Corey [98,99] and Lygo [100] as catalysts for alkylation reactions of aldimines. Aldimines (or Schiff bases) are derived from amino acid esters such as alanine *t*Bu ester. Catalyst **186** was optimal for benzylation reactions but had a poor substrate scope for other alkylating agents resulting in lower *ee*. However, PTC **187** with 2-naphthyl aldimines **188** gave excellent selectivity for many electrophiles with the enantiomeric excess improved by lower temperatures and using RbOH as a base (Scheme 29).[100,101]



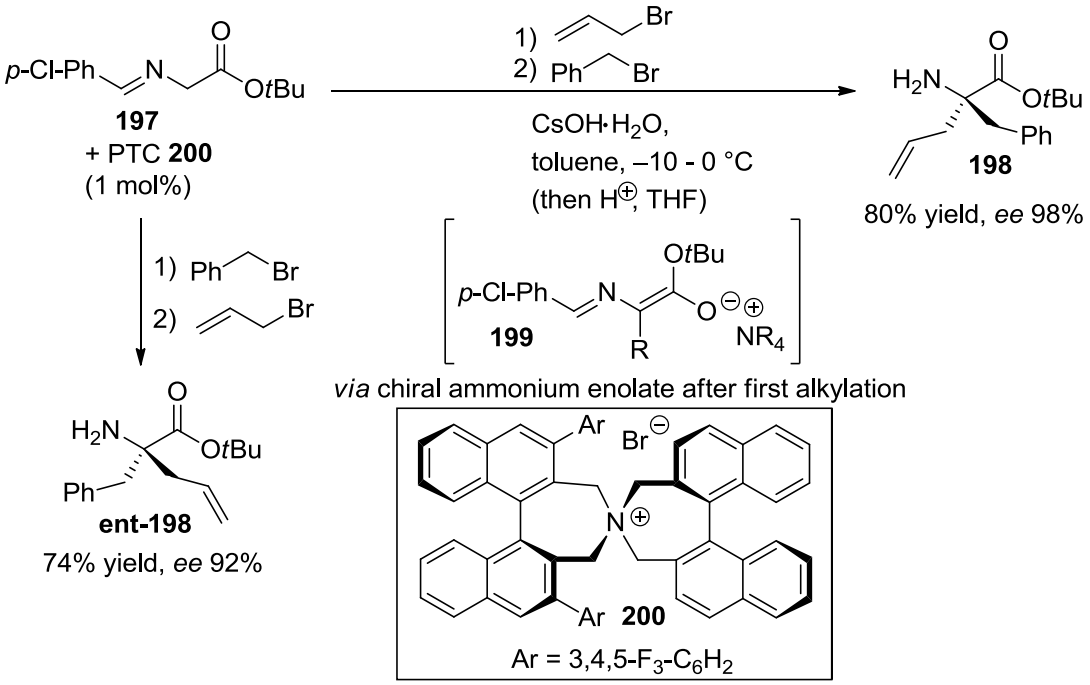

**Scheme 29: Alkylation of aldimides using ammonium salts as PTC**

Itoh *et al.* used PTC for the asymmetric alkylation of malonic-diesters (**190**). The α,α-disubstituted malonic diester products **193** were converted into (*R*)- and (*S*)-α-allylphenylalanine derivatives **196** (Scheme 30).[102] This was achieved through deprotection of one of the esters (TFA for *t*Bu ester and LiOH for Me ester) followed by a Curtius rearrangement to form amine **195** and hydrolysis of the second ester. The order of ester hydrolysis determines which enantiomer of the amino acid is formed.[102]




**Scheme 30: Asymmetric alkylation of malonate ester and formation of allylphenylalanine**

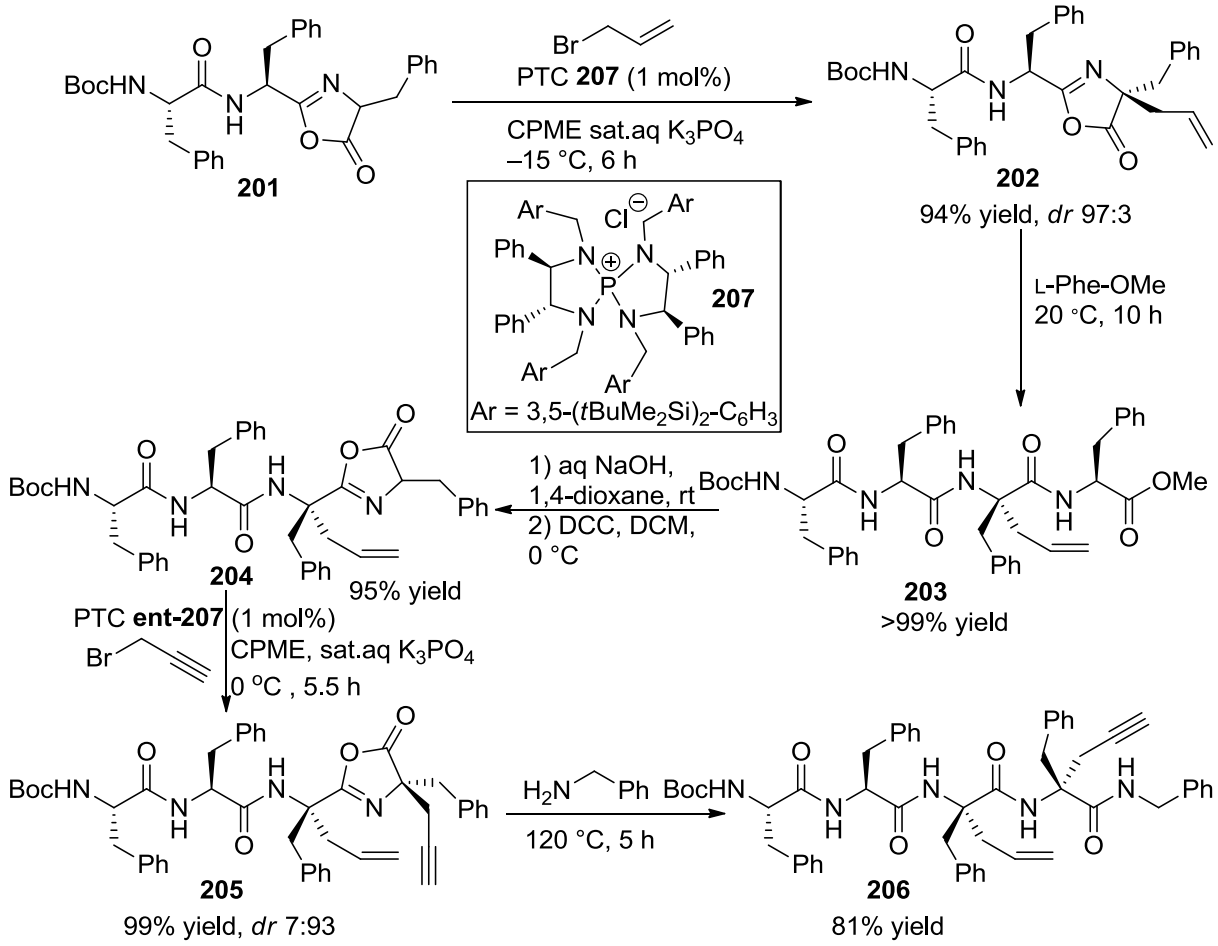
Maruoka *et al.* developed $C_2$-symmetric chiral quaternary ammonium salts (**200**)[103] as PTCs made from binaphthol, which is commercially available in both its (*R*) and (*S*) forms. This catalyst was used in the synthesis of quaternary amino acid derivatives in a double alkylation process of aldimine Schiff base **197** derived from glycine (Scheme 31).[104,105] PTC **200** directs the second alkylation step by forming a chiral ammonium enolate **199** that controls the addition of the electrophile to one face of the enolate. The role of the PTC was confirmed by inverse addition of the alkyl halides, which resulted in the formation of the opposite enantiomer **ent-198** in 92% *ee*.[105]




**Scheme 31: Maruoka's PTC in the formation of quaternary amino acid derivatives**

The asymmetric alkylation using a chiral PTC was also applied to imines derived from phenylalanine, alanine, and leucine with >93% *ee*.[106] Maruoka has also shown asymmetric alkylation using PTC **200** to be successful for methyl and ethyl esters of *N*-protected α-amino acids,[107] and the formation of 5-membered cyclic α-amino acids.[108] In 2013, a similar catalyst to **200** was used for the asymmetric synthesis of ≥ 6-membered cyclic amino acids.[109]

The formation of quaternary amino acids from azlactones is also possible with PTC. Ooi *et al*. developed a method of adding quaternary amino acids at sites on a peptide strand. [110] The C-terminus of the peptide was activated as an azlactone and under biphasic conditions using tetraaminophosphonium chloride PTC **207** a quaternary stereocentre was generated (Scheme 32). The product could then undergo repetition of the activation, alkylation and ligation sequence, allowing the peptide chain to be extended. This methodology represents a very impressive and useful synthesis of oligopeptides containing quaternary α-amino acid residues.




**Scheme 32: Formation of an oligopeptide containing quaternary amino centres using a PTC**

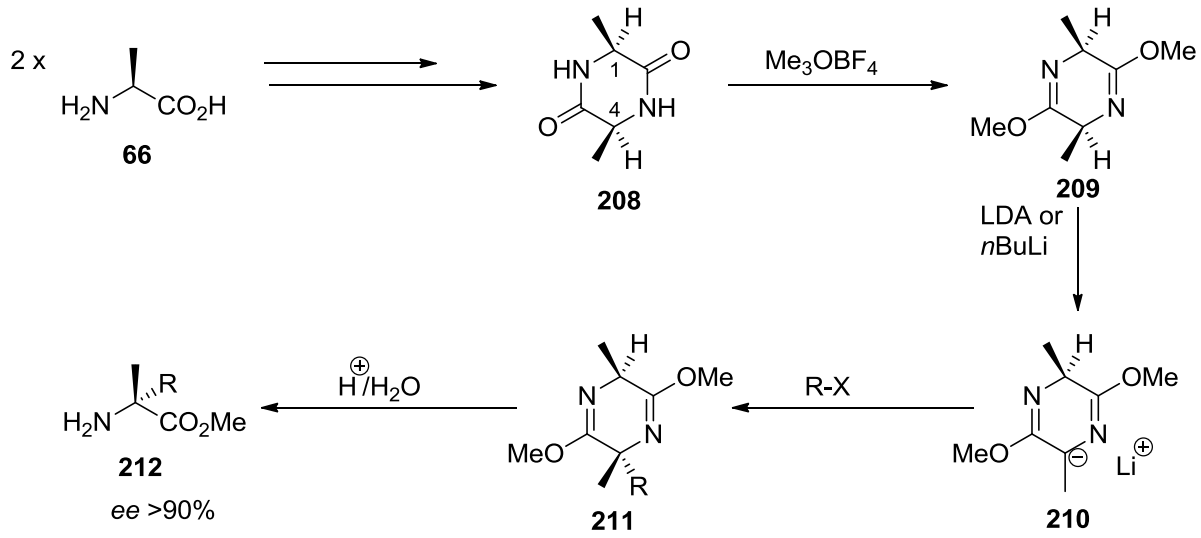
These catalytic approaches represent a selection of examples that have used an external source (i.e. the catalyst) to asymmetrically generate quaternary amino acids and their precursors from starting materials that are based on α-tertiary amino acids.

## 1.4.3.2 Chiral Auxiliaries

### 1.4.3.2.1 The Schöllkopf Approach

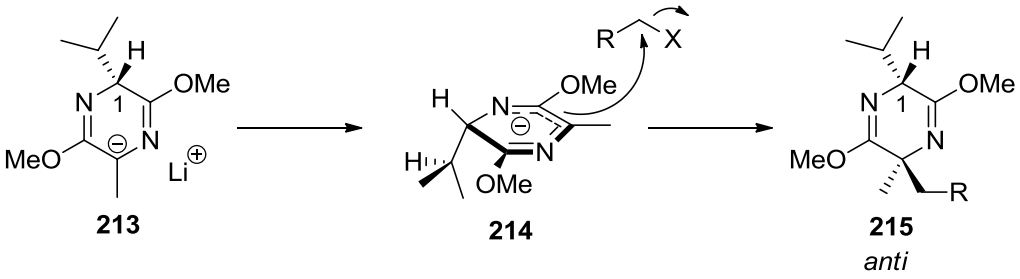
Alongside chiral catalysts, chiral auxiliaries can be used to perform asymmetric reactions. Schöllkopf's approach uses natural amino acids from the chiral pool to form an intermediate bis-lactim ether, which is used to control the formation of a new stereocentre. The deprotonated intermediate undergoes an asymmetric alkylation reaction with 1,4 asymmetric induction. The first synthesis of bis-lactim ether **209** was reported in 1979, with the combination of two alanine molecules leading to a *cyclo*-(L-Ala-L-Ala) intermediate **208** followed by reaction with trimethyloxonium tetrafluoroborate to generate bis-lactim ether **209**. This could then undergo lithiation followed by diastereoselective alkylation that was controlled by the C1 substituent (**208**) (Scheme 33). The substituent on C1 shields one face of the molecule and the electrophile adds to the least hindered side *anti* to the C1 substituent. The amino acid derivatives (**212**) containing a

quaternary centre were obtained through hydrolysis of **211** using HCl. The enantiomeric enrichment obtained for various electrophiles were all >90%.[111] In addition to the product, one equivalent of the L-alanine ester was also recovered.




**Scheme 33: 1,4-Stereoselective inductive alkylation from a Schöllkopf bis-lactim ether**

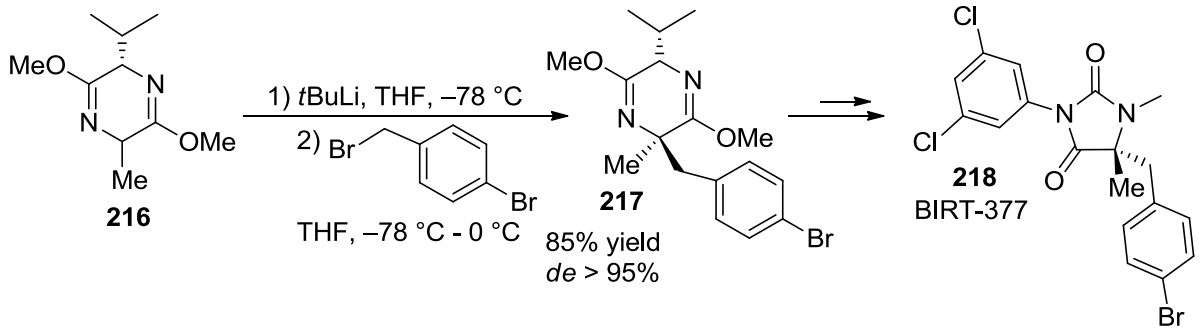
This approach was developed further to the use of mixed bis-lactim ethers for example with *cyclo*-(L-Val-L-Ala) intermediates **213**. In this case the isopropyl group of the valine controls the alkylation, meaning one equivalent of L-Val-OMe acts as an auxiliary and is recovered. The L-Ala component is deprotonated as this stereocentre is the least hindered, with the planar anion (**214**) generated by lithiation attacking the electrophile from the less shielded side (Scheme 34). This yields product **215** in which the electrophile has added *anti* to the C1 substituent (Scheme 33 and Scheme 34).[112,113]




**Scheme 34: The anionic intermediate formed that gives the *anti* product**

The base used to form anion **213** from **216** is important, using *t*BuLi gave a yield of 72% compared with a 24% yield using *n*BuLi for the synthesis of bis-lactim ether **217**. The improved yields are attributed to the fact that *t*BuLi is bulkier and less nucleophilic than *n*BuLi. This was further exemplified when the modified Schöllkopf procedure was used for the synthesis of an *N*-aryl

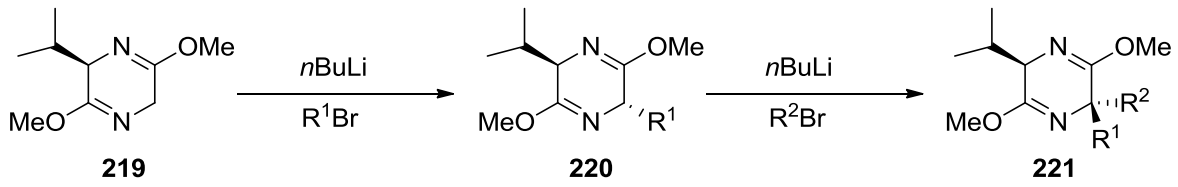
hydantoin BIRT-377 (**218**), which is a potential agonist for treatment of autoimmune diseases such as Crohn's disease (Scheme 35).[114]




**Scheme 35: Application of Schöllkopf methodology for the synthesis of BIRT-377**

Carbonyl compounds can be added as acylating agents[115] and through the use of other mixed bis-lactim ethers such as *cyclo*-(L-Val-Gly) and *cyclo*-(L-*t*Leu-Gly), (*R*)-serine and (*R*)-cystein derivatives could be synthesised.[113,116] This methodology has been applied to the synthesis of precursors to (*R*)-α-methylcysteine, which is a potential enzyme inhibitor. The alkylated bis-lactim ether intermediate was obtained in 80% yield with greater than 95% *de* and the final product was isolated with greater than 95% *ee*.[117] Other synthetic uses included the application of *cyclo*-(L-Val-L-Ala) to the formation of optically pure (*R*)-isovaline, which is an important starting material in the synthesis of amphiphilic peptide antibiotics.[118]

Using glycine as part of the bis-lactim ether (**219**) allowed a double alkylation to occur. The order in which the electrophiles are added can control which stereoisomer of product is formed. The first alkylation occurs *anti* to the sterically demanding isopropyl group as it fully shields one face of the intermediate anion. When the carbon centre is deprotonated for the second time the next electrophile also adds *anti* to the controlling group, inverting the first stereocentre formed (Scheme 36). In this case both substituents that form the quaternary centre have been introduced stereoselectively.[119]



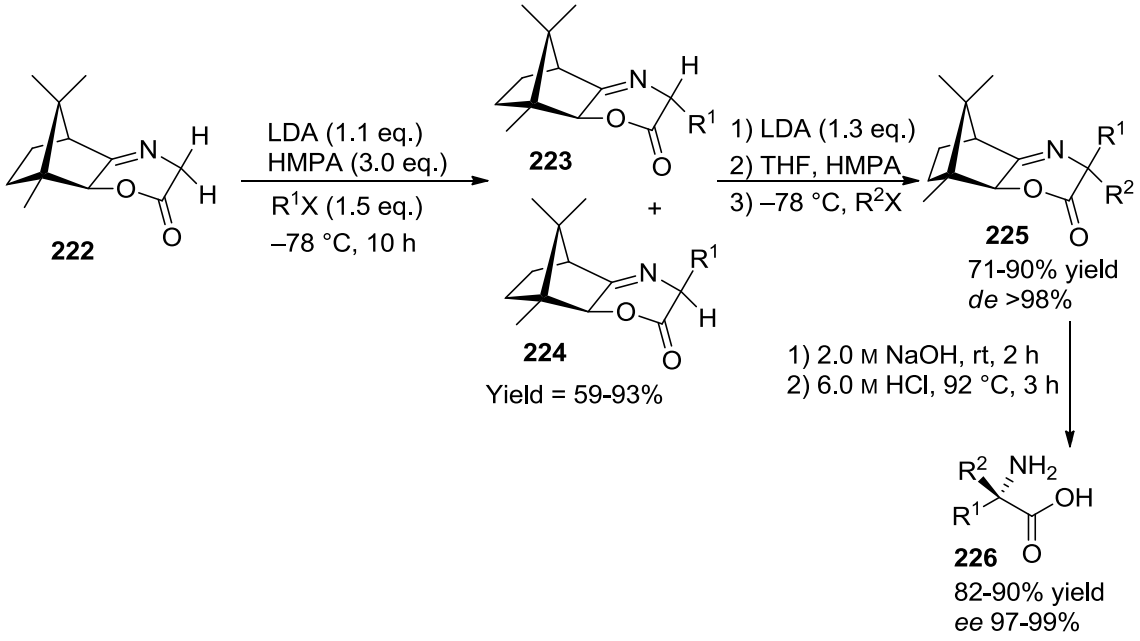

**Scheme 36: Double alkylation of a glycine based bis-lactim ether**

Schöllkopf's approach has used natural tertiary amino acids from the chiral pool to form an intermediate bis-lactim ether, which acts as an auxiliary in the formation of a new stereocentre.

### 1.4.3.2.2 Alternative Auxiliaries

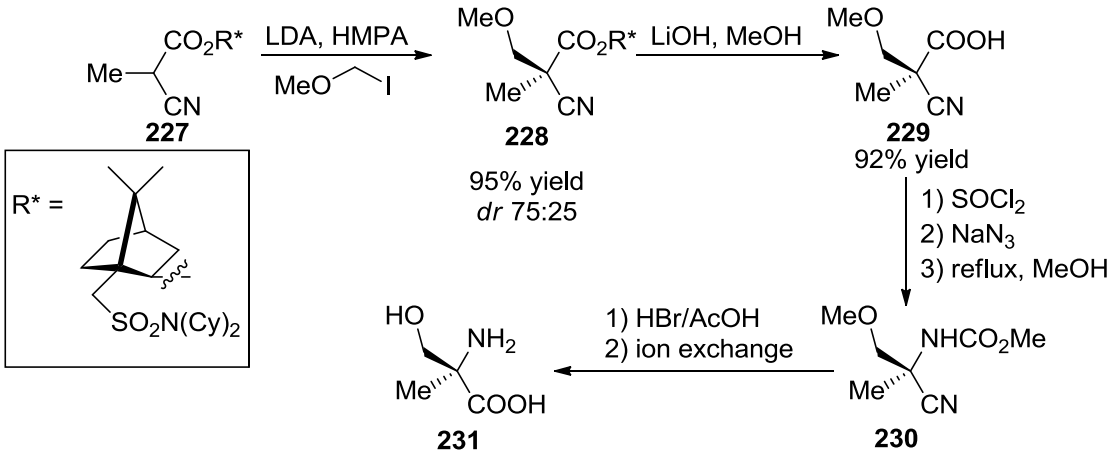
There are many other chiral auxiliaries that can be used to induce stereocontrol in a reaction to form quaternary amino acids from tertiary amino acid starting materials that can be removed after completion of the reaction.

A widely known class of auxiliary are those derived from camphor.[120] Xu *et al.* developed a tricycloiminolactone **222** from camphor that has been used to control the selectivity of alkylation reactions to form α,α-disubstituted amino acids after auxiliary removal. LDA and HMPA at –78 °C gave the best facial selectivity during the alkylation and removal of the auxiliary was achieved by hydrolysis. To obtain α,α-disubstituted amino acids a double alkylation process was necessary, and regardless of the electrophile, the enolate always reacted from its *endo* face. A diastereomeric mixture of monoalkylated products **223** and **224** could be subjected to the reaction conditions to generate a single diastereomer of product **225**. The configuration of the final product **226** could be controlled by the order of the alkylation (Scheme 37).[121]



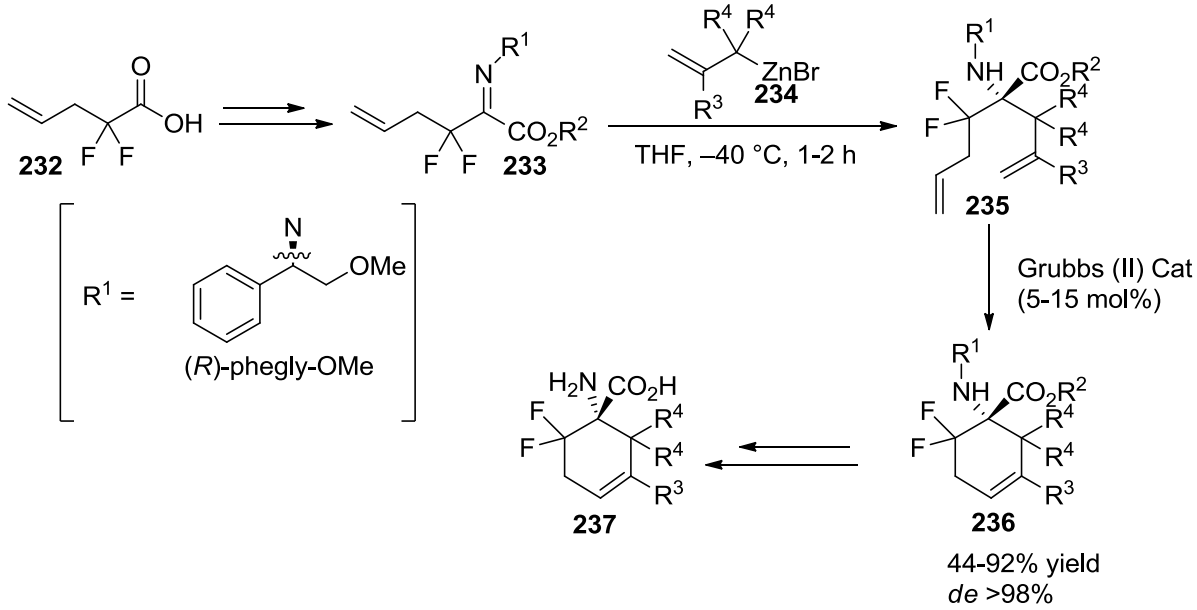

**Scheme 37: Dialkylation controlled by a camphor derived auxiliary**

A 10-dicyclohexysulfamoyl group has shown reasonable control in α-alkylations, the electrophile is added to the *Z*-enolate of **227** and on the opposite side of the sulfamoyl group.[122] The optimum conditions use LDA as a base and either HMPA or LiCl as an additive. Bases such as LiHMDS, KHMDS and NaHMDS gave poor diastereoselectivity (Scheme 38).




**Scheme 38: Use of a sulfamoyl group as an auxiliary for control in an alkylation**

(*R*)-Phenylglycinol methyl ester has been used as a chiral auxiliary for the formation of β,β-difluorinated cyclic quaternary α-amino acids. Cyclic amino acids are more conformationally rigid and can give higher selectivity for certain biological receptors.[123,124] A chemoselective allylation takes place from chiral imine ester **233** as the zinc coordinates to both the imine nitrogen and the oxygen of the auxiliary. The allyl group is added from the opposite side to the phenyl group of the auxiliary. Ring closure by Grubb's metathesis and protecting group removal yielded the β,β-difluorinated cyclic quaternary α-amino acids **237** (Scheme 39).[123] More recently Fustero *et al.* used similar methodology for intramolecular additions of allyl and propargylsilanes to chiral imines derived from (*R*)-phenylglycinol to form cyclic and bicyclic quaternary amino acids.[125]




**Scheme 39: Formation of β,β-difluorinated cyclic quaternary α-amino acids**

There are many other methods that have used various chiral auxiliaries such as ribonolactone,[126] sulfinyloxiranes,[127] and (*S*)-(+)-3-carene[128] for stereocontrolled transformations in the formation of α,α-disubstituted amino acids. In summary the methods described show the typical alkylation procedures of tertiary amino acid derived starting materials with stereochemical induction achieved using an auxiliary that was removed after the reaction.

### 1.4.4 Conclusion

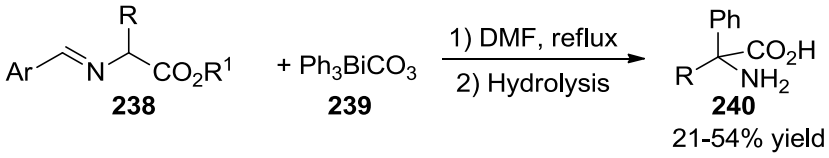
In conclusion, the asymmetric α-alkylation of tertiary amino acids and their derivatives to generate a wide variety of α,α-disubstituted quaternary amino acids is well established. The asymmetry of the reaction has been accomplished through two routes, firstly using the configuration of the starting material (chiral memory) and secondly using external sources to control the asymmetry such as chiral catalysts and auxiliaries.

## 1.5 α-Arylation

### 1.5.1 Arylation using Metals

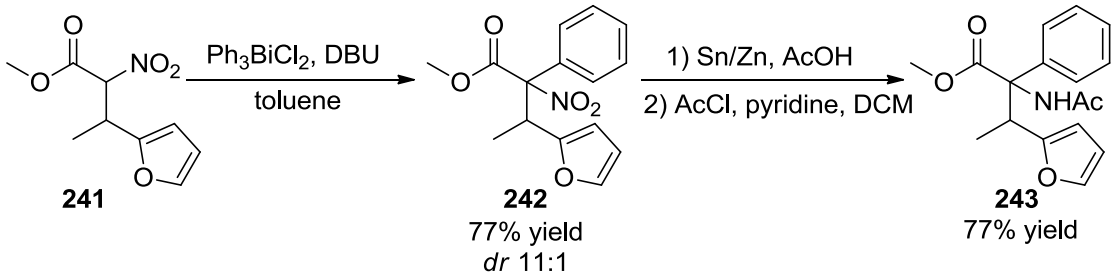
The synthesis of α-arylated quaternary amino acids is challenging and until recently there was little progress made in the area of α-arylation. Currently, there are a limited number of methods available to carry out α-arylations of α-amino acid derivatives and very few that are also asymmetric.

One of the earliest methods of arylation to generate α-arylated α-amino acids was reported in 1989 by O'Donnell *et al.* who showed phenylation through use of triphenylbismuth carbonate (**239**), at reflux in DMF followed by direct hydrolysis. This reaction was successful for methyl and ethyl esters and nine different R groups, unfortunately the reaction was not selective and the yields were low to moderate (21-54%, Scheme 40).[129]



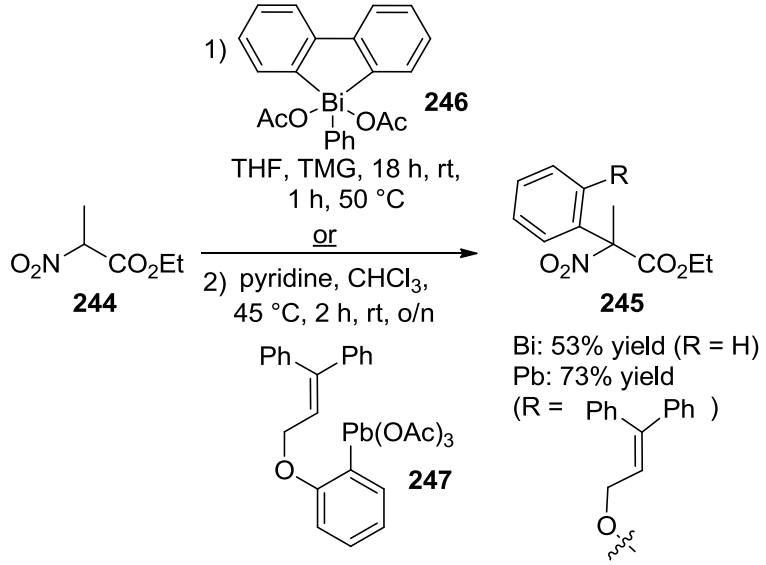

**Scheme 40: Early phenylation using triphenylbismuth carbonate**

In 1998, Montgomery *et al*. also used triphenylbismuth dichloride to carry out a diastereoselective arylation of amino acid derivatives. The reaction was successful with DBU as a base leading to **242** with a reasonable 11:1 *dr* and the authors showed intermediate **242** could be converted into amino acid derivative **243** through reduction and derivatisation (Scheme 41).[130] The advantage of this method was it showed some selectivity and a good yield, but the reaction was only demonstrated for one example.




**Scheme 41:Arylation using $Ph_3BiCl_2$ and conversion into amino acid derivative**[i]

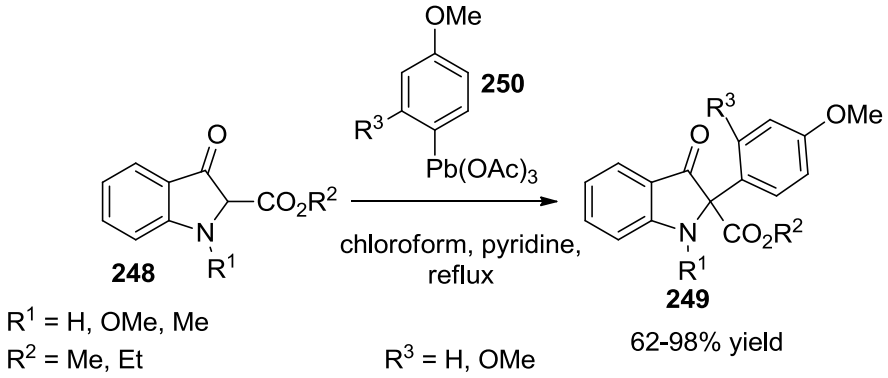
Finet *et al.* showed that penta-coordinate biphenylbismuth derivatives also performed α-arylations. A synthesis of bismuth derivative **246** was established and phenylation was attempted under basic conditions for different substrates including **244** generating **245** that could be converted into an amino acid. These conditions were milder and bismuth species **246** has a lower reactivity compared with triphenylbismuth derivative **239**. Only one example of α-arylation was given and the product was racemic (Scheme 42).[131]




**Scheme 42: α-Arylation with penta-coordinate biphenylbismuth**

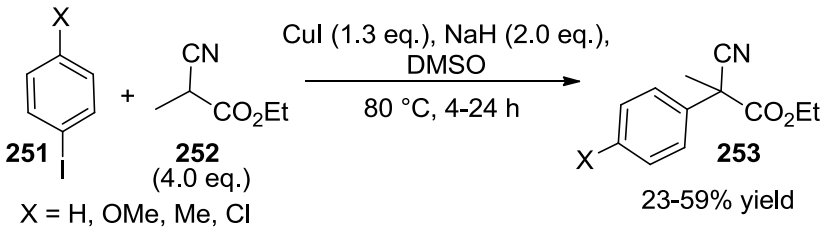
In addition to bismuth, Finet also showed this transformation (Scheme 42) to be possible using aryllead species **247** that contained a free radical trap. The yield for the reaction was improved (73%), but lead is more toxic than bismuth.[132] Finet also showed lead triacetate compounds **250** catalyse α-arylations in the formation of 2,3-dihydroindoles (Scheme 43).[133] The advantage was the method was applicable to different substrates and two different aromatic rings, giving arylation products in a good yield.

[i] Relative stereochemistry of the major isomer of **242** not determined



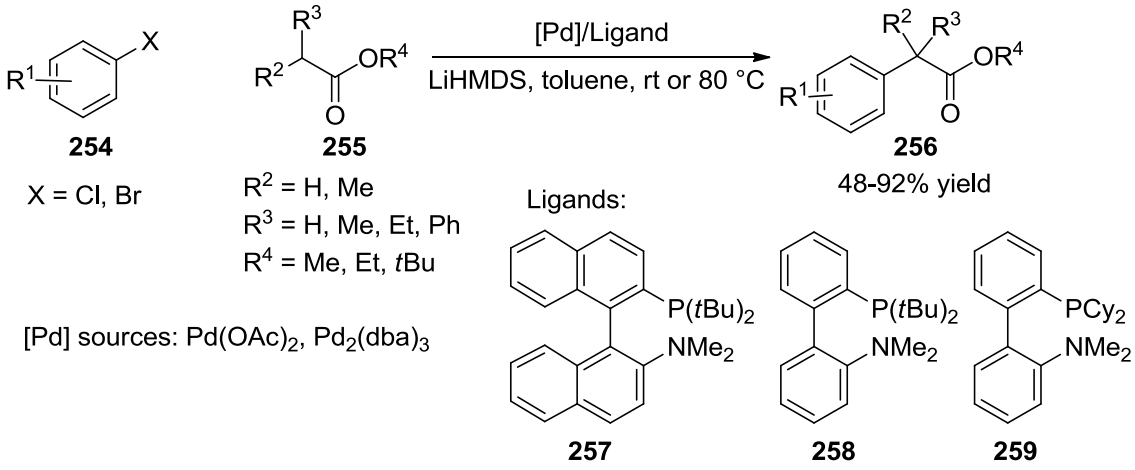

**Scheme 43: α-Arylation using lead triacetate compounds**

Transition metals have been used to catalyse α-arylations, in 1996 CuI was used in combination with aryl iodides to generate quaternary cyanoesters **253** (Scheme 44).[134] A variety of different aryl iodides were successful but unfortunately the reaction was low-yielding and not enantioselective.



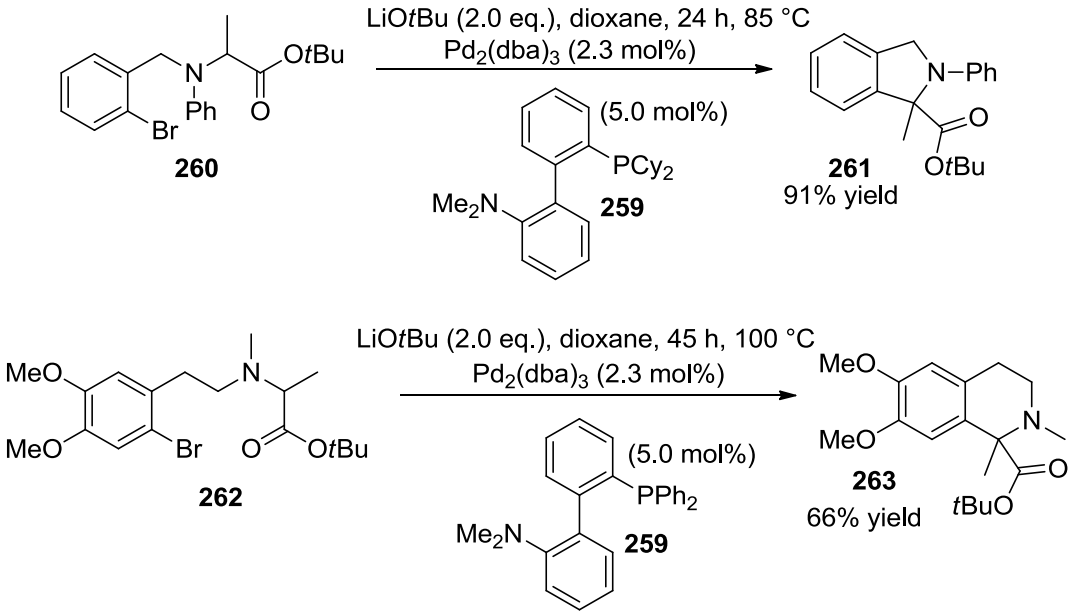

**Scheme 44: Copper mediated arylation**

The biggest advance in transition metal-catalysed α-arylation was achieved through use of palladium catalysis.[135,136] In 2001, both Buchwald[137] and Hartwig[138] developed methodologies for the arylation of esters with aryl halides. Buchwald reported a one-pot procedure for the arylation of esters that was simple and applicable to a wide range of commercially available starting materials and achieved high yields. The optimised conditions used LiHMDS, which was crucial for obtaining the monoarylated products selectively. The reaction conditions are mild and tolerate many functional groups and require just 3 mol% palladium (Scheme 45).[137]



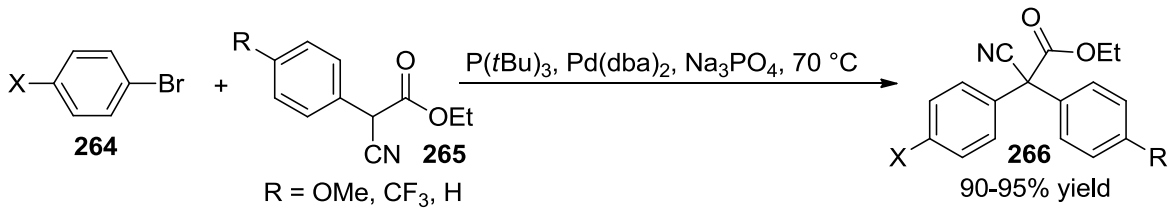

**Scheme 45: α-Arylation of esters to generate quaternary centres**

This methodology was extended in 2002 to amino acid esters generating dihydroisoindoles **261** and tetrahydroisoquinolines **263** in good yield under mild conditions (Scheme 46).[139]



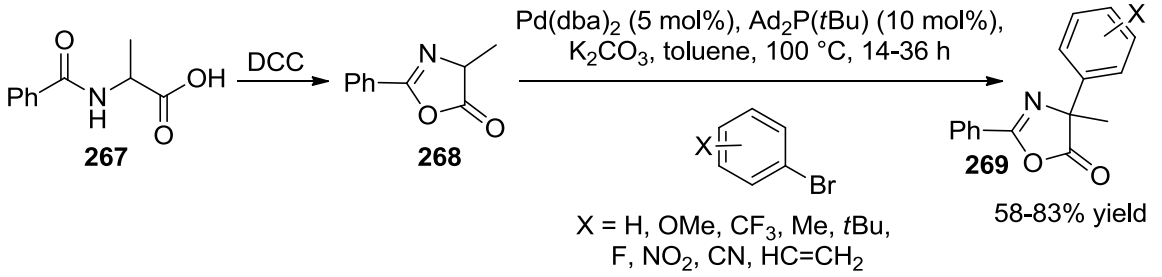

**Scheme 46: α-Arylation to generate dihydroisoindoles and tetrahydroisoquinolines**

At the same time Hartwig described the palladium-catalysed α-arylation of esters.[138,140] This was extended to protected amino acids and a range of racemic cyanoesters **266** were synthesised in excellent yields through a coupling using palladium and an aryl halide (Scheme 47).[141]




**Scheme 47: Synthesis of α-arylated cyanoesters**

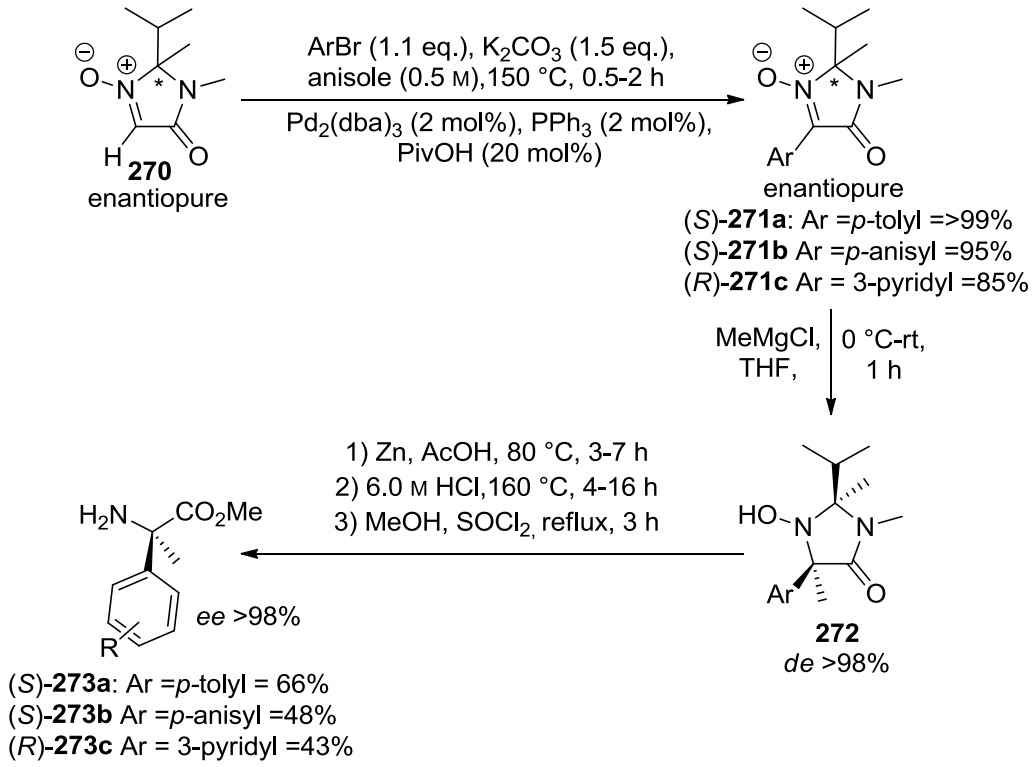
Hartwig also showed the α-arylation of azlactone derivatives of alanine through use of palladium catalysis for a wide variety of aromatic rings (Scheme 48).[142] This methodology was extended to valine, phenylalanine, phenylglycine and leucine derivatives all in good yields.




**Scheme 48: α-Arylation of azlactones of alanine**

In 2013, Hartwig *et al.* applied their palladium-catalysed α-arylation to zinc enolates of esters, although this was not applied to amino acid derivatives. The zinc enolates allow for an extension of the reaction scope to a large variety of bromoarenes, incorporating a variety of functionality including bromopyridines.[143]

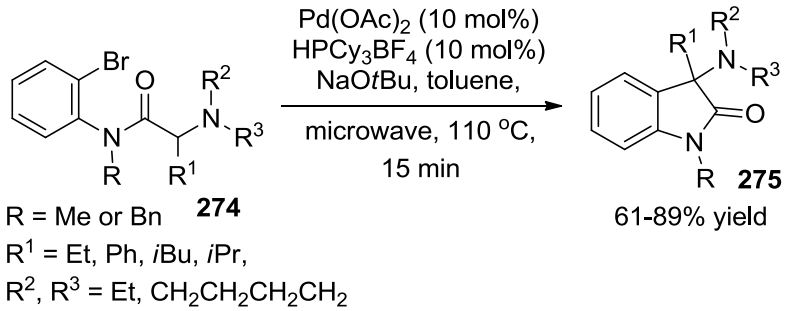
Blandin *et al.* used palladium for a fast, efficient and high yielding arylation of cyclic nitrones.[144] This generated a number of arylated nitrones that could be converted into quaternary amino acid derivatives. The formation of enantiopure quaternary α-amino esters was achieved through a chiral version of this reaction generating tertiary nitrones **271a-c** that were then subjected to a Grignard reagent to form a quaternary centre. Intermediates **272** could then be reduced, hydrolysed and esterified to generate **273a-c** in reasonable yields with >98% *ee* (Scheme 49).




**Scheme 49: Arylation of nitrones**

This method showed a large substrate scope and that the arylation could be applied to enantiopure starting materials. However, the quaternary centre was actually formed through a Grignard reaction and the starting material has to be enantiopure to begin with.

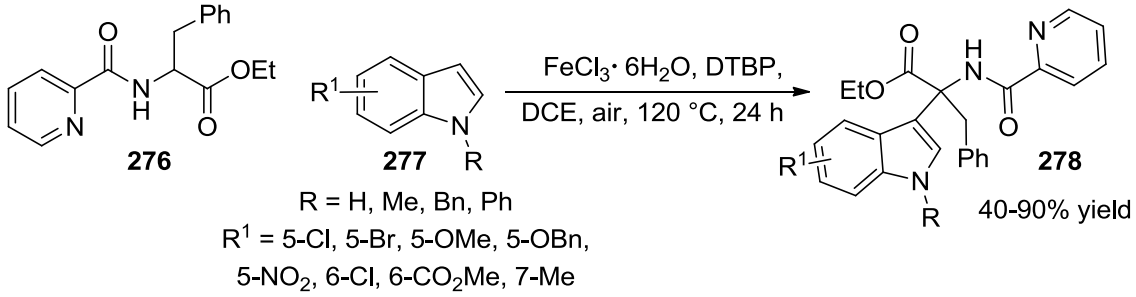
3,3-Disubstituted oxindole products are biologically valuable and have been synthesised by Marsden *et al.* through an intramolecular arylation of enolate derived amino acids **274** using palladium catalysis (Scheme 50),[145] generating a range of 3-aminooxindoles **275** in good yield.




**Scheme 50: Intramolecular arylation to generate 3-aminooxindole products**

Methods of α-arylation that use palladium catalysts can be expensive and trace metals can be problematic if a method is for use in the pharmaceutical industry due to strict guidelines for the limits allowed in the final drug product. Some of the methods described access a large substrate scope of quaternary amino acid derivatives, but most are not asymmetric.

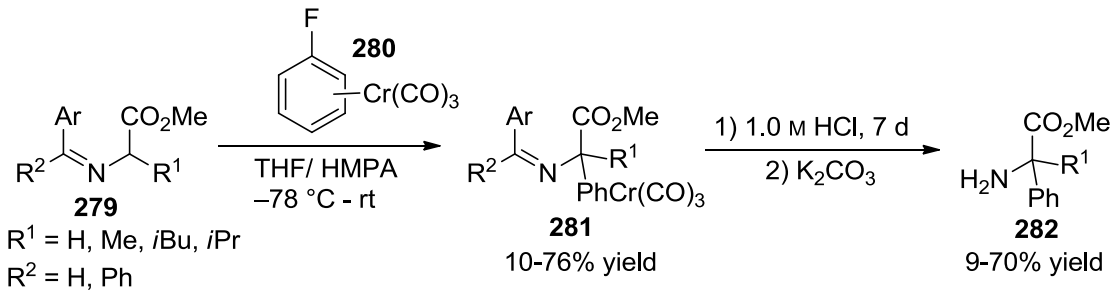
You *et al.* reported α-arylation of tertiary α-amino esters through use of oxidative C-H cross coupling using an iron (III) catalyst to give products **278** in good yields.[146] The reaction was successful for a variety of substituted indoles, including halogen substituents that have the potential for further functionalization of product **278** (Scheme 51).




**Scheme 51: α-Arylation through iron catalysis**

The phenylalanine side chain could be altered to various chains including phenylglycine, allyl, tryptophan and 1-naphthyl. The phenyl ring of the phenylalanine could also be substituted. The scope of nucleophiles was large with heterocycles such as thiophenes and furans also being successful. The mechanism for this reaction was proposed to occur *via* single electron transfer (SET). Coordination of **276** to Fe(III) *via* both nitrogen atoms allows a *t*BuO radical from DTBP to abstract an α-proton. Next, intramolecular SET generates a ketimine intermediate that can be nucleophilically attacked.

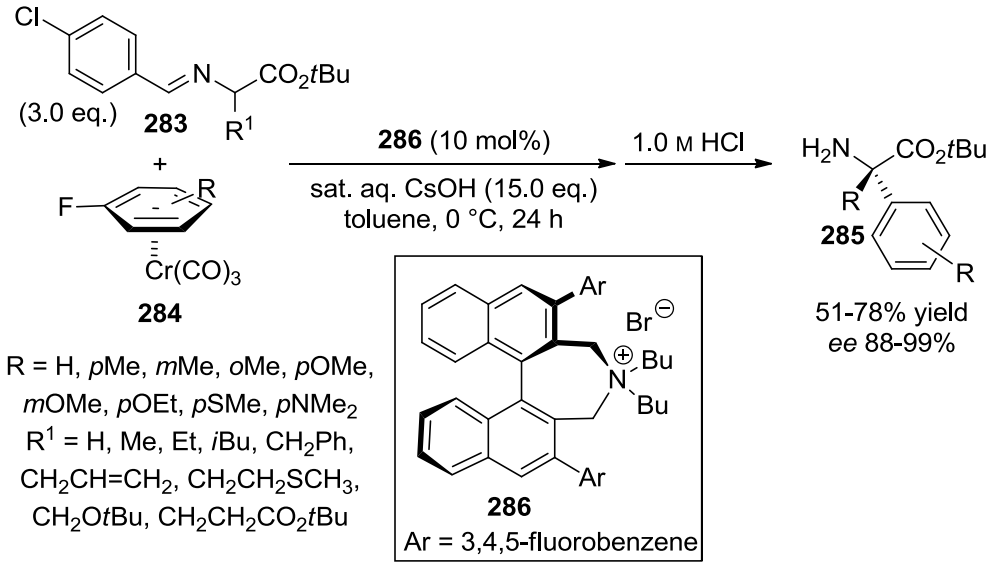
Chromium has also been utilised for α-arylations, although it is considerably more toxic than either palladium or iron and is not used catalytically. Arene-chromium tricarbonyl complexes (**280**) were used in 1989 to facilitate the α-arylation of amino acid derivatives to generate chromate Schiff bases **279**.[147] The yields were reasonable, but the hydrolysis and de-complexation required long reaction times (Scheme 52).[148,149]




**Scheme 52: α-Arylation using fluorobenzene tricarbonylchromium complex**

In 2015, Maruoka and co-workers reported one of the few enantioselective catalytic methods for α-arylation of amino acid derivatives.[150] This method used phase transfer catalysis and overcomes

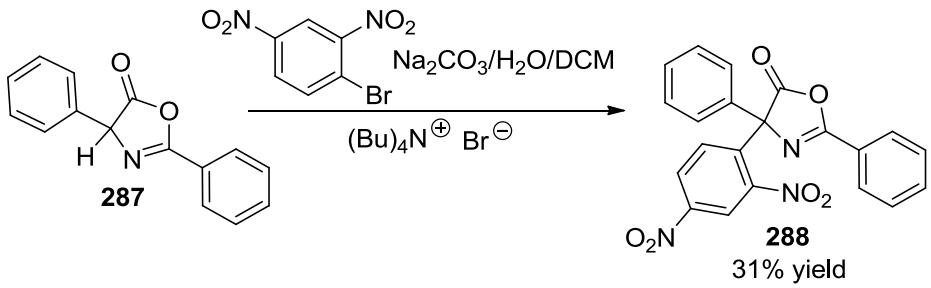
previous limitations of arylation often only being successful for electron deficient rings such as nitroarenes. The authors described an $S_NAr$ reaction using arene-chromium tricarbonyl complexes of fluorobenzenes (**284**) promoted by phase transfer catalysis. The reaction was successful for a variety of rings, both electron donating and electron withdrawing and for several amino acid derivatives but the major drawback is that the reaction requires stoichiometric chromium and an excess of tertiary amino acid derivative **283** (Scheme 53).




**Scheme 53: PTC $S_NAr$ reaction using a chromium complex**

## 1.5.2 Metal-free Arylation

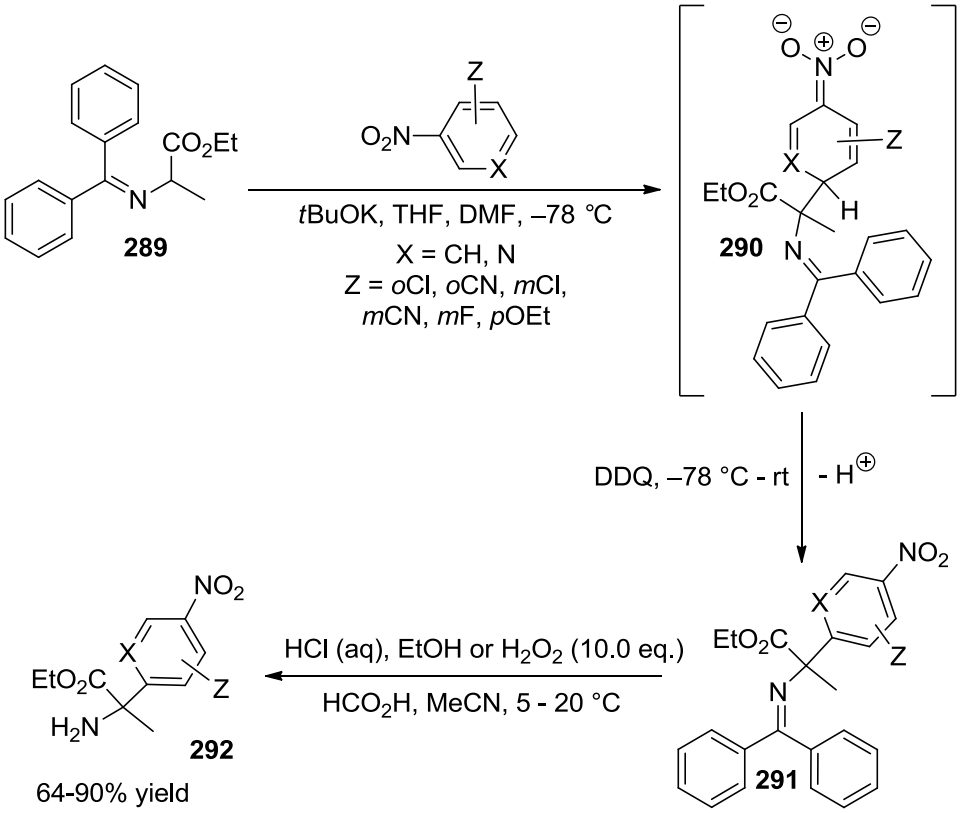
Arylations are possible without either metal catalysts or organometallic reagents,[151] but the majority of reported arylations have been successful for only electron poor aromatic rings such as nitroarenes. In 1984, Gelmi *et al.* reported the alkylation of azlactones using PTC, one of the examples was an arylation with a 2,4-nitro substituted ring (Scheme 54)[152] and the method was subsequently extended to 3,5-dinitro-2-pyridyl rings.[153]




**Scheme 54: PTC α-arylation of azlactones**

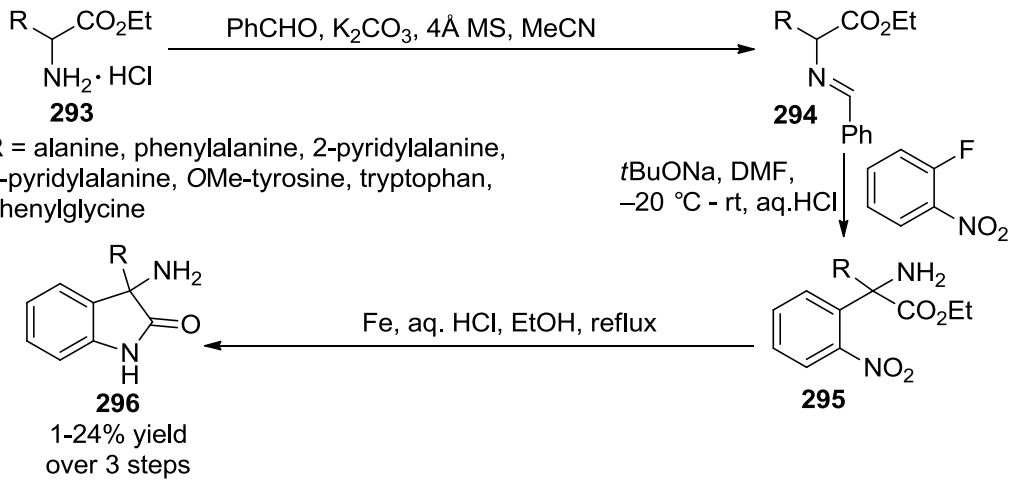
Makosza *et al.* showed α-arylation was possible with substituted *p*-nitroarenes, the reaction generated racemic alanine derivatives **292** in good yields through use of oxidative nucleophilic substitution of the hydrogen in the nitro-arene (Scheme 55).[154] The scope was limited to electron

poor rings and was only applicable to alanine and serine derivatives. The scope has since been extended to include proline derivatives[155] and protected threonine esters.[156]



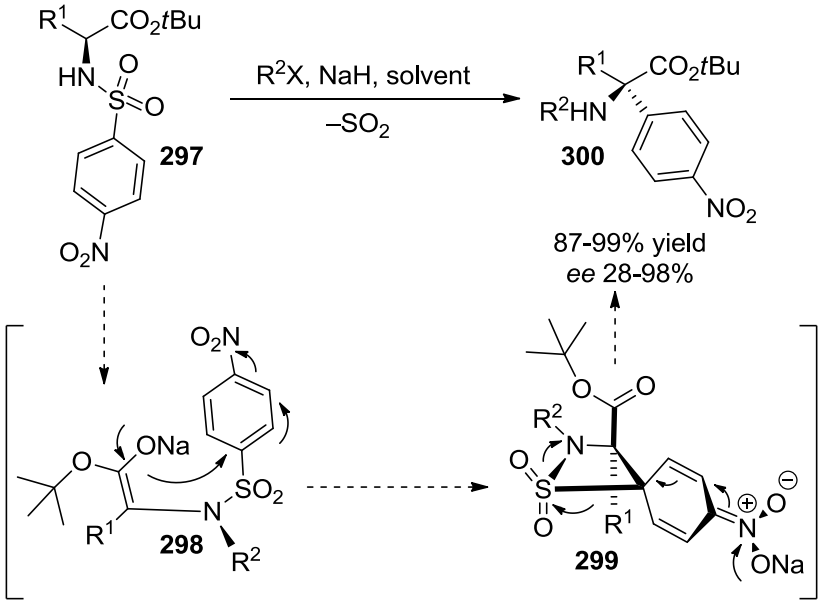

**Scheme 55: Oxidative nucleophilic substitution of nitroarenes**

The synthesis of sterically hindered 3-amino-2-oxindoles has been achieved through α-arylation with electron poor aromatic rings (*o*-$NO_2$ arene).[157] Nucleophilic aromatic substitution followed by acidic hydrolysis of the imine functional group yielded **295**. These quaternary amino acid derivatives were conveniently converted into oxindole products **296** using iron. The yields were moderate over the three steps (Scheme 56). The method showed a successful α-arylation of complex amino acids, but the yields for some were very low and scale up of the route required further optimisation. Additionally, the reaction was not enantioselective but the authors proposed this may be possible by PTC.




**Scheme 56: Synthesis of oxindoles through α-arylation of hindered amino acid derivatives**

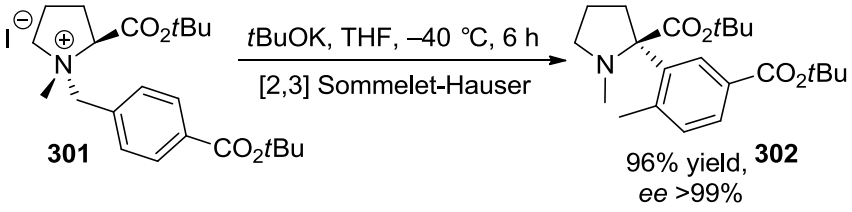
Penso *et al.* demonstrated the synthesis of enantiomerically enriched α-arylated quaternary amino acid derivatives through a stereoselective intramolecular arylation.[158] The reaction was demonstrated for *p*-nitroarenes for various amino acid side chains. The reaction was a one-pot alkylation followed by migration of the *p*-nitro ring with loss of $SO_2$, the reaction takes place *via* a non-racemic enolate. Facial control was achieved through chiral memory (similar to Kawabata and Kouklovsky) with addition of the aromatic ring to enolate **298** generating a spiro-Meisenheimer intermediate **299** that rearomatised and lost $SO_2$ to generate amino acid derivatives **300** in excellent yield and a range of *ee* (Scheme 57). Although this method was limited to electron poor aromatic rings it is one of the few enantioselective α-arylation reactions of amino acid derivatives and has since been extended to proline derivatives.[159]




**Scheme 57: Alkylation, ring migration and loss of $SO_2$ to generate quaternary amino acid derivatives**

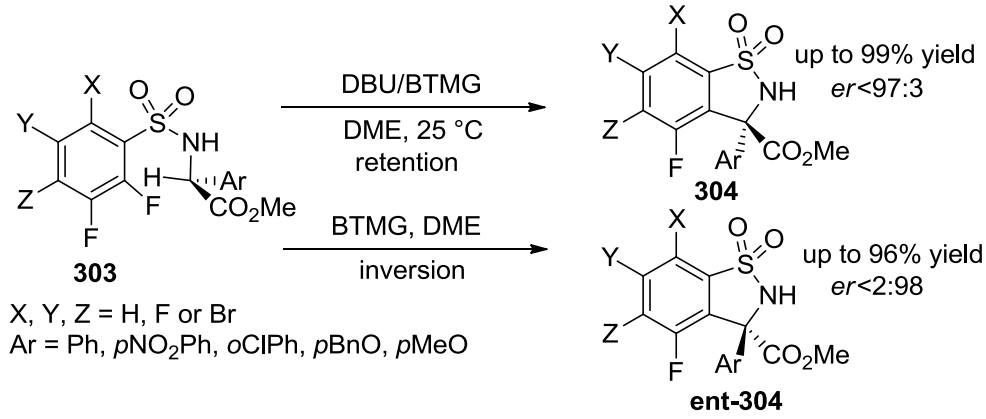
A similar method that involved an aryl migration with loss of $SO_2$ was described by Krchňák in 2014, in this case the aromatic ring had an *o*-$NO_2$ substitutent.[160]

There are other methods to carry out α-arylations that do not require a nitro substitutent on the aromatic ring. An asymmetric Sommelet-Hauser rearrangement was reported by Tayama *et al.*, with the rearrangement of *N*-benzylic ammonium salt **301** generating enantiomerically enriched proline derivative **302** (Scheme 58).[161] This was applied to the synthesis of enantiomerically enriched glycine and alanine derivatives[162] and more recently has been applied in the synthesis of racemic pipecolinic acid derivatives.[163] This method gave good enantioselectivity but was only demonstrated for a limited number of quaternary examples.




**Scheme 58: Sommelet-Hauser rearrangement of proline derivative**

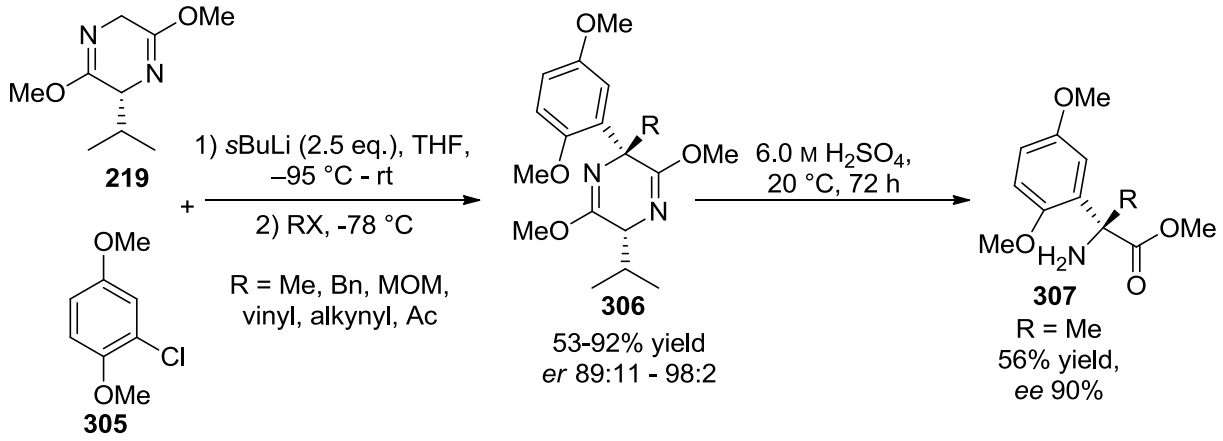
Another memory of chirality approach was used to generate chiral benzo[*d*]sultams through α-arylation, with the enantiomer of product formed dependent on the base used (**304** or **ent-304**) (Scheme 59).[164] This method was successful for halogenated aromatic rings attached to an $SO_2$ group. This demonstrated memory of chirality was possible to generate arylated quaternary amino acid derivatives, but is limited to a very specific system.




**Scheme 59: Memory of chirality to generate benzo[*d*]sultams**

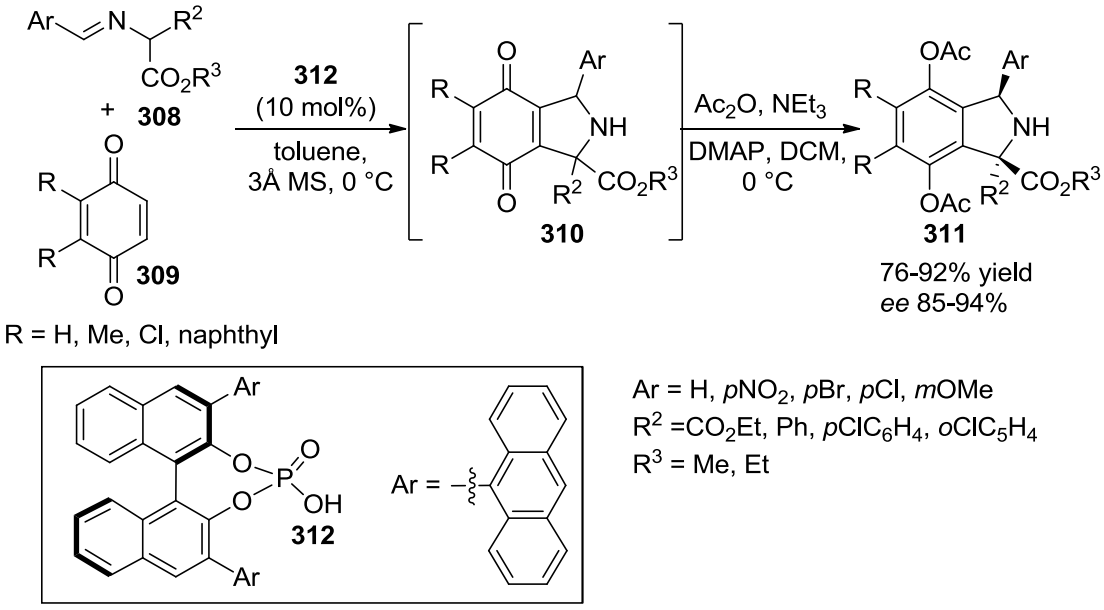
Additionally, the bis-lactim ether approach described for α-alkylation by Schöllkopf as an external source to introduce asymmetry was used by Jones *et al.* for the synthesis of α-arylated quaternary Schöllkopf adducts **306** (Scheme 60). Initially, a benzyne species is formed from **305**, the bis-lactim ether **219** adds to the benzyne introducing the aryl ring before addition to RX. The products

**306** were hydrolysed using 6.0 M $H_2SO_4$ for 72 h to give quaternary amino acid derivatives **307** in reasonable yields.[165,166] The selectivity and yield for this reaction was good, there was only a limited number of aromatic rings demonstrated but the reaction was applicable to a range of electrophiles.




**Scheme 60: Schöllkopf approach to α-arylated quaternary amino acids**

Finally, organocatalysis has been used to achieve a double α-arylation to generate isoindoline derivatives. Wang *et al.* showed an asymmetric method through reaction of an imine with a quinone that aromatises to give isoindole products **311** in good yields and good *ee* using Brønsted acid **312** as a catalyst (Scheme 61).[167]




**Scheme 61: Double α-arylation using organocatalysis**

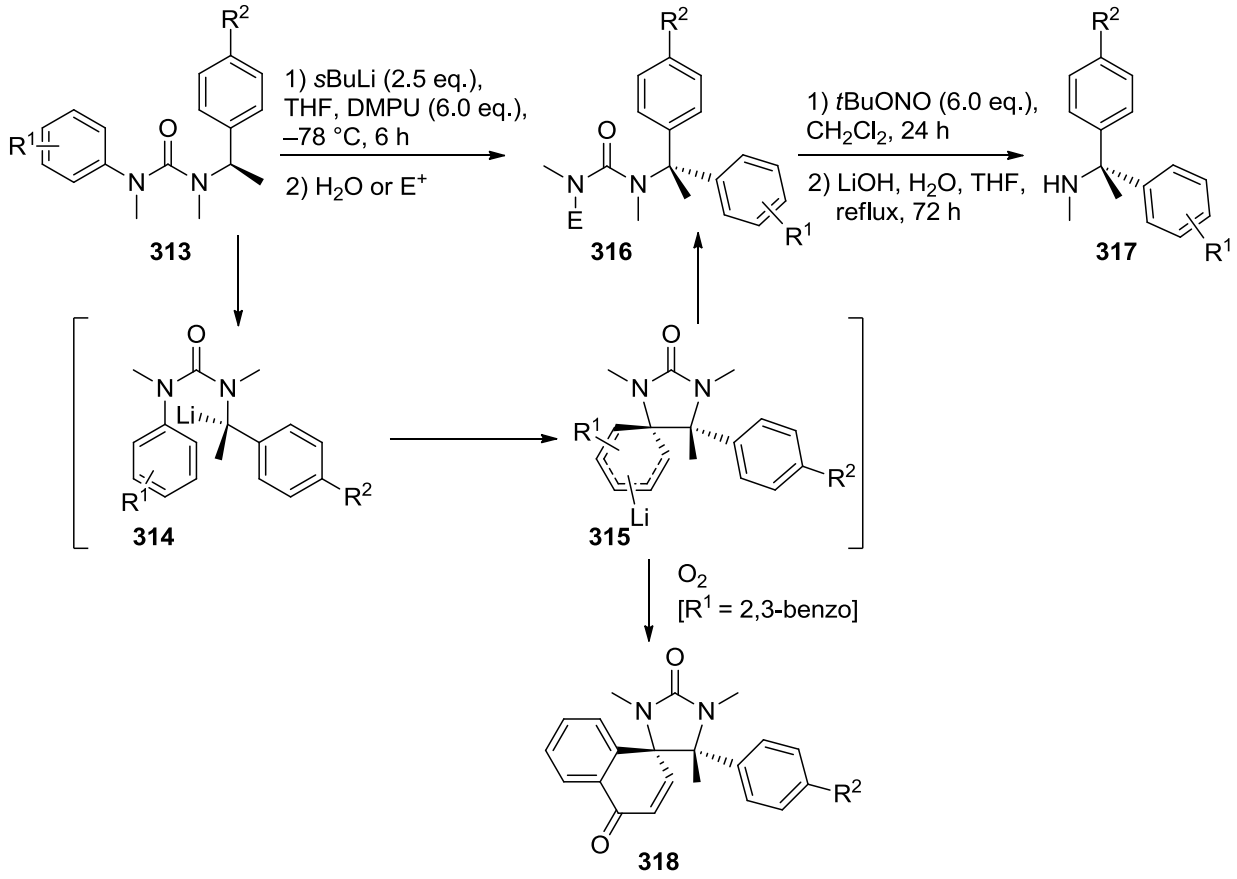
## 1.5.3 Conclusion

In conclusion, the early methods for α-arylation of α-amino acids used bismuth and lead complexes, while recent developments involve metal-catalysis with the most successful methods

being demonstrated by Buchwald, Hartwig and You using palladium or iron catalysts. These methods were efficient and accessed wide substrate scopes, but the major disadvantage was the reactions were not enantioselective. Arene-chromium complexes with PTC were successfully used by Maruoka for the asymmetric α-arylation of tertiary amino acid derivatives for a variety of amino acids and aromatic rings, but the reactions required stoichiometric chromium and a three-fold excess of the tertiary amino acid derivative. A transition-metal-free method would avoid problems of expensive or toxic metals and early methods showed α-arylation to be possible for electron poor rings such as nitroarenes. More recent methods using rearrangement, memory of chirality, Schöllkopf bis-lactim ethers or organocatalysis have shown asymmetric α-arylation of α-amino acid derivatives is possible, but all these methods have very specific requirements and have not shown a wide substrate scope. Overall, none of these methods provide a general protocol for the asymmetric α-arylation of α-amino acid derivatives to access α,α-disubstituted quaternary amino acids.

## 1.6 Rearrangement Chemistry

In 2007, Clayden *et al.* reported an unexpected stereospecific intramolecular aryl transfer reaction, found whilst studying the regioselective lithiation of *N*-aryl ureas.[168] *N*-Benzyl-*N'*-aryl ureas (**313**) can be transformed into tertiary amines (**317**), forming a quaternary centre *via* this rearrangement chemistry (Scheme 62).




**Scheme 62: Proposed rearrangement of *N*-benzyl-*N'*-aryl ureas into tertiary amines**

The rearrangement occurred upon addition of *s*BuLi in THF and DMPU was used as an additive to help solvent coordination, which increases the reactivity of the organolithium. The reaction was quenched with either water or an electrophile ($E^+$) generating a urea containing a quaternary centre (**316**). The second step was removal of the urea functionality to generate a tertiary amine (**317**).

When the reaction was carried out using enantiomerically pure starting material there was retention of the stereochemistry with minimal loss of enantiomeric purity after rearrangement. The migration worked for both electron rich and electron deficient rings. The stereospecificity is proposed to be due to the configurational stability of the intermediate dipole-stabilised organolithium **314** and retention of the stereochemistry was confirmed through the X-ray crystal structure of **318**.[169]

The proposed mechanism involves a benzylic lithiation (**314**) followed by addition of the organolithium centre to the 'distal' aryl ring. This may go *via* a dearomatised intermediate **315** and finally ring-opening gives urea **316**. This unexpected nucleophilic attack of the lithiated benzyl group on the aromatic ring was termed an *ipso* $S_NAr$ displacement of the urea nitrogen by the

lithiated benzyl group. The migration of the naphthyl ring was the only case the dearomatised intermediate was observed and trapped through exposure to air resulting in oxidation (**318**).

Further investigation of the mechanism was carried out using *in situ* NMR, IR and DFT calculations.[170] The NMR experiment containing DMPU suggested a transient dearomatised intermediate for the 1-naphthyl ring (as proposed in Scheme 62) but *in situ* IR performed in the absence of DMPU showed no detectable dearomatised intermediate. The DFT calculations also indicated the importance of coordinated lithium cations for the reaction to take place. The calculations suggested movement of the solvated lithium cation to the remote migrating ring during the reaction to stabilise the developing negative charge. This work also suggested the position of the solvated lithium cation was related to whether the reaction went with retention or inversion of stereochemistry. Further, coordination of lithium to the carbonyl of **315** when the ring migrates from the nitrogen atom to the α-carbon with elimination of urea functionality is vital. Finally, DFT calculations showed that attack on the urea carbonyl by the organolithium reagent would require a significantly higher energy pathway and therefore the aryl migration is more favourable.[170]

Further DFT calculations showed that the rearrangement reaction is possible due to the conformation adopted by the urea. A bond rotation takes place that allows the carbanion and the phenyl ring to be close enough in space for attack on the electron rich ring to be possible, this overcomes any electronic repulsion preventing the reaction taking place. In the case of ureas a retentive reaction is observed due to the solvated lithium cation existing between the two aromatic rings (**319**) (Figure 14).[171]

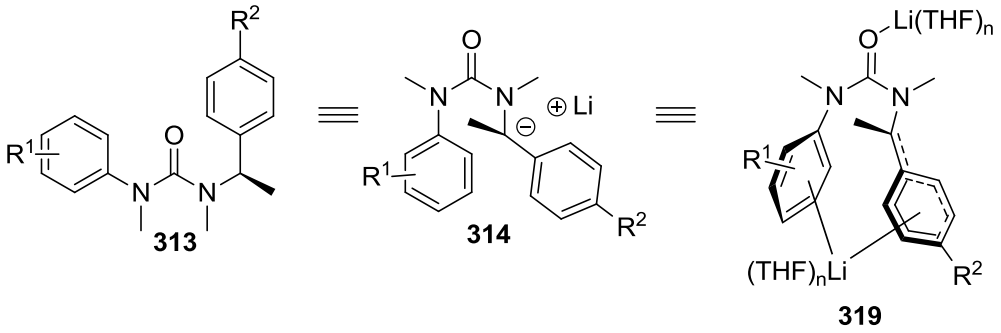
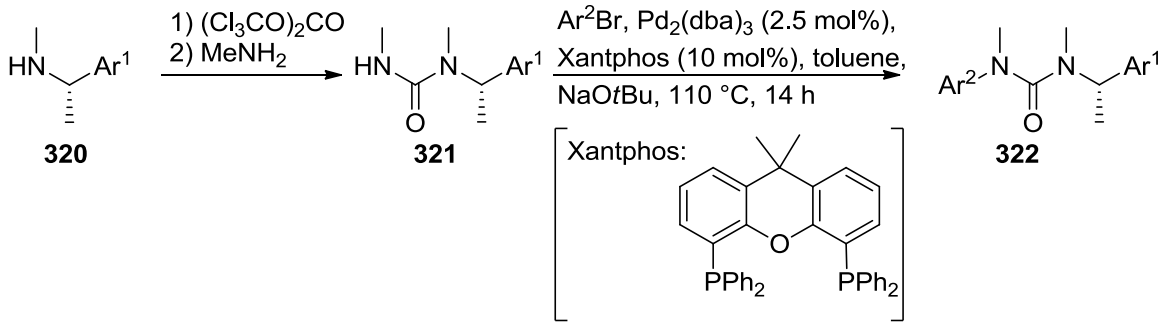


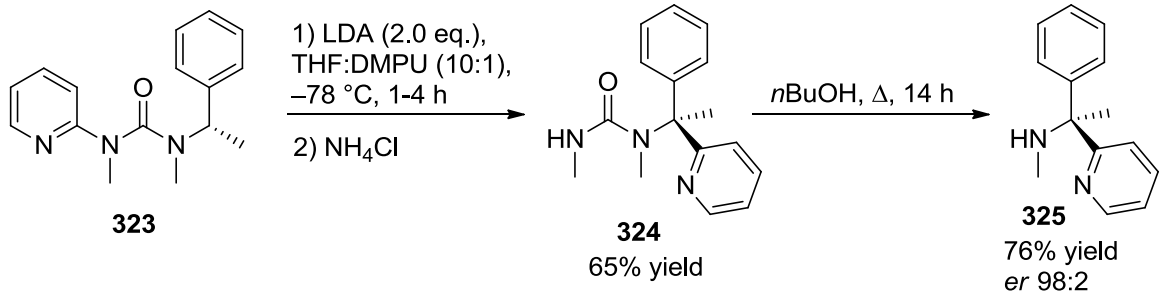

**Figure 14: Conformation allowing 1,4-aryl migration to occur**

This methodology was extended to the rearrangement of *N*-benzyl-*N'*-pyridyl ureas because chiral pyridyl-containing targets (e.g. nicotine) are biologically interesting and attractive in the pharmaceutical industry. Previously the ureas had been synthesised from isocyanates and amines, but due to the poor reactivity of pyridyl amines and the limited availability of pyridyl isocyanates, an alternative route was designed. The synthesis was achieved using a palladium coupling reaction of urea **321** with bromopyridines.[172]




**Scheme 63: Synthesis of pyridine containing ureas**

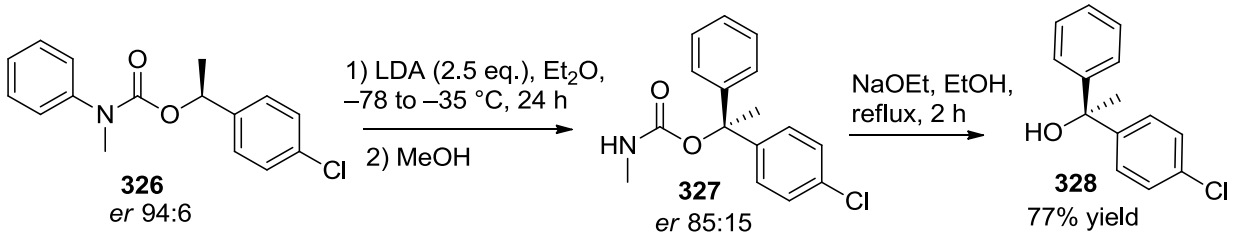
The rearrangement was successful and gave an efficient enantioselective synthesis of pyridines bearing an aminated quaternary stereogenic centre. LDA was used as a base with DMPU as an additive, *s*BuLi could not be used because it lithiated the pyridine ring rather than performing the rearrangement. The reaction was stereospecific and successful for various pyridine substituents with enantiomeric ratios up to 98:2 obtained (Scheme 64).[172]




**Scheme 64: Rearrangement of *N*-benzyl-*N'*-pyridyl ureas**

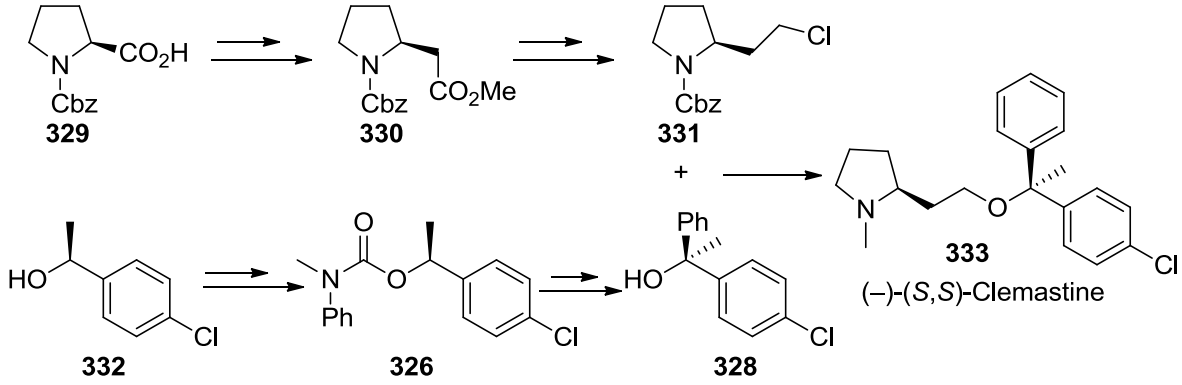
This α-arylation chemistry was also applied to the synthesis of cyclic amines. However, the rearrangement was non-stereospecific and enantiomerically enriched starting materials generated racemic products. The rearrangement was slower than for acyclic substrates meaning racemisation of the intermediate organolithium competed with the rearrangement due to the constrained system.[173]

In addition to ureas, alternative heteroatoms α to the benzylic position were investigated. Clayden *et al.* have shown the rearrangement reaction proceeds from carbamates to generate α-arylated secondary and tertiary alcohols.[174] The enantioselectivity of the reaction was lowered by the use of DMPU in THF, yet $Et_2O$ gave high *ee* (Scheme 65). Inversion at the lithium bearing centre was observed and DFT calculations suggest this is because one of the lowest energy transition states has the lithium cation bound to the carbamate oxygen rather than the carbanionic centre. 1,2 Migration of the lithium cation allows for rotation and inversion of the stereochemistry.[175]



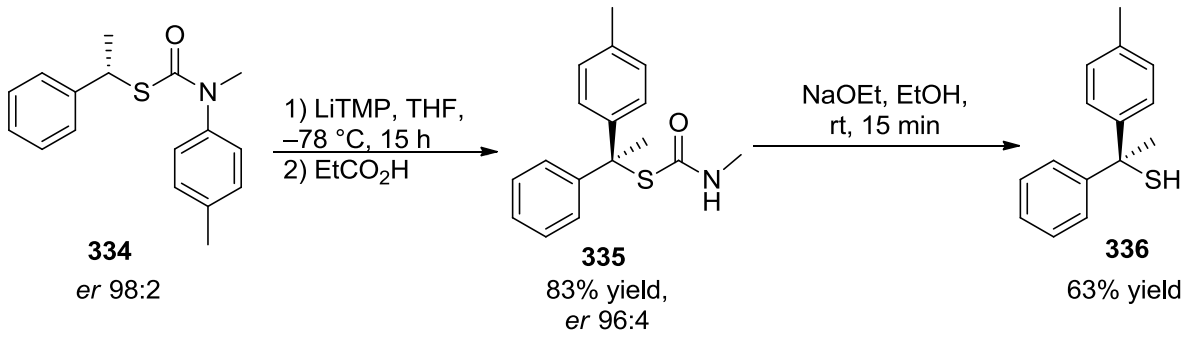

**Scheme 65: Generation of a tertiary alcohol from the aryl migration by lithiation**

Carbamate rearrangement was used in the synthesis of (–)-(*S*,*S*)-clemastine (**333**), which is an antihistamine agent (Scheme 66). The synthesis was achieved through reaction of a proline derived chloroethylpyrrolidine (**331**) and enantiomerically enriched tertiary alcohol **328** formed by the stereospecific aryl migration of lithium carbamates.[176]



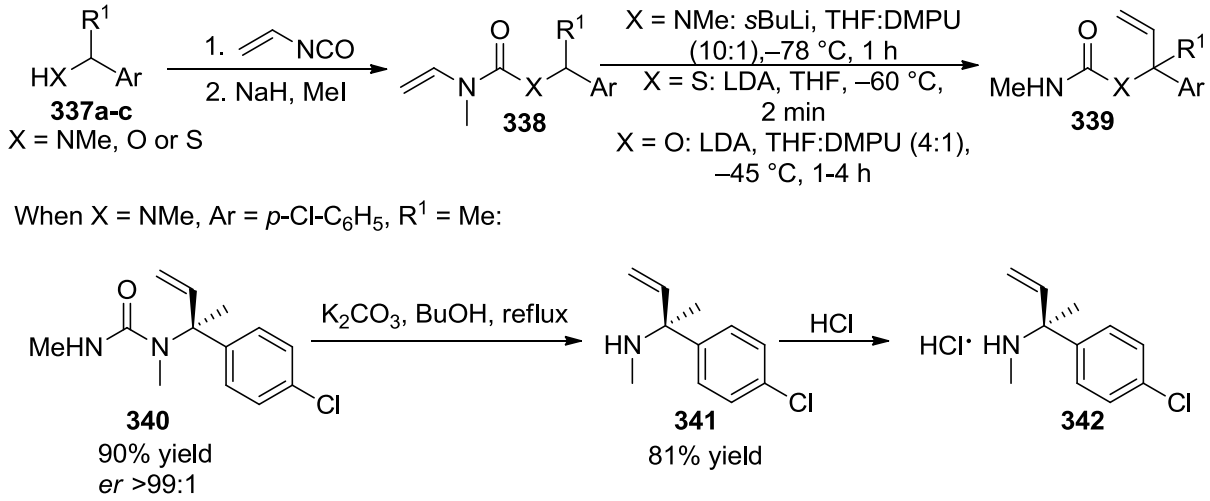

**Scheme 66: The synthesis of (–)-(*S*,*S*)-Clemastine using carbamate rearrangement chemistry**

Additionally, thiocarbamates can undergo intramolecular arylation to generate tertiary thiols. For these substrates, retention of stereochemistry is observed in the migration of the *N*-aryl ring to the anionic centre α to the sulphur. Electron deficient and moderately electron rich aryl rings migrate with good yield and selectivity. LiTMP gave an almost completely stereospecific reaction, but longer reaction times were required due to a slower lithiation step. Increasing the steric bulk of the base improved the enantioselectivity by giving high configurational stability to the intermediate (Scheme 67).[177]




**Scheme 67: Rearrangement of a thiocarbamate into a tertiary thiol**

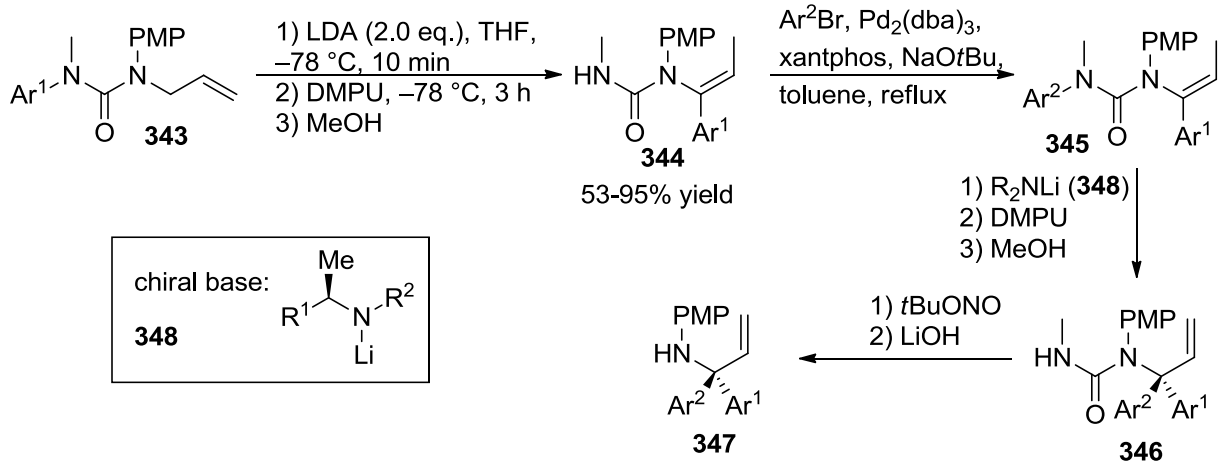
Direct arylation of organolithiums is challenging and this unexpected migration methodology gave a useful method to overcome this problem. Since intramolecular nucleophilic aromatic substitution was successful even with electron-rich rings for *N'*-aryl substrates, investigations into the migration of electron-rich alkenyl groups were carried out. Vinyl migration occurred at the benzylic position in ureas, carbamates and thiocarbamates (**337a-c**) (Scheme 68). For ureas this occurred with *s*BuLi with retention of stereochemistry but milder LDA was used as a base for the carbamates and thiocarbamates to minimise attack of the base on their carbonyl groups.[178]




**Scheme 68: Vinyl migration of ureas, carbamates, and thiocarbamates**

The one-pot operation (formation, rearrangement, and deprotection) followed by addition of anhydrous HCl led to crystalline amines (**342**), allowing unambiguous determination of the stereochemistry by X-ray crystallography. Computational models show coordination of the lithium cation to the π system of the phenyl group, whilst in the carbon-carbon bond forming transition state the lithium cation migrates to the terminal carbon of the vinyl group. This stabilises the forming negative charge leading to retention of stereochemistry in the product. Following the carbon-nitrogen bond breakage the lithium cation coordinates to the urea functionality to stabilise the negative charge.

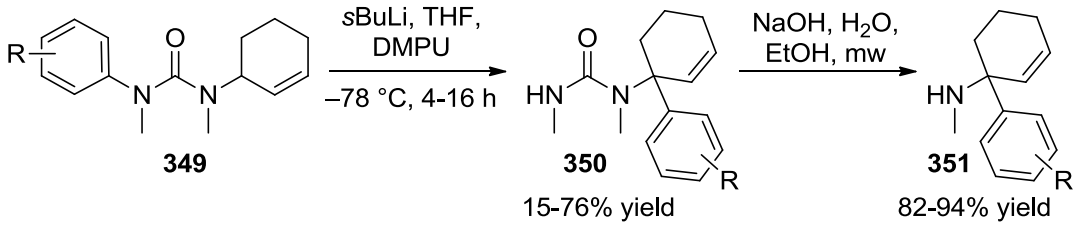
This rearrangement chemistry has evolved to double α-arylation migrations, which was demonstrated on *N*-allyl ureas.[179] In this case the anion generated from deprotonation is sufficiently stabilised by the allyl group in place of the benzyl group used previously. Following the first rearrangement, a secondary aromatic ring can be introduced and if a chiral lithium base **348** is used an enantioselective secondary rearrangement can occur generating 1,1-diarylallyl amine derivatives **347** (Scheme 69).




**Scheme 69: Double α-arylation of *N*-allylureas**

The optimum results were observed when lithiation occurred in a coordinating solvent with a DMPU additive, but for the synthesis of enantiomerically enriched amines it was necessary to remove DMPU and add LiCl to the reaction. The products (**347**) were obtained with enantioselective ratios between 84:16 and 92:8.

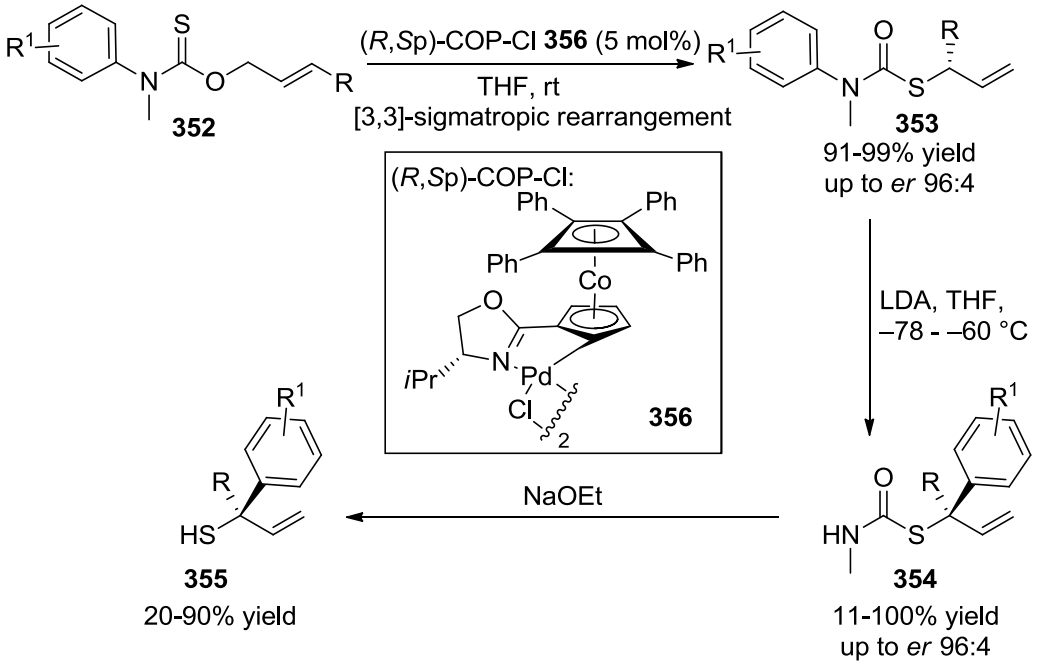
Other single arylations have been carried out using allyl stabilising group rather than benzylic groups. The synthesis of 1-arylcycloalkenamines **351** has been achieved through aryl migration followed by urea cleavage in moderate to good yields (Scheme 70).[180]




**Scheme 70: Aryl migration with allylic stabilising groups**

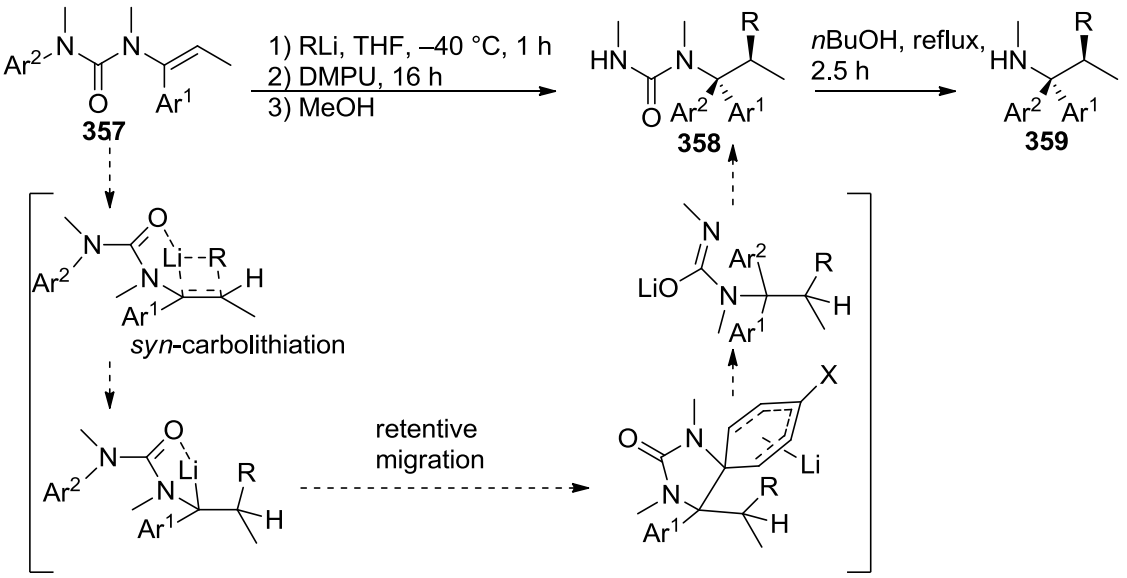
In 2014, α-arylated tertiary thiols were generated from allylic thiocarbamates, the precursors to the rearrangement were synthesised by a [3,3]-sigmatropic rearrangement that was carried out in tandem with the aryl migration (Scheme 71).[181] The products **355** from this reaction were *S*-

allylated under standard conditions and converted into dihydrothiophenes containing quaternary centres using ring closing metathesis.[182]



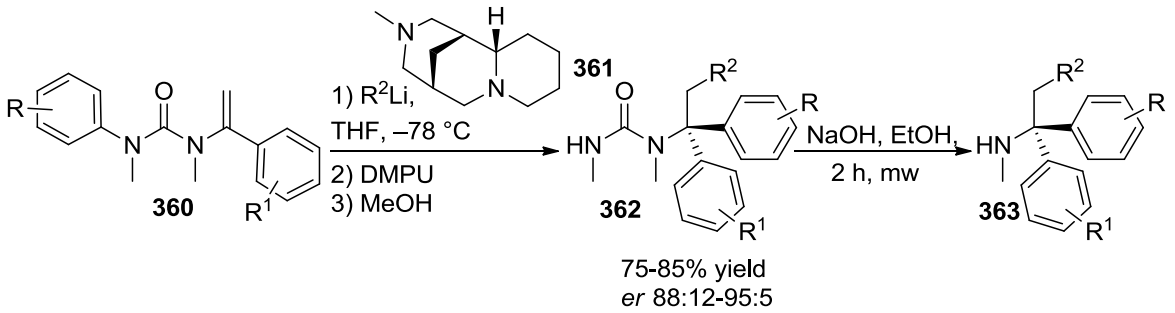

**Scheme 71: α-Arylated thiols from allylic thiocarbamates**

The rearrangement chemistry has been combined with carbolithiation to involve a β-alkylation-α-arylation process. Carbolithiation followed by *N*-aryl migration led to the addition of two carbon substituents across electron rich enamine double bonds. The reaction was stereospecific for both carbolithiation and rearrangement, resulting in a *syn* lithiation and retentive migration based on the starting material being an (*E*)-alkenyl urea (**357**). The carbolithiation occurred at –40 °C in toluene and by adding DMPU this enforced the rearrangement after carbolithiation (Scheme 72).[183]




**Scheme 72: Proposed *syn* carbolithiation followed by retentive migration**

This has also been applied to *O*-vinylcarbamates to provide tertiary alcohols with two new carbon-carbon bonds forming in a one-pot reaction,[184] and to *S*-alkenyl-*N*-aryl-thiocarbamates providing tertiary thiols.[185] In 2013, this tandem carbolithiation-rearrangement was applied to achiral starting materials generating enantiomerically enriched products through use of (–)-sparteine or (+)-sparteine surrogate (**361**) as a chiral ligand (Scheme 73)[186] and amides **362** with α-quaternary centres were obtained in good yield and *er*.



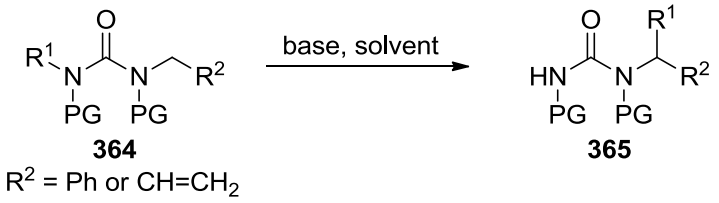

**Scheme 73: Tandem carbolithiation and rearrangement using (+)-sparteine surrogate**

In conclusion, this rearrangement chemistry has been useful for synthesising enantiomerically enriched amines, alcohols, and thiols with α-quaternary centres. This methodology is unusual as it allows nucleophilic aromatic substitution using nucleophilic addition to aromatic rings that are electron rich and not usually considered electrophilic. This discovery of a method that involves a '$Ph^+$' electrophilic species and generation of a quaternary centre could be used as a new method for generating α-arylated quaternary amino acids.

# 2 Results and Discussion

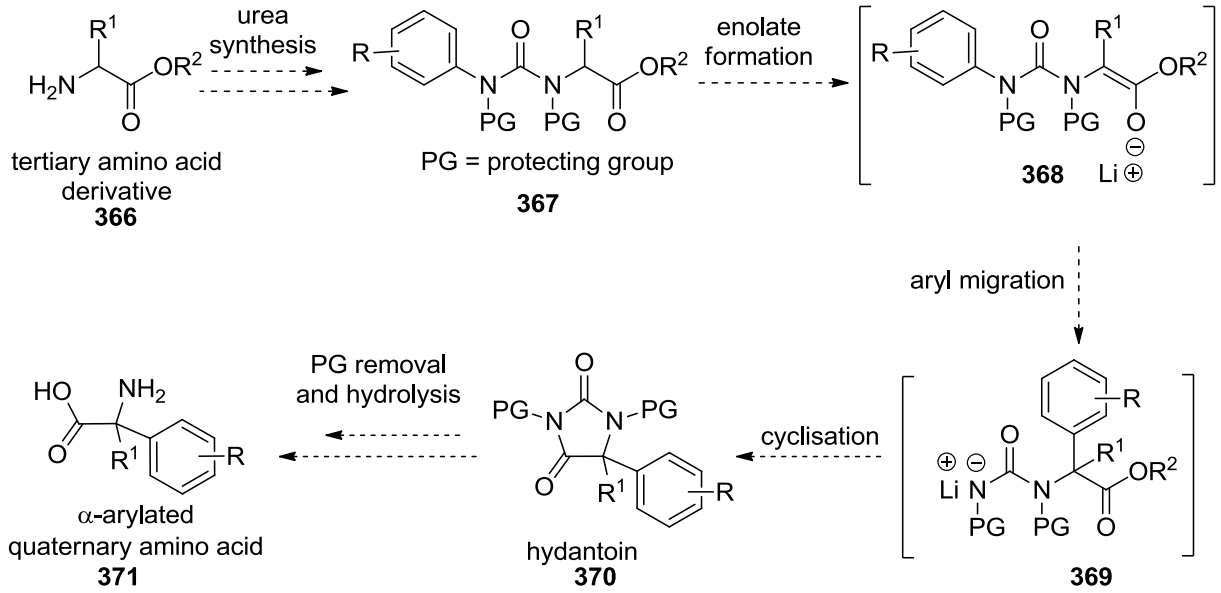
## 2.1 Aims of the Project

Clayden *et al.* have previously investigated various migrating groups ($R^1$) in rearrangement reactions of protected ureas, but to date only benzylic and allylic stabilising groups have been explored (Scheme 74). These are needed to stabilise the anion formed after basic deprotonation prior to migration and act as the nucleophile in the intramolecular nucleophilic aromatic substitution.




**Scheme 74: General migration reaction**

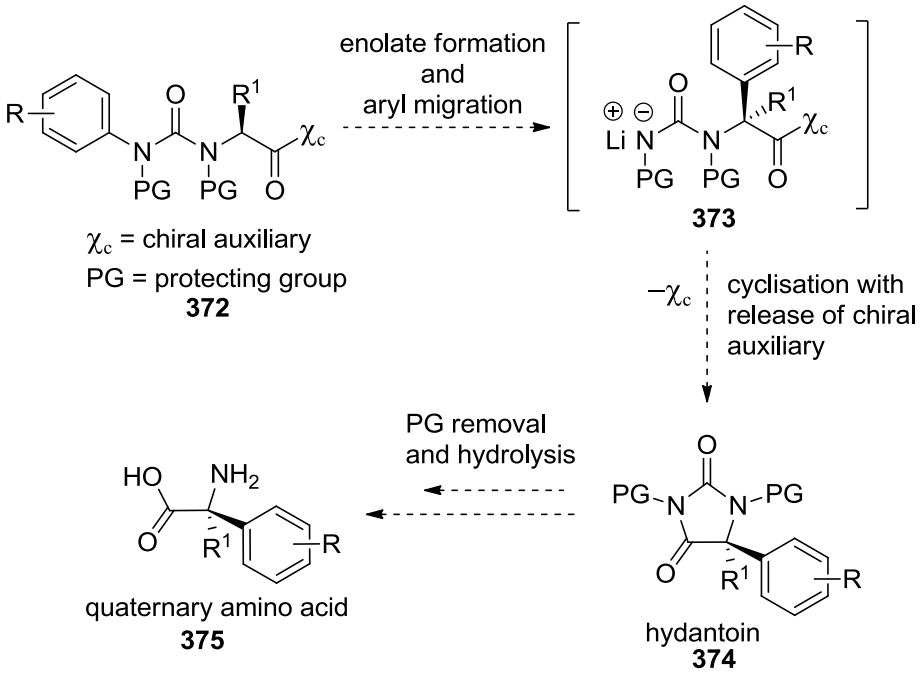
The aim of this project was to investigate enolates as a new class of nucleophile for the urea rearrangement chemistry. The overall goal was to develop a method for the synthesis of α-arylated quaternary amino acids through transition-metal-free intramolecular arylation of amino acid enolates. The first part of the project was to examine whether the rearrangement was possible with enolate nucleophiles and explore the scope and limitations of this process (Scheme 75).




**Scheme 75: The first aim of the project**

Initially, carboxylic urea derivatives **367** synthesised from tertiary amino acid derivatives **366** were investigated in the rearrangement with deprotonation proceeding *via* a planar enolate anion to

generate racemic products. The second part of the project aimed to introduce asymmetry into the reaction through use of a chiral auxiliary ($\chi_c$), allowing access to enantiomerically enriched α-arylated quaternary amino acid derivatives (Scheme 76).




**Scheme 76: The second aim of the project**

An advantage of this method is that the auxiliary will be released in the hydantoin formation, avoiding the need for a separate auxiliary removal step, which can sometimes be a problem. This also leads to the potential for the capture and recycling of the auxiliary at the end of the reaction.

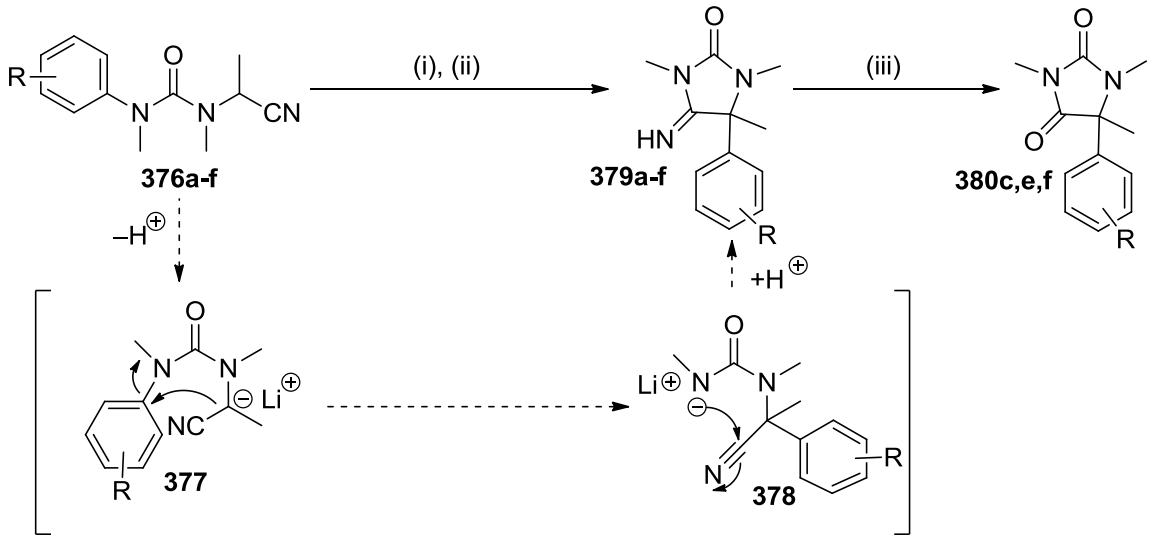
Quaternary α-amino acids are very important as they have improved metabolic stability compared with tertiary α-amino acids.[6,187] Their derivatives are important building blocks, or precursors to, many pharmaceutical targets and natural products.[188,189] The biological function of proteins is highly dependent on the secondary and tertiary structures adopted. It is useful to be able to synthesise peptidic chains with particular conformational properties utilising quaternary amino acids,[7] as conformation and structure can alter physiological effects.[9,10]

Quaternary amino acids can currently be made from their naturally occurring proteinogenic tertiary counterparts through methods such as alkylation. There are many methods available for the asymmetric α-alkylation of amino acids,[8,113,190-195] but fewer for α-arylation. There has been progress in metal-catalysed methods for the arylation of enolates.[135,136,141] Additionally, a small number of methods for the arylation of amino acids have been developed (see Chapter 1.5).[138,139,142,196,197] However, many arylation methods use expensive palladium catalysts that can lead to trace metals being present in the final products, which is a particular disadvantage if these

methods are to be used in the pharmaceutical industry. Moreover these methods are far from general, access only a limited substrate scope and the majority generate racemic products. Consequently, there is a need for a general asymmetric method for the synthesis of α-arylated quaternary amino acids that accesses a wide substrate scope.

## 2.2 Previous Work

Preliminary studies carried out by Dr Nicole Volz showed that anions derived from nitriles (metallonitriles) undergo rearrangement with *s*BuLi. The rearrangement produces iminohydantoins (**379a-f**) that can be converted into hydantoins in moderate yields (**380c,e,f**) using 3.0 M HCl in EtOH (Scheme 77, Table 4).[ii]



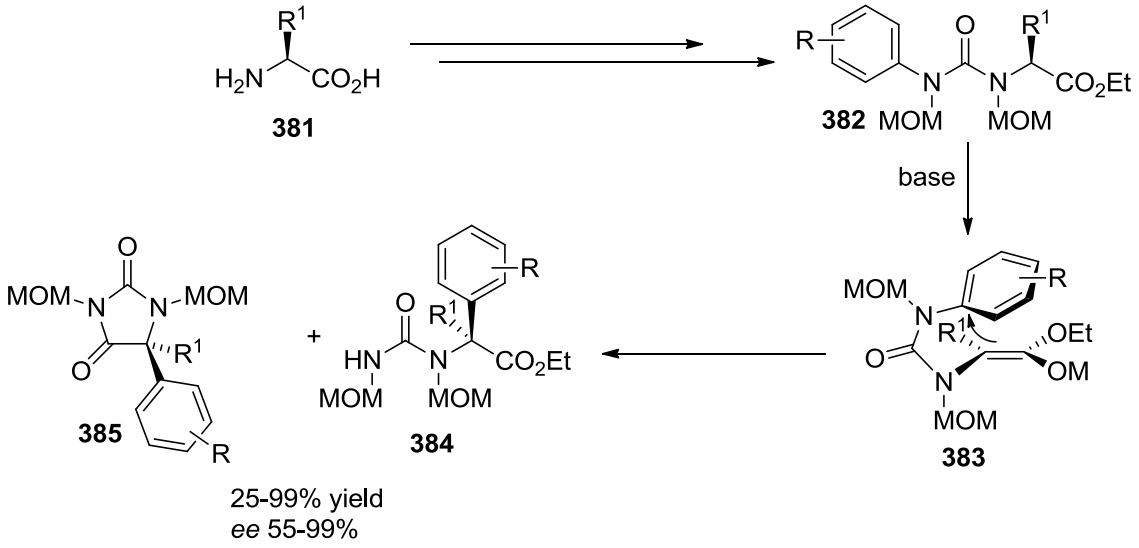

**Scheme 77: Reagent and conditions: (i) 2.0 eq. *s*BuLi, THF, −78 °C, 1 h; (ii) MeOH; (iii) 3.0 M HCl, EtOH, reflux, 8 h**

**Table 4: Rearrangement of metallonitriles to give iminohydantoins and hydantoins**

| Entry | R | Iminohydantoin | Yield (%) | Hydantoin | Yield (%) |
|---|---|---|---|---|---|
| 1 | H | **379a** | 85 | - | - |
| 2 | *p*-Cl | **379b** | 98 | - | - |
| 3 | *m*-F | **379c** | 86 | **380c** | 56 |
| 4 | *o*-OMe | **379d** | 76 | - | - |
| 5 | *p*-$CF_3$ | **379e** | 97 | **380e** | 50 |
| 6 | *m*-Cl | **379f** | 85 | **380f** | 51 |

This initial work suggested the rearrangement should be possible for anions less reactive than benzylic anions (α-H to nitrile p$K_a$ ~ 25, α-H to benzyl p$K_a$ ~ 35). However this method produces iminohydantoins that require an additional step to convert them into biologically interesting hydantoins. Secondly, asymmetry cannot be introduced into this reaction as the chiral auxiliary cannot be coupled to the nitrile functionality. During the course of this project Kawabata *et al.*[198] reported the combination of the Clayden group's rearrangement chemistry with their chiral memory work to perform asymmetric α-arylations of amino acids (Scheme 78).

[ii] With thanks to Dr Nicole Volz for carrying out these preliminary studies




**Scheme 78: Rearrangement and chiral memory**

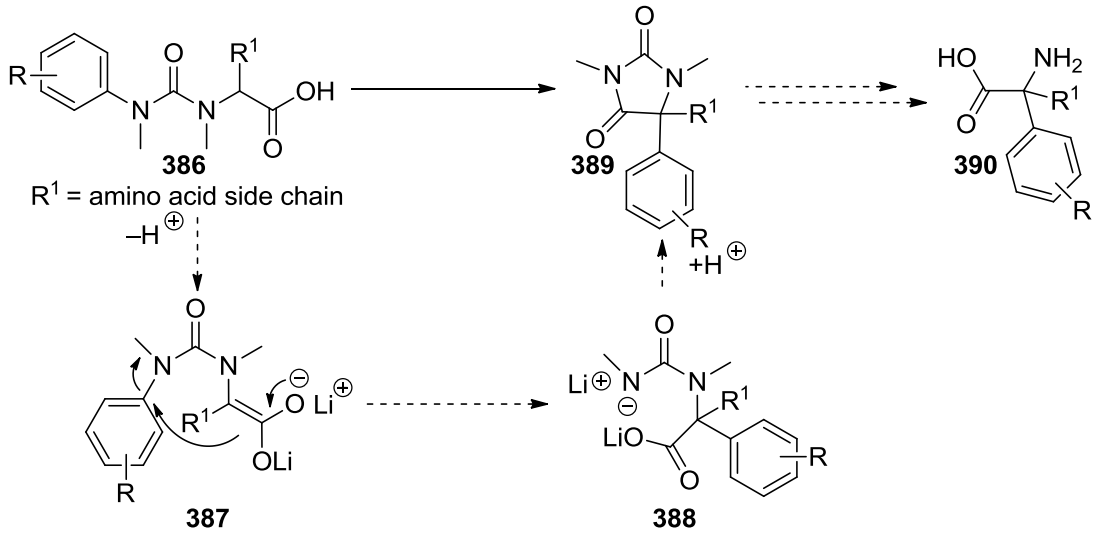
Although Kawabata's methodology was successful in generating enantiomerically enriched hydantoins, there are limitations. Firstly, only a small variety of amino acids were used, with most examples using phenylalanine and a few using either valine or methionine. Only five aromatic migrating groups were demonstrated and all were electron deficient. The reaction conditions were also not general and required optimisation for each substrate. In addition, for asymmetric induction using chiral memory MOM *N*-protecting groups were critical for formation of an axially chiral enolate. Furthermore, the method is stereospecific, not stereoselective, so a configurationally-defined chiral centre was required in the starting amino acid, therefore the synthesis of the starting material must avoid racemisation and racemic unnatural amino acids cannot be used. Finally, there was no proof that the MOM groups could be removed from the hydantoin and none of the examples were converted into quaternary amino acids.

## 2.3 Rearrangement of Amino Acid Enolates

### 2.3.1 *N*-Methyl Protected Hydantoins

#### 2.3.1.1 Rearrangement Reaction

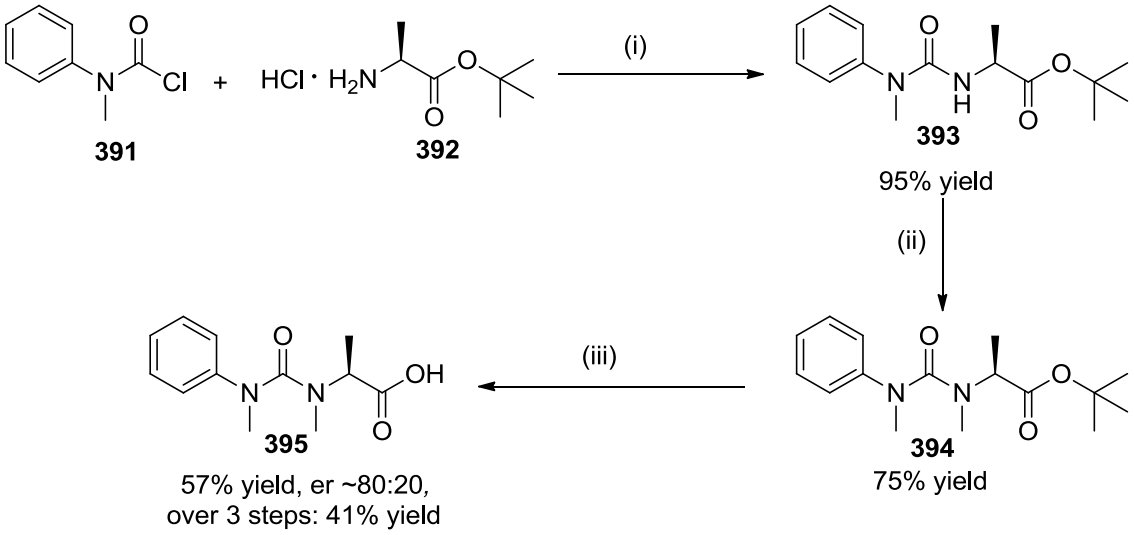
The first aim was to apply the rearrangement chemistry developed in the Clayden group to enolate nucleophiles. After preliminary studies showed success rearranging nitrile derivatives (Table 4) we set out to apply this anionic arylation to equally reactive, but more readily available, enolates of amino acid carboxylate salts (Scheme 79).




**Scheme 79: Arylation of enolates of a variety of amino acids**

It was expected that urea carboxylic acid **386** would be deprotonated, forming firstly a carboxylate anion followed by a second deprotonation at the α-position to generate an enolate **387**. This enolate would undergo rearrangement, with the aryl ring migrating from the nitrogen onto the α-carbon atom (**388**). In this case, if the same cyclisation was observed as with the nitrile series, hydantoins **389** would be directly formed through attack of the anionic nitrogen onto the carbonyl of the carboxylic acid.

The first task was to synthesise a starting material containing the aromatic ring for rearrangement and the amino acid linked by a urea tether through a three-step procedure. The first step was acylation of L-alanine *tert*-butyl ester (**392**) with *N*-methyl-*N*-phenyl carbamoyl chloride (**391**), affording **393** in an excellent 95% yield. Secondly, *N*-methylation using sodium hydride and methyl iodide led to the dimethylated urea **394** in 75% yield and partial racemisation of the stereocentre occurred during this step (100% *ee* to 60% *ee*). The final step was removal of the *tert*-butyl group using TFA in DCM, giving product **395**, obtained in 41% yield over the three steps (Scheme 80).



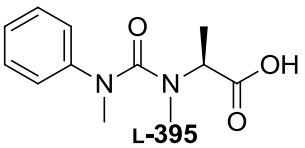

**Scheme 80: Reagents and conditions: (i) 2.3 eq. $Et_3N$, DMAP (cat), DCE, reflux, 20 h; (ii) 3.0 eq. MeI, 2.0 eq. NaH, DMF, 20 h; (iii) TFA, DCM, 2 h[iii]**

With a route to the desired starting material (**395**) established, the conditions for the rearrangement were investigated and optimised. In the case of the nitrile derivatives, the rearrangement occurred readily at –78 °C using 2 eq. of *s*BuLi but for the amino acid substrates an extra equivalent of base was necessary as the carboxylic acid needs to be deprotonated in the reaction mixture.

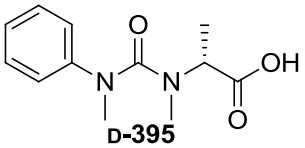
The first conditions tried were 3 eq. of *s*BuLi at –78 °C, but this led to decomposition of the starting material (entry 1, Table 5). LDA was investigated as a milder base and at –78 °C a small amount of product was observed by $^1$H NMR, with the remaining material being starting material (entry 2, Table 5). There are two possible reasons for the remaining starting material under these conditions. Firstly, the rate of deprotonation to form the enolate could be slow, preventing the reaction going to completion at low temperature. Alternatively, the starting material could be fully deprotonated but the rearrangement step may be slow, resulting in no reaction.

To investigate the rates of the deprotonation and rearrangement, urea carboxylic acid **395** was synthesised from both L and D-alanine according to the conditions in Scheme 80. The synthesis resulted in partial racemisation of the α stereocentre but the urea carboxylic acid was still predominantly one enantiomer (*er* ~80:20) shown by chiral HPLC analysis (Figure 15).

[iii] The stereochemistry is shown for the major enantiomer




From L-alanine: *er* = 80:20 (*S*:*R*)
*ee* = 60%
Retention times: 19.0 min and 22.5 min



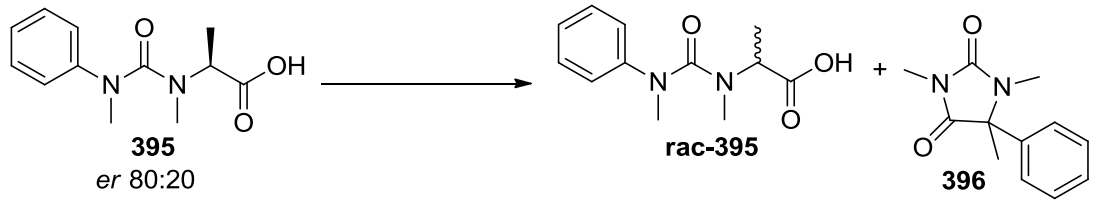

From D-alanine: *er* = 14:86 (*S*:*R*)
*ee* = 72%
Retention times: 19.0 min and 23.0 min

**Figure 15: HPLC analysis of two enantiomers; chiralpak® AD-H column, 262 nm, 1 mL/min, 5 µl, 95:5 hexane:IPA**

The starting material synthesised from L-alanine was used in the optimisation of the rearrangement reaction, with conversion into product determined by $^{1}$H NMR. If incomplete conversion occurred HPLC analysis indicated whether α-deprotonation of the starting material had occurred, this was shown by a decrease in the starting material's *er*. The percentage of the remaining starting material that had racemised could then be calculated, which gave an indication of the relative rate of deprotonation at different temperatures. The results with various reagents and conditions are detailed in Table 5.[iv]

[iv] Optimisation carried out in collaboration with Dr Daniele Castagnolo

**Table 5: Conditions and optimisation of the urea amino acid rearrangement[iv]**



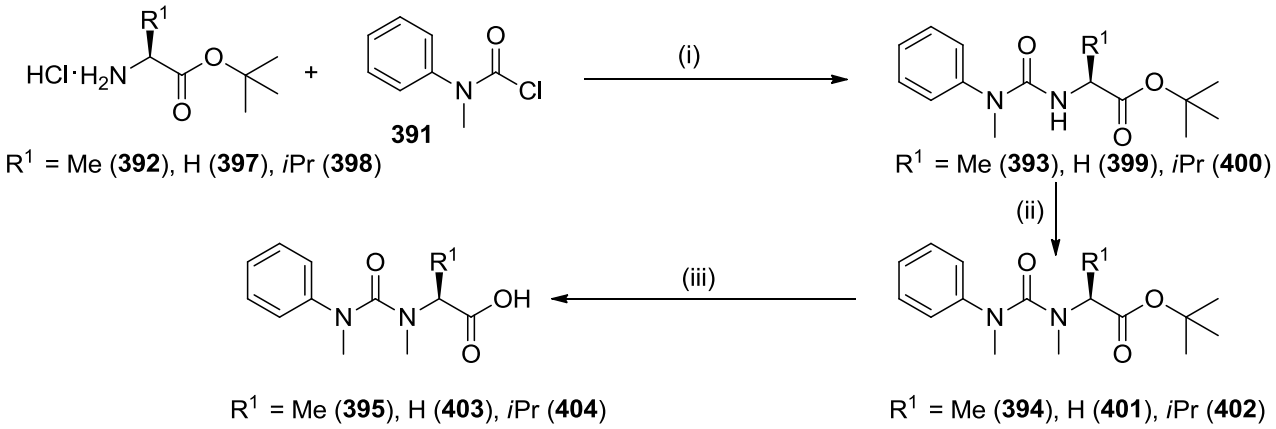

| Entry | Base, n° eq. | Conditions (T °C, t h) | % loss of *ee*[a] for remaining SM 395 | Yield 396 (%)[b] |
|---|---|---|---|---|
| 1 | *s*BuLi, 3.0 | –78 °C, 1 h | – | 0 |
| 2 | LDA, 3.0 | –78 °C, 1 h | 15 | 18 |
| 3 | LDA, 3.0 | –40 °C, 1 h | 31 | 43 |
| 4 | LDA, 3.0 | –15 °C, 1 h | 62 | 86 |
| 5 | LDA, 3.0 | 0 °C, 2 h | 9 | 83 |
| 6 | LDA, 3.0[c] | 0 °C, 1 h | 64 | 59 |
| 7 | LiTMP, 3.0 | 0 °C, 2 h | – | 50 |
| 8 | LDEA, 3.0 | 0 °C, 2 h | – | 75 |
| 9 | LDA, 7.0 | 0 °C, 2 h | – | 90 |
| 10 | LDA, 3.0 | –78 - 20 °C, 20 h | – | 96 |
| 11 | LDA, 3.0 + LiCl, 3.0[d] | –78 - 20 °C, 3 h | – | 98 (89)[e] |

All reactions were carried out in THF (0.1 M) (except entry 6). [a] *ee* of the starting material **395** = 60%, 'x'% *ee* of recovered starting material **rac-395** after the reaction, therefore ('x'/60)×100 = y% not racemised and (100–y) = % loss of *ee*. [b] NMR yield. [c] $Et_2O$ used as solvent. [d] an excess of LiCl was also successful. [e] isolated yield (0.5 g scale).

When LDA was used as a base at –78 °C a small amount of rearrangement took place (entry 2, Table 5). HPLC analysis of the recovered starting material showed lack of racemisation, suggesting that at –78 °C deprotonation to form the enolate was slow. Increasing the temperature to –40 °C and to –15 °C (entries 3 and 4, Table 5) improved the yield, and the amount of racemisation of remaining starting material increased. This showed that both the rate of enolate formation and the rate of rearrangement increased with temperature. The temperature was increased further to 0 °C (entry 5, Table 5) and although the yield was good the remaining starting material showed little racemisation, which indicated incomplete deprotonation. Using $Et_2O$ as a solvent (entry 6, Table 5) instead of THF resulted in reduced rates of both deprotonation and rearrangement. Changing the base to more basic LiTMP or less sterically hindered LDEA, (entries 7 and 8, Table 5) gave no improvement in the yield. However, an improvement in yield was observed when an excess of LDA was used or the reaction was warmed to a higher temperature (entries 9 and 10, Table 5). This suggested that solvation of the reaction intermediates with lithium ions ($Li^+$) could facilitate the rearrangement. Finally using 3 eq. of LDA with 3 eq. of LiCl to increase the lithium content of the reaction was optimal (entry 11, Table 5). These conditions gave excellent conversion 98% when

the reaction was warmed to room temperature after the LDA addition and left for 3 h at room temperature, allowing **396** to be isolated in 89% yield.

Having established optimal rearrangement conditions an investigation into the scope of α-amino acids and different migrating groups tolerated was carried out. A number of urea carboxylic acids containing different amino acid side chains was synthesised using the general method shown in Scheme 81. Acylation of *tert*-butyl amino esters with *N*-methyl-*N*-phenyl carbamoyl chloride (**391**) followed by methylation of the free nitrogen atom using methyl iodide and sodium hydride and finally, removal of the *tert*-butyl group using TFA in DCM gave the required urea amino acids (**395**, **403**, **404**). Following this method, urea derivatives of glycine, alanine and valine were synthesised in reasonable yields over the three steps (Table 6).

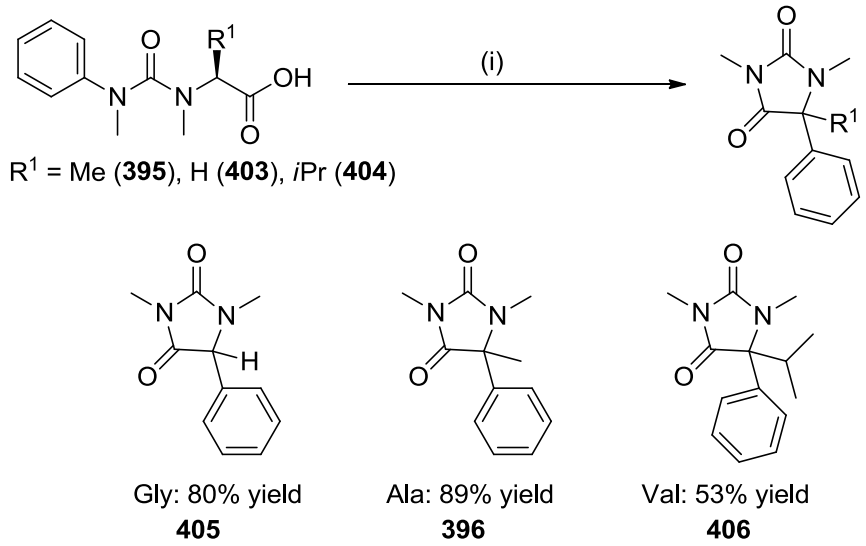



**Scheme 81: Reagents and conditions: (i) DMAP (cat), $Et_3N$, DCE; (ii) MeI, NaH, DMF; (iii) TFA, DCM**

**Table 6: Yields for the synthesis of the starting urea amino acids**

| Entry | SM | Acylation yield (%) | Methylated yield (%) | Deprotected yield (%) | Overall yield (%) |
|---|---|---|---|---|---|
| 1 | Ala (**392**) | 95 (**393**) | 75 (**394**) | 57 (**395**) | 41 |
| 2 | Gly (**397**) | >99 (**399**) | 99 (**401**) | 60 (**403**) | 59 |
| 3 | Val (**398**) | 95 (**400**) | 93 (**402**) | 92 (**404**) | 81 |

These derivatives were successfully rearranged using the optimised conditions of 3 eq. of LDA and 3 eq. of LiCl added at –78 °C and warmed to room temperature for 3 h (Scheme 82).

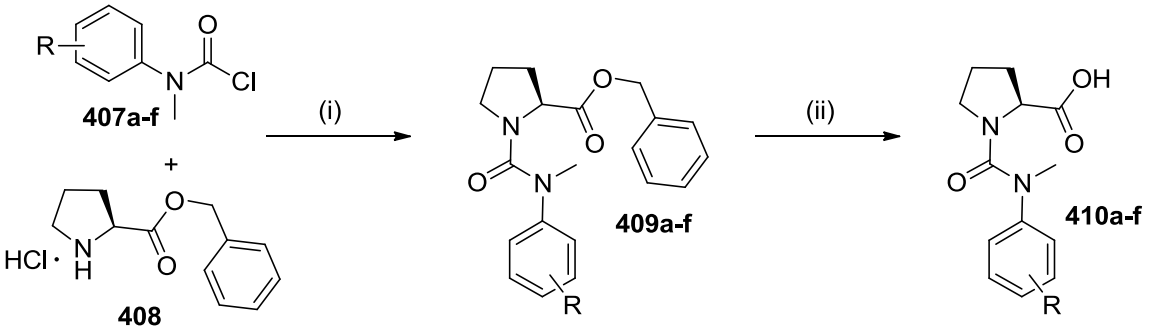



**Scheme 82: Reagents and conditions: (i) 3.0 eq. LDA, 3.0 eq. LiCl, THF, –78 °C – rt, 3 h**

The derivatives of glycine (**403**) and alanine (**395**) rearranged to give hydantoins **405** and **396** in excellent yields of 80% and 89%, respectively. The valine derivative **404** rearranged to give **406** in a more moderate isolated yield of 53% but the crude $^{1}$H NMR showed 22% of remaining starting material (**404**:**406** = 1:3.5). In order to push the reaction to completion the reaction was left overnight but there was no improvement in the yield. Finally the reaction conditions were changed to 6 eq. of LDA and 6 eq. of LiCl, but this gave a lower yield. In this case the reaction mixture may be too basic, which could cause decomposition of either the starting material or product. Overall the yield was lower for the valine derivative (**404**) as it is more difficult to deprotonate at the α-position due to the steric effects of the branched side chain.

Following on from the success with simple tertiary amino acids and migrating phenyl rings, proline was investigated in the rearrangement with a variety of aryl migrating rings. The synthesis of the urea starting materials was modified according to Scheme 83. Firstly an acylation reaction was performed between a carbamoyl chloride (**407a-f**) containing the appropriate migrating ring and proline benzyl ester (**408**). Secondly, the *N*-benzyl protecting group was removed by hydrogenolysis to give the free carboxylic acids (**410a-f**).

The coupled products (**409a-d**) containing different aryl migrating groups were synthesised in excellent yields of 90-99% (Table 7).

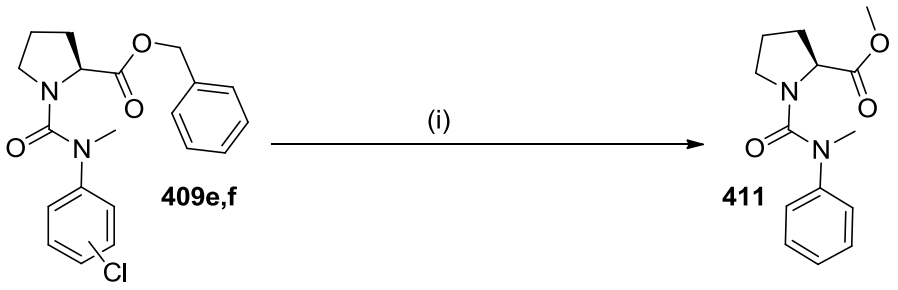



**Scheme 83: Reagents and conditions: (i) DMAP (cat), $Et_3N$, DCE, 70 °C, 20 h; (ii) $H_2$ (1 atm), Pd/C (10%), MeOH, rt, 20 h**

**Table 7: Yields for the synthesis of proline derived ureas**

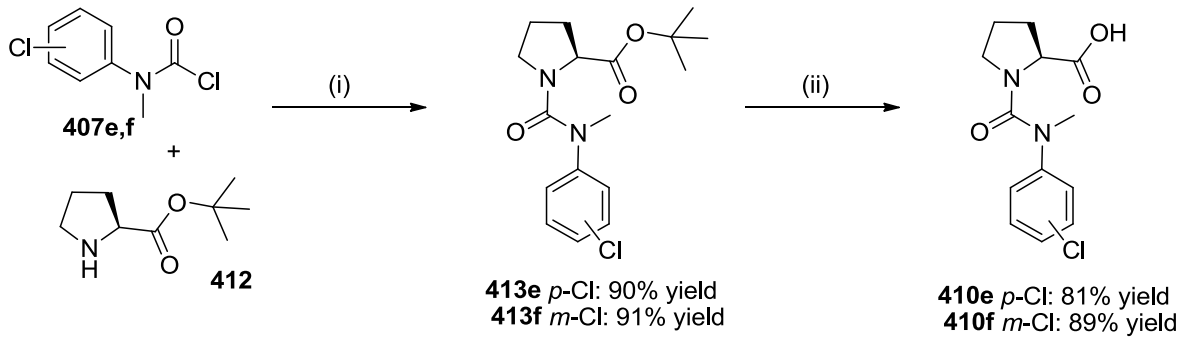
| Entry | R = | Coupled benzyl ester 409 | Yield (%) | Carboxylic acid 410 | Yield (%) |
|---|---|---|---|---|---|
| 1 | H | **409a** | >99 | **410a** | 93 |
| 2 | *m*-F | **409b** | 94 | **410b** | 97 |
| 3 | *o*-OMe | **409c** | 98 | **410c** | >99 |
| 4 | *o*-Me | **409d** | 96 | **410d** | 99 |
| 5 | *p*-Cl | **409e** | 93 | **410e** | 0 |
| 6 | *m*-Cl | **409f** | 90 | **410f** | 0 |

Unfortunately, when the chlorine-containing coupled products **409e** and **409f** were subjected to the hydrogenation conditions the palladium catalyst facilitated dehalogenation of the aromatic ring. This generated hydrochloric acid *in situ*, which in combination with the MeOH solvent led to transesterification of the benzyl ester into methyl ester **411** (Scheme 84).




**Scheme 84: Reagents and conditions: (i) Pd/C (10%), $H_2$ (1 atm), MeOH, rt, 20 h**

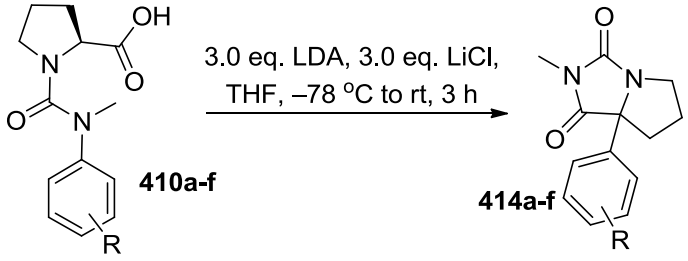
Therefore, an alternative route for the synthesis of chlorinated aromatics **410e** and **410f** was used. Acylation of proline *tert*-butyl ester (**412**) with carbamoyl chlorides **407e** and **407f**, followed by cleavage of the *tert*-butyl group using TFA in DCM gave the required carboxylic acids (**410e,f**) in high yields (Scheme 85).




**Scheme 85: Reagents and conditions: (i) DMAP (cat), DCE, $Et_3N$, 45 °C, 20 h, (ii) 1:1 TFA:DCM, rt, 2-4 h**

The various proline derivatives (**410a-f**) were then subjected to the optimised rearrangement conditions. Pleasingly, all of the proline-derived substrates rearranged in moderate to good yields of 55-75% (**414a-f**) (Table 8). This is particularly interesting as it represents cyclic amino acids undergoing rearrangement to create bicyclic hydantoin structures.

**Table 8: Rearrangement of the proline derived ureas:**




| Entry | R = | Hydantoin 414 | Yield (%) |
|---|---|---|---|
| 1 | H | **414a** | 70 |
| 2 | *m*-F | **414b** | 55 |
| 3 | *o*-OMe | **414c** | 75 |
| 4 | *o*-Me | **414d** | 60 |
| 5 | *p*-Cl | **414e** | 72 |
| 6 | *m*-Cl | **414f** | 65 |

These optimised conditions were also applied to other amino acids and other migrating groups (Figure 16).[v]

[v] With thanks to Dr Daniele Castagnolo and Dr Julien Maury for applying the conditions to these substrates.

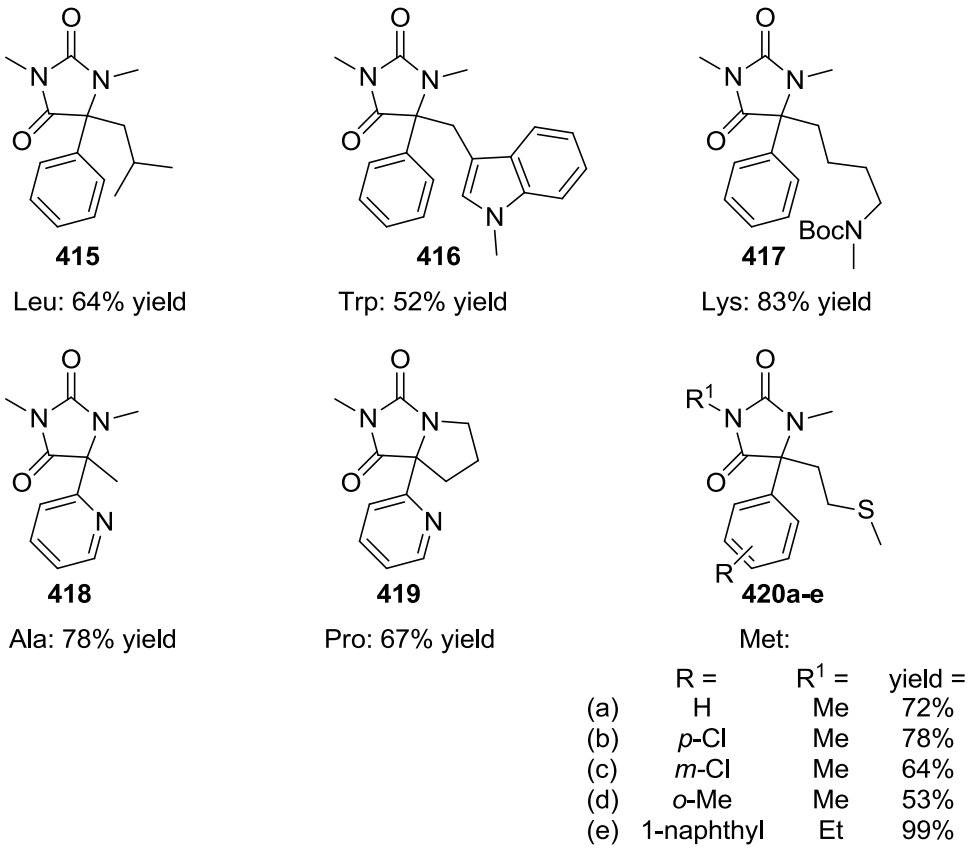
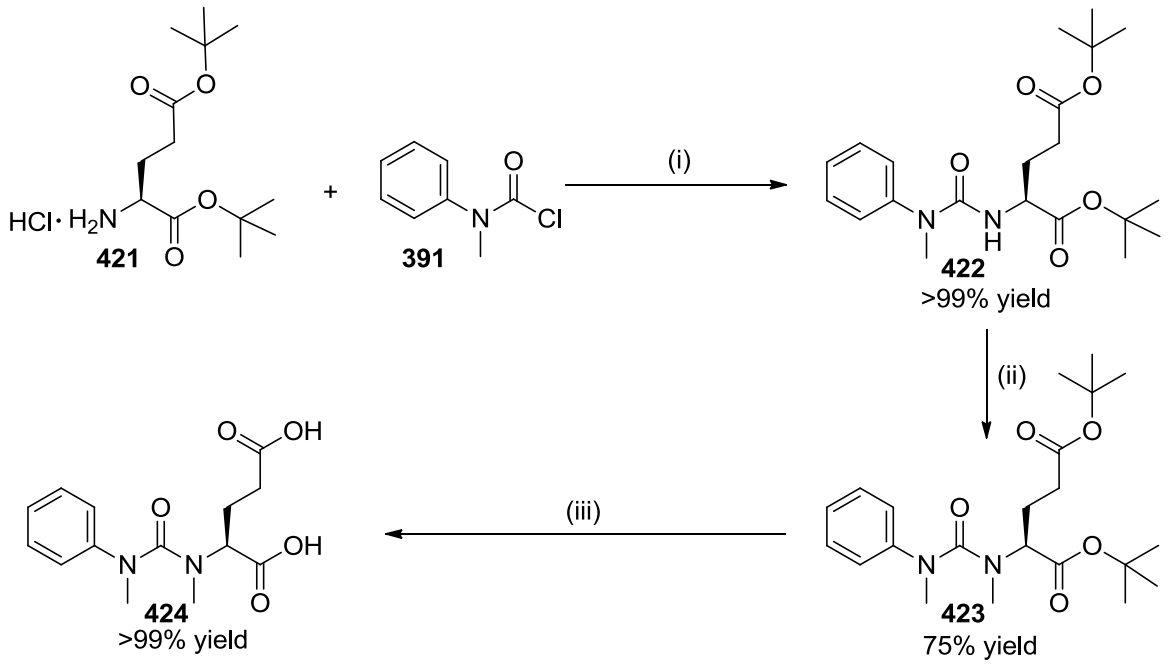



**Figure 16: Other amino acid substrates and rings used with the optimised conditions**[v]

These examples show that more complex amino acids are tolerated in the rearrangement. Leucine derivative **415** gave a moderate yield, similar to that observed for valine derivative **406**, probably due to the branched nature of the substrate making the deprotonation more difficult. Tryptophan derivative **416** rearranged in a moderate yield, with 15% of the starting material being recovered. *Nε*-Boc protected lysine derivative **417** rearranged successfully in a high 83% yield. Migration of pyridine rings was successful for alanine **418** and proline **419** and a wide variety of migrating groups rearranged successfully with the methionine derivative **420a-e**.

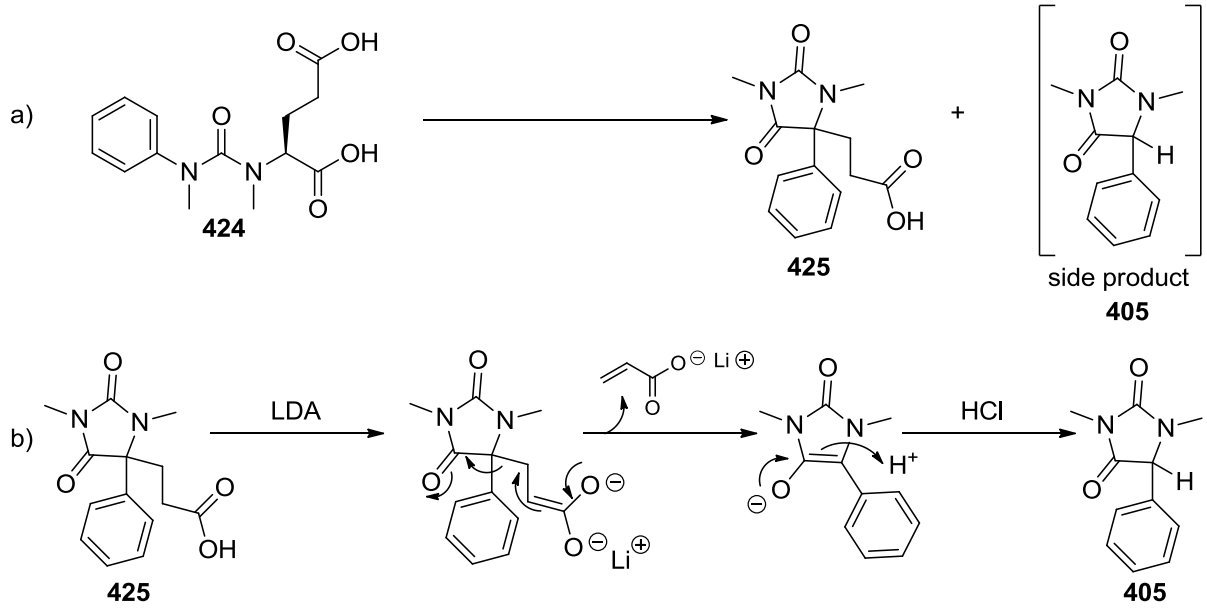
Based on the fact that more complex amino acid derivatives underwent rearrangement, glutamic acid was investigated in the enolate arylation. The standard method for generating the urea carboxylic acid was used (Scheme 86). The acylation step was successful giving product **422** in >99% yield. The methylation conditions were modified to use 2 eq. of methyl iodide and 1.5 eq. of sodium hydride forming **423** in a 75% yield. The conditions for the *tert*-butyl removal were also modified as two esters now needed to be hydrolysed. The best conditions found were use of 1:2 TFA:DCM and to leave the reaction for only a short period of time to prevent degradation of the product. This allowed product **424** to be isolated in a >99% yield, but it was very acid sensitive and, underwent degradation in chlorinated solvents.




**Scheme 86: Reagents and conditions: (i) 2.3 eq. $Et_3N$, DMAP (cat), DCE, 70 °C, 20 h; (ii) 2.0 eq. MeI, 1.5 eq. NaH, DMF, 0 °C – rt, 20 h; (iii) 1:2 TFA:DCM, rt, 30 min**

The rearrangement of glutamic acid derivative **424** requires more base than the previously optimised conditions as there is an additional carboxyl group that will be deprotonated. The standard conditions were modified to 4 eq. of LDA with 4 eq. of LiCl, but low conversion into hydantoin **425** was observed.

The reaction conditions were further modified to try and improve the conversion but in all cases starting material remained. An increase in LDA led to decomposition while an increase in LiCl led to side product **405** (Scheme 87a). The side product **405** is thought to arise from a retro-Michael reaction of the desired product **425**. Lower temperatures minimised formation of the side product **405** but prevented a complete reaction. Re-subjecting a crude reaction mixture that had minimal **405** present to the reaction conditions, subsequently gave side product **405** as the major component. (Scheme 87b).

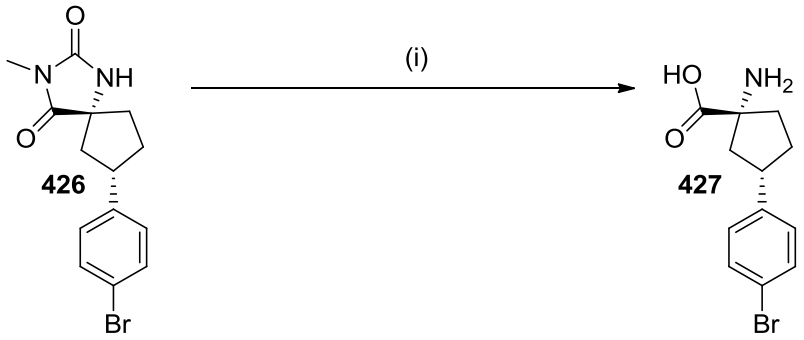



**Scheme 87: Retro-Michael reaction generating side product 405 from desired product 425**

The optimum conditions found for the rearrangement of glutamic acid derivative **424** were 5 eq. of LDA, 10 eq. of LiCl for 3 h with addition at –78 °C and warming to room temperature. The product **425** was present along with the side product **405** and starting material **424**. ($^1$H NMR showed 50% **425**: 25% **405**: 25% **424**). Unfortunately, the reaction could not be pushed further as conditions that minimised the impurity formation gave low conversions and left mainly starting material, but when more forcing conditions were used the major product was the impurity **405**.

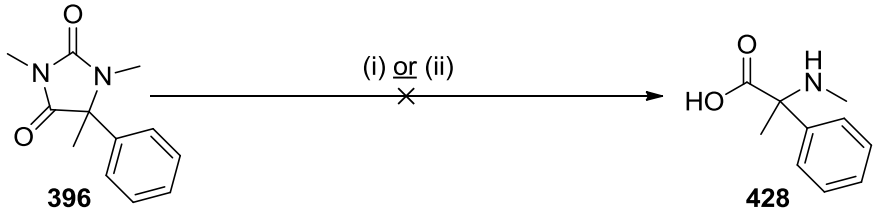
### 2.3.1.2 Attempted Cleavage of *N*-Methyl Protected Hydantoins

The optimised rearrangement conditions were successful on a wide variety of urea amino acid derivatives, ranging from glycine to tryptophan. A large selection of aromatic rings were also shown to migrate successfully. Hydantoin structures are themselves biologically interesting, especially ones containing a quaternary centre.[32,36-39] However, being able to cleave the hydantoins into the corresponding α-arylated quaternary amino acids would be valuable. The next step was to cleave the hydantoins to generate quaternary amino acids. There is literature precedent to suggest that unprotected hydantoins can be hydrolysed to generate amino acids (Scheme 88).[31,199-201]




**Scheme 88: Reagents and conditions: (i) 2.0 M NaOH, dioxane, reflux, 24 h[201]**

Unfortunately, there are no known literature methods to remove the *N*-methyl protecting groups from the hydantoins. A direct hydrolysis of the alanine derived *N*-methyl protected hydantoin **396** was attempted (Scheme 89) using NaOH with dioxane at reflux for an extended period of time (8 days) or alternatively using NaOH in EtOH with microwave heating. Using these similar and harsher conditions to the literature only starting material remained after a given time. This suggested that the *N*,*N*'-disubstituted hydantoins were very difficult to hydrolyse. If it was possible to cleave *N*,*N*'-dimethyl protected hydantoins the product obtained would not be a free quaternary amino acid as the nitrogen would still be methylated (**428**).



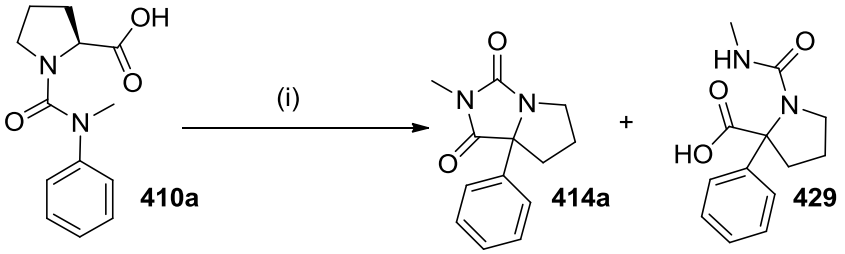

**Scheme 89: Reagents and conditions: (i) 10.0 eq. NaOH, dioxane, reflux, 8 d or (ii) 20% NaOH solution in EtOH, 130 °C, microwave (μw), 2.5 h**

Although the *N*-methyl groups cannot be chemically removed, a sample of alanine hydantoin **396** was sent for testing and preliminary experiments suggested that it may be possible to demethylate them biocatalytically using cytochrome P450 enzymes.[vi] Literature from 1963[202] showed the demethylation of hydantoins using the liver of rats that were treated with phenobarbital or nikethamide, but the rate of demethylation varied hugely depending on the substrate suggesting biocatalysis would not be a general method.

The proline-derived hydantoin is the only hydantoin formed that is not *N*,*N*'-methyl protected as it is bicyclic and contains two fused five-membered rings. Occasionally, uncyclised rearranged product **429** was observed as a mixture with cyclised hydantoin **414a** (Scheme 90). The bicyclic

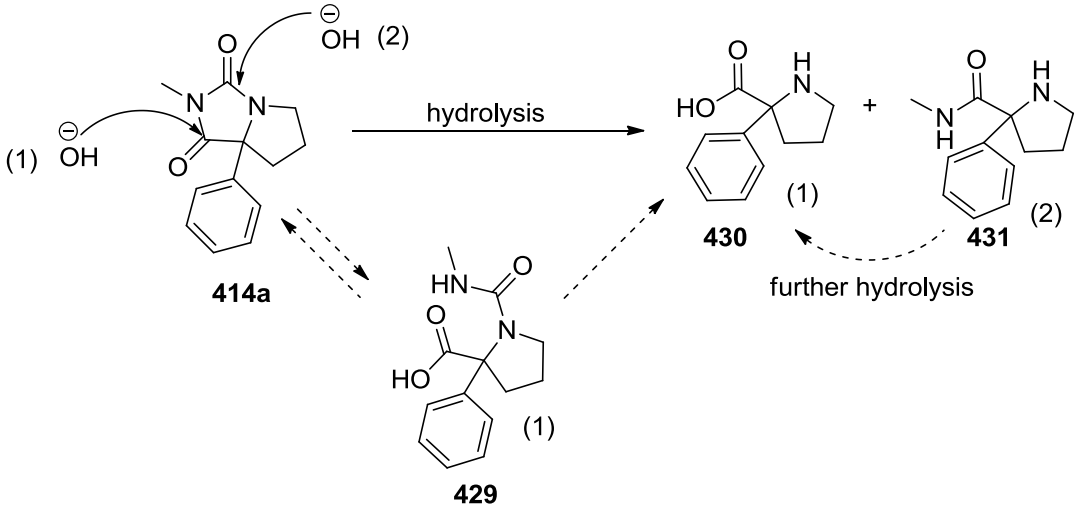
[vi] With thanks to Paul Kelly and Professor Nicholas Turner from the Manchester Institute of Biotechnology.

structure introduces ring strain into the product making it less favourable to form than in all the other cases.



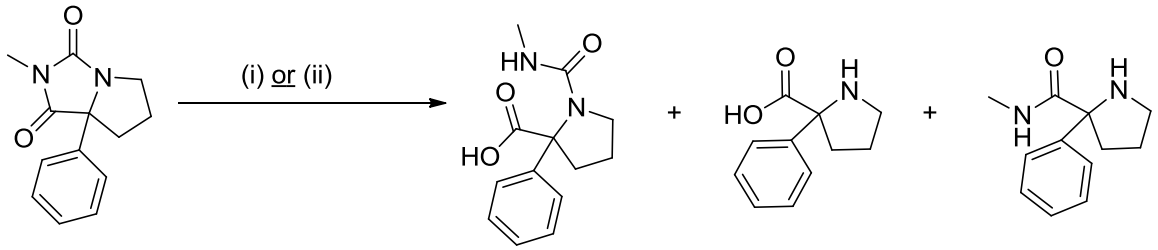

**Scheme 90: Reagents and conditions: (i) 3.0 eq. LDA, 3.0 eq. LiCl, THF, −78 °C – rt, 3 h**

This suggested that it may be easier to hydrolyse the proline derived hydantoin **414a** as this would relieve the ring strain introduced through the cyclisation (Scheme 91). There are two possible routes by which the hydrolysis could occur. One possibility is hydrolysis to form ring-opened urea **429**, which can be cleaved to form the quaternary amino acid **430** (1). Alternatively, if the opposite carbonyl group was attacked, amide **431** would be generated that could be further hydrolysed into the desired quaternary amino acid **430** (2).



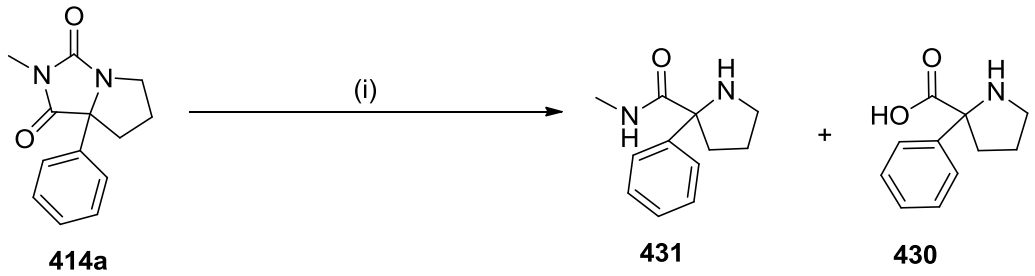

**Scheme 91: Hydrolysis of proline hydantoin to generate a quaternary amino acid**

The initial hydrolysis conditions attempted are shown in Scheme 92. Hydantoin **414a** was treated with either NaOH or $Ba(OH)_2$ and heated at 100 °C for 18 h.[203,204] In both cases a mixture of **429**, **430** and **431** were detected. These initial attempts showed that it was possible to open the hydantoin, but the hydrolysis required more forcing conditions to obtain solely the quaternary amino acid **430**.




**Scheme 92: Reagents and conditions: (i) 1:1 EtOH: 5.0 M NaOH solution, 100 °C, 18 h; (ii) 3.4 eq. $Ba(OH)_2 \cdot (H_2O)_8$ in 1:1 EtOH:$H_2O$, 100 °C, 18 h**

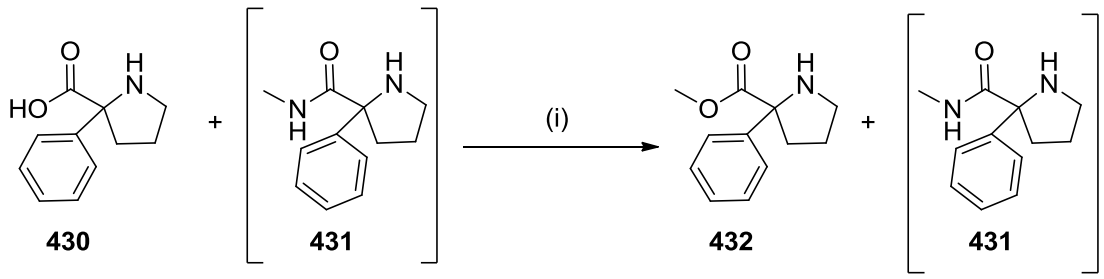
The reaction with NaOH was repeated using microwave heating, but again only a mixture of **430** and **431** was obtained. This suggested that the ring-opening of the hydantoin was fast to give **429** and this could easily be converted into the quaternary amino acid **430**. However, the difficult step was hydrolysis of the quaternary amide **431** into quaternary amino acid **430** (Scheme 93).




**Scheme 93: Reagents and conditions: (i) 5.0 M NaOH solution, 150 °C, 7 h, microwave (μw)**

Many other conditions were attempted to give complete hydrolysis of amide **431**. The best conditions found were hydantoin **414a** in 5.0 M NaOH solution, heating at 150 °C in the microwave for 7 h. The first time this was carried out the majority of the product was quaternary amino acid **430**, but when repeated a 1:1 mixture of **430**:**431** was obtained. In order to obtain an isolated yield the reaction was scaled up from 0.22 mmol to 0.52 mmol, but the increased volume used under the harsh conditions led to a rapid explosion of the microwave vial. This is hypothesised to be due to etching of the glass due to the concentration of NaOH or the ions causing hot spots in the glass during heating. Unfortunately, this meant that this process was not viable to be carried out in the microwave and scale up of this procedure could be dangerous.

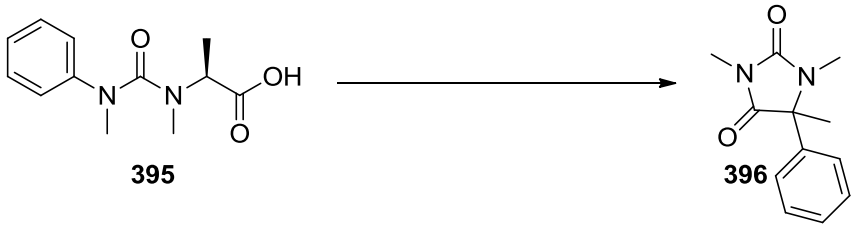
One further problem identified during these studies was that the isolation of the quaternary amino acid can be difficult. The mixture of amide **431** and acid **430** was dissolved in MeOH and treated with thionyl chloride at reflux. This converted the quaternary amino acid **430** into methyl ester **432** that could be readily isolated as a mixture with **431** (Scheme 94).




**Scheme 94: Reagents and conditions: (i) 15.0 eq. $SOCl_2$, MeOH, 0 °C – 85 °C, 18 h**

### 2.3.1.3 *In situ* ReactIR Mechanistic Study

To study the mechanism of the intramolecular enolate arylation in more detail, the rearrangement of alanine derivative **395** was followed by *in situ* infra-red spectroscopy (ReactIR). It was proposed that the reaction and the formation of intermediates could be followed through changes in the carbonyl stretching frequencies (Scheme 95).




**Scheme 95: Rearrangement of the alanine urea acid derivative to be studied by *in situ* ReactIR[vii]**

Initially the optimised reaction conditions (3.0 eq. LDA, 3.0 eq. LiCl, –78 °C to rt) were investigated, but practically LiCl led to disruption of the IR signal as the solution was saturated and therefore contained insoluble LiCl. The change in temperature was also problematic because it was large temperature change (–78 °C – rt) over a short period of time resulting in a disrupted IR signal. A clearer signal was observed when the LiCl was removed and the reaction was monitored at a constant temperature of 0 °C. The reaction was carried out in THF using 3 eq. of LDA at 0 °C. Despite the trace being clearer, the reaction occurred too quickly for any of the reaction intermediates to be observed. There were two clear carbonyl peaks observed at the start of the reaction for the starting material and two clear carbonyl peaks for the hydantoin upon quenching. This indicated the hydantoin did not form until the quench, but no further information of reactive intermediates could be gained (Figure 17).

[vii] The stereochemistry is shown for the major enantiomer of **395**

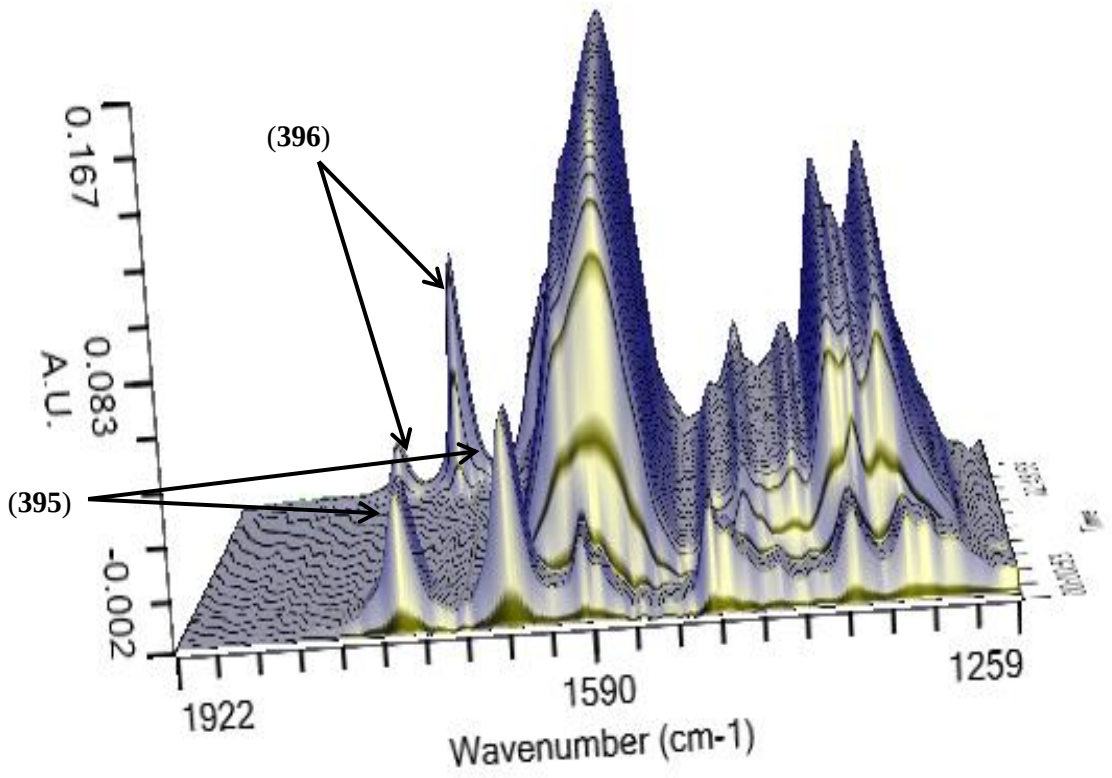



**Figure 17: Overall 3D-ReactIR trace for 395 in THF at 0 °C with 3.0 eq. LDA**

To observe the reaction intermediates it was necessary to slow the rate of both the deprotonation and the rearrangement. During optimisation of the rearrangement we had noted that carrying out the reaction in $Et_2O$ slowed the rate of the reaction (59% product observed, entry 6, Table 5) and the remaining starting material had undergone a good degree of racemisation (64%), indicating formation of the enolate.

The slower rate of reaction in $Et_2O$ at 0 °C allowed more detailed observation of the reaction intermediates. The changes in the carbonyl stretching frequencies were monitored using the internal IR probe during the LDA addition and throughout the course of the reaction. The reaction was quenched with MeOH after 1 h at 0 °C before an acidic work up was carried out (for full details see experimental section).

Throughout the experiment, IR spectra were recorded at varying time intervals (detailed timings are shown in the experimental section). Figure 18-Figure 20 show the 3D-ReactIR traces obtained that show the changes observed in the portion of the IR spectrum centred on the carbonyl absorptions throughout the reaction.

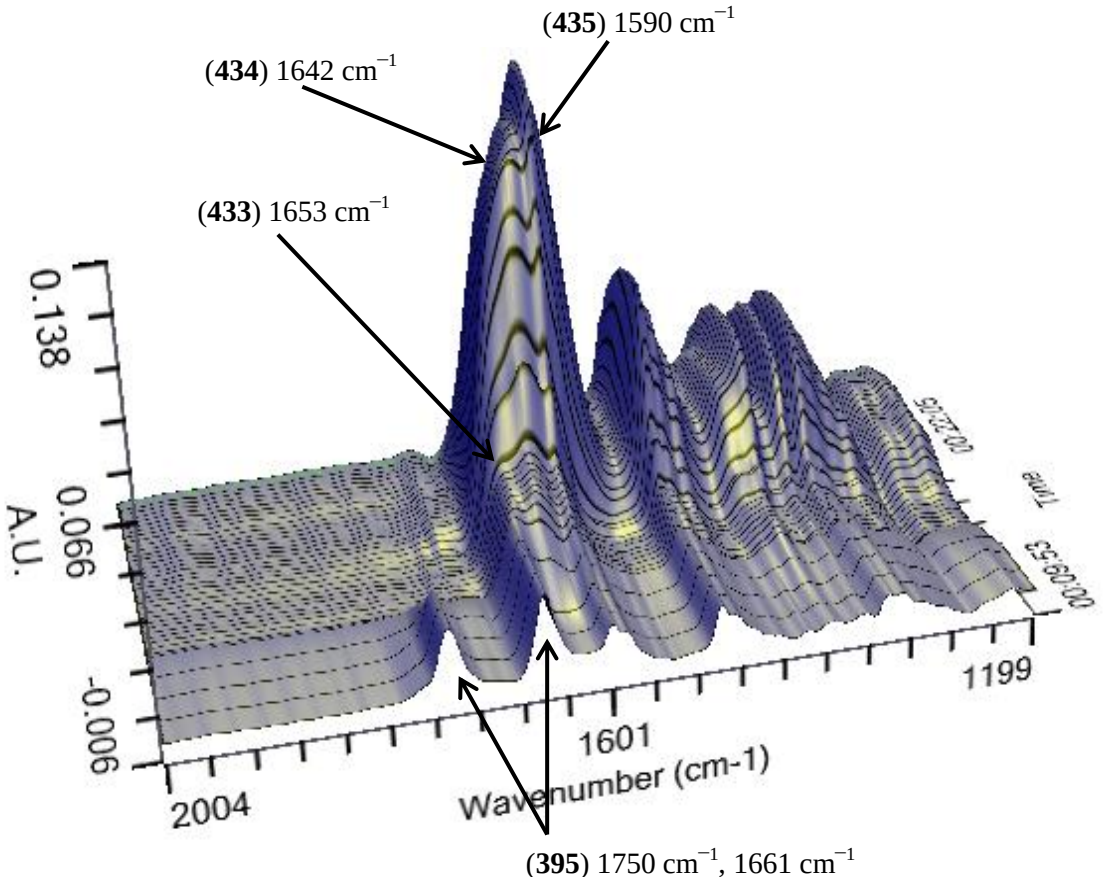



**Figure 18: 3D- ReactIR trace for 395 in $Et_2O$ at 0 °C during the addition of LDA over 10 min**

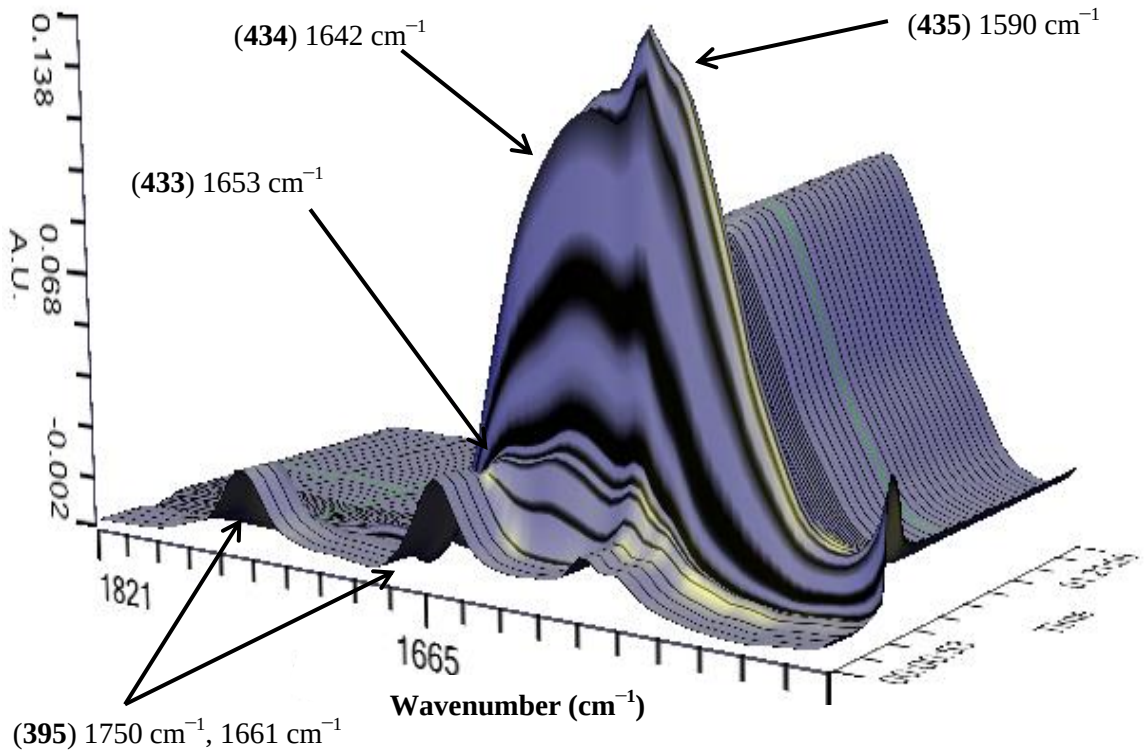



**Figure 19: 3D-ReactIR trace for 395 in $Et_2O$ at 0 °C during LDA addition over 10 min and 1 h reaction at 0 °C**

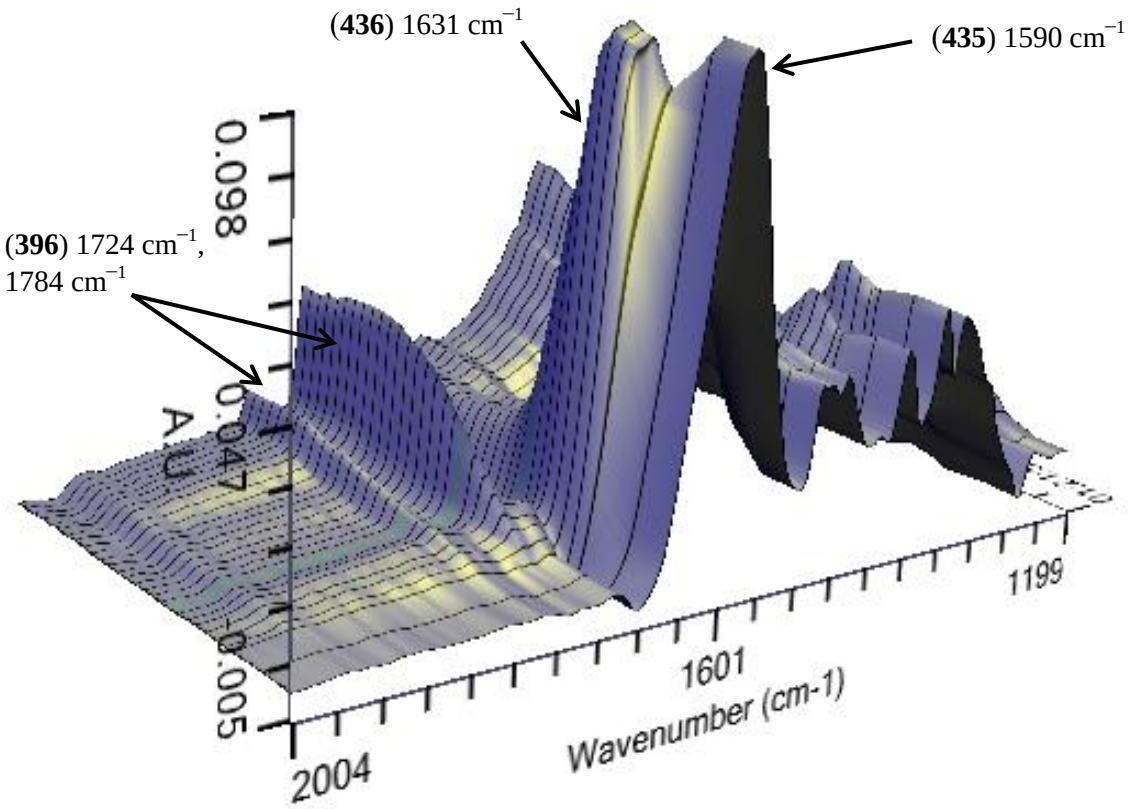



**Figure 20: 3D-ReactIR trace from the end of the 1 h reaction period at 0 °C through the quench with MeOH**

Using the IR data acquired over different time periods, difference spectra allowed reaction intermediates to be identified by shifts in the C=O stretching frequencies. The spectra shown in Figure 21-Figure 24 have the spectrum of **395** subtracted. The spectra shown in Figure 21 also has the spectrum of **435** (taken at the end of the 1 h reaction period) subtracted. These subtractions meant any new peaks forming could be clearly identified and attributed to different reaction intermediates.

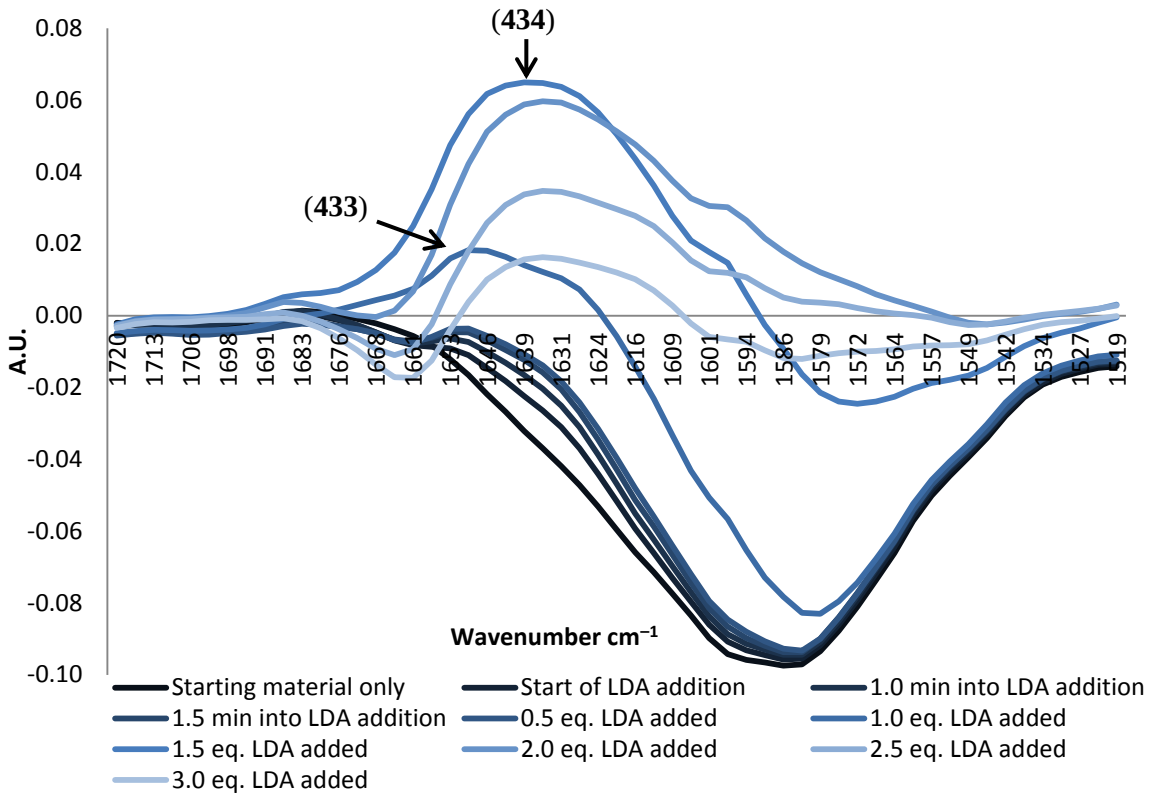



**Figure 21: IR difference spectra for the period during the addition of 3.0 eq. LDA over 10 min at 0 °C (spectrum of 395 and 435 subtracted)**

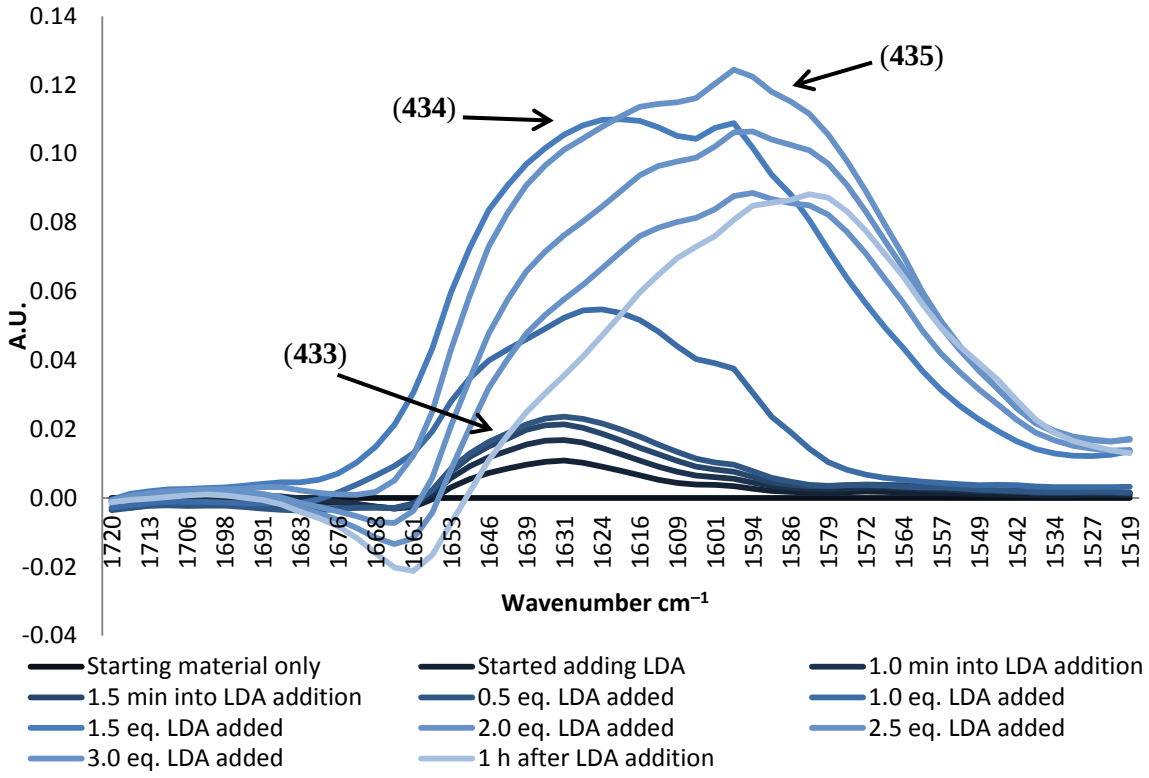



**Figure 22: IR difference spectra for the period during the addition of 3.0 eq. LDA over 10 min at 0 °C and the 1 h reaction period at 0 °C (spectrum of 395 subtracted)**

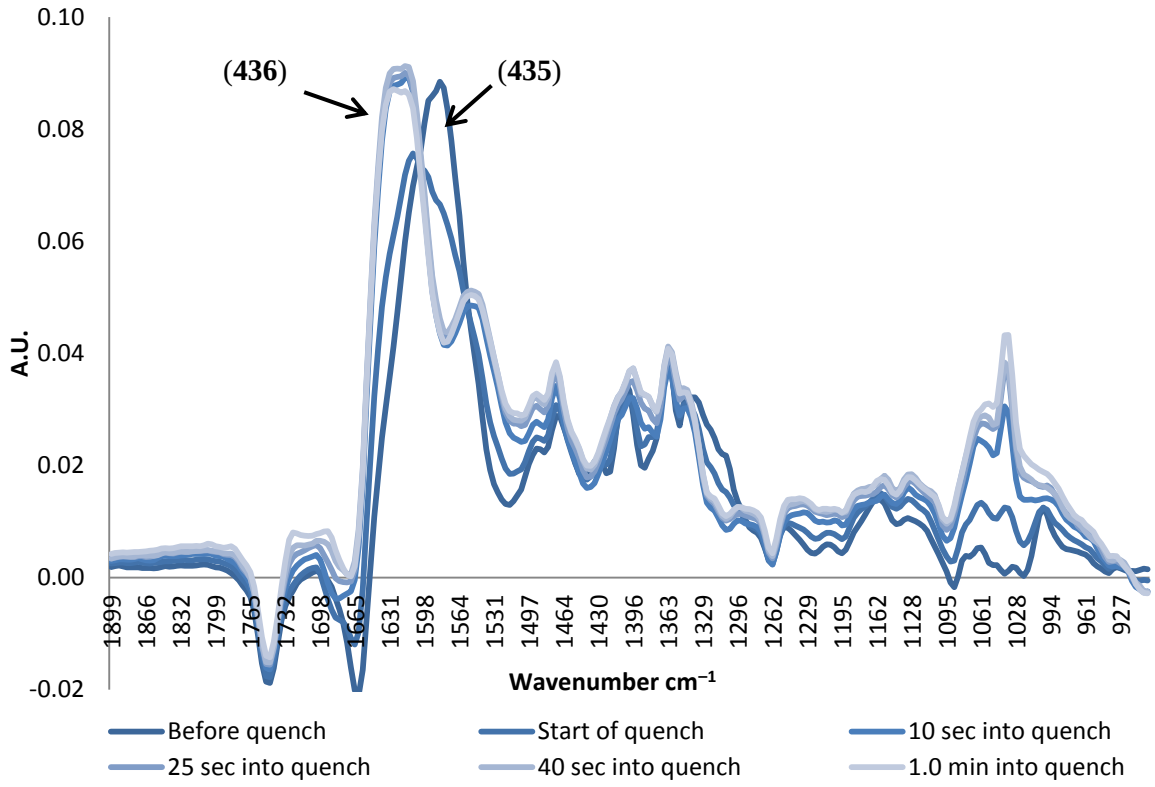



**Figure 23: IR difference spectra for the period after the 1 h reaction at 0 °C and during the first min of the quench with MeOH (spectrum of 395 subtracted)**

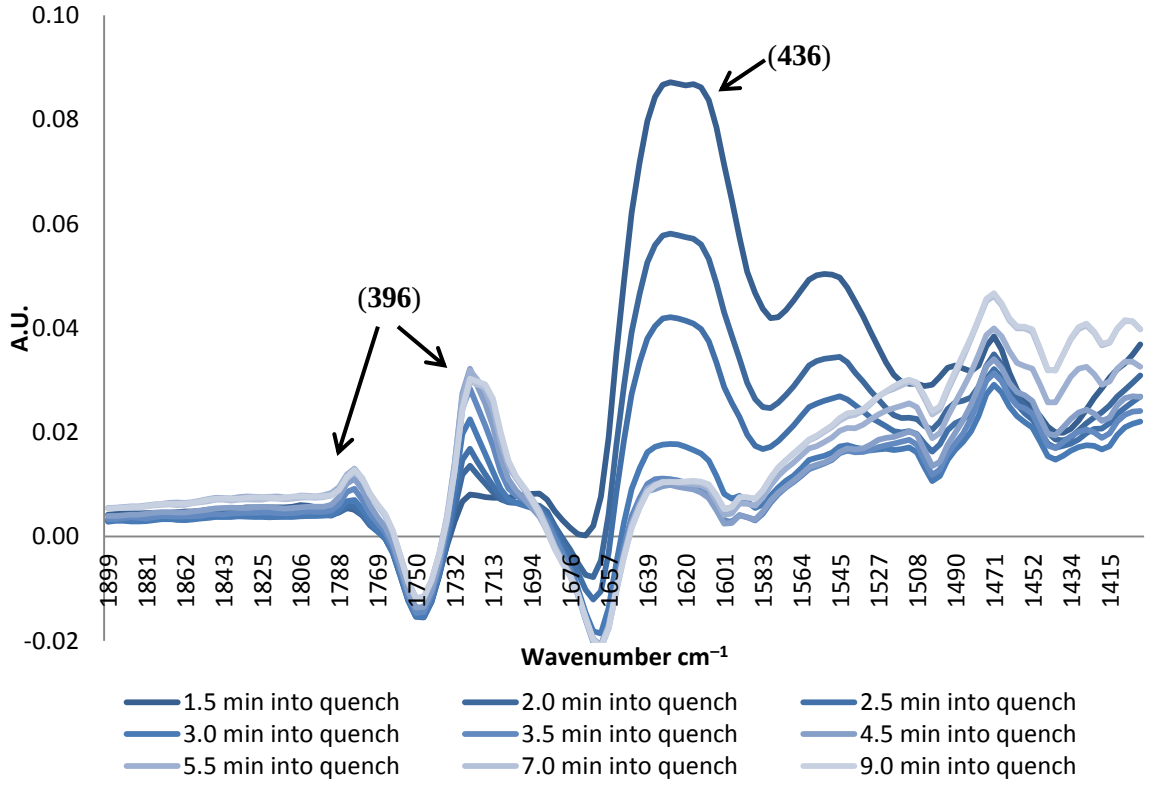



**Figure 24: IR difference spectra for the period 1.5 min into the MeOH addition until the end of the quench (spectrum of 395 subtracted)**

The difference spectra at specific time points during the reaction were also plotted. These allowed an estimation of the C=O stretching frequencies for the proposed intermediate species formed during the reaction. The spectra shown in Figure 26-Figure 30 have the spectrum of **395** subtracted. The spectra shown in Figure 26 and Figure 27 also have the spectrum of **435** (taken at the end of the 1 h reaction period) subtracted, this made any new peaks easier to identify.

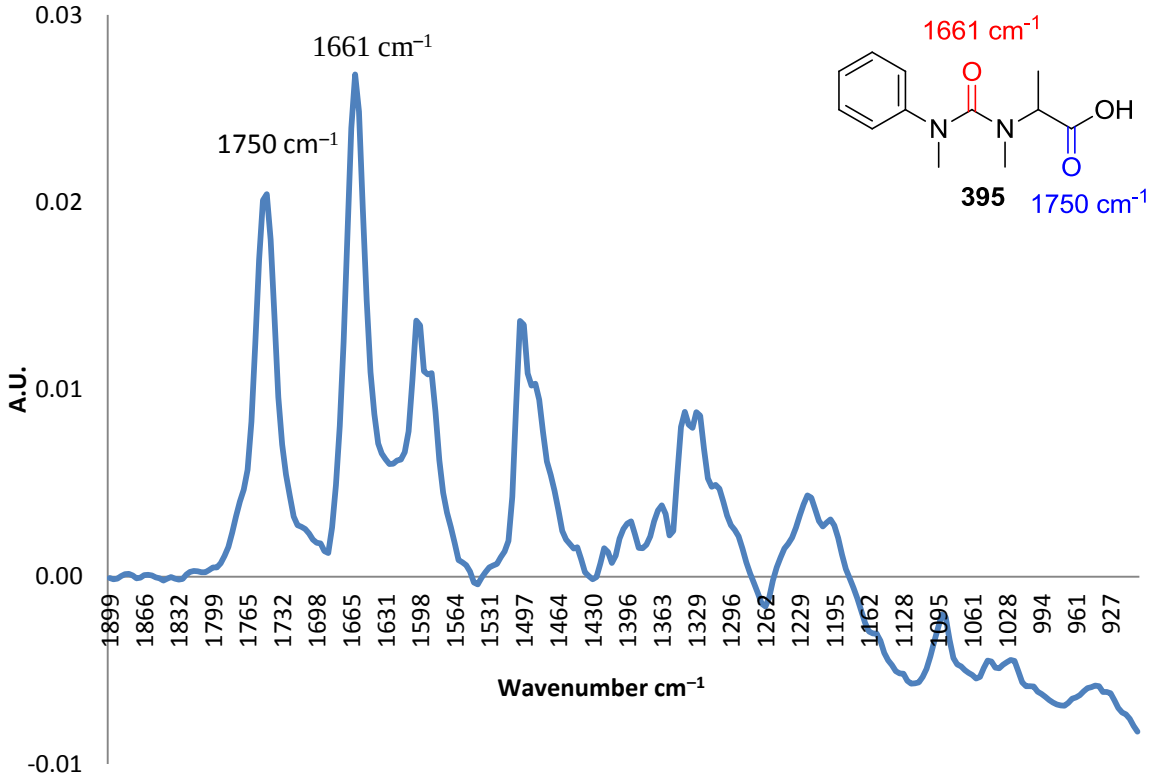



**Figure 25: Starting material 395 in $Et_2O$ at 0 °C prior to the addition of LDA**

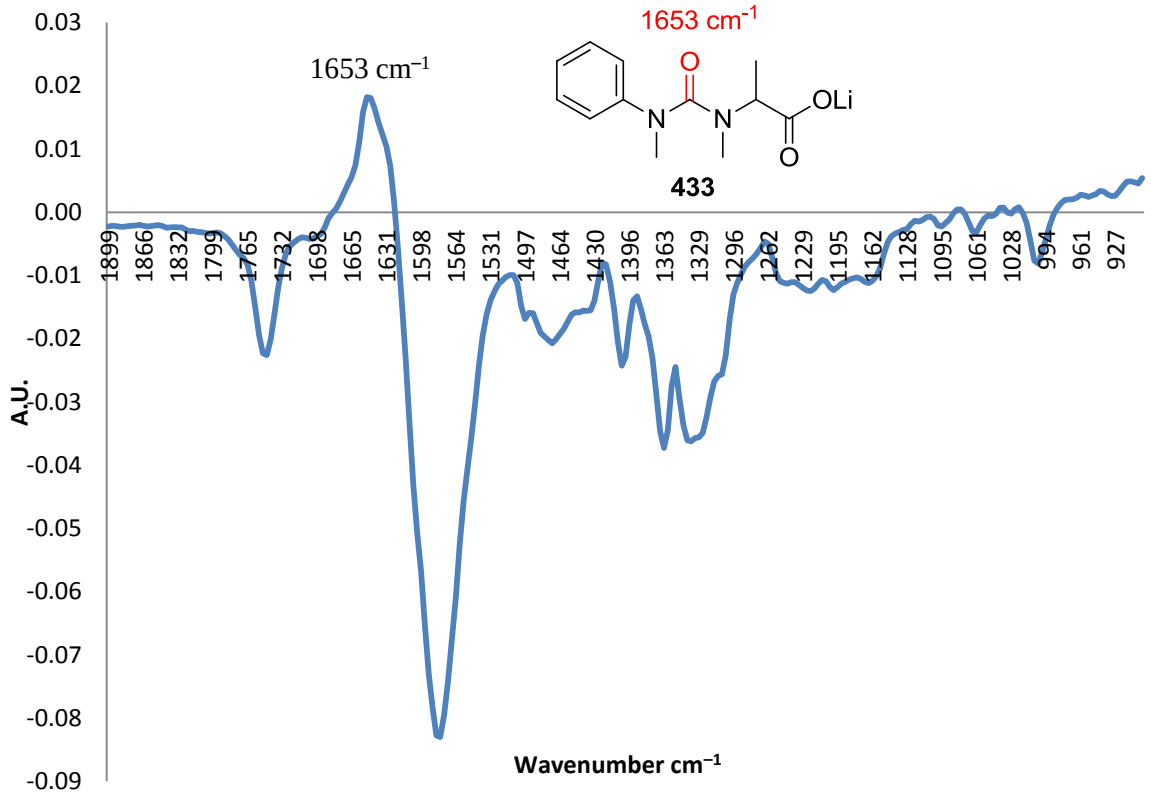



**Figure 26: IR difference spectrum after addition of *ca.* 1.0 eq. LDA (spectrum of 395 and 435 subtracted)**

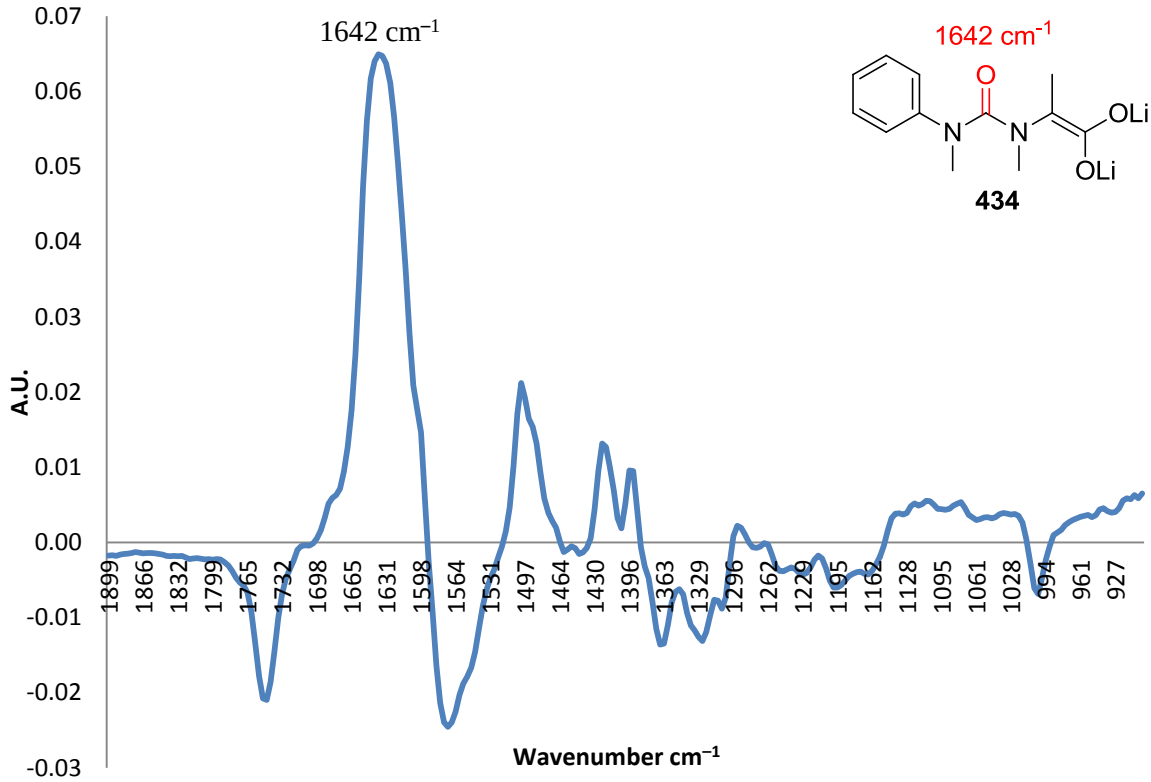



**Figure 27: IR difference spectrum after addition of *ca.* 1.5 eq. LDA (spectrum of 395 and 435 subtracted)**

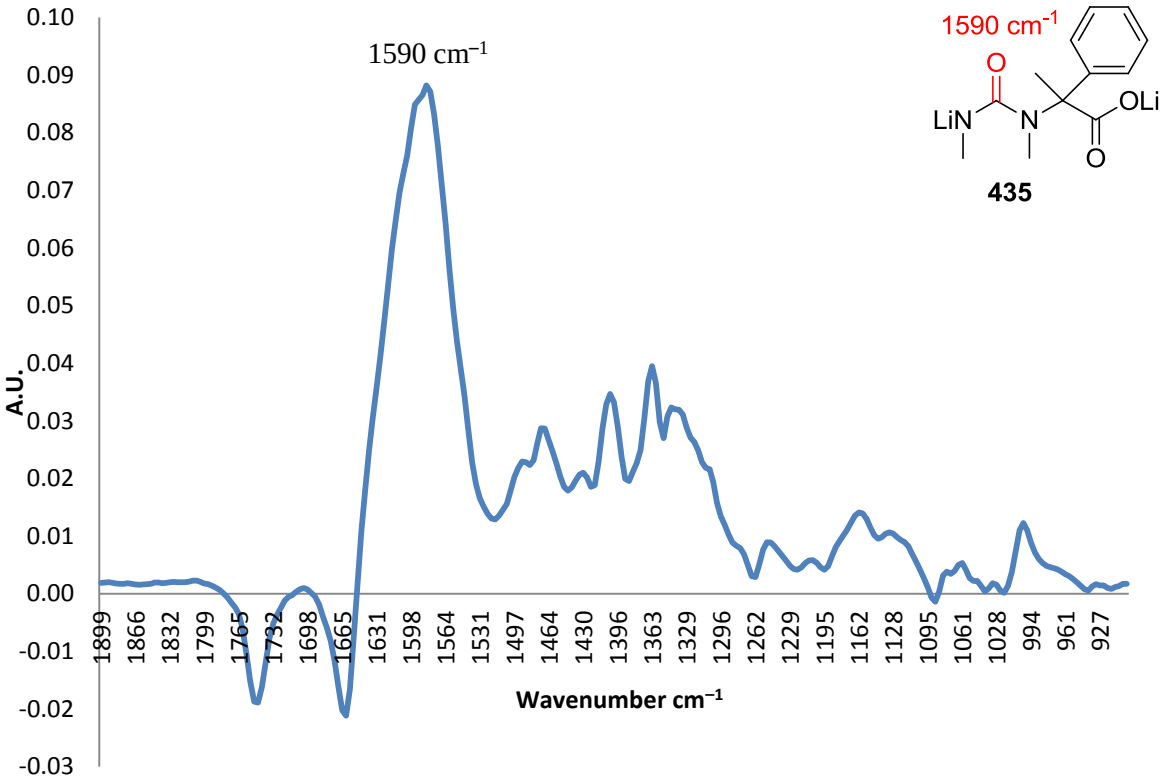



**Figure 28: IR difference spectrum after 1 h reaction time at 0 °C (spectrum of 395 subtracted)**

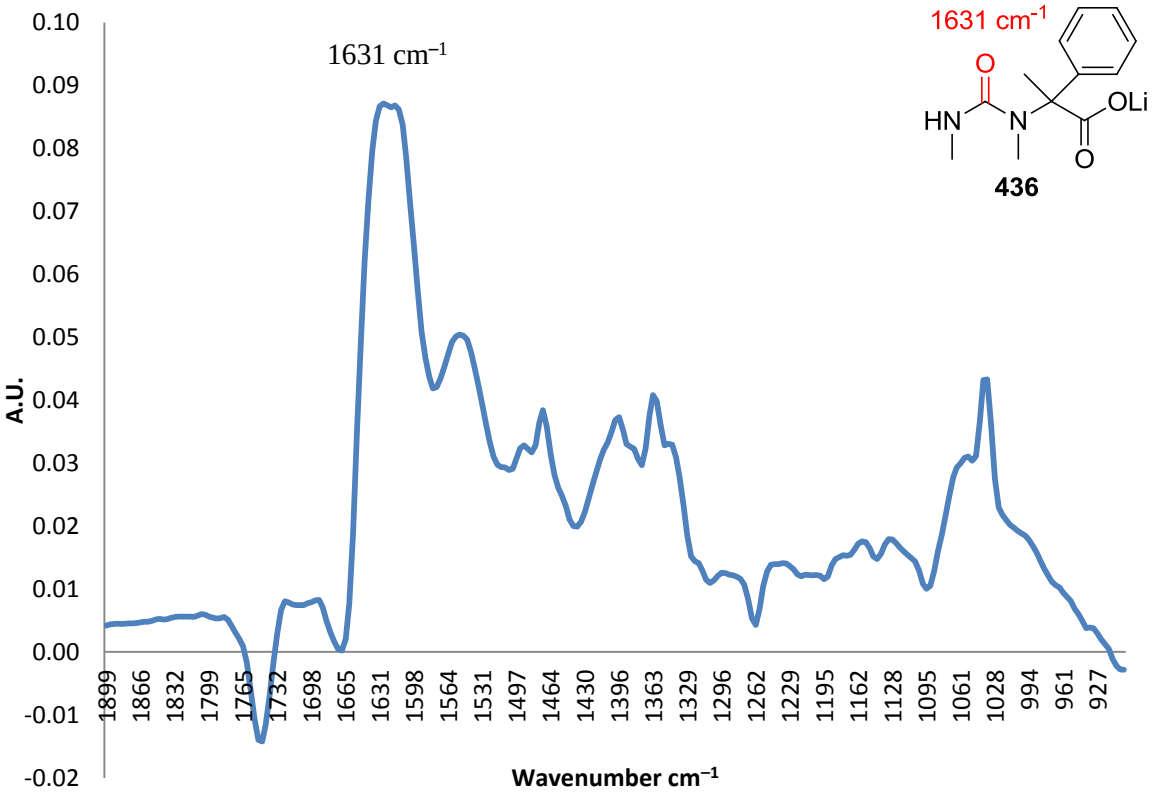



**Figure 29: IR difference spectrum 1 min after the start of the quench with MeOH (spectrum of 395 subtracted)**

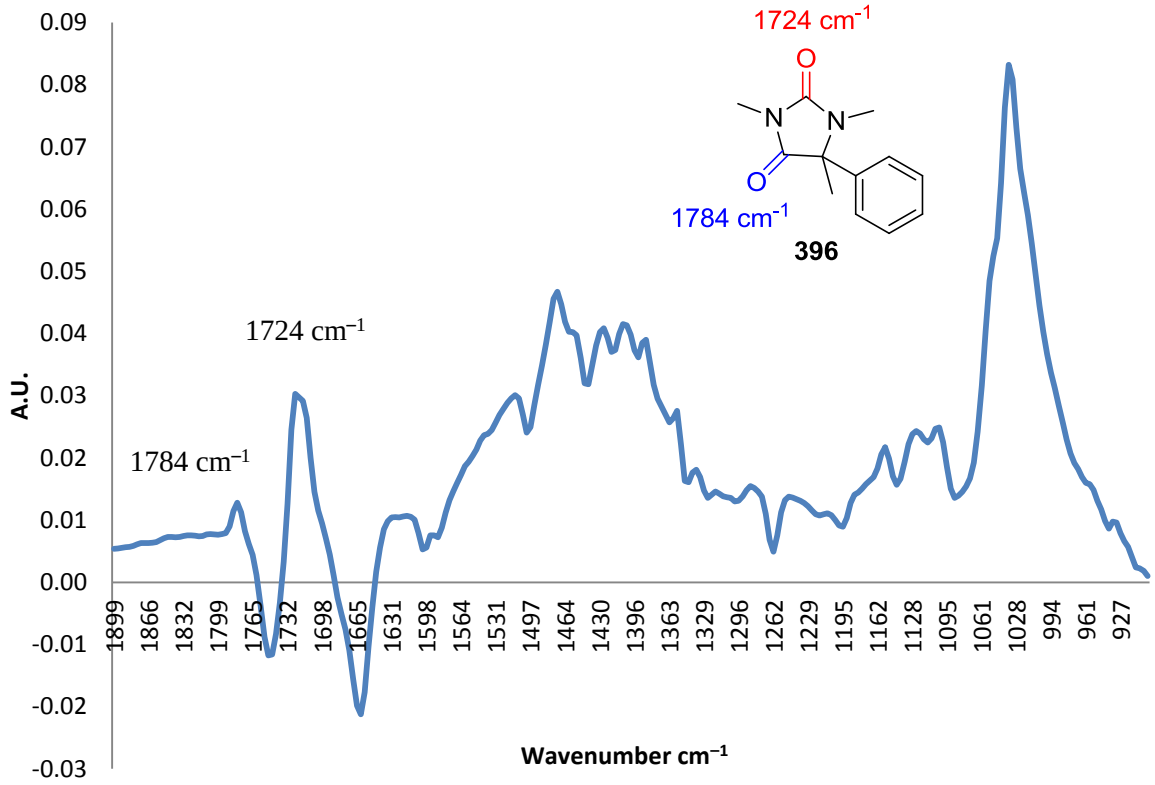



**Figure 30: IR difference spectrum 9 min after the quench with MeOH (spectrum of 395 subtracted)**

Based upon this data, a number of potential reaction intermediates were identified (Scheme 96). For the urea starting material **395** in $Et_2O$ at 0 °C, the two carbonyl absorptions at 1750 $cm^{-1}$ and 1661 $cm^{-1}$ were assigned to $\nu_{C=O}$ for the carboxylic acid and urea respectively (Figure 25). Upon addition of the first equivalent of LDA there was immediate loss of the absorption at 1750 $cm^{-1}$ corresponding to the carbonyl of the carboxylic acid, this suggested formation of a carboxylate anion. A change from the starting material **395** was further indicated by a small shift in the urea carbonyl absorption at 1661 $cm^{-1}$ to 1653 $cm^{-1}$ that was assigned to carboxylate **433** (Figure 26).

During the addition of the remaining LDA, the 1653 $cm^{-1}$ absorption disappeared and an absorption appeared at a lower wavenumber of 1642 $cm^{-1}$. A carboxylic acid carbonyl absorption was still absent. This new stretching frequency was assigned to enolate **434** (Figure 27) and this species was dominant between the addition of 1 and 2 eq. of LDA (Figure 21).

Towards the end of the LDA addition there was a decay in the intensity of the absorption at 1642 $cm^{-1}$ assigned to enolate **434**, but at the same time a new absorption at 1590 $cm^{-1}$ grew (Figure 18, Figure 19 and Figure 22). This significant shift in the carbonyl stretching frequency to a lower wavenumber is consistent with formation of the deprotonated urea and can be assigned to the absorption of the urea function of dianion **435** (Figure 28). A negative charge on the nitrogen atom

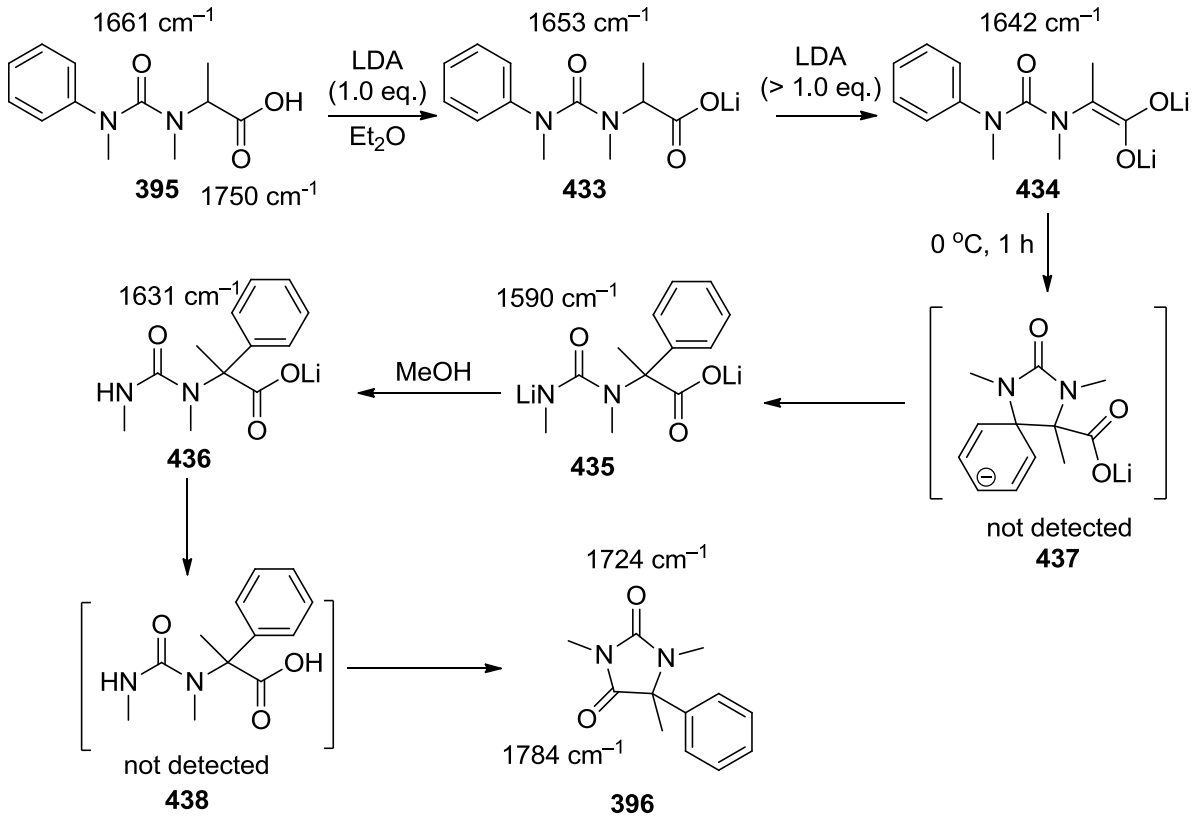
donating into the adjacent carbonyl group is expected to weaken the carbonyl stretching frequency significantly, and the shift to a wavenumber of 1550-1600 $cm^{-1}$ is consistent with data reported for related anionic ureas.[170,178] Throughout the addition the absorption assigned to enolate **434** reduced and the absorption assigned to dianion **435** increased.

During the hour that the reaction was at 0 °C, the peak for dianion **435** remained constant (Figure 19 and Figure 22). At no point during the reaction was a higher frequency carbonyl absorption observed that would be expected for a 5-membered-ring cyclic intermediate **437**. If such an intermediate was formed it did not accumulate to any significant concentration during the reaction.

After 1 h the reaction was quenched by dropwise addition of MeOH, which immediately caused the absorption at 1590 $cm^{-1}$, assigned to the dianion **435**, to shift back to a higher wavenumber, reappearing at 1631 $cm^{-1}$. This is consistent with reprotonation of the anionic urea. No absorbance appeared with a stretching frequency indicative of a carboxylic acid C=O. The peak at 1631 $cm^{-1}$ was assigned to a rearranged carboxylate species **436**. No intermediate with both the nitrogen and carboxylate protonated **438** was observed (Figure 20, Figure 23 and Figure 29). Species **436** was present for the 1.5 min of the quench, after which time the absorption at 1631 $cm^{-1}$ decreased in intensity and finally disappeared.

Approximately 1 min into the quench two new absorptions appeared at 1724 $cm^{-1}$ and 1784 $cm^{-1}$ corresponding to $\nu_{C=O}$ for **396** (Figure 20, Figure 24 and Figure 30). This was confirmed through comparison of the IR data with an isolated sample of hydantoin **396**, obtained in the solid state, that gave stretching frequencies of 1704 $cm^{-1}$ and 1770 $cm^{-1}$[viii]. No carboxylic acid C=O absorption was evident before the cyclisation that gave hydantoin **396**, suggesting that the hydantoin must form, even under basic conditions, directly from the carboxylate (Scheme 96).

[viii] Difference in values due to solid state *vs* in solution. $^1$H NMR of product confirmed it was hydantoin **396**




**Scheme 96: The six reaction species identified on the pathway from 395 to 396 in $Et_2O$**

To check the reaction mechanism was the same in THF as in $Et_2O$, the ReactIR experiment was repeated in THF but at –40 °C to slow the reaction enough to observe the reaction intermediates. The urea was disolved in THF and cooled to –40 °C, LDA was added slowly over 25 min and the IR spectra were followed for the LDA addition period. The reaction was left for 1 h before being quenched with MeOH (for full details see the experimental section).

Throughout the experiment IR spectra were recorded at varying time intervals (detailed timings are shown in the experimental section). A difference spectrum was constructed using the IR data collected over the 25 min LDA addition (Figure 31). The spectrum of **395** was subtracted to allow clearer identification of new species.

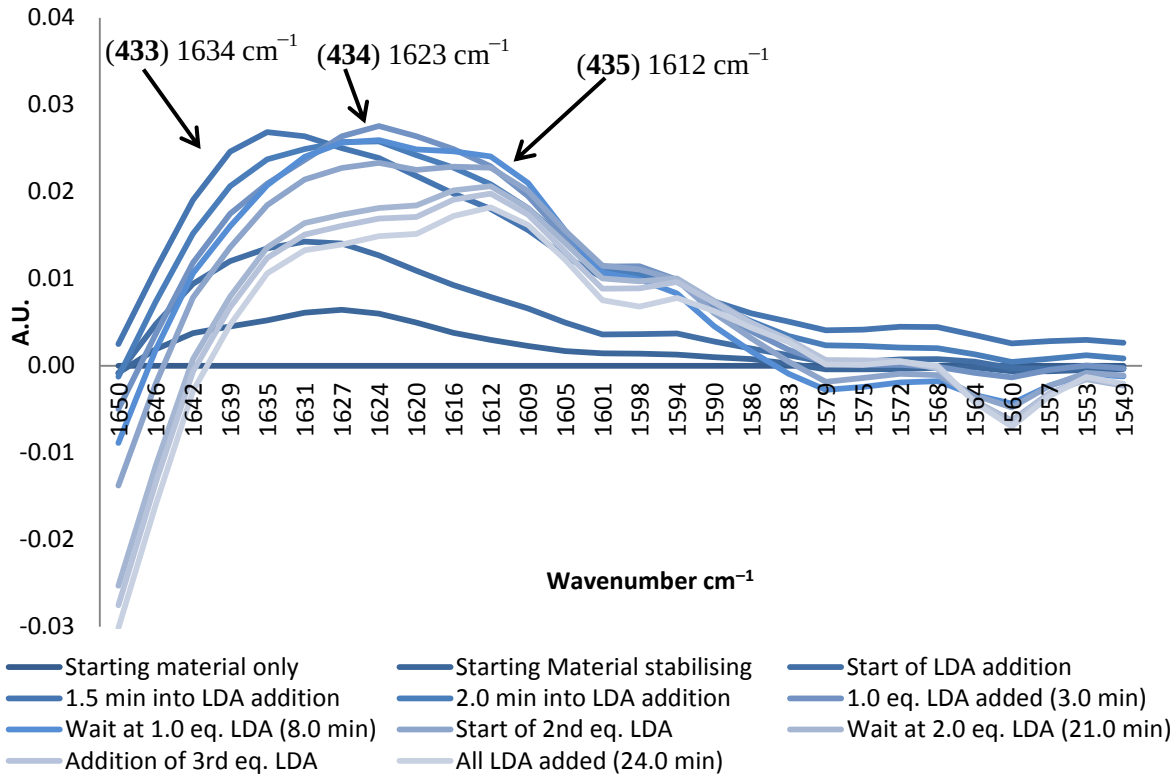
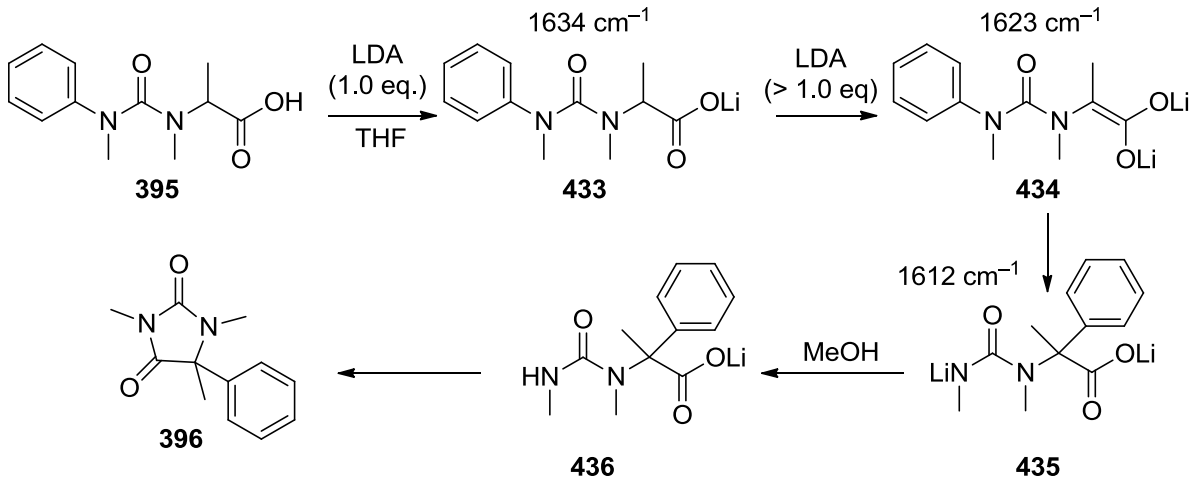



**Figure 31: IR difference spectrum for the 25 min addition of LDA to 395 at –40 °C in THF (spectrum of 395 subtracted)**

The graph shows an absorption at 1634 $cm^{-1}$ that appeared at the start of the LDA addition, which is assigned to carboxylate **433**. At the end of the addition of the first equivalent of LDA and during the 5 min wait enolate **434** started to form and continued to form throughout the addition of the second equivalent of LDA, with the absorption at 1623 $cm^{-1}$ appearing and the absorption at 1634 $cm^{-1}$ reducing in intensity. Finally, between the addition of the second and the third equivalents, a third absorption was observed at 1612 $cm^{-1}$, which was assigned to **435**. Throughout the addition the carbonyl absorption for **433** increases then reduces in intensity as the carbonyl absorption for **434** increases. At the end of the addition the carbonyl absorption for **434** reduces and the carbonyl peak for **435** was dominant (Figure 31).

The same pattern was observed in the $Et_2O$ ReactIR experiments, confirming the reaction undergoes the same pathway in both $Et_2O$ and THF. The values of the stretching frequencies were different due to the two different solvents, but the same general shifts in the carbonyl stretching frequencies were consistent with a similar series of reaction intermediates (Scheme 97).

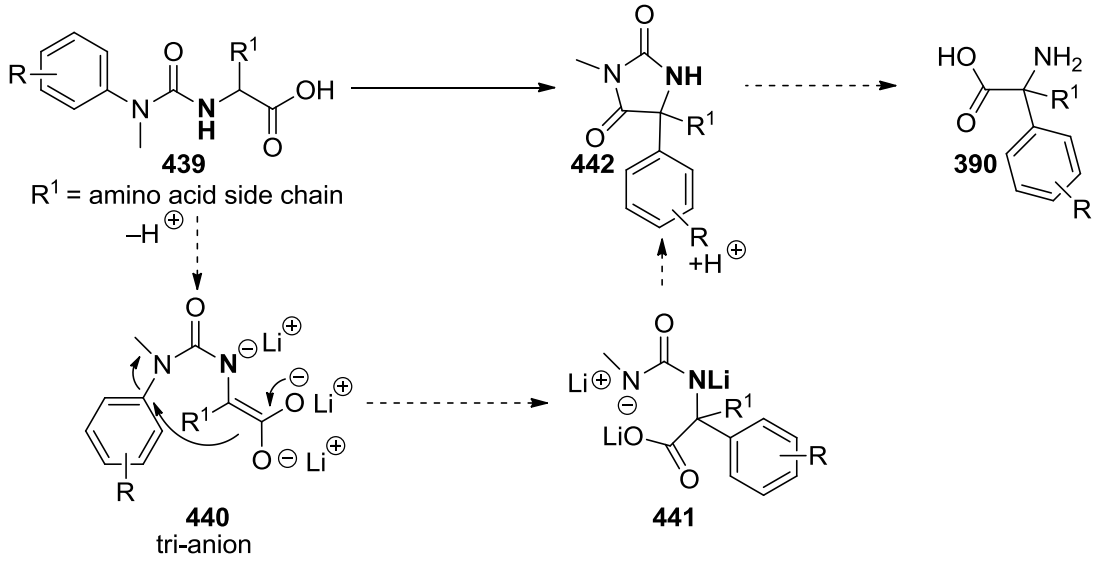



**Scheme 97: The observed reaction species on the pathway from 395 to 396 in THF**

## 2.3.2 *N*-Unprotected Hydantoins

### 2.3.2.1 Rearrangement Reaction

Since hydantoins that were *N,N'*-protected were not cleavable, an alternative strategy was necessary for the synthesis of quaternary amino acids. It is known that when one of the nitrogen atoms is free from a protecting group the hydantoin can be hydrolysed.[31,199-201] The aim was to investigate whether the rearrangement reaction would still take place without a protecting group on one of the nitrogen atoms (Scheme 98).

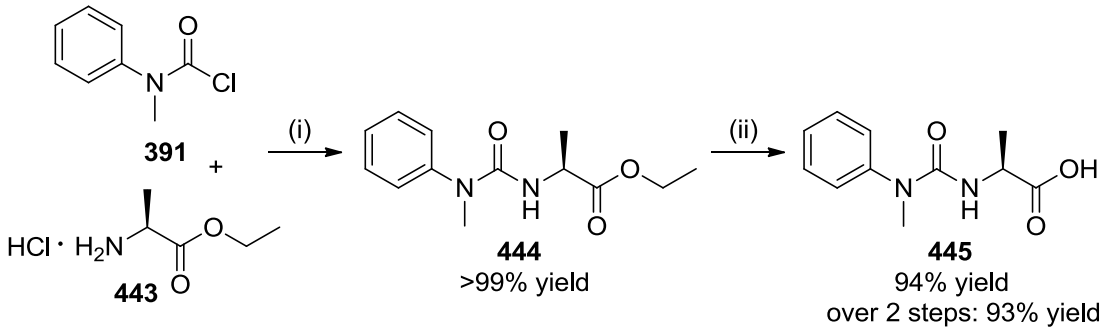



**Scheme 98: Arylation of substrates free from a protecting group**

This would be likely to involve the formation of a tri-anion (**440**) prior to rearrangement with deprotonation of the carboxylic acid to generate a carboxylate, deprotonation of the NH and finally, deprotonation at the α-carbon to generate an enolate (**440**). This enolate would undergo

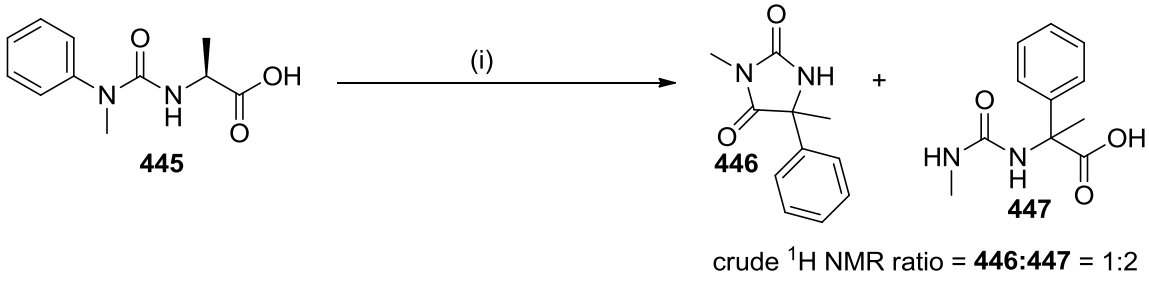
rearrangement, with the aryl ring migrating from the nitrogen onto the α-carbon atom (**441**). It was expected that cyclisation would take place giving hydantoin **442**, which should be hydrolysable into a quaternary amino acid.

The starting material for the alanine derivative was synthesised by a two step procedure, similar to the method for methylated starting material **395**. The first step was acylation of L-alanine ethyl ester (**443**) with *N*-methyl-*N*-phenyl carbamoyl chloride (**391**). The monomethylated urea **444** was obtained in an excellent yield of >99%. Secondly, saponification of the ethyl ester through basic hydrolysis with LiOH yielded the unprotected starting material in 94% yield. The final product **445** was obtained in an excellent 93% yield over the two steps (Scheme 99).




**Scheme 99: Reagents and conditions: (i) 2.3 eq. $Et_3N$, MeCN, reflux, 20 h; (ii) 15.0 eq. LiOH, 2:1 THF:$H_2O$, 45 °C, 20 h**

With a route to the unprotected starting material (**445**) established, conditions for the rearrangement were investigated. The first conditions attempted were similar to those for the previous rearrangement (Scheme 82) but with an extra equivalent of base and LiCl due to the presence of the deprotonable NH (Scheme 100).

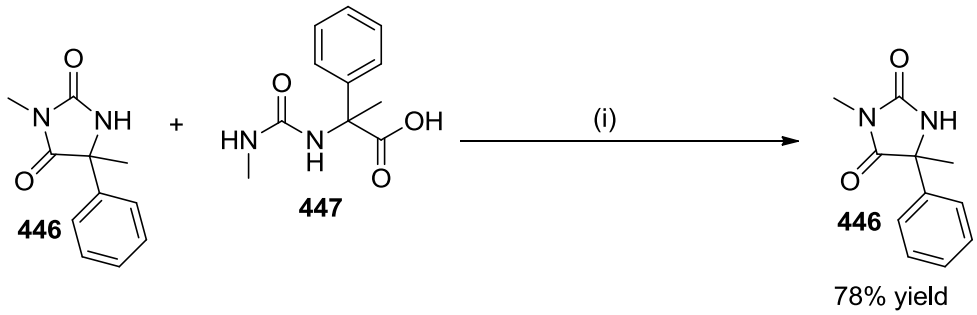



**Scheme 100: Reagents and conditions: 4.0 eq. LDA, 4.0 eq. LiCl, THF, –78 °C – rt, 3 h**

Pleasingly these conditions yielded the desired hydantoin **446**, showing remarkably that the rearrangement worked for tri-anionic species. However, the product was accompanied by uncyclised product **447**, similar to that observed occasionally in the di-anionic series for the proline derivatives (Scheme 90). This suggested that it was less favourable to form the hydantoin starting from a tri-anion than from the di-anion. If it were possible to avoid hydantoin **446** the cleavage of

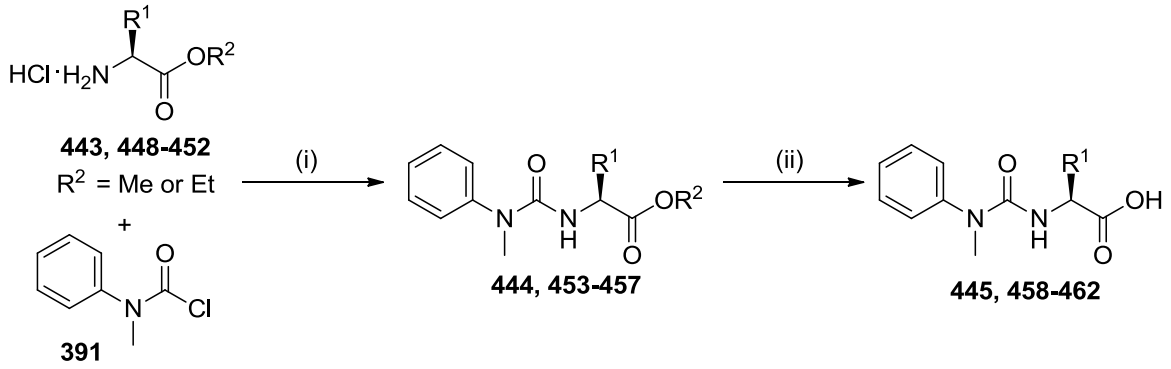
the urea in **447** would be a lot easier to achieve than the hydrolysis of the hydantoin to generate quaternary amino acids.

The reaction shown in Scheme 100 was quenched with MeOH and acidified to pH 1 and the ratio of **446**:**447** was 1:2. The reaction was repeated and quenched with an aqueous saturated $NH_4Cl$ solution and acidified to just pH 4. It was hoped that just the uncyclised product **447** would be obtained but the ratio of **446**:**447** was 1:3.5 showing even under mild conditions some of the uncyclised product was converted into hydantoin **446**. Additionally, an attempted separation of uncyclised product **447** from hydantoin **446** resulted in the conversion of the uncyclised product **447** into hydantoin **446**. Therefore, to ensure the maximum yield for the rearrangement reaction the mixture of **446** and **447** was stirred overnight with thionyl chloride in MeOH to ensure complete conversion into hydantoin **446** which was obtained in an excellent yield of 78% (Scheme 101).




**Scheme 101: Reagents and conditions: $SOCl_2$, MeOH, rt, 16 h**

To assess the scope of this reaction a number of unprotected urea starting materials containing different amino acid side chains were synthesised using the method shown in Scheme 99. Acylation of ethyl or methyl amino esters with *N*-methyl-*N*-phenyl carbamoyl chloride (**391**) followed by hydrolysis of the ester functionality (Scheme 102). Using this method urea derivatives of alanine (**445**), butyrine (R = ethyl) (**458**), valine (**459**), leucine (**460**), methionine (**461**) and phenylalanine (**462**) were synthesised in excellent yields over the two steps (Table 9).




**Scheme 102: (i) 2.3 eq. $Et_3N$, MeCN, reflux, 20 h; (ii) 15.0 eq. LiOH, 2:1 THF:$H_2O$, 45 °C, 20 h**[ix]

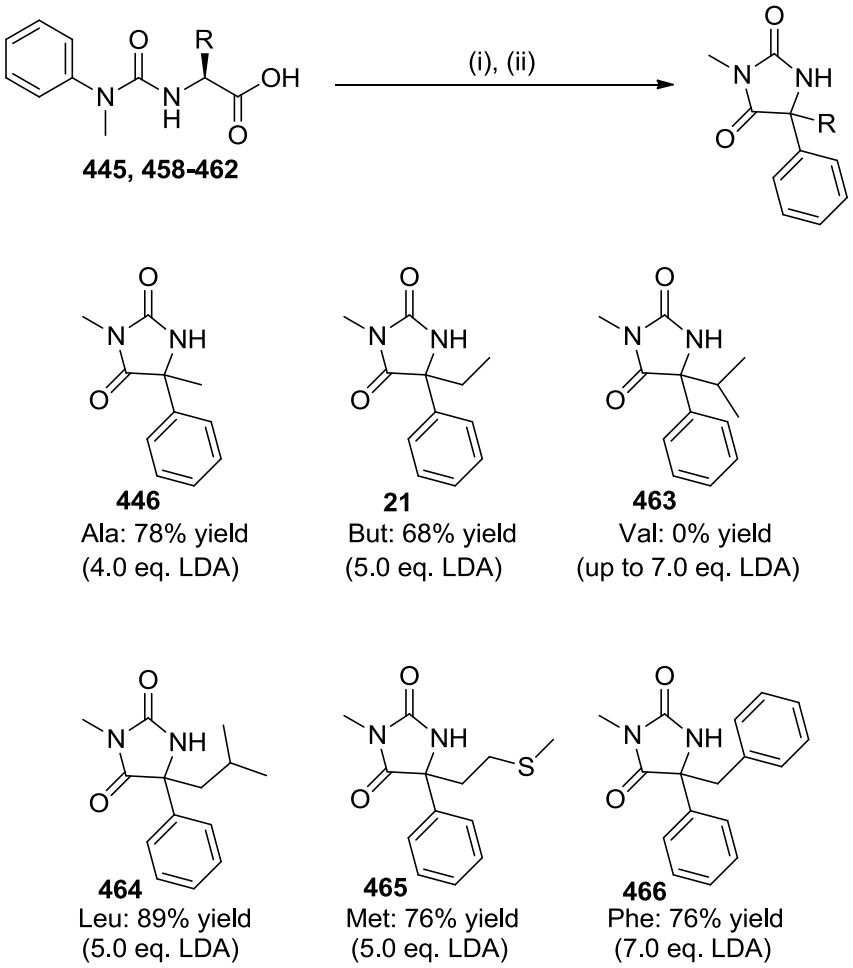
**Table 9: Yields for the synthesis of unprotected starting materials**

| Entry | SM | Coupled yield (%) | Saponification yield (%) | Overall yield (%) |
|---|---|---|---|---|
| 1 | Ala (**443**) | >99 (**444**) | 94 (**445**) | 93 |
| 2 | But (**448**) | >99 (**453**) | >99 (**458**) | 98 |
| 3 | Val (**449**) | >99 (**454**) | 89 (**459**) | 88 |
| 4 | Leu (**450**) | 93 (**455**) | >99 (**460**) | 92 |
| 5 | Met (**451**) | >99 (**456**) | >99 (**461**) | 98 |
| 6 | Phe (**452**) | 93 (**457**) | >99 (**462**) | 92 |

These derivatives were subjected to the conditions used for alanine derivative **445** ((i) 4.0 eq. LDA, 4.0 eq. LiCl, THF, –78 °C – rt, 3 h, (ii) $SOCl_2$, MeOH, rt, 16 h). Unfortunately, using just 4 eq. of LDA led to incomplete conversion, with starting material remaining in all cases.

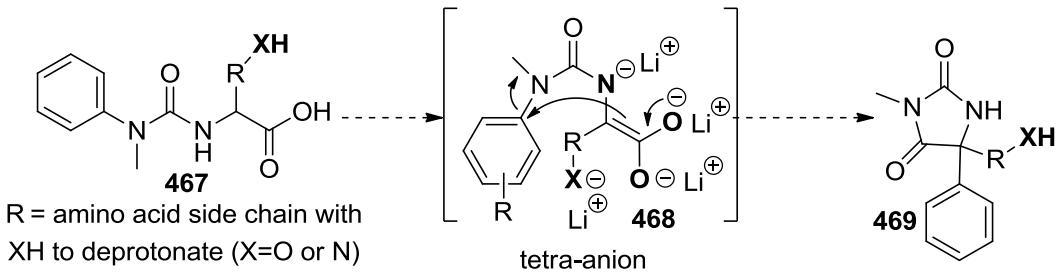
For the butyrine (**458**), leucine (**460**) and methionine (**461**) derivatives, using 5 eq. of LDA ensured a complete reaction. However, as the steric bulk of the α-amino acid side chain increased, more LDA was needed for the reaction to go to completion. For example phenylalanine derivative (**462**) required 7 eq. of LDA for complete conversion. However, for valine derivative (**459**), which has the branch point directly attached to the α-carbon, the reaction returned just starting material even with an excess of 7 eq. of LDA (Scheme 103).

[ix] Ethyl derivative synthesised from racemic methyl-DL-α-aminobutyrate hydrochloride



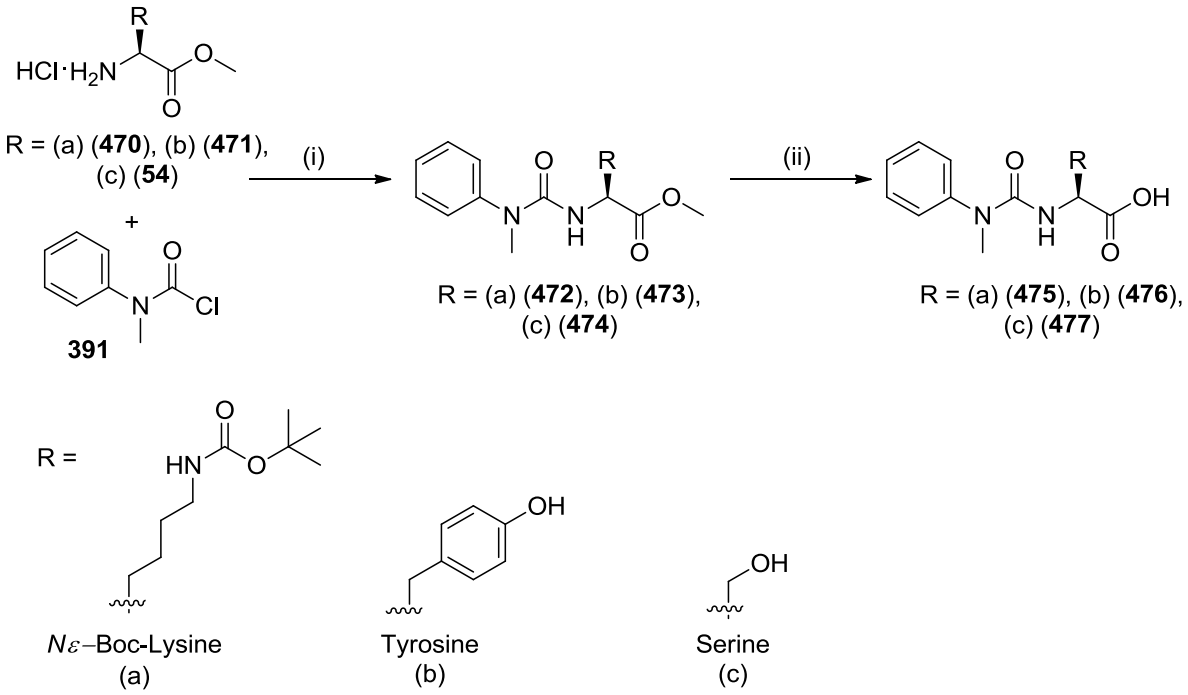

**Scheme 103: Reagents and conditions: (i) 4.0-7.0 eq. LDA, 4.0 eq. LiCl, THF, −78 – rt, 3 h; (ii) $SOCl_2$, MeOH, rt, 16 h**

Derivatives of amino acids with acidic β-protons such as phenylalanine had been unsuccessful in the dianionic rearrangement due to β-deprotonation and elimination of the urea functionality prior to rearrangement. However, the phenylalanine derivative **462** rearranged giving **466** in an excellent yield of 76% in this system, the negative charge on the unsubstituted nitrogen is proposed to prevent the elimination due to electron repulsion. To further assess the limits and scope of this rearrangement reaction, even more complex amino acids were investigated. Amino acids were chosen that had a further deprotonable position in the side chain (**467**) and would conceivably generate a tetra-anion (**468**) prior to rearrangement (Scheme 104).




**Scheme 104: Formation of tetra-anion prior to rearrangement**

The starting materials for the rearrangement were synthesised according to the general procedure used previously (Scheme 105). Derivatives of *Nε*-Boc-lysine (**475**), tyrosine (**476**) and serine (**477**) were formed through the acylation with *N*-methyl-*N*-phenyl carbamoyl chloride (**391**) and hydrolysis of the methyl ester in excellent yield (Table 10).



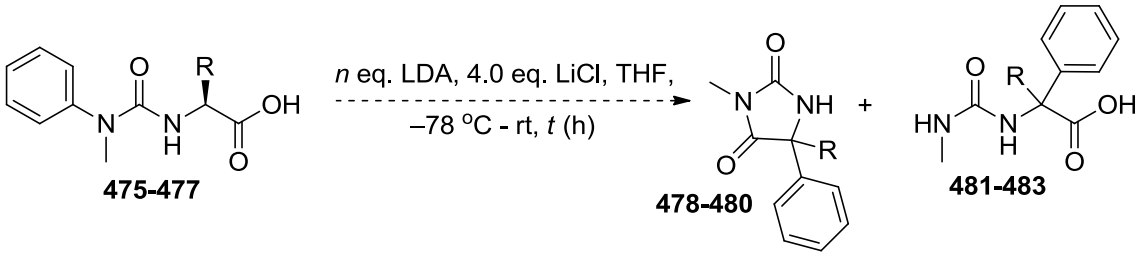

**Scheme 105: Reagents and conditions: 2.3 eq. $Et_3N$, MeCN, reflux, 20 h; (ii) 15.0 eq. LiOH, 2:1 THF:$H_2O$, 45 °C, 20 h**

**Table 10: Yield for synthesis of more complex amino acid derivatives**

| Entry | SM | Coupled yield (%) | Saponification yield (%) | Overall yield (%) |
|---|---|---|---|---|
| 1 | *Nε*-Boc-Lysine (**470**) | >99 (**472**) | 96 (**475**) | 95 |
| 2 | Tyrosine (**471**) | 98 (**473**) | 97 (**476**) | 95 |
| 3 | Serine (**54**) | 92 (**474**) | 86 (**477**) | 79 |

Considering the results from the tri-anionic rearrangement and due to the complexity of the amino acid side chains it was decided a large excess of LDA would be necessary for any reaction to occur. The conditions investigated are shown in Table 11 for the different amino acid derivatives.

**Table 11: Rearrangement conditions attempted for tetra-anionic species**



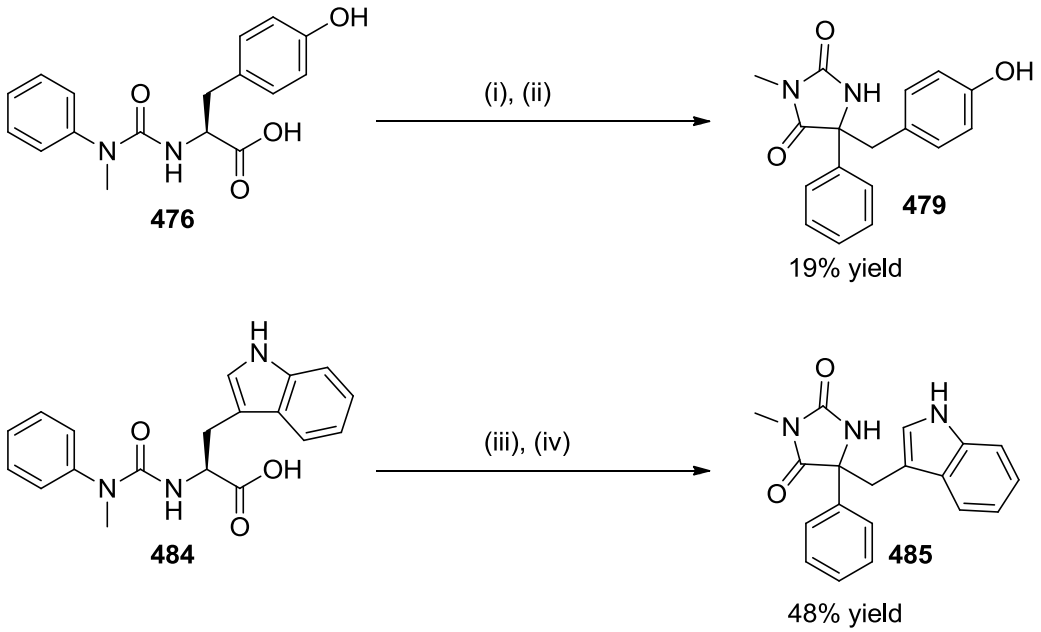

| Entry | Amino Acid | LDA (eq.), *t* (h) | **SM:Product** (cyclised+uncyclised) |
|---|---|---|---|
| 1 | *N*ε-Boc-Lysine (**475**) | LDA (6.0 eq.), 3 h | 0.0:0.0 (**478**:**481**) |
| 2 | Tyrosine (**476**) | LDA (7.0 eq.), 3 h | 1.0:0.8 (**479**:**482**) |
| 3 | Tyrosine (**476**) | LDA (8.0 eq.), 15 h | 1.0:2.6 (**479**:**482**) |
| 4 | Tyrosine (**476**) | LDA (12.0 eq.), 15 h | 1.0:2.6 (**479**:**482**) |
| 5 | Serine (**477**) | LDA (8.0 eq.), 4 h | 2.0:1.0 (**480**:**483**) |

For the *N*ε-Boc-lysine derivative **475** the starting material was consumed but no product returned. Instead a complex mixture of different species was observed (entry 1, Table 11) suggesting a number of unwanted side reactions occur in this system. Tyrosine derivative **476** was subjected to the same reaction conditions as the phenylalanine derivative **462** (entry 2, Table 11), but the reaction was incomplete. Increasing the number of equivalents of LDA (entry 3, 4, Table 11) resulted in a maximum ratio of 1.0:2.6 **479**:**482**. This suggests a further deprotonation (OH on the aromatic ring) slowed the reaction down due to the tetra-anion present. Serine derivative (**477**) was also treated with a large excess of LDA (entry 5, Table 11), but the main component after the reaction was the starting material. Remarkably these results suggested that it was possible to carry out the rearrangement for some tetra-anionic species, but a large excess of LDA was required and incomplete conversion was observed in all cases.

Despite incomplete conversion, the reaction of the tyrosine derivative **476** (entry 3, Table 11) was acidified to yield hydantoin **479** as the sole product and separated from the starting material by flash column chromatography. Hydantoin **479** was isolated in a low yield of 19%, but considering the transformation taking place without any protecting groups the yield was acceptable (Scheme 106). In addition to this example tryptophan derivative **484**[x] was subjected to the rearrangement

[x] With thanks to Dr. Fernando Fernández-Nieto for synthesising the tryptophan starting material **476** using the general procedure used for the other amino acid derivatives.

conditions shown in Scheme 106 and the hydantoin product **485** was returned in a reasonable 48% yield with no protection of either nitrogen atom required.

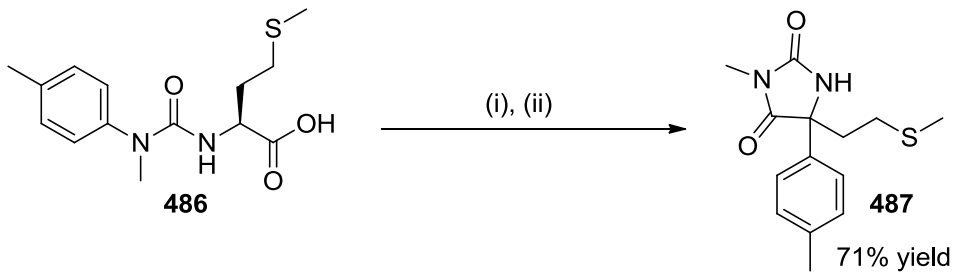



**Scheme 106: Reagents and conditions: (i) 8.0 eq. LDA, 4.0 eq. LiCl, THF, −78 °C – rt, 15 h; (ii) $SOCl_2$, MeOH, rt, 16 h; (iii) 6.0 eq. LDA, 4.0 eq. LiCl, THF, −78 °C – rt, 3 h; (iv) $SOCl_2$, MeOH, rt, 16 h**

In summary, the scope of amino acids that can be used in this unprotected rearrangement is broad. From simple aliphatic amino acids such as alanine and butyrine to branched aliphatic amino acids such as leucine, the rearrangement works well. The scope was extended to amino acids that contained heteroatoms such as methionine and aromatic amino acids such as phenylalanine still giving excellent rearrangement results. The scope was stretched further to amino acids that contained either an OH or NH as part of their chain, introducing a further deprotonable position. The reaction worked less well in these cases with incomplete conversion being observed for many examples, but hydantoins for tryptophan and tyrosine derivatives were isolated in reasonable yields for a tetra-anionic process.

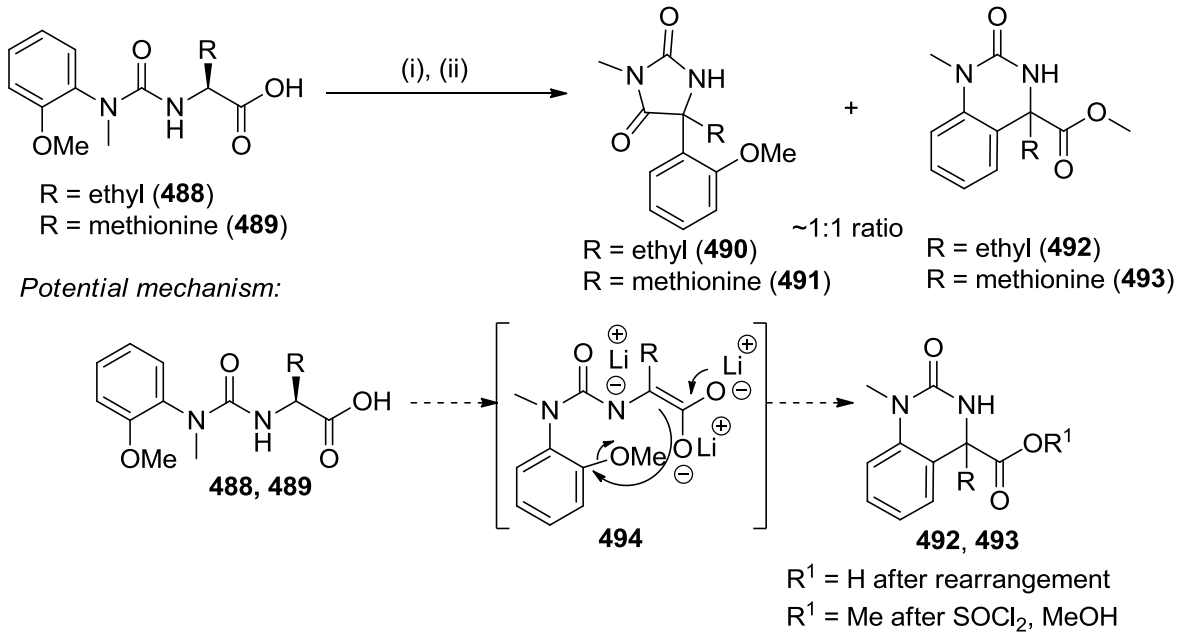
The final area of scope for investigation was the nature of the migrating ring. Various starting materials were synthesised using the same general procedure as previously described (Scheme 102) using carbamoyl chlorides containing different aromatic rings.[xi] Simple migrating rings such as tolyl rearranged well using similar conditions to those optimised for the phenyl ring, with the hydantoin **487** isolated in 71% yield (Scheme 107).

[xi] With thanks to Dr. Fernando Fernández-Nieto and Mary Okoh for synthesising the starting materials




**Scheme 107: Reagents and conditions: (i) 5.5 eq. LDA, 4.0 eq. LiCl, THF, −78 °C – rt, 3 h; (ii) $SOCl_2$, MeOH, rt, 16 h**

However, when aromatic rings substituted with an *o*-OMe group were investigated a mixture of the desired product **490** or **491** in combination with side product **492** or **493** was observed (Scheme 108).

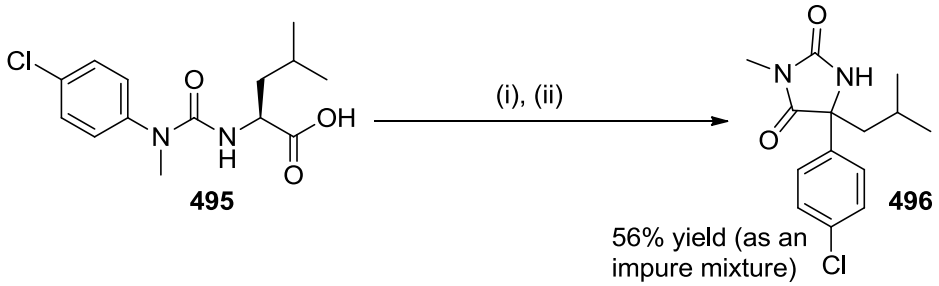



**Scheme 108: Reagents and conditions; (i) 5.5 eq. LDA, 4.0 eq. LiCl, THF, −78 °C – rt, 3 h; (ii) $SOCl_2$, MeOH, rt, 16 h**

Side products **492** and **493** could have come from an $S_NAr$ reaction in which the enolate (**494**) attacks the OMe-carbon instead of the desired *ipso*-carbon (Scheme 108). Alternatively a radical mechanism could be in operation. Side product **493** had very similar signals in the $^1H$ NMR spectrum to the desired product **491** and the mass for both products was identical. The differences were observed in the IR spectrum where a stretch at 1677 $cm^{-1}$ was found for the side product **493** that corresponds to an ester carbonyl. Additionally, there was a significant shift for one of the aromatic carbons observed in the $^{13}C$ NMR spectra. In the desired product **491** the carbon on the aromatic ring with the OMe group attached comes at 150-160 ppm. In the side product **493**,

without the OMe group present, this carbon was now attached to a quaternary carbon centre and was observed at a lower value of 130-140 ppm.

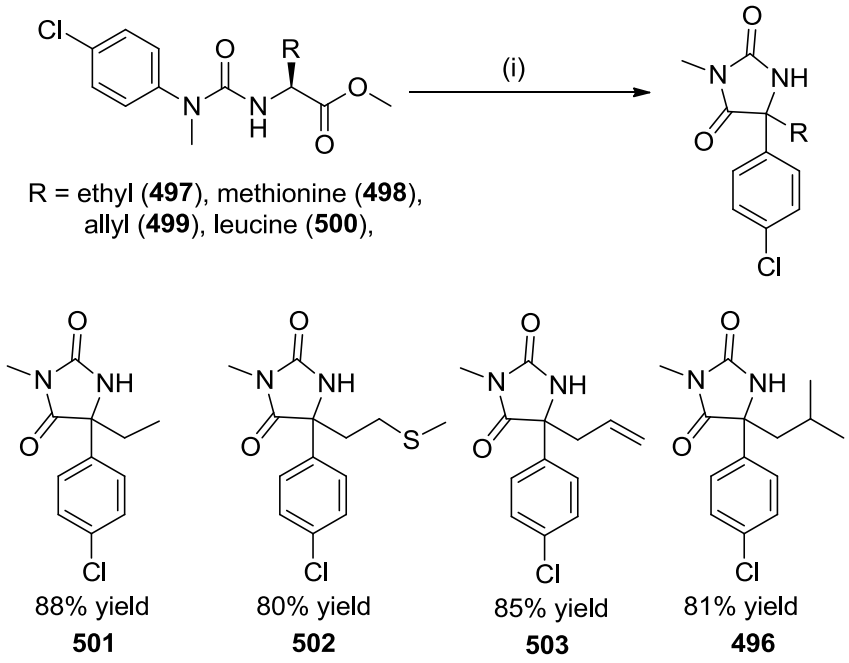
In addition to *o*-OMe substituted aromatic rings being problematic *p*-Cl substituted aromatic rings were also challenging. When leucine derivative **495** with a *p*-Cl ring was treated under rearrangement conditions the desired product **496** was observed by $^{1}$H NMR, but it could only be isolated along with an unidentifiable inseparable impurity (Scheme 109).




**Scheme 109: Reagents and conditions; (i) 5.5 eq. LDA, 4.0 eq. LiCl, THF, −78 °C – rt, 3 h; (ii) $SOCl_2$, MeOH, rt, 16 h**

These *o*-OMe and *p*-Cl substituted aryl rings migrated successfully in the di-anionic series, but with the trianion being more reactive competing side reactions were observed. Kawabata *et al.*[198] reported mono-anionic rearrangements of protected ureas from ester starting materials using milder silazide bases. Since the increased reactivity of the tri-anionic system was problematic the rearrangements were attempted from the ester rather than the carboxylic acid. In this case only a dianion would be expected to form in the reaction, making the starting material less reactive and allowing the use of a milder base such as KHMDS. The reaction was attempted with different amino acid side chains and a *p*-Cl substituted aromatic ring as the migrating group (Scheme 110).[xii]

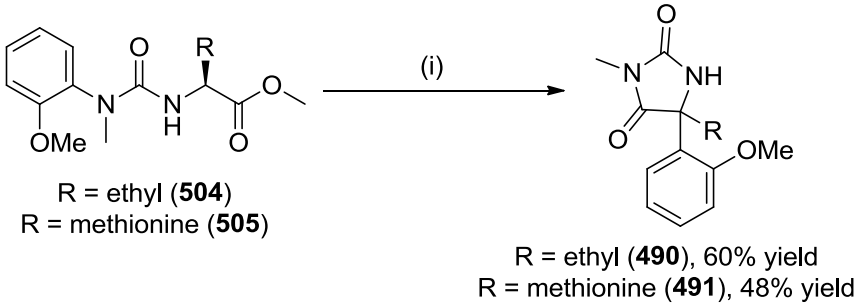
[xii] With thanks to Dr. Fernando Fernández-Nieto for carrying out these preliminary studies on the esters with *p*-Cl migrating rings




**Scheme 110: Reagents and conditions: 4.0 eq. KHMDS, THF, −78 °C – rt, 4 h**[xii,xiii]

The rearrangement from the ester (**497-500**) using 4 eq. of KHMDS gave the hydantoins (**496**, **501-503**) in excellent yields. The reaction resulted solely in the hydantoin with none of the uncyclised product observed. Pleasingly no side reactions were observed under these conditions either.

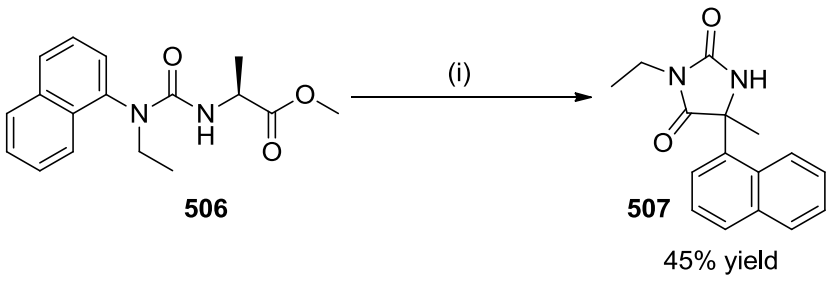
Applying the milder KHMDS conditions to previously problematic *o*-OMe substituted ester ureas **504** and **505** gave hydantoins **490** and **491** in good yield (Scheme 111). Pleasingly, none of side product **492** or **493** arising from unwanted $S_NAr$ reactions was observed under these conditions.




**Scheme 111: Reagents and conditions: 4.0 eq. KHMDS, THF, −78 °C – rt, 3.5 h**

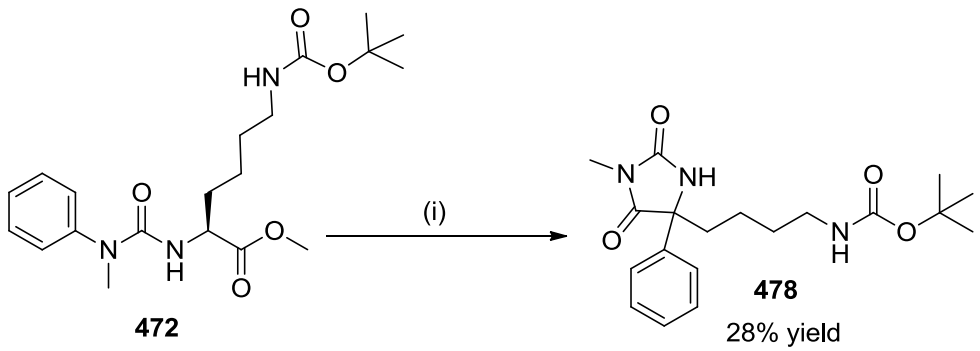
More complex rings such as the 1-naphthyl migrated in a reasonable yield from ester **506** using KHMDS as a base, forming **507** in 45% yield (Scheme 112).

[xiii] Ethyl- and allyl-substituted starting materials were synthesised from racemic starting materials




**Scheme 112: Reagents and conditions: 4.0 eq. KHMDS, THF, −78 °C – rt, 3.5 h**

Finally, *Nε*-Boc-lysine derivative, which gave a complex mixture from the acid **475** under the LDA rearrangement conditions, was investigated. Using ester **472** and KHMDS as a base (5.0 eq. due to the NH in the side chain), hydantoin **478** could be isolated in 28% yield. Although the rearrangement took place in a low yield, this was an improvement on the LDA reaction and reasonable considering no additional protection of the Boc protected side chain was necessary (Scheme 113).




**Scheme 113: Reagents and conditions: 5.0 eq. KHMDS, THF, −78 °C – rt, 3.5 h**

In conclusion, a variety of aromatic rings can undergo this migration, either from the carboxylic acid or the ester. The hydantoin products generated contain an unsubstituted nitrogen atom that should aid the hydrolysis to form quaternary amino acids. This method is simple for production of a large variety of hydantoins that are themselves biologically interesting. For example product **21** is a known anti-epileptic drug, mephenytoin, that is expensive to buy (Sigma-Aldrich, 10 mg (±)-mephenytoin, £428.50). This method avoids the need for protection of the starting materials and the need for a deprotection step after the reaction, prior to hydrolysis. A summary of the hydantoins synthesised by the two methods is shown below (Figure 32). Chiral HPLC analysis proved all these hydantoins were racemic showing no chiral memory effects in this system.[198]

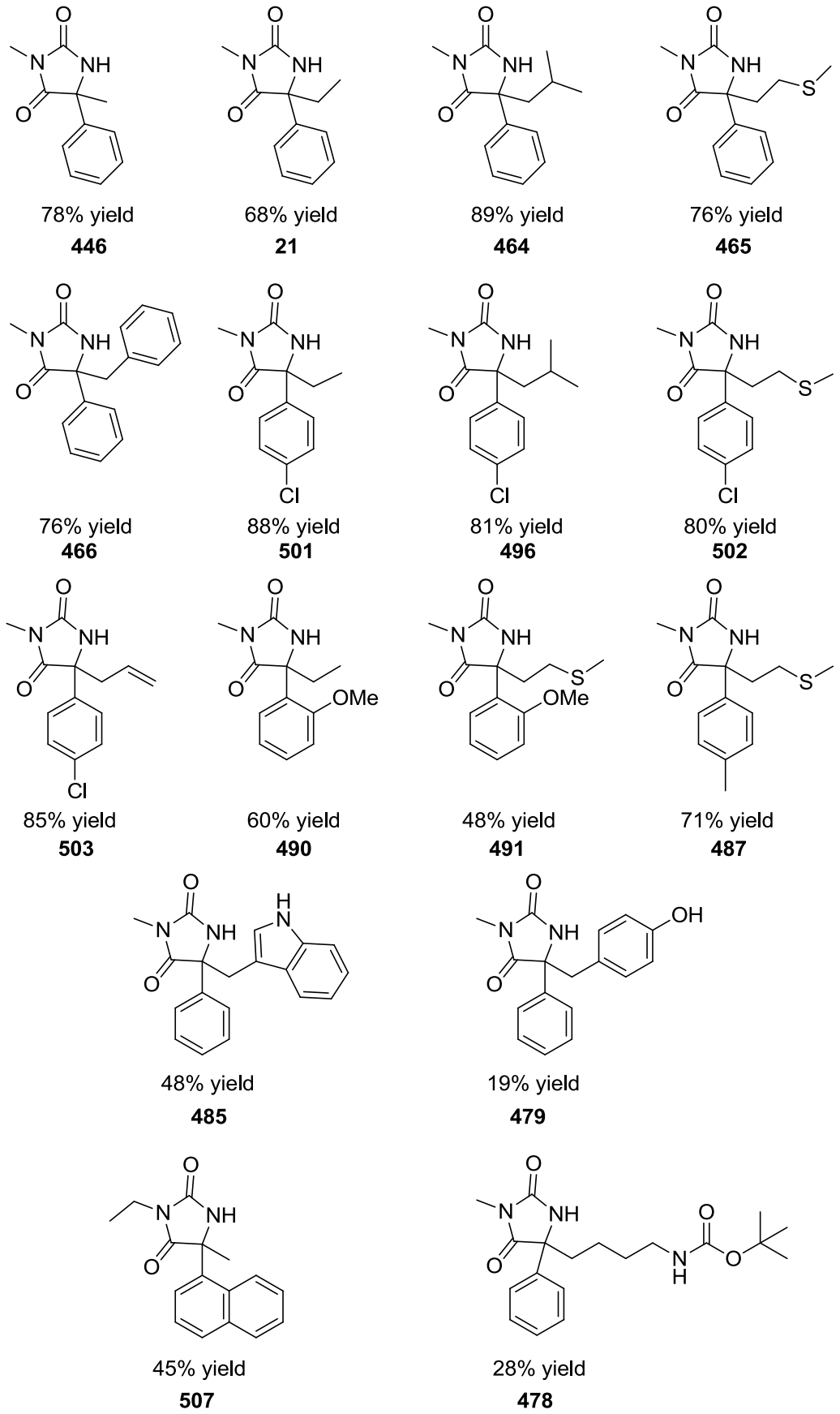


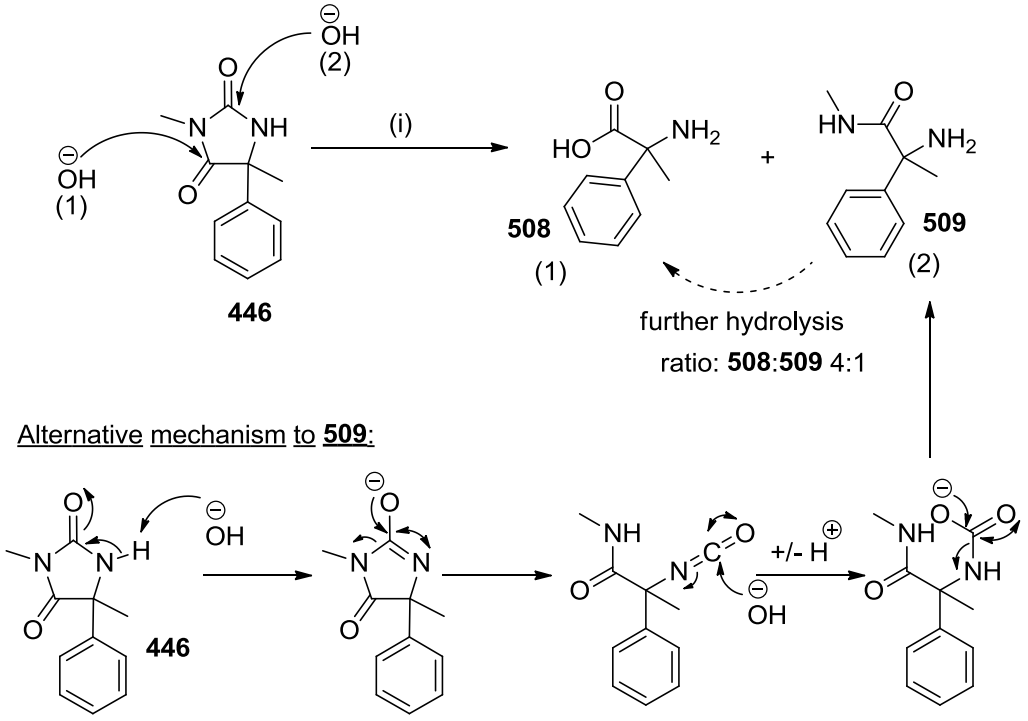

**Figure 32: Scope of hydantoins synthesised from unprotected urea carboxylic acids and esters**

### 2.3.2.2 Cleavage of *N*-Unprotected Hydantoins

Having successfully developed the rearrangement reaction from the *N*-unprotected ureas the final goal was to demonstrate that the hydantoin products could be hydrolysed to the corresponding α-arylated quaternary amino acids.

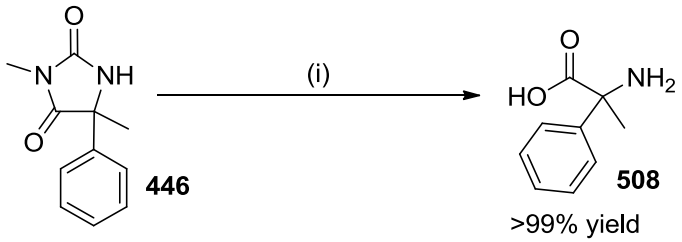
For hydantoins protected on both nitrogen atoms there are two possible routes by which the hydrolysis could occur, (1) and (2), both of which involve attack on one of the carbonyl groups. However, if a hydantoin is *N*-unprotected (**446**), there is a further route available for hydantoin cleavage. The proposed mechanism involves deprotonation of the NH, opening of the ring and formation of an isocyanate that is hydrolysed to give quaternary amino amide **509** (Scheme 114).

Hydantoin **446** derived from alanine was subjected to similar conditions suggested by the literature.[201] Heating **446** with 4.0 M NaOH solution in dioxane at reflux for 25 h gave a mixture of the desired quaternary amino acid **508** along with a small amount of quaternary amino amide **509**, **508**:**509** 4:1 (Scheme 114).




**Scheme 114: Reagents and conditions: (i) 3:1 NaOH (4.0 M): dioxane, reflux, 25 h**

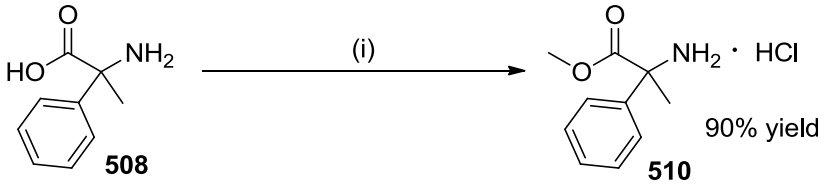
The quaternary amino amide **509** should hydrolyse to give quaternary amino acid **508** under more forceful conditions. Therefore hydantoin **446** was treated with 4.0 M NaOH with no co-solvent and the solution was heated at reflux for 43.5 h. After this time full conversion into quaternary amino acid **508** was observed. The quaternary amino acid **508** was isolated in an excellent >99% yield after acidification followed by purification using a Dowex® ion exchange resin (Scheme 115).




**Scheme 115: Reagents and conditions: (i) 4.0 M NaOH solution, reflux, 43.5 h**

### 2.3.2.3 Isolation of Quaternary Amino Acids as Quaternary Amino Esters

This proved that quaternary amino acids could be synthesised from hydantoins containing one unsubstituted nitrogen atom. Quaternary amino acids are often difficult to isolate and work with and are not very soluble. For convenience, amino acid **508** was converted into amino ester **510** using thionyl chloride and MeOH at reflux. The quaternary amino ester **510** was obtained in 90% yield after suspension in EtOH and filtration over cotton wool (Scheme 116).




**Scheme 116: Reagents and conditions: (i) $SOCl_2$, MeOH, 0 °C – reflux, 20 h**

## 2.3.3 Conclusion

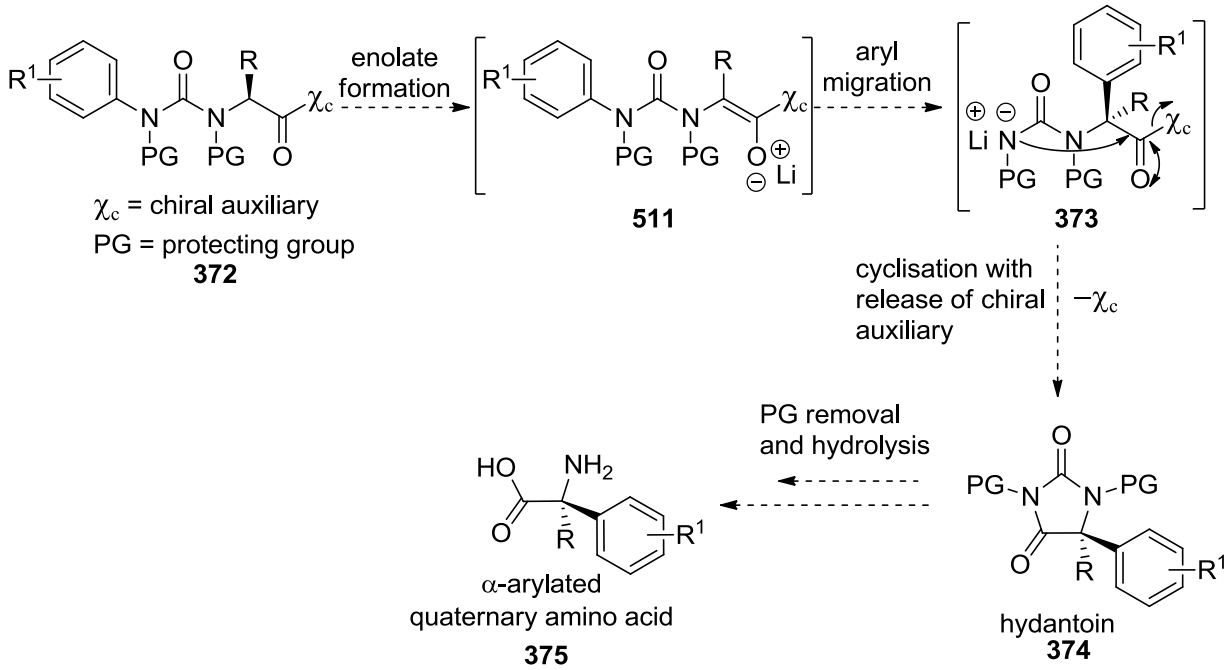
Urea-substituted amino acid enolates undergo intramolecular aryl ring migration under basic conditions. This methodology has established a synthesis of racemic α-arylated quaternary amino acid derivatives, which would be difficult to achieve by other methods. Advantages of this method include the facts that the reaction is transition-metal-free and has a large substrate scope.

Initially, a method was developed that allowed dianionic enolates formed from urea derivatives of tertiary amino acids to undergo ring migration to generate fully protected hydantoins with a quaternary centre. The mechanism for this reaction was elucidated through use of *in situ* ReactIR through analysis of the carbonyl stretching frequencies and six successive reaction intermediates were identified. This method suffered from the fact that *N,N'*-protected hydantoins could not be hydrolysed into quaternary amino acids. Consequently, a new method was developed that involved a rearrangement reaction free from protecting groups. Generation of trianionic enolates from the carboxylic acid or dianionic enolates from the ester, followed by ring migration resulted in the formation of hydantoins with α-arylated quaternary centres but with one of the nitrogen atoms free from a protecting group. This allowed direct hydrolysis to α-arylated quaternary amino acids that for convenience were isolated as α-arylated quaternary amino esters.

## 2.4 *N*-Protecting Groups and Enantioselective Rearrangement using Pseudoephedrine

### 2.4.1 Introduction to Pseudoephedrine

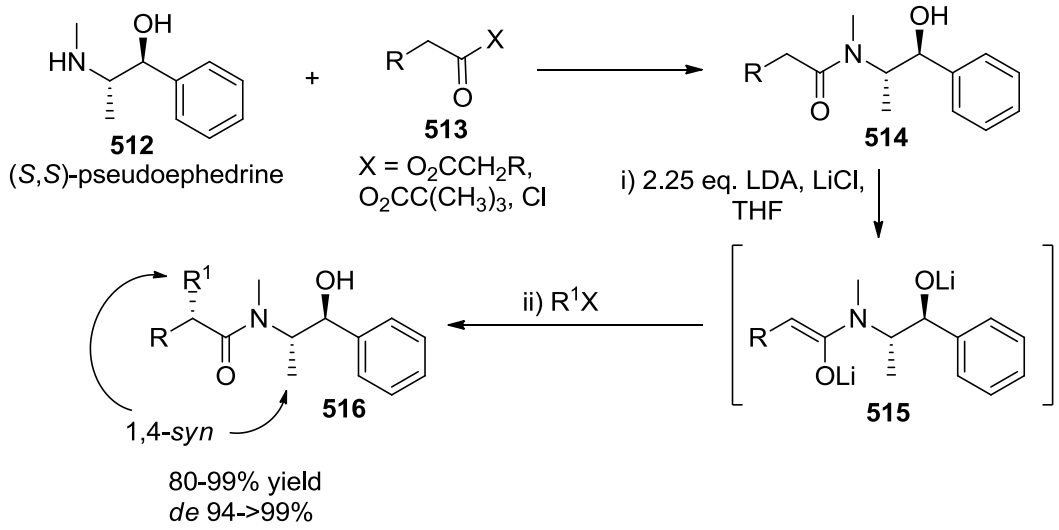
The first part of the project proved the rearrangement was possible with an enolate but this also generates a planar species, leading to racemic products. The second part of the project was to introduce asymmetry into the reaction. By introducing a chiral auxiliary into the starting material it was anticipated this could control the facial addition of the migrating ring, leading to enantiomerically enriched α-arylated quaternary amino acids (Scheme 117).




**Scheme 117: The introduction of asymmetry through use of a chiral auxiliary**

The aim was to attach the auxiliary *via* the carboxylic acid, with α-deprotonation generating the required enolate. It was hoped that rearrangement would occur using the auxiliary to induce stereoselectivity. After the ring migration, if cyclisation to the hydantoin occurs as observed in the racemic series (Chapter 2.3), this would result in release of the chiral auxiliary. This is advantageous as many processes that use chiral auxiliaries have difficulty removing them. In this case the auxiliary would be released during the reaction, allowing it to be isolated and recycled at the end of the reaction.

The auxiliary chosen to investigate was pseudoephedrine (**512**) as it is readily available in both enantiomeric forms and is relatively inexpensive. Pseudoephedrine has been developed by Myers and co-workers as a chiral auxiliary for asymmetric alkylation reactions (Scheme 118).[205]




**Scheme 118: Myers' preparation of pseudoephedrine amides followed by asymmetric alkylation**[205]

Tertiary amide derivatives **514** are formed through *N*-acylation of pseudoephedrine (**512a**) with acid chlorides or acid anhydrides. The asymmetric alkylation of pseudoephedrine amides **514** is achieved through formation of a di-anion **515** using LDA as a base. The reaction is carried out in THF with 6 eq. of LiCl and after deprotonation an alkylating agent ($R^1X$) is added. LiCl accelerates the alkylation rate, is essential for a complete reaction, suppresses unwanted alkylation of the secondary alcohol and leads to improved stereoselectivity. The pseudoephedrine can subsequently be removed by acidic or basic hydrolysis.

The proposed stereochemical model for the alkylation process is shown in Figure 33. The major product for this secondary to tertiary system arises from alkylation of the (*Z*)-enolate (R *syn* to the enolate oxygen) from the same face (1,4-*syn*) as the 2-methyl group of the pseudoephedrine auxiliary in **515**.[206,207]

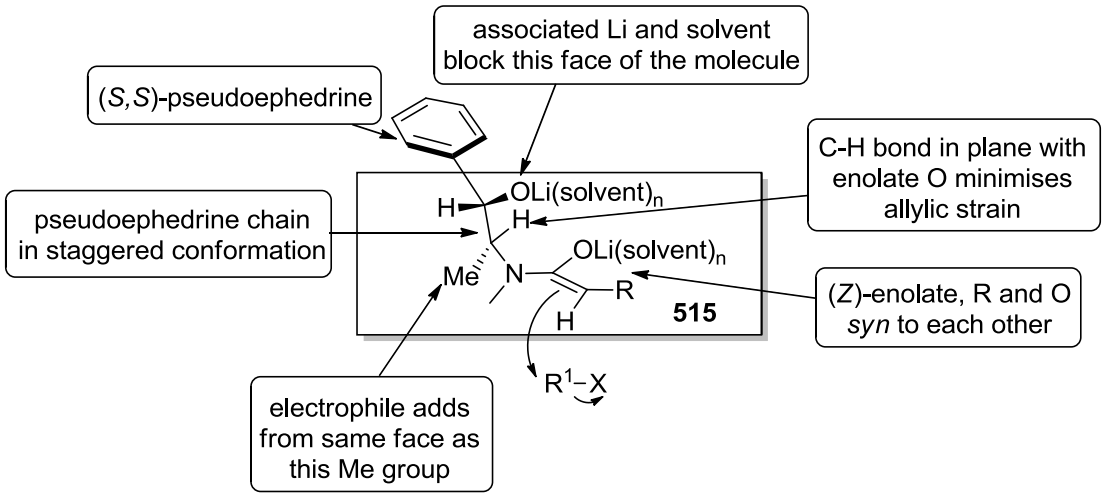



**Figure 33: Enolate in an extended planar conformation reacting to give 1,4-*syn* product**[206,207]

The lithium alkoxide and the solvent molecules associated with the pseudoephedrine oxyanion block one face of the (*Z*)-enolate forcing the alkylation to occur from the opposite face. In Figure 33 the pseudoephedrine side chain is in a staggered conformation and the C-H bond α to nitrogen lies in the same plane as the enolate oxygen to avoid allylic strain. These predictions are based on crystal structures of pseudoephedrine glycinamide hydrate **517** (Figure 34) and modelling. In this model it is also possible for the two oxyanions (enolate oxygen and pseudoephedrine oxygen) to share one or more lithium cations.

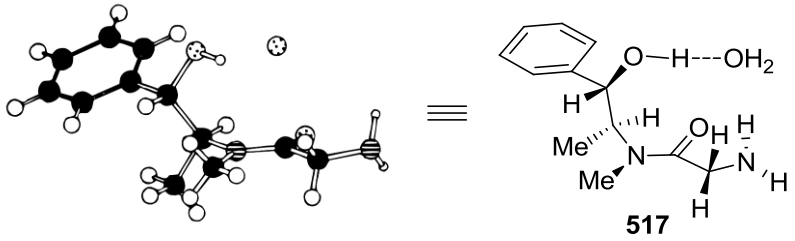



**Figure 34: Predictions based on crystal structure of pseudoephedrine glycinamide hydrate (crystal structure taken from ref 207)**

The case is more complicated for the formation of a quaternary from a tertiary centre. Myers suggests that stereospecific enolisation can occur, with the favoured conformation having the alkoxide side chain of the pseudoephedrine and base on opposite faces of the developing enolate and the α-C-H bond aligned for deprotonation (Figure 35).[208]

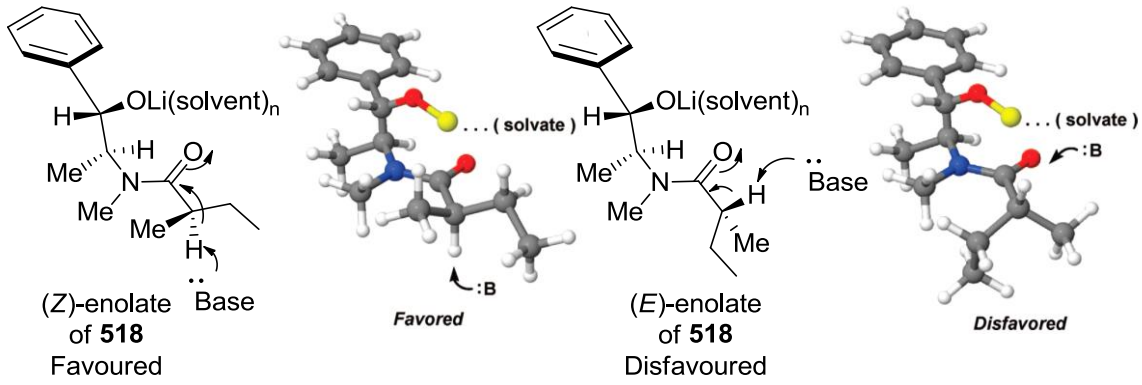
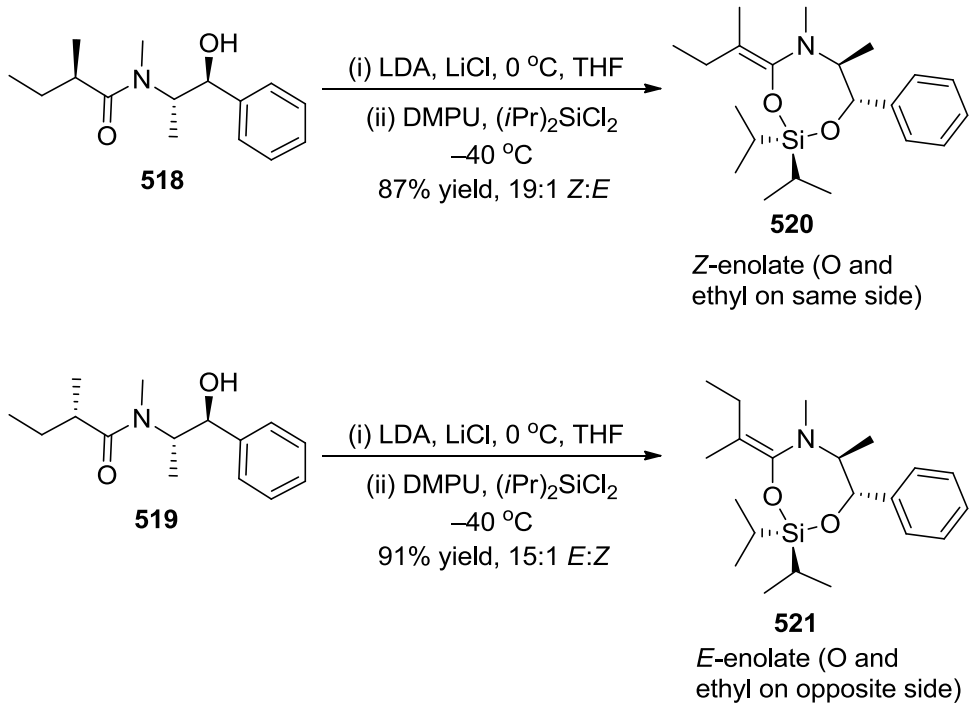


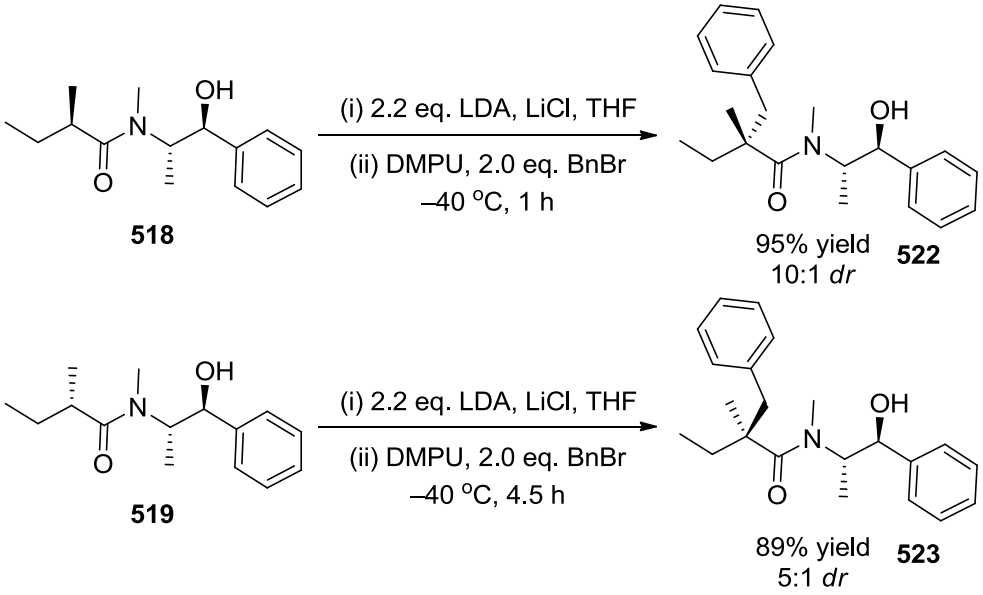

**Figure 35: Favoured and disfavoured conformations for deprotonation (figure taken from ref 208)**

As evidence, enolates of **518** and **519** were trapped at –40 °C using dichlorodiisopropylsilane. In this case the two diastereomers (**518** and **519**) gave different enolate geometries upon trapping (**520** and **521**) (Scheme 119).



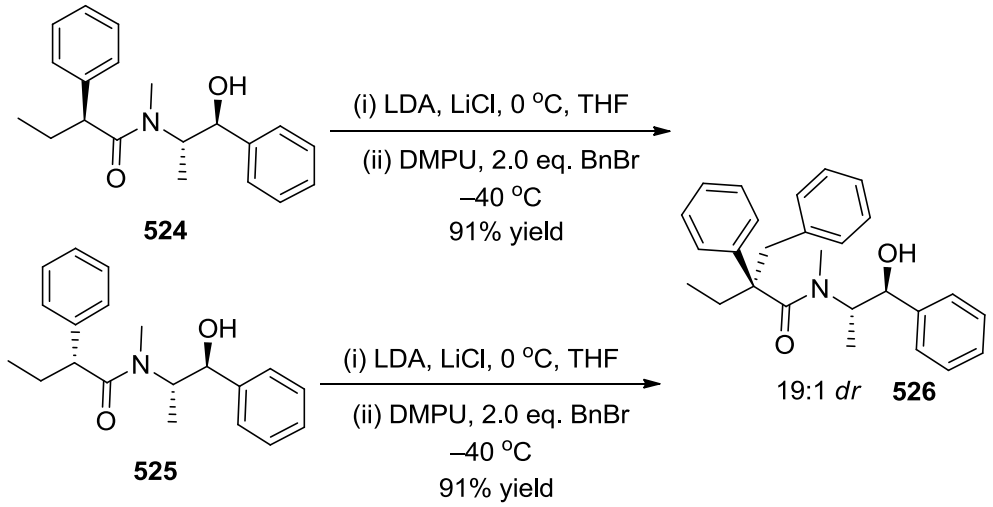

**Scheme 119: Trapped (*Z*) and (*E*)-enolates[208]**

The stereospecificity of the alkylation was shown when **518** and **519** were reacted with benzyl bromide and net retention of the stereochemistry was observed, with the α-C-H bond directly being replaced by the C-electrophile bond. However, the diastereomer leading to the (*Z*)-enolate was more reactive than the (*E*)-enolate, with the reaction occurring four times as fast and with better diastereoselectivity (Scheme 120).




**Scheme 120: Benzylation of both the (*Z*) and (*E*)-enolates[208]**

However, this is not always the case, as in certain examples starting from either the (*R*) or (*S*) tertiary centre affords the same major alkylation product (Scheme 121). This suggests that (*Z*) and (*E*)-enolates can interconvert under the reaction conditions. The enolate for **524** and **525** were both trapped using dichlorodiisopropylsilane and the (*E*)-enolate was formed in a 2.5:1 preference over the (Z) in both cases (Figure 36).




**Scheme 121: Reaction *via* the same enolate to generate one major product** [208]

In this case the major enolate formed from both diastereomers (**524** and **525**) has the ethyl substituent *syn* to the enolate oxygen. However, as the phenyl has higher priority (Cahn-Ingold-Prelog) this is now an (*E*)-enolate (**527**) (Figure 36)

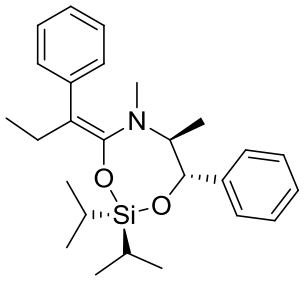



**Figure 36: Most reactive enolate conformation**

During this project, Myers reported pseudoephenamine as a new auxiliary containing a phenyl substituent α to the nitrogen in place of the α-methyl in pseudoephedrine.[209,210] Myers reported the α-alkylation of amino acid derivatives to form α-alkylated quaternary amino acids using the new auxiliary. The same interconversion into the most reactive enolate was observed, with diastereoisomers **528** and **529** both reacting to give enolate **530** (Figure 37). This suggests that the

(*Z*)-enolate is higher in energy, possibly due to repulsive interactions between the enolate oxygen and the imino lone pair in the conformation required to form the (*Z*)-enolate.

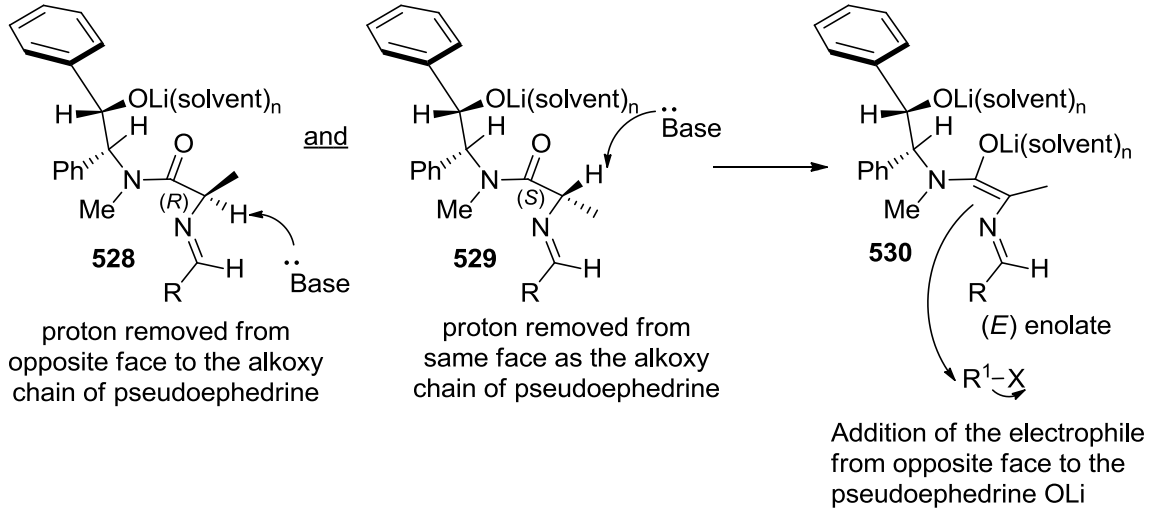


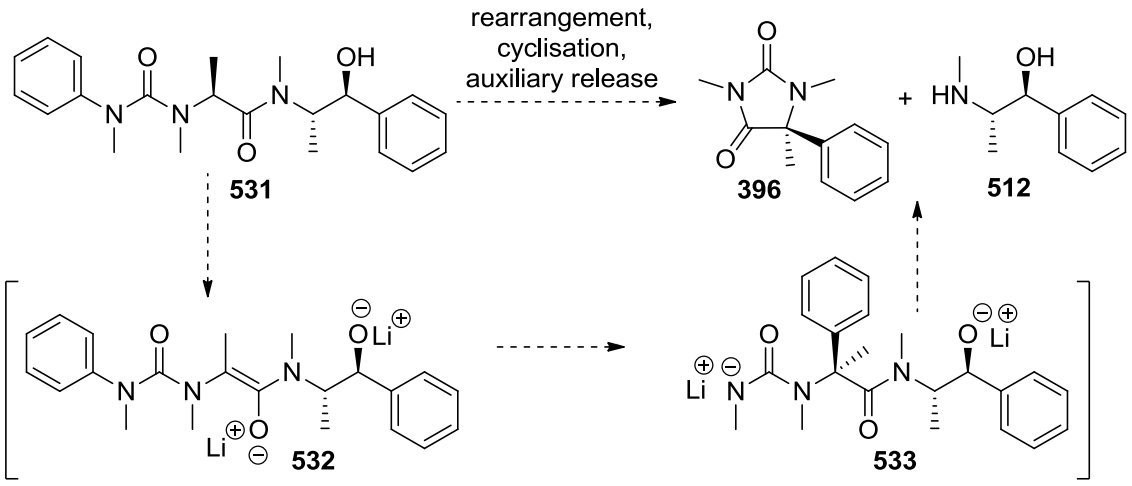

**Figure 37: The formation of an (*E*)-enolate from both (*R*) and (*S*) starting materials[210]**

In all cases the electrophile adds from the face opposite to the alkoxy chain of the auxiliary. For the formation of tertiary centres starting from glycine the (*Z*)-enolate is formed and has the amino acid nitrogen *syn* to the enolate oxygen. The formation of quaternary centres is more complex and the enolate geometry formed can depend on the stereochemistry of the starting material. However, in most cases, the most reactive enolate is formed even if the removal of the proton occurs from a hindered trajectory. Myers' latest paper shows the formation of quaternary amino acid derivatives from (*E*)-enolates, in this case the nitrogen of the amino acid derivative is *anti* to the enolate oxygen (Figure 37).[210]

It was hoped that the excellent stereocontrol shown by pseudoephedrine in asymmetric α-alkylation reactions for the formation of both tertiary and quaternary centres could be mimicked in the aryl migration reaction for the intramolecular rearrangement from amino acid enolates.

### 2.4.2 *N*-Methyl Protected Ureas with Pseudoephedrine

To determine whether using pseudoephedrine as an auxiliary would induce any stereocontrol in the rearrangement reaction *N,N'*-dimethyl urea **531** was initially studied. The reaction is expected to pass through a dianionic intermediate due to α-deprotonation to form the enolate and deprotonation of the pseudoephedrine OH also occurring under the reaction conditions (Scheme 122).

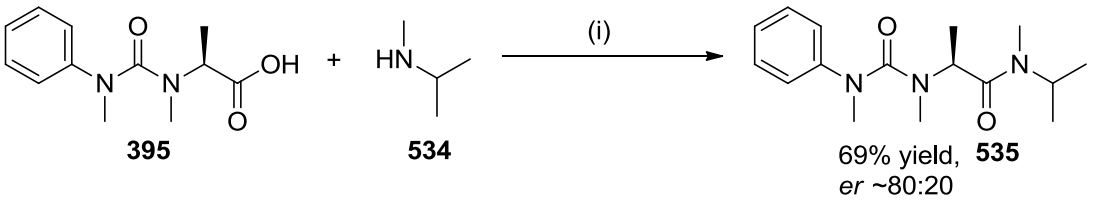



**Scheme 122: Rearrangement with pseudoephedrine incorporated**

### 2.4.2.1 Model Amide System

When the pseudoephedrine is coupled to the carboxylic acid an amide is formed. The first part of the project showed carboxylic acids and esters undergo rearrangement (Chapter 2.3), but amides were never attempted. Before trying the rearrangement reaction on a complex amide such as **531**, a model amide **535** was synthesised and tested to ensure rearrangement occurs.

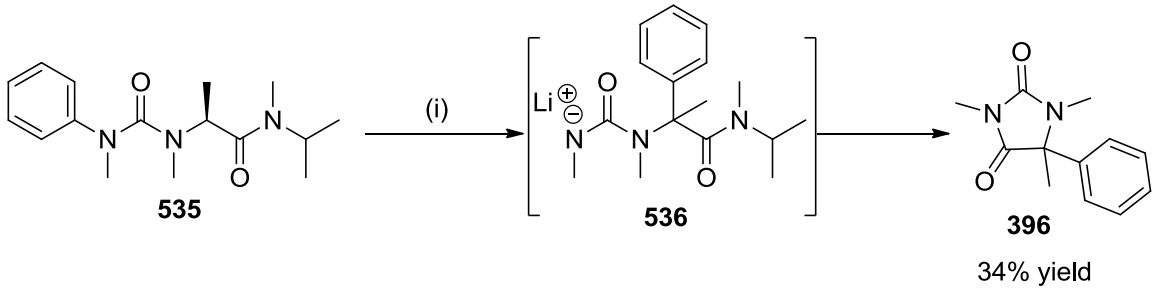
*N*-isopropyl-*N*-methyl amine (**534**) was coupled to urea carboxylic acid **395** that had been used in the racemic series (synthesised according to Chapter 2.3, Scheme 80) using standard coupling conditions of EDC, HOBt and DiPEA in DCM. The product containing an isopropyl group to add steric bulk and mimic pseudoephedrine was formed in a moderate 69% yield (Scheme 123).




**Scheme 123: Reagents and conditions: (i) 1.0 eq. HOBt, 1.2 eq. EDC, 2.3 eq. DiPEA, DCM, rt, 96 h**[xiv]

To establish whether ureas with amide enolates undergo rearrangement reactions, model amide **535** was subjected to the rearrangement conditions previously reported in the benzylic rearrangement.[168] Lithiation and rearrangement occurred upon addition of 3 eq. of *s*BuLi in THF at –78 °C followed by addition of DMPU after 3.5 h and warming to room temperature overnight. The migration of the phenyl ring occurred followed by cyclisation of the nitrogen onto the amide carbonyl, releasing *N*-isopropyl-*N*-methyl amine (**534**) and generating hydantoin **396** in 34% yield after flash column chromatography (Scheme 124).

[xiv] The stereochemistry is shown for the major enantiomer as the stereocentre was partially racemised during the synthesis

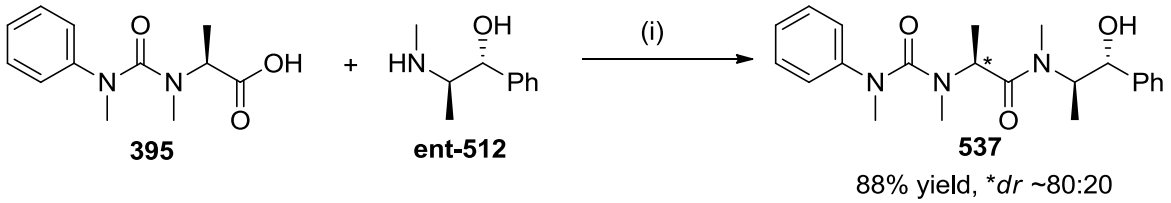



**Scheme 124: Reagents and conditions: (i) 3.0 eq. *s*BuLi, 0.1 M THF, −78 °C, DMPU (after 3.5 h), warm to rt**

The rearrangement was also possible in the absence of DMPU using 4.5 eq. of *n*BuLi and LiCl in THF for 30 min at –78 °C and warming to room temperature for 3 h, hydantoin **396** was obtained in 33% yield. Chiral HPLC analysis confirmed that hydantoin **396** was racemic, showing there was no memory of chirality from the starting materials in this case.[198]

### 2.4.2.2 Enantioselective Reaction of *N*-Methyl Protected Ureas

The starting material containing pseudoephedrine was synthesised from urea acid **395**, which itself was synthesised over three steps in an overall 41% yield using the previously established route (synthesised according to Chapter 2.3, Scheme 80). Carboxylic acid **395** was activated using EDC·HCl, HOBt·$H_2O$ and DiPEA and pseudoephedrine (**ent-512**) was successfully coupled using these standard peptide coupling conditions. The desired product **537** was obtained as a mixture of diastereomers (*dr*~80:20) in a good yield of 88% (Scheme 125). A mixture of diastereomers was not a problem as the partially racemised centre (*) is destroyed during the rearrangement reaction. This fact should also allow this methodology to be applied to racemic and non-natural amino acids, unlike other approaches such as the memory of chirality methodology[198] that require an enantiopure stereocentre.



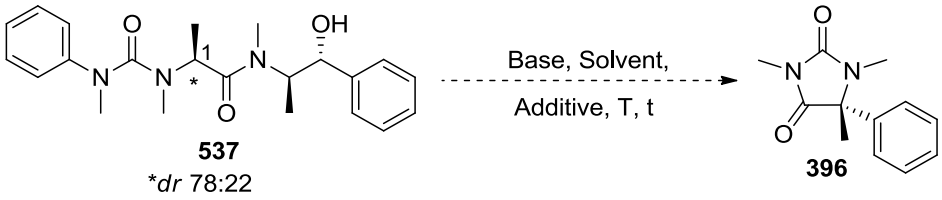

**Scheme 125: Reagents and conditions: (i) 1.5 eq. (*R*,*R*)-pseudoephedrine (ent-512), 1.2 eq. EDC·HCl, 1.0 eq. HOBt·$H_2O$, 2.3 eq. DiPEA, DCM, rt, 65 h**

The $^1$H NMR spectrum of compound **537** was very complicated as it contained two diastereomers that were both also present as a mixture of rotamers due to the tertiary amide (created by pseudoephedrine). The presence of two diastereomers was confirmed through the coupling of urea carboxylic acid **395** with (*S*,*S*)-pseudoephedrine (**512**) rather than (*R*,*R*)-pseudoephedrine (**ent-512**). This gave a similar $^1$H NMR spectrum but with the opposite diastereomer being the major component (**531**). The assignment of the two different diastereomers and rotamers was

achieved using NOESY experiments. The ratio of the diastereomers and the rotamers varied slightly each time **531** or **537** was synthesised, however the *dr* was always greater than 75:25.

Pseudoephedrine starting material **537** was subjected to conditions developed previously for the enantioselective benzylic rearrangements.[168] Unfortunately, the rearrangement was unsuccessful using either *s*BuLi or LDA in the presence of DMPU (Table 12). DMPU was added as a coordinating solvent to increase the reactivity of the organolithium, in an attempt to increase the reaction rate. However, $^{1}$H NMR analysis of the crude reaction showed the quartet for the proton on C1 of **537** remained.

**Table 12: Dimethylated starting material under standard rearrangement conditions**



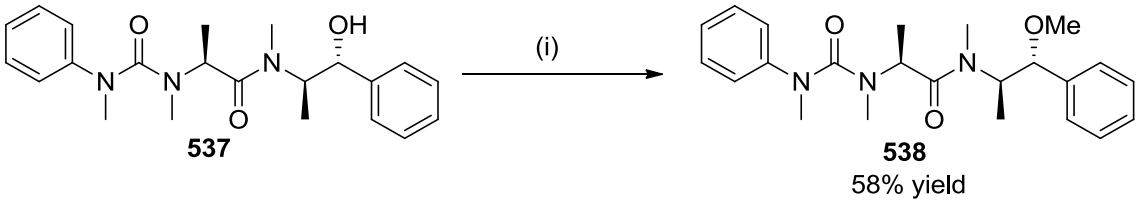

**537**
**dr* 78:22

**396**

| Entry | Base | T (°C) + t (h) | Additive | SM 537 (%) | Hydantoin 396 (%) |
|---|---|---|---|---|---|
| 1 | *s*BuLi | –78 (7 h) to rt (o/n) | DMPU (4.5 h)[a] | 100[b] | 0 |
| 2 | LDA | –78 (6 h) to rt (o/n) | DMPU (5.0 h)[a] | 100[b] | 0 |

Solvent used was 0.1 M THF, 3.0 eq. base, quench at −78 °C with MeOH. [a] Time after which 20.0 eq. DMPU was added. [b] Determined by $^{1}$H NMR.

The free OH group on pseudoephedrine in **537** may have been interfering with the rearrangement. To test this, the OH group was methylated using KO*t*Bu and methyl iodide in THF, forming **538** in 58% yield (Scheme 126).

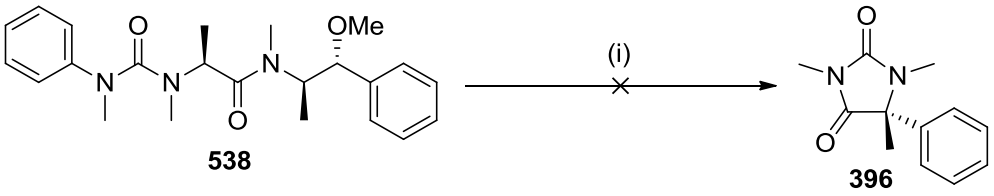



**537**

**538**
58% yield

**Scheme 126: Reagents and conditions: (i) 1.2 eq. KO*t*Bu, 1.3 eq. MeI, THF, o/n**

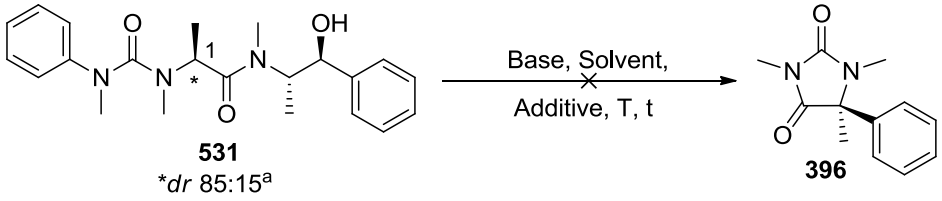
Methylated starting material **538** was treated with *s*BuLi in THF at –78 °C with the addition of DMPU after 2.5 h then warming to room temperature (Scheme 127). However, no reaction was observed under these conditions.




**Scheme 127: Reagents and conditions: (i) 2.5 eq. *s*BuLi, 0.1 M THF, DMPU (after 2.5 h), –78 °C to rt after 4.5 h**

This suggested the overall problem with the rearrangement was not related to the free OH group in **537** and further studies were performed with substrate **537**. To assess if there was any evidence of enolate formation under the reaction conditions and if there was any difference between the reactivity of the starting materials that contained the (*R*,*R*)- or (*S*,*S*)-pseudoephedrine (**537** or **531**), starting material **531** formed from reaction with (*S*,*S*)-pseudoephedrine (**512**) was subjected to various basic conditions.

**Table 13: Basic conditions for the (*S*,*S*) starting material**




| Entry | Base | T (°C) + t (h) | Additive | SM 531 (%) | Hydantoin 396 (%) |
|---|---|---|---|---|---|
| 1 | *s*BuLi | –78 (7 h) to rt (o/n) | DMPU (3.0 h)[b] | 100[c] | 0 |
| 2 | *s*BuLi | –78 (5 h) to rt (o/n) | DMPU | 100[c] | 0 |

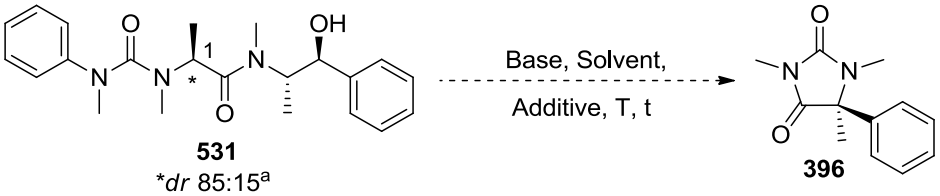
THF (0.1 M), 3.0 eq. base, quench at –78 °C with MeOH. [a] Determined by HPLC analysis. [b] Time after which 20.0 eq. DMPU was added. [c] Determined by $^1$H NMR.

Under the reaction conditions previously used only the starting material was recovered. However, the crude $^1$H NMR spectrum showed a change in the ratio of the two diastereomers through a difference in the relative intensities of the quartets for the C1 proton of **531**. This result was positive as it indicated starting material **531** was undergoing deprotonation at the correct position. This was difficult to quantify by $^1$H NMR due to the presence of rotamers so the *dr* of **531** before and after reaction was determined by HPLC. For Table 13 entry 2 the *dr* of the starting material **531** was 85:15 *vs*. 70:30 after reaction proving some deprotonation had occurred. Further HPLC analysis during the experiment showed that at –78 °C the *dr* of starting material **531** remained the same and that deprotonation only occurred upon warming.

As temperature seemed to be important for deprotonation various experiments were performed changing the final reaction temperature both with and without DMPU as an additive (Table 14). Starting material **531** in THF was cooled to –78 °C and 3 eq. of *s*BuLi were added. After stirring

for 30 min, the temperature was adjusted and left for a period of time stated. Gratifyingly, changing the temperature resulted in the rearrangement reaction occurring and subsequent hydantoin **396** formation. HPLC analysis using an OD-H chiral stationary phase showed that the auxiliary was inducing stereocontrol in the reaction. Table 14 showed the reaction occurred at room temperature and 0 °C (entries 2, 3, Table 14) and also at –20 °C, but the lower the temperature the longer the reaction took with no improvement in *er* (entry 5, Table 14). There was also no improvement in the *er* when DMPU was added (entries 1, 4, Table 14) and at lower temperatures it had a negative impact on the *er* (entry 6, Table 14).

**Table 14: Investigation of temperature effects on the rearrangement reaction**




**531**
**dr* 85:15[a]

**396**

| Entry | Additive | T (°C) + t (h) | Yield of 396 (%)[a] | *er*[b,c] |
|---|---|---|---|---|
| 1 | DMPU | –78 (0.5 h) to rt (3 h 20) | 47% | 22:78 |
| 2 | - | –78 (0.5 h) to rt (3 h 20) | 30% | 22:78 |
| 3 | - | –78 (0.5 h) to 0 (5 h 15) | 68% | 20:80 |
| 4 | DMPU | –78 (0.5 h) to 0 (5 h 15) | 31% | 23:77 |
| 5 | - | –78 (0.5 h) to –20 (o/n) | 32% | 24:76 |
| 6 | DMPU | –78 (0.5 h) to –20 (o/n) | 49% | 28:72 |

3.0 eq. *s*BuLi, THF (0.1 M), Scale ~ 0.13 mmol, quench at –78 °C with MeOH. [a]Yield after purification by flash column chromatography. [b] Determined by HPLC analysis. [c] Absolute stereochemistry not determined.

The next factor investigated was the base. The typical lithium bases were trialled along with disilazide bases that were used by Kawabata *et al.* in their chiral memory work (Table 15).[198]

**Table 15: The effect of base on the rearrangement**

| Entry | Base | T (°C) + t (h) | Yield of 396 (%)[a] | *er*[b] |
|---|---|---|---|---|
| 1 | *s*BuLi | –78 (0.5 h) to rt (3 h 20) | 30% | 22:78 |
| 2 | *n*BuLi | –78 (0.5 h) to rt (3 h 20) | 68% | 22:78 |
| 3 | LDA | –78 (0.5 h) to rt (3 h 20) | 56% | 23:77 |
| 4 | KHMDS | –78 (0.5 h) to rt (3 h 20) | 41% | 60:40 |
| 5 | NaHMDS | –78 (0.5 h) to rt (3 h 20) | 50% | 39:61 |
| 6 | LiHMDS | –78 (0.5 h) to rt (3 h 20) | 44% | 32:68 |

3.0 eq. base, THF (0.1 M), Scale ~ 0.13 mmol, quench at –78 °C with MeOH. [a]Yield after purification by flash column chromatography. [b] Determined by HPLC analysis.

Similar enantioselectivities were observed for *s*BuLi, *n*BuLi and LDA with an *er* ~ 22:78 (entries 1-3, Table 15), but using the disilazide bases the selectivity was lower and for the potassium base the opposite enantiomer was formed in excess (entries 4-6, Table 15).

Solvent can often have an effect on a reaction, so rearrangement was carried out under the same conditions as in Table 15, entry 1, in different solvents. No reaction was observed in either $Et_2O$ or toluene after 3 h. However, HPLC analysis indicated that deprotonation had occurred in both solvents. The best results were obtained using THF and the reaction occurred at a reasonable rate.

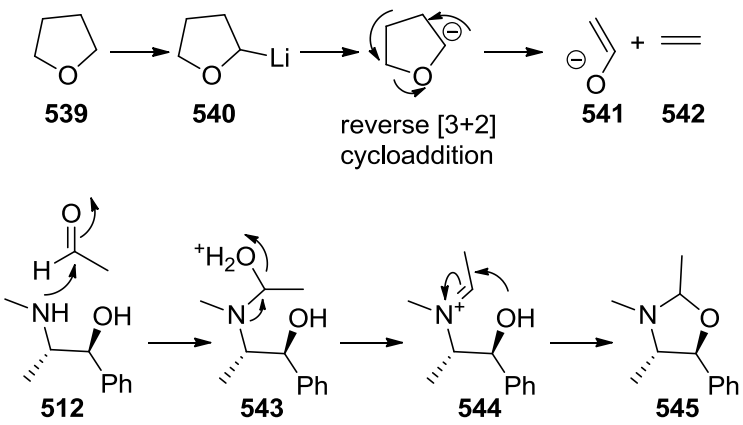
Myers *et al.* suggest that LiCl (>6.0-7.0 eq.) helped to coordinate to the deprotonated OH group of the pseudoephedrine blocking one face of the molecule.[207] Therefore, LiCl was tested as an additive to try and improve the *er* of the rearrangement reaction (Table 16).

**Table 16: Optimisation of the rearrangement reaction**

| Entry | Base | Eq. Base | Solvent (M) | T (°C) + t (h) | Additive[d] | Yield of 396 (%)[a] | *er*[b] |
|---|---|---|---|---|---|---|---|
| 1 | *s*BuLi | 3.0 | THF (0.1) | –78 (0.5 h) to rt (3 h 20) | - | 30% | 22:78 |
| 2 | *s*BuLi | 3.0 | THF (0.1) | –78 (0.5 h) to rt (3 h 20) | LiCl | 56% | 17:83 |
| 3 | *s*BuLi | 3.0 | THF (0.05) | –78 (0.5 h) to rt (3 h 20) | LiCl | 53% | 17:83 |
| 4 | *n*BuLi | 4.5 | THF (0.1) | –78 (0.5 h) to rt (3 h 20) | - | 68% | 14:86 |
| 5 | *n*BuLi | 4.5 | THF (0.1) | 0 (3 h 20) | - | 4% | 13:87 |
| 6 | *n*BuLi | 4.5 | THF (0.1) | –78 (0.5 h) to rt (3 h 20) | LiCl | 49% | 8:92 |
| 7a | LDA | 3.0 | THF (0.1) | –78 (0.5 h) to rt (3 h 20) | LiCl | 51% | 9:91 |
| 7b[c] | LDA | 3.0 | THF (0.1) | –78 (0.5 h) to rt (3 h 20) | LiCl | 72%[c] | 12:88 |
| 8 | LDA | 3.0 | THF (0.1) | 0 (3 h 20) | LiCl | 0% | - |
| 9 | LiTMP | 3.0 | THF (0.1) | –78 (0.5 h) to rt (3 h 20) | LiCl | 64% | 8:92 |

THF (0.1 M), Scale ~ 0.13 mmol except entry 7b, quench at –78 °C with MeOH. [a]Yield after purification by flash column chromatography. [b]Determined by HPLC analysis. [c]Scale up ~0.34 mmol. [d]12.0 eq. LiCl.

The addition of LiCl to the reaction did improve the *er* from 22:78 to 17:83 (Table 16, entry 2). Lowering the reaction concentration had no impact on the enantioselectivity (Table 16, entry 3). Having a larger excess of base (Table 16, entry 4) further improved the *er* and a combination of LiCl and 4.5 eq. of *n*BuLi led to the best *er* of 8:92 (Table 16, entry 6). When this reaction was performed on a larger scale, an inseparable impurity was observed that was identified as **545** (Scheme 128). The structure was confirmed by comparison of $^{1}$H NMR data with literature data.[211] Impurity **545** formed after the rearrangement through reaction of the pseudoephedrine (**512**) released in cyclisation, with acetaldehyde (**541**), which is generated from the decomposition of THF (**539**) by excess *n*BuLi. Excess base under these conditions was therefore problematic.




**Scheme 128: The formation of an impurity from pseudoephedrine and acetaldehyde**

The combination of 3 eq. of LDA with LiCl (Table 16, entry 7a) resulted in an *er* of 9:91, which was comparable with entry 6 (Table 16). This reaction was scaled up (entry 7b, Table 16) and after purification a good yield of 72% and a reasonable *er* of 12:88 was obtained. The importance of adding the base at –78 °C was confirmed by repeating the experiment at 0 °C. In this case no product was observed (entry 8, Table 16). LiTMP also gave the same *er* as LDA in combination with LiCl (entry 9, Table 16). This result was useful for future work when optimising rearrangement reactions of different starting materials, as LiTMP works at a lower temperature than LDA.

To complete the optimisation final experiments were carried out using LDA and LiCl. These are detailed in the table below (Table 17).

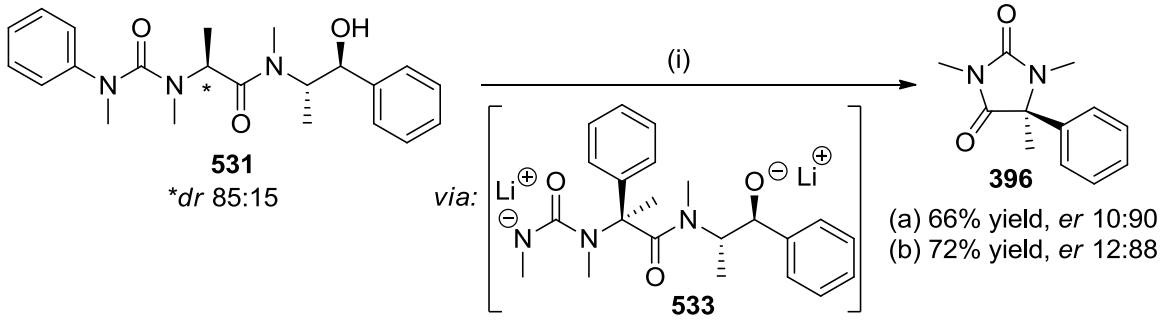
**Table 17: Final optimisation reactions**

| Entry | Eq. LDA | T (°C) + t (h) | Yield of 396 (%)[a] | *er*[b] |
|---|---|---|---|---|
| 1a | 3.0 | –78 (0.5 h) to rt (3 h 20) | 51% | 9:91 |
| 1b[c] | 3.0 | –78 (0.5 h) to rt (3 h 20) | 72%[c] | 12:88 |
| 2 | 3.0 | –78 (0.5 h) to 0 (3 h 20) | 69% | 13:87 |
| 3 | 3.0 | –78 (0.5 h) to –20 (3 h 20) | 0% | - |
| 4 | 3.0 | –78 (0.5 h) to rt (1.0 h) | 66% | 10:90 |
| 5 | 3.0 | –78 (0.5 h) to 0 (4 min)[d] | 0% | - |
| 6 | 3.0 | –78 (0.5 h) to 0 (1.0 h) | 38%[e] | 10:90 |
| 7 | 4.5 | –78 (0.5 h) to rt (1.0 h) | 65% | 15:85 |

LDA, 12.0 eq. LiCl, THF (0.1 M), Scale ~ 0.13 mmol except 1b, quench at –78 °C with MeOH. [a]Yield after purification by flash column chromatography. [b]Determined by HPLC analysis. [c]Scale up ~0.34 mmol. [d]Warm to 0 °C and quenched straight away. [e]Crude NMR contained starting material.

Warming the reactions using LDA and LiCl to lower than room temperature gave no improvement in yield or *er* (entry 2, 3, Table 17). The reaction was carried out in a shorter time period giving a good yield and *er* (entry 4, Table 17). To establish if the rearrangement reaction occurred during the warm up to room temperature, the reaction was quenched as soon as it reached 0 °C (entry 5, Table 17). No hydantoin product was found suggesting that the rearrangement takes place after a period of time at 0 °C or at room temperature. The reaction was not complete after 1 h at 0 °C (entry 6, Table 17) and a lower temperature gave no improvement in the *er*. Finally, an excess of LDA gave a good yield but no improvement in *er* (entry 7, Table 17).

In summary, whilst previously reported benzylic rearrangements[168] occurred at –78 °C, this reaction required a temperature of –20 °C or above. There was no improvement in *er* at lower temperature and the reaction times were longer. Various bases have been investigated, with LDA optimal for this reaction in terms of both yield and *er*. Solvent and concentration were explored; the rearrangement only took place in THF and the concentration had no effect. DMPU and LiCl were investigated as additives; DMPU had no advantageous effects but LiCl proved crucial to obtaining the high *er*. The overall optimised conditions for this rearrangement reaction are shown in Scheme 129, giving the hydantoin **396** in a good yield (66-72%) with a good *er* (12:88-10:90).



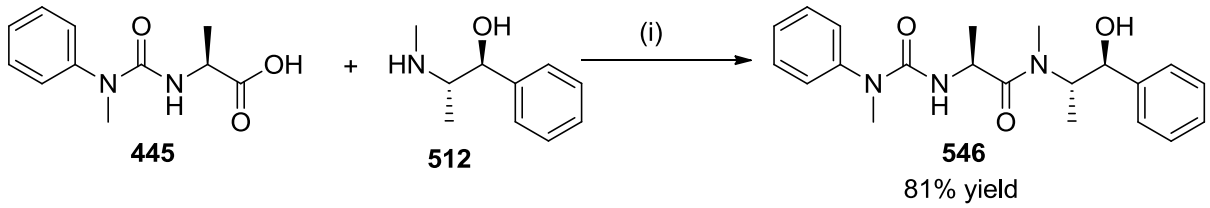

**Scheme 129: Reagents and conditions: (i) 3.0 eq. LDA, 12.0 eq. LiCl, 0.1 M THF, –78 °C (0.5 h) – rt, (a) 1 h at rt, 0.13 mmol scale, (b) 3 h at rt, 0.34 mmol scale**

This proved that pseudoephedrine is a suitable chiral auxiliary that can induce stereocontrol in this rearrangement reaction. The absolute configuration of the hydantoin **396** was not determined at this stage, but will be discussed in the end of this chapter (Chapter 2.4.9, page 165).

### 2.4.3 *N*-Unprotected Ureas with Pseudoephedrine

With the knowledge that pseudoephedrine was a suitable chiral auxiliary this was applied to the unprotected version of the rearrangement. This would not only allow enantiomerically enriched hydantoins to be generated but also cleavage into enantiomerically enriched quaternary amino acids.

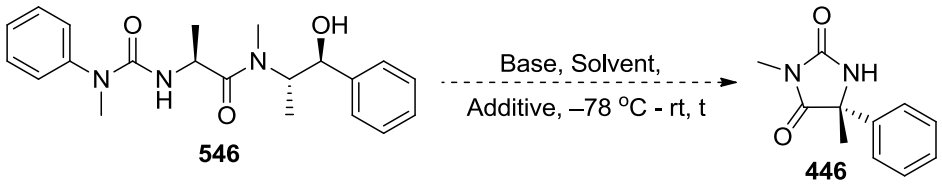
The (*S*,*S*)-pseudoephedrine (**512**) was coupled to urea derived carboxylic acid **445** free from a nitrogen protecting group, which was synthesised over two steps in an overall 93% yield (synthesised according to Chapter 2.3, Scheme 99). To introduce the (*S*,*S*)-pseudoephedrine (**512**), the carboxylic acid **445** was activated using EDC·HCl, HOBt·$H_2O$ and DiPEA giving the desired product **546** as a single diastereomer in a yield of 81% (Scheme 130). The $^1$H NMR spectrum for **546** was a mixture of rotamers due to the tertiary amide formed through introduction of pseudoephedrine.




**Scheme 130: Reagents and conditions: (i) 1.5 eq. (*S*,*S*)-pseudoephedrine (512), 1.2 eq. EDC·HCl, 1.0 eq. HOBt·$H_2O$, 1.2 eq. DiPEA, DCM, rt, 19 h**

The unprotected pseudoephedrine starting material **546** was subjected to similar rearrangement conditions to the protected starting material **531**, but 4 eq. of base were needed due to the additional NH deprotonation (Table 18).

**Table 18: Attempted rearrangement conditions for the unprotected pseudoephedrine starting material**

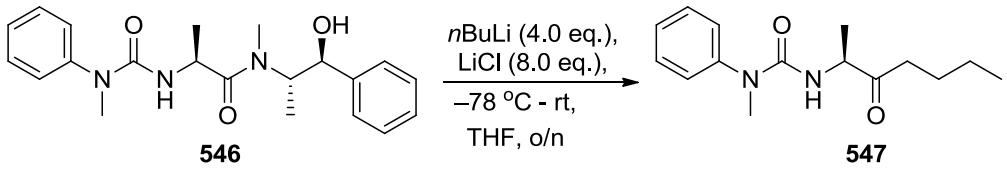



546 446

| Entry | Base | Eq. Base | Eq. LiCl | t (h) at rt | Yield of 446 (%)[a] | *er*[b] |
|---|---|---|---|---|---|---|
| 1 | LDA | 4.0 | 5.0 | 3.0 | - | - |
| 2 | LDA | 4.0 | 7.0 | o/n | 54% | 50:50 |
| 3 | LDA | 4.0 | 12.0 | o/n | 45% | 50:50 |
| 4 | LDA | 6.0 | 7.0 | o/n | -[c] | - |
| 5 | *n*BuLi | 4.0 | 8.0 | o/n | -[d] | - |
| 6 | LiTMP | 4.0 | 7.0 | o/n | 43% | 55:45 |
| 7 | LiHMDS | 4.0 | 7.0 | o/n | - | - |
| 8[c] | LiHMDS[e] | 4.0 | - | o/n | - | - |

–78 °C – rt, THF (0.1 M) except entry 8, $NH_4Cl$ quench at –78 °C, warm to rt and acidify with 1.0 M HCl. [a]Yield after purification by flash column chromatography. [b]Determined by HPLC analysis. [c]Decomposition occurred. [d]*n*BuLi added into the amide carbonyl of the starting material rather than carrying out the rearrangement, **547** in Scheme 131. [e]Reaction solvent was 5:1 DMF:THF.

Using 4 eq. of LDA for 3 h at room temperature returned only starting material (entry 1, Table 18). Pleasingly, leaving the reaction overnight resulted in some product formation but disappointingly product **446** was racemic (entry 2, Table 18). Addition of more LiCl did not improve the *er* and **446** was still racemic and the yield was lower (entry 3, Table 18). Using more base resulted in decomposition of the starting material (entry 4, Table 18). Changing to a more reactive base, *n*BuLi, resulted in **547**, where the base attacked the carbonyl of the starting material rather than the desired α-carbon (entry 5, Table 18, Scheme 131). Trying LiTMP gave a similar result to entries 2 and 3, the yield was moderate but product **446** was virtually racemic (entry 6, Table 18). Finally, using LiHMDS as a milder base returned just starting material in both THF and a 5:1 DMF:THF mixture (entries 7, 8, Table 18).

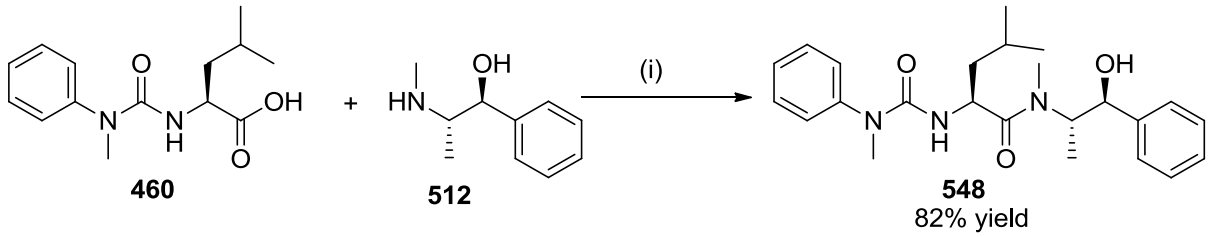



546 547

**Scheme 131: Reaction with *n*BuLi, attack on carbonyl**

To check the problem was not with the stability of alanine derived substrate **546**, (*S*,*S*)-pseudoephedrine (**512**) was coupled to the unprotected leucine derivative **460** (synthesised

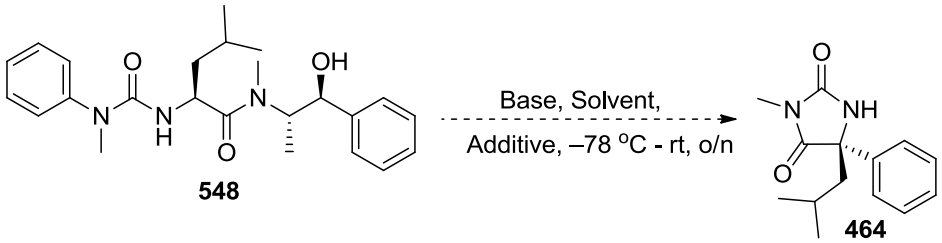
according to Chapter 2.3, Scheme 102) using EDC·HCl, HOBt·$H_2O$ and DiPEA. The desired product **548** was obtained as a single diastereomer in a yield of 82% (Scheme 132).




**Scheme 132: Reagents and conditions: (i) 1.5 eq. (*S*,*S*)-pseudoephedrine (512), 1.2 eq. EDC·HCl, 1.0 eq. HOBt·$H_2O$, 1.2 eq. DiPEA, DCM, rt, 16 h**

The unprotected leucine derivative **548** was subjected to various rearrangement conditions shown in Table 19.

**Table 19: Attempted rearrangement conditions for the unprotected leucine derivative**

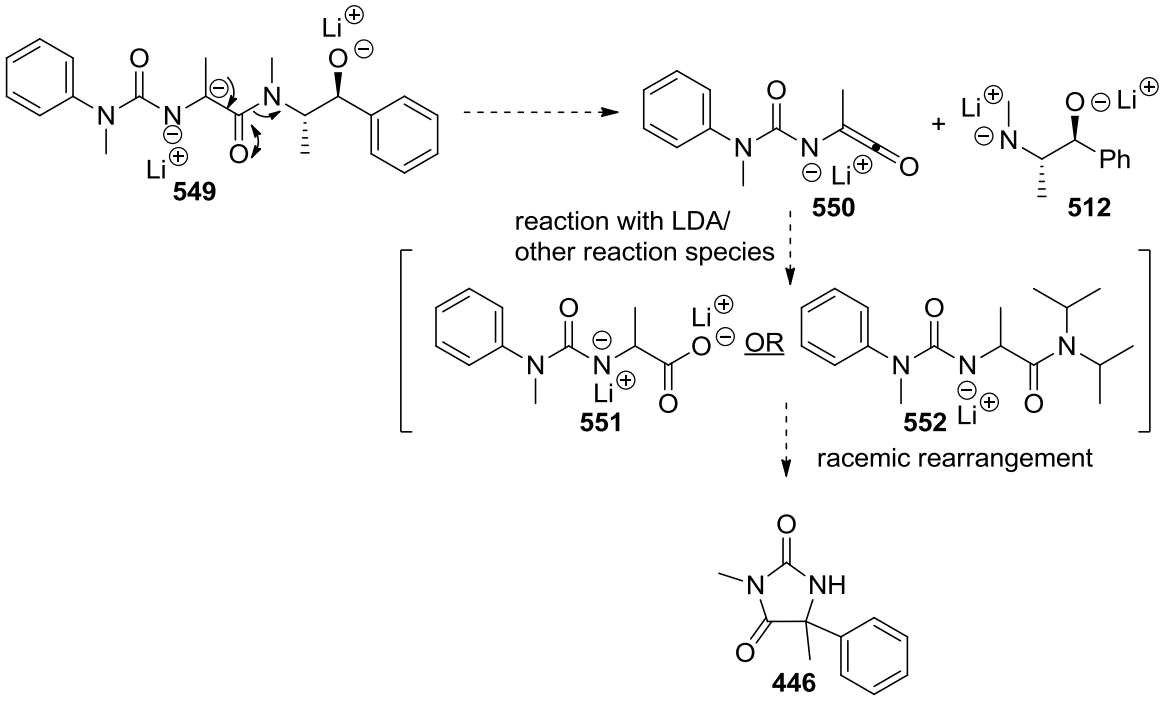



| Entry | Base | Eq. Base | Eq. LiCl | Yield of 464 (%) | *er* |
|---|---|---|---|---|---|
| 1 | LDA | 4.0 | 6.0 | - | - |
| 2 | LDA | 6.0 | 7.0 | - | - |
| 3 | *n*BuLi | 5.0 | 7.0 | -[a] | - |
| 4 | LiHMDS | 5.0 | 5.0 | - | - |
| 5 | LiHMDS[b] | 4.0 | - | - | - |

–78 °C – rt, overnight, THF (0.1 M) except entry 8, $NH_4Cl$ quench at –78 °C, warm to rt and acidify with 1.0 M HCl. [a]*n*BuLi added into the amide carbonyl of the starting material rather than carrying out the rearrangement (similar to product **547**, Scheme 131). [b]Reaction solvent was 5:1 DMF:THF.

Unfortunately under all conditions (entries 1-5, Table 19) no reaction was observed and starting material was recovered, except for entry 3, when *n*BuLi was used and this added into the carbonyl of the starting material (similar to product **547**, Scheme 131). Since similar results were obtained for the alanine **546** and leucine **548** derivatives, disappointingly this suggested an enantioselective rearrangement reaction was not possible with one of the nitrogen atoms unprotected.

The free NH in starting material **546** is likely to be deprotonated under the reaction conditions, putting a negative charge next to the α-carbon, which itself is deprotonated to form enolate **549** (Scheme 133). Two negative charges in such close proximity would lead to repulsion that may decompose the starting material. It is hypothesised that the pseudoephedrine chiral auxiliary can be eliminated from starting material **546** to generate ketene **550**, which under the reaction conditions could become many other species including **551** and **552**. These can then undergo rearrangement to give product **446**, but in the absence of the chiral auxiliary the product is racemic (Table 18). This was not a problem in the reaction described in Chapter 2.3.2.1 that generated racemic products, because ketene formation would have required loss of $O^{2-}$, which is bad leaving group.




**Scheme 133: Proposed reason for the racemic product in the auxiliary controlled reaction**

Alternatively, deprotonation of the NH could result in formation of an azlactone accompanied by elimination of the chiral auxiliary. There is potential for α-deprotonation of the azlactone followed by rearrangement providing an alternative explanation for the unselective reaction.

### 2.4.4 Alternative *N*-Protecting Groups with Pseudoephedrine

The rearrangement from unprotected starting materials was unsuccessful, but an enantioselective rearrangement was possible from *N*,*N'*-protected starting materials. This suggested N protection was necessary for an enantioselective reaction, therefore alternative protecting groups to methyl groups were investigated. The aim was to generate enantiomerically enriched protected hydantoins, which after the removal of the protecting group(s) could be hydrolysed into enantiomerically enriched quaternary amino acids.

The protecting group had to be base-stable for the rearrangement and had to be easily removed after the rearrangement under conditions that would not compromise any other functionality.

#### 2.4.4.1 *N*-Benzyl Protected Ureas

The first protecting group considered was *N*-benzyl, which can be removed by hydrogenation (Figure 38).

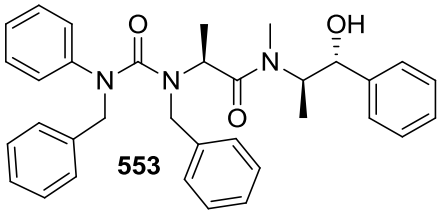
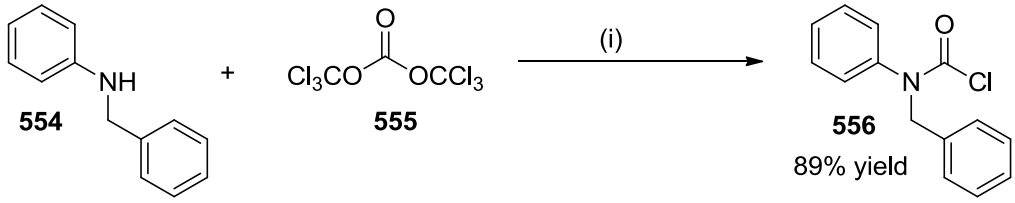


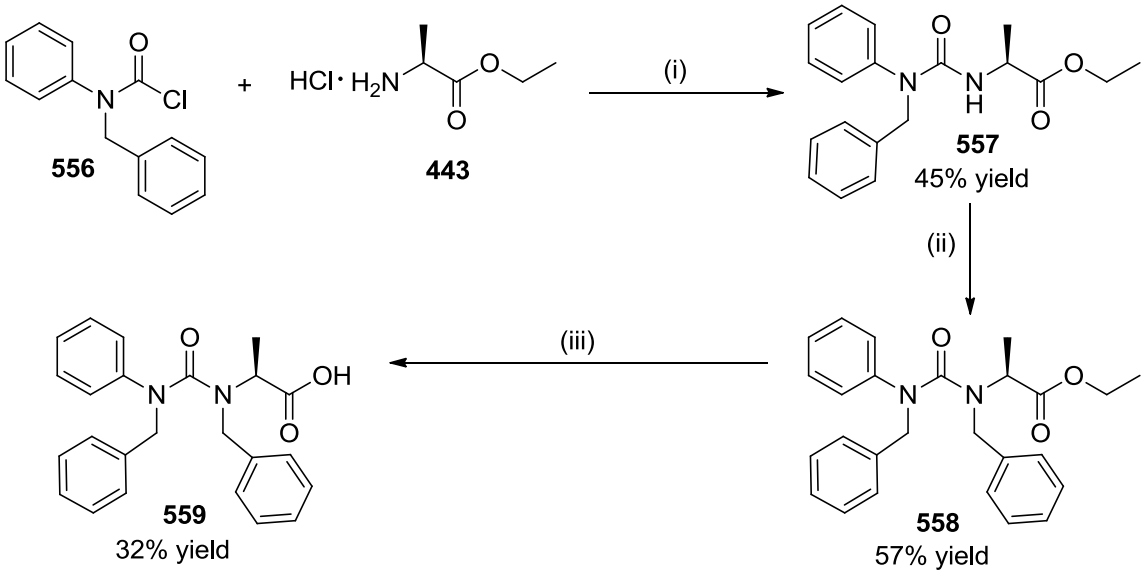

**Figure 38: Benzyl protected starting material target**

The required starting material **553** was synthesised from *N*-benzyl-*N*-phenyl carbamoyl chloride (**556**). This was made by reaction of *N*-benzylaniline (**554**) with triphosgene (**555**) in the presence of pyridine. Product **556** was isolated after 2 h in a yield of 89% (Scheme 134).




**Scheme 134: Reagents and conditions: (i) 2.2 eq. pyridine, DCM, –78 °C - rt, 2 h**

Carbamoyl chloride **556** was coupled to L-alanine ethyl ester (**443**) in a moderate 45% yield. Urea **557** was then benzylated using benzyl bromide and sodium hydride at 0 °C, giving doubly benzylated urea **558** in 57% yield. Finally, removal of the ethyl group to give free acid **559** was achieved in a poor crude yield of 32% (Scheme 135).

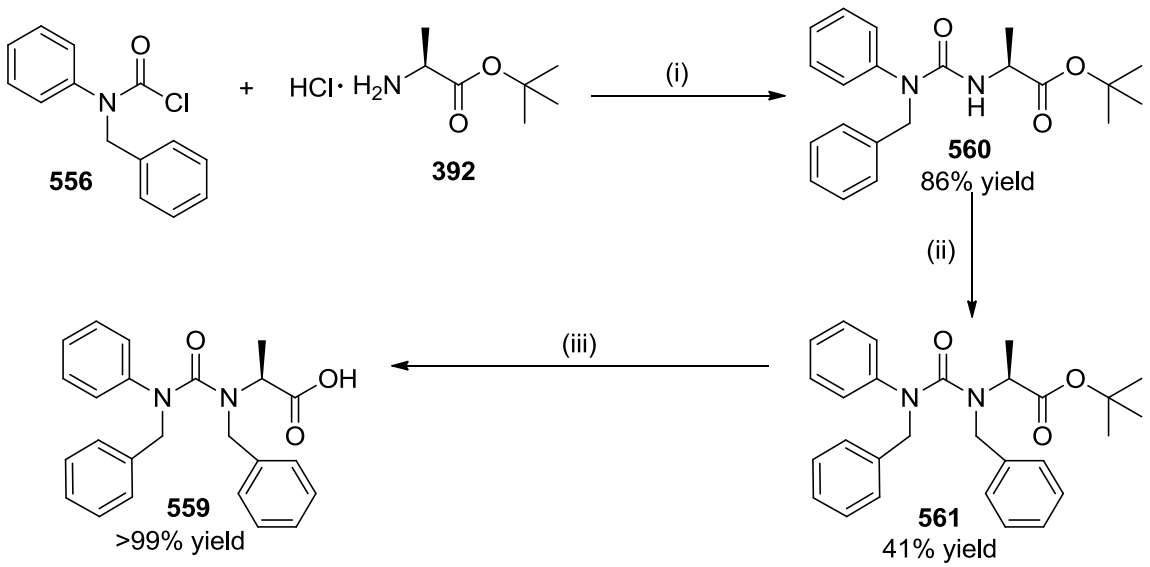



**Scheme 135: Reagents and conditions: (i) 2.3 eq. $Et_3N$, DMAP (cat), DCE, 70 °C, 2 d; (ii) 3.0 eq. BnBr, 2.0 eq. NaH, DMF, 0 °C – rt, o/n; (iii) 8.0 eq. KOH, 3:2 EtOH:$H_2O$, 70 °C, 1.5 h**[xv]

The overall yield for the three steps was a poor 8%, making this route unfeasible for the synthesis of the pseudoephedrine containing starting material. The bulky benzyl group meant the acylation reaction was lower yielding than with the *N*-methyl carbamoyl chloride and increased hindrance close to the NH led to a moderate yield for the benzylation step too. Additionally, a poor saponification yield resulted in an overall poor yield.

An alternative approach was taken using L-alanine *tert*-butyl ester (**392**), because *tert*-butyl groups can be easily removed using TFA (Scheme 136).

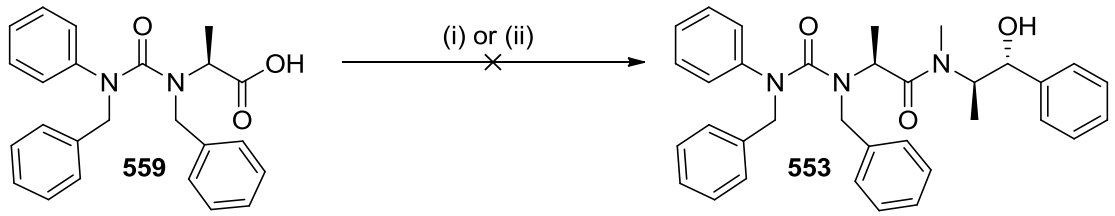
[xv] The stereochemistry is shown for the major enantiomer, partial racemisation of the alanine centre occurred during the synthesis




**Scheme 136: Reagents and conditions: (i) 2.3 eq. $Et_3N$, DMAP (cat), DCE, 70 °C, 20 h; (ii) 2.0 eq. BnBr, 2.0 eq. NaH, DMF, 0 °C – rt, 2 d; (iii) DCM, TFA, rt, 2.5 h**[xvi]

Firstly L-alanine *tert*-butyl ester HCl (**392**) was coupled to carbamoyl chloride **556**. Pleasingly, the monobenzylated urea **560** was obtained in a good yield of 86%, this may be due to *t*Bu esters being less volatile than ethyl esters. Urea **560** was benzylated, yielding the doubly benzylated product **561** in low yield of 41% after flash column chromatography. The final step was deprotection of the *tert*-butyl group using TFA in DCM. Pleasingly, this afforded carboxylic acid **559** in a quantitative yield without the need for further purification. Over three steps the acid **559** was obtained in a 35% yield with just one purification step.

The final step in the synthesis was to couple pseudoephedrine auxiliary (**ent-512**) to carboxylic acid **559** (Scheme 137). Activation of the carboxylic acid using conditions such as oxalyl chloride (Scheme 137 (i)) to generate an acid chloride, or pivaloyl chloride (Scheme 137 (ii)) to form a mixed anhydride were attempted.



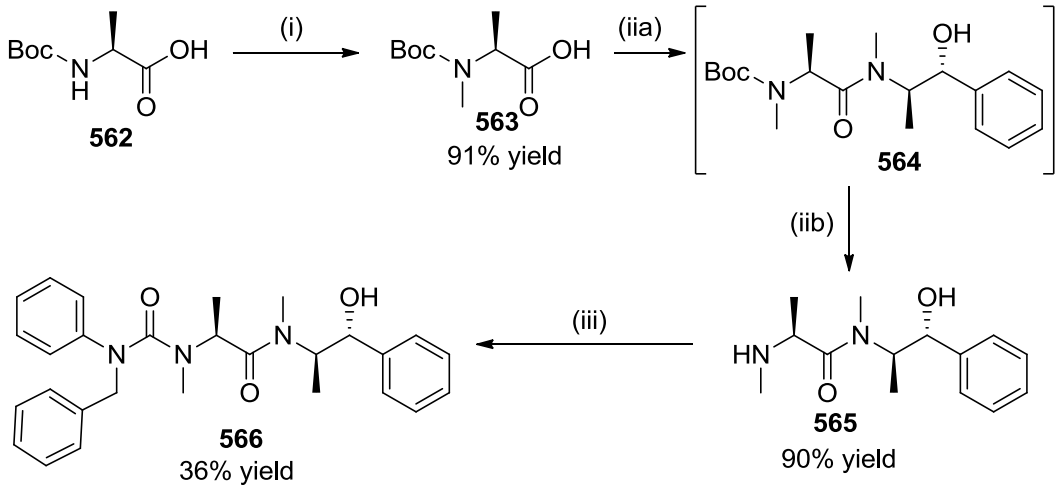

**Scheme 137: Reagents and conditions: (i) 5.0 eq. oxalyl chloride, 3.0 eq. $Et_3N$, 1.5 eq. (*R*,*R*)-pseudoephedrine (ent-512); (ii) 1.5 eq. PivCl, 2.5 eq. $Et_3N$, 1.0 eq. (*R*,*R*)-pseudoephedrine (ent-512)**

Both of these approaches were unsuccessful in generating the desired product. A proposed reason for this was that the activated species was too reactive and underwent a cyclisation reaction before

[xvi] The stereochemistry is shown for the major enantiomer, partial racemisation of the alanine centre occurred during the synthesis

it reacted with the pseudoephedrine. Alternatively, the steric bulk of the benzyl group on the nitrogen of the amino acid may be preventing a successful coupling.

A different route was explored that introduced the pseudoephedrine earlier in the synthesis and the urea functionality at the end. The benzylation of the urea NH was consistently poor yielding (41-57%) compared with the methylation used previously (>75%). To firstly establish if the rearrangement worked with a benzyl group present and if it could be removed, the system was simplified to containing one benzyl group **566** (Scheme 138).

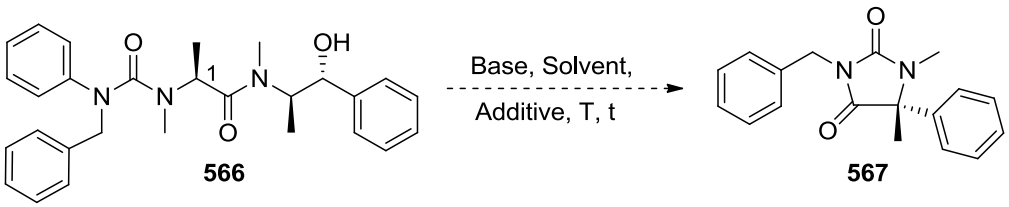



**Scheme 138: Reagents and conditions: (i) 10.0 eq. MeI, 10.0 eq. NaH, THF, o/n; (iia) 1.2 eq. $Et_3N$ (×2), 1.0 eq. PivCl, 1.0 eq. (*R*,*R*)-pseudoephedrine (ent-512), DCM, 2.5 h; (iib) TFA, DCM, 1.5 h, rt; (iii) 1.0 eq. *N*-benzyl-*N*-phenyl carbamoyl chloride (556), DMAP (cat), DCE, rt, o/n**

*N*-Methylation of Boc-L-alanine (**562**) was achieved following a procedure used by Malkov *et al.*[212] forming *N*-Boc-*N*-methyl protected alanine **563** without the need for further purification in 91% yield. This was subjected to conditions similar to those reported by Myers[206] to introduce the pseudoephedrine (**ent-512**) and removal of the Boc group was achieved using TFA. Methylated amine **565** was obtained in an excellent 90% yield over two steps. Introduction of the benzyl group was achieved through acylation with carbamoyl chloride **556** to obtain **566** in a 36% yield. The low yield was due to two purifications, one by flash column chromatography and one by recrystallisation. However, this route led to the desired product in three steps with an overall yield of 29%.

*N*-Methylated-*N*-benzylated starting material **566** was then subjected to various rearrangement conditions (Table 20).

**Table 20: Rearrangement conditions investigated for benzylated starting material 566**




**566** **567**

| Entry | Base | Eq. Base | Conc (M) | Additive | T (°C)[a] | t (h) | 567 (%) |
|---|---|---|---|---|---|---|---|
| 1 | *s*BuLi | 3.0 | 0.1 | - | –78 to –60 to –40 | o/n | 0[b] |
| 2 | *s*BuLi | 3.0 | 0.1 | LiCl | –78 to –60 to rt | o/n | 0[b] |
| 3[c] | *s*BuLi | 3.0 | 0.1 | DMPU (1 h 10) | –40 to rt | o/n | 0 |
| 4 | *n*BuLi | 3.0 | 0.1 | DMPU (2 h 30) | –78 to rt | o/n | 0[b] |
| 5 | LDA | 3.0 | 0.1 | - | –78 to –40 | o/n | 0[b] |
| 6 | LDA[d] | 2.0 | 0.1 | - | –78 to 0 to rt | 2.0 | 0 |

THF (except entry 4), all reactions were quenched with MeOH at –78 °C. [a]Last temperature given is the temperature the time column relates to. [b]Reverse phase HPLC analysis showed an additional peak: Column: Kinetex 2.6 μm XB-C18, Pore diameter (Å): 82-102, solvent system 20:80 $H_2O$:MeOH, λ = 220 nm and 254 nm, flow 1 ml/min, retention times: 1.7 min (SM) and 2.4 min. [c]Reaction in toluene.[d]Same outcome with LiCl.

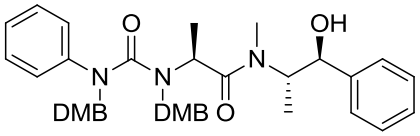
When 3 eq. of base were used in THF, the desired rearrangement reaction did not occur (entries 1-2 and 4-5, Table 20). This was clear because the quartet for the proton on C1 of **566** was still present in the $^1$H NMR spectrum. However, there was a shift for some of the aromatic protons in the $^1$H NMR spectrum suggesting that an alternative reaction was occurring. HPLC analysis showed the starting material and an additional unidentified major signal. To assess if 3 eq. of base were promoting an alternative reaction over the rearrangement just 2 eq. of base was used (entry 6, Table 20). In this case, just starting material was found suggesting that 2 eq. were insufficient for any reaction to occur. A change in solvent to toluene (entry 3, Table 20) or the addition of additives such as DMPU (entries 3-4, Table 20) or LiCl (entry 2, Table 20) led to no improvement.

A proposed reason for the failure was due to the benzyl protecting group leading to complications. The base could be deprotonating the benzylic position of the protecting group rather than the desired position, leading to an alternative migration site. This would explain why the quartet for the proton on C1 of **566** remained and why some of the aromatic protons appeared to be in an alternative environment in the crude $^1$H NMR. Considering the difficulties in synthesising this starting material and the complications introduced by the benzyl group when the rearrangement was attempted an alternative protecting group was considered.

### 2.4.4.2 Initial *N*-DMB Protected Ureas

The next protecting group investigated was DMB, as it is more electron rich than benzyl making the benzylic positions less susceptible to deprotonation. In addition DMB should be easier to

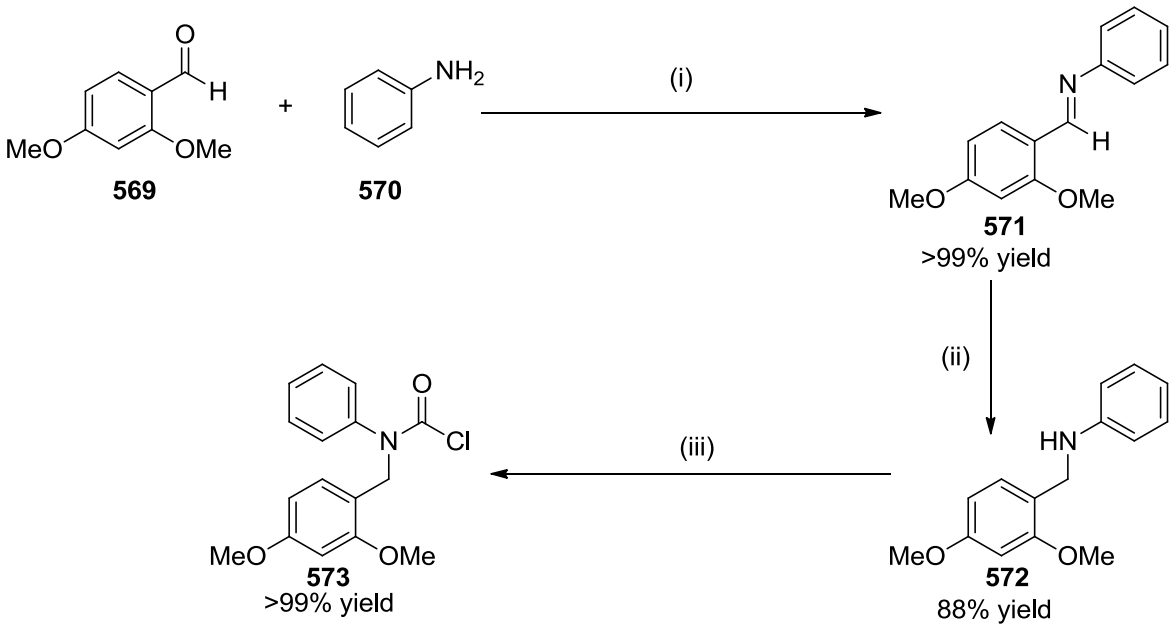
deprotect than a benzyl group, as it can be oxidatively cleaved using either CAN or DDQ. The target starting material **568** is shown in Figure 39




**568**

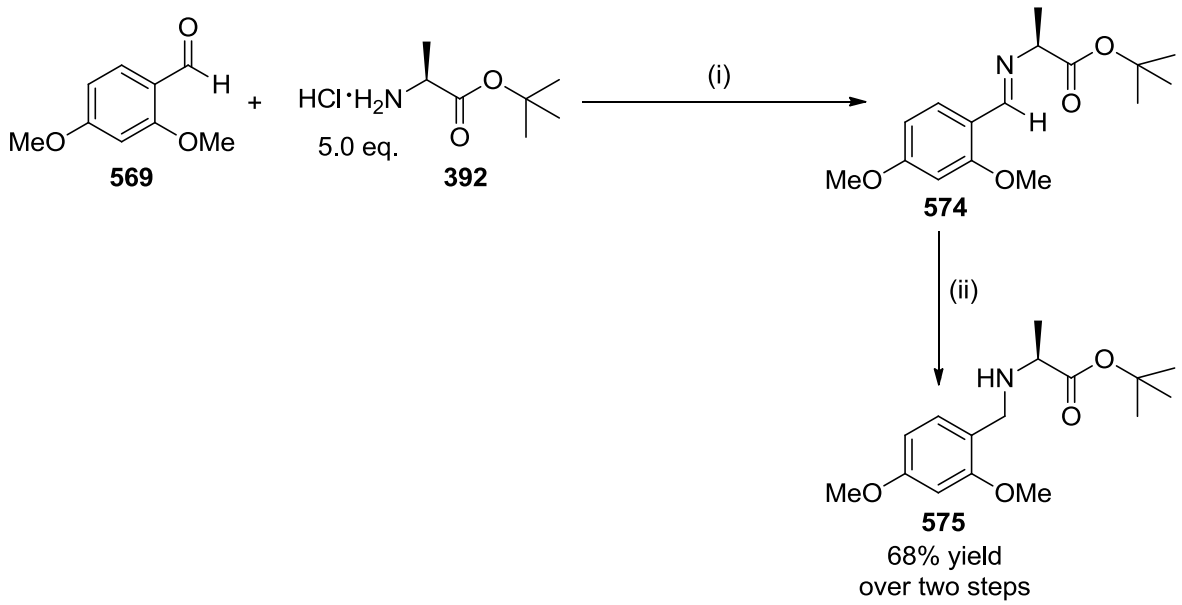
**Figure 39: Target starting material containing DMB protecting groups**

Firstly, carbamoyl chloride **573** containing a DMB group was synthesised (Scheme 139). Imine **571** was generated in a quantitative yield through a reaction of aniline (**570**) and 2,4-dimethoxybenzaldehyde (**569**). Reduction using sodium borohydride in a 1:1 DCM:EtOH mixture generated secondary amine **572** in an 88% yield. Finally, carbamoyl chloride **573** was formed by reaction of amine **572** with triphosgene in the presence of pyridine. The desired product was isolated after two days in a quantitative yield.



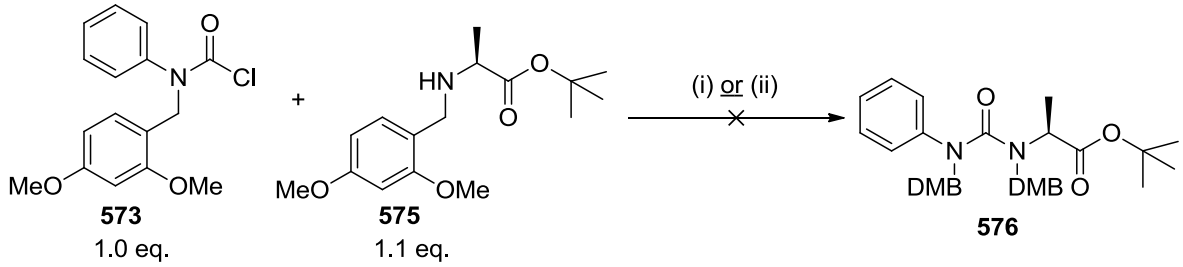

**Scheme 139: Reagents and conditions: (i) toluene, Dean-Stark, 160 °C, 20 h; (ii) 1.6 eq. $NaBH_4$, 1:1 DCM:EtOH, 0 °C – rt, 20 h; (iii) 1.0 eq. triphosgene, 2.2 eq. pyridine, DCM, −78 °C – rt, 2 d**

Secondly, DMB protected secondary amine **575** was synthesised by a reductive amination (Scheme 140). Imine **574** was generated through a reaction of L-alanine *tert*-butyl ester hydrochloride (**392**) and 2,4-dimethoxybenzaldehyde (**569**). Imine **574** was reduced with sodium borohydride to generate secondary amine **575** in a moderate 68% yield over the two steps.




**Scheme 140: Reagents and conditions: (i) 5.0 eq. $Et_3N$, DCM, MS (4 Å), rt, 20 h; (ii) 1.6 eq. $NaBH_4$, 1:1 DCM:EtOH, 0 °C – rt, 20 h**

To form DMB protected urea (**576**) it was necessary to couple secondary amine **575** and DMB carbamoyl chloride **573** (Scheme 141). The standard acylation conditions of heating at reflux in DCE with $Et_3N$ and DMAP were unsuccessful, as were variations on these conditions, including using sodium hydride in DMF.

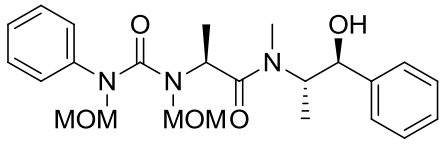



**Scheme 141: Reagents and conditions: (i) $Et_3N$, DCE, DMAP, reflux, 20 h, 3 d or (ii) NaH, DMF, rt, 20 h**

Therefore it seems the two components **573** and **575** are too sterically demanding to allow them to react with one another.

### 2.4.4.3 *N*-MOM Protected Ureas

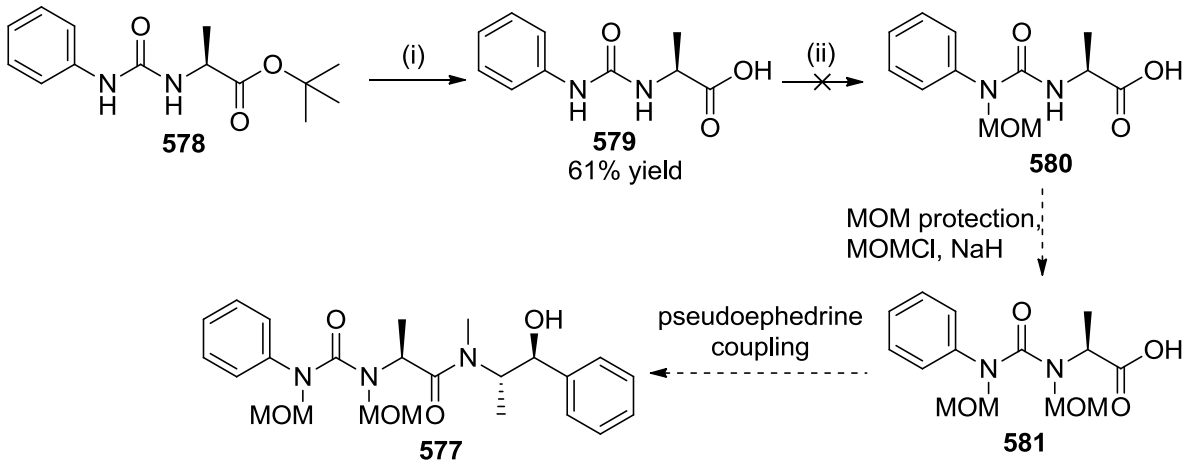
The next protecting group considered was MOM, which is base stable and removable under acidic conditions. MOM is sterically less demanding compared with the benzylic protecting groups and avoids an alternative deprotonation site. Kawabata *et al*. used MOM protecting groups in their rearrangement with chiral memory work,[198] although they provided no evidence that the MOM groups could be removed. The target starting material **577** contained both nitrogen atoms protected by MOM groups (Figure 40).




**577**

**Figure 40: Target MOM protected starting material**

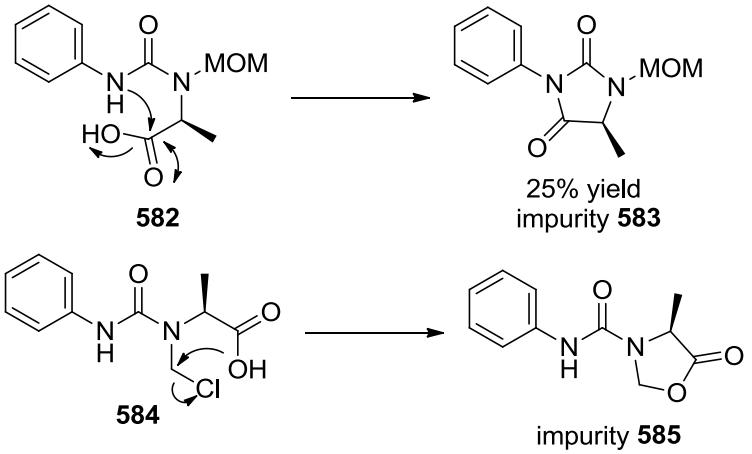
The proposed route for the synthesis of **577** is shown in Scheme 142. The first step was removal of the *tert*-butyl group from Boc-protected urea **578**. This was achieved using TFA in DCM and product **579** was obtained in 61% yield without the need for further purification. The first MOM protection was attempted following a procedure used by Kawabata *et al*.,[198, 213] TMSCl was added to a mixture of urea carboxylic acid **579** in DCM with paraformaldehyde and stirred before quenching with MeOH to generate the MOM group. The second MOM protection was then to be carried out using MOMCl and NaH (**581**) before coupling the pseudoephedrine to give **577**.




**578** **579** 61% yield **580** **581** **577**

**Scheme 142: Reagents and conditions: (i) TFA, DCM, 2 h, rt; (ii) 6.0 eq. paraformaldehyde, 6.0 eq. TMSCl, DCM, 0 °C-rt, 4.5 h, MeOH, 0.5 h**

The mono-MOM protected urea **580** expected was not isolated and instead hydantoin **583** was isolated in 25% yield (Scheme 143). This was formed through MOM protection occurring on the amino acid nitrogen followed by cyclisation of the free nitrogen onto the carbonyl group under the reaction conditions. Additional signals in the crude $^{1}$H NMR also suggested formation of a second impurity **585**. If the protection happened on the amino acid nitrogen then prior to quenching with MeOH it is possible for the hydroxyl group of the carboxylic acid to react to form impurity **585** (Scheme 143).



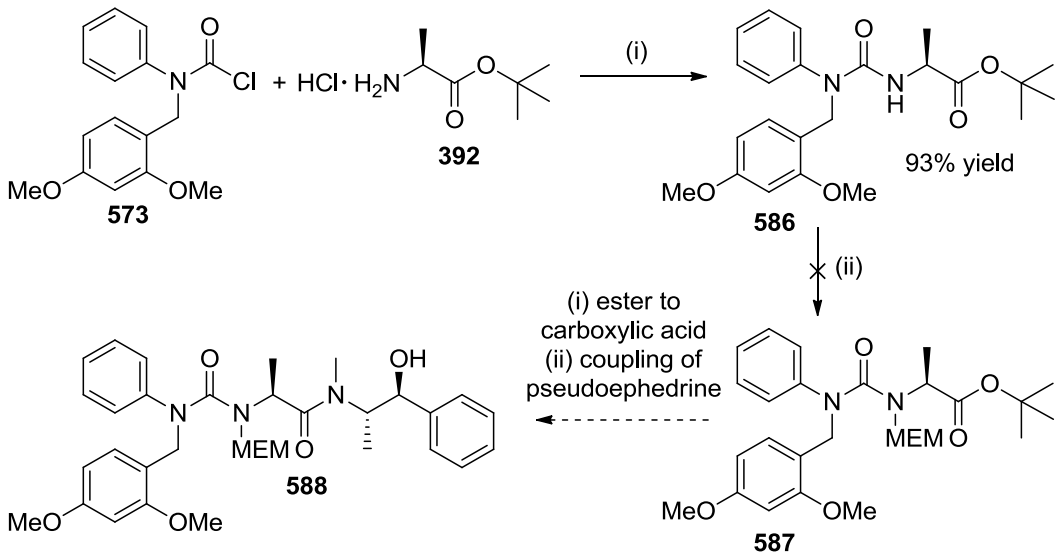

**Scheme 143: Hydantoin generated in MOM protection and proposed impurity formation**

Considering the problems with unwanted reactions occurring early on in this route it was deemed unviable to reach the doubly MOM protected starting material **577** and therefore an alternative strategy was needed.

### 2.4.4.4 *N*-MEM and *N*-DMB Protected Ureas

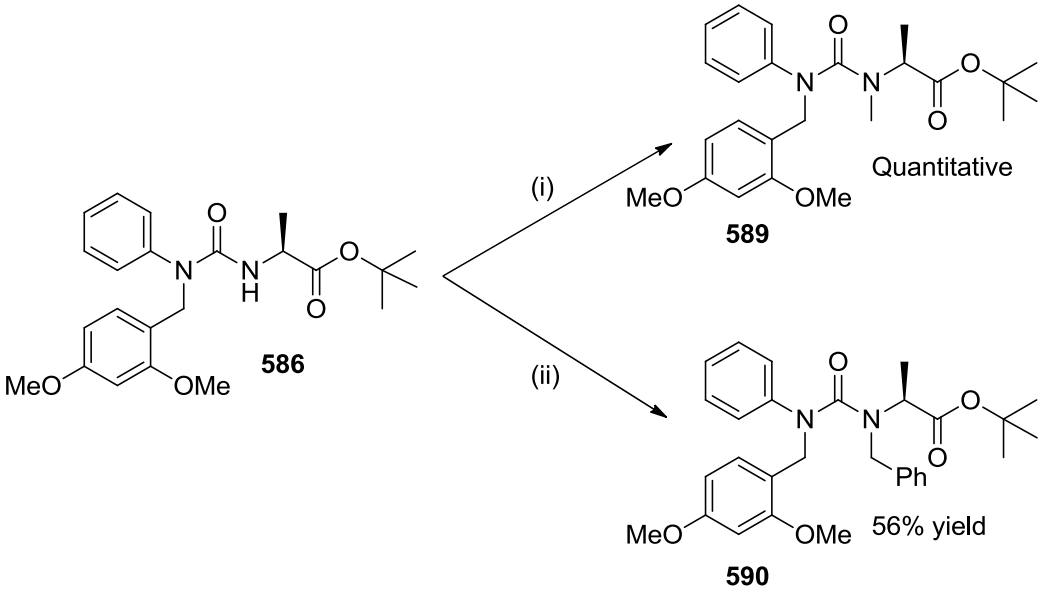
The alternative strategy was to use a benzylic protecting group in combination with a removable protecting group that could be introduced by alkylation. It has been established that the benzylic protecting group can be easily introduced through use of a carbamoyl chloride to protect the nitrogen containing the migrating ring. With one nitrogen atom pre-protected this should avoid problems with free nitrogen atoms carrying out alternative reactions during the second protection step. DMB was chosen as the benzylic protecting group due to increased electron density at the benzylic position, in combination with a MEM protecting group that can be removed under acid conditions and is introduced using a less toxic reagent, MEMCl compared with MOMCl.

The proposed synthesis route is shown in Scheme 144, acylation of L-alanine *tert*-butyl ester hydrochloride (**392**) with DMB carbamoyl chloride **573** gave urea **586** in an excellent yield of 93%. The alkylation of the second nitrogen using MEMCl was attempted. Sadly, using different bases such as NaH, $Et_3N$ and KHMDS and different solvents such as THF and DMF the protection of **586** was unsuccessful.




**Scheme 144: Reagents and conditions: (i) 2.3 eq. $Et_3N$, DMAP, DCE, 70 °C, 20 h**

To investigate if the MEM group was causing the problem, urea **586** was subjected to methylation and benzylation conditions. Methylation occurred in a quantitative yield and benzylation in 56% yield. (Scheme 145). These results suggested the amide NH can be deprotonated using sodium hydride, but as the steric bulk of the electrophile increases the yield decreases.




**Scheme 145: Reagents and conditions: (i) DMF, 0 °C, 2.0 eq. NaH, 30 min, 3.0 eq. MeI, 1 h;[xvii] (ii) DMF, 0 °C, 2.0 eq. NaH, 30 min, 3.0 eq. BnBr, 20 h[xvii]**

In conclusion, *N*-benzyl protection was problematic due to suspected benzylic deprotonation of the protecting group providing an alternative migration site to the desired one. The starting material

[xvii] The major enantiomer is shown for clarity but under the reaction conditions partial racemisation occurs

containing a MOM group was unable to be synthesised due to the conditions required for its protection leading to a complex mixture of other reactions taking place. Methoxybenzyl groups showed potential as a protecting group as their removal conditions are desirable, but two DMB groups proved too sterically demanding meaning the starting material could not be synthesised. However, the strategy of using groups like DMB in combination with another protecting group seemed promising.

### 2.4.5 *N*-PMB Protected Ureas

Having removable protecting groups on both nitrogen atoms would lead to *N*,*N*'-unsubstituted hydantoins that are known to hydrolyse easily.[31] This was proving difficult and given that the literature[199-201] suggests and it was shown in Chapter 2.3.2.2 that with one free NH the hydantoin can be hydrolysed, use of a removable protecting group on just the nitrogen atom that would end up in the quaternary amino acid was considered.

The literature suggests that PMB protecting groups can be removed oxidatively using reagents such as CAN.[214,215] PMB is more electron rich than benzyl, but is sterically less demanding than DMB. If the PMB protecting group is on the nitrogen that is present in the final amino acid product, the other urea nitrogen can be protected with a methyl group as this will be lost as part of the hydantoin hydrolysis reaction. The target starting material **591** is shown below (Figure 41).

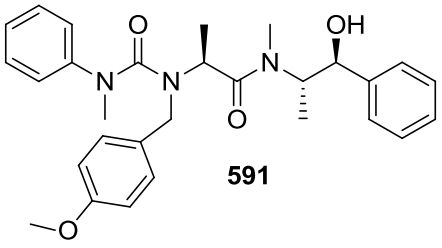
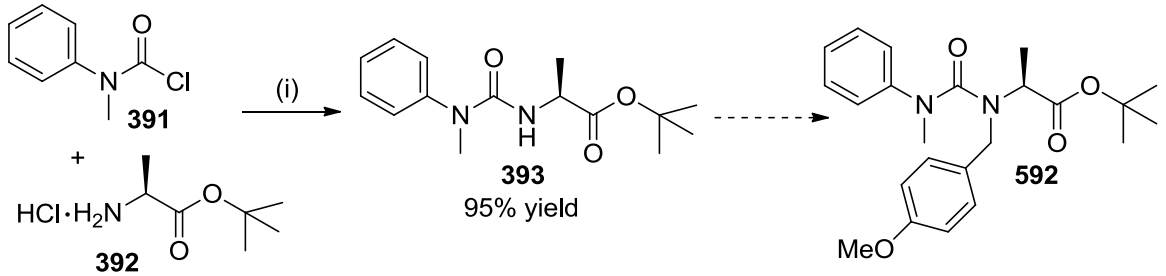



**Figure 41: The target starting material containing PMB**

Firstly, *N*-methyl-*N*-phenyl carbamoyl chloride (**391**) was coupled with L-alanine *tert*-butyl ester hydrochloride (**392**) to generate urea **393** in a 95% yield (Scheme 146) (Chapter 2.3, Scheme 80).

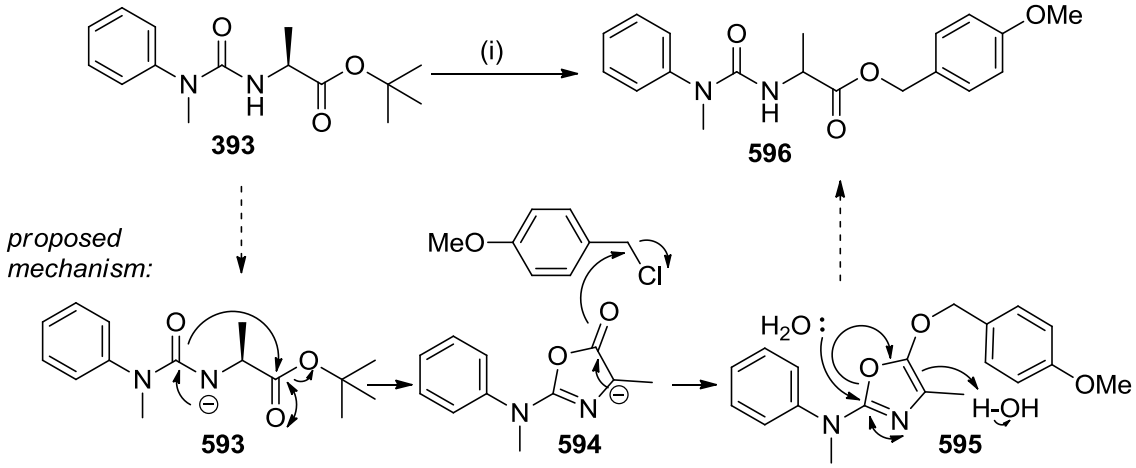



**Scheme 146: Reagents and conditions: (i) 2.3 eq. $Et_3N$, DMAP, DCE, 70 °C, 20 h**

**Table 21: Conditions for PMB alkylation**

| Entry | Conditions | Yield 592 (%) |
|---|---|---|
| 1 | DMF, 0 °C, 2.0 eq. DBU, 1.5 eq. PMBCl, 3 h, 0 °C – rt 20 h | 0 |
| 2 | DMF, 1.0 eq. $K_2CO_3$, 1.2 eq. PMBCl, 60 °C, 20 h | 0 |
| 3 | DMF, 0 °C, 1.5 eq. NaH, 1.5 eq. PMBCl, rt, 20 h | 0 |
| 4 | DMF, 0 °C, 3.0 eq. NaH, 30 min, 3.0 eq. PMBCl, NaI (cat), rt, 20 h | 0 |

The second step was introduction of the PMB group by alkylation. The conditions investigated are shown in Table 21. Unfortunately under all these conditions the desired product **592** was not formed (entry 1-4, Table 21). Interestingly, when using sodium hydride as a base this returned starting material in addition to PMB ester **596** (Scheme 147) (entry 3, Table 21). This suggested that the high reactivity of the deprotonated nitrogen seen previously when methyl iodide was used as an electrophile was not replicated with PMBCl. A proposed mechanism for the formation of product **596** is shown in Scheme 147. Instead of the deprotonated nitrogen atom reacting directly with the electrophile an internal cyclisation reaction of the deprotonated starting material could occur followed by a second deprotonation and reaction with the PMBCl through the oxygen of cyclic intermediate **594**, followed by hydrolysis upon workup to give **596**.

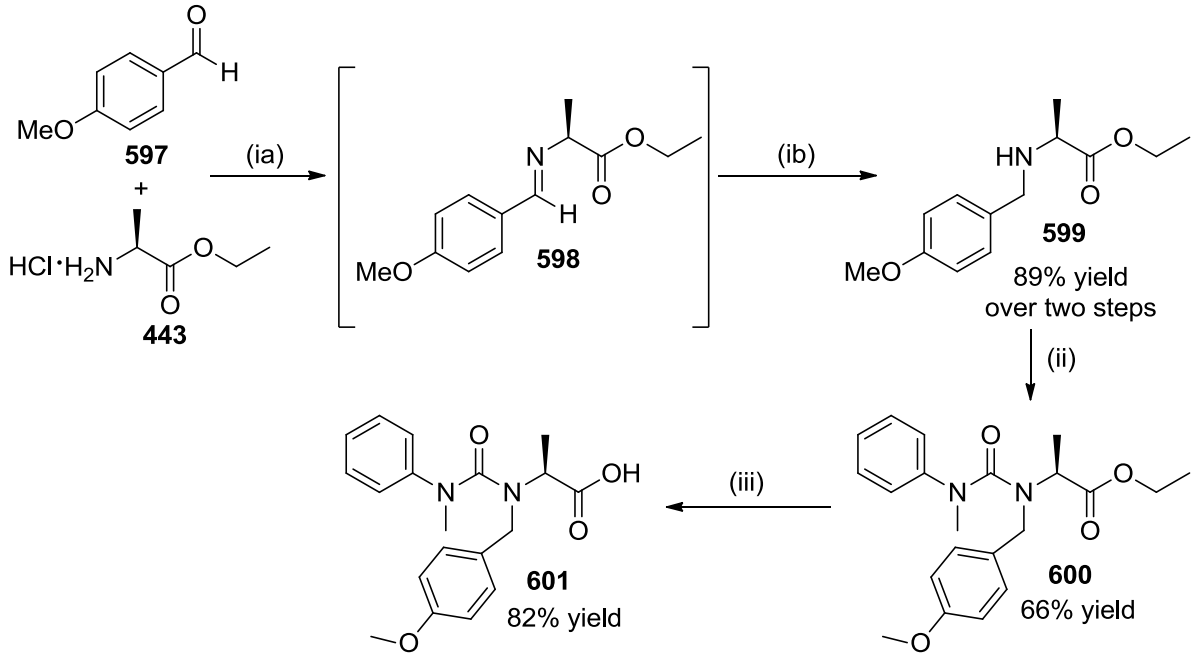



**Scheme 147: Reagents and conditions: (i) 1.5 eq. NaH, 1.5 eq. PMBCl, DMF, 0 °C – rt, 20 h**

Based on all the problems observed previously and the knowledge gained, an alternative approach for the introduction of the PMB group was used. Rather than alkylation, the PMB was introduced by reductive amination as this had been successful for introducing DMB. To avoid potential issues with the PMB also being removed during the acidic removal of the *tert*-butyl ester to obtain the free acid, the ethyl amino ester was used that could be removed under basic conditions.

Firstly, PMB secondary amine **599** was synthesised by a reductive amination (Scheme 148). Imine **598** was generated through reaction of L-alanine ethyl ester hydrochloride (**443**) and *p*-

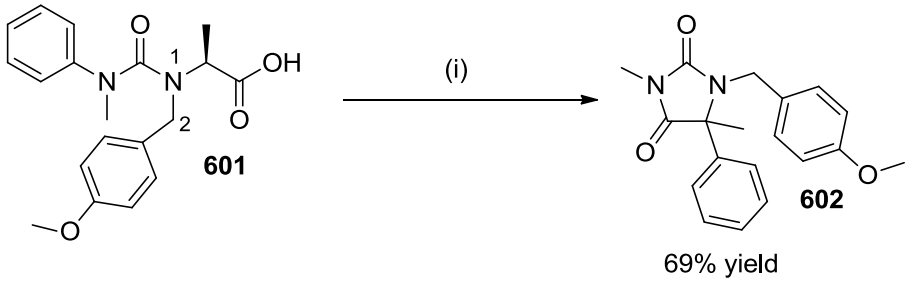
anisaldehyde (**597**). Imine **598** was used directly in the reduction and this generated secondary amine **599** in 89% yield over two steps. PMB secondary amine **599** was then acylated with *N*-methyl-*N*-phenyl carbamoyl chloride (**391**) and urea product **600** was isolated in 66% yield. The free carboxylic acid was formed through saponification of the ethyl ester using LiOH in THF and water forming carboxylic acid **601** in 82% yield.




**Scheme 148: Reagents and conditions: (ia) 1.8 eq. $Et_3N$, DCM, MS (4 Å), rt, 20 h; (ib) 1.6 eq. $NaBH_4$, 1:1 DCM:EtOH, 0 °C – rt, 23 h; (ii) 1.0 eq. *N*-methyl-*N*-phenyl carbamoyl chloride (391), DMAP (cat), 1.3 eq. $Et_3N$, DCE, 70 °C, 20 h; (iii) 50.0 eq. LiOH, 2:1 THF:$H_2O$, 45 °C, 20 h**

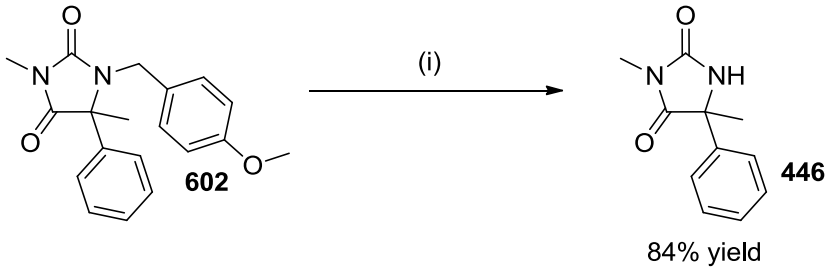
### 2.4.5.1 Rearrangement of *N*-PMB Protected Ureas

Before coupling pseudoephedrine to PMB carboxylic acid **601**, a rearrangement was attempted from the carboxylic acid to ensure deprotonation at the benzylic position of the PMB would not be problematic before continuing. PMB carboxylic acid **601** was subjected to the optimised conditions for the dianionic rearrangement. Using 3 eq. of LDA and 3 eq. of LiCl the rearrangement proceeded to hydantoin **602** in a yield of 69% (Scheme 149). Importantly, the migration occurred solely at the α-carbon with no unwanted migration to the benzylic position observed.




**Scheme 149: Reagents and conditions: (i) 3.0 eq. LDA, 3.0 eq. LiCl, THF, −78 °C to rt, 3 h**

The PMB group can also be removed from hydantoin product **602** using CAN, generating unprotected hydantoin **446** in 84% yield (Scheme 150). Hydantoin **446** was shown to hydrolyse into a quaternary amino acid in chapter 2.3.2.2 (Scheme 115).[xviii]



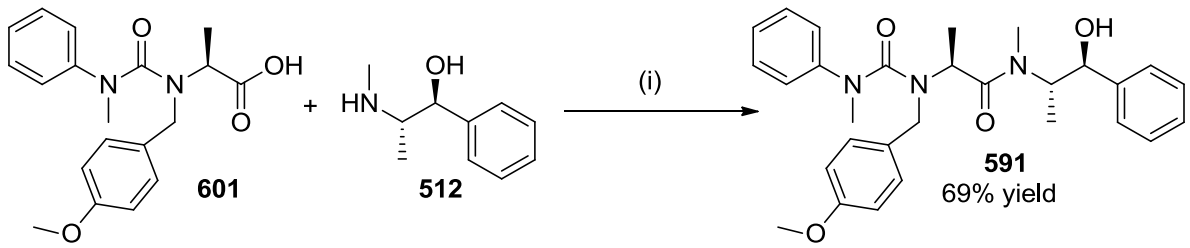

**Scheme 150: Reagents and conditions: (i) 4.0 eq. CAN, $H_2O$, MeCN, 0 °C, 1 h**[xviii]

Before the selective reaction was attempted, HPLC conditions were optimised to separate the two enantiomers of product **602** (Scheme 149). Surprisingly, product **602** was not racemic, but had an *er* of 77:23, showing two non-equivalent peaks on both the OD-H and AD-H chiral columns and an $[\alpha]_D^{21}$ was observed. The reaction was repeated with similar conditions but using *s*BuLi instead of LDA and an *er* of 63:37 was obtained. Repetition of the reaction using the LDA conditions on another occasion showed an *er* of 50:50, suggesting the reaction *er* is capricious. However, these results suggested that chiral memory could be playing a role under certain conditions with the PMB group inducing the memory in a given conformation leading to an axially chiral enolate due to restricted rotation about the C-N bond (N(1)-C(2) in **601**) or through a transient deprotonation. [53,198] This was outside the scope of this project but may be investigated in the future.

### 2.4.5.2 Enantioselective Reaction of *N*-PMB Protected Ureas

The (*S*,*S*)-pseudoephedrine (**512**) was coupled to PMB carboxylic acid **601** using the EDC, HOBt·$H_2O$ and DiPEA coupling conditions forming starting material **591** in a 69% yield (Scheme 151).

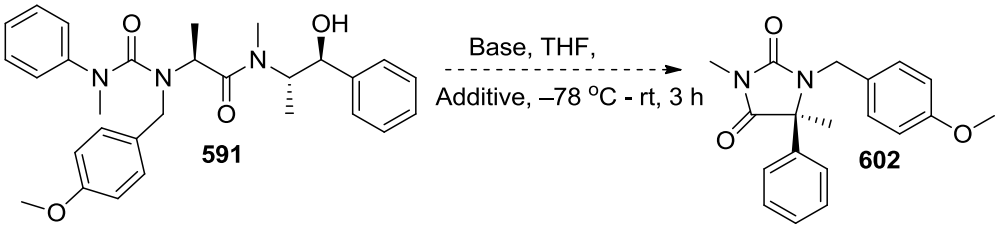
[xviii] With thanks to Dr Julien Maury for carrying out the CAN deprotection




**Scheme 151: Reagents and conditions: (i) 1.5 eq. (*S*,*S*)-pseudoephedrine (512), 1.2 eq. EDC, 1.0 eq. HOBt·$H_2O$, 1.2 eq. DiPEA, DCM, rt, 18 h**

Different rearrangement conditions were applied to determine whether the rearrangement took place and if any control in selectivity was observed (Table 22).

**Table 22: Rearrangement conditions investigated for PMB starting material 591**



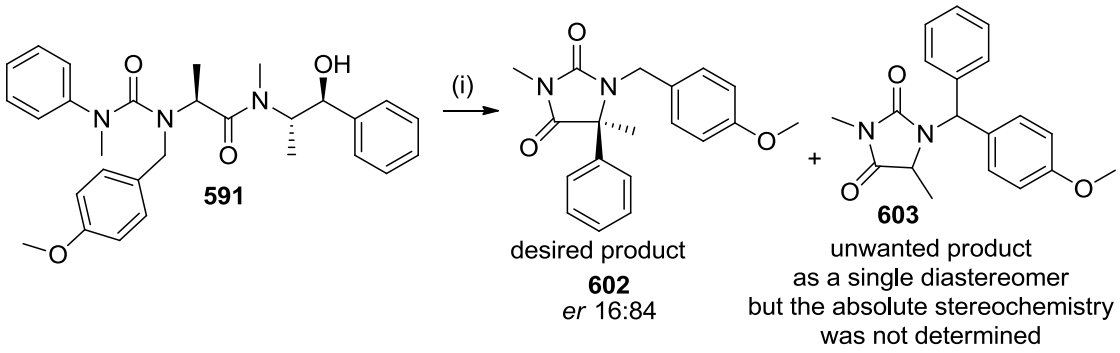

| Entry | Base | Eq. Base | Additive (eq.) | *er* of 602[a] |
|---|---|---|---|---|
| 1 | *s*BuLi | 3.0 | - | 33:67 |
| 2[b] | *s*BuLi | 3.0 | LiCl (3.0) | - |
| 3 | *n*BuLi | 3.0 | - | 34:66 |
| 4[c] | *n*BuLi | 3.0 | LiCl (8.0) | - |
| 5 | LDA | 3.0 | - | 22:78 |
| 6 | LDA | 4.5 | LiCl (11.0) | 23:77 |
| 7 | LDA | 3.0 | LiCl (8.5) | 16:84 |

THF, –78 °C – rt (except entry 2), 3 h. [a]Determined by HPLC analysis: Chiral OD-H, Hexane:IPA = 85:15, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 11.4, 14.4 min. [b] –78 °C – 0 °C.

Various reaction conditions were explored, with different bases and additives and gratifyingly the rearrangement worked. However, a side product was present under all the reaction conditions with the amount formed depending on the conditions used. Although side product **603** was inseparable from desired product **602** the *er* could still be determined by HPLC analysis of the mixture. The results in Table 22 show that using *s*BuLi and *n*BuLi as bases (entries 1 and 3, Table 22) a moderate *er* of ~34:66 is found, but in both these cases a significant amount of side product was obtained. When the reaction was carried out at 0 °C (entry 2, Table 22) only the starting material was recovered. A combination of *n*BuLi and LiCl (entry 4, Table 22) led to a mixture of starting material and product and the *er* could not be determined. The amount of side product was lowered when LDA was used, and an improvement in *er* for hydantoin **602** was seen using either 3 eq. or an

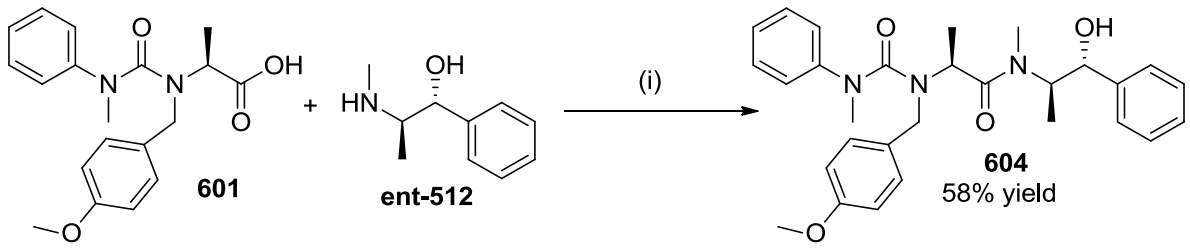
excess of 4.5 eq. (entries 5,6, Table 22). Finally, 3 eq. of LDA in combination with an excess of LiCl gave the best *er* for this reaction of 16:84 (entry 7, Table 22). Disappointingly under all these conditions the inseparable impurity was present and the best *er* was lower than in the doubly methylated case.

The side product was identified as the unwanted migration product **603**, in which the aromatic ring had migrated to the benzylic position of the PMB rather than the α-carbon (Scheme 152). This was not observed in the racemic case, but for the amide **591** that contains pseudoephedrine the α-position could be more sterically hindered making it more favourable to deprotonate at the benzylic position than it was in the case of the carboxylic acid **601**.




**Scheme 152: Reagents and conditions: (i) 3.0 eq. LDA, 8.5 eq. LiCl, THF, –78 °C – rt, 3 h**

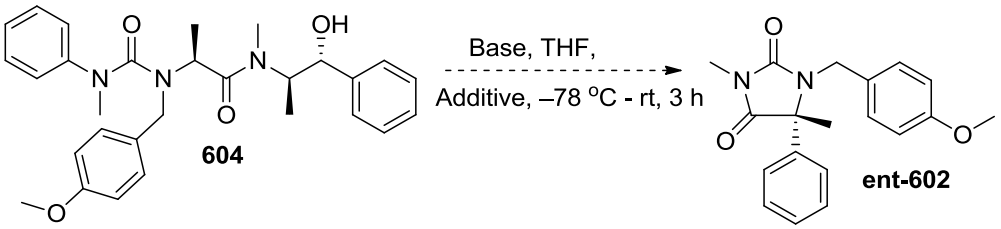
There is potential that the PMB group is inducing chiral memory control in this reaction, if this control was opposite to the control induced by the pseudoephedrine auxiliary this could explain the highest *er* being only 16:84. Secondly, Myers suggests that there is potential for stereospecific enolisation, implying the deprotonation step to form the enolate could also affect the selectivity. Myers showed (*R*) and (*S*)-amino acids with (*S*,*S*)-pseudoephedrine reacted *via* the same enolate to give the same diastereomeric product. However, the yield and *dr* was better for the (*R*)-amino acids with (*S*,*S*)-pseudoephedrine (matched case) and (*S*)-amino acids with (*S*,*S*)-pseudoephedrine gave lower yield and *dr* (mis-matched case) (Figure 37).[210] To investigate this proposal, (*R*,*R*)-pseudoephedrine (**ent-512**) was coupled to (*S*)-PMB carboxylic acid **601** creating a 'matched case' and forming **604** in a 58% yield (Scheme 153).




**Scheme 153: Reagents and conditions: 1.5 eq. (*R*,*R*)-pseudoephedrine (ent-512), 1.2 eq. EDC, 1.0 eq. HOBt·$H_2O$, 1.2 eq. DiPEA, DCM, rt, 18 h**

Similar rearrangement conditions were applied to (*R*,*R*) starting material **604** and again the product **ent-602** was observed along with side product **ent-603** in all cases (Table 23).

**Table 23: Rearrangement conditions investigated for (*R*,*R*) PMB starting material 604**




| Entry | Base | Eq. Base | Additive (eq.) | *er* of ent-602[a] |
|---|---|---|---|---|
| 1 | LDA | 3.0 | LiCl (12.0) | 74:26 |
| 2[b] | LDA | 3.0 | LiCl (16.0) | 74:26 |
| 3 | LDA | 4.5 | LiCl (10.5) | 92:8 |

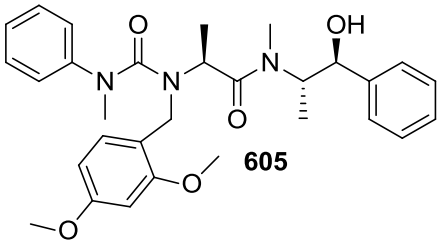
THF, −78 °C – rt, 3 h (except entry 2). [a]Determined by HPLC analysis. [b] At rt overnight.

Using the standard conditions of 3 eq. of LDA with an excess of LiCl and leaving the reaction for 3 h or overnight (entries 1, 2, Table 23) the *er* for the hydantoin **ent-602** was the same as previously observed, but the opposite enantiomer was formed as expected. However, when the reaction was carried out with an excess of LDA the *er* of **ent-602** increased to 92:8 (entry 3, Table 23). This *er* was the best observed for reactions with PMB and pseudoephedrine and it suggested the 'mis-matched' effect did have a role in this reaction and therefore needed to be kept in mind for future optimisation of the rearrangement. Unfortunately, despite this good *er* the desired product **ent-602** was accompanied by a large amount of impurity **ent-603** (1:1 **ent-602**: **ent-603**).

In conclusion, despite changing the reaction conditions the problem of migration to the benzylic position of the PMB could not be overcome and the search continued for a protecting group compatible with this reaction.

### 2.4.6 *N*-DMB Protected Ureas

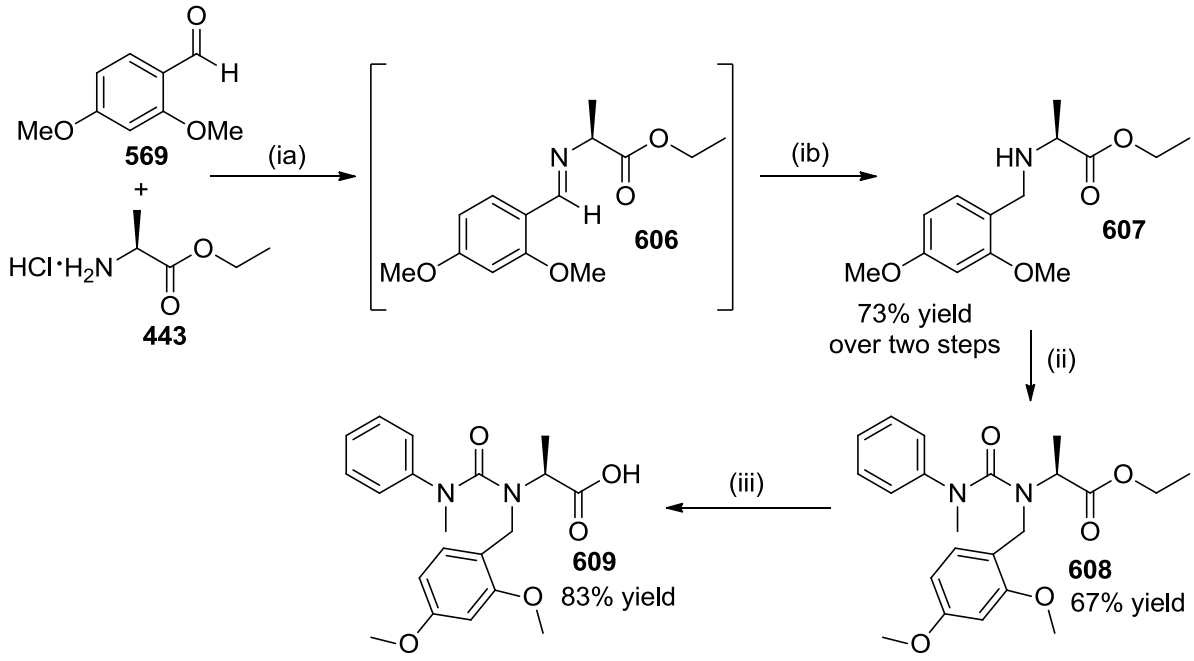
Since the DMB protecting group was similar to PMB but was more electron rich and bulkier it was less likely to undergo benzylic deprotonation. The only disadvantage observed from the earlier work (Chapter 2.4.4.2) was its steric bulk in relation to synthesising the starting material but in combination with a small *N*-methyl protecting group this could potentially be overcome. The target starting material **605** is shown below (Figure 42).




**605**

**Figure 42: The target starting material containing DMB**

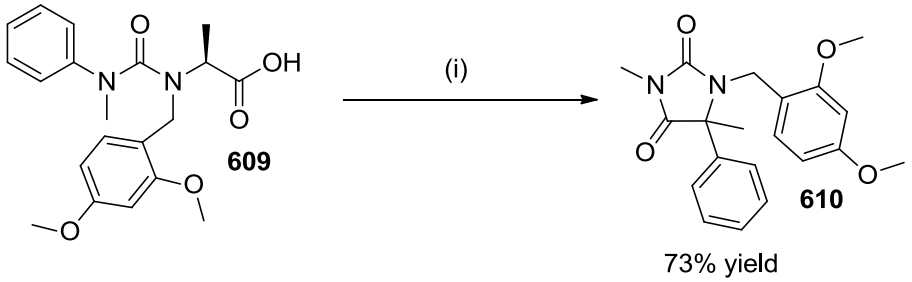
DMB starting material **605** was synthesised according to the same procedure as the PMB target **591.** Imine **606** was generated through reaction of L-alanine ethyl ester hydrochloride (**443**) and 2,4-dimethoxybenzaldehyde (**569**). The imine **606** was used directly in the reduction using sodium borohydride generating secondary amine **607** in 73% yield over two steps. DMB secondary amine **607** was acylated with *N*-methyl-*N*-phenyl carbamoyl chloride (**391**) and urea product **608** was isolated in 67% yield. Carboxylic acid **609** was formed through saponification of ethyl ester **608** using LiOH in THF and water. Carboxylic acid **609** was obtained in 83% yield to which the pseudoephedrine chiral auxiliary could now be coupled (Scheme 154).




**Scheme 154: Reagents and conditions: (ia) 1.8 eq. $Et_3N$, DCM, MS (4 Å), rt, 25 h; (ib) 1.6 eq. $NaBH_4$, 1:1 DCM:EtOH, 0 °C – rt, 18 h; (ii) 1.0 eq. *N*-methyl-*N*-phenyl carbamoyl chloride (391), DMAP (cat), 1.3 eq. $Et_3N$, DCE, 70 °C, 23 h; (iii) 50.0 eq. LiOH, 2:1 THF:$H_2O$, 45 °C, 22 h**

### 2.4.6.1 Rearrangement of *N*-DMB Protected Ureas

Before coupling pseudoephedrine to DMB carboxylic acid **609**, the rearrangement was attempted from the carboxylic acid to check if competitive deprotonation at the benzylic position of the DMB was problematic before continuing. DMB carboxylic acid **609** was subjected to the optimised conditions for the dianionic rearrangement. Using 3 eq. of LDA and 3 eq. of LiCl the rearrangement proceeded in a good yield of 73% giving **610** (Scheme 155). As with the PMB protected species **601**, the migration occurred solely at the α-carbon with no unwanted migration to the benzylic position observed.



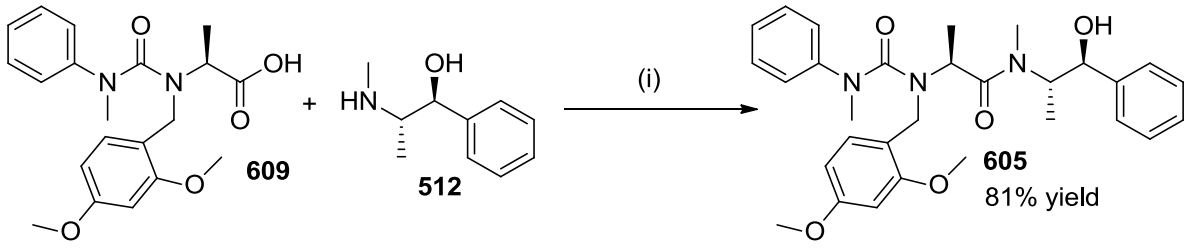

**Scheme 155: Reagents and conditions: (i) 3.0 eq. LDA, 3.0 eq. LiCl, THF, −78 °C to rt, 3 h**

Since the PMB hydantoin **602** had shown an *ee* for a reaction to supposedly give racemic product, the chiral HPLC conditions were optimised to separate the two enantiomers of hydantoin **610**. In

this case hydantoin **610** was formed in an *er* of 50:50 as was expected. This showed no memory of chirality was involved in reactions involving a DMB protecting group.

### 2.4.6.2 Enantioselective Rearrangement of *N*-DMB Protected Ureas

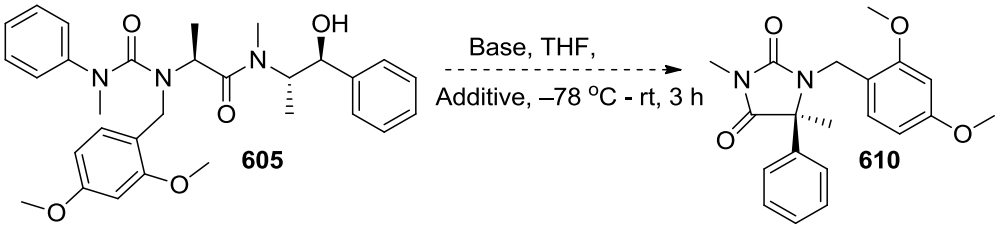
(*S*,*S*)-Pseudoephedrine (**512**) was coupled to DMB carboxylic acid **609** using the EDC·HCl, HOBt·$H_2O$ and DiPEA coupling conditions. Starting material **605** for the enantioselective rearrangement was formed in an 81% yield (Scheme 156).




**Scheme 156: Reagents and conditions: (i) 1.5 eq. (*S*,*S*)-pseudoephedrine (512), 1.2 eq. EDC·HCl, 1.0 eq. HOBt·$H_2O$, 2.3 eq. DiPEA, DCM, rt, 18 h**

Different rearrangement conditions were applied to **605** in order to determine whether the rearrangement took place, if any control in selectivity was observed and if any unwanted migration took place (Table 24).

**Table 24: Rearrangement conditions investigated for DMB starting material 605**



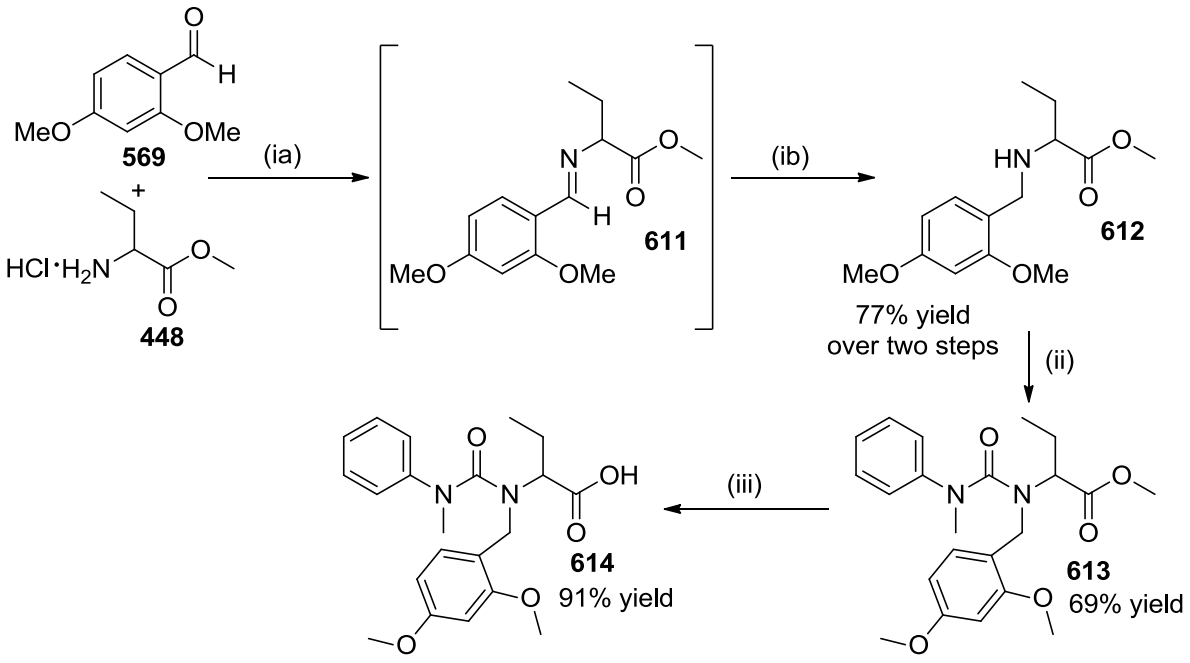

| Entry | Base | Eq. Base | Additive (eq.) | Yield (%) 610 | *er* of 610[a] |
|---|---|---|---|---|---|
| 1 | LDA | 3.0 | - | -[b] | 21:79 |
| 2 | *n*BuLi | 3.0 | - | -[b] | 29:71 |
| 3 | LDA | 3.0 | LiCl (3.0) | 37[c] | 21:79 |
| 4[c] | LDA[d] | 3.0 | LiCl (10.0) | 68 | 15:85 |
| 5 | LDA | 3.0 | LiCl(11.0) | 71 | 15:85 |
| 6 | LDA[e] | 3.0 | LiCl (11.0) | 39 | 21:79 |
| 7 | LiTMP | 3.0 | LiCl (11.0) | 72 | 15:85 |
| 8 | LDA | 3.5 | LiCl (10.0) | 87 | 16:84 |
| 9 | LDA | 4.5 | LiCl (12.0) | 77 | 15:85 |
| 10 | LDA | 6.0 | LiCl (10.0) | 43 | 1:99 |
| 11 | LDA | 8.0 | - | -[f] | - |
| 12 | LDA | 3.0 | LiCl (10.0) + LiOH (1.0)[g] | 85 | 15:85 |
| 13 | LDA | 3.0 | LiCl (10.0) + LiO*t*Bu (1.0)[h] | 71 | 14:86 |

THF, –78 °C – rt (except entry 6), 3 h (except entry 4). [a]Determined by HPLC analysis. [b] Mix of SM and product. [c]Isolated yield remainder of material SM. [d]Left at rt overnight. [e]Reaction warmed to 0 °C and did not go to completion. [f]Degradation. [g]Through addition of 1.0 eq. $H_2O$ and 1.0 eq. extra base. [h]Through addition of 1.0 eq. butanol and 1.0 eq. extra base.

Using 3 eq. of *n*BuLi or LDA gave a moderate *er* and the reaction did not go to completion, the same was observed for LDA in combination with 3 eq. of LiCl (entries 1-3, Table 24). As the number of equivalents of LiCl were increased the yield and *er* improved (entries 4, 5, Table 24). Warming to a lower temperature of 0 °C led to no improvement in the *er* (entry 6, Table 24) and LiTMP gave a similar yield and *er* to LDA (entry 7, Table 24). As the number of equivalents of LDA were increased to 3.5-4.5 the *er* remained the same and the yield was similar at 77-87% (entries 8, 9, Table 24). A major improvement in *er* to an excellent 1:99 was found using 6 eq. of LDA, but the yield was considerably lower at 43% (entry 10, Table 24). Unfortunately adding more LDA led to decomposition (entry 11, Table 24). The low yield may be due to the large excess of LDA required, but the excellent *ee* could have been due to increased addition of other salts that are variably present in bottles of *n*BuLi. Therefore, different additives such as LiOH and LiO*t*Bu were added to the reaction mixture in combination with just 3 eq. of LDA (entries 12, 13, Table 24) in the hope a better yield would be observed with high *er*. Disappointingly the *er* was only 15:85 in these cases suggesting it was in fact the increased amount of LDA or a new lithium aggregate

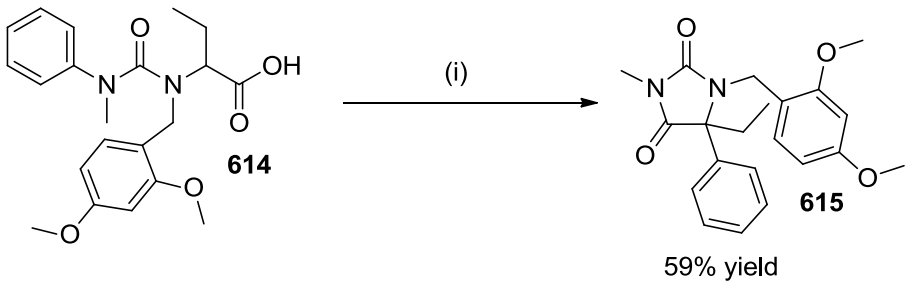
created with 6 eq. that improved *er*. Pleasingly unwanted migration side product similar to **603** was not seen in any of the reactions.

Despite the low yield obtained, the ethyl derivative of the starting material was synthesised to assess if these conditions were general and if the low yield was specific to the alanine case. The synthesis followed the same route as for the alanine starting material with a reductive amination, acylation then saponification yielding carboxylic acid **614** in a 48% yield over three steps (Scheme 157).



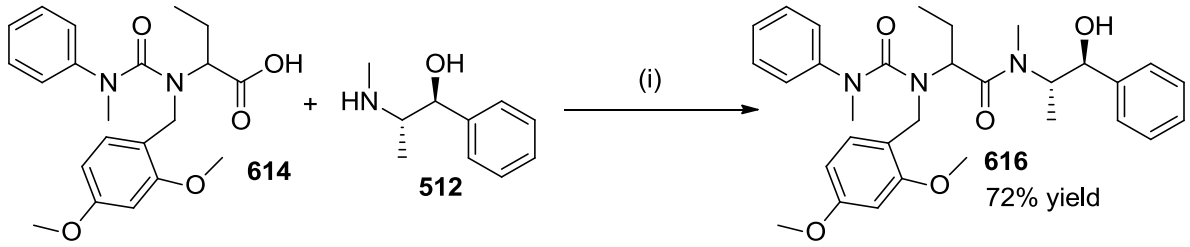

**Scheme 157: Reagents and conditions: (ia) 1.8 eq. $Et_3N$, DCM, molecular sieves (4 Å), rt, 18 h; (ib) 1.6 eq. $NaBH_4$, 1:1 DCM:EtOH, 0 °C – rt, 20 h; (ii) 1.0 eq. *N*-methyl-*N*-phenyl carbamoyl chloride (391), DMAP (cat), 1.3 eq. $Et_3N$, DCE, 70 °C, 16 h; (iii) 35.0 eq. LiOH, 2:1 THF:$H_2O$, 45 °C, 22 h**

The rearrangement was carried out from the carboxylic acid **614** to ensure no side products were observed and resulted in a racemic sample of hydantoin **615** for the HPLC analysis. The same rearrangement conditions were applied as used previously, shown in Scheme 158, but the reaction was left overnight to ensure completion giving racemic hydantoin **615** in a 59% yield after 21.5 h.




**Scheme 158: Reagents and conditions: (i) 3.0 eq. LDA, 3.0 eq. LiCl, THF, −78°C – rt, 21.5 h**

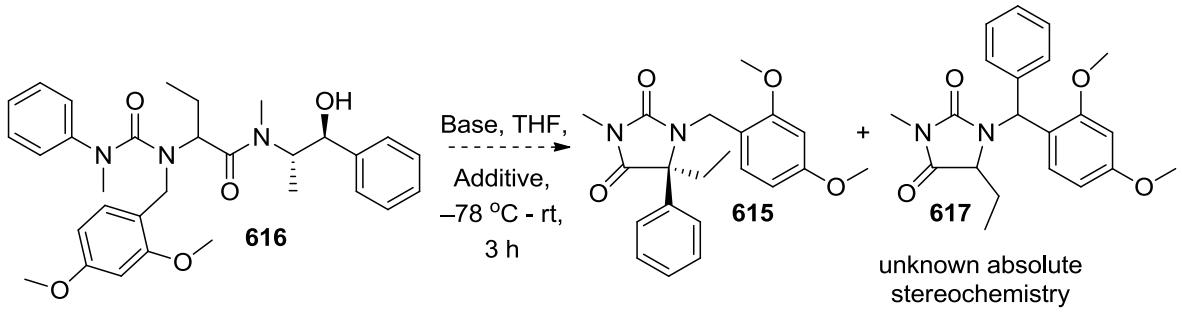
Pseudoephedrine was coupled to ethyl carboxylic acid **614**, using the peptide coupling conditions previously optimised product **616** was obtained in a 72% yield after 69 h (Scheme 159).




**Scheme 159: Reagents and conditions: (i) 1.5 eq. (*S*,*S*)-pseudoephedrine (512), 1.2 eq. EDC·HCl, 1.0 eq. HOBt·$H_2O$, 2.3 eq. DiPEA, DCM, rt, 69 h**

Ethyl derivative **616** was subjected to similar conditions to alanine derivative **605**. The conditions are shown in Table 25 using a combination of LDA with a large excess of LiCl.

**Table 25: Rearrangement conditions investigated for ethyl DMB starting material 616**




| Entry | Base | Eq. Base | Additive (eq.) | Ratio 616:615:617[a] | *er* of 615[b] |
|---|---|---|---|---|---|
| 1[c] | LDA | 3.0 | LiCl (10.0) | 3.0:1.0:0.0 | - |
| 2[c] | LDA | 3.75 | LiCl (10.0) | 1.0:2.0:0.0 | 20:80 |
| 3 | LDA | 4.5 | LiCl (10.0) | 0.0:1.0[d]:0.4 | 7:93 |
| 4 | LDA | 6.5 | LiCl (10.0) | 0.0:1.0:0.8[e] | - |

THF, –78 °C – rt, 3 h (except entry 1,2). [a]From crude $^1$H NMR. [b]Determined by HPLC analysis. [c]Left at rt overnight. [d]32% isolated product yield. [e]The reaction was very messy.

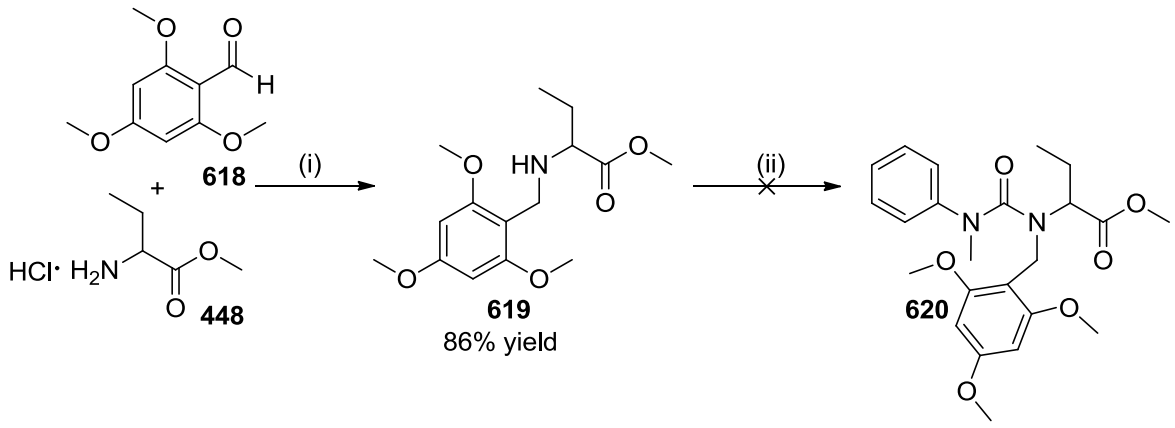
Unfortunately, using 3 eq. of LDA the reaction gave mainly starting material (**616**:**615** 3:1) (entry 1, Table 25). Increasing the equivalents of base to 3.75 gave an improvement in the ratio of 1:2 **616**:**615** but hydantoin **615** had a low *er* of 20:80 (entry 2, Table 25). Increasing further to 4.5 eq. gave a good *er* of 7:93 but the yield was low at 32% and unfortunately the reason for the low yield was the formation of unwanted migration product **617** present in a 1.0:0.4 **615**:**617** ratio (entry 3, Table 25). Using 6.5 eq. of LDA, similar to the best conditions for alanine derivative **605**, the reaction was very messy and the crude $^{1}$H NMR showed a mix of hydantoin **615** in combination with side product **617** in an increased ratio of 1.0:0.8 **615**:**617** (entry 4, Table 25). These results suggested changing the side chain of the amino acid had resulted in more steric bulk around the α-position that created more opportunity for deprotonation and rearrangement at the unwanted benzylic position. The best conditions for ethyl derivative **616** gave a good *er* but a low yield, this was comparable with alanine derivative **605**, but in this case the unwanted migration product **617** was present in the reaction mixture.

Disappointingly, this showed this method not to be applicable to a wide range of substrates and as the complexity of the amino acid side chain increased the rearrangement was slower and more unwanted side reactions were observed. More complex amino acids were investigated, but the rearrangement led to decomposition with such an excess of LDA. For bulky amino acids such as valine the starting material could not be synthesised.[xix]

### 2.4.7 *N*-TMB Protected Ureas

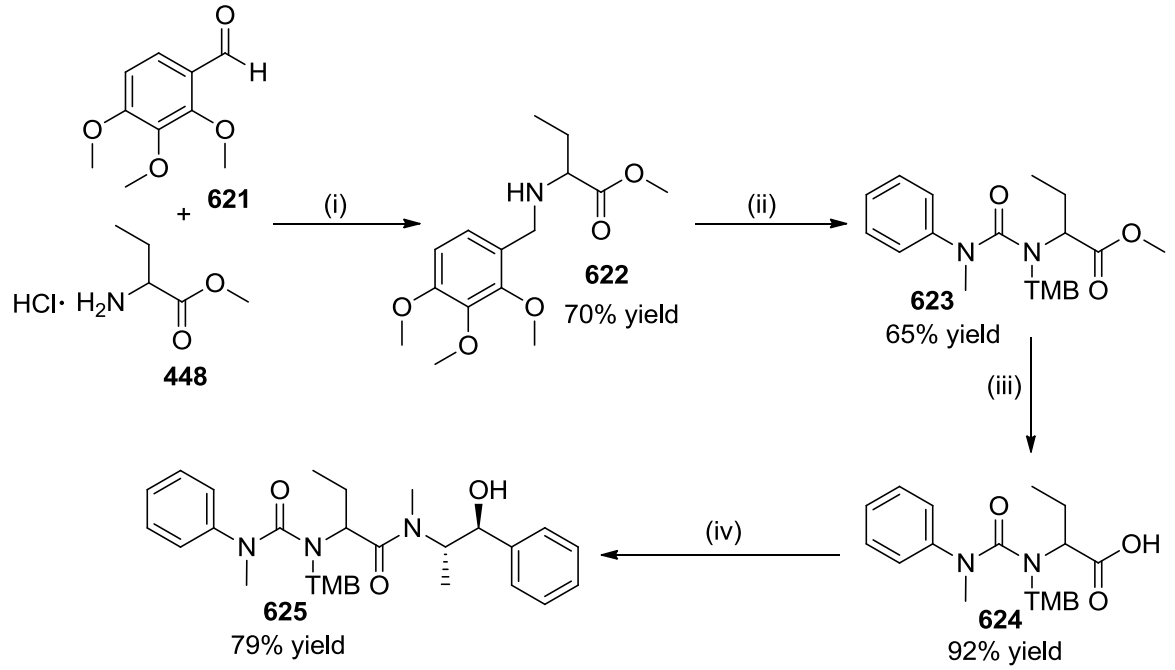
To complete the exploration of benzylic protecting groups, trimethoxylbenzyl (TMB) was investigated. This had a further OMe group on the ring, increasing the electron density at the benzylic position and also the steric bulk. The 2,3,4-TMB and 2,4,6-TMB were considered with the starting materials synthesised by the same route used previously, reductive amination to insert the protecting group, acylation to create the urea functionality and saponification to give the carboxylic acid prior to peptide coupling of the pseudoephedrine auxiliary. The ethyl derivative was chosen as this was the first example in the DMB case where alternative migration was seen. The 2,4,6-TMB underwent reductive amination in a one step procedure using sodium triacetoxyborohydride with sodium acetate in MeOH successfully in an 86% yield. Unfortunately secondary amine **619** when coupled with carbamoyl chloride **391** decomposed upon purification suggesting the protecting group was too electron rich and causing stability problems even at this early stage in the synthesis (Scheme 160).

[xix] With thanks to Dr. Fernando Fernández-Nieto for exploring amino acids more complex than alanine and the ethyl chain




**Scheme 160: Reagents and conditions: (i) 1.0 eq. 2,4,6-trimethoxybenzaldehyde, 2.0 eq. NaOAc, 2.0 eq. $NaBH(OAc)_3$, MeOH, rt, 20 h; (ii) 1.0 eq. *N*-methyl-*N*-phenyl carbamoyl chloride (391), DMAP (cat), 1.3 eq. $Et_3N$, DCE, 70 °C, 16 h**

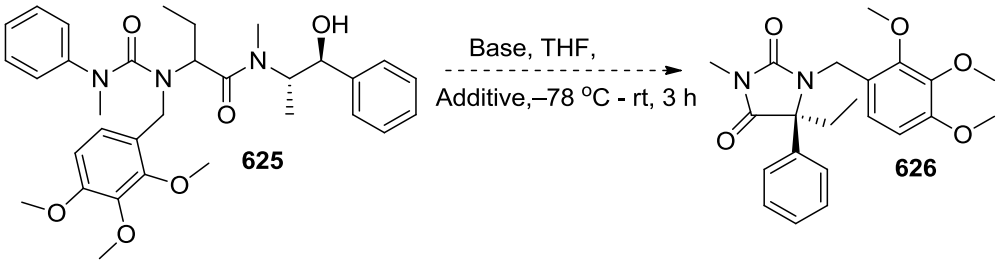
The 2,3,4-TMB protecting group behaved differently and starting material **625** was successfully synthesised in a 34% yield over four steps (Scheme 161).




**Scheme 161: Reagents and conditions: (i) 1.0 eq. 2,3,4-trimethoxybenzaldehyde, 2.0 eq. NaOAc, 2.0 eq. $NaBH(OAc)_3$, MeOH, rt, 23 h; (ii) 1.0 eq. *N*-methyl-*N*-phenyl carbamoyl chloride (391), DMAP (cat), 1.3 eq. $Et_3N$, DCE, 70 °C, 19 h; (iii) 17.0 eq. LiOH, 2:1 THF:$H_2O$, 45 °C, 22 h; (iv) 1.5 eq. (*S*,*S*)-pseudoephedrine (512), 1.2 eq. EDC·HCl, 1.0 eq. HOBt·$H_2O$, 2.3 eq. DiPEA, DCM, rt, 17 h**

A variety of rearrangement conditions were then applied to the TMB substrate **625** (Table 26)

**Table 26: Rearrangement conditions investigated for ethyl TMB starting material 625**




| Entry | Base | Eq. Base | Additive (eq.) | Yield 626 (%) |
|---|---|---|---|---|
| 1 | LDA | 3.0 | LiCl (11.0) | 0 |
| 2 | LDA | 4.5 | LiCl (10.0) | 0 |
| 3 | LDA | 6.0 | LiCl (10.0) | 0 |
| 4 | *s*BuLi | 3.0 | LiCl (10.0) | 0 |
| 5 | LDA | 10.0 | LiCl (10.0) | 0 |

THF, –78 °C – rt, 3 h.

Disappointingly, using 3-6 eq. of LDA (entries 1-3, Table 26) only starting material was returned. Under more forcing conditions of 3 eq. of *s*BuLi (entry 4, Table 26) starting material was returned and using 10 eq. of LDA (entry 5, Table 26) the starting material decomposed with no rearrangement observed. Since under a variety of conditions there was no evidence of rearrangement this suggested the protecting group was too large and causing steric hindrance of the α-carbon preventing deprotonation.

### 2.4.8 Conclusion

Pseudoephedrine is a successful chiral auxiliary for inducing control in the rearrangement reaction leading to enantiomerically enriched hydantoins. Methylated starting material **531** was rearranged into hydantoin **396** in a 66-72% yield and with an *er* of 10:90-12:88. It was already known that *N*-methyl hydantoin **396** cannot be hydrolysed, but unfortunately the unprotected rearrangement led to racemic hydantoins as it is suspected the chiral auxiliary is lost under the reaction conditions prior to rearrangement. The MOM and MEM protecting groups could not be inserted and the benzyl protecting group gave unwanted rearrangement to the benzylic position of the protecting group. Other methoxy-benzyl protecting groups were investigated, PMB gave desired hydantoin **ent-602** in a good *er* of 92:8 using the (*R*,*R*)-pseudoephedrine, but hydantoin **ent-602** was in combination with an inseparable side product of unwanted migration **603**. The DMB protection was successful for alanine derivative **605**, giving hydantoin **610** in an excellent *er* of 1:99 but a moderate 43% yield. When the scope was investigated with other amino acid side chains, the reaction suffered from competing migration to the benzylic position of the protecting group along with the desired product, but ethyl derivative **615** was separated from the impurity and **616** isolated in a 32% yield and with an *er* of 7:93. Finally, the TMB protected substrates were too bulky to

undergo rearrangement. A summary of the racemic and enantioenriched hydantoins synthesised in this chapter are shown in Figure 43 below.

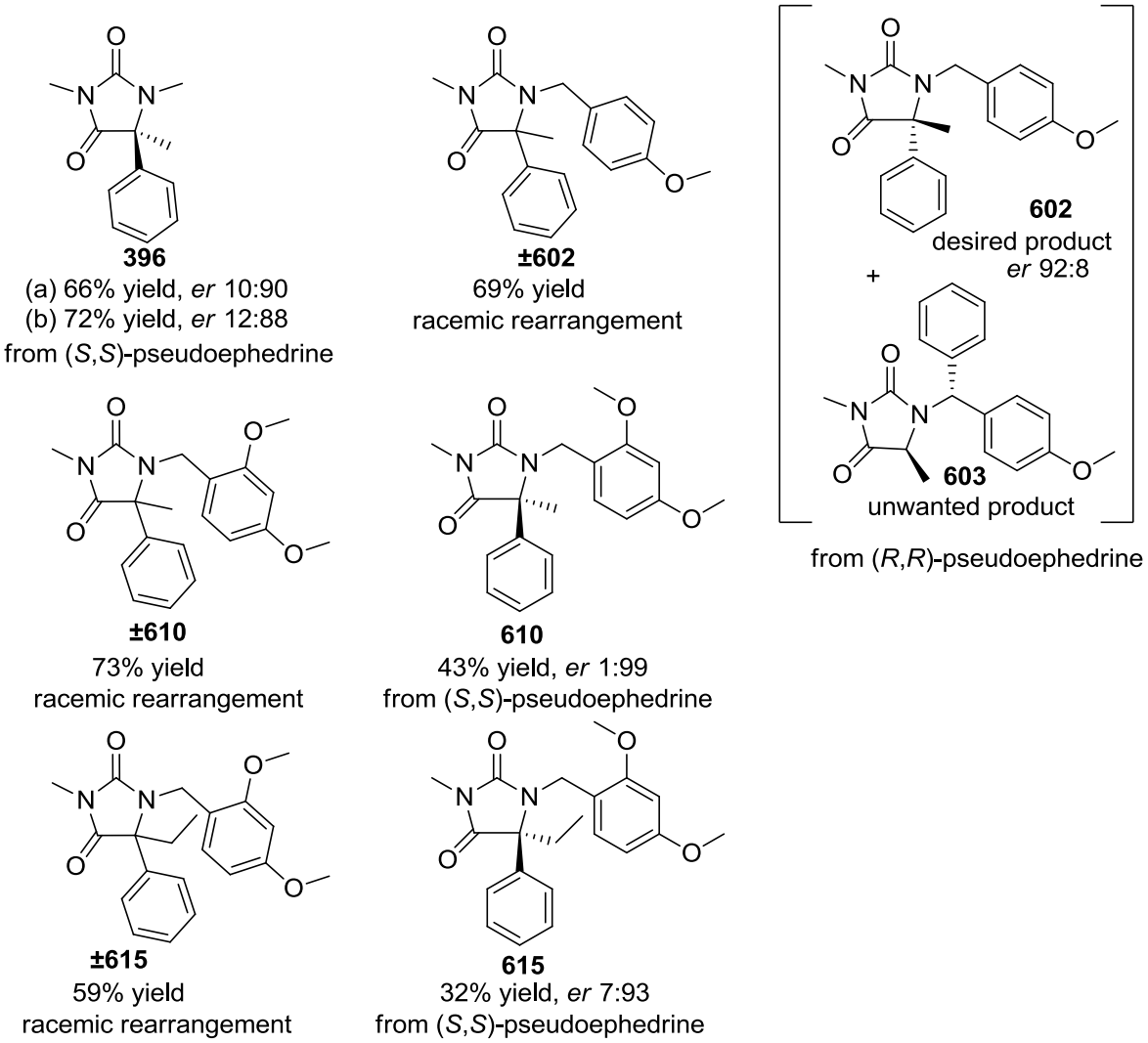



**Figure 43: Summary of racemic and enantioenriched hydantoins synthesised**

### 2.4.9 Absolute Configuration of the Products

The absolute configuration for the *N*-DMB and *N*-methyl protected hydantoins were confirmed through comparison of specific rotations with literature values. The *N*-DMB-substituted hydantoin **610** (*er* 1:99) synthesised from (*S*,*S*)-pseudoephedrine had $[\alpha]_D^{21}$ = +57.9 (*c* = 1.1, $CHCl_3$). *N*-DMB-substituted hydantoin **ent-610** (*er* 99:1) was also synthesised using (*R*,*R*)-pseudoephedrine and had $[\alpha]_D^{23}$ = –54.4 (*c* = 1.0, $CHCl_3$). This hydantoin was deprotected, hydrolysed and converted into methyl ester HCl **510**[xx] and $[\alpha]_D^{23}$ = –61.1 (*c* = 1.0, MeOH) was found. The hydrochloride salt of quaternary methyl ester **510** has a literature value[216] of $[\alpha]_D^{20}$ = –51.8 (*c* = 0.5, MeOH) for its (*R*)

[xx] With thanks to Romain Costil for synthesising the opposite enantiomer from the (*R*,*R*)-pseudoephedrine (**ent-512**) and converting this into the amino ester

enantiomer. In this case the (*R*,*R*)-pseudoephedrine had formed the (*R*) enantiomer selectively. The DMB hydantoin **610** synthesised using the (*S*,*S*)-pseudoephedrine has the opposite sign showing the (*S*) enantiomer was formed selectively using the (*S*,*S*)-pseudoephedrine derivative (Figure 44).

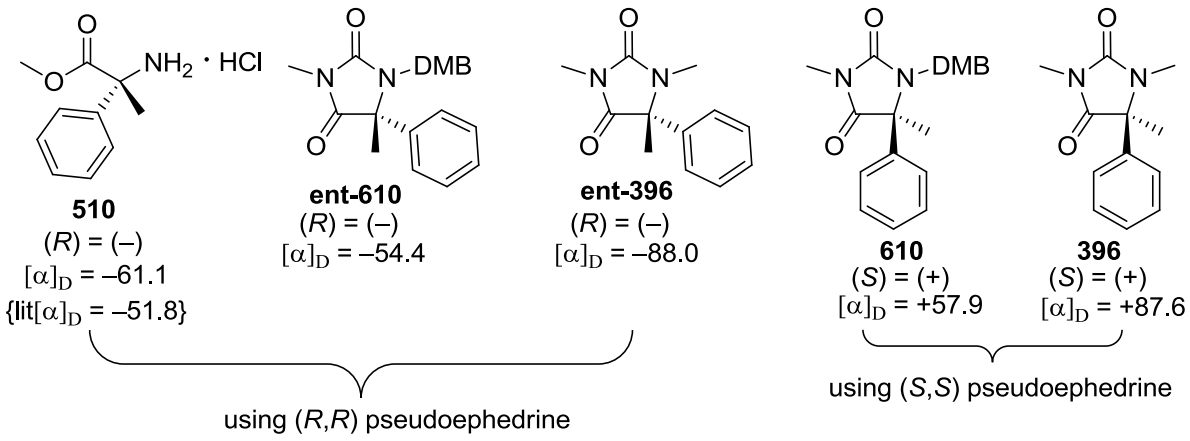



**Figure 44: The absolute configuration of the hydantoins from protected rearrangements**

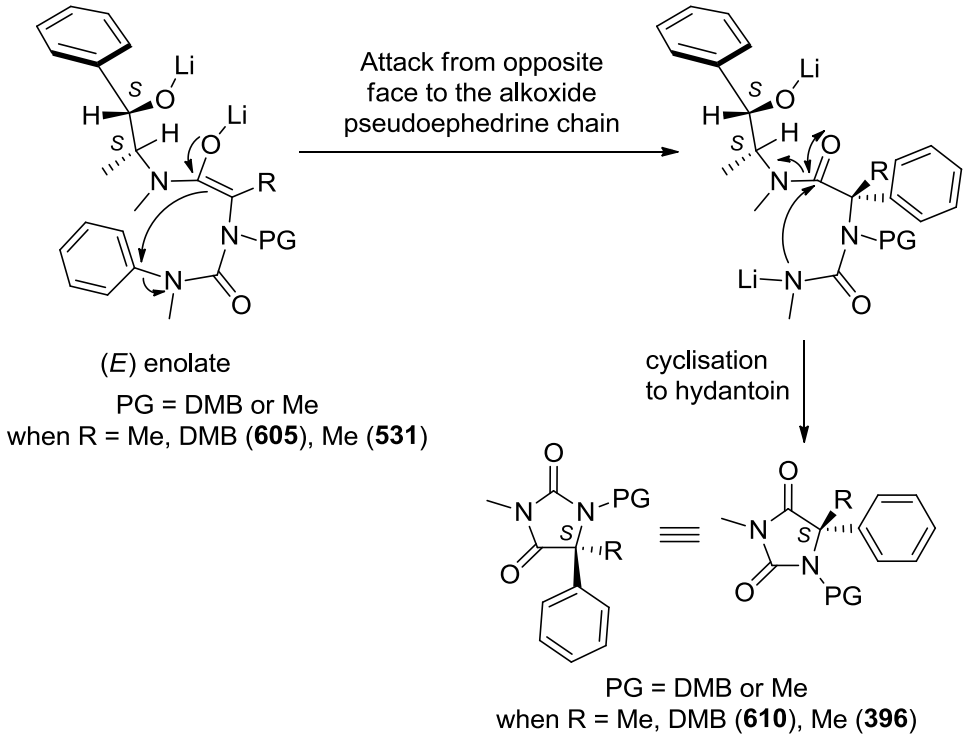
The (*R*,*R*)- and (*S*,*S*)-pseudoephedrine were both coupled to L-alanine, but gave a different enantiomers of the product. This showed the absolute stereochemistry of the amino acid centre (in this case the alanine centre) was unimportant. The outcome of the reaction had no dependence on the relative stereochemistry of the starting material and was purely determined by the enantiomer of pseudoephedrine used.

Finally, *N*-methyl hydantoin **396** (*er* 12:88), synthesised using (*S*,*S*)-pseudoephedrine had $[\alpha]_D^{21}$ = +87.6 (*c* = 1.1, $CHCl_3$). To determine the absolute configuration a sample of the (*R*)-hydantoin **446** (*er* 88:12) (see Chapter 2.5) was methylated on nitrogen to give a sample of **ent-396** with $[\alpha]_D^{22}$ = –88.0 (*c* = 1.0, $CHCl_3$).[xxi] This confirmed the (*S*)-enantiomer was formed selectively using the (*S*,*S*)-pseudoephedrine (Figure 44). The same result was observed in the DMB case suggesting reaction *via* a similar transition state for *N*-protected rearrangements.

The stereochemical outcome can be rationalised by considering the enolate geometry and the face the rearrangement is directed from by the pseudoephedrine. The transition state suggested is based on models that Myers proposes. Myers suggests it is possible for tetra-substituted enolates to form both (*Z*) and (*E*)-enolates,[208] but showed in his asymmetric α-alkylation of amino acids[210] usually the (*E*)-enolate is more reactive.

[xxi] With thanks to Dr. Fernando Fernández-Nieto for carrying out the methylation

For rearrangements of pre-*N*-protected starting materials, it is proposed the transition state involves an (*E*)-enolate, as suggested by Myers in his asymmetric α-alkylation of amino acids. This geometry is favourable due to minimisation of repulsive interactions between the enolate oxygen and the urea nitrogen lone pair and minimisation of steric hindrance. In this conformation the aromatic ring can undergo the intramolecular nucleophilic aromatic substitution with attack of the aromatic ring from the bottom face of the enolate. This avoids the alkoxide chain of the pseudoephedrine blocking the opposite face through coordination to lithium and solvent. The ring adds to the same face as the methyl group α to the nitrogen of the pseudoephedrine (1,4–*syn*). This results in the (*S*)-configuration present in the hydantoin after cyclisation and release of the pseudoephedrine (Scheme 162).




**Scheme 162: Proposed transitions state involving an (*E*)-enolate**

## 2.5 Enantioselective Rearrangement of Amino Acid Enolates through *in situ N*-Protection

### 2.5.1 Reaction Optimisation with *in situ N*-Protection

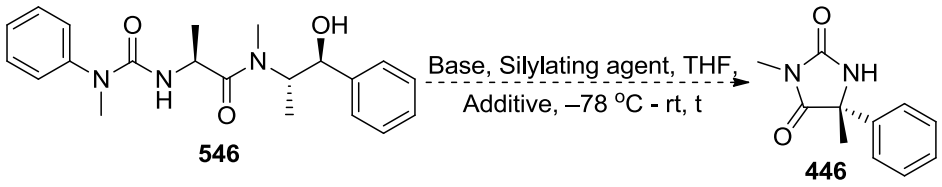
The previous chapters have described the development of N to C aryl migration from amino acid enolates. Numerous nitrogen protecting groups were investigated, but none fully satisfied the overall aim for the project of developing an asymmetric rearrangement that generated enantiomerically enriched α-arylated hydantoins that could be converted into quaternary amino acids and was applicable to a wide substrate scope. An efficient method for the preparation of racemic hydantoins across a large substrate scope that could be converted into quaternary amino acids was developed (Chapter 2.3.2). Unfortunately, when pseudoephedrine was attached to the unprotected starting materials the rearrangement was not selective and racemic products were obtained (Chapter 2.4.3).

These results showed that a *N*-protecting group is essential for asymmetric rearrangement, but this introduced an extra step in the synthesis of the starting materials and a further step after the rearrangement to remove the protecting group prior to hydrolysis. However, introduction of various benzylic protecting groups was unsuccessful due to either difficulties in the starting material synthesis or unwanted benzylic deprotonations leading to alternative migration sites.

To overcome these issues an *in situ N*-protection with a small, non-benzylic, protecting group that was base stable and easily removed was next investigated. The starting material would be synthesised over the minimum number of steps and would contain a free NH on the amino acid nitrogen. Through addition of a silylating agent to the rearrangement conditions it was hoped the NH would be protected *in situ* preventing the loss of the auxiliary prior to rearrangement and the silyl group could be removed as part of the work up. Therefore the development of a procedure in which protection, enolisation, rearrangement, cyclisation and deprotection took place in one pot was explored.

Starting material **546** (used in Chapter 2.4.3, synthesised in Scheme 130) was subjected to various rearrangement conditions in the presence of a silylating agent. The silylating agent was added to a pre-cooled solution of base and LiCl at −78 °C before substrate **546** was added in THF. The reaction was quenched with $NH_4Cl$ and acidified with 1.0 M HCl to hydrolyse any *N*-silylated positions. The results are shown in Table 27.

**Table 27: Rearrangement of 546 with *in situ* protection**




546 446

| Entry | Base (n° eq.) | Silylating agent (n° eq.) | Additive (n° eq.) | t (h) at rt | Yield 446 (%)[a] | *er*[b] |
|---|---|---|---|---|---|---|
| 1 | LDA (4.0) | - | LiCl (7.0) | o/n | 54 | 50:50 |
| 2 | LDA (4.0) | TMSCl (1.0) | LiCl (7.0) | o/n | 60 | 75:25 |
| 3 | LDA (4.0) | TMSCl (2.0) | LiCl (7.0) | o/n | 65 | 92:8 |
| 4 | LDA (4.0) | TMSCl (3.0) | LiCl (7.0) | o/n | -[c] | - |
| 5 | LDA (4.0) | TMSCl (4.0) | LiCl (7.0) | o/n | -[d] | - |
| 6 | LiTMP (4.0) | TMSCl (2.0) | LiCl (7.0) | o/n | -[e] | 75:25 |
| 7 | KHMDS (4.0) | TMSCl (2.0) | - | o/n | -[c] | - |
| 8 | LDA (4.0) | TMSCl (2.0) | LiCl (7.0) | 3.0 | 59 | 91:9 |
| 9 | LDA (4.0) | TMSCl (2.0) | - | 3.0 | 45 | 91:9 |
| 10[f] | LDA (4.0) | TMSCl (2.0) | LiCl (7.0) | 3.0 | 58 | 91:9 |
| 11 | LDA (4.0) | TMSOTf (2.0) | LiCl (7.0) | o/n | 57 | 89:11 |
| 12 | LDA (4.0) | TBDMSCl (2.0) | LiCl (7.0) | o/n | -[e] | 78:22 |
| 13 | LDA (4.0) | TBDMSOTf (2.0) | LiCl (7.0) | o/n | -[g] | 83:17 |

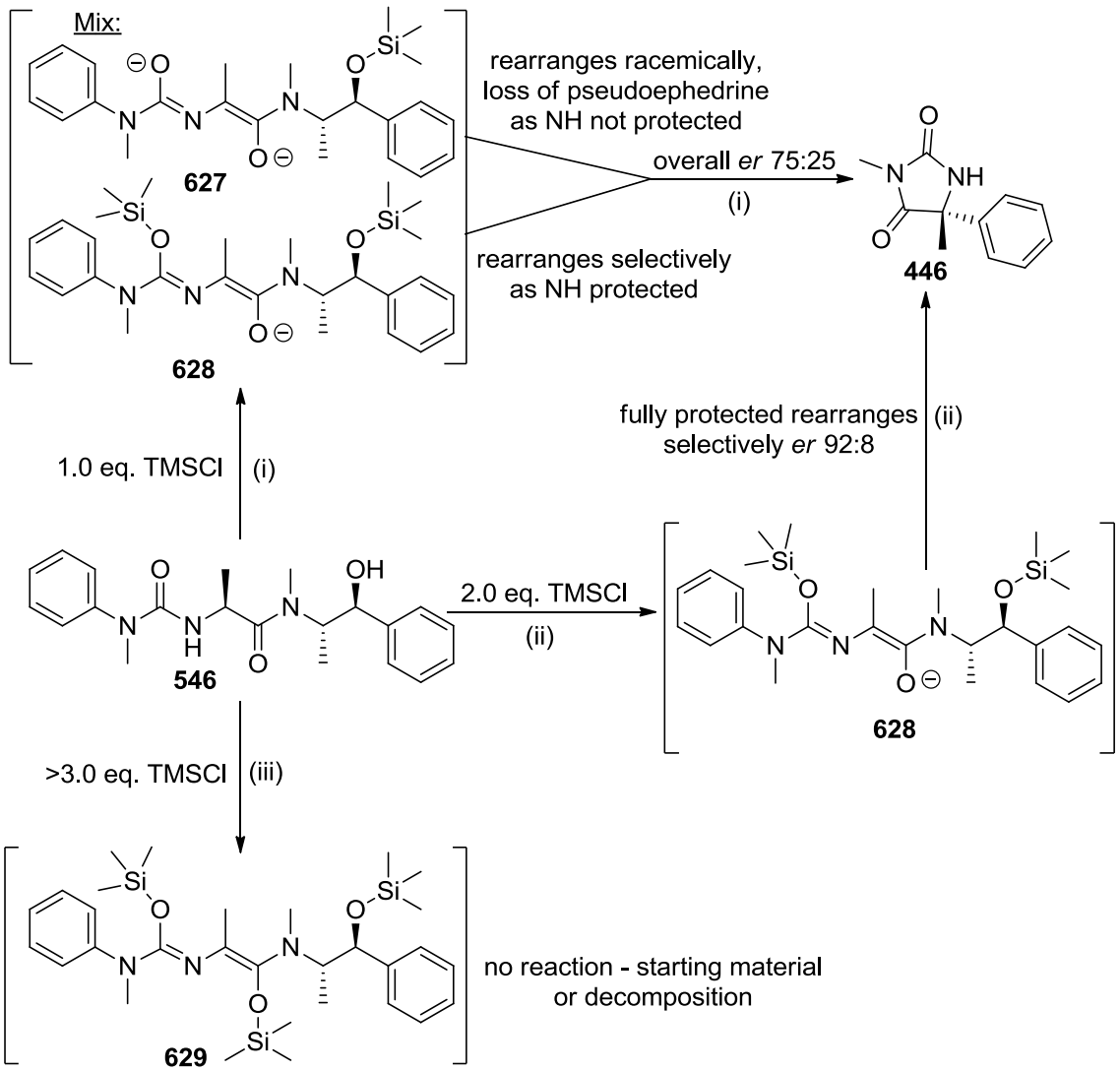
–78 °C – rt (except entry 10), THF (0.1 M), Method: base + LiCl cooled to –78 °C, silylating agent added, stir 5 mins, substrate in THF added, stir 30 min at –78°C warm to room temp, stir for time period stated, quench with $NH_4Cl$, acidify with 1.0 M HCl, stir 30 mins. [a]Yield after purification by flash column chromatography. [b]Determined by HPLC analysis. [c]Starting material recovered. [d]Messy reaction, many silylated species in $^1$H NMR spectra. [e]Mainly starting material but *er* determined for any product formed. [f]Reaction warmed to 0 °C, did not go to completion. [g]Mix of starting material with the pseudoephedrine protected by TBS group and some product formed.

With no silylating agent present the reaction occurred in a 54% yield but hydantoin **446** was racemic (entry 1, Table 27). Adding 1 eq. of TMSCl gave a 60% yield, but showed some evidence of stereoselectivity as the *er* of **446** was 75:25 (entry 2, Table 27) and the crude $^1$H NMR showed 1:2 carboxylic acid **445**: hydantoin **446**, suggesting some elimination of the pseudoephedrine auxiliary (described in Chapter 2.4.3, Scheme 133) and incomplete reaction. Pleasingly, when 2 eq. of TMSCl was added the *er* of **446** improved to 92:8 and the reaction reached completion with a good yield of 65% (entry 3, Table 27). This suggested the TMSCl was able to protect the NH *in situ* and prevent elimination of the pseudoephedrine prior to rearrangement. However, when 3 or more equivalents of TMSCl were added the starting material was recovered as mixture of epimers (entries 4, 5, Table 27). Changing the base to LiTMP with 2 eq. of TMSCl returned mainly starting

material and any product formed had a lower *er* of 75:25 (entry 6, Table 27). KHMDS returned only starting material **546** suggesting it was not a strong enough base for the reaction (entry 7, Table 27). This showed that only LDA in combination with a silylating reagent was successful with the reaction complete after 3 h giving **446** in 59% yield and 91:9 *er* (entry 8, Table 27). Surprisingly, without LiCl present a high *er* for **446** was obtained (entry 9, Table 27), suggesting silylation of the OH was enough to block one face of the molecule and induce selectivity. Carrying out the reaction at 0 °C resulted in a similar *er*, but the reaction did not go to completion (entry 10, Table 27). Alternative silylating reagents were considered, with TMSOTf giving a slightly lower *er* and yield than TMSCl (entry 11, Table 27). TBDMSCl and TBDMSOTf gave mainly starting material and any product formed had a lower *er* of 78:22 and 83:17, respectively (entries 12, 13, Table 27). Furthermore, the starting material recovered in entry 13 was silylated on the OH of the pseudoephedrine. The best conditions found are shown in entry 3 giving a good 65% yield for protection, enolisation, rearrangement, cyclisation and deprotection in one pot, with a good *er* of 92:8 for unprotected hydantoin **446**, which can be hydrolysed into α-arylated quaternary amino acid **508**.

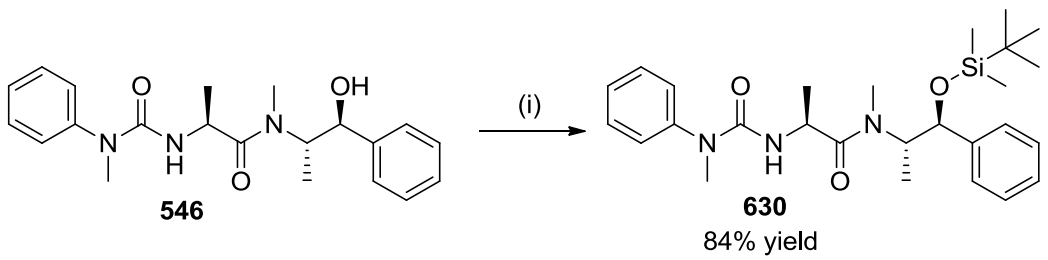
### 2.5.2 Proposed Reaction Mechanism

The results in Table 27 show that TMSCl is the best silylating agent and that the selectivity depends on the number of equivalents used. The TMSCl was added to protect the free NH *in situ*, but under the reaction conditions the OH of the pseudoephedrine will be deprotonated and it is likely the OH will be protected before the NH. When 1 eq. of TMSCl was used a moderate *er* of 75:25 was observed (entry 2, Table 27). This suggests some stereoselective rearrangement, but if unsilylated species **546** or monosilyated species **627** are present they can lead to a competing rearrangement without any selectivity due to elimination of the auxiliary prior to rearrangement. A mix of these two outcomes (racemic and selective) would result in product **446** with a moderate *er*. However, when 2 eq. of TMSCl were added this allowed complete protection of both the OH and NH generating species **628** that rearranged selectively generating hydantoin **446** in a 92:8 *er* (entry 3, Table 27). Finally, with more than 3 eq. of TMSCl only starting material or decomposition was observed. One possibility is that an excess of TMSCl protects the both OH and NH but also the enolate formed can be trapped as a silyl enol ether **629**, which could be unreactive to rearrangement (entry 4, 5, Table 27) (Scheme 163). The literature suggests that the silylation of a urea anion is likely to occur on oxygen rather than nitrogen.[217] Itoh *et al.* suggests $SiMe_3$ groups have a higher affinity for oxygen over nitrogen, the proposed order of affinity is $O>S\geq N$.[218]




**Scheme 163: Proposed mechanism for the *in situ* protection with TMSCl**

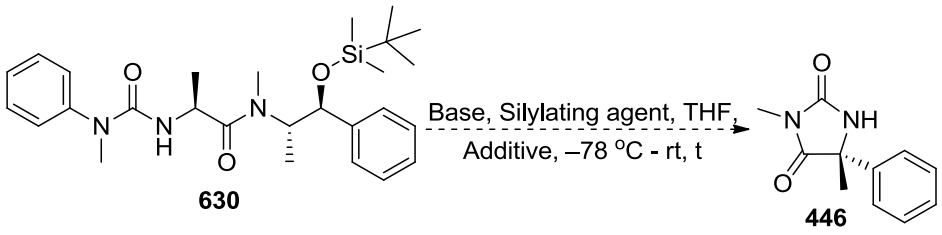
To probe this hypothesis starting material **546** was pre-protected on the OH of the pseudoephedrine with a TBDMS group using TBDMSOTf in the presence of 2,6-lutidine in DCM with TBDMS, protected product **630** was obtained in 84% yield (Scheme 164).




**Scheme 164: Reagents and conditions: (i) 1.5 eq. TBDMSOTf, 2.0 eq. 2,6-Lutidine, DCM, 0 °C – rt, 4 h**

The pre-protected product **630** was then subjected to the rearrangement conditions shown in Table 28 to determine if a similar outcome was observed.

**Table 28: Rearrangement of OH protected 630 with *in situ* protection**




| Entry | Base (n° eq.) | Silylating agent (n° eq.) | Additive (n° eq.) | t (h) at rt | 630:446 [a] | *er*[b] |
|---|---|---|---|---|---|---|
| 1 | LDA (3.0) | - | LiCl (7.0) | o/n | 1.0:0.0 | - |
| 2 | LDA (3.0) | TMSCl (1.0) | LiCl (7.0) | o/n | 1.0:1.0 | 86:14 |
| 3 | LDA (3.0) | TMSCl (2.0) | LiCl (7.0) | o/n | 1.0:0.0 | - |

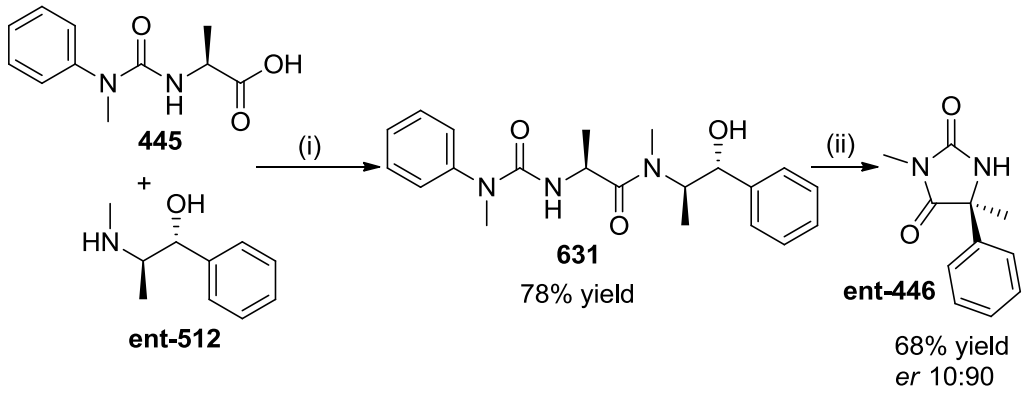
–78 °C – rt, THF (0.1 M), Method: base + LiCl cooled to –78°C, TMSCl added, stir 5 mins, substrate in THF added, stir 30 min at –78 °C warm to room temp, stir for time period stated, quench with $NH_4Cl$, acidify with 1.0 M HCl, stir 30 mins. [a]Ratio based on crude $^1H$ NMR. [b]Determined by HPLC analysis.

When no TMSCl is added (entry 1, Table 28), only starting material was obtained, which was expected as the reaction with TBDMSOTf gave mainly starting material previously (Table 27, entry 13). It is likely starting material **630** is more stable in this case and rather than elimination of the auxiliary and unselective rearrangement, no reaction occurs. This also fits with the trend that with less silylating agent the reaction was slower and did not reach completion. However, using 1 eq. of TMSCl (entry 2, Table 28) mimics the optimum conditions for starting material **546** (entry 3, Table 27). In this case the maximum *er* for a TBDMS protected species was observed (86:14) and the reaction showed more conversion into product **446**. Finally, with 2 eq. of TMSCl, only starting material was observed (entry 3, Table 28). This fits with the hypothesis that more than 3 eq. of TMSCl for unprotected starting material **546** leads to formation of a silyl enol ether that is unreactive (entry 4, 5, Table 27). These results support the proposed mechanistic hypothesis and because the OH of the pseudoephedrine was already protected one less equivalent of LDA and one less equivalent of TMSCl should give similar results to those in Table 27, this was the case and the general trend was the same.

### 2.5.3 Alternative Auxiliaries to (*S*,*S*)-Pseudoephedrine

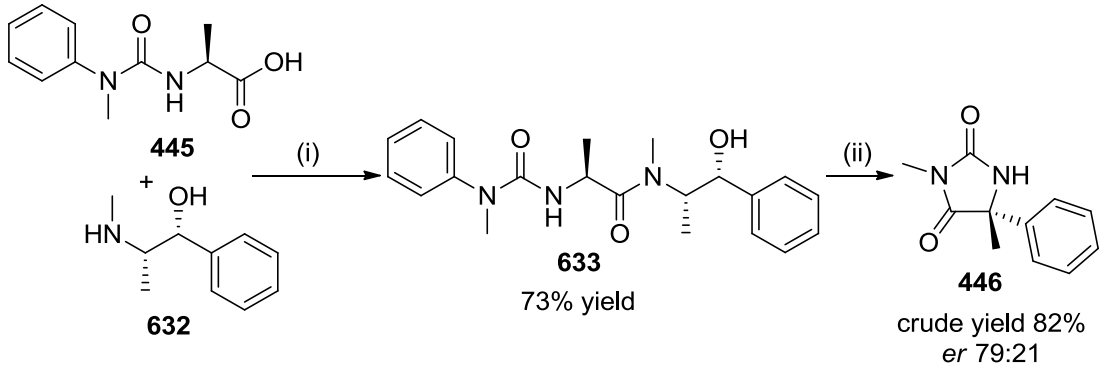
Before applying the optimised conditions (4.0 eq. LDA, 2.0 eq. TMSCl – *er* 92:8, 65% yield) to a range of substrates, other auxiliaries were investigated to ensure (*S*,*S*)-pseudoephedrine was optimum for this reaction. Since this reaction was now significantly different from the α-alkylations performed by Myers using (*S*,*S*)-pseudoephedrine this may not be the optimum auxiliary, therefore auxiliaries similar to (*S*,*S*)-pseudoephedrine were considered.

To ensure that there was no mis-matched effect between the L-amino acids and the (*S*,*S*)-pseudoephedrine as described by Myers for amino acid alkylations (discussed in Chapter 2.4.1),[210] (*R*,*R*)-pseudoephedrine (**ent-512**) was coupled to unprotected carboxylic acid **445** using the standard coupling conditions forming **631** in a 78% yield. After rearrangement hydantoin **ent-446** was obtained in a 68% yield with an *er* of 10:90, confirming that (*R*,*R*)-pseudoephedrine induces opposite enantioselectivity, but showing comparable yield and *er* to the (*S*,*S*)-pseudoephedrine. This allowed the mis-matched effect and any dependence on the starting materials relative stereochemistry to be eliminated as a potential problem (Scheme 165).



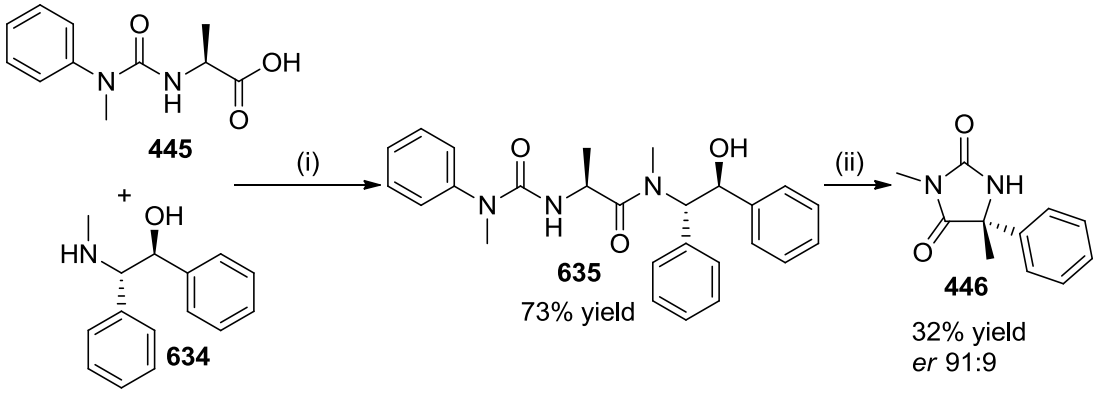

**Scheme 165: Reagents and conditions: (i) 1.5 eq. (*R*,*R*)-pseudoephedrine (ent-512), 1.2 eq. EDC·HCl, 1.0 eq. HOBt·$H_2O$, 1.2 eq. DiPEA, DCM, rt, 18 h; (ii) 4.0 eq. LDA, 2.0 eq. TMSCl, 7.0 eq. LiCl, THF, −78 °C – rt, 16 h**

In addition, (1*R*,2*S*)-(–)-ephedrine (**632**) was investigated. Firstly ephedrine was coupled using the peptide conditions shown in Scheme 166, giving product **633** in a 73% yield. The rearrangement conditions were applied, but the reaction returned some starting material. By omitting the LiCl the reaction produced mainly hydantoin **446** with a crude *er* of 79:21, which was significantly lower than from (*S*,*S*)-pseudoephedrine and therefore no further purification or conditions were tried (Scheme 166).




**Scheme 166: Reagents and conditions: (i) 1.5 eq. (1*R*,2*S*)-(–)-ephedrine (632), 1.2 eq. EDC·HCl, 1.0 eq. HOBt·$H_2O$, 1.2 eq. DiPEA, DCM, rt, 16 h; (ii) 4.0 eq. LDA, 2.0 eq. TMSCl, THF, −78 °C – rt, 16 h**

During this project Myers published a route to an alternative auxiliary, pseudoephenamine **634** that is similar in structure to pseudoephedrine **512** but has a phenyl ring in place of the methyl group α to the nitrogen. The advantage of this auxiliary over pseudoephedrine is that it has no regulatory restrictions, but is it is not commercially available and has to be synthesised over three steps. (*S*,*S*)-Pseudoephenamine[xxii] was synthesised according to Myers protocol[209] then coupled to carboxylic acid **445** giving starting material **635** in a 73% yield (Scheme 167). After rearrangement a similar *er* was obtained for hydantoin **446** as with the (*S*,*S*)-pseudoephedrine (91:9), but the isolated yield was significantly lower at 32%. This may be due to competing benzylic deprotonation of the auxiliary as there is a phenyl ring α to the nitrogen leading to unwanted reactions. This was further indicated by the many colour changes that took place upon addition of the substrate.

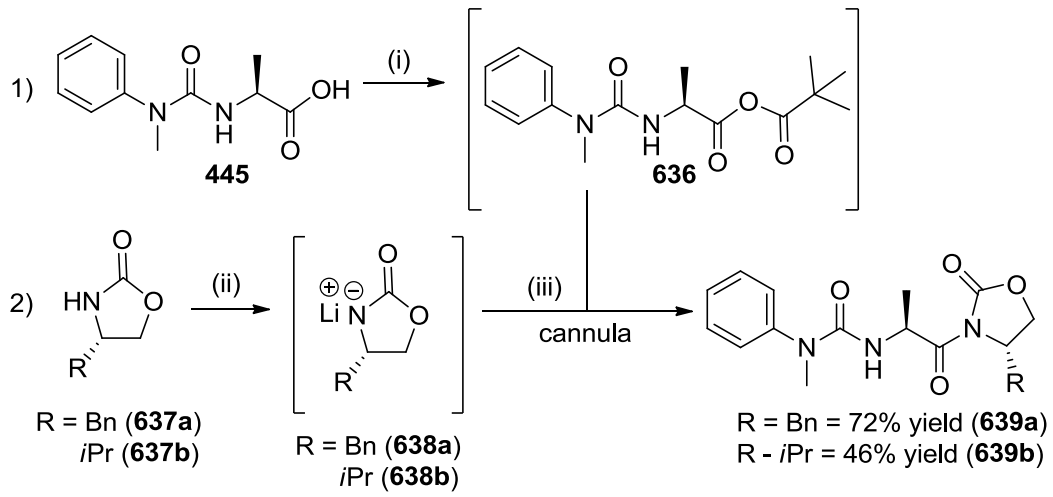



**Scheme 167: Reagents and conditions: (i) 1.5 eq. (*S*,*S*)-pseudoephenamine (634), 1.2 eq. EDC·HCl, 1.0 eq. HOBt·$H_2O$, 1.2 eq. DiPEA, DCM, rt, 16 h; (ii) 4.0 eq. LDA, 2.0 eq. TMSCl, 7.0 eq. LiCl, THF, −78 °C – rt, 16 h**

In conclusion, of the auxiliaries that are similar to (*S*,*S*)-pseudoephedrine, (*R*,*R*)-pseudoephedrine gives comparable results showing there are no matched/mis-matched effects, (1*R*,2*S*)-ephedrine gives lower selectivity and (*S*,*S*)-pseudoephenamine gives comparable selectivity but a significantly lower yield.

Next, other common chiral auxiliaries such as Evans' oxazolidinones were investigated. Attempts to couple the benzyl version of Evans' oxazolidinones **637a** to unprotected carboxylic acid **445** using the standard peptide coupling conditions of EDC·HCl, HOBt·$H_2O$ and DiPEA were unsuccessful. Even with deprotonation of the auxiliary with sodium hydride prior to coupling, these conditions were unsuccessful. For a successful coupling, carboxylic acid **445** had to be activated with pivaloyl chloride to form mixed anhydride **636** and auxiliary **637a** was deprotonated with *n*BuLi giving **638a**. The two components were combined *via* cannula to give benzyl product **639a** in a 72% yield (Scheme 168).

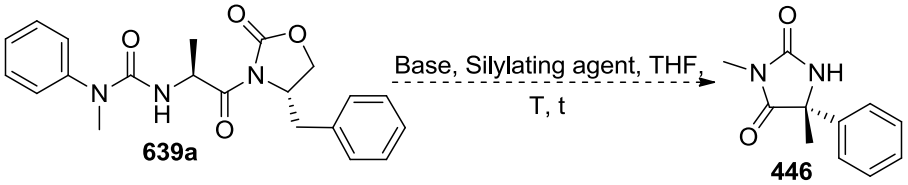
[xxii] With thanks for Dr. Fernando Fernández-Nieto for assisting with the synthesis of the pseudoephenamine




**Scheme 168: Reagents and conditions: (i) 1.2 eq. $Et_3N$, THF, 1.05 eq. PivCl, −78 °C – rt, 3 h then −78 °C; (ii) 1.1 eq. *n*BuLi, THF, −78 °C, 30 min; (iii) cannula at −78 °C, stir at −78 °C, 1 h 30, warm to rt, stir 18 h**

Starting material **639a** was subjected to different rearrangement conditions. It was expected that only 1 eq. of TMSCl would be needed as there was only the NH to protect (Table 29).

**Table 29: Rearrangement of 639a containing the benzyl Evans auxiliary**




| Entry | Base (n° eq.) | Silylating agent (n° eq.) | T (°C) | t (h) at rt | Yield 446 (%) |
|---|---|---|---|---|---|
| 1 | LDA (4.0) | TMSCl (1.0) | –78 – rt | o/n | 0 |
| 2 | LDA (3.0) | TMSCl (1.0) | –78 – 0[a] | 3.0 | 0 |
| 3 | LDA (3.0) | - | –78 - rt | o/n | 0 |
| 4 | LDA (3.0) | TMSCl (2.0) | –78 - 0 | 3.0 | 0 |
| 5 | LDA (4.0)[b] | TMSCl (2.0) | –78 | 3.0 | 0 |
| 6 | KHMDS (3.0) | TMSCl (1.0) | –78 - rt | o/n | 0 |
| 7 | NaHMDS (3.0) | TMSCl (1.0)[c] | –78 | 3.0 | 0 |

THF (0.1 M), Method: base + LiCl cooled to –78 °C, silylating agent added, stir 5 mins, substrate in THF added, stir 30 min at –78°C warm to temp stated, stir for time period stated. [a]Reaction repeated and left -78 °C throughout. [b]Reaction repeated with 5.0 eq. LDA. [c]Reaction repeated with no TMSCl.

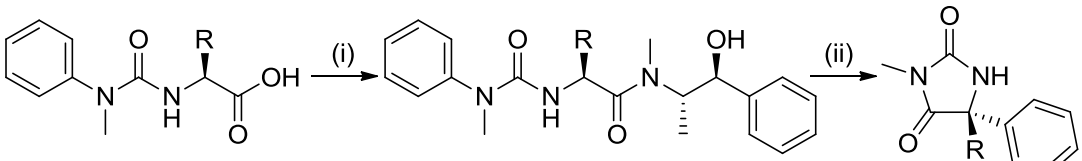
Unfortunately, under all the conditions trialled (entries 1-7, Table 29) starting material **639a** was unstable and the auxiliary was eliminated giving carboxylic acid **445** (isolated as a methyl ester due to a MeOH quench) and free auxiliary **637a**. Using LDA (3.0-5.0 eq.) in combination with TMSCl (1.0 - 2.0 eq.) at different temperatures was unsuccessful (entries 1-2, 4-5, Table 29). LDA without TMSCl (entry 3, Table 29) and using milder disilazide bases (entries 6-7, Table 29) gave the same outcome. To ensure this was not specific to the benzyl Evans auxiliary, isopropyl Evans auxiliary **637b** was coupled to carboxylic acid **445** to give **639b** in 46% yield (Scheme 168). Under similar rearrangement conditions the auxiliary **637b** was eliminated and no rearrangement occurred.

In conclusion, Evans oxazolidinones under the basic rearrangement conditions are eliminated and other chiral auxiliaries are likely to be the same as by their very nature they are good leaving groups. Pseudoephedrine is an exception to this as it is more stable due to the hydroxyl group (protected *in situ*) and is less likely to be eliminated. This work proved (*S*,*S*)-pseudoephedrine to be the best auxiliary for this reaction.

### 2.5.4 Enantioselective Rearrangement of Ureas with *in situ N*-Protection

The optimised conditions for alanine derivative **546** were: 4.0 eq. LDA, 2.0 eq. TMSCl, 7.0 eq. LiCl, THF, –78 °C – rt, o/n, giving hydantoin **446** in 65% yield and 92:8 *er*. These were applied to different amino acid derivatives to explore the scope of the reaction.

(*S*,*S*)-Pseudoephedrine (**512**) was coupled to the unprotected carboxylic acids of butyrine (R = ethyl) (**458**), leucine (**460**) and methionine (**461**) (synthesised in Chapter 2.3, Scheme 102) using peptide coupling conditions. These examples were then subjected to the rearrangement protocol (Scheme 169). For α-aminobutyric acid derivative **640**, 4.0 eq. of LDA were used. In the racemic version of this process (Chapter 2.3.2.1) more complex chains required more LDA, therefore 5 eq. of LDA were used for leucine **548** and methionine **641** examples. Table 9 shows the yields for the coupling, and the conditions, yield and *er* for the rearrangement.




But: **458**
Leu: **460**
Met: **461**

But: **640**
Leu: **548**
Met: **641**

But: **21**
Leu: **464**
Met: **465**

**Scheme 169: Reagents and conditions: (i) 1.5 eq. (*S*,*S*)-pseudoephedrine (512), 1.2 eq. EDC·HCl, 1.0 eq. HOBt·$H_2O$, 1.2 eq. DiPEA, DCM, rt, 16-20 h; (ii) 4.0-5.0 eq. LDA, 2.0 eq. TMSCl, 7.0 eq. LiCl, THF, –78 °C – rt, 16 h**

**Table 30: Yields for the coupling and rearrangement of other amino acids**

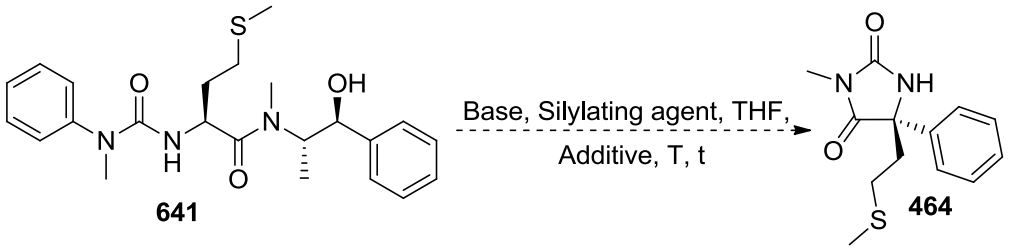
| Entry | SM | Coupled yield (%) | Rearrangement conditions[a] | Rearrangement yield (%)[b] | Rearrangement *er*[c] |
|---|---|---|---|---|---|
| 1 | But (**458**) | 66 (**640**) | LDA (4.0 eq.), TMSCl (2.0 eq.) | 49 | 94:6 |
| 2 | Leu (**460**) | 82 (**548**) | LDA (5.0 eq.), TMSCl (2.0 eq.) | 37[d] | 77:23 |
| 3 | Met (**461**) | 72 (**641**) | LDA (5.0 eq.), TMSCl (2.0 eq.) | 24 | 92:8 |

Method: base + LiCl cooled to –78 °C, TMSCl added, stir 5 mins, substrate in THF added, stir 30 min at –78 °C warm to room temp, stir for 16 h, quench with $NH_4Cl$, acidify with 1.0 M HCl, stir 30 mins. [a]All carried out with 7.0 eq. LiCl, THF, –78 – rt, o/n. [b]After purification by flash column chromatography. [c]Determined by HPLC. [d]Messy reaction.

(*S*,*S*)-Pseudoephedrine (**512**) was successfully coupled to all the corresponding carboxylic acids in good yields (66-82%). Pleasingly the rearrangement took place for all the examples with good *er*s obtained for the butyrine and methionine derivatives (entries 1, 3, Table 9). The *er* was lower for the leucine case (entry 2, Table 9), potentially due to the branched chain leading to additional steric bulk that may prevent the ring adding from the desired face, alternatively the reaction may go *via* a mixture of both (*Z*) and (*E*)-enolates leading to a moderate *er*. The yields for all three substrates were low (24-49%) and the methionine derivative **641** (entry 3, Table 9) significantly lower than alanine derivative **546** (24% *vs* 65%). This suggested that as the amino acids got more complex these conditions were not optimum, but it did prove that this *in situ* protection-rearrangement method should be applicable to a range of substrates.

To optimise the conditions further and have a standard set of conditions for all substrates, the methionine derivative **641** was chosen as it had given the lowest yield. The crude $^1$H NMR spectrum showed a number of other species alongside hydantoin **465**, indicating starting material **641** was decomposing under the reaction conditions before rearranging. The reaction is complex as it is a one pot protection, enolisation, rearrangement, cyclisation and deprotection. Under the conditions above (Table 30) the substrate was added to the LDA and TMSCl, but if deprotonation and protection do not occur immediately this could lead to complications. For example, there is potential for enolisation and rearrangement before all the starting material was N and O silyl protected (Method 1, Table 31). The protocol was modified to ensure protection of both the N and O prior to enolate formation. Substrate **641** was first added to 2 eq. of the LDA to deprotonate the NH and OH without deprotonation of the α-carbon. Then 2 eq. of TMSCl were added to protect both the urea anion and pseudoephedrine oxygen. To ensure protection had occurred the reaction was stirred for 30 min before a further 2 eq. of LDA were added to induce enolisation and rearrangement (Method 2, Table 31).

**Table 31: Optimisation of rearrangement conditions based on methionine derivative 641**



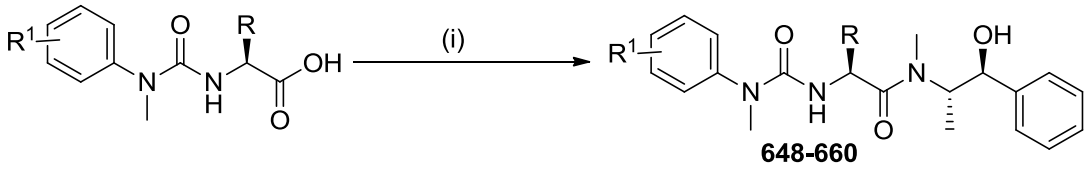

| Entry | Method | Conditions | Yield (464) (%)[a] | *er*[b] |
|---|---|---|---|---|
| 1 | 1[c] | 5.0 eq. LDA, 2.0 eq. TMSCl, 7.0 eq. LiCl, o/n, quench: 1.0 M HCl | 24 | 92:8 |
| 2 | 2[d] | [2.0 + 2.0]eq. LDA, 2.0 eq. TMSCl, 7.0 eq. LiCl, o/n, quench: 1.0 M HCl | 45 | 92:8 |
| 3 | 2[d] | [2.0 + 2.0]eq. LDA, 2.0 eq. TMSCl, 7.0 eq. LiCl, 3 h, quench: $K_2CO_3$, MeOH | 64 | 92:8 |
| 4 | 2[d] | [2.0 + 2.0]eq. LDA, 2.1 eq. TMSCl, 3 h, quench: $K_2CO_3$, MeOH | 70 | 93:7 |

All reactions carried out in THF, –78 °C – rt. [a]After purification by flash column chromatography. [b]Determined by HPLC [c]Method 1: All LDA + LiCl cooled to –78 °C, TMSCl added, stir 5 mins, substrate in THF added, stir 30 min at –78 °C warm to rt, stir o/n, quench with $NH_4Cl$, acidify with 1.0 M HCl, stir 30 mins. [d]Method 2: 2.0 eq. LDA + LiCl, cooled to –78 °C, substrate in THF added, stir for 15 mins, TMSCl added, stir 30 mins, further 2.0 eq. LDA added, stir 15 mins, warm to rt, stir for specified time period, quench as detailed.

Carrying out the reaction in a more controlled manner improved the yield from 24% to 45% with only 4 eq. of LDA needed (entry 2, Table 31). The crude $^1$H NMR using this method was cleaner than previously, but still contained silyl peaks between 0-1 ppm suggesting the quench to remove any protecting groups needed improving. The quench was changed from acidic to basic conditions using $K_2CO_3$ in MeOH, this generated methoxide that is known to cleanly remove TMS groups.[219] Additionally the reaction time was reduced to 3 h to prevent decomposition over time. These modifications further improved the yield of hydantoin **464** to 64% and the *er* was still good (entry 3, Table 31). Finally, since the OH of the pseudoephedrine was silyl protected the need for LiCl to block that face of the molecule is avoided. Therefore, LiCl was omitted from the reaction conditions leading to a final improvement to form **464** in an excellent 70% yield and 93:7 *er* for this complex one pot procedure (entry 4, Table 31). Since these conditions gave such a great improvement for the methionine example **641** these were the new optimised conditions and the substrate scope was explored.

(*S*,*S*)-Pseudoephedrine (**512**) was coupled using EDC·HCl, HOBt·$H_2O$ and DiPEA to a variety of different unprotected carboxylic acids with different amino acid side chains and different migrating

rings (carboxylic acids synthesised according to the procedure in Chapter 2.3, Scheme 102).[xxiii] The yields for starting materials of butyrine (R = ethyl) (**640**), leucine (**548**) and methionine (**641**) are shown in Table 30. The yield and conditions for the coupling of other unprotected carboxylic acids are shown in Scheme 170 and Table 32.




**648-660**

**Scheme 170: Reagents and conditions: (i) 1.5 eq. (*S*,*S*)-pseudoephedrine (512), 1.2 eq. EDC·HCl, 1.0 eq. HOBt·$H_2O$, 1.2 eq. DiPEA, DCM, rt, 17-69 h**

**Table 32: Yields for the coupling of pseudoephedrine to carboxylic acids with other amino acid side chains and migrating rings**

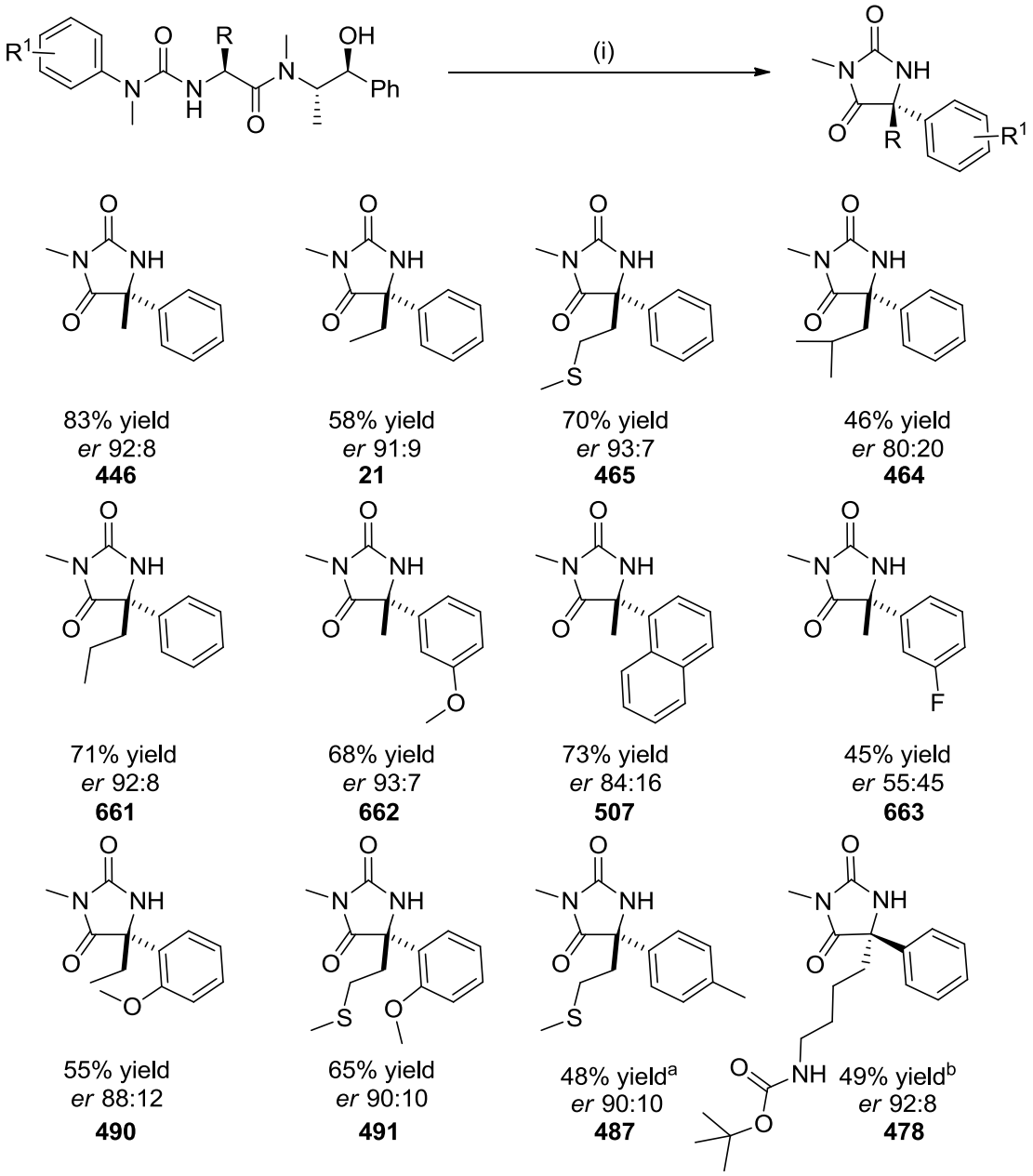
| Entry | R (SM) | $R^1$ | Yield (%)[a] | Product |
|---|---|---|---|---|
| 1 | Allyl (**642**) | H | 80 | **648**[b] |
| 2 | Ala (**643**) | *m*-OMe | 72 | **650** |
| 3 | Ala (**644**) | 1-naphthyl | 82 | **651** |
| 4 | Ala (**645**) | *m*-Cl | 75 | **652** |
| 5 | Ethyl (**488**) | *o*-OMe | 79 | **653** |
| 6 | Ethyl (**646**) | *p*-Cl | 70 | **654** |
| 7 | Met (**489**) | *o*-OMe | 76 | **655** |
| 8 | Met (**486**) | *p*-Me | 72 | **656** |
| 9 | Met (**647**) | *p*-Cl | 78 | **657** |
| 10 | Phe (**462**) | H | 75 | **658** |
| 11 | Tyr (**476**) | H | 26 | **659** |
| 12 | *Nε*-Boc-Lys (**475**) | H | 72 | **660** |

[a]After purification by flash column chromatography. [b]Propyl derivative **649** was synthesised through hydrogenation of the allyl **648** example with 18% by weight Pd/C (10%) + $H_2$ in MeOH, rt, 25 h in a 89% yield.

All the examples were successfully coupled to (*S*,*S*)-pseudoephedrine (**512**) in 72-80% yield, except tyrosine derivative **476**, which gave **659** in a poor 26% yield (entry 12, Table 32). The propyl chain in **649** was introduced through hydrogenation of the allyl chain of **648** using palladium on carbon under a hydrogen atmosphere in an 89% yield (entry 2, Table 32).

*N*-unprotected urea pseudoephedrine starting materials were subjected to the optimised rearrangement conditions ([2.0 + 2.0] eq. LDA, 2.1 eq. TMSCl, THF, –78 – rt, 3 h). Gratifyingly, a variety of amino acid side chains with several aromatic rings have been successfully rearranged under the standard set of optimised conditions (Scheme 171).

[xxiii] With thanks for Dr. Fernando Fernández-Nieto and Mary Okoh for synthesising many of the unprotected carboxylic acids




**Scheme 171: Reagents and conditions (i) [2.0 + 2.0]eq. LDA, 2.1 eq. TMSCl, THF, −78 – rt, 3-4 h, [a] 16.5 h, [b] [3.0 + 2.0]eq. LDA, 3.1 eq. TMSCl due to NH on lysine chain**

For a number of amino acid side chains the phenyl ring migrated successfully in an excellent yield and *er*. For the alanine **446**, methionine **465** and propyl **661** hydantoins the reaction was highly successful with yields above 70% and *er*s of greater than 92:8 observed. For ethyl derivative **21** the *er* was excellent but the yield lower due to some of the starting material decomposing to give eliminated urea **666** (Scheme 172) before rearrangement occurred. Leucine derivative **464** was obtained in a moderate yield and *er* due to its branched side chain making it the limit of the reaction scope. *Nε*-Boc-lysine derivative **660** required an extra equivalent of LDA and TMSCl to protect the NH in the side chain. The rearrangement took place in a good 49% yield and the

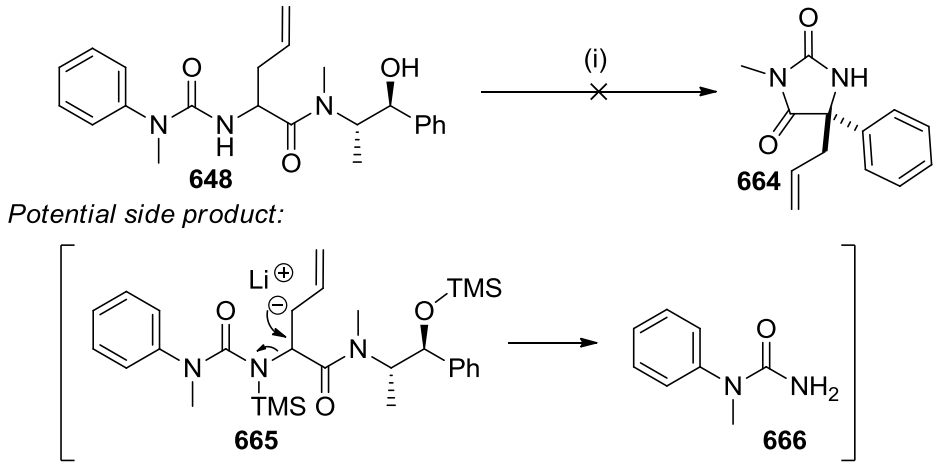
product **478** was obtained in an excellent *er* of 92:8. This showed remarkably that more complex amino acids were successful under these conditions and that pre-protection of the NH of the side chain was unnecessary.

Different migrating aromatic rings (Scheme 171):

- *m*-OMe ring rearranged in a good yield and *er* to give alanine derivative **661**.
- 1-Naphthyl ring rearranged in an excellent yield of 73% but the product had a slightly lower *er* of 84:16 in alanine derivative **507**.
- *m*-F ring rearranged in a moderate yield but the product **663** was virtually racemic (*er* 55:45). It could be that for electron deficient rings the reaction goes *via* a competing mechanism and potentially a reversible one leading to lower selectivity.[xxiv]
- *o*-OMe ring rearranged in good yields and *er*s to give butyrine **490** and methionine **491** derivatives, this was pleasing as these rings are often highly challenging to insert.[220]
- *p*-Me ring rearranged in a reasonable 48% yield but the product had an excellent *er* giving methionine derivative **487**.
- *m*-Cl or *p*-Cl rings (in starting materials **652**, **654**, **657**) were unsuccessful in the rearrangement resulting in decomposition. TMSCl and LDA with chlorine-containing rings may result in lithium-halogen exchange causing unwanted reactions.

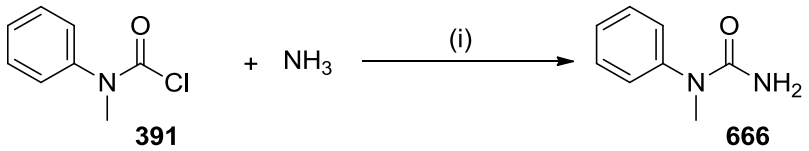
Substrates with acidic β-protons, such as allyl-substituted **648**, phenylalanine **658** and tyrosine **659** derivatives led to complex mixtures in the crude $^{1}$H NMR spectrum. A plausible reason for the failure of these reactions is due to deprotonation occurring at the β-carbon (**665**) rather than the α-carbon leading to elimination of the urea functionality to give **666** and decomposition of the other fragment (Scheme 172). This elimination was not observed in the rearrangements without the TMS protection because the urea nitrogen was deprotonated and contained a negative charge making a less favourable leaving group meaning this mechanism was unlikely.

[xxiv] With thanks for Dr. Fernando Fernández-Nieto for synthesising the starting material of the *m*F analogue with pseudoephedrine




**Scheme 172: Reagents and conditions: (i) [2.0 + 2.0]eq. LDA, 2.1 eq. TMSCl, THF, −78 – rt, 3 h**

To further prove this proposal an authentic sample of elimination product **666** was synthesised through reacting *N*-methyl-*N*-phenyl carbamoyl chloride (**391**) with an aqueous $NH_3$ solution (Scheme 173). Product **666** was isolated in an 86% yield and the $^1$H NMR spectrum was similar to the peaks observed in the crude $^1$H NMR spectrum of the allyl reaction, with a peak at ~ 3.3 ppm for the NMe (downfield of where the NMe is expected for hydantoin **664**).




**Scheme 173: Reagents and conditions: (i) 1.0 eq. *N*-methyl-*N*-phenyl carbamoyl chloride (391), 1.3 eq. $Et_3N$, 35% $NH_3$ solution, DCM, rt, 48.5 h**

Despite these limitations, the aim of synthesising enantiomerically enriched α-arylated quaternary amino acid derivatives across a wide substrate scope has been achieved successfully through development of an *in situ* protection-rearrangement protocol. This one pot method incorporates protection, enolisation, rearrangement, cyclisation and deprotection. Protection of the urea nitrogen was required for starting material stability when the pseudoephedrine was in place and protection of the pseudoephedrine oxygen blocked one face of the molecule leading to enantiomerically enriched products. Enolisation was achieved in a controlled fashion through addition of a second portion of LDA and rearrangement was stereoselective. Cyclisation occurred eliminating the chiral auxiliary and generating the hydantoin product. Deprotection was cleanly achieved upon work-up under basic conditions of $K_2CO_3$ in MeOH. The advantage of this *in situ* method is that it avoids the need for a separate protection step prior to rearrangement and a separate deprotection step prior to hydantoin hydrolysis. Additionally, there are very few other methods for the formation of enantiomerically enriched α-arylated quaternary amino acids. The few methods that do exist are mostly successful for only electron-deficient aryl rings, but this method is optimum for electron-

rich aryl rings. Currently, there is only one alternative method for the asymmetric α-arylation of amino acid derivatives with electron-rich rings. This was developed by Maruoka in 2015, but requires the use of stoichiometric chromium and a three-fold excess of the nucleophile.[150]

#### 2.5.4.1 Recovery of the Pseudoephedrine Chiral Auxiliary

One advantage of this method is the potential to recover the chiral auxiliary after the rearrangement reaction, as cyclisation occurs generating the hydantoin product and releasing the auxiliary. In an attempt to recover the pseudoephedrine (**512**) after the reaction the rearrangement of **546** was scaled up to 2.5 mmol. Unfortunately, scaling-up the reaction led to a lower 59% yield of hydantoin **446**, potentially due to a large volume of LDA being added that could have led to warming of the reaction. Despite this, the *er* for hydantoin **446** was 96:4 and 98% of the pseudoephedrine was recovered (based on the yield of hydantoin **446** formed). Recovery was possible during the work up through acidification of the aqueous layer, extraction of hydantoin **446** into EtOAc leaving the pseudoephedrine (**512**) in the aqueous. Basifying the acidic layer and extracting with DCM allowed the pseudoephedrine to be isolated, with the $^{1}$H NMR data matching an authentic sample. The recovered (*S*,*S*)-pseudoephedrine (**512**) was recrystallised from toluene leading to a melting point of 117-118 °C and $[\alpha]_D^{21}$ = +53.9 (*c* = 0.66, EtOH) consistent with a commercial sample of (*S*,*S*)-pseudoephedrine (mp: 118-120 °C, $[\alpha]_D^{20}$ = +52.0 (*c* = 0.6, EtOH) – Sigma Aldrich). This showed it was possible to recover the pseudoephedrine and there is potential to recycle the auxiliary and re-use it in the synthesis.

Finally, the *er* of hydantoin **446** was improved through crystallisation from chloroform. The racemate crystallised and the mother liquors contained enantiomerically enriched hydantoin **446** with an enhanced *er* of 99:1. The crystal structure for the racemate is shown below in Figure 45 (CCDC deposition number 1051080).

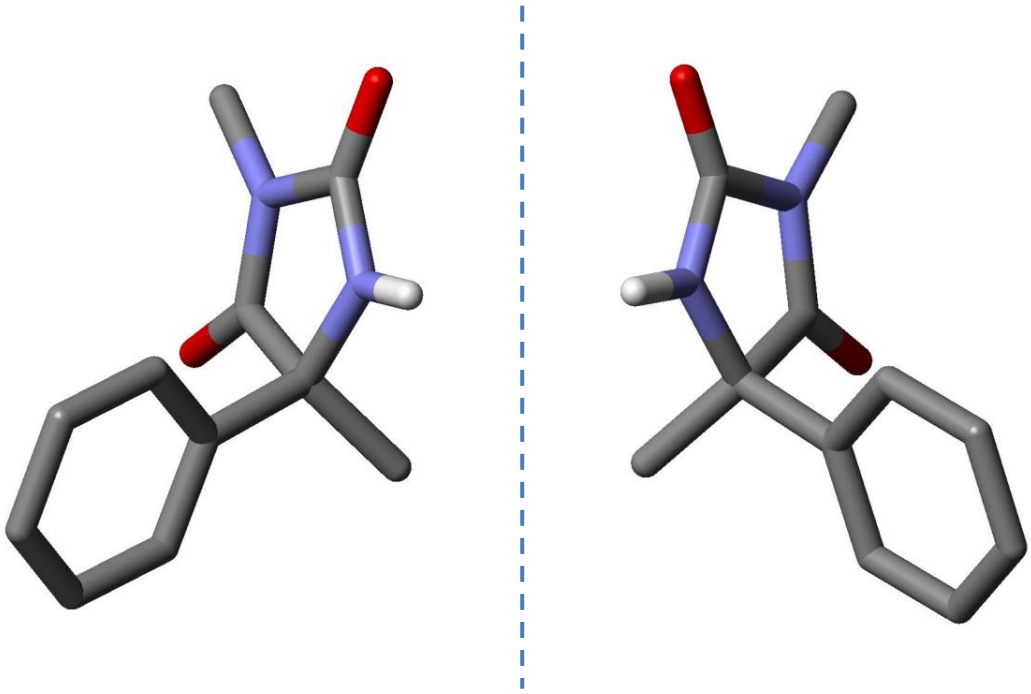


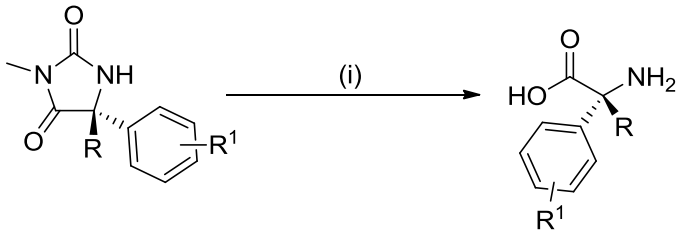
**Figure 45: Crystal structure of the racemate of 446**

### 2.5.5 Cleavage of *N*-Unprotected Hydantoins into Quaternary Amino Acids

To complete the aim of this project a few enantiomerically enriched hydantoin examples were hydrolysed into their quaternary amino acids under basic conditions (optimised in Chapter 2.3.2.2).

#### 2.5.5.1 Hydrolysis of *N*-Unprotected Hydantoins

The optimised conditions for hydantoin hydrolysis were refluxing the hydantoin in neat 4.0 M NaOH solution. The length of time depended on the hydantoin, as the amino acid side chain became more complex the reaction time also increased. Hydantoin cleavage occurred very quickly, but longer reaction times were required to convert the quaternary amino amide generated into the desired quaternary amino acid. The quaternary amino acids were isolated after acidification followed by purification using a Dowex® ion exchange resin. The yields and conditions are shown in Scheme 174 and Table 33.



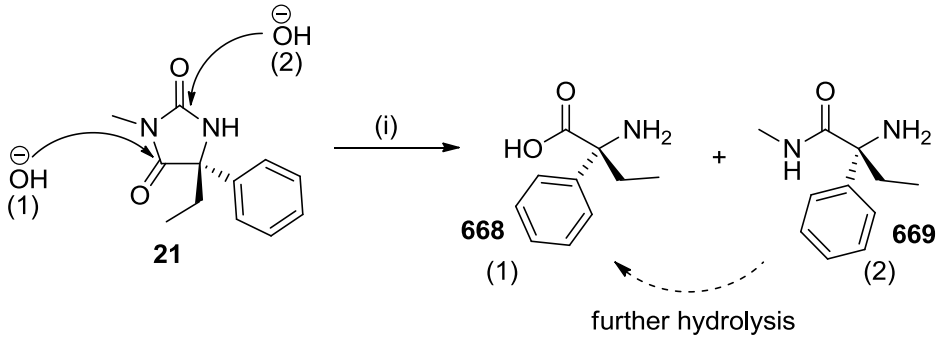

**Scheme 174: Reagents and conditions: (i) 4.0 M NaOH solution, reflux, 40 h – 7 d**

**Table 33: Yields for hydrolysis of hydantoins to quaternary amino acids**

| Entry | R | $R^1$ | SM | Time (h or d) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | Ala | H | **446** | 65 h | 92 (**508**) |
| 2 | Ala | *m*-OMe | **662** | 40 h | >99 (**667**) |
| 3 | Ethyl | H | **21** | 7 d | >99 (**668**) |

[a]After purification with Dowex® 50WX8 hydrogen form (100-200 mesh) ion exchange resin to remove any inorganics.

All the examples were successfully hydrolysed into enantiomerically enriched quaternary amino acids in excellent yields 92->99%. The length of time varied depending on the substrate, for the alanine examples **446** and **662** (entries 1, 2, Table 33) the hydrolysis was complete after 40-65 h but the ethyl example **21** required longer at reflux (entry 3, Table 33). After 96 h a mixture of the quaternary amino acid **668** and quaternary amino amide **669** was isolated (Scheme 175).




**Scheme 175: Reagents and conditions: (i) 4.0 M NaOH solution, reflux, 96 h**

To fully convert quaternary amino amide **669** into quaternary amino acid **668** a longer period was required under basic reflux. After seven days the conversion was complete and quaternary amino acid **668** isolated in an excellent yield of >99% (entry 3, Table 34).

### 2.5.5.2 Isolation of Quaternary Amino Acids as Quaternary Methyl Esters

Quaternary amino acids can be difficult to isolate and work with and are not very soluble. For convenience, quaternary amino acids **508**, **667**, **668** were converted into their corresponding quaternary amino esters **510**, **670**, **671**. Methyl ester formation was achieved using thionyl chloride in MeOH at reflux (Scheme 176).


**Scheme 176: Reagents and conditions: (i) $SOCl_2$, MeOH, 0 °C – reflux, 36 - 44.5 h**

**Table 34: Yields for methyl ester formation of the quaternary amino acids**

| Entry | R | $R^1$ | Time (h) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | Ala | H | 36 h | **510** = >99 |
| 2 | Ala | *m*-OMe | 36 h | **670** = 97 |
| 3 | Ethyl | H | 44.5 h | **671** = 96 |

[a]After purification through suspension in EtOH and filtration over cotton wool to remove any inorganics.

The quaternary amino acids **508**, **667**, **668** were conveniently converted into quaternary amino esters **510**, **670**, **671** in excellent yields (96->99%). The reaction was complete after 36 h for the alanine derivatives **508** and **667** (entries 1, 2, Table 34) and 44.5 h for the ethyl derivative **668** (entry 3, Table 34).

### 2.5.6 Absolute Configuration of the Products

The absolute configuration for the products was confirmed through comparison of their specific rotations with literature data. The hydrochloride salt of quaternary methyl ester **510**, synthesised from alanine derivative **446** has a literature value[216] of $[\alpha]_D^{20}$ = –51.8 (*c* = 0.5, MeOH) for its (*R*)-enantiomer. The specific rotation of enantiomerically enriched quaternary methyl ester **510** isolated after rearrangement (*er* 92:8), hydrolysis and methyl ester formation was $[\alpha]_D^{21}$ = –46.4 (*c* = 0.5, MeOH), proving **446** isolated from the *in situ* protection-rearrangement has a (*R*)-configuration. Hydantoin **21** is mephentoin, a known anti-epileptic drug that has a literature specific rotation[221] of $[\alpha]_D^{20}$ = –101.6 (*c* = 0.13, EtOH) for the (*R*)-enantiomer. The value for enantiomerically enriched hydantoin **21** isolated after the rearrangement (*er* 91:9), was $[\alpha]_D^{21}$ = –71.4 (*c* = 0.14, EtOH)[xxv] further confirming the (*R*)-configuration (Figure 46). The absolute configuration of all other hydantoins made from the *in situ* protection-rearrangement using the (*S*,*S*)-pseudoephedrine were assigned as (*R*) by analogy.

This was the inverse to the observation made for the pre-*N*-protected rearrangements (described in Chapter 2.4.9). The stereochemical outcome is opposite but about equal in magnitude, therefore this is most simply explained by a switch in enolate geometry leading to a different transition state.

[xxv] Also run in chloroform as a higher concentration could be achieved, $[\alpha]_D^{21}$ = –102.5 (*c* = 1.3, $CHCl_3$)

To prove there was no dependence on the stereochemistry of the starting amino acid and that the enantiomeric pseudoephedrine gave the opposite enantiomer, the reaction was carried out with the (*R*,*R*)-pseudoephedrine. Using (*S*,*S*)-pseudoephedrine (*R*)-hydantoin **446** (*er* 92:8) had $[\alpha]_D^{21}$ = –85.3 (*c* = 1.1, $CHCl_3$). The (*R*,*R*)-pseudoephedrine gave enriched hydantoin **ent-446** (*er* 10:90) with $[\alpha]_D^{21}$ = +73.5 (*c* = 0.8, $CHCl_3$), the opposite sign confirming the (*S*)-enantiomer was formed (Figure 46).

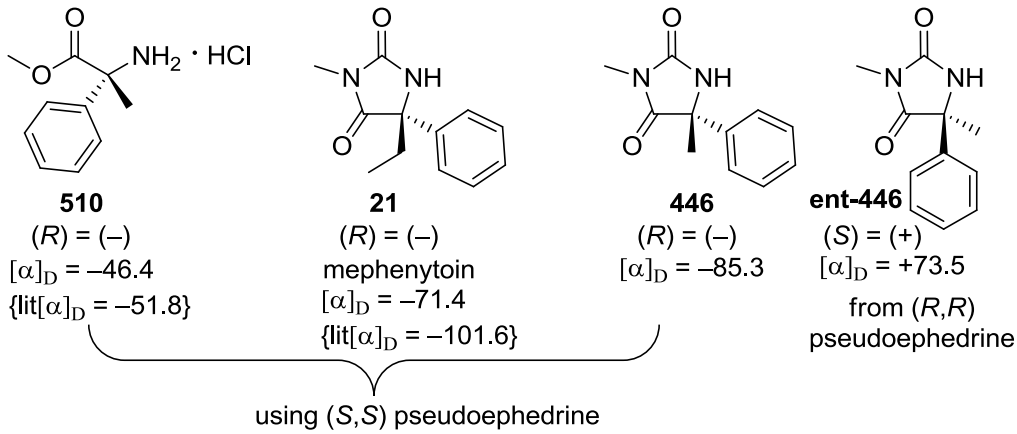
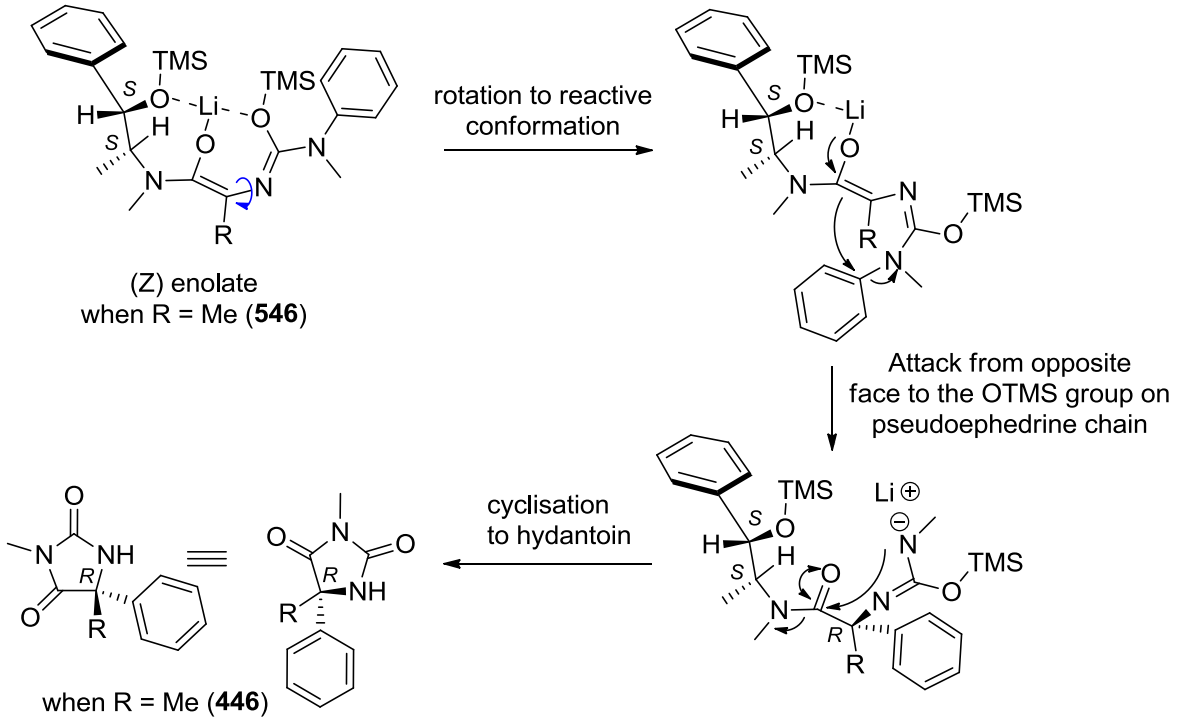



**Figure 46: The absolute configuration of the hydantoins from *in situ* protected rearrangements**

The stereochemical outcome can be rationalised by considering the enolate geometry and the face the rearrangement is directed from by the pseudoephedrine. The transition state suggested is based on models that Myers proposes. Myers suggests it is possible for tetra-substituted enolates to form both (*Z*) and (*E*)-enolates,[208] but showed in his asymmetric α-alkylation of amino acids[210] usually the (*E*)-enolate is formed preferentially.

For the *in situ* protection-rearrangement the urea anion is protected with TMSCl and the literature suggests the TMS group has a higher affinity for urea oxygen over the nitrogen[217,218] leading to a different environment compared with a urea that has a pre-protected nitrogen atom. It is proposed the transition state involves a (*Z*)-enolate, which is favourable as all three oxygen atoms can share one or more lithium cation(s) through coordination. Once the enolate geometry is set there is rotation of the urea into a reactive conformation. The aromatic ring then undergoes the intramolecular nucleophilic aromatic substitution with attack of the aromatic ring from the bottom face of the enolate. This is the same face as the methyl group α to the nitrogen of the pseudoephedrine and opposite to the bulky oxygen of the pseudoephedrine that is protected by the TMS group and co-ordinated to lithium and solvent. This results in the (*R*) configuration of the hydantoin after cyclisation and release of the pseudoephedrine (Scheme 177).




**Scheme 177: Proposed transitions state involving a (*Z*)-enolate**

In conclusion, when the nitrogen is protected (by either DMB or methyl) the rearrangement goes *via* an (*E*)-enolate meaning (*S*,*S*)-pseudoephedrine generates (*S*)-products and the (*R*,*R*)-pseudoephedrine generates (*R*)-products. The opposite is true for the *in situ* unprotected rearrangement that is proposed to go *via* a (*Z*)-enolate meaning (*S*,*S*)-pseudoephedrine generates (*R*)-products and the (*R*,*R*)-pseudoephedrine generates (*S*)-products.

## 2.6 Conclusion

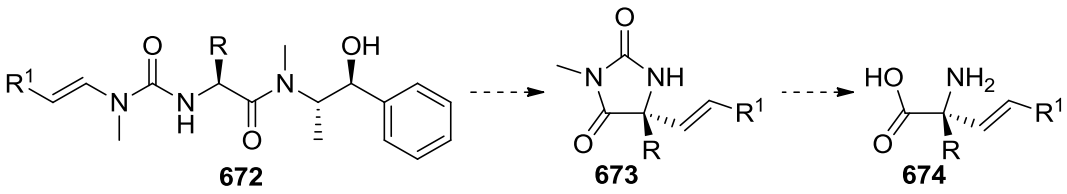
In conclusion, amino acid enolates have been thoroughly investigated as a new class of nucleophile for the rearrangement chemistry. This has led to a new synthetic method for the asymmetric α-arylation of readily available amino acids. This is one of only a few asymmetric α-arylation protocols and demonstrates one of the first methods that is optimum with electron-rich aromatic rings, in addition to being transition-metal free.

Initially, a method was developed for the synthesis of racemic α-arylated quaternary amino acid derivatives through intramolecular arylation of amino acid enolates and the reaction mechanism was studied by *in situ* ReactIR. This method is one of very few transition-metal free amino acid arylation procedures and is achieved through an intramolecular delivery of an aromatic ring using a urea tether.[222] Modification of the methodology allowed the synthesis of racemic α-arylated quaternary amino acids through an unprotected rearrangement, showing a large substrate scope for the hydantoin products. This work fulfilled the first aim of the project of establishing if the rearrangement was possible for enolate nucleophiles and exploring the reaction scope.

Since the deprotonation to form an enolate proceeds *via* a planar enolate anion, the reaction from a carboxylate generated racemic products due to the absence of a chiral controller within the system. The second aim of the project was to synthesise enantiomerically enriched α-arylated quaternary amino acid derivatives through enantioselective rearrangement with a chiral auxiliary. Various protecting groups were investigated and the rearrangement was successful with both nitrogen atoms protected; double methyl protection or alternatively one methyl and the other DMB protected. Both methods generated enantiomerically enriched hydantoins but neither method gave good yields and enantiomeric ratios across a large substrate scope. Gratifyingly, a method was developed that involved an *in situ* protection using TMSCl and generated α-arylated quaternary amino acid derivatives across a wide substrate range with good yields and enantiomeric ratios. The auxiliary was released at the end of the reaction and was successfully recovered. The enantiomerically enriched unprotected hydantoins generated from this rearrangement were successfully hydrolysed to give α-arylated quaternary amino acids and conveniently converted into α-arylated quaternary methyl esters. Finally, the absolute configuration of the products was established and rationalised through consideration of the enolate geometry and pseudoephedrine's control.

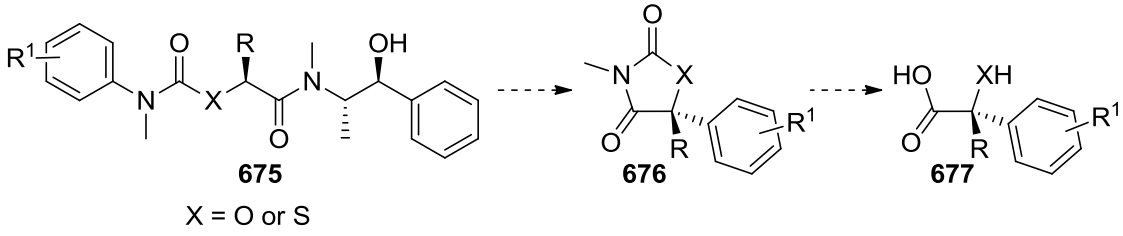
## 2.7 Future Work

The future work for this project will be to investigate vinyl group migration in combination with enolate nucleophiles **672** to extend the scope even further and give a handle for further functionalisation (**674**) (Scheme 178).



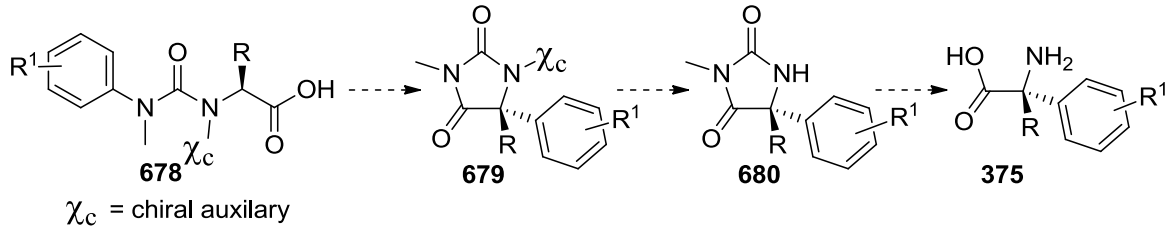

**Scheme 178: Vinyl migration with enolate nucleophiles**

In addition, the urea functionality will be substituted for carbamate or thiocarbamate functionality as these structures were successful in the rearrangement with benzylic nucleophiles.[174,177] This will give access to enantiomerically enriched α-arylated quaternary α-hydroxy carboxylic acids and α-arylated quaternary α-sulfuryl carboxylic acids (**677**) (Scheme 179). The vinyl migration can also be applied to enolates in combination with carbamates and thiocarbamates.



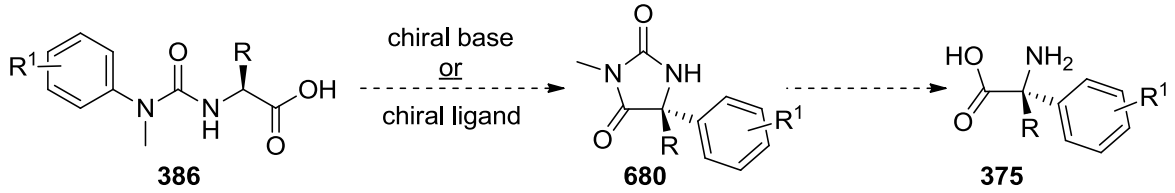

**Scheme 179: α-Arylation of carbamate and thiocarbamate derivatives**

Alternatively, the auxiliary could be changed but located in a different position on the starting material to prevent its loss prior to rearrangement. For example, an auxiliary could be placed on one of the nitrogen atoms and the rearrangement performed from the free carboxylic acid. This would involve an additional step for removal of the auxiliary after rearrangement but with the auxiliary being closer to the reactive centre this could lead to even higher enantiomeric ratios of the final products. Incorporation of the auxiliary in the hydantoin product **679** would lead to diasteromeric rather than enantiomeric hydantoin products meaning there would be potential for improving the *de* by purification (Scheme 180).




**Scheme 180: An alternative auxiliary at a different position in the starting material**

Finally, alternative approaches could be investigated to induce asymmetry into this reaction. Firstly, further work into the PMB protecting group as a mediator of chiral memory to generate enantiomerically enriched products from carboxylic acids (Chapter 2.4.5.1). Secondly, external sources such as chiral ligands and chiral bases will be explored as alternatives to auxiliaries or groups that are incorporated as part of the starting material (Scheme 181).




**Scheme 181: Asymmetry introduced through a chiral base or chiral ligand**

# 3 Experimental

## 3.1 General Information

All reactions were performed under a nitrogen atmosphere in flame-dried apparatus. All reagents and chemicals were bought from chemical suppliers and used without further purification (unless otherwise stated). Tetrahydrofuran (THF) was distilled under nitrogen from sodium wire using benzophenone as an indicator. Dichloromethane (DCM) was obtained by distillation from calcium hydride under nitrogen. Toluene and $Et_2O$ were collected under inert conditions from an Innovative Technologies PureSolve PS-MP-5 solvent purification system. Pet.Ether indicates fractions of petroleum ether boiling at 40-60 °C. All solvents were removed under vacuum using a rotary evaporator. Diisopropylamine (DiPA) was obtained by distillation from calcium hydride under nitrogen. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) was distilled under reduced pressure from calcium hydride and stored over 4Å molecular sieves. Trimethylsilyl chloride (TMSCl) was distilled under reduced pressure from calcium hydride and stored under argon. Triethylamine ($Et_3N$) was stored over KOH. Lithium chloride (LiCl) was dried in the oven (>150 °C) and used directly. *n*-Butyllithium was used as a solution in hexanes (1.6 M from Sigma-Aldrich or 2.5 M from Acros Organics) and *s*-butyllithium was used as a solution in cyclohexane and hexane. They were titrated prior to use with *N*-benzylbenzamide in anhydrous THF.[223] Acetone/dry ice cooling baths were used to obtain –78 °C, acetonitrile/dry ice cooling baths were used to obtain –40 °C and other low temperatures were reached using a Thermo Scientific Haake Immersion Cooler EK90. Room temperature is between 16-24 °C.

Thin layer chromatography (TLC) was performed using commercially available pre-coated plates (Macherey-Nagel alugram SIL G/UV254). Visualisation was *via* UV light (at 254 nm) or by staining with phosphomolybdic acid or 'Seebach' dip (2.50 g phosphomolybdic acid hydrate, 1.00 g cerium (IV) sulphate tetrahydrate, 3.20 mL conc. $H_2SO_4$, 90.50 mL $H_2O$) followed by heating. Flash column chromatography used chromatography grade silica, 60Å particle size, 40-63 microns from Sigma-Aldrich and compounds were loaded as saturated solutions in the column eluent.

Capillary melting points were determined on a Stuart Scientific melting point SMP 10 apparatus and are uncorrected.

Optical rotations $[\alpha]_{\lambda}^{T}$ were recorded on a Perkin-Elmer 341 polarimeter with a path length of 1 dm or on an AA-100 polarimeter using a cell with a pathlength of 0.25 dm at 18-22 °C with the solvent and concentration (*c*) quoted in g/100 mL.

Nuclear Magnetic Resonance (NMR) spectra ($^{1}$H NMR and $^{13}$C NMR) were recorded on either Bruker Ultrashield 300 (Avance), 400 (Avance III or Avance III HD fitted with nitrogen cooled prodigy cold probe) or 500 MHz (Avance II) spectrometers. Chemical shifts, δ, are quoted in parts per million (ppm) downfield of trimethylsilane. Spectra were calibrated using the residual solvent peak for $CDCl_3$ ($\delta_H$: 7.26 ppm; $\delta_C$: 77.16 ppm), $CD_3OD$ ($\delta_H$: 3.31 ppm; $\delta_C$: 49.00 ppm), $D_2O$ ($\delta_H$: 4.79 ppm) and $(CD_3)_2SO$ ($\delta_H$: 2.50 ppm; $\delta_C$: 39.52 ppm) as appropriate.[224] Coupling constants (*J*) are reported to the nearest 0.1 Hz. The splitting patterns for the spectra assignment are abbreviated to: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin.), septet (sept.), multiplet (m), broad (br.) and some as a combination of these. Major and minor diastereomers are assigned as Maj D and Min D respectively and rotamers are assigned as Rot A and Rot B.

Infrared spectra were recorded on a Thermo Scientific iD5 ATR, FT-IR spectrometer, using a Universal ATR accessory for sampling, with absorption of most relevance quoted as ν in $cm^{-1}$ and the samples were run as solids or evaporated films.

Low and high resolution mass spectra were recorded mainly by staff at the University of Manchester. ESI were recorded on a Micromass Platform II or Waters QTOF; high resolution mass spectra (HRMS) were recorded on a Thermo Finnigan MAT95XP mass spectrometer or Waters QTOF. A small number of HRMS were recorded at the EPSRC UK National Mass Spectrometry Facility at Swansea University using the LTQ Orbitrap XL.

Enantiomeric and diastereomeric ratios were determined by chiral HPLC on a Hewlett-Packard system series 1050 or Agilent 1100 series or Agilent Technologies 1260 Infinity with UV detection at 254, 230 and 210 nm. A Daicel Chiralcel OD-H or Daicel ChiralPak® AD-H column with hexane:2-propanol (IPA) as the eluent was used for all separations, unless otherwise stated. If the temperature could be set the separation was performed at 25 °C, otherwise room temperature.

Microwave reactions were carried out in a Biotage Initiator microwave synthesizer.

The ReactIR *i*C10, made by Mettler Toledo was used for the *in situ* IR experiments. It was fitted with a K6 conduit, that is a silicon tipped 16mm probe, and uses an MCT detector. The data was collected using *i*C IR software (version 4.1.882) as supplied by Mettler Toledo. Nitrogen purge of the probe was used throughout the experiment and this was subtracted from all spectra as the background. Further to this, solvent spectra at the appropriate temperature for each experiment were taken and this was also subtracted from the data. Each spectrum represents 256 scans measured at a spectral resolution of 8 $cm^{-1}$ although provides data points approximately every 4 $cm^{-1}$.

During the synthesis of some alanine derived starting materials partial racemisation (ca. 60% *ee*) occurred. For clarity the structures are drawn as the major enantiomer rather than a mixture.[(a)]

## 3.2 General Procedures

**Procedure 1a:** *Urea formation from an amine and a carbamoyl chloride*

Amine·HCl (1.1 eq.), anhydrous 1,2-DCE (0.2-0.6 M) and $Et_3N$ (2.3 eq.) were combined and stirred for 10 min at room temperature. The carbamoyl chloride (1.0 eq.) and DMAP (catalytic amount) were added. The reaction mixture was then heated at reflux and left until TLC analysis showed the reaction was complete. The reaction mixture was cooled to room temperature then quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with DCM (×2). The combined organic layers were washed with 1.0 M HCl and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

**Procedure 1b:** *Urea formation from an amino ester and a carbamoyl chloride*

Ester·HCl (1.0 eq.) was dissolved in MeCN (0.34- 0.40 M) and $Et_3N$ (2.3 eq.) was added. The reaction mixture was stirred for 15 min at room temperature before the carbamoyl chloride (1.1 eq.) was added. The reaction mixture was heated to reflux and left overnight. The reaction mixture was cooled to room temperature when TLC analysis showed the reaction was complete. The reaction mixture was concentrated *in vacuo* then diluted with DCM and a saturated aqueous $NaHCO_3$ solution. This mixture was stirred for 10 min before the organic layer was separated and the aqueous layer extracted with DCM (×2). The combined organic layers were then washed once with 1.0 M HCl and once with brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was used without any further purification.

**Procedure 1c:** *Urea formation from a pre-made protected amine and a carbamoyl chloride*

Protected amine (1.1 eq.), anhydrous 1,2-DCE (0.2-0.6 M) and $Et_3N$ (1.3 eq.) were combined and stirred for 10 min at room temperature. The carbamoyl chloride (1.0 eq.) and DMAP (catalytic amount) were added. The reaction mixture was then heated at reflux and left until TLC analysis showed the reaction was complete. The reaction mixture was cooled to room temperature then quenched with saturated aqueous $NaHCO_3$ solution, the organic layer was separated and the aqueous layer was extracted with DCM (×2). The combined organic layers were washed with 1.0 M HCl and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

**Procedure 2a:** *Methylation of ureas*

The appropriate urea (1.0 eq.) was dissolved in anhydrous DMF (0.3 M) and MeI (3.0 eq.) was added. The solution was cooled to 0 °C before NaH (2.0 eq., 60% suspension in mineral oil) was added. The reaction was allowed to warm to room temperature and was monitored by TLC. Upon completion, the reaction mixture was quenched with MeOH and saturated aqueous $NH_4Cl$ solution was added before extracting with $Et_2O$ (×3). The combined organic extracts were washed with water (×2) and once with brine then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by removal of grease through washing with pentane, filtration over a plug of silica and extraction with EtOAc.

**Procedure 2b:** *Methylation of ureas with basified workup*

The appropriate urea (1.0 eq.) was dissolved in anhydrous DMF (0.1-0.4 M) and MeI (3.0 eq.) was added. The solution was cooled to 0 °C before NaH (2.0 eq., 60% suspension in mineral oil) was added. The reaction was allowed to warm to room temperature and was monitored by TLC. Upon completion, the reaction mixture was quenched with water and basified before extracting with $Et_2O$ (×3). The combined organic layers were washed with water (×2) and washed once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

**Procedure 3:** *Removal of tert-butyl group (TFA deprotection)*

The appropriate urea (1.0 eq.) was dissolved in anhydrous DCM (0.5-0.7 M) and TFA (0.5-0.7 M) was added dropwise. The reaction mixture was left to stir at room temperature and monitored by TLC. When the reaction was complete, the reaction mixture was diluted with DCM (3 × starting amount) and washed with water (×3). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

**Procedure 4:** *Removal of benzyl group (hydrogenation)*

Urea ester (1.0 eq.) was dissolved in MeOH (0.2 M) and nitrogen was bubbled through the solution before 10% palladium on carbon (10% by weight) was added. The reaction mixture was placed under a hydrogen atmosphere through use of a balloon and was left to stir at room temperature, monitoring by TLC. When the reaction was complete the solution was filtered over Celite®, washed with EtOAc and concentrated *in vacuo*. The crude product was used without any further purification.

**Procedure 5:** *Saponification of methyl/ether esters to a carboxylic acid*

The appropriate urea (1.0 eq.) was dissolved in a 2:1 THF:$H_2O$ mixture (0.05-0.08 M) and LiOH (15.0 eq.) was added. The reaction mixture was heated to 45 °C and left overnight and was cooled to room temperature when TLC analysis showed the reaction was complete. The mixture was then acidified with 3.0 M HCl and extracted with EtOAc (×3). The combined organic layer was washed once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was used without any further purification.

**Procedure 6:** *Rearrangement to form protected hydantoins*

To urea acid (1.0 eq.) was added anhydrous LiCl (3.0 eq.) and anhydrous THF (0.1 – 0.2 M relative to urea). The reaction mixture was cooled to –78 °C. In a separate flask LDA was prepared; anhydrous THF (0.6 – 1.6 M relative to DiPA) and DiPA (3.0 eq.) were cooled to 0 °C, *n*BuLi (3.0 eq.) was added dropwise and stirred for 10 min. The LDA was added dropwise to the reaction mixture and a colour change was observed. The reaction mixture was stirred at –78 °C for 5 min before being allowed to warm to room temperature and stirred for 3 h. The reaction was quenched *via* dropwise addition of 1.0 M HCl and stirred for 15-30 min, ensuring that the pH was acidic. The reaction mixture was extracted with EtOAc (×3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

**Procedure 7:** *Rearrangement and cyclisation to form racemic free hydantoins from carboxylic acids*

Urea acid (1.0 eq.) and LiCl (4.0 eq.) were dissolved in anhydrous THF (0.1 – 0.2 M relative to urea) and cooled to –78 °C. In a separate flask LDA (4.0-7.0 eq.) was prepared; anhydrous THF (1.4-2.6 M relative to DiPA) and DiPA (4.0-7.0 eq.) were cooled to 0 °C, *n*BuLi (4.0-7.0 eq.) was added dropwise and stirred for 10-15 min. LDA was then added dropwise to the flask cooled at –78 °C. The reaction mixture was then stirred for 10 min at –78 °C before warming to room temperature and stirring for 3 h. The reaction was then quenched with MeOH, stirred for 15 min, acidified with 1.0 M HCl and stirred for 30-50 min. The aqueous layer was extracted with EtOAc (×3) and the combined organic layers dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in anhydrous MeOH and thionyl chloride was added. The reaction mixture was stirred overnight to ensure full cyclisation. The reaction was then concentrated *in vacuo* and the crude product was purified by flash column chromatography.

**Procedure 8:** *Rearrangement to form racemic free hydantoins from esters*

Urea ester (1.0 eq.) was dissolved in anhydrous THF (0.1 M) and cooled to –78 °C. KHMDS solution (4.0 eq., 1.0 M in THF) was added dropwise and the reaction was stirred for 15 min at –78 °C before warming to room temperature and stirring until TLC analysis showed completion. The reaction was quenched with an aqueous saturated $NH_4Cl$ solution, stirred for 10 min and concentrated *in vacuo*. The residue was then dissolved in water and the aqueous layer was extracted with EtOAc (×3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was either triturated with $Et_2O$ or used without any further purification.

**Procedure 9:** *Coupling of the pseudoephedrine chiral auxiliary*

The appropriate urea (1.0 eq.) was dissolved in DCM (0.10-0.25 M) and cooled to 0 °C. HOBt·$H_2O$ (1.0 eq.), EDC·HCl (1.2 eq.) and DiPEA (1.2 eq.) were added and the reaction mixture was stirred until the solution was clear (15-40 min). (*S*,*S*)-Pseudoephedrine (1.5 eq.) was added and the mixture was stirred for 30 min at 0 °C before the reaction was warmed to room temperature. The pH was checked to ensure the reaction mixture was basic before the reaction was left overnight. The reaction was worked up once TLC analysis showed the reaction was complete. The reaction mixture was concentrated *in vacuo* and diluted with EtOAc, the organic layer was washed with a 5% aqueous $KHSO_4$ solution (×3), then with a saturated aqueous $NaHCO_3$ solution (×3) and once with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo.* The crude product was purified by flash column chromatography.

**Procedure 10:** *Benzylation of ureas*

The appropriate urea (1.0 eq.) was dissolved in anhydrous DMF (0.3 M) and benzyl bromide (3.0 eq.) was added. The solution was cooled to 0 °C before NaH (2.0 eq., 60% suspension in mineral oil) was added. The reaction was stirred at room temperature until complete by TLC analysis. The reaction mixture was quenched with MeOH and saturated aqueous $NH_4Cl$ solution was added, the aqueous layer was extracted with $Et_2O$ (×3). The combined organic extracts were washed with water (×3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

**Procedure 11:** *Reductive amination to insert protecting group*

$Et_3N$ (1.8 eq.) was added to amino ester hydrochloride (1.2 eq.) in anhydrous DCM (0.20-0.50 M) with molecular sieves (4Å). The reaction mixture was stirred for 10 min then aldehyde (1.0 eq.) was added. The reaction was stirred at room temperature overnight. The mixture was filtered and the organic layer was concentrated *in vacuo*. The crude residue was dissolved in anhydrous DCM:EtOH (1:1), cooled to 0 °C and $NaBH_4$ (1.6 eq.) was added portionwise. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was cooled to 0 °C and quenched with ice water followed by a solution of conc. HCl, then basified using a solution of 5.0 M NaOH. The organic layer was separated and the aqueous layer extracted with DCM (×2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

**Procedure 12:** *Selective rearrangement with in situ protection and deprotection*

A stock solution of LDA (8.0 eq.) was prepared; anhydrous THF (1.2-1.5 M relative to *n*BuLi) and DiPA (8.1 eq.) were cooled to 0 °C, *n*BuLi (8.0 eq.) was added dropwise and stirred for 20 min. A separate flask (reaction flask) was cooled to 0 °C and LDA (2.0 eq.) from the stock solution was added. The flask was placed under an argon atmosphere and cooled to –78 °C. In another flask the urea pseudoephedrine (1.0 eq.) was dissolved in anhydrous THF (0.15 M relative to urea) and added dropwise to the reaction flask. The reaction was stirred for 15 min then TMSCl (2.1 eq.) was added dropwise and the reaction was stirred for a further 30 min. Further LDA (2.0 eq.) was added from the stock solution and the reaction stirred for 15 min at –78 °C before warming to room temperature. The reaction was stirred for 3 h or until TLC showed the reaction was complete. The reaction was quenched *via* dropwise addition of MeOH (0.1 M) and stirred for 5 min before $K_2CO_3$ (5.0 eq.) was added and stirred for a further 30 min. The reaction mixture was concentrated *in vacuo* to remove the MeOH and THF, then water and EtOAc were added. The reaction mixture was extracted with EtOAc (×3), washed once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

**Procedure 13:** *Hydrolysis of hydantoins*

A freshly made NaOH solution (4.0 M) was added to the hydantoin (1.0 eq.) and the reaction was heated to reflux (probe set to 130 °C). The reaction mixture was heated until $^{1}$H NMR analysis (9:1 $D_2O$:MeOD NMR solvent) showed completion. The reaction mixture was then cooled to room temperature and the solvent was removed *in vacuo*. The residue was diluted with water and the reaction mixture acidified with 3.0 M HCl, an insoluble solid was formed that was filtered off using a sinter funnel under vaccum. The liquor containing the quaternary amino acid was then purified using a Dowex® 50WX8 hydrogen form (100-200 mesh) ion exchange resin. The acidic liquor was loaded onto the dowex (pre-washed with 3.0 M HCl) then the resin bound with the product was washed with water, then dioxane and further with water before the compound was eluted using a 35% aqueous $NH_3$ solution. This solution was then concentrated *in vacuo* to yield the title compound.

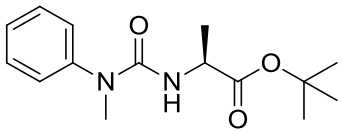
**Procedure 14:** *Derivatisation of the amino acids to amino esters*

Quaternary amino acid (1.0 eq.) was dissolved in MeOH (1.50-10.00 mL), cooled to 0 °C and thionyl chloride (0.15-0.80 mL) added dropwise. The reaction was then warmed to room temperature and heated to reflux. The reaction was heated until $^{1}$H NMR analysis (MeOD NMR solvent) showed completion. The reaction was then cooled to room temperature and concentrated *in vacuo.* To ensure all inorganic salts had been removed the product was dissolved in EtOH and filtration over cotton wool removed any salts. The filtrate was concentrated *in vacuo* to yield the title compound.

## 3.3 Experimental Data

**Synthesis of 395:**[xxvi]

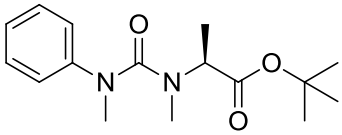
**(*S*)-*tert*-Butyl 2-(3-methyl-3-phenylureido)propanoate (393)**



Following general procedure **1a**, *N*-methyl-*N*-phenylcarbamoyl chloride (3.49 g, 20.58 mmol) and DMAP (cat.) were added to a pre-stirred solution of L-alanine *tert*-butyl ester hydrochloride (4.00 g, 22.08 mmol) and $Et_3N$ (6.59 mL, 47.30 mmol) in DCE (41.0 mL). The reaction was complete after 20 h at reflux. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (5.42 g, 19.47 mmol, 95%). **393: $R_f$** (4:1 Pet.Ether:EtOAc) 0.29; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.40-7.34 (2H, m, Ph*H*), 7.26-7.20 (3H, m, Ph*H*), 4.82 (1H, br. d, *J* = 7.0, N*H*CH), 4.33 (1H, quin., *J* = 7.0, NHC*H*$CH_3$), 3.21 (3H, s, NC$H_3$), 1.34 (9H, s, OC(C$H_3$)$_3$), 1.21 (3H, d, *J* = 7.0, CHC$H_3$); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 172.9 (*C*=O), 156.4 (*C*=O), 143.3 (Ar*C*N), 130.0 (2×Ar*C*H), 127.2 (Ar*C*H), 127.2 (2×Ar*C*H), 81.4 (*C*$(CH_3)_3$), 49.9 (NH*C*H$CH_3$), 37.1 (N*C*$H_3$), 28.0 (C(*C*$H_3$)$_3$), 19.2 (*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3343 (NH), 2978, 2934, 2879 (C-H), 1731 (C=O ester), 1664 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 279 ($[M+H]^+$, 60%), 301 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{15}H_{22}O_3N_2Na$ $[M+Na]^+$ 301.1523, found 301.1516.

*NMR file: $^1$H NMR = 2011-05-05-jpc-60 (20), $^{13}$C NMR = 2011-05-05-jpc-60 (21).*

**(*S*)-*tert*-Butyl 2-(1,3-dimethyl-3-phenylureido)propanoate (394)**



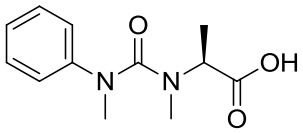
Following a similar method to general procedure **2a**, NaH (1.94 g, 48.75 mmol, 2.5 eq., 60% suspension) was added to urea **393** (5.42 g, 19.50 mmol) in DMF (48.8 mL). After 30 min MeI (3.64 mL, 58.50 mmol) was added. The reaction was left at 0 °C for 1 h before warming to room temperature. The reaction was complete after 22 h at room temperature. Purification by flash column chromatography ($SiO_2$, 9:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (4.27 g, 14.61 mmol, 75%). **394: $R_f$** (1:1 Pet.Ether:EtOAc) 0.69; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.34-7.30 (2H, m, Ph*H*), 7.16-7.08 (3H, m, Ph*H*), 4.66 (1H, q, *J* = 7.0, NC*H*$CH_3$), 3.23 (3H, s, NC$H_3$), 2.45 (3H, s, NC$H_3$), 1.45 (9H, s, OC(C$H_3$)$_3$), 1.27 (3H, d, *J* = 7.0, CHC$H_3$); **$^{13}$C {$^1$H} NMR**

[xxvi] During the synthesis partial racemisation (ca. 60% *ee*) occurred, structures drawn as the major enantiomer.[(a)]

(100 MHz, $CDCl_3$): $\delta_C$ = 171.3 (*C*=O), 161.6 (*C*=O), 146.7 (Ar*C*N), 129.4 (2×Ar*C*H), 124.4 (Ar*C*H), 124.0 (2×Ar*C*H), 81.2 (*C*($CH_3$)$_3$), 55.7 (N*C*H$CH_3$), 39.8 (N*C*$H_3$), 32.5 (N*C*$H_3$), 28.1 (C(*C*$H_3$)$_3$), 14.3 (*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2976, 2926, 2872, 2854 (C-H), 1732 (C=O ester), 1649 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 293 ([M+H]$^+$, 50%), 315 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{24}O_3N_2Na$ [M+Na]$^+$ 315.1680 found 315.1667.

*NMR file: $^1$H NMR = 2011-05-06-jpc-55 (11), $^{13}$C NMR = 2011-05-05-jpc-55 (12).*

**(*S*)-2-(1,3-Dimethyl-3-phenylureido)propanoic acid (395)**

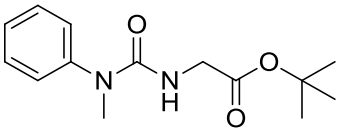


Following general procedure **3**, anhydrous DCM (20.0 mL) and TFA (20.0 mL) were added to urea **394** (4.27 g, 14.62 mmol). The reaction was complete after 4 h. Purification by flash column chromatography ($SiO_2$, 1:1 Pet.Ether:EtOAc to 100% EtOAc) yielded the title compound as a white solid (1.97 g, 8.33 mmol, 57%). **395: $R_f$** (1:1 Pet.Ether:EtOAc) 0.19; **mp**: 104-107 °C (recrystallised from EtOAc and Pet.Ether); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.40-7.37 (2H, m, Ph*H*), 7.23-7.20 (1H, m, Ph*H*), 7.15-7.13 (2H, m, Ph*H*), 4.48 (1H, q, *J* = 7.2, NC*H*$CH_3$), 3.33 (3H, s, NC$H_3$), 2.35 (3H, s, NC$H_3$), 1.35 (3H, d, *J* = 7.2, CHC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.7 (*C*=O), 162.8 (*C*=O), 145.5 (Ar*C*N), 129.5 (2×Ar*C*H), 125.2 (Ar*C*H), 124.3 (2×Ar*C*H), 55.5 (N*C*H$CH_3$), 39.7 (N*C*$H_3$), 33.5 (N*C*$H_3$), 13.9 (*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2982 (OH broad), 2938 (C-H), 1710 (C=O acid), 1644 (C=O urea); **MS** (ESI$^-$, MeOH): *m/z* = 235 ([M–H]$^-$, 100%); **HRMS**: (ESI$^+$) *m/z* calcd for $C_{12}H_{17}O_3N_2$ [M+H]$^+$ 237.1234, found 237.1239; **HPLC**: *er* 80:20, ChiralPak® AD-H, Hexane:IPA = 95:5, flow = 1.0 mL/min, λ = 262 nm, $t_R$ = 19 (major), 22 (minor) min.

*NMR file: $^1$H NMR = 2012-02-10-jpc-1 (10), $^{13}$C NMR = 2012-02-10-jpc-1 (11).*

**<u>Synthesis of 403:</u>**

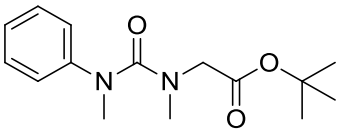
***tert*-Butyl 2-(3-methyl-3-phenylureido)acetate (399)**



Following general procedure **1a**, *N*-methyl-*N*-phenylcarbamoyl chloride (473 mg, 2.79 mmol) and DMAP (cat.) were added to a pre-stirred solution of glycine *tert*-butyl ester hydrochloride (500 mg, 2.98 mmol) and $Et_3N$ (0.89 mL, 6.41 mmol) in DCE (9.30 mL). The reaction was complete after 20 h at reflux. The title compound was yielded as a yellow oil without further purification (736 mg, 2.79 mmol, >99%). **399: $R_f$** (4:1 Pet.Ether:EtOAc) 0.15; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.46-7.41 (2H, m, Ph*H*), 7.33-7.28 (3H, m, Ph*H*), 4.79 (1H, br. s, N*H*CH), 3.86 (2H, d, *J* = 4.8,

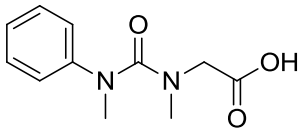
NHC*H*$_2$), 3.28 (3H, s, NC*H*$_3$), 1.43 (9H, s, OC(C*H*$_3$)$_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 170.0 (*C*=O), 156.8 (*C*=O), 143.0 (Ar*C*N), 130.0 (2×Ar*C*H), 127.4 (Ar*C*H), 127.3 (2×Ar*C*H), 81.7 (*C*(CH$_3$)$_3$), 43.3 (NH*C*H$_2$), 37.3 (N*C*H$_3$), 28.0 (C(*C*H$_3$)$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3370 (NH), 2977 (C-H), 1740 (C=O ester), 1657 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 287 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{20}O_3N_2Na$ [M+Na]$^+$ 287.1367, found 287.1377.
*NMR file: $^1$H NMR = 2012-06-21-jpc-32 (10), $^{13}$C NMR = 2012-06-21-jpc-32 (12).*

**_tert_-Butyl 2-(1,3-dimethyl-3-phenylureido)acetate (401)**



Following general procedure **2b**, MeI (0.52 mL, 8.36 mmol) and NaH (223 mg, 5.58 mmol) were added to urea **399** (736 mg, 2.79 mmol) in DMF (14.0 mL). The reaction was complete after 2 h at 0 °C. The reaction mixture was quenched with MeOH and saturated aqueous $NH_4Cl$ solution. The title compound was yielded as a yellow oil without further purification (775 mg, 2.79 mmol, > 99%). **401: $R_f$** (2:1 Pet.Ether:EtOAc) 0.42; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.36-7.31 (2H, m, Ph*H*), 7.20-7.17 (2H, m, Ph*H*), 7.13-7.09 (1H, m, Ph*H*), 3.85 (2H, s, NC*H*$_2$), 3.23 (3H, s, NC*H*$_3$), 2.60 (3H, s, NC*H*$_3$), 1.45 (9H, s, OC(C*H*$_3$)$_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 169.0 (*C*=O), 161.5 (*C*=O), 146.4 (Ar*C*N), 129.5 (2×Ar*C*H), 124.6 (Ar*C*H), 124.2 (2×Ar*C*H), 81.5 (*C*(CH$_3$)$_3$), 52.5 (N*C*H$_2$), 40.0 (N*C*H$_3$), 37.9 (N*C*H$_3$), 28.1 (C(*C*H$_3$)$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2927 (C-H), 1740 (C=O ester), 1650 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 301 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{22}O_3N_2Na$ [M+Na]$^+$ 301.1523, found 301.1521.
*NMR file: $^1$H NMR = 2012-06-21-jpc-33 (20), $^{13}$C NMR = 2012-06-21-jpc-33 (21).*

**2-(1,3-Dimethyl-3-phenylureido)acetic acid (403)**



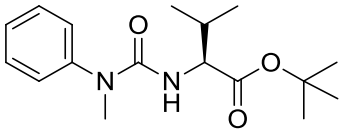
Following general procedure **3**, anhydrous DCM (5.00 mL) and TFA (5.00 mL) were added to urea **401** (769 mg, 2.77 mmol). The reaction was complete after 5 h. Purification by removal of grease through washing with pentane, filtration over a silica plug and extraction with EtOAc yielded the title compound as a white solid (369 mg, 1.66 mmol, 60%). **403: $R_f$** (2:1 Pet.Ether:EtOAc) 0.06; **mp** 104-107 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ =11.01 (1H, br. s, COO*H*), 7.34-7.30 (2H, m, Ph*H*), 7.18-7.10 (3H, m, Ph*H*), 3.95 (2H, s, NC*H*$_2$), 3.23 (3H, s, NC*H*$_3$), 2.56 (3H, s, NC*H*$_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 173.1 (*C*=O), 162.1 (*C*=O), 145.6 (Ar*C*N), 129.5 (2×Ar*C*H), 125.1 (Ar*C*H), 124.4 (2×Ar*C*H), 51.8 (N*C*H$_2$), 40.0 (N*C*H$_3$), 38.0 (N*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2931 (OH broad), 2931 (C-H), 1736 (C=O acid), 1592 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 223

([M+H]$^+$, 100%), 245 ([M+Na]$^+$, 40%); **HRMS** (ESI$^-$): *m/z* calcd for $C_{11}H_{13}O_3N_2$ [M–H]$^-$ 221.0931, found 221.0921.

*NMR file: $^1$H NMR = 2012-06-21-jpc-21 (11), $^{13}$C NMR = 2012-06-21-jpc-21 (13).*

**Synthesis of 404:**

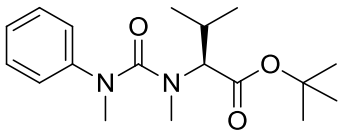
**(*S*)-*tert*-Butyl 3-methyl-2-(3-methyl-3-phenylureido)butanoate (400)**



Following general procedure **1a**, *N*-methyl-*N*-phenylcarbamoyl chloride (378 mg, 2.23 mmol) and DMAP (cat.) were added to a pre-stirred solution of L-valine *tert*-butyl ester hydrochloride (500 mg, 2.38 mmol) and $Et_3N$ (0.71 mL, 5.12 mmol) in DCE (11.2 mL). The reaction was complete after 20 h at reflux. The title compound was yielded as a yellow oil without further purification (647 mg, 2.11 mmol, 95%). **400: $R_f$** (4:1 Pet.Ether:EtOAc) 0.23; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.47-7.41 (2H, m, Ph*H*), 7.33-7.28 (3H, m, Ph*H*), 4.81 (1H, br. d, *J* = 8.4, N*H*CH), 4.34 (1H, dd, *J* = 8.7, 4.5, NHC*H*CH), 3.28 (3H, s, NC$H_3$), 2.11-2.00 (1H, m, C*H*$(CH_3)_2$), 1.42 (9H, s, OC(C$H_3$)$_3$), 0.89 (3H, d, *J* = 6.9, CH(C$H_3$)$_2$), 0.71 (3H, d, *J* = 6.9, CH(C$H_3$)$_2$); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 171.8 (*C*=O), 156.9 (*C*=O), 143.3 (Ar*C*N), 130.0 (2×Ar*C*H), 127.3 (Ar*C*H), 127.2 (2×Ar*C*H), 81.4 (*C*$(CH_3)_3$), 58.7 (N*C*H), 37.2 (N*C*$H_3$), 31.5 (*C*H$(CH_3)_2$), 28.3 (C(*C*$H_3$)$_3$), 27.6 (CH(*C*$H_3$)$_2$), 17.4 (CH(*C*$H_3$)$_2$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3428 (NH), 2966, 2933, 2874 (C-H), 1728 (C=O ester), 1670 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 329 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{26}O_3N_2Na$ [M+Na]$^+$ 329.1836 found 329.1834.

*NMR file: $^1$H NMR = 2012-10-03-jpc-51 (10), $^{13}$C NMR = 2013-03-25-jpc-50 (11).*

**(*S*)-*tert*-Butyl 2-(1,3-dimethyl-3-phenylureido)-3-methylbutanoate (402)**

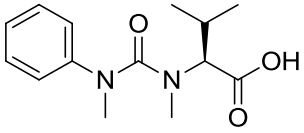


Following a similar method to general procedure **2b**, NaH (206 mg, 5.15 mmol, 2.5 eq., 60% suspension) was added to urea **400** (630 mg, 2.06 mmol) in DMF (10.3 mL). After 20 min MeI (0.38 mL, 6.18 mmol) was added. The reaction was left at 0 °C for 1 h before warming to room temperature. The reaction was complete after 1 h at room temperature. The reaction was quenched with water. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a white solid (610 mg, 1.91 mmol, 93%). **402: $R_f$** (4:1 Pet.Ether:EtOAc) 0.49; **mp**: 72-74 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.33-7.29 (2H, m, Ph*H*), 7.13-7.08 (3H, m, Ph*H*), 4.27 (1H, d, *J* = 10.4, NC*H*CH), 3.20 (3H, s, NC$H_3$), 2.49 (3H, s, NC$H_3$), 2.14-2.01 (1H, m, C*H*$(CH_3)_2$), 1.45 (9H, s, OC(C$H_3$)$_3$), 0.96 (3H, d, *J* = 6.8, CH(C$H_3$)$_2$), 0.85 (3H, d, *J* = 6.8,

CH(C*H*$_3$)$_2$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 170.8 (*C*=O), 162.6 (*C*=O), 146.7 (Ar*C*N), 129.4 (2×Ar*C*H), 124.6 (Ar*C*H), 124.4 (2×Ar*C*H), 81.1 (*C*(CH$_3$)$_3$), 65.3 (N*C*HCO$_2$C(CH$_3$)$_3$), 40.2 (N*C*H$_3$), 32.3 (N*C*H$_3$), 28.1 (C(*C*H$_3$)$_3$), 27.6 (*C*H(CH$_3$)$_2$), 19.8 (CH(*C*H$_3$)$_2$), 19.3 (CH(*C*H$_3$)$_2$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2970, 2933, 2875 (C-H), 1728 (C=O ester), 1651 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 343 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{18}H_{28}O_3N_2Na$ [M+Na]$^+$ 343.1993 found 343.1998.

*NMR file: $^1$H NMR = 2012-10-04-jpc-15 (10), $^{13}$C NMR = 2012-10-04-jpc-15 (11).*

**(*S*)-2-(1,3-Dimethyl-3-phenylureido)-3-methylbutanoic acid (404)**

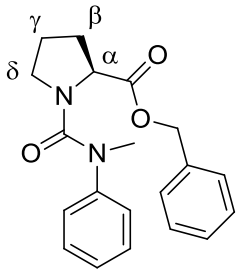



Following general procedure **3**, anhydrous DCM (2.50 mL) and TFA (2.50 mL) were added to urea **402** (400 mg, 1.25 mmol). The reaction was complete after 2 h. Purification by flash column chromatography ($SiO_2$, 1:1 Pet.Ether:EtOAc to 100% EtOAc) yielded the title compound as a pale yellow oil (304 mg, 1.15 mmol, 92%). **404: R$_f$** (1:1 Pet.Ether:EtOAc) 0.27; $[\alpha]_D^{20}$ = –207.4 (*c* = 1.5 in $CHCl_3$); **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 10.89 (1H, br. s, COO*H*), 7.39-7.34 (2H, m, Ph*H*), 7.23-7.13 (3H, m, Ph*H*), 3.91 (1H, d, *J* = 10.8, NC*H*CH), 3.29 (3H, s, NC*H*$_3$), 2.36 (3H, s, NC*H*$_3$), 2.22-2.10 (1H, m, C*H*(CH$_3$)$_2$), 1.01 (3H, d, *J* = 6.3, CH(C*H*$_3$)$_2$), 0.84 (3H, d, *J* = 6.6, CH(C*H*$_3$)$_2$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 171.4 (*C*=O), 164.7 (*C*=O), 144.6 (Ar*C*N), 129.7 (2×Ar*C*H), 126.3 (Ar*C*H), 125.4 (2×Ar*C*H), 67.3 (N*C*H), 40.2 (N*C*H$_3$), 34.1 (N*C*H$_3$), 26.6 (*C*H(CH$_3$)$_2$), 20.3 (CH(*C*H$_3$)$_2$), 19.5 (CH(*C*H$_3$)$_2$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2965 (OH broad), 2931, 2875 (C-H), 1726 (C=O acid), 1639 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 265 ([M+H]$^+$, 50%), 287 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{21}O_3N_2$ [M+H]$^+$ 265.1547 found 265.1548.

*NMR file: $^1$H NMR = 2013-03-26-jpc-58 (11), $^{13}$C NMR = 2012-10-04-jpc-52 (10).*

**<u>Synthesis of 410a:</u>**

**(*S*)-Benzyl 1-(methyl(phenyl)carbamoyl)pyrrolidine-2-carboxylate (409a)**

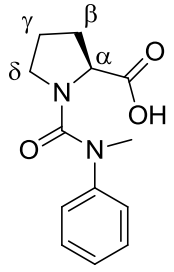



Following general procedure **1a**, *N*-methyl-*N*-phenylcarbamoyl chloride (983 mg, 5.80 mmol) and DMAP (cat.) were added to a pre-stirred solution of L-proline benzyl ester hydrochloride (1.50 g,

6.21 mmol) and $Et_3N$ (1.86 mL, 13.35 mmol) in DCE (9.70 mL). The reaction was complete after 20 h at reflux. The title compound was yielded as a yellow oil without further purification (1.96 g, 5.80 mmol, >99%). **409a: $R_f$** (1:1 Pet.Ether:EtOAc) 0.5; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.49-7.43 (5H, m, Ph*H*), 7.37-7.30 (4H, m, Ph*H*), 7.24-7.18 (1H, m, Ph*H*), 5.33 (1H, d, *J* = 12.3, OC$H_A$$H_B$Ph), 5.26 (1H, d, *J* = 12.3, OC$H_A$$H_B$Ph), 4.68-4.63 (1H, m, NC*H*CO(α)), 3.32 (3H, s, NC$H_3$), 3.09-3.02 (1H, m, NC$H_A$$H_B$(δ)), 2.81-2.73 (1H, m, NC$H_A$$H_B$(δ)), 2.30-2.20 (1H, m, C$H_A$$H_B$(β)), 1.89-1.72 (3H, m, C$H_2$(γ) + C$H_A$$H_B$(β)); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 173.0 (*C*=O), 159.3 (*C*=O), 145.8 (Ar*C*N), 135.9 (Ar*C*), 129.4 (2×Ar*C*H), 128.6 (2×Ar*C*H), 128.3 (3×Ar*C*H), 125.4 (2×Ar*C*H), 125.0 (Ar*C*H), 66.7 (O*C*$H_2$Ph), 60.4 (N*C*HCO(α)), 49.0 (N*C*$H_2$(δ)), 39.6 (N*C*$H_3$), 29.4 (*C*$H_2$(β)), 25.4 (*C*$H_2$(γ)); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2925, 2877 (C-H), 1742 (C=O ester), 1641 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 339 ([M+H]$^+$, 50%), 361 ([M+Na]$^+$, 100%), 377 ([M+K]$^+$, 80%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{22}O_3N_2Na$ [M+Na]$^+$ 361.1523, found 361.1519.

*NMR file: $^1$H NMR = 2012-08-20-jpc-5 (10) or 2012-08-07-jpc-8 (10), $^{13}$C NMR = 2012-08-20-jpc-5 (13).*

**(*S*)-1-(Methyl(phenyl)carbamoyl)pyrrolidine-2-carboxylic acid (410a)**

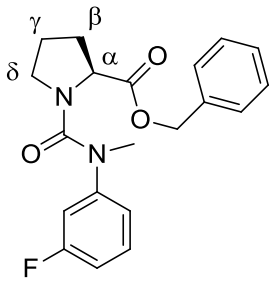



Following general procedure **4**, urea ester **409a** (1.47 g, 4.35 mmol) was dissolved in MeOH (20.0 mL) and palladium on carbon (150 mg) was added. The reaction was complete after 20 h. The title compound was yielded as a white solid without further purification (1.00 g, 4.03 mmol, 93%). **410a: $R_f$** (1:1 Pet.Ether:EtOAc) 0.1; **mp** 158-160 °C; $[\alpha]_D^{20}$ = –122.0 (*c* = 0.2 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.39-7.35 (2H, m, Ph*H*), 7.24-7.18 (3H, m, Ph*H*), 4.53 (1H, dd, *J* = 7.2, 4.8, NC*H*CO(α)), 3.28 (3H, s, NC$H_3$), 2.76-2.70 (1H, m, NC$H_A$$H_B$(δ)), 2.67-2.61 (1H, m, NC$H_A$$H_B$(δ)), 2.26-2.18 (1H, m, C$H_A$$H_B$(β)), 1.94-1.86 (1H, m, C$H_A$$H_B$(β)), 1.83-1.72 (1H, m, C$H_A$$H_B$(γ)), 1.71-1.61 (1H, m, C$H_A$$H_B$(γ)); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 174.2 (*C*=O), 160.7 (*C*=O), 144.9 (Ar*C*N), 129.7 (2×Ar*C*H), 126.0 (Ar*C*H), 125.7 (2×Ar*C*H), 61.0 (N*C*HCO(α)), 49.2 (N*C*$H_2$(δ)), 40.3 (N*C*$H_3$), 28.1 (*C*$H_2$(β)), 25.2 (*C*$H_2$(γ)); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3002 (OH broad), 2976, 2948, 2876 (C-H), 1721 (C=O acid), 1644 (C=O urea); **MS** (ESI$^-$, MeOH): *m/z* = 247 ([M–H]$^-$, 100%); **HRMS** (ESI$^-$): *m/z* calcd for $C_{13}H_{15}O_3N_2$ [M–H]$^-$ 247.1088, found 247.1088.

*NMR file: $^1$H NMR = 2012-08-20-jpc-6 (10), $^{13}$C NMR = 2012-08-20-jpc-6 (11).*

**Synthesis of 410b:**

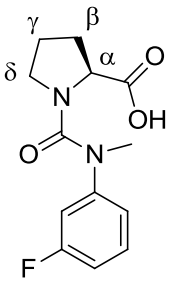
**(*S*)-Benzyl 1-((3-fluorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylate (409b)**



Following general procedure **1a**, *N*-(3-fluorophenyl)-*N*-methylcarbamoyl chloride (362 mg, 1.93 mmol) and DMAP (cat.) were added to a pre-stirred solution of L-proline benzyl ester hydrochloride (500 mg, 2.07 mmol) and $Et_3N$ (0.62 mL, 4.45 mmol) in DCE (4.80 mL). The reaction was complete after 20 h at reflux. Purification by flash column chromatography ($SiO_2$, 4:1 to 3:2 Pet.Ether:EtOAc) yielded the title compound as a yellow oil (649 mg, 1.82 mmol, 94%). **409b: $R_f$** (4:1 Pet.Ether:EtOAc) 0.13; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.38-7.31 (5H, m, Ph*H*), 7.21 (1H, dt, *J* = 6.4, 8.0, FAr*H*), 7.02 (1H, ddd, *J* = 8.0, 2.0, 0.8, FAr*H*), 6.97 (1H, dt, *J* = 10.4, 2.4, FAr*H*), 6.81 (1H, tdd, *J* = 8.0, 2.8, 0.8, FAr*H*), 5.23 (1H, d, *J* = 12.4, OC$H_A$H$_B$Ph), 5.17 (1H, d, *J* = 12.4, OCH$_A$$H_B$Ph), 4.58-4.54 (1H, m, NC*H*CO(α)), 3.22 (3H, s, NC$H_3$), 3.04-2.99 (1H, m, NC$H_A$H$_B$(δ)), 2.80-2.73 (1H, m, NCH$_A$$H_B$(δ)), 2.26-2.16 (1H, m, C$H_A$H$_B$(β)), 1.82-1.66 (3H, m, C$H_2$(γ) + CH$_A$$H_B$(β)); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 172.7 (*C*=O), 163.1 (d, $^1J_{C\text{-}F}$ = 245.0, Ar*C*F), 158.8 (*C*=O), 147.3 (Ar*C*N), 135.7 (Ar*C*), 130.3 (d, $^3J_{C\text{-}F}$ = 9.2, FAr*C*H), 128.5 (2×Ar*C*H), 128.3 (Ar*C*H), 128.2 (2×Ar*C*H), 120.4 (d, $^4J_{C\text{-}F}$ = 3.0, FAr*C*H), 112.0 (d, $^2J_{C\text{-}F}$ = 30.0, FAr*C*H), 111.5 (d, $^2J_{C\text{-}F}$ = 20.0, FAr*C*H), 66.7 (O*C*H$_2$Ph), 60.3 (N*C*HCO(α)), 49.0 (N*C*H$_2$(δ)), 39.2 (N*C*H$_3$), 29.4 (*C*H$_2$(β)), 25.4 (*C*H$_2$(γ)); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3064, 2953, 2879 (C-H), 1741 (C=O ester), 1645 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 357 ([M+H]$^+$, 100%), 379 ([M+Na]$^+$, 50%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{21}O_3N_2FNa$ [M+Na]$^+$ 379.1433, found 379.1436.

*NMR file: $^1$H NMR = 2013-01-16-jpc-2 (10), $^{13}$C NMR = 2013-01-16-jpc-2 (12).*

**(*S*)-1-((3-Fluorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylic acid (410b)**



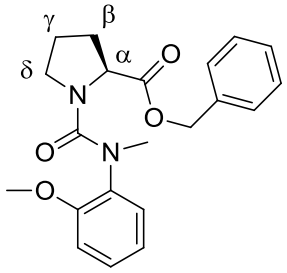
Following general procedure **4**, urea ester **409b** (602 mg, 1.69 mmol) was dissolved in MeOH (10.0 mL) and palladium on carbon (60 mg) was added. The reaction was complete after 20 h. The

title compound was yielded as a white solid without further purification (435 mg, 1.64 mmol, 97%). **410b: $R_f$** (1:1 Pet.Ether:EtOAc) 0.18; **mp** 143-145 °C; $[\alpha]_D^{20}$ = +92.4 (*c* = 1.0 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.32 (1H, dt, *J* = 6.8, 8.0, Ar*H*), 7.03 (1H, ddd, *J* = 8.0, 2.0, 0.8, Ar*H*), 6.98 (1H, dt, *J* = 10.0, 2.0, Ar*H*), 6.90 (1H, tdd, *J* = 8.0, 2.4, 0.8, Ar*H*), 4.57-4.53 (1H, m, NC*H*CO(α)), 3.27 (3H, s, NC$H_3$), 2.86-2.74 (2H, m, NC$H_2$(δ)), 2.15-2.01 (2H, m, C$H_2$(β)), 1.87-1.78 (1H, m, C$H_A$H$_B$(γ)), 1.76-1.66 (1H, m, CH$_A$$H_B$(γ)); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 175.3 (*C*=O), 163.2 (d, $^1J_{C\text{-}F}$ = 245.9, Ar*C*F), 159.9 (*C*=O), 146.8 (d, $^3J_{C\text{-}F}$ = 9.8, Ar*C*N), 130.6 (d, $^3J_{C\text{-}F}$ = 9.3, Ar*C*H), 120.9 (d, $^4J_{C\text{-}F}$ = 3.0, Ar*C*H), 112.6 (d, $^2J_{C\text{-}F}$ = 12.2, Ar*C*H), 112.3 (d, $^2J_{C\text{-}F}$ = 10.4, Ar*C*H), 60.7 (N*C*HCO(α)), 49.2 (N*C*H$_2$(δ)), 39.8 (N*C*H$_3$), 28.6 (*C*H$_2$(β)), 25.3 (*C*H$_2$(γ)); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2976 (OH broad), 2881 (C-H), 1740 (C=O acid), 1589 (C=O urea); **MS** (ESI$^-$, MeOH): *m/z* = 265 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{16}O_3N_2F$ [M+H]$^+$ 267.1140, found 267.1135.

*NMR file: $^1$H NMR = 2013-01-16-jpc-18 (11), $^{13}$C NMR = 2013-03-24-jpc-49 (10).*

**Synthesis of 410c:**

**(*S*)-Benzyl 1-((2-methoxyphenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylate (409c)**

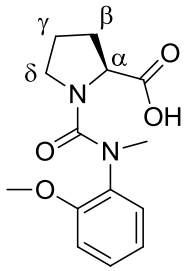



Following general procedure **1a**, *N*-(2-methoxyphenyl)-*N*-methylcarbamoyl chloride (385 mg, 1.93 mmol) and DMAP (cat.) were added to a pre-stirred solution of L-proline benzyl ester hydrochloride (500 mg, 2.07 mmol) and $Et_3N$ (0.62 mL, 4.45 mmol) in DCE (4.80 mL). The reaction was complete after 20 h at reflux. Purification by flash column chromatography ($SiO_2$, 3:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (694 mg, 1.88 mmol, 98%). **409c: $R_f$** (1:1 Pet.Ether:EtOAc) 0.35; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.38-7.30 (5H, m, Ph*H*), 7.21-7.17 (2H, m, OMeAr*H*), 6.91 (1H, dd, *J* = 8.8, 1.2, OMeAr*H*), 6.84 (1H, td, *J* = 7.6, 1.2, OMeAr*H*), 5.21 (1H, d, *J* = 12.4, OC$H_A$H$_B$Ph), 5.12 (1H, d, *J* = 12.4, OCH$_A$$H_B$Ph), 4.53-4.50 (1H, m, NC*H*CO(α)), 3.87 (3H, s, OC$H_3$), 3.08 (3H, s, NC$H_3$), 2.90-2.84 (1H, m, NC$H_A$H$_B$(δ)), 2.58-2.52 (1H, m, NCH$_A$$H_B$(δ)), 2.14-2.09 (1H, m, C$H_A$H$_B$(β)), 1.76-1.63 (3H, m, C$H_2$(γ) + CH$_A$$H_B$(β)); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 173.0 (*C*=O), 159.7 (*C*=O), 154.3 (Ar*C*OMe), 135.9 (Ar*C*N), 133.8 (Ar*C*), 128.6 (Ar*C*H), 128.5 (2×Ar*C*H), 128.1 (3×Ar*C*H), 127.5 (Ar*C*H), 121.1 (Ar*C*H), 111.5 (Ar*C*H), 66.5 (O*C*H$_2$Ph), 60.4 (N*C*HCO(α)), 55.4 (O*C*H$_3$), 48.0 (N*C*H$_2$(δ)), 37.7 (N*C*H$_3$), 29.5 (*C*H$_2$(β)), 25.3 (*C*H$_2$(γ)); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2957, 2880 (C-H), 1743 (C=O ester),

1639 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 369 ($[M+H]^+$, 100%), 391 ($[M+Na]^+$, 70%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{21}H_{25}O_4N_2$ $[M+H]^+$ 369.1809, found 369.1800.

*NMR file: $^1$H NMR = 2013-01-16-jpc-3 (21), $^{13}$C NMR = 2013-01-20-jpc-3 (23).*

**(*S*)-1-((2-Methoxyphenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylic acid (410c)**

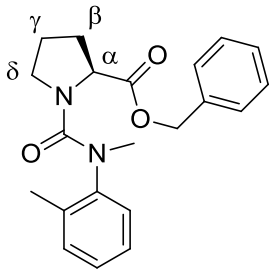



Following general procedure **4**, urea ester **409c** (678 mg, 1.84 mmol) was dissolved in MeOH (10.0 mL) and palladium on carbon (70 mg) was added. The reaction was complete after 20 h. The title compound was yielded as a white solid without further purification (511 mg, 1.84 mmol, >99%). **410c: $R_f$** (1:1 Pet.Ether:EtOAc) 0.21; **mp** 136-138 °C; $[\alpha]_D^{20}$ = –105.5 (*c* = 1.1 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 11.50 (1H, br. s, COO*H*), 7.27-7.23 (1H, m, Ar*H*), 7.20-7.18 (1H, m, Ar*H*) 6.98-6.93 (2H, m, Ar*H*), 4.53-4.50 (1H, m, NC*H*CO(α)), 3.87 (3H, s, OC$H_3$), 3.15 (3H, s, NC$H_3$), 2.66-2.55 (2H, m, NC$H_2$(δ)), 2.25-2.17 (1H, m, C$H_A$H$_B$(β)), 1.89-1.80 (1H, m, CH$_A$$H_B$(β)), 1.77-1.68 (1H, m, C$H_A$H$_B$(γ)), 1.68-1.59 (1H, m, CH$_A$$H_B$(γ)); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 173.6 (*C*=O), 161.4 (*C*=O), 154.4 (Ar*C*OMe), 132.8 (Ar*C*N), 128.5 (Ar*C*H), 128.4 (Ar*C*H), 121.4 (Ar*C*H), 111.9 (Ar*C*H), 61.3 (N*C*HCO(α)), 55.8 (O*C*H$_3$) 48.5 (N*C*H$_2$(δ)), 39.0 (N*C*H$_3$), 27.7 (*C*H$_2$(β)), 25.2 (*C*H$_2$(γ)); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2969 (OH broad), 2881 (C-H), 1740 (C=O acid), 1593 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 279 ($[M+H]^+$, 100%), 301 ($[M+Na]^+$, 40%), ($ESI^-$, MeOH): *m/z* = 277 ($[M–H]^-$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{14}H_{19}O_4N_2$ $[M+H]^+$ 279.1340, found 279.1343.

*NMR file: $^1$H NMR = 2013-01-17-jpc-36 (10), $^{13}$C NMR = 2013-01-17-jpc-36 (12).*

**<u>Synthesis of 410d:</u>**

**(*S*)-Benzyl 1-(methyl(2-methylphenyl)carbamoyl)pyrrolidine-2-carboxylate (409d)**

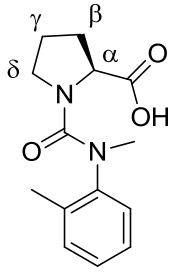



Following general procedure **1a**, *N*-methyl-*N*-(2-methylphenyl)carbamoyl chloride (355 mg, 1.93 mmol) and DMAP (cat.) were added to a pre-stirred solution of L-proline benzyl ester

hydrochloride (500 mg, 2.07 mmol) and $Et_3N$ (0.62 mL, 4.45 mmol) in DCE (4.80 mL). The reaction was complete after 20 h at reflux. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (654 mg, 1.85 mmol, 96%). **409d: $R_f$** (7:3 Pet.Ether:EtOAc) 0.32; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.37-7.30 (5H, m, Ph*H*), 7.22-7.20 (1H, m, $CH_3$Ar*H*), 7.17-7.08 (3H, m, $CH_3$Ar*H*), 5.23 (1H, d, *J* = 12.4, OC$H_A$$H_B$Ph), 5.12 (1H, d, *J* = 12.4, OC$H_A$$H_B$Ph), 4.53-4.49 (1H, m, NC*H*CO(α)), 3.08 (3H, s, NC$H_3$), 2.76-2.70 (1H, m, NC$H_A$$H_B$(δ)), 2.55-2.50 (1H, m, NC$H_A$$H_B$(δ)), 2.28 (3H, s, C$H_3$) 2.13-2.03 (1H, m, C$H_A$$H_B$(β)), 1.77-1.62 (3H, m, C$H_2$(γ) + C$H_A$$H_B$(β)); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 173.0 (*C*=O), 159.5 (*C*=O), 144.1 (Ar*C*N + Ar*C*), 135.9 (Ar*C*$CH_3$), 131.1 ($CH_3$Ar*C*H), 128.5 (2×Ar*C*H), 128.1 (2×Ar*C*H + $CH_3$Ar*C*H), 127.9 (Ar*C*H), 127.1 ($CH_3$Ar*C*H), 126.7 ($CH_3$Ar*C*H), 66.6 (O*C*$H_2$Ph), 60.7 (N*C*HCO(α)), 48.0 (N*C*$H_2$(δ)), 38.6 (N*C*$H_3$), 29.2 (*C*$H_2$(β)), 25.2 (*C*$H_2$(γ)), 17.7 (*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3029, 2957, 2880 (C-H), 1742 (C=O ester), 1638 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 353 ([M+H]$^+$, 100%), 375 ([M+Na]$^+$, 80%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{25}O_3N_2$ [M+H]$^+$ 353.1860, found 353.1867.

*NMR file: $^1$H NMR = 2013-01-17-jpc-37 (10), $^{13}$C NMR = 2013-01-17-jpc-37 (12).*

**(*S*)-1-(Methyl(2-methylphenyl)carbamoyl)pyrrolidine-2-carboxylic acid (410d)**

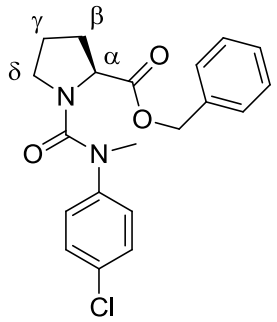



Following general procedure **4**, urea ester **409d** (617 mg, 1.75 mmol) was dissolved in MeOH (10.0 mL) and palladium on carbon (62 mg) was added. The reaction was complete after 20 h. The title compound was yielded as a white solid without further purification (454 mg, 1.73 mmol, 99%). **410d: $R_f$** (1:1 Pet.Ether:EtOAc) 0.14; **mp** 152-154 °C; $[\alpha]_D^{20}$ **=** –120.0 (*c* = 1.0 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 10.50 (1H, br. s, COO*H*), 7.24-7.17 (4H, m, Ar*H*), 4.51-4.47 (1H, m, NC*H*CO(α)), 3.14 (3H, s, NC$H_3$), 2.62-2.56 (1H, m, NC$H_A$$H_B$(δ)), 2.52-2.46 (1H, m, NC$H_A$$H_B$(δ)), 2.27 (3H, s, $CH_3$) 2.13-2.06 (1H, m, C$H_A$$H_B$(β)), 2.94-2.86 (1H, m, C$H_A$$H_B$(β)), 1.81-1.71 (1H, m, C$H_A$$H_B$(γ)), 1.69-1.59 (1H, m, C$H_A$$H_B$(γ)); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.7 (*C*=O), 160.5 (*C*=O), 143.2 (Ar*C*N), 135.0 (Ar*C*), 131.3 (Ar*C*H), 127.8 (Ar*C*H), 127.3 (Ar*C*H), 127.2 (Ar*C*H), 61.3 (N*C*HCO(α)), 48.2 (N*C*$H_2$(δ)), 39.2 (N*C*$H_3$), 28.0 (*C*$H_2$(β)), 25.2 (*C*$H_2$(γ)), 17.6 (*C*$H_3$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2971 (OH broad), 2881 (C-H), 1740 (C=O acid), 1576 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 263 ([M+H]$^+$, 30%), 285 ([M+Na]$^+$, 100%), (ESI$^-$, MeOH): *m/z* = 261 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{18}O_3N_2Na$ [M+Na]$^+$ 285.1210, found 285.1222.
*NMR file: $^1$H NMR = 2013-02-07-jpc-1 (10), $^{13}$C NMR = 2013-02-07-jpc-1 (11).*

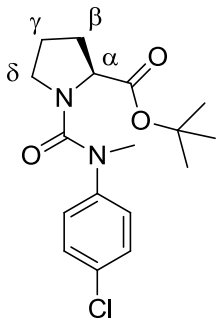
**Synthesis of 410e:**

**(S)-Benzyl 1-((4-chlorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylate (409e)**




Following general procedure **1a**, *N*-(4-chlorophenyl)-*N*-methylcarbamoyl chloride (394 mg, 1.93 mmol) and DMAP (cat.) were added to a pre-stirred solution of L-proline benzyl ester hydrochloride (500 mg, 2.07 mmol) and $Et_3N$ (0.62 ml, 4.45 mmol) in DCE (4.8 mL). The reaction was complete after 20 h at reflux. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (670 mg, 1.79 mmol, 93%). **409e:** **$R_f$** (7:3 Pet.Ether:EtOAc) 0.35; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.41-7.32 (5H, m, Ph*H*), 7.24-7.20 (2H, m, Ar*H*), 7.17-7.14 (2H, m, Ar*H*), 5.22 (1H, d, *J* = 12.4, OC$H_A$H$_B$Ph), 5.15 (1H, d, *J* = 12.4, OCH$_A$$H_B$Ph), 4.58-4.54 (1H, m, NC*H*CO(α)), 3.19 (3H, d, *J* = 1.5, NC$H_3$), 3.01-2.96 (1H, m, NC$H_A$H$_B$(δ)), 2.72-2.66 (1H, m, NCH$_A$$H_B$(δ)), 2.25-2.15 (1H, m, C$H_A$H$_B$(β)), 1.81-1.64 (3H, m, C$H_2$(γ) + CH$_A$$H_B$(β)); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 172.8 (*C*=O), 159.1 (*C*=O), 144.4 (Ar*C*N), 135.7 (Ar*C*Cl), 130.2 (Ar*C*), 129.4 (2×ClAr*C*H), 128.6 (2×Ar*C*H), 128.3 (Ar*C*H), 128.2 (2×Ar*C*H), 126.5 (2×ClAr*C*H), 66.8 (O*C*H$_2$Ph) 60.3 (N*C*HCO(α)), 49.1 (N*C*H$_2$(δ)), 39.4 (N*C*H$_3$), 29.4 (*C*H$_2$(β)), 25.4 (*C*H$_2$(γ)); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3034, 2971, 2879 (C-H), 1742 (C=O ester), 1645 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 373 ([M+H]$^+$, 100%), 395 ([M+Na]$^+$, 30%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{22}O_3N_2{}^{35}Cl$ [M+H]$^+$ 373.1313, found 373.1309.
*NMR file: $^1$H NMR = 2013-01-18-jpc-8 (12), $^{13}$C NMR = 2013-01-18-jpc-8 (10).*

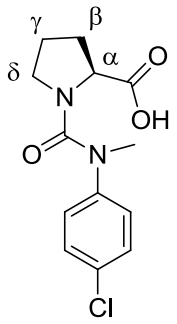
**(*S*)-*tert*-Butyl 1-((4-chlorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylate (413e)**



Following a similar method to general procedure **1a**, *N*-(4-chlorophenyl)-*N*-methylcarbamoyl chloride (530 mg, 2.60 mmol) and DMAP (cat.) were added to a pre-stirred solution of L-proline *tert*-butyl ester (446 mg, 2.60 mmol, 1.0 eq.) and $Et_3N$ (0.47 mL, 3.38 mmol, 1.3 eq.) in DCE (5.2 mL). The reaction was complete after 20 h at 45 °C. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a white solid (792 mg, 2.34 mmol, 90%). **413e: $R_f$** (4:1 Pet.Ether:EtOAc) 0.16; **mp** 115-117 °C; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.31-7.22 (4H, m, Ar*H*), 4.37-4.32 (1H, m, NC*H*CO(α)), 3.20 (3H, d, *J* = 1.5, NC$H_3$), 3.03-2.97 (1H, m, NC$H_A$H$_B$(δ)), 2.77-2.69 (1H, m, NCH$_A$$H_B$(δ)), 2.22-2.09 (1H, m, C$H_A$H$_B$(β)), 1.77-1.62 (3H, m, C$H_2$(γ) + CH$_A$$H_B$(β)), 1.48 (9H, d, *J* = 1.8, OC(C$H_3$)$_3$); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 172.0 (*C*=O), 158.9 (*C*=O), 144.5 (Ar*C*N), 129.8 (Ar*C*Cl), 129.3 (2×Ar*C*H), 126.1 (2×Ar*C*H), 80.9 (O*C*(CH$_3$)$_3$), 60.8 (N*C*HCO(α)), 49.0 (N*C*H$_2$(δ)), 39.2 (N*C*H$_3$), 29.5 (*C*H$_2$(β)), 28.0 (OC(*C*H$_3$)$_3$), 25.2 (*C*H$_2$(γ)); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2976, 2877 (C-H), 1735 (C=O ester), 1645 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 339 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{23}O_3N_2{}^{35}ClNa$ [M+Na]$^+$ 361.1289, found 361.1289.

*NMR file: $^1$H NMR = 2013-01-28-jpc-23 (10), $^{13}$C NMR = 2013-01-28-jpc-23 (11).*

**(*S*)-1-((4-Chlorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylic acid (410e)**



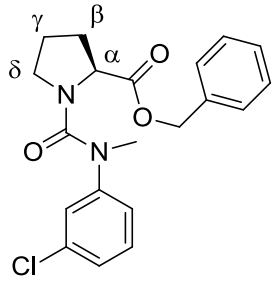
Following general procedure **3**, anhydrous DCM (3.00 mL) and TFA (3.00 mL) were added to urea **413e** (611 mg, 1.81 mmol). The reaction was complete after 4 h. The title compound was yielded as a pale yellow solid without further purification (413 mg, 1.45 mmol, 81%). **410e: $R_f$** (1:1 Pet.Ether:EtOAc) 0.08; **mp** 150-152 °C; $[\alpha]_D^{20}$ = +104.7 (*c* = 1.2 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 9.90 (1H, br. s, COO*H*), 7.34-7.30 (2H, m, Ar*H*), 7.23-7.20 (2H, m, Ar*H*), 4.54-4.50

(1H, m, NC*H*CO(α)), 3.24 (3H, s, NC$H_3$), 2.89-2.84 (1H, m, NC$H_A$H$_B$(δ)), 2.74-2.68 (1H, m, NC$H_A$H$_B$(δ)), 2.18-2.09 (1H, m, C$H_A$H$_B$(β)), 1.99-1.90 (1H, m, CH$_A$$H_B$(β)), 1.86-1.78 (1H, m, C$H_A$H$_B$(γ)), 1.76-1.65 (1H, m, CH$_A$$H_B$(γ)); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.7 (*C*=O), 159.9 (*C*=O), 143.8 (Ar*C*N), 130.9 (Ar*C*Cl), 129.6 (2×Ar*C*H), 126.8 (2×Ar*C*H), 60.6 (N*C*HCO(α)), 49.3 (N*C*H$_2$(δ)), 39.9 (N*C*H$_3$), 28.7 (*C*H$_2$(β)), 25.4 (*C*H$_2$(γ)); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2976 (OH broad), 2879 (C-H), 1737 (C=O acid), 1606 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 283 ([M+H]$^+$, 90%), 305 ([M+Na]$^+$, 100%), (ESI$^-$, MeOH): *m/z* = 281 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{15}O_3N_2{}^{35}ClNa$ [M+Na]$^+$ 305.0663, found 305.0663.

*NMR file: $^1$H NMR = 2013-02-05-jpc-52 (10), $^{13}$C NMR = 2013-02-05-jpc-23 (11).*

**Synthesis of 410f:**

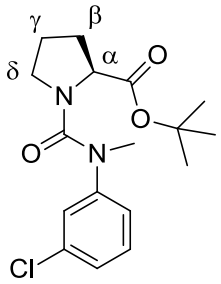
**(S)-Benzyl 1-((3-chlorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylate (409f)**




Following general procedure **1a**, *N*-(3-chlorophenyl)-*N*-methylcarbamoyl chloride (394 mg, 1.93 mmol) and DMAP (cat.) were added to a pre-stirred solution of L-proline benzyl ester hydrochloride (500 mg, 2.07 mmol) and $Et_3N$ (0.62 ml, 4.45 mmol) in DCE (4.80 mL). The reaction was complete after 20 h at reflux. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (646 mg, 1.74 mmol, 90%). **409f:** **$R_f$** (7:3 Pet.Ether:EtOAc) 0.42; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.38-7.31 (5H, m, Ph*H*), 7.24-7.23 (1H, t, *J* = 2.0, Ar*H*), 7.20-7.13 (2H, m, Ar*H*), 7.08 (1H, dt, *J* = 7.2, 2.0, Ar*H*), 5.23 (1H, d, *J* = 12.4, OC$H_A$H$_B$Ph), 5.17 (1H, d, *J* = 12.4, OCH$_A$$H_B$Ph), 4.58-4.54 (1H, m, NC*H*CO(α)), 3.21 (3H, s, NC$H_3$), 3.03-2.98 (1H, m, NC$H_A$H$_B$(δ)), 2.78-2.72 (1H, m, NCH$_A$$H_B$(δ)), 2.26-2.16 (1H, m, C$H_A$H$_B$(β)), 1.82-1.67 (3H, m, C$H_2$(γ) + CH$_A$$H_B$(β)); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 172.7 (*C*=O), 158.8 (*C*=O), 147.0 (Ar*C*N), 135.7 (Ar*C*Cl), 134.7 (Ar*C*), 130.3 (ClAr*C*H), 128.6 (2×Ar*C*H), 128.2 (3×Ar*C*H), 124.9 (ClAr*C*H), 124.8 (ClAr*C*H), 123.1 (ClAr*C*H), 66.8 (O*C*H$_2$Ph), 60.3 (N*C*HCO(α)), 49.1 (N*C*H$_2$(δ)), 39.3 (N*C*H$_3$), 29.4 (*C*H$_2$(β)), 25.4 (*C*H$_2$(γ)); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2972, 2879 (C-H), 1742 (C=O ester), 1646 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 395 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{21}O_3N_2{}^{35}ClNa$ [M+Na]$^+$ 395.1133, found 395.1134.

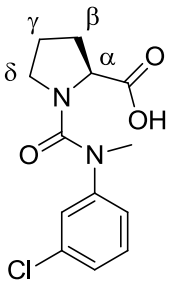
*NMR file: $^1$H NMR = 2013-01-17-jpc-38 (20), $^{13}$C NMR = 2013-01-17-jpc-38 (23).*

**(*S*)-*tert*-Butyl 1-((3-chlorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylate (413f)**



Following a similar method to general procedure **1a**, *N*-(3-chlorophenyl)-*N*-methylcarbamoyl chloride (498 mg, 2.44 mmol) and DMAP (cat.) were added to a pre-stirred solution of L-proline *tert*-butyl ester (418 mg, 2.44 mmol, 1.0 eq.) and $Et_3N$ (0.44 mL, 3.17 mmol, 1.3 eq.) in DCE (4.90 mL). The reaction was complete after 20 h at 45 °C. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (753 mg, 2.22 mmol, 91%). **413f: $R_f$** (4:1 Pet.Ether:EtOAc) 0.21; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.30-7.23 (3H, m, Ar*H*), 7.11-7.09 (1H, m, Ar*H*), 4.37-4.34 (1H, m, NC*H*CO(α)), 3.24 (3H, s, NC$H_3$), 3.06-3.01 (1H, m, NC$H_A$H$_B$(δ)), 2.84-2.78 (1H, m, NCH$_A$$H_B$(δ)), 2.23-2.14 (1H, m, C$H_A$H$_B$(β)), 1.83-1.67 (3H, m, C$H_2$(γ) + CH$_A$$H_B$(β)), 1.51 (9H, s, OC(C$H_3$)$_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 171.9 (*C*=O), 158.7 (*C*=O), 147.1 (Ar*C*N), 134.6 (Ar*C*Cl), 130.2 (Ar*C*H), 124.5 (Ar*C*H), 124.4 (Ar*C*H), 122.7 (Ar*C*H), 81.0 (O*C*(CH$_3$)$_3$), 60.9 (N*C*HCO(α)), 49.1 (NCH$_2$(δ)), 39.1 (NCH$_3$), 29.5 (*C*H$_2$(β)), 28.0 (OC(*C*H$_3$)$_3$), 25.2 (*C*H$_2$(γ)); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2977, 2877 (C-H), 1736 (C=O ester), 1649 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 339 ([M+H]$^+$, 100%), 361 ([M+Na]$^+$, 30%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{23}O_3N_2{}^{35}ClNa$ [M+Na]$^+$ 361.1289, found 361.1289.
*NMR file: $^1$H NMR = 2013-02-04-jpc-53 (20), $^{13}$C NMR = 2013-02-04-jpc-53 (23).*

**(*S*)-1-((3-Chlorophenyl)(methyl)carbamoyl)pyrrolidine-2-carboxylic acid (410f)**



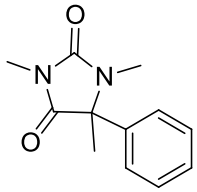
Following general procedure **3**, anhydrous DCM (3.00 mL) and TFA (3.00 mL) were added to urea **413f** (688 mg, 2.04 mmol). The reaction was complete after 2 h. The title compound was yielded as an off-white solid without further purification (514 mg, 1.82 mmol, 89%). **410f: $R_f$** (1:1 Pet.Ether:EtOAc) 0.08; **mp** 132-134 °C; $[\alpha]_D^{20}$ = +100.9 (*c* = 1.3 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 10.92 (1H, br. s, COO*H*), 7.29-7.25 (2H, m, Ar*H*), 7.22-7.19 (1H, m, Ar*H*), 7.14-7.11 (1H, m, Ar*H*), 4.56-4.52 (1H, m, NC*H*CO(α)), 3.24 (3H, s, NC$H_3$), 2.95-2.90 (1H, m, NC$H_A$H$_B$(δ)),

2.75-2.69 (1H, m, NCH$_A$*H$_B$*(δ)), 2.22-2.14 (1H, m, C*H$_A$*H$_B$(β)), 1.96-1.87 (1H, m, CH$_A$*H$_B$*(β)), 1.86-1.77 (1H, m, C*H$_A$*H$_B$(γ)), 1.77-1.66 (1H, m, CH$_A$*H$_B$*(γ)); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 176.2 (*C*=O), 159.5 (*C*=O), 146.5 (Ar*C*N), 134.8 (Ar*C*Cl), 130.4 (Ar*C*H), 125.3 (2×Ar*C*H), 123.5 (Ar*C*H), 60.4 (N*C*HCO(α)), 49.2 (N*C*H$_2$(δ)), 39.6 (N*C*H$_3$), 28.9 (*C*H$_2$(β)), 25.4 (*C*H$_2$(γ)); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2976 (OH broad), 2879 (C-H), 1738 (C=O acid), 1610 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 283 ([M+H]$^+$, 100%), 305 ([M+Na]$^+$, 60%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{15}O_3N_2{}^{35}ClNa$ [M+Na]$^+$ 305.0663, found 305.0659.

*NMR file: $^1$H NMR = 2013-02-05-jpc-54 (10), $^{13}$C NMR = 2013-02-05-jpc-54 (11).*

**Synthesis of racemic methylated hydantoins:**

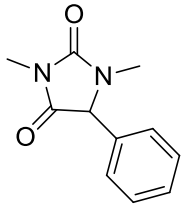
**1,3,5-Trimethyl-5-phenylimidazolidine-2,4-dione (±396)**



Following general procedure **6**, LiCl (276 mg, 6.52 mmol) and THF (17.0 mL) were added to urea acid **395** (513 mg, 2.17 mmol). LDA was prepared with DiPA (0.91 mL, 6.52 mmol), THF (5.00 mL) and *n*BuLi (2.61 mL, 6.52 mmol, 2.5 M in hexanes). Upon addition of LDA the reaction mixture turned yellow. Purification by flash column chromatography ($SiO_2$, 3:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow solid (422 mg, 1.93 mmol, 89%). ±**396: R$_f$** (1:1 Pet.Ether:EtOAc) 0.44; **mp** 81-83 °C;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **396**

**1,3-Dimethyl-5-phenylimidazolidine-2,4-dione (405)**[225]

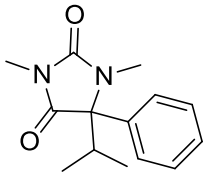


Following general procedure **6**, LiCl (67 mg, 1.57 mmol) and THF (4.20 mL) were added to urea acid **403** (116 mg, 0.52 mmol). LDA was prepared with DiPA (0.22 mL, 1.57 mmol), THF (1.00 mL) and *n*BuLi (1.30 mL, 1.57 mmol, 1.2 M in hexanes). Upon addition of LDA the reaction mixture turned pale yellow and with warming to room temperature turned orange. Purification by flash column chromatography ($SiO_2$, 3:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (85 mg, 0.42 mmol, 80%). **405: R$_f$** (3:2 Pet.Ether:EtOAc) 0.41; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.45-7.34 (3H, m, Ph*H*), 7.26-7.23 (2H, m, Ph*H*), 4.79 (1H, s, NC*H*C=O), 3.06 (3H, s, NC*H$_3$*), 2.89 (3H, s, NC*H$_3$*); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 171.3 (*C*=O), 156.9 (*C*=O),

132.5 (Ar*C*), 129.3 (3×Ar*C*H), 127.2 (2×Ar*C*H), 65.9 (N*C*H), 28.1 (N*C*H$_3$), 25.1 (N*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2918 (C-H), 1770 (C=O amide), 1702 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 227 ([M+Na]$^+$, 20%), 259 ([M+Na+MeOH]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{12}O_2N_2Na$ [M+Na]$^+$ 227.0791, found 227.0796. Matches literature data.

*NMR file: $^1$H NMR = 2012-07-17-jpc-48 (10), $^{13}$C NMR = 2012-07-17-jpc-48 (13).*

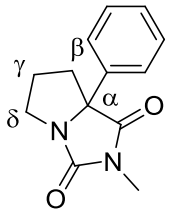
**5-Isopropyl-1,3-dimethyl-5-phenylimidazolidine-2,4-dione (406)**



Following general procedure **6**, LiCl (28 mg, 0.65 mmol) and THF (1.20 mL) were added to urea acid **404** (57 mg, 0.22 mmol). LDA was prepared with DiPA (0.09 mL, 0.65 mmol), THF (1.00 mL) and *n*BuLi (0.26 mL, 0.65 mmol, 2.5 M in hexanes). Upon addition of LDA the reaction mixture turned yellow. Purification by flash column chromatography ($SiO_2$, 3:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (28 mg, 0.11 mmol, 53%). **406: $R_f$** (3:2 Pet.Ether:EtOAc) 0.55; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.44-7.31 (3H, m, Ph*H*), 7.29-7.26 (2H, m, Ph*H*), 3.04 (3H, s, NC*H*$_3$), 2.97 (3H, s, NC*H*$_3$), 2.99-2.90 (1H, m, C*H*(CH$_3$)$_2$), 1.02 (3H, d, *J* = 5.4, CH(C*H*$_3$)$_2$), 0.99 (3H, d, *J* = 6.0, CH(C*H*$_3$)$_2$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.3 (*C*=O), 156.9 (*C*=O), 135.2 (Ar*C*), 129.1 (2×Ar*C*H), 128.4 (Ar*C*H), 126.7 (2×Ar*C*H), 73.8 (N*C*C=O), 32.0 (*C*H(CH$_3$)$_2$), 27.6 (N*C*H$_3$), 24.9 (N*C*H$_3$), 17.1 (CH(*C*H$_3$)$_2$), 16.7 (CH(*C*H$_3$)$_2$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2969 (C-H), 1768 (C=O amide), 1704 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 247 ([M+H]$^+$, 100%), 269 ([M+Na]$^+$, 70%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{18}O_2N_2Na$ [M+Na]$^+$ 269.1261, found 269.1262.

*NMR file: $^1$H NMR = 2012-10-05-jpc-38 (10), $^{13}$C NMR = 2012-10-08-jpc-26 (13).*

**2-Methyl-7*a*-phenyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (414a)**

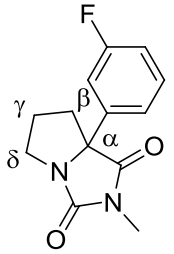



Following general procedure **6**, LiCl (66 mg, 1.56 mmol) and THF (3.20 mL) were added to urea acid **410a** (129 mg, 0.52 mmol). LDA was prepared with DiPA (0.22 mL, 1.56 mmol), THF (2.00 mL) and *n*BuLi (0.78 mL, 1.56 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned yellow and with warming to room temperature turned orange. Purification by flash column chromatography ($SiO_2$, 3:2 Pet.Ether:EtOAc) yielded the title compound as a colourless oil

(84 mg, 0.36 mmol, 70%). **414a: $R_f$** (7:3 Pet.Ether:EtOAc) 0.28; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.59-7.56 (2H, m, Ph*H*), 7.41-7.31 (3H, m, Ph*H*), 3.86-3.79 (1H, m, NC$H_A$H$_B$(δ)), 3.43-3.37 (1H, m, NCH$_A$$H_B$(δ)), 2.97 (3H, s, NC$H_3$), 2.42-2.34 (1H, m, C$H_A$H$_B$(β)), 2.16-2.07 (2H, m, CH$_A$$H_B$(β)+ C$H_A$H$_B$(γ)), 1.96-1.84 (1H, m, CH$_A$$H_B$(γ)); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.5 (*C*=O), 160.2 (*C*=O), 137.4 (Ar*C*), 128.6 (2×Ar*C*H), 128.3 (Ar*C*H), 125.7 (2×Ar*C*H), 74.5 (*C*(α)), 45.0 (N*C*H$_2$(δ)), 36.1 (*C*H$_2$(β)), 26.0 (*C*H$_2$(γ)), 25.2 (N*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2952, 2899 (C-H), 1771 (C=O amide), 1705 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 253 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{14}O_2N_2Na$ [M+Na]$^+$ 253.0948, found 253.0951.

*NMR file: $^1$H NMR = 2012-08-23-jpc-60 (10), $^{13}$C NMR = 2012-08-23-jpc-60 (12).*

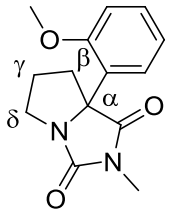
**7*a*-(3-Fluorophenyl)-2-methyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (414b)**




Following general procedure **6**, LiCl (48 mg, 1.13 mmol) and THF (1.80 mL) were added to urea acid **410b** (100 mg, 0.38 mmol). LDA was prepared with DiPA (0.16 mL, 1.13 mmol), THF (2.00 mL) and *n*BuLi (0.56 mL, 1.13 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned bright yellow. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (52 mg, 0.21 mmol, 55%). **414b: $R_f$** (7:3 Pet.Ether:EtOAc) 0.27; **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.38-7.33 (2H, m, Ar*H*), 7.30-7.28 (1H, m, Ar*H*), 7.04-7.00 (1H, m, Ar*H*), 3.86-3.80 (1H, m, NC$H_A$H$_B$(δ)), 3.42-3.37 (1H, m, NCH$_A$$H_B$(δ)), 2.98 (3H, s, NC$H_3$), 2.36-2.31 (1H, m, C$H_A$H$_B$(β)), 2.16-2.09 (2H, m, CH$_A$$H_B$(β)+ C$H_A$H$_B$(γ)), 1.95-1.85 (1H, m, CH$_A$$H_B$(γ)); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.0 (*C*=O), 162.9 (d, $^1J_{C\text{-}F}$ = 245.5, Ar*C*F), 160.1 (*C*=O), 140.1 (d, $^3J_{C\text{-}F}$ = 7.3, Ar*C*), 130.2 (d, $^3J_{C\text{-}F}$ = 8.1, Ar*C*H), 121.4 (d, $^4J_{C\text{-}F}$ = 3.0, Ar*C*H), 115.3 (d, $^2J_{C\text{-}F}$ = 20.9, Ar*C*H), 113.1 (d, $^2J_{C\text{-}F}$ = 22.9, Ar*C*H), 74.5 (*C*(α)), 45.2 (N*C*H$_2$(δ)), 36.3 (*C*H$_2$(β)), 26.0 (*C*H$_2$(γ)), 25.3 (N*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2953 (C-H), 1774 (C=O amide), 1707 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 249 ([M+H]$^+$, 30%), 271 ([M+Na]$^+$, 100%), 287 ([M+K]$^+$, 40%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{14}O_2N_2F$ [M+H]$^+$ 249.1034, found 249.1045.

*NMR file: $^1$H NMR = 2013-01-23-jpc-39 (10), $^{13}$C NMR = 2013-01-23-jpc-39 (12).*

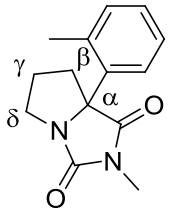
**7*a*-(2-Methoxyphenyl)-2-methyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (414c)**



Following general procedure **6**, LiCl (69 mg, 1.62 mmol) and THF (3.40 mL) were added to urea acid **410c** (150 mg, 0.54 mmol). LDA was prepared with DiPA (0.23 mL, 1.62 mmol), THF (2.00 mL) and *n*BuLi (0.81 mL, 1.62 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned orange/brown. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a white solid (106 mg, 0.41 mmol, 75%). **414c: $R_f$** (7:3 Pet.Ether:EtOAc) 0.18; **mp** 148-150 °C; **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.36-7.31 (2H, m, Ar*H*), 6.97-6.93 (2H, m, Ar*H*), 3.85-3.80 (1H, m, NC$H_A$H$_B$(δ)), 3.82 (3H, s, OC$H_3$) 3.18-3.13 (1H, m, NCH$_A$$H_B$(δ)), 3.03 (3H, s, NC$H_3$), 2.85 (1H, ddd, *J* = 13.5, 7.0, 2.5, C$H_A$H$_B$(β)), 2.22-2.14 (1H, m, C$H_A$H$_B$(γ)) 2.12-2.05 (1H, m, CH$_A$$H_B$(γ)), 1.95-1.88 (1H, m, CH$_A$$H_B$(β)); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 175.1 (*C*=O), 160.5 (*C*=O), 158.2 (Ar*C*OMe) 130.2 (Ar*C*H), 127.3 (Ar*C*H), 124.5 (Ar*C*), 120.5 (Ar*C*H), 112.5 (Ar*C*H), 72.9 (*C*(α)), 56.0 (O*C*H$_3$), 44.2 (N*C*H$_2$(δ)), 31.7 (*C*H$_2$(β)), 26.7 (*C*H$_2$(γ)), 25.1 (N*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2949, 2839 (C-H), 1770 (C=O amide), 1703 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 261 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{16}O_3N_2Na$ [M+Na]$^+$ 283.1053, found 283.1042.

*NMR file: $^1$H NMR = 2013-01-23-jpc-38 (10), $^{13}$C NMR = 2013-01-23-jpc-38 (13).*

**2-Methyl-7*a*-(2-methylphenyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (414d)**

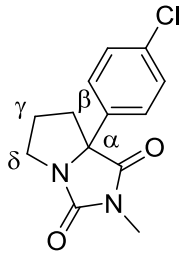


Following general procedure **6**, LiCl (24 mg, 0.57 mmol) and THF (1.00 mL) were added to urea acid **410d** (50 mg, 0.19 mmol). LDA was prepared with DiPA (0.08 mL, 0.57 mmol), THF (0.90 mL) and *n*BuLi (0.29 mL, 0.57 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned orange/brown. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (28 mg, 0.12 mmol, 60%). **414d: $R_f$** (7:3 Pet.Ether:EtOAc) 0.34; **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.51-7.49 (1H, m, Ar*H*), 7.26-7.21 (2H, m, Ar*H*), 7.18-7.15 (1H, m, Ar*H*), 3.95-3.90 (1H, m, NC$H_A$H$_B$(δ)), 3.22-3.16 (1H, m, NCH$_A$$H_B$(δ)), 2.98 (3H, s, NC$H_3$), 2.68 (3H, s, ArC$H_3$) 2.66-2.61 (1H, m, C$H_A$H$_B$(β)), 2.28-2.22 (1H, m, CH$_A$$H_B$(β)), 2.10-2.02 (1H, m, C$H_A$H$_B$(γ)), 1.95-1.86 (1H, m, CH$_A$$H_B$(γ)); **$^{13}$C {$^1$H} NMR**

(125 MHz, $CDCl_3$): $\delta_C$ = 174.7 (*C*=O), 159.8 (*C*=O), 136.9 (Ar*C*), 135.4 (Ar*C*), 133.0 (Ar*C*H), 128.5 (Ar*C*H), 126.1 (Ar*C*H), 125.9 (Ar*C*H), 75.1 (*C*(α)), 44.3 (N*C*$H_2$(δ)), 34.6 (*C*$H_2$(β)), 26.5 (*C*$H_2$(γ)), 25.2 (N*C*$H_3$), 21.5 (*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2952 (C-H), 1771 (C=O amide), 1706 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 267 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{16}O_2N_2Na$ [M+Na]$^+$ 267.1104, found 267.1101.

*NMR file: $^1$H NMR = 2013-01-23-jpc-37 (10), $^{13}$C NMR = 2013-01-23-jpc-37 (12).*

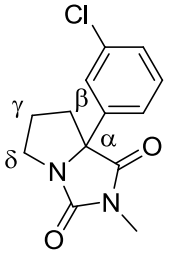
**7*a*-(4-Chlorophenyl)-2-methyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (414e)**




Following general procedure **6**, LiCl (22 mg, 0.53 mmol) and THF (1.00 mL) were added to urea acid **410e** (50 mg, 0.18 mmol). LDA was prepared with DiPA (0.07 mL, 0.53 mmol), THF (0.80 mL) and *n*BuLi (0.26 mL, 0.53 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned bright yellow. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a white solid (34 mg, 0.13 mmol, 72%). **414e: $R_f$** (7:3 Pet.Ether:EtOAc) 0.25; **mp** 107-109 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.53-7.49 (2H, m, Ar*H*), 7.37-7.34 (2H, m, Ar*H*), 3.85-3.78 (1H, m, NC$H_A$$H_B$(δ)), 3.41-3.35 (1H, m, NC$H_A$$H_B$(δ)), 2.97 (3H, s, NC$H_3$), 2.36-2.28 (1H, m, C$H_A$$H_B$(β)), 2.17-2.08 (2H, m, C$H_A$$H_B$(β)+ C$H_A$$H_B$(γ)), 1.96-1.81 (1H, m, C$H_A$$H_B$(γ)); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.1 (*C*=O), 160.1 (*C*=O), 136.0 (Ar*C*), 134.5 (Ar*C*Cl), 128.8 (2×Ar*C*H), 127.2 (2×Ar*C*H), 74.1 (*C*(α)), 45.2 (N*C*$H_2$(δ)), 36.2 (*C*$H_2$(β)), 26.0 (*C*$H_2$(γ)), 25.3 (N*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2952, 2900 (C-H), 1772 (C=O amide), 1705 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 265 ([M+H]$^+$, 20%), 287 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{14}O_2N_2{}^{35}Cl$ [M+H]$^+$ 265.0738, found 265.0728.

*NMR file: $^1$H NMR = 2013-02-04-jpc-52 (10), $^{13}$C NMR = 2013-02-04-jpc-60 (12).*

**7*a*-(3-Chlorophenyl)-2-methyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (414f)**



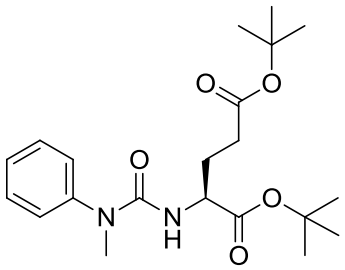

Following general procedure **6**, LiCl (22 mg, 0.53 mmol) and THF (1.00 mL) were added to urea acid **410f** (50 mg, 0.18 mmol). LDA was prepared with DiPA (0.07 mL, 0.53 mmol), THF (0.80

mL) and *n*BuLi (0.26 mL, 0.53 mmol, 2.0 M in hexanes). Upon addition of LDA the reaction mixture turned bright yellow. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a pale pink oil (31 mg, 0.12 mmol, 65%). **414f: $R_f$** (7:3 Pet.Ether:EtOAc) 0.30; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.59-7.55 (1H, m, Ar*H*), 7.49-7.44 (1H, m, Ar*H*), 7.39-7.29 (2H, m, Ar*H*), 3.87-3.78 (1H, m, NC$H_A$H$_B$(δ)), 3.44-3.36 (1H, m, NCH$_A$$H_B$(δ)), 2.98 (3H, s, NC$H_3$), 2.41-2.29 (1H, m, C$H_A$H$_B$(β)), 2.18-2.07 (2H, m, CH$_A$$H_B$(β)+ C$H_A$H$_B$(γ)), 1.99-1.82 (1H, m, CH$_A$$H_B$(γ)); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 173.9 (*C*=O), 160.1 (*C*=O), 139.5 (Ar*C*), 134.6 (Ar*C*Cl), 130.0 (Ar*C*H), 128.6 (Ar*C*H), 126.0 (Ar*C*H), 124.1 (Ar*C*H), 74.2 (*C*(α)), 45.2 (N*C*H$_2$(δ)), 36.2 (*C*H$_2$(β)), 26.0 (*C*H$_2$(γ)), 25.3 (N*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2952, 2900 (C-H), 1773 (C=O amide), 1705 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 265 ([M+H]$^+$, 30%), 287 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{14}O_2N_2{}^{35}Cl$ [M+H]$^+$ 265.0738, found 265.0733.

*NMR file: $^1$H NMR = 2013-02-04-jpc-40 (10), $^{13}$C NMR = 2013-02-04-jpc-41 (12).*

**Synthesis of 424:**

**(S)-Di-*tert*-butyl 2-(3-methyl-3-phenylureido)pentanedioate (422)**

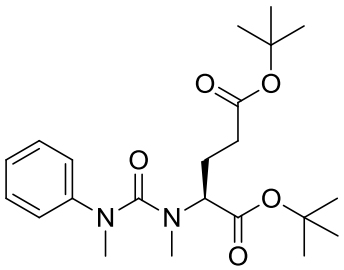


Following general procedure **1a**, *N*-methyl-*N*-phenylcarbamoyl chloride (536 mg, 3.16 mmol) and DMAP (cat.) were added to a pre-stirred solution of L-glutamic acid di-*tert*-butyl ester hydrochloride (1.00 g, 3.38 mmol) and $Et_3N$ (1.01 mL, 7.27 mmol) in DCE (15.8 mL). The reaction was complete after 20 h at reflux. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (1.24 g, 3.16 mmol, >99%). **422: $R_f$** (4:1 Pet.Ether:EtOAc) 0.21; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.39-7.34 (2H, m, Ph*H*), 7.26-7.21 (3H, m, Ph*H*), 4.87 (1H, br. d, *J* = 7.8, N*H*CH), 4.33 (1H, dt, *J* = 8.1, 4.8, NHC*H*CH$_2$), 3.20 (3H, s, NC$H_3$), 2.25-2.07 (2H, m, C$H_2$C=O), 2.02-1.91 (1H, m, CHC$H_A$H$_B$CH$_2$), 1.75-1.62 (1H, m, CHCH$_A$$H_B$CH$_2$), 1.35 (9H, s, C(C$H_3$)$_3$), 1.34 (9H, s, C(C$H_3$)$_3$); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 172.2 (*C*=O), 171.8 (*C*=O), 156.0 (*C*=O), 143.1 (Ar*C*N), 130.0 (2×Ar*C*H), 127.3 (Ar*C*H), 127.1 (2×Ar*C*H), 81.7 (*C*(CH$_3$)$_3$), 80.4 (*C*(CH$_3$)$_3$), 53.6 (NH*C*H), 37.2 (N*C*H$_3$), 31.6 (CH$_2$*C*H$_2$C=O), 28.2 (CH*C*H$_2$CH$_2$), 28.0 (C(*C*H$_3$)$_3$), 27.9 (C(*C*H$_3$)$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3420 (NH), 2976, 2933 (C-H), 1726 (C=O ester), 1664 (C=O ester), 1596 (C=O urea); **MS** (ESI$^+$,

MeOH): *m/z* = 415 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{32}O_5N_2Na$ [M+Na]$^+$ 415.2203, found 415.2208.

*NMR file: $^1$H NMR = 2013-03-20-jpc-33 (11), $^{13}$C NMR = 2013-03-20-jpc-33 (12).*

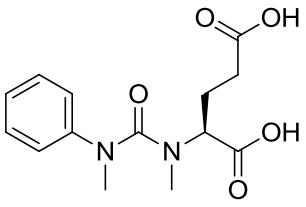
**(S)-Di-*tert*-butyl 2-(1,3-dimethyl-3-phenylureido)pentanedioate (423)**



Following a similar method to general procedure **2b**, MeI (0.39 mL, 6.32 mmol, 2.0 eq.) was added to urea **422** (1.24 g, 3.16 mmol) in DMF (15.8 mL) at 0 °C. NaH (189 mg, 4.74 mmol, 1.5 eq.) was added to the reaction mixture and the reaction was left at 0 °C for 1 h before warming to room temperature. The reaction was complete after 20 h at room temperature. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (965 mg, 2.37 mmol, 75%). **423: $R_f$** (9:1 Pet.Ether:EtOAc) 0.26; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.35-7.30 (2H, m, Ph*H*), 7.15-7.10 (3H, m, Ph*H*), 4.59-4.54 (1H, m, NC*H*$CH_2$), 3.20 (3H, s, NC$H_3$), 2.44 (3H, s, NC$H_3$), 2.26-2.12 (3H, m, C$H_2$C=O + CHC$H_A$H$_B$CH$_2$), 1.89-1.79 (1H, m, CHCH$_A$$H_B$CH$_2$), 1.44 (9H, s, C(C$H_3$)$_3$), 1.43 (9H, s, C(C$H_3$)$_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 172.1 (*C*=O), 170.5 (*C*=O), 162.0 (*C*=O), 146.5 (Ar*C*N), 129.4 (2×Ar*C*H), 124.7 (Ar*C*H), 124.4 (2×Ar*C*H), 81.4 (*C*(CH$_3$)$_3$), 80.5 (*C*(CH$_3$)$_3$), 58.9 (N*C*H), 40.2 (N*C*H$_3$), 32.6 (N*C*H$_3$), 32.2 (CH$_2$*C*H$_2$C=O), 28.1 (C(*C*H$_3$)$_3$), 28.0 (C(*C*H$_3$)$_3$), 24.4 (CH*C*H$_2$CH$_2$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2976, 2932 (C-H), 1727 (C=O ester), 1649 (C=O ester), 1596 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 429 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{34}O_5N_2Na$ [M+Na]$^+$ 429.2360, found 429.2348.

*NMR file: $^1$H NMR = 2013-03-07-jpc-34 (10), $^{13}$C NMR = 2013-03-07-jpc-34 (12).*

**(S)-2-(1,3-Dimethyl-3-phenylureido)pentanedioic acid (424)**



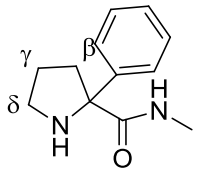
Following a similar method to general procedure **3**, anhydrous DCM (4.00 mL) and TFA (2.00 mL) were added to urea **423** (310 mg, 0.76 mmol). The reaction was complete after 35 min and the solvent was removed *in vacuo* yielding the title compound as a pale pink solid without further purification (224 mg, 0.76 mmol, >99%). **424: $R_f$** (3:7 Pet.Ether:EtOAc) 0.07; **mp** 140-142 °C;

$[\alpha]_D^{21}$ = –88.4 (*c* = 0.9 in MeOH); **$^1$H NMR** (300 MHz, 0.05 M NaOH in $D_2O$): $\delta_H$ = 7.46-7.41 (2H, m, Ph*H*), 7.26-7.21 (3H, m, Ph*H*), 4.26 (1H, br. d, *J* = 11.1, NC*H*$CH_2$), 3.18 (3H, s, NC$H_3$), 2.61 (3H, s, NC$H_3$), 2.07 (3H, br. s, C$H_2CO_2H$ + CHC$H_A$$H_B$$CH_2$), 1.86-1.74 (1H, m, $CHCH_AH_BCH_2$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 177.3 (*C*=O), 173.8 (*C*=O), 163.9 (*C*=O), 145.0 (Ar*C*N), 129.8 (2×Ar*C*H), 126.1 (Ar*C*H), 125.1 (2×Ar*C*H), 58.8 (N*C*H$CH_2$), 40.2 (N*C*$H_3$), 33.9 (N*C*$H_3$), 30.3 ($CH_2CH_2$C=O), 23.4 (CH*C*$H_2CH_2$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2976, 2932 (C-H), 1730 (C=O acid), 1705 (C=O acid), 1573 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 317 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{18}O_5N_2Na$ [M+Na]$^+$ 317.1108, found 317.1121.

*NMR file: $^1$H NMR = 2013-04-12-jpc-32 (11), $^{13}$C NMR = 2013-03-27-jpc-47 (21).*

**Synthesis of quaternary amino amide 431:**

***N*-Methyl-2-phenylpyrrolidine-2-carboxamide (431)**



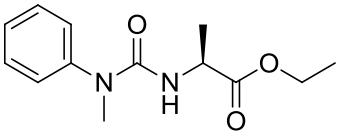

1-(Methylcarbamoyl)-2-phenylpyrrolidine-2-carboxylic acid (68 mg, 0.27 mmol, 1.0 eq.) was disolved in EtOH (2.00 mL) and transferred into a 10.0 mL microwave vial. A solution of 2.0 M aqueous NaOH (2.00 mL) was added and the microwave vial was sealed. The reaction was heated in a microwave reactor for 2.5 h at 130 °C under 4 bar pressure. The reaction was then cooled to room temperature and the pressure released before the solution was neutralised with 1.0 M HCl to pH = 5 and the solvent removed *in vacuo*. The residue was re-disolved in anhydrous MeOH (10.0 mL) and cooled to 0 °C. Thionyl chloride (0.20 mL, 2.74 mmol, 10.0 eq.) was added dropwise and stirred for 10 min before the reaction was heated to reflux for 20 h. The reaction mixture was then cooled to room temperature and the solvent removed *in vacuo*. The residue was disolved in EtOAc and dilute NaOH solution was added. The organic layer was separated and the aqueous layer extracted with EtOAc (×2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography ($SiO_2$, 3:97 (9:1 (MeOH:$NH_3$):DCM) yielded the title compound as a colourless oil (35 mg, 0.17 mmol, 63%). **431:** **$R_f$** (5:95 MeOH:DCM) 0.38; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.99 (1H, br. s, $CH_3$N*H*C=O), 7.50-7.45 (2H, m, Ph*H*), 7.37-7.31 (2H, m, Ph*H*), 7.29-7.24 (1H, m, Ph*H*), 3.20-3.11 (1H, m, NC$H_A$$H_B$(δ)), 3.00-2.88 (2H, m, $NCH_AH_B$(δ)+ C$H_A$$H_B$(β)), 2.80 (3H, d, *J* = 5.1, HNC$H_3$), 2.05-1.95 (2H, m, N*H* + $CH_AH_B$(β)), 1.90-1.77 (2H, m, $NCHCH_2CH_2$(γ)); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 175.3 (*C*=O), 143.4 (Ar*C*N), 128.4 (2×Ar*C*H), 127.3 (Ar*C*H), 125.9 (2×Ar*C*H), 73.6 (N*C*CO(α)), 46.6 (N*C*$H_2$(δ)), 36.4 (*C*$H_2$(β)), 26.2 (HN*C*$H_3$), 25.9 ($NCHCH_2CH_2$(γ)); **IR (film,**

**cm$^{-1}$)**: $\nu_{max}$ = 3337 (NH broad), 2945, 2875 (C-H), 1658 (C=O amide); **MS** (ESI$^+$, MeOH): *m/z* = 205 ([M+H]$^+$, 20%), 227 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{16}ON_2Na$ [M+Na]$^+$ 227.1155, found 227.1152.

*NMR file: $^1$H NMR = 2013-03-04-jpc-23 (20), $^{13}$C NMR = 2013-03-04-jpc-23 (22).*

**Synthesis of 445:**

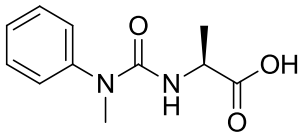
**(*S*)-Ethyl 2-(3-methyl-3-phenylureido)propanoate (444)**



Following general procedure **1b**, *N*-methyl-*N*-phenylcarbamoyl chloride (2.43 g, 14.32 mmol) was added to a pre-stirred solution of L-alanine ethyl ester hydrochloride (2.00 g, 13.02 mmol) and $Et_3N$ (4.17 mL, 29.90 mmol) in MeCN (30.0 mL). The reaction was complete after 20 h at reflux. The title compound was yielded as a pale yellow oil without further purification (3.26 g, 13.02 mmol, >99%). **444**: **R$_f$** (1:1 Pet.Ether:EtOAc) 0.5; $[\alpha]_D^{21}$= +62.4 (*c* = 1.5 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.44-7.40 (2H, m, Ph*H*), 7.31-7.26 (3H, m, Ph*H*), 4.85 (1H, br. d, *J* = 7.5, N*H*), 4.47 (1H, quin., *J* = 7.2, NHC*H*$CH_3$), 4.13 (2H, q, *J* = 7.1, OC*H*$_2$$CH_3$), 3.25 (3H, s, NC*H*$_3$), 1.27 (3H, d, *J* = 7.2, NHCHC*H*$_3$), 1.23 (3H, t, *J* = 7.1, $OCH_2$C*H*$_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.0 (*C*=O), 156.6 (*C*=O), 143.2 (Ar*C*), 130.1 (2×Ar*C*H), 127.5 (Ar*C*H), 127.3 (2×Ar*C*H), 61.3 (O*C*H$_2$$CH_3$), 49.4 (*C*H$CH_3$), 37.2 (N*C*H$_3$), 18.9 (CH*C*H$_3$), 14.2 ($OCH_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3424 (NH), 2981, 2838 (C-H), 1736 (C=O ester), 1660 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 251 ([M+H]$^+$, 100%), 273 ([M+Na]$^+$, 80%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{18}N_2O_3Na$ [M+Na]$^+$ 273.1215, found 273.1219.

*NMR file: $^1$H NMR = 2013-11-22-jpc-47 (10), $^{13}$C NMR = 2013-11-22-jpc-47 (11).*

**(*S*)-2-(3-Methyl-3-phenylureido)propanoic acid (445)**

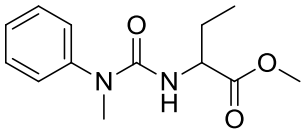


Following general procedure **5**, LiOH (4.68g, 195.60 mmol) was added to urea **444** (3.26 g, 13.02 mmol) in 2:1 THF:$H_2O$ (140 mL: 70.0 mL). The reaction was complete after 20 h at 45 °C. The title compound was yielded as an off white solid without further purification (2.73 g, 12.28 mmol, 94%). **445**: **R$_f$** (1:1 Pet.Ether:EtOAc) 0.36; **mp**: 156-157 °C; $[\alpha]_D^{21}$= +28.1 (*c* = 1.7 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 10.59 (1H, br. s, O*H*), 7.46-7.42 (2H, m, Ph*H*), 7.34-7.32 (1H, m, Ph*H*), 7.30-7.28 (2H, m, Ph*H*), 4.84 (1H, br. d, *J* = 7.0, N*H*), 4.43 (1H, quin., *J* = 7.1, NHC*H*$CH_3$), 3.26 (3H, s, NC*H*$_3$), 1.31 (3H, d, *J* = 7.2, NHCHC*H*$_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ =

176.3 (*C*=O), 157.6 (*C*=O), 142.7 (Ar*C*), 130.3 (2×Ar*C*H), 127.9 (Ar*C*H), 127.3 (2×Ar*C*H), 49.8 (*C*HCH$_3$), 37.6 (N*C*H$_3$), 18.1 (CH*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3413 (NH), 2981, 2940 (C-H), 1732 (C=O acid), 1621 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 223 ([M+H]$^+$, 100%), 245 ([M+Na]$^+$, 80%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{15}N_2O_3$ [M+H]$^+$ 223.1077, found 223.1077.
*NMR file: $^1$H NMR = 2014-02-24-jpc-2 (10), $^{13}$C NMR = 2013-11-26-jpc-14 (10).*

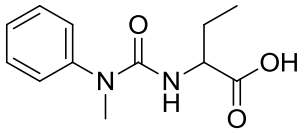
**Synthesis of 458:**

**Methyl 2-(3-methyl-3-phenylureido)butanoate (453)**



Following general procedure **1b**, *N*-methyl-*N*-phenylcarbamoyl chloride (2.43 g, 14.32 mmol) was added to a pre-stirred solution of methyl 2-aminobutanoate hydrochloride (2.00 g, 13.02 mmol) and Et$_3$N (4.17 mL, 29.95 mmol) in MeCN (33.0 mL). The reaction was complete after 21 h at reflux. The title compound was yielded as a yellow oil without further purification (3.26 g, 13.02 mmol, >99%). **453**: **R$_f$** (7:3 Pet.Ether:EtOAc) 0.45; **$^1$H NMR** (400 MHz, CDCl$_3$): $\delta_H$ = 7.46-7.42 (2H, m, Ph*H*), 7.34-7.30 (3H, m, Ph*H*), 4.79 (1H, br. d, *J* = 7.7, N*H*), 4.48-4.43 (1H, m, NHC*H*CH$_2$), 3.70 (3H, s, OC*H$_3$*), 3.27 (3H, s, NC*H$_3$*), 1.84-1.73 (1H, m, CHC*H$_A$*H$_B$CH$_3$), 1.62-1.51 (1H, m, CHCH$_A$*H$_B$*CH$_3$), 0.81 (3H, t, *J* = 7.5, CH$_2$C*H$_3$*); **$^{13}$C {$^1$H} NMR** (100 MHz, CDCl$_3$): $\delta_C$ = 174.0 (*C*=O), 156.8 (*C*=O), 143.2 (Ar*C*), 130.2 (2×Ar*C*H), 127.6 (Ar*C*H), 127.4 (2×Ar*C*H), 54.7 (*C*HCH$_2$), 52.3 (O*C*H$_3$), 37.3 (N*C*H$_3$), 25.9 (*C*H$_2$CH$_3$), 9.8 (CH$_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3430 (NH), 2969, 2878 (C-H), 1738 (C=O ester), 1659 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 251 ([M+H]$^+$, 100%), 273 ([M+Na]$^+$, 70%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{19}N_2O_3$ [M+H]$^+$ 251.1390, found 251.1391.
*NMR file: $^1$H NMR = 2014-03-04-jpc-44 (10), $^{13}$C NMR = 2014-03-04-jpc-44 (11).*

**2-(3-Methyl-3-phenylureido)butanoic acid (458)**



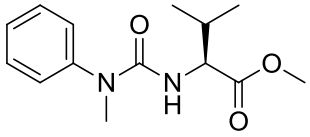
Following general procedure **5**, LiOH (3.98 g, 166.20 mmol) was added to urea **453** (2.77 g, 11.08 mmol) in 2:1 THF:H$_2$O (130 mL: 65.0 mL). The reaction was complete after 18 h at 45 °C. The title compound was yielded as a pale yellow solid without further purification (2.62 g, 11.08 mmol, >99%). **458**: **R$_f$** (1:1 Pet.Ether:EtOAc) 0.10; **mp**: 118-120 °C; **$^1$H NMR** (400 MHz, CDCl$_3$): $\delta_H$ = 7.47-7.44 (2H, m, Ph*H*), 7.37-7.33 (1H, m, Ph*H*), 7.31-7.29 (2H, m, Ph*H*), 4.72 (1H, br. d, *J* = 7.2, N*H*), 4.30 (1H, dt, *J* = 7.5, 5.6, NHC*H*CH$_2$), 3.28 (3H, s, NC*H$_3$*), 1.92-1.81 (1H, m, CHC*H$_A$*H$_B$CH$_3$), 1.65 -1.54 (1H, m, CHCH$_A$*H$_B$*CH$_3$), 0.85 (3H, t, *J* = 7.4, CH$_2$C*H$_3$*); **$^{13}$C {$^1$H} NMR**

(100 MHz, $CDCl_3$): $\delta_C$ = 175.5 (*C*=O), 157.9 (*C*=O), 142.6 (Ar*C*), 130.4 (2×Ar*C*H), 128.0 (Ar*C*H), 127.3 (2×Ar*C*H), 55.4 (*C*HCH$_2$), 37.6 (N*C*H$_3$), 24.9 (*C*H$_2$CH$_3$), 10.0 (CH$_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3415 (NH), 2969 (OH broad), 2936, 2878 (C-H), 1730 (C=O ester), 1622 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 237 ([M+H]$^+$, 80%), 259 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{17}N_2O_3$ [M+H]$^+$ 237.1234, found 237.1234.

*NMR file: $^1$H NMR = 2014-03-06-jpc-55 (10), $^{13}$C NMR = 2014-03-06-jpc-55 (11).*

**Synthesis of 459:**

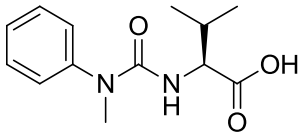
**(*S*)-Methyl 3-methyl-2-(3-methyl-3-phenylureido)butanoate (454)**



Following general procedure **1b**, *N*-methyl-*N*-phenylcarbamoyl chloride (2.22 g, 13.10 mmol) was added to a pre-stirred solution of L-valine methyl ester hydrochloride (2.00 g, 11.90 mmol) and Et$_3$N (3.82 mL, 27.40 mmol) in MeCN (30.0 mL). The reaction was complete after 23 h at reflux. The title compound was yielded as a pale yellow oil without further purification (3.14 g, 11.88 mmol, >99%). **454**: **R$_f$** (1:1 Pet.Ether:EtOAc) 0.53; $[\alpha]_D^{21}$= +31.2 (*c* = 1.1 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.47-7.43 (2H, m, Ph*H*), 7.34-7.30 (3H, m, Ph*H*), 4.77 (1H, br. d, *J* = 8.6, N*H*), 4.41 (1H, dd, *J* = 8.7, 5.0, NHC*H*CH), 3.69 (3H, s, OC*H*$_3$), 3.28 (3H, s, NC*H*$_3$), 2.08-1.99 (1H, m, C*H*(CH$_3$)$_2$), 0.88 (3H, d, *J* = 6.8, CH(C*H*$_3$)$_2$), 0.72 (3H, d, *J* = 6.9, CH(C*H*$_3$)$_2$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 173.6 (*C*=O), 157.0 (*C*=O), 143.2 (Ar*C*), 130.2 (2×Ar*C*H), 127.6 (Ar*C*H), 127.4 (2×Ar*C*H), 58.7 (NH*C*HCH), 52.1 (O*C*H$_3$), 37.3 (N*C*H$_3$), 31.2 (*C*H(CH$_3$)$_2$), 19.2 (CH(*C*H$_3$)$_2$), 17.8 (CH(*C*H$_3$)$_2$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3432 (NH), 2962, 2875 (C-H), 1738 (C=O ester), 1667 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 265 ([M+H]$^+$, 100%), 287 ([M+Na]$^+$, 80%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{21}N_2O_3$ [M+H]$^+$ 265.1547, found 265.1548.

*NMR file: $^1$H NMR = 2014-01-30-jpc-9 (20), $^{13}$C NMR = 2014-01-30-jpc-9 (21).*

**(*S*)-3-Methyl-2-(3-methyl-3-phenylureido)butanoic acid (459)**



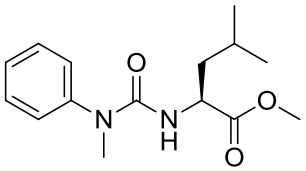
Following general procedure **5**, LiOH (3.77 g, 157.40 mmol) was added to urea **454** (2.77 g, 10.49 mmol) in 2:1 THF:$H_2O$ (90.0 mL: 45.0 mL). The reaction was complete after 17.5 h at 45 °C. The title compound was yielded as a pale yellow solid without further purification (2.33 g, 9.30 mmol, 89%). **459**: **R$_f$** (1:1 Pet.Ether:EtOAc) 0.15; **mp**: 126-128 °C; $[\alpha]_D^{21}$= +31.5 (*c* = 1.3 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 10.22 (1H, br. s, O*H*), 7.46-7.42 (2H, m, Ph*H*), 7.34-7.30 (3H, m,

Ph*H*), 4.81 (1H, br. d, *J* = 8.5, N*H*), 4.34 (1H, dd, *J* = 8.5, 5.0, NHC*H*CH), 3.27 (3H, s, NC$H_3$), 2.15-2.07 (1H, m, C*H*($CH_3$)$_2$), 0.91 (3H, d, *J* = 6.8, CH(C$H_3$)$_2$), 0.74 (3H, d, *J* = 6.9, CH(C$H_3$)$_2$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 176.0 (*C*=O), 157.7 (*C*=O), 142.8 (Ar*C*), 130.2 (2×Ar*C*H), 127.8 (Ar*C*H), 127.3 (2×Ar*C*H), 58.9 (NH*C*HCH), 37.5 (N*C*H$_3$), 30.6 (*C*H($CH_3$)$_2$), 19.3 (CH(*C*H$_3$)$_2$), 17.7 (CH(*C*H$_3$)$_2$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3422 (NH), 2962 (OH broad), 2933, 2875 (C-H), 1729 (C=O acid), 1623 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 251 ([M+H]$^+$, 100%), 273 ([M+Na]$^+$, 50%), (ESI$^-$, MeOH): *m/z* = 249 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{19}N_2O_3$ [M+H]$^+$ 251.1390, found 251.1397.

*NMR file: $^1$H NMR = 2014-01-31-jpc-10 (10), $^{13}$C NMR = 2014-01-31-jpc-10 (11).*

**Synthesis of 460:**

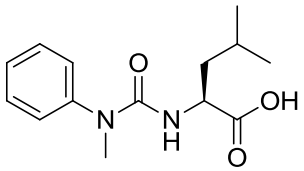
**(*S*)-Methyl 4-methyl-2-(3-methyl-3-phenylureido)pentanoate (455)**



Following general procedure **1b**, *N*-methyl-*N*-phenylcarbamoyl chloride (1.03 g, 6.05 mmol) was added to a pre-stirred solution of L-leucine methyl ester hydrochloride (1.00 g, 5.50 mmol) and Et$_3$N (1.76 mL, 12.70 mmol) in MeCN (14.0 mL). The reaction was complete after 22.5 h at reflux. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (1.42 g, 5.10 mmol, 93%). **455**: **$R_f$** (7:3 Pet.Ether:EtOAc) 0.28; $[\alpha]_D^{21}$= +21.6 (*c* = 1.0 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.46-7.42 (2H, m, Ph*H*), 7.34-7.29 (3H, m, Ph*H*), 4.65 (1H, br. d, *J* = 8.4, N*H*), 4.54-4.48 (1H, m, NHC*H*CH$_2$), 3.70 (3H, s, OC$H_3$), 3.27 (3H, s, NC$H_3$), 1.62-1.47 (2H, m, CHC$H_A$H$_B$CH + CH$_2$C*H*($CH_3$)$_2$), 1.38-1.31 (1H, m, CHCH$_A$$H_B$CH), 0.90 (3H, d, *J* = 6.3, CH(C$H_3$)$_2$), 0.87 (3H, d, *J* = 6.4, CH(C$H_3$)$_2$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.8 (*C*=O), 156.9 (*C*=O), 143.2 (Ar*C*), 130.2 (2×Ar*C*H), 127.6 (Ar*C*H), 127.4 (2×Ar*C*H), 52.3 (O*C*H$_3$), 52.2 (NH*C*HCH$_2$), 41.7 (*C*H$_2$), 37.4 (N*C*H$_3$), 25.0 (*C*H($CH_3$)$_2$), 23.0 (CH(*C*H$_3$)$_2$), 22.0 (CH(*C*H$_3$)$_2$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3431 (NH), 2955, 2870 (C-H), 1741 (C=O ester), 1663 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 279 ([M+H]$^+$, 60%), 301 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{23}N_2O_3$ [M+H]$^+$ 279.1703, found 279.1695.

*NMR file: $^1$H NMR = 2014-01-08-jpc-27 (10), $^{13}$C NMR = 2014-02-21-jpc-27 (11).*

**(*S*)-4-Methyl-2-(3-methyl-3-phenylureido)pentanoic acid (460)**

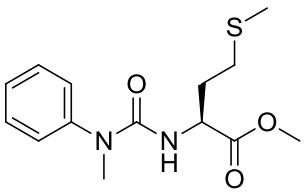


Following general procedure **5**, LiOH (1.20 g, 50.00 mmol) was added to urea **455** (927 mg, 3.33 mmol) in 2:1 THF:$H_2O$ (30.0 mL: 15.0 mL). The reaction was complete after 22.5 h at 45 °C. The title compound was yielded as a pale yellow oil without further purification (880 mg, 3.33 mmol, >99%). **460**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc) 0.14; $[\alpha]_D^{21} = -17.2$ (*c* = 1.0 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 8.38 (1H, br. s, O*H*), 7.47-7.43 (2H, m, Ph*H*), 7.37-7.33 (1H, m, Ph*H*), 7.31-7.29 (2H, m, Ph*H*), 4.61 (1H, br. d, *J* = 7.7, N*H*), 4.40-4.35 (1H, m, NHC*H*$CH_2$), 3.28 (3H, s, NC$H_3$), 1.65-1.50 (2H, m, CHC$H_A$$H_B$CH + $CH_2$C*H*$(CH_3)_2$), 1.43-1.36 (1H, m, CHC$H_A$$H_B$CH), 0.88 (6H, t, *J* = 6.1, CH(C$H_3$)$_2$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 176.3 (*C*=O), 158.0 (*C*=O), 142.6 (Ar*C*), 130.4 (2×Ar*C*H), 128.0 (Ar*C*H), 127.4 (2×Ar*C*H), 52.7 (NH*C*H$CH_2$), 40.5 (*C*$H_2$), 37.6 (N*C*$H_3$), 25.0 (*C*H$(CH_3)_2$), 23.0 (CH(*C*$H_3$)$_2$), 21.9 (CH(*C*$H_3$)$_2$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3423 (NH), 2956 (OH broad), 2956, 2870 (C-H), 1729 (C=O acid), 1622 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 287 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{20}N_2O_3Na$ [M+Na]$^+$ 287.1372, found 287.1371.

*NMR file: $^1$H NMR = 2014-01-13-jpc-26 (10), $^{13}$C NMR = 2014-01-13-jpc-26 (11).*

**Synthesis of 461:**

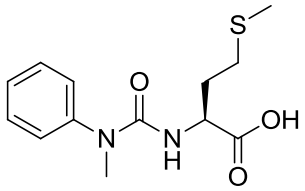
**(*S*)-Methyl 2-(3-methyl-3-phenylureido)-4-(methylthio)butanoate (456)**



Following general procedure **1b**, *N*-methyl-*N*-phenylcarbamoyl chloride (1.87 g, 11.02 mmol) was added to a pre-stirred solution of L-methionine methyl ester hydrochloride (2.00 g, 10.02 mmol) and $Et_3N$ (3.20 mL, 23.03 mmol) in MeCN (25.0 mL). The reaction was complete after 21 h at reflux. The title compound was yielded as an orange oil without further purification (2.97 g, 10.02 mmol, >99%). **456**: $\mathbf{R_f}$ (7:3 Pet.Ether:EtOAc) 0.36; $[\alpha]_D^{21}$ = +8.9 (*c* = 1.5 in $CHCl_3$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.46-7.42 (2H, m, Ph*H*), 7.33-7.28 (3H, m, Ph*H*), 5.00 (1H, br. d, *J* = 8.0, N*H*), 4.60 (1H, td, *J* = 7.9, 4.9, NHC*H*$CH_2$), 3.70 (3H, s, OC$H_3$), 3.26 (3H, s, NC$H_3$), 2.43 (2H, t, *J* = 7.4, SC$H_2$$CH_2$), 2.09-2.01 (1H, m, CHC$H_A$$H_B$$CH_2$), 2.01 (3H, s, SC$H_3$), 1.86-1.79 (1H, m, CHC$H_A$$H_B$$CH_2$); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 173.5 (*C*=O), 156.8 (*C*=O), 143.1 (Ar*C*), 130.2 (2×Ar*C*H), 127.7 (Ar*C*H), 127.4 (2×Ar*C*H), 53.1 (*C*H$CH_2$), 52.4 (OC$H_3$), 37.4 (NC$H_3$), 31.9

(CH*C*H$_2$CH$_2$), 30.3 (S*C*H$_2$CH$_2$), 15.5 (S*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3421, 3342 (NH), 2950, 2916 (C-H), 1738 (C=O ester), 1657 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 297 ([M+H]$^+$, 100%), 319 ([M+Na]$^+$, 80%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{21}N_2O_3S$ [M+H]$^+$ 297.1267, found 297.1258.
*NMR file: $^1$H NMR = 2014-01-06-jpc-54 (10), $^{13}$C NMR = 2014-01-06-jpc-54 (11).*

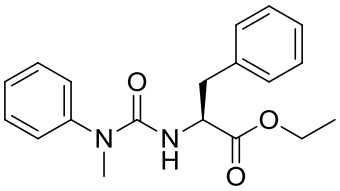
**(*S*)-2-(3-Methyl-3-phenylureido)-4-(methylthio)butanoic acid (461)**



Following general procedure **5**, LiOH (3.12 g, 130.20 mmol) was added to urea **456** (2.57 g, 8.68 mmol) in 2:1 THF:$H_2O$ (100 mL: 50.0 mL). The reaction was complete after 18 h at 45 °C. The title compound was yielded as a yellow oil without further purification (2.45 g, 8.68 mmol, >99%). **461**: **R$_f$** (1:1 Pet.Ether:EtOAc) 0.15; $[\alpha]_D^{21}$ = –24.1 (*c* = 1.6 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 8.81 (1H, br. s, OH), 7.47-7.43 (2H, m, Ph*H*), 7.37-7.33 (1H, m, Ph*H*), 7.31-7.29 (2H, m, Ph*H*), 5.15 (1H, br. d, *J* = 7.3, N*H*), 4.49 (1H, td, *J* = 7.6, 5.0, NHC*H*CH$_2$), 3.28 (3H, s, NC*H$_3$*), 2.48 (2H, br. s, SC*H$_2$*CH$_2$), 2.14-2.05 (1H, m, CHC*H$_A$*H$_B$CH$_2$ ), 1.99 (3H, br. s, SC*H$_3$*), 1.93-1.85 (1H, m, CHCH$_A$*H$_B$*CH$_2$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.9 (*C*=O), 158.0 (*C*=O), 142.5 (Ar*C*), 130.4 (2×Ar*C*H), 128.1 (Ar*C*H), 127.5 (2×Ar*C*H), 53.6 (*C*HCH$_2$), 37.6 (N*C*H$_3$), 30.6 (CH*C*H$_2$CH$_2$), 30.2 (S*C*H$_2$CH$_2$), 15.4 (S*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3410 (NH), 2916 (OH broad), 2916 (C-H), 1728 (C=O acid), 1620 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 305 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{18}N_2O_3SNa$ [M+Na]$^+$ 305.0936, found 305.0923.
*NMR file: $^1$H NMR = 2014-01-09-jpc-16 (10), $^{13}$C NMR = 2014-02-21-jpc-26 (20).*

**<u>Synthesis of 462:</u>**

**(*S*)-Ethyl 2-(3-methyl-3-phenylureido)-3-phenylpropanoate (457)**

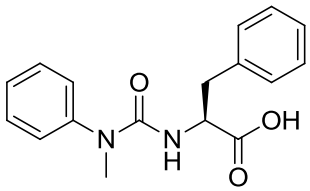


Following general procedure **1b**, *N*-methyl-*N*-phenylcarbamoyl chloride (812 mg, 4.79 mmol) was added to a pre-stirred solution of L-phenylalanine ethyl ester hydrochloride (1.00 g, 4.35 mmol) and $Et_3N$ (1.39 mL, 10.00 mmol) in MeCN (11.0 mL). The reaction was complete after 25 h at reflux. Purification by flash column chromatography ($SiO_2$, 4:1-7:3 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (1.32g, 4.05 mmol, 93%). **457**: **R$_f$** (4:1 Pet.Ether:EtOAc) 0.26; $[\alpha]_D^{21}$ = +3.7 (*c* = 1.1 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.39-7.35 (2H, m, Ph*H*), 7.31-

7.27 (1H, m, Ph*H*), 7.22-7.20 (3H, m, Ph*H*), 7.17-7.15 (2H, m, Ph*H*), 7.00-6.98 (2H, m, Ph*H*), 4.77-4.73 (2H, m, N*H* + NHC*H*$CH_2$), 4.14 (2H, q, *J* = 7.1, OC$H_2CH_3$), 3.26 (3H, s, NC$H_3$), 3.08-3.03 (1H, m, CHC$H_A$$H_B$), 3.00-2.95 (1H, m, CHC$H_A$$H_B$), 1.23 (3H, t, *J* = 7.1, $OCH_2CH_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 172.5 (*C*=O), 156.4 (*C*=O), 142.8 (Ar*C*), 136.2 (Ar*C*), 130.0 (2×Ar*C*H), 129.1 (2×Ar*C*H), 128.4 (2×Ar*C*H), 127.4 (Ar*C*H), 127.2 (2×Ar*C*H), 126.9 (Ar*C*H), 61.2 ($OCH_2CH_3$), 54.4 (*C*H$CH_2$), 38.2 (*C*$H_2$Ph), 37.1 (N*C*$H_3$), 14.1 ($OCH_2CH_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3428 (NH), 3062, 3028, 2980, 2937 (C-H), 1736 (C=O ester), 1659 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 349 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{22}N_2O_3Na$ [M+Na]$^+$ 349.1528, found 349.1521.

*NMR file: $^1$H NMR = 2014-01-13-jpc-27 (10), $^{13}$C NMR = 2014-01-13-jpc-27 (11).*

**(*S*)-2-(3-Methyl-3-phenylureido)-3-phenylpropanoic acid (462)**

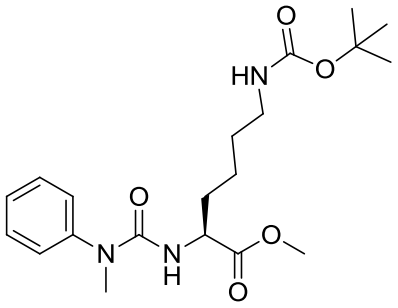



Following general procedure **5**, LiOH (821 mg, 34.30 mmol) was added to urea **457** (746 mg, 2.29 mmol) in 2:1 THF:$H_2O$ (20.0 mL: 10.0 mL). The reaction was complete after 17.5 h at 45 °C. The title compound was yielded as a pale yellow oil without further purification (682 mg, 2.29 mmol, >99%). **462**: **R$_f$** (1:1 Pet.Ether:EtOAc) 0.11; $[\alpha]_D^{21}$ = –44.4 (*c* = 1.1 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 10.8 (1H, br. s, O*H*), 7.35-7.28 (3H, m, Ph*H*), 7.21-7.19 (3H, m, Ph*H*), 7.05-7.03 (2H, m, Ph*H*), 7.00-6.97 (2H, m, Ph*H*), 4.68 (1H, br. d, *J* = 7.2, N*H*), 4.63 (1H, td, *J* = 7.4, 5.1, NHC*H*$CH_2$), 3.22 (3H, s, NC$H_3$), 3.14 (1H, dd, *J* = 14.0, 5.1, CHC$H_A$$H_B$), 2.95 (1H, dd, *J* = 14.1, 7.5, CHC$H_A$$H_B$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.9 (*C*=O), 157.4 (*C*=O), 142.2 (Ar*C*), 136.1 (Ar*C*), 130.1 (2×Ar*C*H), 129.2 (2×Ar*C*H), 128.6 (2×Ar*C*H), 127.7 (Ar*C*H), 127.1 (2×Ar*C*H), 126.9 (Ar*C*H), 54.7 (*C*H$CH_2$), 37.3 (*C*$H_2$Ph), 37.2 (N*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3421 (NH), 3062 (OH broad), 3029, 2934 (C-H), 1731 (C=O acid), 1620 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 321 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{18}N_2O_3Na$ [M+Na]$^+$ 321.1215, found 321.1203.

*NMR file: $^1$H NMR = 2014-01-20-jpc-3 (10), $^{13}$C NMR = 2014-01-17-jpc-7 (11).*

**Synthesis of 475:**

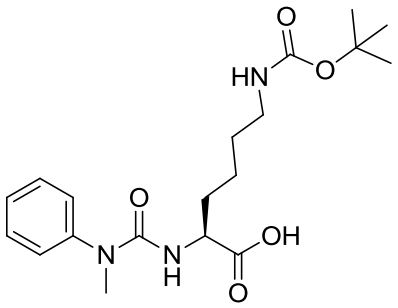
**Methyl $N^6$-(*tert*-butoxycarbonyl)-$N^2$-(methyl(phenyl)carbamoyl)-*L*-lysinate (472)**



Following general procedure **1b**, *N*-methyl-*N*-phenylcarbamoyl chloride (1.20 g, 7.08 mmol) was added to a pre-stirred solution of $N_\varepsilon$-Boc-*L*-lysine methyl ester hydrochloride (2.00 g, 6.74 mmol) and $Et_3N$ (2.16 mL, 15.50 mmol) in MeCN (20.0 mL). The reaction was complete after 15 h at reflux. The title compound was yielded as a pale yellow oil without further purification (2.65 g, 6.73 mmol, >99%). **472**: $\mathbf{R_f}$ (7:3 Pet.Ether:EtOAc) 0.15; $[\alpha]_D^{21}$ = +7.3 (*c* = 1.2 in $CHCl_3$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.45-7.42 (2H, m, Ph*H*), 7.33-7.28 (3H, m, Ph*H*), 4.78 (1H, br. d, *J* = 8.1, N*H*), 4.57 (1H, br. s, BocN*H*), 4.49 (1H, td, *J* = 8.1, 5.2, NHC*H*$CH_2$), 3.69 (3H, s, OC$H_3$), 3.26 (3H, s, NC$H_3$), 3.06-3.05 (2H, m, C$H_2$NHBoc), 1.78-1.71 (1H, m, HCC$H_A$$H_B$$(CH_2)_3$NH), 1.55-1.45 (3H, m, HCC$H_A$$H_B$$(CH_2)_3$NH + C$H_2$$CH_2$NH), 1.43 (9H, s, OC(C$H_3$)$_3$), 1.33-1.22 (2H, m, HCC$H_2$C$H_2$$(CH_2)_2$NH); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.0 (*C*=O), 156.8 (*C*=O), 156.1 (*C*=O), 143.1 (Ar*C*), 130.2 (2×Ar*C*H), 127.6 (Ar*C*H), 127.3 (2×Ar*C*H), 79.2 (*C*$(CH_3)_3$), 53.4 (NH*C*HC$H_2$), 52.3 (O*C*$H_3$), 40.4 (*C*$H_2$NHBoc), 37.4 (N*C*$H_3$), 32.5 (HC*C*$H_2$$(CH_2)_3$NH), 29.5 (*C*$H_2$$CH_2$NH), 28.6 (C(*C*$H_3$)$_3$), 22.7 (HCC$H_2$*C*$H_2$$(CH_2)_2$NH); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3338 (NH), 2973, 2933, 2864 (C-H), 1740 (C=O ester), 1709 (C=O carbamate), 1657 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 416 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{31}N_3O_5Na$ [M+Na]$^+$ 416.2156, found 416.2166.

*NMR file: $^1$H NMR = 2014-07-22-jpc-36 (20) 500a, $^{13}$C NMR = 2014-07-22-jpc-36 (21) 500a.*

**$N^6$-(*tert*-Butoxycarbonyl)-$N^2$-(methyl(phenyl)carbamoyl)-*L*-lysine (475)**



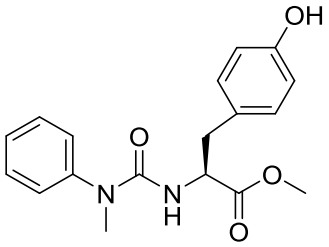
Following general procedure **5**, LiOH (2.26g, 94.54 mmol) was added to urea **472** (2.48 g, 6.30 mmol) in 2:1 THF:$H_2O$ (79.0 mL: 39.5 mL). The reaction was complete after 15 h at 45 °C. The

title compound was yielded as a white gum without further purification (2.29 g, 6.03 mmol, 96%). **475**: $\mathbf{R}_f$ (1:4 Pet.Ether:EtOAc) 0.23; $[\alpha]_D^{21}$ = –7.8 (*c* = 1.2 in $CHCl_3$); **$^1$H NMR** (400 MHz, MeOD): $\delta_H$ = 7.49-7.45 (2H, m, Ph*H*), 7.36-7.33 (3H, m, Ph*H*), 4.28 (1H, dd, *J* = 8.3, 4.9, NHC*H*$CH_2$), 3.25 (3H, s, NC$H_3$), 3.00 (2H, t, *J* = 6.9, C$H_2$NHBoc), 1.85-1.76 (1H, m, HCC$H_A$$H_B$$(CH_2)_3$NH), 1.66-1.56 (1H, m, HCC$H_A$$H_B$$(CH_2)_3$NH), 1.49-1.40 (2H, m, C$H_2$$CH_2$NH), 1.43 (9H, s, OC(C$H_3$)$_3$), 1.34-1.27 (2H, m, HCC$H_2$C$H_2$$(CH_2)_2$NH); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.5 (*C*=O), 157.4 (*C*=O), 156.2 (*C*=O), 142.7 (Ar*C*), 130.2 (2×Ar*C*H), 127.7 (Ar*C*H), 127.2 (2×Ar*C*H), 79.3 (*C*$(CH_3)_3$), 53.5 (NH*C*HC$H_2$), 40.4 (*C*$H_2$NHBoc), 37.5 (N*C*$H_3$), 32.0 (HC*C*$H_2$$(CH_2)_3$NH), 29.4 (*C*$H_2$$CH_2$NH), 28.5 (C(*C*$H_3$)$_3$), 22.6 (HCC$H_2$*C*$H_2$$(CH_2)_2$NH); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3334 (NH), 2976, 2933, 2865 (C-H), 1705 (C=O acid), 1651 (C=O carbamate), 1594 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 380 ([M+H]$^+$, 30%), 402 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{29}N_3O_5Na$ [M+Na]$^+$ 402.2005, found 402.2022.

*NMR file: $^1$H NMR = 2014-07-07-jpc-31 (20) 400c, $^{13}$C NMR = 2014-08-06-jpc-50 (11) 400c.*

**Synthesis of 476:**

**Methyl (methyl(phenyl)carbamoyl)-*L*-tyrosinate (473)**

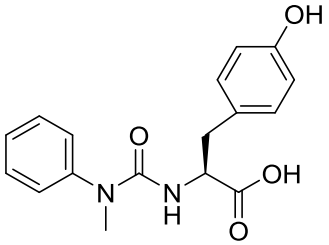



Following general procedure **1b**, *N*-methyl-*N*-phenylcarbamoyl chloride (1.54 g, 9.06 mmol) was added to a pre-stirred solution of L-tyrosine methyl ester hydrochloride (2.00 g, 8.63 mmol) and Et$_3$N (2.77 mL, 19.8 mmol) in MeCN (22.0 mL). The reaction was complete after 15 h at reflux. The title compound was yielded as a white solid without further purification (2.79 g, 8.50 mmol, 98%). **473**: $\mathbf{R}_f$ (7:3 Pet.Ether:EtOAc) 0.08; **mp**: 155-157 °C; $[\alpha]_D^{21}$ = –6.4 (*c* = 1.1 in $CHCl_3$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.39-7.36 (2H, m, Ph*H*), 7.31-7.28 (1H, m, Ph*H*), 7.15-7.13 (2H, m, Ph*H*), 6.78 (2H, d, *J* = 8.4, OHAr*H*), 6.75 (1H, br.s, O*H*), 6.65 (2H, d, *J* = 8.5, OHAr*H*), 4.74-4.67 (2H, m, N*H* + NHC*H*$CH_2$), 3.69 (3H, s, OC$H_3$), 3.24 (3H, s, NC$H_3$), 2.97 (1H, dd, *J* = 14.0, 5.4, CHC$H_A$$H_B$), 2.82 (1H, dd, *J* = 14.0, 6.7, CHC$H_A$$H_B$); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 173.4 (*C*=O), 156.9 (*C*=O), 155.6 (Ar*C*OH), 142.7 (Ar*C*N), 130.2 (2×Ar*C*H + 2×OHAr*C*H), 127.7 (Ar*C*H), 127.4 (Ar*C*), 127.3 (2×Ar*C*H), 115.6 (2×OHAr*C*H), 54.8 (*C*H$CH_2$), 52.4 (O*C*$H_3$), 37.5 (CH*C*$H_2$Ar*C*H), 37.3 (N*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3422 (NH), 3194 (OH broad), 2954, 2939 (C-H), 1751 (C=O ester), 1640 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 329 ([M+H]$^+$, 20%), 351

([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{18}H_{20}N_2O_4Na$ [M+Na]$^+$ 351.1315, found 351.1303.

*NMR file: $^1$H NMR = 2014-07-22-jpc-35 (20) 500a, $^{13}$C NMR = 2014-07-22-jpc-35 (21) 500a.*

**(Methyl(phenyl)carbamoyl)-*L*-tyrosine (476)**

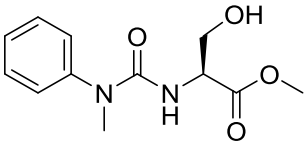



Following general procedure **5**, LiOH (2.87 g, 120.00 mmol) was added to urea **473** (2.63 g, 8.00 mmol) in 2:1 THF:$H_2O$ (100 mL: 50.0 mL). The reaction was complete after 15 h at 45 °C. The title compound was yielded as a white solid without further purification (2.43 g, 7.73 mmol, 97%). **476**: **R$_f$** (1:4 Pet.Ether:EtOAc) 0.21; **mp**: 205-207 °C; $[\alpha]_D^{21}$= –24.5 (*c* = 1.0 in MeOH); **$^1$H NMR** (500 MHz, MeOD): $\delta_H$ = 7.40-7.37 (2H, m, Ph*H*), 7.33-7.30 (1H, m, Ph*H*), 7.16-7.15 (2H, m, Ph*H*), 6.83-6.81 (2H, m, OHAr*H*), 6.63-6.61 (2H, m, OHAr*H*), 4.47 (1H, dd, *J* = 6.9, 5.3, NHC*H*CH$_A$H$_B$), 3.18 (3H, s, NC*H$_3$*), 2.98 (1H, dd, *J* = 13.9, 5.3, CHC*H$_A$*H$_B$), 2.82 (1H, dd, *J* = 13.9, 7.0, CHCH$_A$*H$_B$*); **$^{13}$C {$^1$H} NMR** (100 MHz, MeOD): $\delta_C$ = 175.5 (*C*=O), 158.8 (*C*=O), 157.4 (Ar*C*OH), 144.0 (Ar*C*N), 131.2 (2×OHAr*C*H), 131.1 (2×Ar*C*H), 128.6 (Ar*C*H), 128.4 (Ar*C*), 128.3 (2×Ar*C*H), 116.3 (2×OHAr*C*H), 55.9 (*C*HCH$_2$), 37.5 (CH*C*H$_2$Ar*C*H), 37.4 (N*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3414 (NH), 3144 (OH broad), 2960, 2937 (C-H), 1760 (C=O acid), 1633 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 315 ([M+H]$^+$, 10%), 337 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{18}N_2O_4Na$ [M+Na]$^+$ 337.1164, found 337.1176.

*NMR file: $^1$H NMR = 2015-01-05-jpc-10 (20) 500a, $^{13}$C NMR = 2015-01-06-jpc-38 (10) 400c, 2D spectra 2014-07-28-jpc-43 (10-14) 400a.*

**<u>Synthesis of 477:</u>**

**Methyl (methyl(phenyl)carbamoyl)-*L*-serinate (474)**

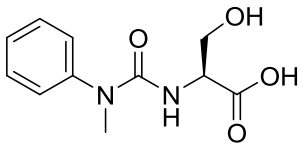



Following general procedure **1b**, *N*-methyl-*N*-phenylcarbamoyl chloride (2.30 g, 13.5 mmol) was added to a pre-stirred solution of L-serine methyl ester hydrochloride (2.00 g, 12.9 mmol) and $Et_3N$ (4.12 mL, 29.6 mmol) in MeCN (32.0 mL). The reaction was complete after 15 h at reflux. The title compound was yielded as a pale yellow oil without further purification (3.00 g, 11.89 mmol, 92%). **474**: **R$_f$** (7:3 Pet.Ether:EtOAc) 0.12; $[\alpha]_D^{21}$= +37.1 (*c* = 1.1 in $CHCl_3$); **$^1$H NMR** (500 MHz,

$CDCl_3$): $\delta_H$ = 7.44-7.41 (2H, m, Ph*H*), 7.32-7.29 (3H, m, Ph*H*), 5.31 (1H, br. d, *J* = 7.0, N*H*), 4.52(1H, dt, *J* = 7.0, 4.0, NHC*H*$CH_2$), 3.84 (2H, d, *J* = 4.0, CHC*H*$_2$OH), 3.72 (3H, s, OC*H*$_3$), 3.26 (3H, s, NC*H*$_3$); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 171.7 (*C*=O), 157.2 (*C*=O), 142.9 (Ar*C*), 130.2 (2×Ar*C*H), 127.7 (Ar*C*H), 127.2 (2×Ar*C*H), 64.1 (CH*C*H$_2$OH), 56.3 (NH*C*HCH$_2$), 52.7 (O*C*H$_3$), 37.4 (N*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3417 (NH), 3417 (OH broad), 2952, 2885 (C-H), 1741 (C=O ester), 1639 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 275 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{16}N_2O_4Na$ [M+Na]$^+$ 275.1002, found 275.1008.

*NMR file: $^1$H NMR = 2014-07-22-jpc-34 (20) 500a, $^{13}$C NMR = 2014-07-22-jpc-34 (21) 500a.*

**(Methyl(phenyl)carbamoyl)-*L*-serine (477)**

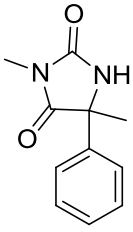



Following general procedure **5**, LiOH (3.94 g, 164.70 mmol) was added to urea **474** (2.77 g, 10.98 mmol) in 2:1 THF:$H_2O$ (138 mL: 69.0 mL). The reaction was complete after 15 h at 45 °C. The title compound was yielded as a yellow gum without further purification (2.26 g, 9.49 mmol, 86%). **477**: **R$_f$** (1:4 Pet.Ether:EtOAc) 0.08; $[\alpha]_D^{21}$ = –14.8 (*c* = 1.0 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.63 (1H, br.s, COO*H*), 7.41-7.38 (2H, m, Ph*H*), 7.29-7.27 (3H, m, Ph*H*), 5.45 (1H, br. d, *J* = 7.1, N*H*), 4.42-4.41 (1H, m, NHC*H*$CH_2$), 3.86 (1H, dd, *J* = 11.0, 3.3, C$H_A$H$_B$OH), 3.72 (1H, dd, *J* = 11.1, 3.1, CH$_A$*H*$_B$OH), 3.22 (3H, s, NC*H*$_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 173.4 (*C*=O), 157.7 (*C*=O), 142.4 (Ar*C*), 130.2 (2×Ar*C*H), 127.7 (Ar*C*H), 127.1 (2×Ar*C*H), 62.9 (CH*C*H$_2$OH), 55.9 (NH*C*HCH$_2$), 37.6 (N*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3420 (NH), 3420 (OH broad), 2942 (C-H), 1732 (C=O acid), 1629 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 239 ([M+H]$^+$, 30%), 261 ([M+Na]$^+$, 100%), 277 ([M+K]$^+$, 30%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{15}N_2O_4$ [M+H]$^+$ 239.1032, found 239.1039.

*NMR file: $^1$H NMR = 2014-08-06-jpc-49 (10) 400c, $^{13}$C NMR = 2014-08-06-jpc-49 (11) 400c.*

**Synthesis of racemic *N*-unprotected hydantoins:**

**3,5-Dimethyl-5-phenylimidazolidine-2,4-dione (±446)**[226]

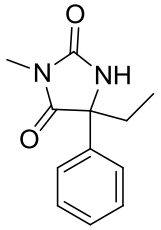



Following a similar method to general procedure **7**, urea acid **445** (95 mg, 0.43 mmol) and LiCl (69 mg, 1.63 mmol, 3.8 eq.) were dissolved in THF (3.30 mL). LDA (4.0 eq.) was prepared with THF

(1.00 mL), DiPA (0.24 mL, 1.71 mmol) and *n*BuLi (1.13 mL, 1.71 mmol, 1.51 M in hexanes). The reaction turned pale yellow upon addition of LDA. After 3 h the reaction was cooled to –78 °C and quenched with saturated aqueous $NH_4Cl$. After stirring for 10 min the reaction was acidified to pH 4 using 1.0 M HCl and stirred for 30 min. After the work up the reaction mixture was dissolved in anhydrous MeOH (4.50 mL) and thionyl chloride (0.04 mL) was added. The reaction was complete after 16 h at room temperature. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc + 1% $Et_3N$) yielded the title compound as a white solid (68 mg, 0.33 mmol, 78%). ±**446**: $\mathbf{R_f}$ (7:3 Pet.Ether:EtOAc + 1% $Et_3N$) 0.39; **mp**: 189-191 °C;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **446**

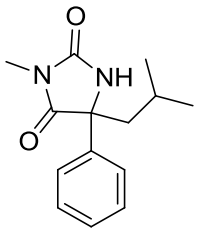
**5-Ethyl-3-methyl-5-phenylimidazolidine-2,4-dione (±21)**[221,227,]




Following general procedure **7**, urea acid **458** (106 mg, 0.45 mmol) and LiCl (71 mg, 1.67 mmol, 3.7 eq.) were dissolved in THF (3.50 mL). LDA (5.0 eq.) was prepared with THF (1.00 mL), DiPA (0.31 mL, 2.25 mmol) and *n*BuLi (1.57 mL, 2.25 mmol, 1.43 M in hexanes). The reaction turned yellow upon addition of LDA. After the work up the reaction mixture was dissolved in anhydrous MeOH (3.00 mL) and thionyl chloride (0.05 mL) was added. The reaction was complete after 17 h at room temperature. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc + 1% $Et_3N$) yielded the title compound as a white solid (67 mg, 0.307 mmol, 68%). ±**21**: $\mathbf{R_f}$ (4:1 Pet.Ether:EtOAc + 1% $Et_3N$) 0.28; **mp**:135-137 °C;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **21**

**5-*iso*Butyl-3-methyl-5-phenylimidazolidine-2,4-dione (±464)**

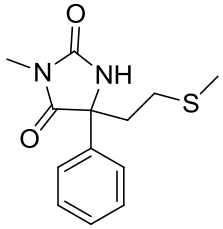



Following general procedure **7**, urea acid **460** (109 mg, 0.41 mmol) and LiCl (70 mg, 1.65 mmol) were dissolved in THF (4.10 mL). LDA (5.0 eq.) was prepared with THF (1.00 mL), DiPA (0.29 mL, 2.06 mmol) and *n*BuLi (1.45 mL, 2.06 mmol, 1.42 M in hexanes). The reaction turned yellow upon addition of LDA. After the work up the reaction mixture was dissolved in anhydrous MeOH

(6.00 mL) and thionyl chloride (0.05 mL) was added. The reaction was complete after 16 h at room temperature. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc + 1% $Et_3N$) yielded the title compound as a white solid (90 mg, 0.37 mmol, 88%). ±**464**: $\mathbf{R_f}$ (4:1 Pet.Ether:EtOAc + 1% $Et_3N$) 0.33; **mp**: 147-149 °C

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **464**

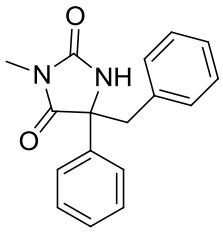
**3-Methyl-5-(2-(methylthio)ethyl)-5-phenylimidazolidine-2,4-dione (±465)**




Following general procedure **7**, urea acid **461** (103 mg, 0.37 mmol) and LiCl (62 mg, 1.46 mmol) were dissolved in THF (2.70 mL). LDA (5.0 eq.) was prepared with THF (1.00 mL), DiPA (0.26 mL, 1.83 mmol) and *n*BuLi (1.29 mL, 1.83 mmol, 1.42 M in hexanes). The reaction turned yellow upon addition of LDA. After the work up the reaction mixture was dissolved in anhydrous MeOH (3.00 mL) and thionyl chloride (0.03 mL) was added. The reaction was complete after 16 h at room temperature. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc + 1% $Et_3N$) yielded the title compound as a white solid (73 mg, 0.28 mmol, 76%). ±**465**: $\mathbf{R_f}$ (4:1 Pet.Ether:EtOAc + 1% $Et_3N$) 0.24; **mp**: 149-151 °C;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **465**

**5-Benzyl-3-methyl-5-phenylimidazolidine-2,4-dione (466)**

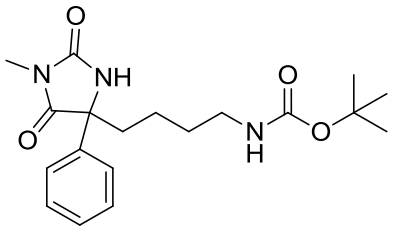



Following general procedure **7**, urea acid **462** (83 mg, 0.28 mmol) and LiCl (56 mg, 1.32 mmol, 4.8 eq.) were dissolved in THF (1.80 mL). LDA (7.0 eq.) was prepared with THF (1.00 mL), DiPA (0.27 mL, 1.95 mmol) and *n*BuLi (1.37 mL, 1.95 mmol, 1.42 M in hexanes). The reaction turned yellow upon addition of LDA and went dark orange over time. After the work up the reaction mixture was dissolved in anhydrous MeOH (5.00 mL) and thionyl chloride (0.05 mL) was added. The reaction was complete after 16 h at room temperature. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a white solid (59 mg, 0.21 mmol, 76%). **466**: $\mathbf{R_f}$ (4:1 Pet.Ether:EtOAc) 0.30; **mp**:199-201 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.61-7.59 (2H, m, Ph*H*), 7.43-7.34 (3H, m, Ph*H*), 7.24-7.21 (3H, m, Ph*H*), 7.05-7.03

(2H, m, Ph*H*), 6.56 (1H, br. s, N*H*), 3.49 (1H, d, *J* = 13.6, C$H_A$$H_B$Ph), 3.29 (1H, d, *J* = 13.6, CH$_A$$H_B$Ph), 2.83 (3H, s, NC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.4 (*C*=O), 156.9 (*C*=O), 137.6 (Ar*C*), 134.0 (Ar*C*), 130.2 (2×Ar*C*H), 128.9 (2×Ar*C*H), 128.7 (Ar*C*H), 125.6 (2×Ar*C*H), 127.8 (Ar*C*H), 125.8 (2×Ar*C*H), 67.9 (*C*$CH_2$), 45.4 (*C*$H_2$), 24.7 (N*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3285 (NH), 3063, 3030 (C-H), 1772 (C=O amide), 1708 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 303 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{16}N_2O_2Na$ [M+Na]$^+$ 303.1109, found 303.1109.

*NMR file: $^1$H NMR = 2014-02-14-jpc-37 (10), $^{13}$C NMR = 2014-02-14-jpc-37 (11).*

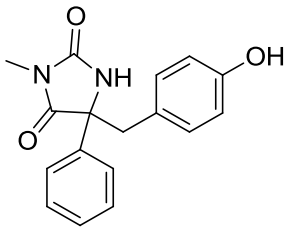
**_tert_-Butyl (4-(1-methyl-2,5-dioxo-4-phenylimidazolidin-4-yl)butyl)carbamate (±478)**



Following a similar method to general procedure **8**, urea ester **472** (79 mg, 0.20 mmol) was dissolved in THF (2.00 mL) and cooled to –78 °C. KHMDS (1.00 mL, 1.00 mmol, 5.0 eq.) was added and the reaction was complete after 3.5 h. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (20 mg, 0.06 mmol, 28%). ±**478**: **R$_f$** (1:2 Pet.Ether:EtOAc) 0.61;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **478**

**5-(4-Hydroxybenzyl)-3-methyl-5-phenylimidazolidine-2,4-dione (479)**



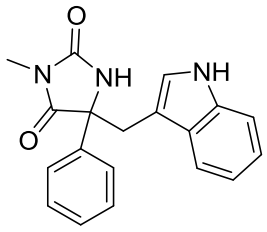
Following a similar method to general procedure **7**, urea acid **476** (100 mg, 0.32 mmol) and LiCl (61 mg, 1.44 mmol, 4.5 eq.) were dissolved in THF (2.20 mL). LDA (8.0 eq.) was prepared with THF (1.00 mL), DiPA (0.36 mL, 2.55 mmol) and *n*BuLi (1.73 mL, 2.55 mmol, 1.47 M in hexanes). The reaction turned yellow upon addition of LDA then became a cloudy yellow solution. The reaction was left at room temperature for 15.5 h. After the work up the reaction mixture was dissolved in anhydrous MeOH (5.00 mL) and thionyl chloride (0.05 mL) was added. The reaction was complete after 16 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:2 Pet.Ether:EtOAc) yielded the title compound as a white solid (18 mg, 0.06 mmol, 19%). **479**: **R$_f$** (1:1 Pet.Ether:EtOAc) 0.51; **mp**: 259-260 °C; **$^1$H NMR** (400 MHz, MeOD): $\delta_H$ = 7.66-7.65 (2H,

m, Ph*H*), 7.43-7.33 (3H, m, Ph*H*), 7.01 (2H, d, *J* = 8.4, OHAr*H*), 6.67 (2H, d, *J* = 8.4, OHAr*H*), 3.50 (1H, d, *J* = 13.7, C$H_A$$H_B$Ar), 3.00 (1H, d, *J* = 13.7, CH$_A$$H_B$Ar), 2.65 (3H, s, NC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, MeOD): $\delta_C$ = 176.4 (*C*=O), 158.4 (*C*=O), 157.9 (Ar*C*OH), 139.9 (Ar*C*), 132.4 (2×OHAr*C*H), 129.7 (2×Ar*C*H), 129.3 (Ar*C*H), 126.8 (2×Ar*C*H), 126.3 (Ar*C*), 115.9 (2×OHAr*C*H), 69.7 (*C*CH$_2$), 45.2 (*C*H$_2$), 24.4 (N*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3337 (NH), 3251 (OH), 2908 (C-H), 1768 (C=O), 1695 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 297 ([M+H]$^+$, 80%), 319 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{16}N_2O_3Na$ [M+Na]$^+$ 319.1059, found 319.1073.

*NMR file: $^1$H NMR = 2015-01-05-jpc-23 (20) 400c, $^{13}$C NMR = 2014-08-06-jpc-55 (14) 400c.*

**5-((1*H*-Indol-3-yl)methyl)-3-methyl-5-phenylimidazolidine-2,4-dione (485)**

(from urea acid **484** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)**(b)**

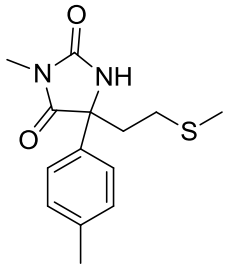



Following general procedure **7**, urea acid **484** (250 mg, 0.74 mmol) and LiCl (122 mg, 2.88 mmol, 3.9 eq.) were dissolved in THF (4.40 mL). LDA (6.0 eq.) was prepared with THF (3.00 mL), DiPA (0.62 mL, 4.45 mmol) and *n*BuLi (3.39 mL, 4.45 mmol, 1.31 M in hexanes). The reaction turned yellow upon addition of LDA then became a cloudy yellow/brown solution. Acidification with 1.0 M HCl to pH 5 during work up. After the work up the reaction mixture was dissolved in anhydrous MeOH (6.00 mL) and thionyl chloride (0.08 mL) was added. The reaction was complete after 16 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:2 Pet.Ether:EtOAc) yielded the title compound as a yellow solid (113 mg, 0.35 mmol, 48%). **485**: **$R_f$** (1:1 Pet.Ether:EtOAc) 0.32; **mp**: 185-187 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 8.05 (1H, br.s, N*H*), 7.62 (2H, d, *J* = 7.0, Ar*H*), 7.42-7.34 (4H, m, Ar*H*), 7.30 (1H, d, *J* = 8.1, Ar*H*), 7.16 (1H, t, *J* = 7.5, Ar*H*), 7.05 (1H, t, *J* = 7.5, Ar*H*), 6.71 (1H, s, Ar*H*), 6.35 (1H, br.s, N*H*), 3.64 (1H, d, *J* = 14.6, C$H_A$$H_B$Ar), 3.52 (1H, d, *J* = 14.6, CH$_A$$H_B$Ar), 2.84 (3H, s, NC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.0 (*C*=O), 157.0 (*C*=O), 137.9 (Ar*C*), 135.8 (Ar*C*), 128.8 (2×Ar*C*H), 128.5 (Ar*C*H), 127.7 (Ar*C*), 125.9 (2×Ar*C*H), 123.9 (Ar*C*H), 122.4 (Ar*C*H), 120.1 (Ar*C*H), 118.7 (Ar*C*H), 111.3 (Ar*C*H), 108.3 (Ar*C*), 68.0 (*C*CH$_2$), 35.5 (*C*H$_2$), 24.8 (N*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3332 (broad NH), 2921 (C-H), 1769 (C=O), 1702 (C=O); **MS** (ESI$^-$, MeOH): *m/z* = 318 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{18}N_3O_2$ [M+H]$^+$ 320.1394, found 320.1396.

*NMR file: $^1$H NMR = 2014-07-11-jpc-45 (20) 400c, $^{13}$C NMR = 2014-07-11-jpc-45 (21) 400c.*

**3-Methyl-5-(2-(methylthio)ethyl)-5-(*p*-tolyl)imidazolidine-2,4-dione (±487)**

(from urea acid **486** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)[(b)]

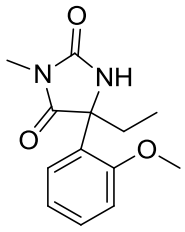



Following a similar method to general procedure **7**, urea acid **486** (146 mg, 0.49 mmol) and LiCl (91 mg, 2.15 mmol, 4.4 eq.) were dissolved in THF (3.00 mL). LDA (5.5 eq.) was prepared with THF (1.90 mL), DiPA (0.38 mL, 2.71 mmol) and *n*BuLi (1.84 mL, 2.71 mmol, 1.47 M in hexanes). The reaction turned orange upon addition of LDA and turned brown over time. After 3 h at room temperature the reaction was quenched with MeOH and stirred for 15 min before the reaction mixture was concentrated *in vacuo*. The reaction mixture was then dissolved in anhydrous MeOH (3.50 mL) and cooled to 0 °C before thionyl chloride (0.35 mL) was added. The reaction was stirred for 10 min at 0 °C and then warmed to room temperature. The reaction was complete after 16 h at room temperature. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a white solid (97 mg, 0.35 mmol, 71%). ±**487**: $\mathbf{R_f}$ (2:1 Pet.Ether:EtOAc) 0.40; **mp**: 141-143 °C;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **487**

**5-(3-Methoxyphenyl)-3,5-dimethylimidazolidine-2,4-dione (±490)**

(from urea ester **504** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)[(b)]

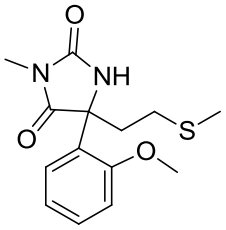



Following general procedure **8**, urea ester **504** (90 mg, 0.32 mmol) was dissolved in THF (3.20 mL) and cooled to –78 °C. KHMDS (1.28 mL, 1.28 mmol) was added and the reaction was complete after 3.5 h. The title compound was yielded as a white solid without further purification (48 mg, 0.19 mmol, 60%). ±**490**: $\mathbf{R_f}$ (1:2 Pet.Ether:EtOAc) 0.59; **mp**: 144-146 °C;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **490**

**5-(2-Methoxyphenyl)-3-methyl-5-(2-(methylthio)ethyl)imidazolidine-2,4-dione (±491)**

(from urea ester **505** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)[(b)]

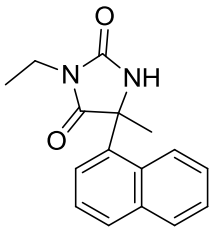


Following general procedure **8**, urea ester **505** (203 mg, 0.62 mmol) was dissolved in THF (6.20 mL) and cooled to –78 °C. KHMDS (2.49 mL, 2.49 mmol) was added and the reaction was complete after 3.5 h. The title compound was yielded as a white solid after trituration with $Et_2O$ (88 mg, 0.30 mmol, 48%). ±**491**: $\mathbf{R_f}$ (3:2 Pet.Ether:EtOAc) 0.42; **mp**: 165-167 °C;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **491**

**3-Ethyl-5-methyl-5-(naphthalen-1-yl)imidazolidine-2,4-dione (±507)**

(from urea ester **506** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)[(b)]

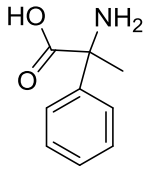


Following a similar method to general procedure **8**, urea ester **506** (200 mg, 0.67 mmol) was dissolved in THF (6.70 mL) and cooled to –78 °C. KHMDS (2.66 mL, 2.66 mmol) was added and the reaction was complete after 3.5 h. Purification by flash column chromatography ($SiO_2$, 1:99 MeOH:DCM) yielded the title compound as a yellow solid (80 mg, 0.30 mmol, 45%). ±**507**: $\mathbf{R_f}$ (3:97 MeOH:DCM) 0.42; **mp**: 142-144 °C;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **507**

**Synthesis of ±510:**

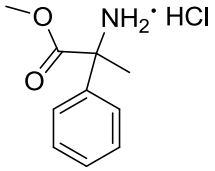
**2-Amino-2-phenylpropanoic acid (±508)**[228]



Following general procedure **13**, 4.0 M NaOH solution (1.00 mL) was added to hydantoin **446** (37 mg, 0.18 mmol) and heated to reflux for 43.5 h. Purification with dowex ion exchange resin yielded the title compound as a white solid (30 mg, 0.18 mmol, >99%). ±**508**: $\mathbf{R_f}$ (1:9 MeOH:DCM) 0.06; **mp**: 267-269 °C;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **508**. Matches literature data.

**Methyl 2-amino-2-phenylpropanoate hydrochloride (±510)**[216]

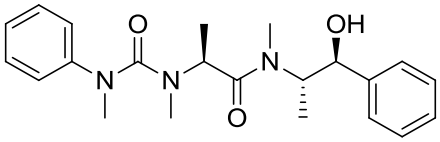


Following general procedure **14**, quaternary amino acid **508** (30 mg, 0.18 mmol) was dissolved in MeOH (6.50 mL), cooled to 0 °C and thionyl chloride (0.15 mL) added. The reaction was complete after 20 h at reflux. The title compound was yielded as a white solid (35 mg, 0.16 mmol, 90%). ±**510**: $\mathbf{R_f}$ (1:9 MeOH:DCM) 0.24; **mp**: 200-202 °C;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **510**. Matches literature data.

**Synthesis of 531 (from synthesis of 395):**[(a)]

**(*S*)-2-(1,3-dimethyl-3-phenylureido)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropanamide (531)**



Following a similar procedure to general procedure **9**, urea **395** (250 mg, 1.06 mmol) was dissolved in DCM (6.00 mL) then (*S*,*S*)-pseudoephedrine (263 mg, 1.59 mmol), HOBt·$H_2O$ (143 mg, 1.06 mmol), EDC·HCl (244 mg, 1.27 mmol) and DiPEA (0.42 mL, 2.44 mmol, 2.3 eq.) were added and stirred for 5 min at 0 °C. The reaction was complete after 65 h at room temperature. Purification by flash column chromatography ($SiO_2$, 1:1 Pet.Ether:EtOAc) yielded the title compound as a white gum (356 mg, 0.93 mmol, 88%). **531: $\mathbf{R_f}$** (1:1 Pet Ether:EtOAc) 0.08;

NMR data is a mixture of diastereomers and rotamers:

Overall: Maj D, Rot B: Maj D, Rot A: Min D, Rot B: Min D, Rot A = 17:12:3:1 = % 52:36:9:3

Major Diastereomer:

**$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.50-7.06 (rot a+b, 10H, m, Ph*H*), 5.24 (rot b, 1H, q, *J* = 7.2 Hz, $CH_3NCHC{=}O$), 5.16 (rot b, 1H, d, *J* = 7.6 Hz, C*H*OH), 5.03 (rot a, 1H, q, *J* = 7.0 Hz, $CH_3NCHC{=}O$), 4.72 (rot a, 1H, br. d, *J* = 8.3 Hz, C*H*OH), 4.60-4.30 (rot a+b, 1H, m, $CH_3NCHCHOH$), 3.24 (rot b, 3H, s, $NCH_3$), 3.19 (rot a, 3H, s, $NCH_3$), 3.05 (rot a, 3H, s, $NCH_3$), 2.95 (rot b, 3H, s, $NCH_3$), 2.66 (rot b, 3H, s, $NCH_3$), 2.45 (rot a, 3H, s, $NCH_3$), 1.29 (rot b, 3H, d, *J* = 7.2 Hz, $NCH(CH_3)C{=}O$), 1.21 (rot a, 3H, d, *J* = 7.1 Hz, $NCH(CH_3)C{=}O$), 1.05 (rot a, 3H, d, *J* = 7.0 Hz, $NCH(CH_3)CHOH$), 1.00 (rot b, 3H, d, *J* = 6.6 Hz, $NCH(CH_3)CHOH$)

Minor Diastereomer:

**$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.50-7.06 (rot a+b, 10H, m, Ph*H*), 5.30 (rot a, 1H, q, *J* = 7.0 Hz, $CH_3NCHC{=}O$), 4.91 (rot b, 1H, q, *J* = 7.1 Hz, $CH_3NCHC{=}O$), 4.60-4.30 (rot a+b, 2H, m, $CH_3NCHCHOH$ and C*H*OH), 3.20 (rot b, 3H, s, $NCH_3$), 3.12 (rot a, 3H, s, $NCH_3$), 3.02 (rot b, 3H, s, $NCH_3$), 2.92 (rot a, 3H, s, $NCH_3$), 2.56 (rot b, 3H, s, $NCH_3$), 2.45 (rot a, 3H, s, $NCH_3$), 1.24 (rot b, 3H, d, *J* = 7.0 Hz, $NCH(CH_3)C{=}O$), 1.23 (rot a, 3H, d, *J* = 7.0 Hz, $NCH(CH_3)C{=}O$), 1.10 (rot a, 3H, d, *J* = 7.2 Hz, $NCH(CH_3)CHOH$), 1.00 (rot b, 3H, d, *J* = 6.6 Hz, $NCH(CH_3)CHOH$)

Only the carbons for the major diastereomer are seen:

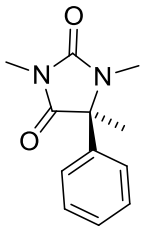
**$^{13}$C {$^{1}$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.2 ($C{=}O_{min}$), 174.1 ($C{=}O_{maj}$), 162.4 ($C{=}O_{maj}$), 161.7 ($C{=}O_{min}$), 146.4 ($ArCN_{min}$), 146.1 ($ArCN_{maj}$), 142.4 ($ArCC_{maj}$), 142.1 ($ArCC_{min}$), 129.5 ($2\times ArCH_{min}$), 129.4 ($2\times ArCH_{maj}$), 128.5 ($2\times ArCH_{maj}$), 128.4 ($2\times ArCH_{min}$), 127.8 ($ArCH_{maj}$), 127.7 ($ArCH_{min}$), 127.1 ($2\times ArCH_{maj}$), 126.6 ($2\times ArCH_{min}$), 124.9 ($ArCH_{min}$), 124.7 ($ArCH_{maj}$), 124.3 ($2\times ArCH_{min}$), 124.2 ($2\times ArCH_{maj}$), 75.8 ($CHOH_{maj}$), 75.8 ($CHOH_{min}$), 58.6 ($NCHCHOH_{maj}$), 52.2 ($NCHC{=}O_{min}$), 51.8 ($NCHCHOH_{min}$), 49.9 ($NCHC{=}O_{maj}$), 40.2 ($NCH_{3min}$), 40.0 ($NCH_{3maj}$), 33.3 ($NCH_{3maj}$), 32.8 ($NCH_{3min}$), 32.2 ($NCH_{3min}$), 26.8 ($NCH_{3maj}$), 16.3 ($NCH(CH_3)CHOH_{maj}$), 15.9 ($NCH(CH_3)C{=}O_{maj}$), 14.4 ($NCH(CH_3)CHOH_{min}$), 14.2 ($NCH(CH_3)C{=}O_{min}$)

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3395 (OH), 3062, 3029 (Aryl-H), 2978, 2934 (C-H), 1624 (C=O amide), 1595 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 384 ($[M+H]^+$, 100%), 406 ($[M+Na]^+$, 60%); **HRMS** ($ESI^+$) *m/z* calcd for $C_{22}H_{30}O_3N_3$ $[M+H]^+$ 384.2282, found 384.2286. Product has been synthesised with both (*R,R*) (**537**) and (*S,S*)-pseudoephedrine (**531**). **HPLC:** Chiralcel OD-H Hexane:IPA = 90:10, flow = 1.0 mL/min, λ = 254 nm, $t_R$ (*R,R*) = 15 (major), 17 (minor) min, $t_R$ (*S,S*) = 19 (major), 23 (minor) min, $dr_{(R,R)}$ = 78:22, $dr_{(S,S)}$ = 85:15 and 80:20.

*NMR file:400MHz service; (S,S): $^{1}$H NMR = 2012-03-13-Administrator-57 (10), $^{13}$C NMR = 2012-03-13-Administrator-57 (11), (R,R): $^{1}$H NMR (300 MHz) = 2012-02-13-jpc-5 (20)*

**Synthesis of hydantoin 396:**

**(S)-1,3,5-Trimethyl-5-phenylimidazolidine-2,4-dione (396)**

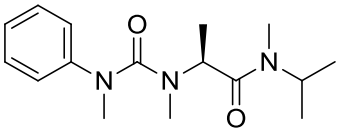


Following a similar method to general procedure **6**, LiCl (188 mg, 4.42 mmol, 12.0 eq.) and THF (2.00 mL) were added to urea pseudo **531** (141 mg, 0.37 mmol). LDA was prepared with DiPA (0.15 mL, 1.10 mmol), THF (1.70 mL) and *n*BuLi (0.69 mL, 1.10 mmol, 1.6 M in hexanes). Upon addition of LDA the reaction mixture turned yellow. The reaction mixture was left to stir at –78 °C for 30 min before warming to room temperature and stirring for 3 h 20 min. After this time the reaction mixture was cooled to –78 °C and quenched with MeOH (1.00 mL). The reaction was allowed to warm to room temperature and saturated aqueous $NH_4Cl$ solution was added. The aqueous layer was extracted using $Et_2O$ (×3). The combined organic layers were washed with water (×2) and once with brine before drying over $MgSO_4$, filtered and concentration *in vacuo*. Purification by flash column chromatography ($SiO_2$, 7:3 Pet. Ether:EtOAc) yielded the title compound as a pale yellow oil (58 mg, 0.26 mmol, 72%). **396: $R_f$** (1:1 Pet.Ether:EtOAc) 0.44; $[\alpha]_D^{21}$= +87.6 (*c* = 1.1 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.42-7.32 (3H, m, Ph*H*), 7.29-7.26 (2H, m, Ph*H*), 3.06 (3H, s, NC$H_3$), 2.84 (3H, s, NC$H_3$), 1.81 (3H, s, CC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.0 (*C*=O), 156.3 (*C*=O), 136.3 (Ar*C*), 129.1 (2×Ar*C*H), 128.7 (Ar*C*H), 125.9 (2×Ar*C*H), 66.7 (*C*$CH_3$), 25.3 (N*C*$H_3$), 25.1 (N*C*$H_3$), 20.2 (C*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2939 (C-H), 1770 (C=O amide), 1704 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 219 ([M+H]$^+$, 20%), 241 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{14}O_2N_2$ [M+Na]$^+$ 241.0948, found 241.0948; **HPLC**: *er* 12:88, Chiralcel OD-H, Hexane:IPA = 95:5, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 18 (minor), 20 (major) min.

*NMR file: $^1$H NMR = 2012-01-26-jpc-58 (11), $^{13}$C NMR = 2012-01-26-jpc-58 (15).*

**Synthesis of 535 (from synthesis of 395):** [xxvii]

**2-(1,3-Dimethyl-3-phenylureido)-*N*-isopropyl-*N*-methylpropanamide (535)**



Following a similar procedure to general procedure **9**, but using EDC not EDC·HCl and *N*-isopropyl-*N*-methyl amine not pseudoephedrine, urea acid **395** (100 mg, 0.42 mmol) was dissolved in DCM (3.00 mL) then *N*-isopropyl-*N*-methyl amine (0.07 mL, 0.64 mmol), HOBt·$H_2O$ (57 mg, 0.42 mmol), EDC (96 mg, 0.50 mmol) and DiPEA (0.17 mL, 0.97 mmol, 2.3 eq.) were added and stirred for 5 min at 0 °C. The reaction was complete after 96 h at room temperature. Purification by flash column chromatography ($SiO_2$, 1:1 Pet.Ether:EtOAc) yielded the title compound as a yellow oil (84 mg, 0.29 mmol, 69%). **535: $R_f$** (1:1 Pet.Ether:EtOAc) 0.14;

Rotamers in a ratio, Major:Minor, Rot A:Rot B, 0.60:0.40, **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.33-7.28 (rot a+b, 2H, m, Ph*H*), 7.13-7.04 (rot a+b, 3H, m, Ph*H*), 5.20 (rot b, 1H, q, *J* = 7.2 Hz, $CH_3NCHC$=O), 5.13 (rot a, 1H, q, *J* = 7.2 Hz, $CH_3NCHC$=O), 4.79 (rot a, 1H, sept., *J* = 6.8 Hz, $NCH(CH_3)_2$), 4.34 (rot b, 1H, sept., *J* = 6.8 Hz, $NCH(CH_3)_2$), 3.19 (rot a, 3H, s, $NCH_3$), 3.18 (rot b, 3H, s, $NCH_3$), 2.89 (rot a, 3H, s, $N(CH_3)CH(CH_3)_2$), 2.75 (rot b, 3H, s, $N(CH_3)CH(CH_3)_2$), 2.46 (rot a, 3H, s, $NCH_3$), 2.45 (rot b, 3H, s, $NCH_3$), 1.22-1.18 (9H, m, rot a+b 3H $CH_3NCHCH_3$ and rot b 6H $N(CH_3)CH(CH_3)_2$), 1.06 (rot a, 6H, t, *J* = 6.4 Hz, $N(CH_3)CH(CH_3)_2$);

**$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 171.2 ($C$=$O_{min}$), 171.1 ($C$=$O_{maj}$), 161.4 ($C$=$O_{min}$), 161.3 ($C$=$O_{maj}$), 146.6 ($ArCN_{maj+min}$), 129.5 ($2\times ArCH_{min1}$), 129.4 ($2\times ArCH_{maj1}$), 124.8 ($ArCH_{maj2}$), 124.7 ($ArCH_{min2}$), 124.2 ($2\times ArCH_{maj3}$), 124.1 ($2\times ArCH_{min3}$), 51.7 ($CH_3NCHC$=$O_{maj}$), 51.2 ($CH_3NCHC$=$O_{min}$), 47.2 ($NCH(CH_3)_{2min}$), 44.2 ($NCH(CH_3)_{2maj}$), 40.3 ($NCH_{3maj}$), 40.2 ($NCH_{3min}$), 32.1 ($NCH_{3min}$), 31.8 ($NCH_{3maj}$), 27.8 ($N(CH_3)CH(CH_3)_{2maj}$), 26.0 ($N(CH_3)CH(CH_3)_{2min}$), 20.7 ($N(CH_3)CH(CH_3)_{2min}$), 20.5 ($N(CH_3)CH(CH_3)_{2maj}$), 19.4 ($N(CH_3)CH(CH_3)_{2min}$), 19.2 ($N(CH_3)CH(CH_3)_{2maj}$), 14.8 ($CH_3NCHCH_{3min}$), 14.3 ($CH_3NCHCH_{3maj}$);

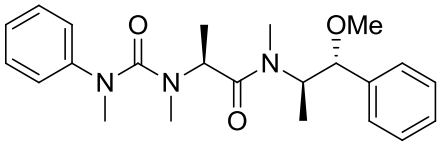
**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2973, 2933 (C-H), 1636 (C=O urea), 1595 (C=O amide); **MS** ($ESI^+$, MeOH): *m/z* = 314 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{16}H_{25}O_2N_3Na$ $[M+Na]^+$ 314.1839, found 314.1836.

*NMR file: $^1$H NMR = 2012-01-31-jpc-3 (11), $^{13}$C NMR = 2012-01-31-jpc-3 (13).*

[xxvii] During the synthesis partial racemisation (ca. 60% *ee*) occurred, structures drawn as the major enantiomer.[(a)]

**Synthesis of 538:**[a]

**(*S*)-2-(1,3-Dimethyl-3-phenylureido)-*N*-((1*R*,2*R*)-1-methoxy-1-phenylpropan-2-yl)-*N*-methylpropanamide (538)**



To KO*t*Bu (18 mg, 0.16 mmol) a solution of urea pseudo **537** (50 mg, 0.13 mmol) in anhydrous THF (1.00 mL) was added resulting in an orange colour change. The reaction was left to stir for 20 min before MeI (0.01 mL, 0.17 mmol) was added dropwise and a white precipitate formed. The reaction was left to stir for 16 h and then quenched with MeOH (1.00 mL). Saturated aqueous $NH_4Cl$ solution was added to the mixture and the product extracted with $Et_2O$ (×3). The combined organic layer was washed with water (×2) and once with brine. The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography ($SiO_2$, 1:1 Pet.Ether:EtOAc) yielded the title compound as a yellow oil (30 mg, 0.08 mmol, 58%). **538: $R_f$** (1:1 Pet Ether:EtOAc) 0.19.

NMR data is a mixture of diastereomers and rotamers:
Overall: Maj D, RotB: Maj D, Rot A: Min D, Rot B: Min D, Rot A = 4:2:3:1 = % 40:20:30:10

Major Diastereomer:
**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.29-7.12 (rot a+b, 6H, m, Ph*H*), 7.02-6.87 (rot a+b, 4H, m, Ph*H*), 5.15-5.06 (rot a+b, 1H, m, $CH_3NCHC$=O), 4.66 (rot a, 1H, br. s, $NCHCHOCH_3$), 4.36 (rot b, 1H, quin., *J* = 7.2, $NCHCHOCH_3$), 3.98 (rot a, 1H, br. d, *J* = 8.1, $CHOCH_3$), 3.90 (rot b, 1H, d, *J* = 8.1, $CHOCH_3$), 3.07 (rot a, 3H, s, $XCH_3$*), 3.00 (rot b, 3H, s, $XCH_3$*), 3.01 (rot b, 3H, s, $XCH_3$*), 2.92 (rot a, 3H, s, $XCH_3$*), 2.86 (rot a, 3H, s, $XCH_3$*), 2.74 (rot b, 3H, s, $XCH_3$*), 2.32 (rot b, 3H, s, $NCH_3$), 2.28 (rot a, 3H, s, $NCH_3$), 1.08 (rot a, 3H, d, *J* = 6.8, $NCH(CH_3)C$=O), 0.94 (rot b, 3H, d, *J* = 6.8, $NCH(CH_3)C$=O), 0.91 (rot b, 3H, d, *J* = 6.8, $NCH(CH_3)CHOCH_3$), 0.79 (rot a, 3H, d, *J* = 7.0, $NCH(CH_3)CHOCH_3$).

Minor Diastereomer:
**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.29-7.12 (rot a+b, 6H, m, Ph*H*), 7.02-6.87 (rot a+b, 4H, m, Ph*H*), 5.32 (rot a, 1H, q, *J* = 6.8, $CH_3NCHC$=O), 5.00 (rot b, 1H, q, *J* = 6.9, $CH_3NCHC$=O), 4.66 (rot b, 1H, br. s, $NCHCHOCH_3$), 4.40-4.38 (rot a, 1H, m, $NCHCHOCH_3$), 4.04 (rot b, 1H, br. d, *J* = 7.9, $CHOCH_3$), 3.94 (rot a, 1H, d, *J* = 8.7, $CHOCH_3$), 3.14 (rot a, 3H, s, $XCH_3$*), 3.07 (rot b, 3H, s, $XCH_3$*), 3.01 (rot b, 3H, s, $XCH_3$*), 2.99 (rot a, 3H, s, $XCH_3$*), 2.85 (rot b, 3H, s, $XCH_3$*), 2.74 (rot a, 3H, s, $XCH_3$*), 2.39 (rot b, 3H, s, $NCH_3$), 2.25 (rot a, 3H, s, $NCH_3$), 1.10 (rot a, 3H, d, *J* =

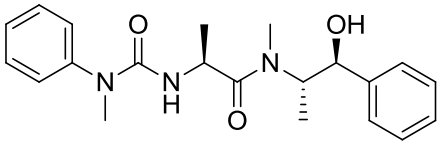
7.0, NCH(C$H_3$)C=O), 1.02 (rot b, 3H, d, *J* = 7.0, NCH(C$H_3$)C=O), 0.85 (rot a, 3H, d, *J* = 7.0, NCH(C$H_3$)CHOC$H_3$), 0.83 (rot b, 3H d, *J* = 7.0, NCH(C$H_3$)CHOC$H_3$).
*XC$H_3$ = NC$H_3$ or OC$H_3$ protons, could not be determined from data.

Only the carbons for the major diastereomer are seen:
**$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 172.6 (*C*=O$_{maj}$), 171.4 (*C*=O$_{min}$), 161.5 (*C*=O$_{maj}$), 161.4 (*C*=O$_{min}$), 146.7 (Ar*C*N$_{maj}$), 146.6 (Ar*C*N$_{min}$), 139.1 (Ar*C*C$_{min}$), 139.0 (Ar*C*C$_{maj}$), 129.5 (Ar*C*H$_{min}$), 129.5 (Ar*C*H$_{min}$), 129.4 (2×Ar*C*H$_{maj}$), 128.6 (Ar*C*H$_{maj}$), 128.5 (Ar*C*H$_{min}$), 128.4 (Ar*C*H$_{min}$), 128.3 (2×Ar*C*H$_{maj}$), 128.2 (Ar*C*H$_{min}$), 127.7 (Ar*C*H$_{min}$), 127.6 (Ar*C*H$_{maj}$), 127.6 (Ar*C*H$_{maj}$), 127.5 (Ar*C*H$_{min}$), 124.9 (Ar*C*H$_{min}$), 124.6 (Ar*C*H$_{min}$), 124.6 (Ar*C*H$_{maj}$), 124.5 (Ar*C*H$_{maj}$), 124.1 (Ar*C*H$_{min}$), 124.0 (Ar*C*H$_{maj}$), 85.1 (*C*HOCH$_{3maj}$), 84.5 (*C*HOCH$_{3min}$), 56.9 (X*C*H$_{3maj/min}$*), 56.7 (X*C*H$_{3maj/min}$*), 56.5 (*C*H$_{maj/min}$), 56.3 (*C*H$_{maj/min}$), 52.5 (*C*H$_{maj/min}$), 51.1 (*C*H$_{maj/min}$), 40.3 (X*C*H$_{3maj/min}$*), 40.1 (X*C*H$_{3maj/min}$*), 38.0 (X*C*H$_{3maj/min}$*), 32.0 (N*C*H$_{3maj/min}$), 31.6 (N*C*H$_{3maj/min}$), 27.5 (X*C*H$_{3maj/min}$*), 15.8 (*C*H$_{3maj/min}$), 15.7 (*C*H$_{3maj/min}$), 14.4 (*C*H$_{3maj/min}$), 14.1 (*C*H$_{3maj/min}$).
*X*C*H$_3$ =either N*C*H$_3$ or O*C*H$_3$ carbons, could not be determined from data.

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3061, 3028 (Aryl-H), 2978, 2934, 2822 (C-H), 1635 (C=O amide), 1595 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 398 ([M+H]$^+$, 60%), 420 ([M+Na]$^+$, 60%), 430 ([M+H+MeOH]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{32}O_3N_3$ [M+H]$^+$ 398.2439, found 398.2443.
*NMR file: $^1$H NMR = 2012-02-20-jpc-55 (10), $^{13}$C NMR = 2012-06-07-jpc-6 (13).*

**Synthesis of 546 (from synthesis of 445):**

**(*S*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-(3-methyl-3-phenylureido)propanamide (546)**




Following general procedure **9**, urea acid **445** (1.30 g, 5.85 mmol) was dissolved in DCM (30.0 mL) then HOBt·$H_2O$ (790 mg, 5.85 mmol), EDC·HCl (1.35 g, 7.02 mmol) and DiPEA (1.22 mL, 7.02 mmol) were added. Stirred for 20 min at 0 °C and (*S*,*S*)-pseudoephedrine (1.45 g, 8.78 mmol) added. The reaction was complete after 19 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:7-2:8 Pet.Ether:EtOAc) yielded the title compound as a white solid (1.75 g, 4.74 mmol, 81%). **546**: **R$_f$** (7:3 Pet.Ether:EtOAc) 0.23; **mp**: 63-65 °C; $[\alpha]_D^{21}$= +123.1 (*c* = 1.2 in $CHCl_3$);

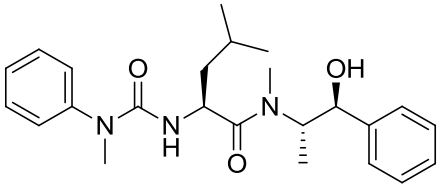
Rotamers in a ratio, Major:Minor, RotA:RotB, 1:0.82, **$^{1}$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.48-7.42 (rot a+b, 3H, m, Ph*H*), 7.40-7.37 (rot a+b, 1H, m, Ph*H*), 7.32-7.30 (rot a+b, 4H, m, Ph*H*), 7.28-7.25 (rot a+b, 2H, m, Ph*H*), 5.28 (rot b, 1H, br. d, *J* = 7.7, N*H*), 5.10 (rot a, 1H, br. d, *J* = 7.7, N*H*), 5.00 (rot a, 1H, quin., *J* = 7.0, NHC*H*$CH_3$), 4.74 (rot b, 1H, quin., *J* = 6.9, NHC*H*$CH_3$), 4.61 (rot b, 1H, d, *J* = 8.0, CHC*H*OH), 4.56-4.51 (rot b, 1H, br. m, $CH_3$C*H*CHOH), 4.48 (rot a, 1H, d, *J* = 9.4, CHC*H*OH), 4.26 (rot a, 1H, dq, *J* = 9.3, 6.7, $CH_3$C*H*CHOH), 3.26 (rot a, 3H, s, NC$H_3$), 3.25 (rot b, 3H, s, NC$H_3$), 2.94 (rot b, 3H, s, NC$H_3$), 2.93 (rot a, 3H, s, NC$H_3$), 1.18 (rot a, 3H, d, *J* = 6.9, NHCHC$H_3$), 1.16 (rot b, 3H, d, *J* = 6.9, NHCHC$H_3$), 1.05 (rot b, 3H, d, *J* = 6.9, C$H_3$CHCHOH), 1.00 (rot a, 3H, d, *J* = 6.7, C$H_3$CHCHOH);

**$^{13}$C {$^{1}$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 175.0 (*C*=$O_{min}$), 174.7 (*C*=$O_{maj}$), 157.7 (*C*=$O_{maj}$), 156.6 (*C*=$O_{min}$), 143.2 (Ar*C*$_{min}$), 142.9 (Ar*C*$_{maj}$), 142.3 (Ar*C*$N_{maj}$), 142.0 (Ar*C*$N_{min}$), 130.2 (2×Ar*C*$H_{maj}$), 130.1 (2×Ar*C*$H_{min}$), 128.8 (2×Ar*C*$H_{min}$), 128.6 (2×Ar*C*$H_{maj}$), 128.1 (Ar*C*$H_{maj}$), 128.0 (Ar*C*$H_{min}$), 127.6 (Ar*C*$H_{maj}$), 127.4 (Ar*C*$H_{min}$), 127.3 (2×Ar*C*$H_{maj}$), 127.2 (2×Ar*C*$H_{min}$), 127.1 (2×Ar*C*$H_{maj}$), 126.6 (2×Ar*C*$H_{min}$), 76.1 (CH*C*$HOH_{min}$), 75.9 (CH*C*$HOH_{maj}$), 58.7 ($CH_3$*C*$HCHOH_{maj+min}$), 47.3 (NH*C*$HCH_{3min}$), 46.1 (NH*C*$HCH_{3maj}$), 37.5 (N*C*$H_{3maj}$), 37.3 (N*C*$H_{3min}$), 27.1 (N*C*$H_{3maj+min}$), 18.8 (NHCH*C*$H_{3min}$), 18.6 (NHCH*C*$H_{3maj}$), 16.1 (*C*$H_3$CHCHO$H_{maj}$), 14.2 (*C*$H_3$CHCHO$H_{min}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3400 (broad NH and OH), 2979, 2935 (C-H), 1627 (C=O amide), 1594 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 370 ($[M+H]^+$, 100%), 392 ($[M+Na]^+$, 90%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{21}H_{27}N_3O_3Na$ $[M+Na]^+$ 392.1945, found 392.1945.
*NMR file: $^{1}$H NMR = 2014-01-06-jpc-55 (10), $^{13}$C NMR = 2014-01-06-jpc-55 (11).*

**<u>Synthesis of 548 (from synthesis of 460):</u>**

**(*S*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*,4-dimethyl-2-(3-methyl-3-phenylureido)pentanamide (548)**




Following general procedure **9**, urea acid **460** (1.66 g, 6.28 mmol) was dissolved in DCM (34.0 mL) then HOBt·$H_2O$ (849 mg, 6.28 mmol), EDC·HCl (1.45 g, 7.54 mmol) and DiPEA (1.31 mL, 7.54 mmol) were added. Stirred for 15 min at 0 °C and (*S*,*S*)-pseudoephedrine (1.57 g, 9.42 mmol) added. The reaction was complete after 16 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:6-3:7 Pet.Ether:EtOAc) yielded the title compound as a white gum (2.13 g, 5.18 mmol, 82%). **548**: $\mathbf{R}_f$ (7:3 Pet.Ether:EtOAc) 0.26; $[\alpha]_D^{21}$ = +80.2 (*c* = 1.9 in $CHCl_3$);

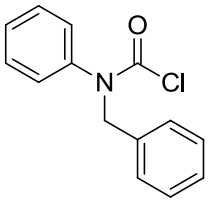
Rotamers in a ratio, Major:Minor, RotA:RotB, 1.00:0.64, **$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.50-7.48 (rot a+b, 1H, m, Ph*H*), 7.44-7.36 (rot a+b, 3H, m, Ph*H*), 7.31-7.23 (rot a+b, 6H, m, Ph*H*), 5.02-4.91 (3H, m, rot a NHC*H*$CH_2$ + rot a+b N*H* + rot a+b OH), 4.76 (rot b, 1H, td, *J* = 9.4, 4.2, NHC*H*$CH_2$), 4.63-4.60 (rot b, 1H, m, CHC*H*OH), 4.57-4.54 (rot b, 1H, br. m, $CH_3$C*H*CHOH), 4.45-4.41 (rot a, 1H, m, CHC*H*OH), 4.37-4.30 (rot a, 1H, m, $CH_3$C*H*CHOH), 3.24 (rot a, 3H, s, NC$H_3$), 3.23 (rot b, 3H, s, NC$H_3$), 2.95 (rot b, 3H, s, NC$H_3$), 2.92 (rot a, 3H, s, NC$H_3$), 1.64-1.56 (rot b, 1H, m, $CH_2$C*H*$(CH_3)_2$), 1.54-1.46 (rot a, 1H, m, $CH_2$C*H*$(CH_3)_2$), 1.42-1.30 (rot a, 2H, m, C$H_2$CH$(CH_3)_2$), 1.20-1.08 (rot b, 2H, m, C$H_2$CH$(CH_3)_2$), 1.05 (rot b, 3H, d, *J* = 6.7, C$H_3$CHCHOH), 0.98 (rot a, 3H, d, *J* = 6.6, C$H_3$CHCHOH), 0.93 (rot b, 3H, *J* = 6.5, CH(C$H_3$)$_2$), 0.88 (rot a, 3H, *J* = 6.5, CH(C$H_3$)$_2$), 0.83 (rot a, 3H, *J* = 6.6, CH(C$H_3$)$_2$), 0.82 (rot b, 3H, *J* = 6.7, CH(C$H_3$)$_2$);

**$^{13}$C {$^{1}$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.1 (*C*=$O_{min}$), 174.4 (*C*=$O_{maj}$), 158.0 (*C*=$O_{maj}$), 157.1 (*C*=$O_{min}$), 143.2 (Ar*C*$_{min}$), 142.7 (Ar*C*$_{maj}$), 142.6 (Ar*C*$N_{maj}$), 142.1 (Ar*C*$N_{min}$), 130.1 (2×Ar*C*$H_{maj}$), 130.0 (2×Ar*C*$H_{min}$), 128.8 (2×Ar*C*$H_{maj}$), 128.4 (2×Ar*C*$H_{min}$), 127.9 (Ar*C*$H_{maj}$), 127.8 (Ar*C*$H_{min}$), 127.6 (Ar*C*$H_{maj}$), 127.3 (Ar*C*$H_{min}$), 127.2 (2×Ar*C*$H_{min}$), 127.2 (2×Ar*C*$H_{maj}$), 127.0 (2×Ar*C*$H_{maj}$), 126.5 (2×Ar*C*$H_{min}$), 76.0 (CH*C*$HOH_{min}$), 75.9 (CH*C*$HOH_{maj}$), 58.6 ($CH_3$*C*$HCHOH_{maj}$), 57.1 ($CH_3$*C*$HCHOH_{min}$), 49.6 (NH*C*$HCH_{2min}$), 48.6 (NH*C*$HCH_{2maj}$), 42.0 (CH*C*$H_2CH_{maj+min}$), 37.5 (N*C*$H_{3maj}$), 37.3 (N*C*$H_{3min}$), 31.7 (N*C*$H_{3maj}$), 27.0 (N*C*$H_{3min}$), 24.8 (*C*H$(CH_3)_{2maj}$), 24.7 (*C*H$(CH_3)_{2min}$), 23.5 (CH(*C*$H_3$)$_{2min}$), 23.0 (CH(*C*$H_3$)$_{2maj}$), 22.3 (CH(*C*$H_3$)$_{2maj}$), 21.8 (CH(*C*$H_3$)$_{2min}$), 16.1 (*C*$H_3$CHCH$OH_{maj}$), 14.2 (*C*$H_3$CHCH$OH_{min}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3395 (broad NH and OH), 2955, 2934 (C-H), 1628 (C=O amide), 1596 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 434 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{34}N_3O_3$ [M+H]$^+$ 412.2600, found 412.2606.
*NMR file: $^{1}$H NMR = 2014-02-18-jpc-17 (10), $^{13}$C NMR = 2014-02-18-jpc-17 (11)*

**Synthesis of carbamoyl chloride 556:**

**Benzyl(phenyl)carbamic chloride (556)**[229]



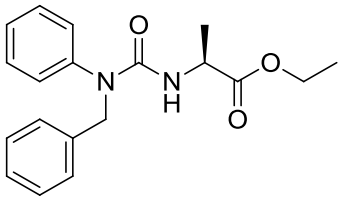

A solution of triphosgene (1.47 g, 4.96 mmol) in DCM (15.0 mL) was cooled to –78 °C under nitrogen before pyridine (0.88 mL, 10.9 mmol) was added. To this pale yellow solution, a solution

of *N*-benzylaniline (2.00 g, 10.9 mmol) in DCM (0.75 mL) was added dropwise over a period of 10 min. The resulting mixture was allowed to warm to room temperature and stirred for 2 h, after which time TLC analysis showed the reaction was complete. The reaction mixture was quenched with 1.0 M HCl (10.0 mL) and extracted with DCM (2 × 30.0 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (40.0 mL) and brine (40.0 mL) then dried over $MgSO_4$, filtered and reduced *in vacuo*. The title compound was yielded as a pale yellow solid and used without further purification (2.38 g, 9.71 mmol, 89%). **556: $R_f$** (5:1 Pet.Ether:EtOAc) 0.53; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.36-7.30 (6H, m, Ph*H*), 7.23-7.20 (2H, m, Ph*H*), 7.04-7.00 (2H, m, Ph*H*), 4.88 (2H, s, C$H_2$Ph); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 149.7 (*C*=O), 141.6 (Ar*C*N), 135.5 (Ar*C*$CH_2$), 129.4 (2×Ar*C*H), 129.0 (2×Ar*C*H), 128.6 (3×Ar*C*H), 128.5(2×Ar*C*H), 128.1 (Ar*C*H), 56.6 (*C*$H_2$Ph); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 1728 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 246 ([M+H]$^+$, 100%); **HRMS** (EI): *m/z* calcd for 245.0602 $C_{14}H_{12}ON^{35}Cl$ [M]$^{\cdot+}$, found 245.0603. Matches literature data.

*NMR file: $^1$H NMR = 2011-09-29-jpc-51 (10), $^{13}$C NMR = 2011-09-30-jpc-24 (12).*

**Synthesis of 558:** [xxviii]

**(*S*)-Ethyl-2-(3-benzyl-3-phenylureido)propanoate (557)**



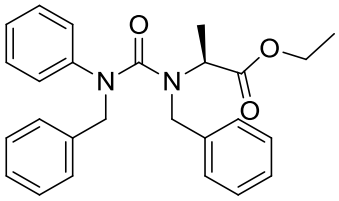

Following general procedure **1a**, L-alanine ethyl ester hydrochloride (335 mg, 2.18 mmol) and $Et_3N$ (0.66 mL, 4.71 mmol) were added to carbamoyl chloride **556** (500 mg, 2.04 mmol) and DMAP (cat.). The reaction was complete after 2 days at reflux. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether: EtOAc) yielded the title compound as a yellow oil (296 mg, 0.91 mmol, 45%). **557: $R_f$** (4:1 Pet.Ether:EtOAc) 0.14; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.30-7.05 (10H, m, Ph*H*), 4.80 (1H, d, *J* = 15.0, C$H_A$$H_B$Ph), 4.78 (1H, d, *J* = 15.0, C$H_A$$H_B$Ph), 4.72 (1H, d, *J* = 7.8, N*H*), 4.45 (1H, quin., *J* = 7.2, NHC*H*C=O), 4.11-4.05 (2H, $ABX_3$ m, OC$H_A$$H_B$$CH_3$), 1.23 (3H, d, *J* = 7.2, HNCHC$H_3$), 1.18 (3H, t, *J* = 7.2, $OCH_2CH_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_c$ = 173.9 (*C*=O), 156.5 (*C*=O), 141.3 (Ar*C*N), 138.4 (Ar*C*$CH_2$), 129.0 (2×Ar*C*H), 128.4 (2×Ar*C*H), 128.3 (2×Ar*C*H), 128.2 (2×Ar*C*H), 127.8 (Ar*C*H), 127.1 (Ar*C*H), 61.2 ($OCH_2CH_3$), 53.1 (*C*$H_2$Ph), 49.4 (NH*C*HC=O), 18.7 (HNCH*C*$H_3$) 14.1 ($OCH_2CH_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3417 (NH), 3326 (NH), 3087, 3060, 3030 (Aryl-H), 2981, 2932 (C-H), 1734 (C=O ester), 1663

[xxviii] During the synthesis partial racemisation (ca. 60% *ee*) occurred, structures drawn as the major enantiomer.[(a)]

(C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 349 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{19}H_{23}N_2O_3$ $[M+H]^+$ 327.1704, found 327.1705.

*NMR file: $^1$H NMR = 2011-10-17-jpc-49 (10), $^{13}$C NMR = 2011-10-17-jpc-49 (11).*

**(*S*)-Ethyl 2-(1,3-dibenzyl-3-phenylureido)propanoate (558)**

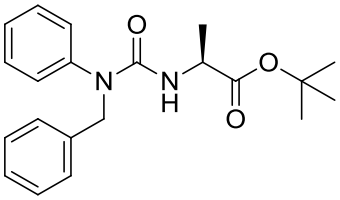



Following general procedure **10**, benzyl bromide (0.21 mL, 1.80 mmol) and NaH (72 mg, 1.80 mmol, 60% suspension) were added to urea **557** (294 mg, 0.90 mmol). The reaction was left to stir for 16 h at room temperature. Purification by flash column chromatography ($SiO_2$, 9:1 Pet.Ether:EtOAc) followed by removal of grease through washing with pentane, filtration over a plug of silica and removal of the compound from the silica with $Et_2O$ yielded the title compound as an colourless oil (212 mg, 0.51 mmol, 57%). **558: $R_f$** (4:1 Pet.Ether:EtOAc) 0.29; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.26-7.02 (15H, m, Ph*H*), 4.88 (1H, d, *J* = 15.2, C$H_{A1}$$H_{B1}$Ph), 4.58 (1H, d, *J* = 15.2, C$H_{A1}$$H_{B1}$Ph), 4.32 (1H, d, *J* = 15.6, C$H_{A2}$$H_{B2}$Ph), 4.31 (1H, q, *J* = 7.2, NC*H*C=O), 4.16-4.11 (2H, $ABX_3$ m, OC$H_A$$H_B$$CH_3$), 4.05 (1H, d, *J* = 16.0, C$H_{A2}$$H_{B2}$Ph), 1.27 (3H, d, *J* = 7.2, $NCH_2CH_3$), 1.24 (3H, t, *J* = 7.2, $OCH_2CH_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 172.3 (*C*=O), 158.7 (*C*=O), 139.4 (Ar*C*N), 138.7 (2×Ar*C*$CH_2$), 129.3 (2×Ar*C*H), 128.7 (Ar*C*H), 128.5 (Ar*C*H), 128.3 (Ar*C*H), 128.2 (4×Ar*C*H), 128.1 (Ar*C*H), 127.4 (Ar*C*H), 126.9 (2×Ar*C*H), 125.4 (Ar*C*H), 125.3 (Ar*C*H), 61.0 ($OCH_2CH_3$), 56.2 ($CH_2$Ph), 55.8 ($CH_2$Ph), 50.5 (N*C*HC=O), 15.0 (PhNCH$CH_3$), 14.2 ($OCH_2CH_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3087, 3063, 3030 (Aryl-H), 2982, 2937, 2872 (C-H), 1713 (C=O ester), 1649 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 439 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{26}H_{29}N_2O_3$ $[M+H]^+$ 417.2173, found 417.2163.

*NMR file: $^1$H NMR = 2011-10-18-jpc-35 (11), $^{13}$C NMR = 2011-10-18-jpc-35 (13).*

**Synthesis of 559:** [xxix]

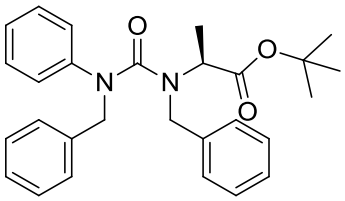
**(*S*)-*tert*-Butyl 2-(3-benzyl-3-phenylureido)propanoate (560)**



Following general procedure **1a**, L-alanine *tert*-butyl ester hydrochloride (1.50 g, 8.25 mmol) and $Et_3N$ (2.47 mL, 17.7 mmol) were added to carbamoyl chloride **556** (1.89 g, 7.71 mmol) and DMAP (cat.). The reaction was complete after 20 h at reflux. The title compound was yielded as an orange oil without further purification (2.52 g, 6.60 mmol, 86%). **560: $R_f$** (4:1 Pet.Ether:EtOAc) 0.24; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.30-7.02 (10H, m, Ph*H*), 4.81 (1H, d, *J* = 15.0, C$H_A$H$_B$Ph), 4.74 (1H, d, *J* = 15.0, CH$_A$$H_B$Ph), 4.71 (1H, d, *J* = 7.5, N*H*), 4.33 (1H, quin., *J* = 7.2, HNC*H*C=O), 1.33 (9H, s, OC(C$H_3$)$_3$), 1.18 (3H, d, *J* = 7.2, HNCHC$H_3$); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 172.9 (*C*=O), 156.4 (*C*=O), 141.5 (Ar*C*N), 138.6 (Ar*C*CH$_2$), 129.9 (2×Ar*C*H), 128.4 (2×Ar*C*H), 128.3 (2×Ar*C*H), 128.2 (2×Ar*C*H), 127.7 (Ar*C*H), 127.0 (Ar*C*H), 81.4 (O*C*(CH$_3$)$_3$), 53.1 (Ph*C*H$_2$), 50.0 (N*C*HC=O), 28.0 (OC(*C*H$_3$)$_3$), 19.0 (HNCH*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3423 (NH), 3062, 3031 (Aryl-H), 2978, 2932, 2875 (C-H), 1732 (C=O ester), 1662 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 355 ([M+H]$^+$, 50%), 377 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{27}N_2O_3$ [M+H]$^+$ 355.2017, found 355.2015.

*NMR file: $^1$H NMR = 2011-11-11-jpc-6 (11), $^{13}$C NMR = 2011-11-11-jpc-6 (13).*

**(*S*)-*tert*-Butyl 2-(1,3-dibenzyl-3-phenylureido)propanoate (561)**



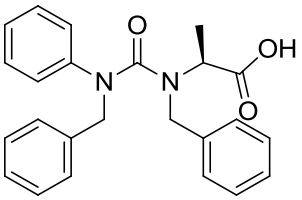
Following general procedure **10**, benzyl bromide (1.69 mL, 14.2 mmol, 2.0 eq.) and NaH (567 mg, 14.2 mmol, 60% suspension) were added to urea **560** (2.52 g, 7.11 mmol). The reaction was left to stir over 2 days. Purification by flash column chromatography ($SiO_2$, 9:1 Pet.Ether:EtOAc) yielded the title compound as a yellow oil (1.28 g, 2.92 mmol, 41%) **561**: **$R_f$** (9:1 Pet.Ether:EtOAc) 0.29; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.25-7.18 (10H, m, Ph*H*), 7.10-7.02 (5H, m, Ph*H*), 4.93 (1H, d, *J* = 15.2, C$H_{A1}$H$_{B1}$Ph), 4.51 (1H, d, *J* = 15.2, CH$_{A1}$$H_{B1}$Ph), 4.37 (1H, d, *J* = 15.6, C$H_{A2}$H$_{B2}$Ph), 4.22 (1H, q, *J* = 7.2, NC*H*C=O), 3.97 (1H, d, *J* = 15.6, CH$_{A2}$$H_{B2}$Ph), 1.43 (9H, s, OC(C$H_3$)$_3$), 1.19 (3H,

[xxix] During the synthesis partial racemisation (ca. 60% *ee*) occurred, structures drawn as the major enantiomer.[(a)]

d, *J* = 7.2, NCHC*H*$_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 171.2 (*C*=O), 161.2 (*C*=O), 145.1 (Ar*C*N), 138.7 (Ar*C*), 138.0 (Ar*C*), 129.1 (2×Ar*C*H), 128.1 (4×Ar*C*H), 128.0 (2×Ar*C*H), 127.4 (2×Ar*C*H), 126.8 (Ar*C*H), 126.8 (Ar*C*H), 125.2 (Ar*C*H), 125.1 (2×Ar*C*H), 81.1 (O*C*(CH$_3$)$_3$), 57.0 (N*C*HC=O), 55.6 (Ph*C*H$_2$)), 50.2 (Ph*C*H$_2$), 27.9 (OC(*C*H$_3$)$_3$), 14.8 (HNCH*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3086, 3063, 3030 (Aryl-H), 3003, 2978, 2932 (C-H), 1732 (C=O ester), 1650 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 467 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{28}H_{33}O_3N_2$ [M+H]$^+$ 445.2486, found 445.2504.

*NMR file: $^1$H NMR = 2011-11-04-jpc-30 (11), $^{13}$C NMR = 2011-11-04-jpc-30 (13).*

**(*S*)-2-(1,3-Dibenzyl-3-phenylureido)propanoic acid (559)**

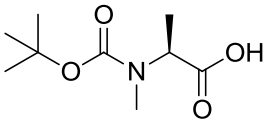



Following general procedure **3**, anhydrous DCM (0.1 M, 39.0 mL) and TFA (0.1 M, 15.6 mL) were added to urea **561** (692 mg, 1.56 mmol). The reaction was complete after 2.5 h. The title compound was yielded as a pale yellow oil without further purification (605 mg, 1.56 mmol, >99%). **559: $R_f$** (4:1 Pet.Ether:EtOAc) 0.03; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.35-7.16 (11H, m Ph*H*), 7.07-7.02 (2H, m, Ph*H*), 6.93-6.90 (2H, m, Ph*H*), 4.87 (1H, d, *J* = 15.0, C*H*$_{A1}$H$_{B1}$Ph), 4.82 (1H, d, *J* = 15.0, CH$_{A1}$*H*$_{B1}$Ph), 4.11 (1H, d, *J* = 15.6, C*H*$_{A2}$H$_{B2}$Ph), 4.09 (1H, q, *J* = 7.5, NC*H*CH$_3$), 3.86 (1H, d, *J* = 15.6, CH$_{A2}$*H*$_{B2}$Ph), 1.49 (3H, d, *J* = 7.2, NCHC*H*$_3$); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 173.5 (*C*=O), 163.7 (*C*=O), 143.4 (Ar*C*N), 137.3(Ar*C*CH$_2$), 135.8 (Ar*C*CH$_2$), 129.7 (2×Ar*C*H), 128.6 (2×Ar*C*H), 128.5 (2×Ar*C*H), 128.4 (2×Ar*C*H), 128.0 (Ar*C*H), 127.6 (2×Ar*C*H), 127.5 (Ar*C*H), 126.4 (Ar*C*H), 125.4 (2×Ar*C*H), 58.2 (Ph*C*H$_2$), 55.7 (Ph*C*H$_2$), 52.7 (N*C*HC=O), 14.5 (NCH*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3062 (OH), 3031 (Aryl-H), 2941 (C-H), 1739 (C=O acid), 1648 (C=O urea); **MS** (ESI$^-$, MeOH): *m/z* = 387 ([M–H]$^-$, 100%); **HRMS** (ESI$^-$): *m/z* calcd for $C_{24}H_{23}O_3N_2$ [M–H]$^-$ 387.1714, found 387.1712.

*NMR file: $^1$H NMR = 2011-11-07-jpc-32 (11), $^{13}$C NMR = 2011-11-07-jpc-32 (13).*

**Synthesis of 566:**

**(*S*)-2-((*tert*-Butoxycarbonl)(methyl)amino)propanoic acid (563)**[212,230]




Following a literature procedure published by Malkov *et al.*,[212] to a solution of Boc-L-alanine (1.68 g, 8.88 mmol) and anhydrous THF (40.0 mL) under argon, MeI (5.50 mL, 88.8 mmol) was added. The reaction mixture was cooled to 0 °C and stirred for 10 min at this temperature. NaH (3.56 g,

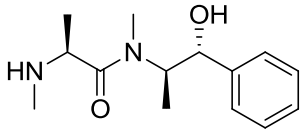
88.8 mmol, 60% suspension in mineral oil) was then added portionwise and the reaction mixture was stirred for a further 20 min at 0 °C before warming to room temperature. More THF (70.0 mL) was added and the reaction mixture was left to stir for 16 h. The reaction mixture was then quenched with water (20.0 mL) and EtOAc (15.0 mL) and the solvent removed *in vacuo*. The concentrated residue was diluted with water (180 mL) and washed with EtOAc (100 mL). The aqueous layer was then acidified to pH 3 with 5% citric acid solution and the product extracted with EtOAc (3 × 200 mL). The combined organic layer was washed with brine and dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The title compound was yielded as a yellow oil without further purification (1.64 g, 8.08 mmol, 91%). **563:** $[\alpha]_D^{21}$= –31.3 (*c* = 1.1 in $CHCl_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 0.55:0.45, **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 4.83 (rot a, 1H, br. q, *J* = 6.5, NC*H*$CH_3$), 4.45 (rot b, 1H, br. q, *J* = 6.5, NC*H*$CH_3$), 2.88 (rot b, 3H, s, NC*H*$_3$), 2.82 (rot a, 3H, s, NC*H*$_3$), 1.46-1.42 (rot a+b, 12H, m, OC(C*H*$_3$)$_3$ and NCHC*H*$_3$);

**$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 177.4 (*C*=O$_{maj+min}$), 156.5 (*C*=O$_{maj+min}$), 80.8 (O*C*(CH$_3$)$_{3min}$), 80.7 (O*C*(CH$_3$)$_{3maj}$), 55.0 (N*C*HCH$_{3min}$), 53.7 (N*C*HCH$_{3maj}$), 31.4 (N*C*H$_{3min}$), 30.8 (N*C*H$_{3maj}$), 28.5 (OC(*C*H$_3$)$_{3maj+min}$), 14.7 (CH*C*H$_{3min}$), 14.3 (CH*C*H$_{3maj}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3094 (OH), 2978, 2935 (C-H), 1744 (C=O acid), 1694 (C=O urethanes); **MS** (ESI$^-$, MeOH): *m/z* = 202 ([M–H]$^-$, 100%); **HRMS** (ESI$^-$): *m/z* calcd for $C_9H_{16}O_4N$ [M–H]$^-$ 202.1084, found 202.1084. Matches literature data given.
*NMR file: $^1$H NMR = 2011-11-21-jpc-8 (10), $^{13}$C NMR = 2011-11-21-jpc-8 (11).*

**(*S*)-*N*-((1*R*,2*R*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-(methylamino)propanamide (565)**




Following a literature procedure published by Myers *et al.*,[231] a solution of *N*-Boc-*N*-methyl-alanine (**563**) (1.64 g, 8.07 mmol) and anhydrous DCM (30.0 mL) were cooled to 0 °C under nitrogen. To this solution was added $Et_3N$ (1.35 mL, 9.69 mmol) and, after 5 min, pivaloyl chloride (1.00 mL, 8.07 mmol) was added dropwise, the reaction mixture became a cloudy white slurry and was stirred for 1.5 h. After this time $Et_3N$ (1.35 mL, 9.69 mmol) was added followed by (*R*,*R*)-pseudoephedrine (1.33 g, 8.07 mmol), the reaction mixture was stirred for 1 h at 0 °C. The solvent was then removed *in vacuo* and the resulting white solid was dissolved in DCM (30.0 mL) before

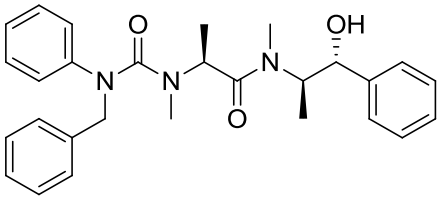
TFA (11.0 mL) was added and the reaction left to stir for 1.5 h. The reaction was quenched with 25% aqueous NaOH solution (30.0 mL) and the product extracted with DCM (×4). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was passed through a silica plug to remove any small impurities and the title compound was yielded as a yellow oil (1.81 g, 7.26 mmol, 90%). **565: $R_f$** (95:5 DCM:MeOH) 0.15; $[\alpha]_D^{21} = -29.6$ (*c* = 1.0 in MeOH);

Rotamers in a ratio, Major:Minor, RotA:RotB, 0.8:0.2; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.31-7.05 (rot a+b, 5H, m, Ph*H*), 5.88 (rot a+b, 2H, br. s, N*H* and O*H*), 5.21 (rot b, 1H, d, *J* = 0.9, C*H*OH), 4.61-4.64 (rot a, 2H, m, HNC*H*$CH_3$ and C*H*OH), 3.79-3.62 (2H, m, rot a $CH_3$NC*H*$CH_3$ and rot b HNC*H*$CH_3$), 2.95 (rot b, 1H, dq, *J* = 7.2, 2.1, $CH_3$NC*H*$CH_3$), 2.86 (rot b, 3H, s, C=ONC*H*$_3$), 2.80 (rot a, 3H, s, C=ONC*H*$_3$), 2.31 (rot a, 3H, d, *J* = 2.4, HNC*H*$_3$), 2.28 (rot b, 3H, d, *J* = 2.4, HNC*H*$_3$), 1.39 (rot b, 3H, d, *J* = 6.6, CC*H*$_3$), 1.17 (rot a, 3H, d, *J* = 6.6, NCHC*H*$_3$CHOH), 0.93 (rot a, 3H, d, *J* = 6.6, HNCHC*H*$_3$), 0.86 (rot b, 3H, d, *J* = 6.6, CC*H*$_3$);

**$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 173.4 (*C*=$O_{maj}$), 172.9 (*C*=$O_{min}$), 141.7 (Ar*C*$_{maj}$), 137.7 (Ar*C*$_{min}$), 128.9 (Ar*C*H$_{min}$), 128.6 (Ar*C*H$_{maj}$), 128.3 (Ar*C*H$_{maj+min}$), 128.1 (Ar*C*H$_{min}$), 127.7 (Ar*C*H$_{maj}$), 126.8 (2×Ar*C*H$_{min}$), 126.6 (2×Ar*C*H$_{maj}$), 75.1 (*C*HOH$_{maj}$), 74.6 (*C*HOH$_{min}$) 58.2 (HN*C*HCH$_{3min}$), 57.1 (HN*C*HCH$_{3maj}$), 55.1 ($CH_3$N*C*HCH$_{maj}$), 45.6 ($CH_3$N*C*HCH$_{3min}$), 32.4 (HN*C*H$_{3maj}$), 30.9 (C=ON*C*H$_{3maj}$), 26.9 (C=ON*C*H$_{3min}$), 21.3 (HN*C*H$_{3min}$), 17.3 (*C*H$_3$CHOH$_{min}$), 16.0 (*C*H$_3$CHOH$_{maj}$), 15.5 (HNCH*C*H$_{3min}$), 14.3 (HNCH*C*H$_{3maj}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3305 (OH/NH), 3063, 3030 (Aryl-H), 2962, 2973, 2924, 2853 (C-H), 1627 (C=O amide); **MS** (ESI$^+$, MeOH): *m/z* = 251 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{23}O_2N_2$ [M+H]$^+$ 251.1755, found 251.1755.
*NMR file: $^1$H NMR = 2011-12-20-jpc-15 (20), $^{13}$C NMR = 2011-12-20-jpc-15 (22).*

**(*S*)-2-(3-Benzyl-1-methyl-3-phenylureido)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropanamide (566)**




Following a similar method to general procedure **1c**, amine **565** (1.81 g, 7.24 mmol), $Et_3N$ (1.04 mL, 7.45 mmol, 1.1 eq) and anhydrous DCE (7.00 mL) were added over 10 min to a solution of carbamoyl chloride **556** (1.66 g, 6.77 mmol) and DMAP (cat.) in anhydrous DCE (7.00 mL). The

reaction mixture was left to stir for 16 h, then quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM (×3). The combined organic layer was washed with 1.0 M HCl and brine. The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The residue was dissolved in DCM (120.0 mL) and washed with $CuSO_4$ solution (2 × 120 mL) to remove DMAP. The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo.* Purification by recrystalisation from EtOAc and petroleum ether yielded the title compound as a yellow solid (1.13 g, 2.44 mmol, 36%). **566: $R_f$** (95:5 DCM:MeOH) 0.22; **mp**: 121-125 °C; $[\alpha]_D^{21}$ = –122.7 (*c* = 0.9 in $CHCl_3$);

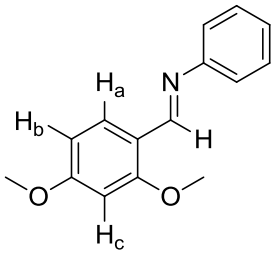
Rotamers in a ratio, Major:Minor, RotA:RotB, 0.7:0.3, **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.48-7.16 (rot a+b, 10H, m, Ph*H*), 7.12-6.96 (rot a+b, 5H, m, Ph*H*), 5.53 (rot b, 1H, q, *J* = 6.9, $CH_3NCHC$=O), 5.02 (rot b, 1H, d, *J* = 15.0, HOC*H*), 4.97 (rot a 1H, q, *J* = 6.9, $CH_3NCHC$=O), 4.83 (rot a, 2H, s, $CH_2$Ph), 4.58 (rot b, 2H, s, $CH_2$Ph), 4.56-4.37 (2H, m, rot a+b NC*H*CHOH + rot a HOC*H*), 4.17 (rot a+b, 1H, br. s, O*H*), 2.93 (rot a, 3H, s, $NCH_3$), 2.88 (rot b, 3H, s, $NCH_3$), 2.57 (rot a, 3H, s, $NCH_3$), 2.38 (rot b, 3H, s, $NCH_3$), 1.22 (rot a, 3H, d, *J* = 6.9, NCH($CH_3$)C=O), 1.19 (rot b, 3H, d, *J* = 6.9, NCH($CH_3$)C=O), 1.02 (rot a, 3H, d, *J* = 6.3, NCH($CH_3$)CHOH), 0.71 (rot b, 3H, d, *J* = 6.3, NCH($CH_3$)CHOH);

Only major rotamer seen for all peaks except Ar*C*H where both the major and minor are seen:
**$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.3 (*C*=O), 161.4 (*C*=O), 145.1 (Ar*C*N), 141.9 (Ar*C*), 138.7 (Ar*C*), 129.5 (2×Ar*C*$H_{min}$), 129.4 (2×Ar*C*$H_{maj}$), 128.7 (2×Ar*C*$H_{min}$), 128.3 (2×Ar*C*$H_{maj}$),128.2 (2×Ar*C*$H_{maj+min}$), 128.2 (Ar*C*$H_{maj+min}$), 128.1 (2×Ar*C*$H_{maj}$), 127.7 (2×Ar*C*$H_{min}$) 127.3 (2×Ar*C*$H_{min}$), 127.0 (Ar*C*$H_{maj}$), 126.9 (Ar*C*$H_{min}$), 126.7 (2×Ar*C*$H_{maj}$), 124.9 (Ar*C*$H_{maj+min}$), 124.6 (2×Ar*C*$H_{maj}$), 124.2 (2×Ar*C*$H_{min}$), 75.9 (*C*HOH), 55.8 ($CH_2$Ph), 52.2 (*C*H), 32.6 ($NCH_3$), 31.6 ($NCH_3$), 27.3 (*C*H), 14.3, ($CH_3$CHCHOH), 14.2 ($CH_3$CHC=O);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3412 (OH), 3062, 3030 (Aryl-H), 2979, 2934 (C-H), 1628 (C=O amide), 1595 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 460 ($[M+H]^+$, 80%), 482 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{28}H_{33}O_3N_3Na$ $[M+Na]^+$ 482.2415, found 482.2409.
*NMR file: $^1$H NMR = 2011-12-19-jpc-14 (11), $^{13}$C NMR = 2011-12-19-jpc-14 (12).*

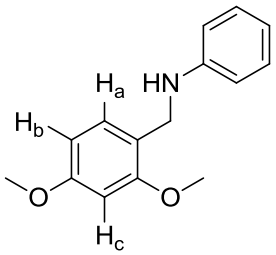
**Synthesis of 573:**

***N*-(2,4-Dimethoxybenzylidene)aniline (571)**[232]




Following a literature procedure by Gauthier *et al.*,[233] to a pre-stirred solution of 2,4-dimethoxybenzaldehyde (1.00 g, 6.02 mmol, 1.0 eq.) in anhydrous toluene (6.00 mL) was added aniline (0.54 mL, 5.90 mmol, 1.0 eq.). Dean-Stark apparatus was connected to remove water from the reaction. The reaction heated to 160 °C and left to stir for 18 h. The reaction was cooled to room temperature and concentrated *in vacuo*. The title compound was yielded as a brown oil and used directly in the next step without further purification (1.42 g, 5.90 mmol, >99%). **571: $\mathbf{R_f}$** (2:1 Pet.Ether:EtOAc) 0.43; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 8.82 (1H, s, N=C*H*), 8.15 (1H, br. d, *J* = 8.4, Ar$H_a$), 7.40-7.35 (2H, m, Ph*H*), 7.23-7.17 (3H, m, Ph*H*), 6.59 (1H, dd, *J* = 8.7, 2.4, Ar$H_b$), 6.47 (1H, d, *J* = 2.4, Ar$H_c$), 3.87 (6H, s, OC$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3002, 2941 (C-H), 1604, 1584 (C=N); **MS** (ESI$^+$, MeOH): *m/z* = 242 ([M+H]$^+$, 100%), 264 ([M+Na]$^+$, 20%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{16}O_2N$ [M+H]$^+$ 242.1176, found 242.1167. Matches literature data.
*NMR file: $^1$H NMR = 2012-06-20-jpc-44 (10).*

***N*-(2,4-Dimethoxybenzyl)aniline (572)**[233]

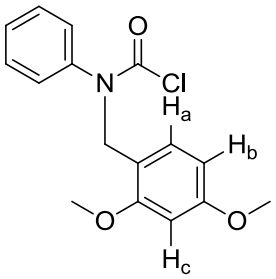



Following a literature procedure by Gauthier *et al.*,[233] $NaBH_4$ (357 mg, 9.44 mmol, 1.6 eq.) was added portion wise to a pre-stirred solution of imine **571** (1.42 g, 5.90 mmol, 1.0 eq.) in anhydrous 1:1 DCM:EtOH (3.00 mL: 3.00 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was poured onto ice water, acidified with conc. HCl, then basified with 5.0 M NaOH. The product was extracted with DCM (×3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was yielded as a pale yellow solid without further purification (1.26 g, 5.19 mmol, 88%). **572: $\mathbf{R_f}$** (2:1 Pet.Ether:EtOAc) 0.6; **mp**: 98-100 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.28-7.22 (3H, m, Ar$H_a$ + Ph*H*), 6.79-6.71 (3H, m, Ph*H*), 6.55 (1H, d, *J* = 2.4, Ar$H_c$), 6.50 (1H, dd, *J* = 8.4, 2.4, Ar$H_b$), 4.32 (2H, s, C$H_2$NH), 3.88 (3H, s, OC$H_3$), 3.85 (3H, s, OC$H_3$); **$^{13}$C {$^1$H} NMR**

(100 MHz, $CDCl_3$): $\delta_C$ = 160.0 (Ar*C*O), 158.3 (Ar*C*O), 148.3 (Ar*C*N), 129.5 (Ar*C*$H_a$), 129.0 (2×Ar*C*H), 119.6 (Ar*C*), 117.1 (Ar*C*H), 113.0 (2×Ar*C*H), 103.7 (Ar*C*$H_b$), 98.4 (Ar*C*$H_c$), 55.2 (O*C*$H_3$), 55.1 (O*C*$H_3$), 43.0 (*C*$H_2$NH); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3372 (NH), 2996, 2964, 2940, 2913, 2836 (C-H); **MS** (ESI$^+$, MeOH): *m/z* = 266 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{18}O_2N$ [M+H]$^+$ 244.1333, found 244.1331. Matches literature data.

*NMR file: $^1$H NMR = 2012-06-21-jpc-35 (10), $^{13}$C NMR = 2012-06-21-jpc-35 (11).*

**(2,4-Dimethoxybenzyl)(phenyl)carbamic chloride (573)**

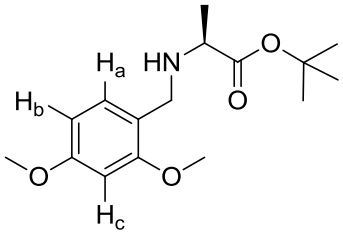



A solution of triphosgene (638 mg, 2.15 mmol, 1.0 eq.) in DCM (6.50 mL) was cooled to –78 °C under nitrogen before pyridine (0.38 mL, 4.73 mmol, 2.2 eq.) was added. To this pale yellow solution, a solution of amine **572** (1.15 g, 4.73 mmol, 2.2 eq.) in DCM (5.00 mL) was added dropwise over a period of 10 min. The resulting mixture was allowed to warm to room temperature and stirred for 3 days, after which time TLC analysis showed the reaction was complete. The reaction mixture was quenched with 1.0 M HCl (10.0 mL) and extracted with DCM (2 × 15.0 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was yielded as a pale yellow solid and used without further purification (1.37 g, 4.49 mmol, 95%). **573: $R_f$** (4:1 Pet.Ether:EtOAc) 0.46; **mp**: 75–78 °C; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.31-7.28 (3H, m, Ar*H$_a$* + Ph*H*), 7.13-7.01 (3H, m, Ph*H*), 6.39 (1H, dd, *J* = 8.4, 2.1, Ar*H$_b$*), 6.35 (1H, br.s, Ar*H$_c$*), 4.87 (2H, s, C*H$_2$*N), 3.78 (3H, s, OC*H$_3$*), 3.56 (3H, s, OC*H$_3$*); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 160.9 (Ar*C*O), 160.3 (Ar*C*O), 158.6 (*C*=O), 141.7 (Ar*C*N), 131.6 (Ar*C*$H_a$), 128.9 (2×Ar*C*H), 128.6 (2×Ar*C*H), 128.2 (Ar*C*H), 116.2 (Ar*C*), 104.1 (Ar*C*$H_b$), 98.3 (Ar*C*$H_c$), 55.3 (O*C*$H_3$), 55.1 (O*C*$H_3$), 50.9 (*C*$H_2$N); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3063, 3002, 2938, 2837 (C-H), 1732 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 328 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{16}O_3N^{35}ClNa$ [M+Na]$^+$ 328.0711, found 328.0715.

*NMR file: $^1$H NMR = 2012-06-28-jpc-28 (11), $^{13}$C NMR = 2012-06-28-jpc-28 (13).*

**Synthesis of DMB on alternative nitrogen 575:**

**(*S*)-*tert*-Butyl 2-((2,4-dimethoxybenzyl)amino)propanoate (575)**

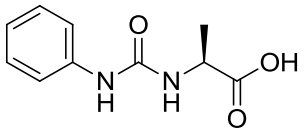



Following a similar method to general procedure **11**, to a mixture of L-alanine *tert*-butyl ester hydrochloride (1.36 g, 7.48 mmol, 5.0 eq.), DCM (7.00 mL) and $Et_3N$ (1.05 mL, 7.48 mmol, 5.0 eq.) was added 2,4-dimethoxybenzaldehyde (250 mg, 1.50 mmol). The reaction was complete after 18 h at room temperature. The crude residue was dissolved in 1:1 DCM:EtOH (2.00 mL:2.00 mL) and $NaBH_4$ (91 mg, 2.40 mmol) added at 0 °C. The reaction was complete after 20 h at room temperature. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc + 1% $Et_3N$) yielded the title compound as a colourless oil (299 mg, 1.01 mmol, 68%). **575: $R_f$** (7:3 Pet.Ether:EtOAc) 0.38; $[\alpha]_D^{21}$= –2.6 (*c* = 1.0 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.15 (1H, d, *J* = 8.7, Ar*H*$_a$), 6.44-6.41 (2H, m, Ar*H*$_b$ + Ar*H*$_c$), 3.81 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 3.74 (1H, d, *J* = 12.9, C*H*$_A$H$_B$Ar), 3.69 (1H, d, *J* = 12.9, CH$_A$*H*$_B$Ar), 3.25 (1H, q, *J* = 6.9, C*H*CH$_3$), 2.43 (1H, br. s, N*H*), 1.45 (9H, s, OC(C*H*$_3$)$_3$), 1.30 (3H, d, *J* = 6.9, CHC*H*$_3$); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 174.5 (*C*=O), 160.3 (Ar*C*O), 158.7 (Ar*C*O), 130.6 (Ar*C*H$_a$), 119.8 (Ar*C*), 103.9 (Ar*C*H$_{b/c}$), 98.5 (Ar*C*H$_{b/c}$), 80.9 (O*C*(CH$_3$)$_3$), 56.6 (*C*HCH$_3$), 55.4 (OCH$_3$), 55.3 (O*C*H$_3$), 46.7 (*C*H$_2$N), 28.0 (OC(*C*H$_3$)$_3$), 18.7 (CH*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3337 (NH), 2976, 2935, 2836 (C-H), 1726 (C=O ester); **MS** (ESI$^+$, MeOH): *m/z* = 296 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{26}O_4N$ [M+H]$^+$ 296.1857, found 296.1862.

*NMR file: $^1$H NMR = 2012-07-19-jpc-31 (10), $^{13}$C NMR = 2012-07-19-jpc-31 (11).*

**Synthesis of 579:**

**(*S*)-2-(3-Phenylureido)propanoic acid (579)**[234]



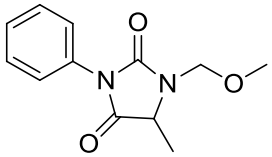

Following general procedure **3**, anhydrous DCM (1.40 mL) and TFA (1.40 mL) were added to *tert*-Butyl 2-(3-phenylureido)propanoate (150 mg, 0.57 mmol). The reaction was complete after 2 h. The product was re-extracted from the water layer with DCM (×6). The title compound was yielded as a white solid without further purification (74 mg, 0.36 mmol, 62%). **579: $R_f$** (1:1 Pet Ether:EtOAc) 0.24; $[\alpha]_D^{21}$= +4.2 (*c* = 0.3 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.50-7.57 (2H, m, Ph*H*), 7.40-7.36 (3H, m, Ph*H*), 7.05 (1H, br. s, N*H*), 4.18 (1H, br. q, *J* = 6.8, HNC*H*CH$_3$),

1.50 (3H, br. d, *J* = 6.8, HNCHC*H*$_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 173.7 (*C*=O), 156.8 (*C*=O), 131.4 (Ar*C*N), 129.1 (2×Ar*C*H), 128.3 (Ar*C*H), 126.2 (2×Ar*C*H), 52.8 (HN*C*HCH$_3$), 17.6 (HNCH*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3292 (NH), 3069 (OH), 2983, 2917, 2849 (C-H), 1772 (C=O acid), 1702 (C=O urea); **MS** (ESI$^-$, MeOH): *m/z* = 207 ([M–H]$^-$, 100%); **HRMS** (ESI$^-$): *m/z* calcd for $C_{10}H_{11}O_3N_2$ [M–H]$^-$ 207.0775, found 207.0772. Matches literature data given.

*NMR file: $^1$H NMR = 2012-05-24-jpc-22 (11), $^{13}$C NMR = 2012-05-24-jpc22 (12).*

**Synthesis of MOM generated impurity 583:**

**1-(Methoxymethyl)-5-methyl-3-phenylimidazolidine-2,4-dione (583)**

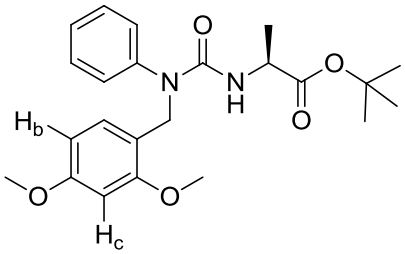


Following a literature procedure published by Barnes *et al.*,[213] a solution of acid **579** (74 mg, 0.36 mmol) and paraformaldehyde (64 mg, 2.13 mmol) in anhydrous DCM (4.00 mL) under nitrogen was cooled to 0 °C. To this solution, anhydrous TMSCl (0.27 mL, 2.13 mmol, distilled over $CaH_2$) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 4.5 h. The reaction mixture was then cooled to 0 °C and anhydrous MeOH (1.00 mL) was added and stirred for 30 min. After this time, the reaction mixture was added to a pre-cooled saturated aqueous $NaHCO_3$ solution at 0 °C with stirring. The aqueous layer was then extracted with EtOAc (×3) and the combined organic layer washed with brine then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (22 mg, 0.09 mmol, 25%). **583: $R_f$** (4:1 Pet.Ether:EtOAc) 0.32; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.48-7.35 (5H, m, Ph*H*), 5.02 (1H, d, *J* = 10.8, $CH_3OC\mathit{H}_A\mathrm{H}_B\mathrm{N}$), 4.76 (1H, d, *J* = 10.8, $CH_3OCH_A\mathit{H}_B\mathrm{N}$), 4.26 (1H, q, *J* = 6.8, NC*H*CH$_3$), 3.39 (3H, s, OC*H*$_3$), 1.58 (3H, d, *J* = 6.8, NCHC*H*$_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 172.3 (*C*=O), 155.5 (*C*=O), 131.5 (Ar*C*N), 129.0 (2×Ar*C*H), 128.2 (Ar*C*H), 126.0 (2×Ar*C*H), 72.6 ($CH_3OC\mathit{H}_2\mathrm{N}$), 56.3 (O*C*H$_3$), 54.3 (HN*C*HCH$_3$), 15.5 (HNCH*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2985, 2934, 2849 (C-H), 1775 (C=O acid), 1711 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 257 ([M+H]$^+$, 100%), 289 ([M+Na]$^+$, 50%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{14}O_3N_2Na$ [M+Na]$^+$ 257.0897, found 257.0889.

*NMR file: $^1$H NMR = 2012-05-31-jpc-14 (21), $^{13}$C NMR = 2012-05-31-jpc-14 (23).*

**Synthesis of 589:**[xxx]

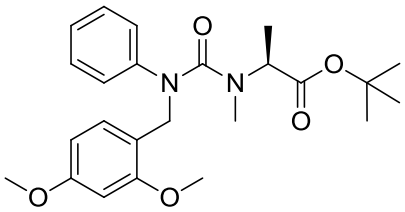
**(*S*)-*tert*-Butyl 2-(3-(2,4-dimethoxybenzyl)-3-phenylureido)propanoate (586)**



Following general procedure **1a**, carbamoyl chloride **573** (200 mg, 0.66 mmol) and DMAP (cat.) were added to a pre-stirred solution of L-alanine *tert*-butyl ester hydrochloride (127 mg, 0.70 mmol) and $Et_3N$ (0.21 mL, 1.51 mmol) in DCE (6.60 mL). The reaction was complete after 20 h at reflux. The title compound was yielded as a yellow oil without further purification (252 mg, 0.61 mmol, 93%). **586: $R_f$** (4:1 Pet.Ether:EtOAc) 0.14; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.35-7.30 (2H, m, Ph*H*), 7.26-7.23 (2H, m, Ph*H*), 7.18-7.15 (2H, m, Ph*H*), 6.41 (1H, dd, *J* = 8.4, 2.4, Ar$H_b$), 6.33 (1H, d, *J* = 2.4, Ar$H_c$), 4.88 (1H, br. d, *J* = 8.1, N*H*), 4.85 (1H, d, *J* = 15.3, C$H_A$H$_B$Ar), 4.81 (1H, d, *J* = 15.3, CH$_A$$H_B$Ar), 4.41 (1H, quin., *J* = 7.5, HNC*H*CH$_3$), 3.76 (3H, s, OC$H_3$), 3.56 (3H, s, OC$H_3$), 1.42 (9H, s, OC(C$H_3$)$_3$), 1.27 (3H, d, *J* = 6.9, CHC$H_3$); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 173.0 (*C*=O), 160.0 (Ar*C*O), 158.2 (Ar*C*O), 156.5 (*C*=O), 142.0 (Ar*C*N), 130.4 (Ar*C*H), 129.4 (2×Ar*C*H), 128.3 (2×Ar*C*H), 127.2 (Ar*C*H), 119.1 (Ar*C*), 104.1 (Ar*C*H$_b$), 98.2 (Ar*C*H$_c$), 81.3 (O*C*(CH$_3$)$_3$), 55.3 (O*C*H$_3$), 55.0 (O*C*H$_3$), 50.0 (HN*C*HCH$_3$), 47.3 (*C*H$_2$N), 27.9 (OC(*C*H$_3$)$_3$), 19.1 (CH*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3422 (NH), 2977, 2836 (C-H), 1730 (C=O ester), 1660 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 437 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{31}O_5N_2$ [M+H]$^+$ 415.2228, found 415.2227.

*NMR file: $^1$H NMR = 2012-06-28-jpc-9 (11), $^{13}$C NMR = 2012-06-28-jpc-9 (13).*

**(*S*)-*tert*-Butyl 2-(3-(2,4-dimethoxybenzyl)-1-methyl-3-phenylureido)propanoate (589)**



Following a similar method to general procedure **2a**, NaH (12 mg, 0.30 mmol) was added to urea **586** (63 mg, 0.15 mmol) in DMF (1.50 mL). After 25 min MeI (0.03 mL, 0.46 mmol) was added. The reaction was complete after 1 h at 0 °C. The title compound was yielded as a yellow oil without further purification (65 mg, 0.15 mmol, >99%). **589: $R_f$** (1:1 Pet.Ether:EtOAc) 0.72; **$^1$H**

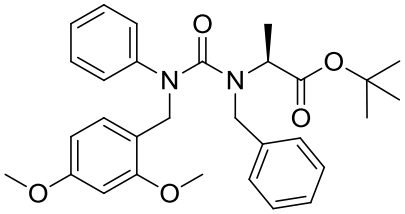
[xxx] During the synthesis partial racemisation (ca. 60% *ee*) occurred, structures drawn as the major enantiomer.[(a)]

**NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.30-7.21 (3H, m, Ph*H*), 7.13-7.10 (2H, m, Ph*H*), 7.06-7.01 (1H, m, Ar*H*), 6.45-6.39 (2H, m, Ar*H*), 4.85 (1H, d, *J* = 15.6, C$H_A$$H_B$Ar), 4.75 (1H, d, *J* = 15.6, C$H_A$$H_B$Ar), 4.67 (1H, q, *J* = 7.2, NC*H*$CH_3$), 3.77 (3H, s, OC$H_3$), 3.72 (3H, s, OC$H_3$), 2.48 (3H, s, $NCH_3$), 1.41 (9H, s, OC(C$H_3$)$_3$), 1.24 (3H, d, *J* = 7.2, CHC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 171.3 (*C*=O), 161.1 (Ar*C*O), 159.8 (Ar*C*O), 158.1 (*C*=O), 146.2 (Ar*C*N), 130.0 (Ar*C*H), 129.0 (2×Ar*C*H), 124.0 (Ar*C*H), 123.8 (2×Ar*C*H), 119.8 (Ar*C*), 103.8 (OMeAr*C*H), 98.2 (OMeAr*C*H), 81.1 (O*C*$(CH_3)_3$), 55.7 (N*C*H$CH_3$), 55.3 (O*C*$H_3$), 55.1 (O*C*$H_3$), 50.1 (*C*$H_2$N), 32.4 ($NCH_3$), 28.0 (OC(*C*$H_3$)$_3$), 14.2 (CH*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2929, 2853 (C-H), 1731 (C=O ester), 1646 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 451 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{33}O_5N_2$ [M+H]$^+$ 429.2384, found 429.2390.

*NMR file: $^1$H NMR = 2012-08-29-jpc-34 (10), $^{13}$C NMR = 2013-05-21-jpc-37 (10).*

**Synthesis of 590 (from synthesis of 586):** [xxxi]

**(*S*)-*tert*-Butyl 2-(1-benzyl-3-(2,4-dimethoxybenzyl)-3-phenylureido)propanoate (590)**



Urea **586** (50 mg, 0.12 mmol, 1.0 eq.) was dissolved in anhydrous DMF (1.20 mL) and cooled to 0 °C. NaH (10 mg, 0.24 mmol, 2.0 eq.) was added and the resulting mixture was stirred for 25 min. Benzyl bromide was added (0.04 mL, 0.36 mmol, 3.0 eq.) and the reaction mixture was allowed to warm to room temperature and stirred for 17 h. The reaction mixture was quenched with water and extracted with $Et_2O$ (×3). The combined organic layers were washed with water (×2) and once with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (34 mg, 0.07 mmol, 56%). **590: $R_f$** (4:1 Pet.Ether:EtOAc) 0.31; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.29 (1H, d, *J* = 8.4, Ph*H*), 7.25-7.17 (5H, m, Ph*H*), 7.14-7.12 (2H, m, Ph*H*), 7.08-7.04 (1H, m, Ph*H*), 7.01-6.99 (2H, m, Ph*H* + Ar*H*), 6.42-6.37 (2H, m, Ar*H*), 4.83 (1H, d, *J* = 14.8, C$H_{A1}$$H_{B1}$Ar), 4.52 (1H, d, *J* = 14.8, C$H_{A1}$$H_{B1}$Ar), 4.37 (1H, d, *J* = 16.0, C$H_{A2}$$H_{B2}$Ar), 4.20 (1H, q, *J* = 7.2, NC*H*$CH_3$), 3.96 (1H, d, *J* = 16.0, C$H_{A2}$$H_{B2}$Ar), 3.79 (3H, s, OC$H_3$), 3.66 (3H, s, OC$H_3$), 1.42 (9H, s, OC(C$H_3$)$_3$), 1.16 (3H, d, *J* = 7.2, CHC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 171.4 (*C*=O), 161.4 (Ar*C*O), 160.0 (Ar*C*O), 158.3 (*C*=O), 145.8 (Ar*C*N), 138.3 (Ar*C*), 131.2 (Ar*C*H), 129.0 (2×Ar*C*H), 128.0 (2×Ar*C*H), 127.5 (2×Ar*C*H), 126.8 (Ar*C*H), 125.0 (2×Ar*C*H), 124.8 (Ar*C*H),

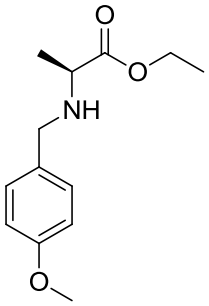
[xxxi] During the synthesis partial racemisation (ca. 60% *ee*) occurred, structures drawn as the major enantiomer.[(a)]

119.3 (Ar*C*), 103.7 (OMeAr*C*H), 98.1 (OMeAr*C*H), 81.1 (O*C*($CH_3$)$_3$), 56.8 (N*C*H$CH_3$), 55.3 (O*C*$H_3$), 55.0 (O*C*$H_3$), 50.4 (*C*$H_2$N), 50.3 (*C*$H_2$N), 28.0 (OC(*C*$H_3$)$_3$), 14.9 (CH*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3062, 2977, 2935 (C-H), 1731 (C=O ester), 1650 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 505 ([M+H]$^+$, 100%), 527 ([M+Na]$^+$, 40%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{30}H_{37}O_5N_2$ [M+H]$^+$ 505.2697, found 505.2695.

*NMR file: $^1$H NMR = 2012-09-05-jpc-24 (11), $^{13}$C NMR = 2012-09-05-jpc-24 (14).*

**Synthesis of 601:**

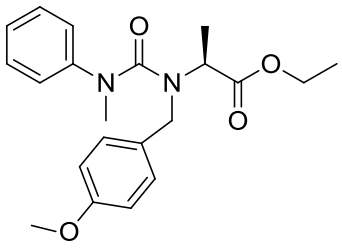
**(*S*)-Ethyl 2-((4-methoxybenzyl)amino)propanoate (599)**




Following general procedure **11**, to a mixture of L-alanine ethyl ester hydrochloride (5.00 g, 32.55 mmol), DCM (60.0 mL) and $Et_3N$ (6.80 mL, 48.82 mmol) was added *p*-anisaldehyde (3.30 mL, 27.12 mmol). The reaction was complete after 20 h at room temperature. The crude residue was dissolved in 1:1 DCM:EtOH (25.0 mL:25.0 mL) and $NaBH_4$ (1.64 g, 43.36 mmol) added at 0 °C. The reaction was complete after 23 h at room temperature. The title compound was yielded as a yellow oil without further purification (5.69 g, 24.01 mmol, 89%). **599: $R_f$** (2:1 Pet.Ether:EtOAc) 0.40; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.29-7.20 (2H, m, Ar*H*), 6.88-6.83 (2H, m, Ar*H*), 4.19 (2H, q, *J* = 7.2, C*H*$_2$CH$_3$), 3.79 (3H, s, OC*H*$_3$), 3.74 (1H, d, *J* = 12.6, C*H*$_A$H$_B$NH), 3.62 (1H, d, *J* = 12.6, CH$_A$*H*$_B$NH), 3.36 (1H, q, *J* = 6.9, C*H*CH$_3$), 2.00 (1H, br. s, N*H*CH), 1.32 (3H, d, *J* = 6.9, CHC*H*$_3$), 1.29 (3H, t, *J* = 7.2, CH$_2$C*H*$_3$); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 175.4 (*C*=O), 158.9 (Ar*C*OMe), 131.5 (Ar*C*), 129.5 (2×Ar*C*H), 113.8 (2×Ar*C*H), 60.7 (O*C*H$_2$), 55.8 (N*C*H), 55.3 (O*C*$H_3$), 51.3 (N*C*H$_2$), 19.0 (*C*$H_3$), 14.3 (*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3327 (NH), 2978, 2935, 2906 (C-H), 1728 (C=O ester), 1245 (C-O ether); **MS** (ESI$^+$, MeOH): *m/z* = 238 ([M+H]$^+$, 5%), 260 ([M+Na]$^+$, 70%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{20}NO_3$ [M+H]$^+$ 238.1438, found 238.1442.

*NMR file: $^1$H NMR = 2013-02-12-jpc-30 (10), $^{13}$C NMR = 2013-02-14-jpc-56 (10).*

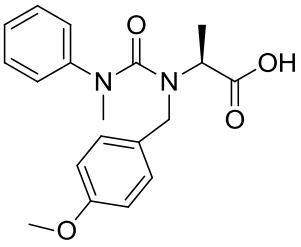
**(*S*)-Ethyl 2-(1-(4-methoxybenzyl)-3-methyl-3-phenylureido)propanoate (600)**



Following general procedure **1a**, *N*-methyl-*N*-phenyl carbamoyl chloride (1.95 g, 11.50 mmol, 1.0 eq.) and DMAP (cat.) were added to a pre-stirred solution of amine **599** (3.00 g, 12.65 mmol, 1.1 eq.) and $Et_3N$ (2.08 mL, 14.95 mmol, 1.3 eq.) in DCE (30.0 mL). The reaction was complete after 20 h. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (2.80 g, 7.56 mmol, 66%). **600: $R_f$** (4:1 Pet.Ether:EtOAc) 0.35; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.31-7.26 (2H, m, Ph*H*), 7.12-7.08 (3H, m, Ph*H*), 6.97-6.94 (2H, m, Ar*H*), 6.78-6.74 (2H, m, Ar*H*), 4.24 (1H, q, *J* = 7.2, C*H*$CH_3$), 4.16-4.11 (2H, $ABX_3$ m, OC$H_AH_B$$CH_3$), 4.18 (1H, d, *J* = 16.0, C$H_A$$H_B$N), 3.97 (1H, d, *J* = 16.0, $CH_A$$H_B$N), 3.76 (3H, s, OC$H_3$), 3.10 (3H, s, NC$H_3$), 1.29 (3H, d, *J* = 6.8, CHC$H_3$), 1.26 (3H, t, *J* = 7.2, $CH_2$C$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 172.2 (*C*=O), 161.6 (*C*=O), 158.5 (Ar*C*OMe), 145.9 (Ar*C*N), 129.8 (Ar*C*), 129.2 (2×Ar*C*H), 128.5 (2×Ar*C*H), 124.9 (Ar*C*H), 124.4 (2×Ar*C*H), 113.4 (2×Ar*C*H), 60.8 (O*C*$H_2$), 55.8 (N*C*H), 55.1 (O*C*$H_3$), 49.9 (N*C*$H_2$), 39.6 (N*C*$H_3$), 14.9 (*C*$H_3$), 14.1 (*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2938 (C-H), 1736 (C=O ester), 1650 (C=O urea), 1244 (C-O ether); **MS** (ESI$^+$, MeOH): *m/z* = 371 ([M+H]$^+$, 5%), 393 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{26}N_2O_4Na$ [M+Na]$^+$ 393.1785, found 393.1792.

*NMR file: $^1$H NMR = 2013-02-14-jpc-38 (20), $^{13}$C NMR = 2013-02-15-jpc-18 (10).*

**(*S*)-2-(1-(4-Methoxybenzyl)-3-methyl-3-phenylureido)propanoic acid (601)**

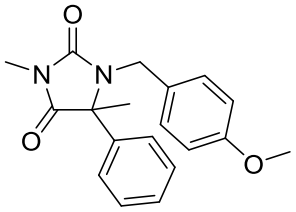


Following a similar method to general procedure **5**, LiOH (3.20 g, 134.00 mmol, 50.0 eq.) was added to urea **600** (992 mg, 2.68 mmol) in 2:1 THF:$H_2O$ (50.0 mL: 25.0 mL). The reaction was complete after 20 h at 45 °C. The title compound was yielded as a pale yellow gum without further purification (748 mg, 2.18 mmol, 82%). **601: $R_f$** (1:1 Pet.Ether:EtOAc) 0.13; $[\alpha]_D^{21}$= +49.0 (*c* = 1.0 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 10.64 (1H, br. s, COO*H*), 7.40-7.33 (2H, m, Ph*H*), 7.23-7.17 (1H, m, Ph*H*), 7.16-7.11 (2H, m, Ph*H*), 6.90-6.85 (2H, m, Ar*H*), 6.79-6.75 (2H, m, Ar*H*), 4.07 (1H, q, *J* = 6.8, C*H*$CH_3$), 4.10 (1H, d, *J* = 14.8, C$H_A$$H_B$N), 3.85 (1H, d, *J* = 14.8, $CH_A$$H_B$N),

3.76 (3H, s, OC$H_3$), 3.23 (3H, s, NC$H_3$), 1.44 (3H, d, $J$ = 7.6, CHC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.9 (*C*=O), 163.1 (*C*=O), 158.9 (Ar*C*OMe), 145.1 (Ar*C*N), 129.6 (2×Ar*C*H), 128.8 (2×Ar*C*H), 128.5 (Ar*C*), 125.7 (Ar*C*H), 124.6 (2×Ar*C*H), 113.7 (2×Ar*C*H), 57.2 (N*C*H), 55.1 (O$CH_3$), 51.3 (N$CH_2$), 39.7 (N$CH_3$), 14.7 ($CH_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2907 (OH broad), 2937 (C-H), 1721 (C=O acid), 1651 (C=O urea), 1246 (C-O ether); **MS** (ESI$^-$, MeOH): *m/z* = 341 ([M–H]$^-$, 15%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{22}N_2O_4Na$ [M+Na]$^+$ 365.1472, found 365.1479.*NMR file: $^1$H NMR = 2013-02-15-jpc-22 (20), $^{13}$C NMR = 2013-02-15-jpc-22 (21).*

**Synthesis of hydantoin 602:**

**1-(4-Methoxybenzyl)-3,5-dimethyl-5-phenylimidazolidine-2,4-dione (602)**

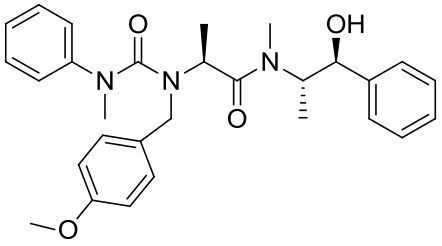


Following general procedure **6**, LiCl (18 mg, 0.43 mmol) and THF (1.00 mL) were added to urea acid **601** (49 mg, 0.14 mmol). LDA was prepared with DiPA (0.06 mL, 0.43 mmol), THF (0.40 mL) and *n*BuLi (0.25 mL, 0.43 mmol, 1.75 M in hexanes). Upon addition of LDA the reaction mixture turned pale yellow and got darker over time. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (32 mg, 0.10 mmol, 69%). **602: $R_f$** (1:1 Pet.Ether:EtOAc) 0.49; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.42-7.33 (3H, m, Ph*H*), 7.24-7.21 (2H, m, Ph*H*), 7.13-7.10 (2H, m, Ar*H*), 6.80-6.77 (2H, m, Ar*H*), 4.90 (1H, d, $J$ = 15.4, C$H_A$H$_B$NH), 3.77 (1H, d, $J$ = 15.4, CH$_A$$H_B$NH), 3.77 (3H, s, OC$H_3$), 3.11 (3H, s, NC$H_3$), 1.58 (3H, s, C$H_3$C); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 175.3 (*C*=O), 159.2 (Ar*C*OMe), 156.9 (*C*=O), 136.6 (Ar*C*), 129.8 (2×Ar*C*H), 129.7 (Ar*C*), 129.3 (2×Ar*C*H), 128.9 (Ar*C*H), 126.4 (2×Ar*C*H), 114.0 (2×Ar*C*H), 67.7 (N*C*C=O), 55.4 (O$CH_3$), 43.9 (N$CH_2$), 25.4 (N$CH_3$), 21.6 ($CH_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2983 (C-H), 1769 (C=O amide), 1705 (C=O urea), 1245 (C-O ether); **MS** (ESI$^+$, MeOH): *m/z* = 347 ([M+Na]$^+$, 100%), **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{20}N_2O_3Na$ [M+Na]$^+$ 347.1366, found 347.1354.

*NMR file: $^1$H NMR = 2013-06-05-40 (10) 300, $^{13}$C NMR = 2013-03-08-jpc-9 (11) 300.*

**Synthesis of 591 and 604 (from synthesis of 601):**

**(*S*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-2-(1-(4-methoxybenzyl)-3-methyl-3-phenylureido)-*N*-methylpropanamide (591)**



Following a similar method to general procedure **9** however EDC rather than EDC·HCl used, urea acid **601** (1.29 g, 3.77 mmol) was dissolved in DCM (17.0 mL), cooled to 0 °C then (*S*,*S*)-pseudoephedrine (933 mg, 5.65 mmol), HOBt·$H_2O$ (509 mg, 3.77 mmol), EDC (0.80 mL, 4.52 mmol) and DiPEA (0.85 mL, 4.90 mmol, 1.3 eq.) were added. Stirred for 25 min at 0 °C then warmed to room temperature. The reaction was complete after 18 h at room temperature. Purification by flash column chromatography ($SiO_2$, 1:1 Pet.Ether:EtOAc) yielded the title compound as a white gum (1.28g, 2.61 mmol, 69%). **591**: $\mathbf{R}_f$ (1:1 Pet.Ether:EtOAc) 0.38; $[\alpha]_D^{21}$= +88.9 (*c* = 1.1 in $CHCl_3$);

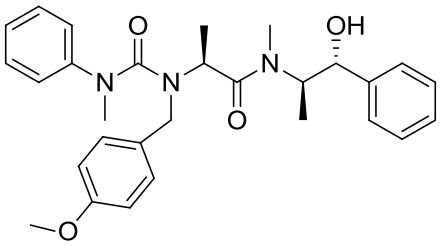
Rotamers in a ratio, Major:Minor, RotA:RotB, 1:0.83, **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.45-7.44 (1H, m, Ar*H*), 7.39-7.25 (7H, m, Ar*H*), 7.16-7.12 (1H, m, Ar*H*), 7.05-6.94 (3H, m, Ar*H*), 6.85-6.79 (2H, m, Ar*H*), 5.40 (rot a, 1H, d, *J* = 6.4, O*H*), 5.12 (rot a, 1H, q, *J* = 6.9, PMBNC*H*$CH_3$), 4.95 (rot b, 1H, q, *J* = 6.7, PMBNC*H*$CH_3$), 4.68 (rot b, 1H, br. d, *J* = 8.4, CHC*H*OH), 4.61-4.55 (2H, m, rot a CHC*H*OH and rot a C$H_AH_B$N), 4.41 (rot b, 1H, br. s, $CH_3$C*H*CHOH), 4.33-4.27 (rot a, 1H, m, $CH_3$C*H*CHOH), 4.15 (rot b, 1H, d, *J* = 16.2, C$H_AH_B$N), 3.90 (rot b, 1H, d, *J* = 16.3, $CH_AH_B$N), 3.79 (rot a, 3H, s, OC$H_3$), 3.78 (rot b, 3H, s, OC$H_3$), 3.74 (rot a, 1H, d, *J* = 16.7, $CH_AH_B$N), 3.61 (rot b, 1H, br. s, O*H*), 3.12 (rot a, 3H, s, NC$H_3$), 3.09 (rot b, 3H, s, NC$H_3$), 3.03 (rot b, 3H, s, NC$H_3$), 3.00 (rot a, 3H, s, NC$H_3$), 1.21 (rot a, 3H, d, *J* = 7.0, PMBNCHC$H_3$), 1.09 (rot b, 3H, d, *J* = 6.9, PMBNCHC$H_3$), 0.95 (rot a+b, 3H, d, *J* = 6.7, C$H_3$CHCHOH);

**$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.0 (*C*=$O_{min}$), 173.6 (*C*=$O_{maj}$), 163.1 (Ar*C*$OMe_{maj}$), 163.2 (Ar*C*$OMe_{min}$), 158.5 (*C*=$O_{maj}$), 158.5 (*C*=$O_{min}$), 145.9 (Ar*C*$_{min}$), 145.4 (Ar*C*$_{maj}$), 142.3 (Ar*C*$N_{maj}$), 142.1 (Ar*C*$N_{min}$), 130.9 (Ar*C*$_{maj}$), 130.7 (Ar*C*$_{min}$), 129.5 (2×Ar*C*$H_{min}$), 129.3 (2×Ar*C*$H_{maj}$), 128.5 (2×Ar*C*$H_{maj}$), 128.5 (2×Ar*C*$H_{min}$), 128.2 (2×Ar*C*$H_{min}$), 127.9 (Ar*C*$H_{maj+min}$), 127.5 (2×Ar*C*$H_{maj}$), 127.2 (2×Ar*C*$H_{min}$), 126.8 (2×Ar*C*$H_{maj}$), 125.2 (Ar*C*$H_{min}$), 124.9 (Ar*C*$H_{maj}$), 124.4 (2×Ar*C*$H_{maj}$), 124.1 (2×Ar*C*$H_{min}$), 113.8 (2×Ar*C*$H_{maj}$), 113.6 (2×Ar*C*$H_{min}$), 76.0 (CH*C*$HOH_{min}$), 75.9 (CH*C*$HOH_{maj}$), 58.9 ($CH_3$*C*$HCHOH_{maj+min}$), 55.3 (O*C*$H_{3maj}$), 55.3 (O*C*$H_{3min}$), 52.9 (PMBN*C*$HCH_{3min}$), 50.3 (PMBN*C*$HCH_{3maj}$), 48.4 (*C*$H_2N_{maj}$), 47.4 (*C*$H_2N_{min}$), 39.9 (N*C*$H_{3min}$),

39.2 (N*C*H$_{3maj}$), 32.3 (N*C*H$_{3min}$), 27.1 (N*C*H$_{3maj}$), 16.3 (PMBNCH*C*H$_{3maj}$ and *C*H$_3$CHCHOH$_{maj}$), 15.3 (PMBNCH*C*H$_{3min}$), 14.4 (*C*H$_3$CHCHOH$_{min}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3402 (OH broad), 3061, 3030, 2975, 2935 (C-H), 1629 (C=O amide), 1594 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 490 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{29}H_{36}N_3O_4$ [M+H]$^+$ 490.2700, found 490.2697.
*NMR file: $^1$H NMR = 2014-12-06-jpc-36 (10) 500a, $^{13}$C NMR = 2014-12-06-jpc-36 (11) 500a.*

**(*S*)-*N*-((1*R*,2*R*)-1-Hydroxy-1-phenylpropan-2-yl)-2-(1-(4-methoxybenzyl)-3-methyl-3-phenylureido)-*N*-methylpropanamide (604)**



Following a similar method to general procedure **9** however EDC rather than EDC·HCl used and (*R*,*R*)-pseudoephedrine used as the chiral auxiliary, urea acid **601** (799 mg, 2.33 mmol) was dissolved in DCM (10.0 mL), cooled to 0 °C then (*S*,*S*)-pseudoephedrine (578 mg, 3.50 mmol), HOBt·H$_2$O (315 mg, 2.33 mmol), EDC (0.50 mL, 2.80 mmol) and DiPEA (0.53 mL, 3.03 mmol, 1.3 eq.) were added. Stirred for 20 min at 0 °C then warmed to room temperature. The reaction was complete after 48 h at room temperature. Purification by flash column chromatography (SiO$_2$, 1:1 Pet.Ether:EtOAc) yielded the title compound as a white gum (667 mg, 1.36 mmol, 58%). **604**: **R$_f$** (1:1 Pet.Ether:EtOAc) 0.35; $[\alpha]_D^{21}$ = –13.3 (*c* = 1.1 in CHCl$_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 1.0:0.33, **$^1$H NMR** (500 MHz, CDCl$_3$): $\delta_H$ = 7.46-7.44 (rot b, 2H, m, Ph*H*), 7.41-7.37 (rot a, 2H, m, Ph*H*), 7.36-7.25 (5H, m, Ph*H*), 7.17-7.11 (rot a, 3H, m, Ph*H*), 7.05-7.03 (rot b, 3H, m, Ph*H*), 6.97-6.94 (2H, m, Ph*H*), 6.83-6.78 (2H, m, Ph*H*), 5.40 (rot b, 1H, d, *J* = 6.4, O*H*), 5.26 (rot b, 1H, q, *J* = 6.6, PMBNC*H*CH$_3$), 4.79 (rot a, 1H, q, *J* = 6.9, PMBNC*H*CH$_3$), 4.72-4.56 (2H, m, rot a+b CHC*H*OH and rot a CH$_3$C*H*CHOH), 4.45-4.40 (rot b, 1H, m, CH$_3$C*H*CHOH), 4.35 (rot a, 1H, br. s, O*H*), 4.30 (rot a, 1H, d, *J* = 16.6, C*H$_A$*H$_B$N), 4.14 (rot b, 1H, d, *J* = 15.7, C*H$_A$*H$_B$N), 3.91 (rot b, 1H, d, *J* = 15.8, CH$_A$*H$_B$*N), 3.90 (rot a, 1H, d, *J* = 16.6, CH$_A$*H$_B$*N), 3.79 (rot a, 3H, s, OC*H$_3$*), 3.78 (rot b, 3H, s, OC*H$_3$*), 3.10 (rot a, 3H, s, NC*H$_{3a}$*), 3.00 (rot a, 3H, s, NC*H$_{3b}$*), 2.95 (rot b, 3H, s, NC*H$_{3a}$*), 2.87 (rot b, 3H, s, NC*H$_{3b}$*), 1.11 (rot a, 3H, d, *J* = 6.9, PMBNCHC*H$_3$*), 1.00-0.98 (rot a+b, 3H, m, C*H$_3$*CHCHOH), 0.91 (rot b, 3H, d, *J* = 6.6, PMBNCHC*H$_3$*);

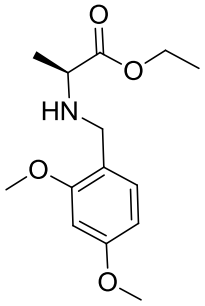
**$^{13}$C {$^{1}$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.5 (*C*=$O_{maj}$), 172.7 (*C*=$O_{min}$), 162.7 (Ar*C*$OMe_{maj}$), 161.9 (Ar*C*$OMe_{min}$), 158.6 (*C*=$O_{maj}$), 158.5 (*C*=$O_{min}$), 146.4 (Ar*C*$_{min}$), 145.8 (Ar*C*$_{maj}$), 142.0 (Ar*C*$N_{maj}$), 141.4 (Ar*C*$N_{min}$), 131.3 (Ar*C*$_{min}$), 131.0 (Ar*C*$_{maj}$), 129.6 (2×Ar*C*$H_{min}$), 129.5 (2×Ar*C*$H_{maj}$), 129.0 (2×Ar*C*$H_{min}$), 128.9 (2×Ar*C*$H_{min}$), 128.5 (2×Ar*C*$H_{maj}$), 128.0 (2×Ar*C*$H_{maj}$), 127.8 (Ar*C*$H_{maj+min}$), 127.1 (2×Ar*C*$H_{min}$), 127.0 (2×Ar*C*$H_{maj}$), 125.4 (Ar*C*$H_{min}$), 125.2 (Ar*C*$H_{maj}$), 124.6 (2×Ar*C*$H_{maj}$), 124.5 (2×Ar*C*$H_{min}$), 113.8 (2×Ar*C*$H_{maj}$), 113.5 (2×Ar*C*$H_{min}$), 76.1 (CH*C*$HOH_{maj}$), 76.0 (CH*C*$HOH_{min}$), 57.5 ($CH_3$*C*$HCHOH_{maj+min}$), 55.4 (O*C*$H_{3maj+min}$), 52.3 (PMBN*C*$HCH_{3maj}$), 52.2 (PMBN*C*$HCH_{3min}$), 48.1 (*C*$H_2N_{maj}$), 46.6 (*C*$H_2N_{min}$), 40.2 (N*C*$H_{3min}$), 39.7 (N*C*$H_{3maj}$), 27.6 (N*C*$H_{3maj}$), 27.1 (N*C*$H_{3min}$), 15.8 (*C*$H_3$CHCHO$H_{min}$), 15.4 (PMBNCH*C*$H_{3min}$), 15.3 (PMBNCH*C*$H_{3maj}$), 14.6 (*C*$H_3$CHCHO$H_{maj}$);

**IR**, **MS** and **HRMS** data the same as **591**

*NMR file: $^{1}$H NMR = 2014-12-06-jpc-37 (10) 500a, $^{13}$C NMR = 2014-12-06-jpc-37 (11) 500a.*

**Synthesis of 609:**

**(*S*)-Ethyl 2-((2,4-dimethoxybenzyl)amino)propanoate (607)**

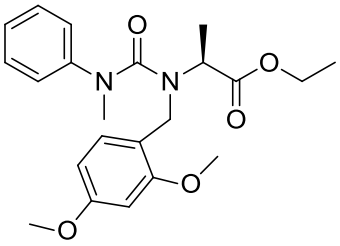



Following general procedure **11**, to a mixture of L-alanine ethyl ester hydrochloride (2.00 g, 13.0 mmol), DCM (30.0 mL) and $Et_3N$ (2.72 mL, 19.51 mmol) was added 2,4-dimethoxybenzaldehyde (1.80 g, 10.84 mmol). The reaction was complete after 25 h at room temperature. The crude residue was dissolved in 1:1 DCM:EtOH (10.0 mL:10.0 mL) and $NaBH_4$ (656 mg, 17.34 mmol) added at 0 °C. The reaction was complete after 18 h at room temperature. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc + 1% $Et_3N$) yielded the title compound as a pale yellow oil (2.10 g, 7.86 mmol, 73%). **607**: $\mathbf{R}_f$ (4:1 Pet.Ether:EtOAc + 1% $Et_3N$) 0.13; $[\alpha]_D^{21}$ = –5.5 (*c* = 1.1 in $CHCl_3$); **$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.11 (1H, d, *J* = 8.0, Ar*H*), 6.42-6.39 (2H, m, Ar*H*), 4.14-4.08 (2H, $ABX_3$ m, O*C*$H_A$*H*$_B$$CH_3$), 3.79 (3H, s, O*C*$H_3$), 3.77 (3H, s, O*C*$H_3$), 3.70 (1H, d, *J* = 13.2, *C*$H_A$$H_B$NH), 3.65 (1H, d, *J* = 13.2, $CH_A$*H*$_B$NH), 3.32 (1H, q, *J* = 7.2, *C*H$CH_3$), 2.20 (1H, br. s, N*H*CH), 1.28 (3H, d, *J* = 7.2, CHC*H*$_3$), 1.24 (3H, t, *J* = 7.2, $CH_2$C*H*$_3$); **$^{13}$C {$^{1}$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.6 (*C*=O), 160.1 (Ar*C*OMe), 158.6 (Ar*C*OMe), 130.3 (Ar*C*H), 120.2 (Ar*C*), 103.6 (Ar*C*H), 98.4 (Ar*C*H), 60.4 (O*C*$H_2$), 55.8 (N*C*H), 55.2 (O*C*$H_3$), 55.2 (O$CH_3$), 46.7 (N*C*$H_2$), 18.9 (*C*$H_3$), 14.1 (*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3338 (NH), 2977, 2937, 2836 (C-H),

1728 (C=O ester); **MS** ($ESI^+$, MeOH): *m/z* = 268 ($[M+H]^+$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{14}H_{22}NO_4$ $[M+H]^+$ 268.1543, found 268.1545.

*NMR file: $^1$H NMR = 2013-05-29-jpc-8 (10), $^{13}$C NMR = 2013-05-29-jpc-8 (11).*

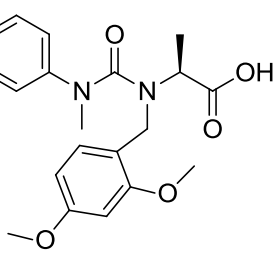
**(*S*)-Ethyl *N*-(2,4-dimethoxybenzyl)-*N*-(methyl(phenyl)carbamoyl)alaninate (608)**



Following general procedure **1c**, *N*-methyl-*N*-phenyl carbamoyl chloride (1.14 g, 6.70 mmol) and DMAP (cat.) were added to a pre-stirred solution of amine **607** (1.97 g, 7.37 mmol) and $Et_3N$ (1.21 mL, 8.72 mmol) in DCE (17.5 mL). The reaction was complete after 23 h. Purification by flash column chromatography ($SiO_2$, 8:2-7:3 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (1.80 g, 4.49 mmol, 67%). **608: $R_f$** (4:1 Pet.Ether:EtOAc) 0.24; $[\alpha]_D^{27}$ = –6.5 (*c* = 1.2 in $CHCl_3$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.26-7.23 (2H, m, Ph*H*), 7.15-7.13 (2H, m, Ph*H*), 7.06-7.03 (1H, m, Ph*H*), 6.98 (1H, d, *J* = 8.3, Ar*H*), 6.37 (1H, dd, *J* = 8.3, 2.4, Ar*H*), 6.33 (1H, d, *J* = 2.4, Ar*H*), 4.21-4.15 (2H, $ABX_3$ m, $OCH_AH_BCH_3$), 4.15 (1H, q, *J* = 7.0, $CHCH_3$), 4.12 (1H, d, *J* = 16.4, $CH_AH_BN$), 4.01 (1H, d, *J* = 16.3, $CH_AH_BN$), 3.78 (3H, s, $OCH_3$), 3.69 (3H, s, $OCH_3$), 3.17 (3H, s, $NCH_3$), 1.29 (3H, t, *J* = 7.2, $CH_2CH_3$), 1.28 (3H, d, *J* = 7.0, $CHCH_3$); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 172.4 (*C*=O), 161.7 (*C*=O), 159.9 (Ar*C*O), 157.9 (Ar*C*O), 146.2 (Ar*C*N), 129.2 (1×OMeAr*C*H), 129.1 (2×Ar*C*H), 124.5 (1×Ar*C*H), 124.1 (2×Ar*C*H), 118.2 (Ar*C*), 103.5 (OMeAr*C*H), 98.0 (OMeAr*C*H), 60.9 ($OCH_2$), 56.2 (N*C*H), 55.3 ($OCH_3$), 55.1 ($OCH_3$), 45.8 ($NCH_2$), 39.6 ($NCH_3$), 14.8 ($CH_3$), 14.2 ($CH_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2980, 2939, 2906 (C-H), 1735 (C=O ester), 1646 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 423 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{22}H_{29}N_2O_5$ $[M+H]^+$ 401.2071, found 401.2069.

*NMR file: $^1$H NMR = 2013-06-04-jpc-20 (20), $^{13}$C NMR = 2013-06-04-jpc-20 (21).*

**(*S*)-*N*-(2,4-dimethoxybenzyl)-*N*-(methyl(phenyl)carbamoyl)alanine (609)**



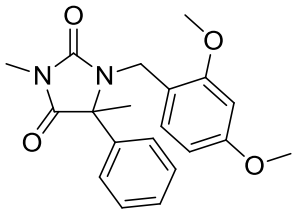
Following a similar method to general procedure **5**, LiOH (5.13g, 214.10 mmol, 50.0 eq.) was added to urea **608** (1.72g, 4.28 mmol) in 2:1 THF:$H_2O$ (80.0 mL: 40.0 mL). The reaction was

complete after 22 h at 45 °C. The title compound was yielded as a pale yellow solid without further purification (1.33g, 3.57 mmol, 83%). **609**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc) 0.26; **mp**: 136-137 °C; $[\alpha]_D^{21}$= +5.2 (*c* = 1.6 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 13.45 (1H, br. s, COO*H*), 7.42-7.37 (2H, m, Ph*H*), 7.23-7.17 (3H, m, Ph*H*), 6.84 (1H, d, *J* = 8.2, Ar*H*), 6.37 (1H, d, *J* = 2.3, Ar*H*), 6.34 (1H, dd, *J* = 8.2, 2.4, Ar*H*), 3.96-3.92 (2H, m, C*H*$CH_3$+ C$H_A$$H_B$N), 3.78 (3H, s, OC$H_3$), 3.75 (3H, s, OC$H_3$), 3.69 (1H, br. d, *J* = 13.9, $CH_AH_B$N), 3.42 (3H, s, NC$H_3$), 1.52 (3H, d, *J* = 7.4, CHC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 173.5 (*C*=O), 164.5 (*C*=O), 161.5 (Ar*C*O), 159.1 (Ar*C*O), 145.1 (Ar*C*N), 131.2 (OMeAr*C*H), 129.8 (2×Ar*C*H), 125.8 (Ar*C*H), 124.3 (2×Ar*C*H), 115.6 (Ar*C*), 103.9 (OMeAr*C*H), 98.6 (OMeAr*C*H), 57.8 (N*C*H), 55.5 (O*C*$H_3$), 55.4 (O*C*$H_3$), 49.5 ($NCH_2$), 39.2 (N*C*$H_3$), 14.7 (*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2999 (OH broad), 2941, 2837 (C-H), 1739 (C=O acid), 1612 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 373 ([M+H]$^+$, 100%), 395 ([M+Na]$^+$, 50%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{25}N_2O_5$ [M+H]$^+$ 373.1758, found 373.1757.

*NMR file: $^1$H NMR = 2014-04-10-jpc-10 (20), $^{13}$C NMR = 2014-04-28-jpc-14 (10).*

**Synthesis of hydantoin 610:**

**1-(2,4-Dimethoxybenzyl)-3,5-dimethyl-5-phenylimidazolidine-2,4-dione (±610)**

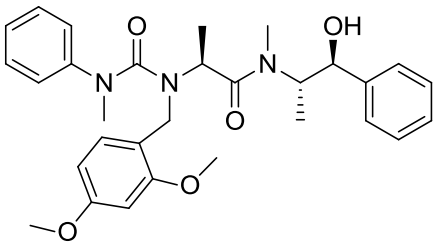


Following general procedure **6**, LiCl (22 mg, 0.52 mmol) and THF (1.00 mL) were added to urea acid **609** (65 mg, 0.18 mmol). LDA was prepared with DiPA (0.07 mL, 0.52 mmol), THF (0.80 mL) and *n*BuLi (0.30 mL, 0.52 mmol, 1.75 M in hexanes). Upon addition of LDA the reaction mixture turned pale yellow. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (45 mg, 0.13 mmol, 73%). ±**610:** $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc) 0.56;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **610**

**Synthesis of 605 (from synthesis of 609):**

**(*S*)-2-(1-(2,4-Dimethoxybenzyl)-3-methyl-3-phenylureido)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropanamide (605)**



Following a similar procedure to general procedure **9**, urea acid **609** (1.55 g, 4.17 mmol) was dissolved in DCM (19.0 mL) then (*S*,*S*)-pseudoephedrine (1.03 g, 6.25 mmol), HOBt·$H_2O$ (563 mg, 4.17 mmol), EDC·HCl (959 mg, 5.00 mmol) and DiPEA (1.67 mL, 9.58 mmol, 2.3 eq.) were added and stirred for 20 min at 0 °C. The reaction was complete after 16 h at room temperature. Purification by flash column chromatography ($SiO_2$, 1:1 Pet.Ether:EtOAc) yielded the title compound as a white gum (1.75 g, 3.36 mmol, 81%). **605**: $\mathbf{R}_f$ (1:1 Pet.Ether:EtOAc) 0.25; $[\alpha]_D^{21}$= +59.4 (*c* = 1.0 in $CHCl_3$);

NMR data is a mixture of 4 rotamers due to the pseudoephedrine and the DMB protecting group
Overall: RotA: RotB: RotC: RotD = 1.00:0.95:0.65:0.21 = % 36:34:23:7

Rotamer A:

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.45-7.23 (8H, m, Ar*H*), 7.11-7.06 (3H, m, Ar*H*), 6.41-6.39 (1H, m, DMBAr$H_a$), 6.35 (1H, d, *J* = 2.3, DMBAr$H_b$), 5.65 (1H, d, *J* = 5.2, O*H*), 4.93-4.86 (1H, m, DMBNC*H*$CH_3$), 4.63-4.56 (1H, m, CHC*H*OH), 4.35 (1H, d, *J* = 17.1, NC$H_A$$H_B$), 4.23-4.11 (1H, m, $CH_3$C*H*CHOH), 4.01 (1H, d, *J* = 17.2, NC$H_A$$H_B$), 3.80 (3H, s, OC$H_3$), 3.68 (3H, s, OC$H_3$), 3.15 (3H, s, NC$H_{3a}$), 2.99 (3H, s, NC$H_{3b}$), 1.18 (3H, d, *J* = 6.9, DMBNCHC$H_3$), 0.92 (3H, d, *J* = 6.7, C$H_3$CHCHOH);

Rotamer B

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.45-7.23 (8H, m, Ar*H*), 7.00-6.91 (3H, m, Ar*H*), 6.41-6.39 (1H, m, DMBAr$H_a$), 6.35 (1H, d, *J* = 2.3, DMBAr$H_b$), 4.75-4.66 (2H, m, $CH_3$C*H*CHOH and DMBNC*H*$CH_3$), 4.63-4.56 (1H, m, CHC*H*OH), 4.23-4.11 (1H, m, NC$H_A$$H_B$), 3.97-3.91 (1H, m, NC$H_A$$H_B$), 3.78 (3H, s, OC$H_3$), 3.69 (3H, s, OC$H_3$), 3.21 (3H, s, NC$H_{3a}$), 2.99 (3H, s, NC$H_{3b}$), 1.82 (1H, br. s, O*H*), 1.15 (3H, d, *J* = 6.9, DMBNCHC$H_3$), 0.96 (3H, d, *J* = 6.8, C$H_3$CHCHOH);

Rotamer C:

**$^{1}$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.45-7.23 (8H, m, Ar*H*), 7.20-7.18 (3H, m, Ar*H*), 6.45 (1H, dd, *J* = 8.3, 2.3, DMBAr$H_a$), 6.41-6.39 (1H, m, DMBAr$H_b$), 4.93-4.86 (1H, m, DMBNC*H*$CH_3$), 4.78 (1H, br. d, *J* = 7.2, CHC*H*OH), 4.53 (1H, br. s, O*H*), 4.27 (1H, br. s, $CH_3$C*H*CHOH), 4.23-4.11 (1H, m, NC$H_A$$H_B$), 3.97-3.91 (1H, m, NC$H_A$$H_B$), 3.78 (3H, s, OC$H_3$), 3.67 (3H, s, OC$H_3$), 3.13 (3H, s, NC$H_{3a}$), 3.06 (3H, s, NC$H_{3b}$), 1.13 (3H, d, *J* = 6.9, DMBNCHC$H_3$), 1.02 (3H, d, *J* = 6.9, C$H_3$CHCHOH);

Rotamer D:

**$^{1}$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.45-7.23 (8H, m, Ar*H*), 7.11-7.06 (3H, m, Ar*H*), 6.45 (1H, dd, *J* = 8.3, 2.3, DMBAr$H_a$), 6.41-6.39 (1H, m, DMBAr$H_b$), 5.29-5.24 (1H, m, $CH_3$C*H*CHOH), 4.63-4.56 (1H, m, CHC*H*OH), 4.49-4.43 (1H, m, DMBNC*H*$CH_3$), 4.23-4.11 (1H, m, NC$H_A$$H_B$), 3.97-3.91 (1H, m, NC$H_A$$H_B$), 3.78 (3H, s, OC$H_3$), 3.65 (3H, s, OC$H_3$), 3.00 (3H, s, NC$H_{3a}$), 2.90 (3H, s, NC$H_{3b}$), 2.35 (1H, br. s, O*H*), 1.13 (3H, d, *J* = 6.9, DMBNCHC$H_3$), 0.96 (rot d, 3H, d, *J* = 6.8, C$H_3$CHCHOH);

Not all the rotamers for each carbon were observed and the rotamers could not be assigned:

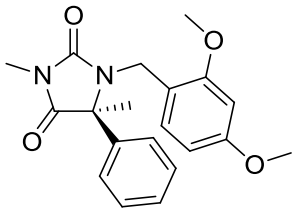
**$^{13}$C {$^{1}$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.9 (*C*=$O_a$), 174.5 (*C*=$O_a$), 174.1 (*C*=$O_a$), 163.6 (Ar*C*OMe), 163.1 (Ar*C*OMe), 162.5 (Ar*C*OMe), 160.0 (Ar*C*OMe), 159.9 (Ar*C*OMe), 159.8 (Ar*C*OMe), 157.9 (*C*=$O_b$), 157.7 (*C*=$O_b$), 146.0 (Ar*C*), 146.0 (Ar*C*), 145.9 (Ar*C*), 142.4 (Ar*C*), 142.3 (Ar*C*), 141.9 (Ar*C*), 129.4 (Ar*C*H), 129.3 (Ar*C*H), 129.3 (Ar*C*H), 128.9 (Ar*C*H), 128.5 (Ar*C*H), 128.5 (Ar*C*H), 128.5 (Ar*C*H), 128.4 (Ar*C*H), 127.9 (Ar*C*H), 127.8 (Ar*C*H), 127.3 (Ar*C*H), 127.2 (Ar*C*H). 127.1 (Ar*C*H), 127.0 (Ar*C*H), 125.1 (Ar*C*H), 125.0 (Ar*C*H), 124.8 (Ar*C*H), 124.7 (Ar*C*H), 124.6 (Ar*C*H), 124.5 (Ar*C*H), 124.4 (Ar*C*H), 119.2 (Ar*C*), 119.1 (Ar*C*), 118.6 (Ar*C*), 103.9 (Ar*C*H), 103.7 (Ar*C*H), 103.7 (Ar*C*H), 103.4 (Ar*C*H), 98.3 (Ar*C*H), 98.2 (Ar*C*H), 98.2 (Ar*C*H), 98.0 (Ar*C*H), 76.0 (CH*C*HOH), 59.1 ($CH_3$*C*HCHOH), 57.5 ($CH_3$*C*HCHOH), 55.6 (O*C*$H_3$), 55.5 (O*C*$H_3$), 55.5 (O*C*$H_3$), 55.3 (O*C*$H_3$), 55.2 (O*C*$H_3$), 55.1 (O*C*$H_3$), 53.0 (DMBNCHC$H_3$), 52.3 (DMBNCHC$H_3$), 52.2 (DMBNCHC$H_3$), 50.7 (DMBNCHC$H_3$), 44.6 (N*C*$H_2$), 43.9 (N*C*$H_2$), 43.3 (N*C*$H_2$), 40.0 (N*C*$H_{3a}$), 39.9 (N*C*$H_{3a}$), 39.3 (N*C*$H_{3a}$), 32.9 (N*C*$H_{3b}$), 31.0 (N*C*$H_{3b}$), 28.2 (N*C*$H_{3b}$), 27.2 (N*C*$H_{3b}$), 16.3 (*C*$H_3$CHCHOH), 16.1 (DMBNCHC$H_3$), 15.1 (DMBNCHC$H_3$), 15.0 (DMBNCHC$H_3$), 14.6 (*C*$H_3$CHCHOH);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3411 (OH broad), 3059, 2937, 2835 (C-H), 1631 (C=O amide), 1593 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 520 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{30}H_{38}N_3O_5$ [M+H]$^+$ 520.2806, found 520.2794.

*NMR file: $^{1}$H NMR = 2014-12-06-jpc-38 (10) 500a, $^{13}$C NMR = 2014-12-06-jpc-38 (11) 500a.*

**Synthesis of hydantoin 610:**

**(*S*)-1-(2,4-Dimethoxybenzyl)-3,5-dimethyl-5-phenylimidazolidine-2,4-dione (610)**



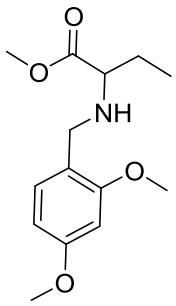
Following a similar method to general procedure **6**, LiCl (95 mg, 2.24 mmol, 10.0 eq.) and THF (1.20 mL) were added to urea pseudo **605** (115 mg, 0.22 mmol). LDA (6.0 eq.) was prepared with DiPA (0.19 mL, 1.33 mmol, 6.0 eq.), THF (1.00 mL) and *n*BuLi (0.90 mL, 1.33 mmol, 1.48 M in hexanes, 6.0 eq.). Upon addition of LDA the reaction mixture turned yellow and over time turned brown. After 3 h at room temperature the reaction was cooled to –78 °C, quenched with MeOH, stirred for 10 min then warmed to room temperature and a saturated aqueous $NH_4Cl$ solution added. The aqueous was extracted with EtOAc (×3) and the combined organic layer was washed with water (×2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography ($SiO_2$, 3:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (34 mg, 0.10 mmol, 43%). **610**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc) 0.56; $[\alpha]_D^{21}$ = +57.9 (*c* = 1.1 in $CHCl_3$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.33-7.27 (3H, m, Ph*H*), 7.21-7.17 (3H, m, 2×Ph*H*+Ar*H*), 6.40 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 6.26 (1H, d, *J* = 2.4, Ar*H*), 4.67 (1H, d, *J* = 15.4, C$H_A$$H_B$NH), 4.14 (1H, d, *J* = 15.4, CH$_A$$H_B$NH), 3.76 (3H, s, OC$H_3$), 3.60 (3H, s, OC$H_3$), 3.10 (3H, s, NC$H_3$), 1.65 (3H, s, C$H_3$C); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.3 (*C*=O), 160.5 (Ar*C*OMe), 157.7 (Ar*C*OMe), 156.7 (*C*=O), 136.7 (Ar*C*), 130.9 (Ar*C*H), 128.7 (2×Ar*C*H), 128.3 (Ar*C*H), 126.0 (2×Ar*C*H), 117.8 (Ar*C*), 104.1 (Ar*C*H), 98.0 (Ar*C*H), 67.4 (N*C*C=O), 55.3 (O*C*H$_3$), 54.9 (O*C*H$_3$), 37.8 (N*C*H$_2$), 25.2 (N*C*H$_3$), 20.3 (*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3062, 2940, 2837 (C-H), 1768 (C=O amide), 1704 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 355 ([M+H]$^+$, 100%), 377 ([M+Na]$^+$, 40%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{20}H_{23}N_2O_4$ [M+H]$^+$ 355.1652, found 355.1651; **HPLC**: *er* 1:99, Chiralcel OD-H, Hexane:IPA = 90:10, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 18.6 (minor), 20.6 (major) min.

**ent-610 (*R*)**: synthesised by another member of the group, $[\alpha]_D^{23}$ = –54.4 (*c* = 1.0 in $CHCl_3$)

*NMR file: $^1$H NMR = 2013-09-25-jpc-36 (10), $^{13}$C NMR = 2013-06-11-jpc-55 (11).*

**Synthesis of 614:**

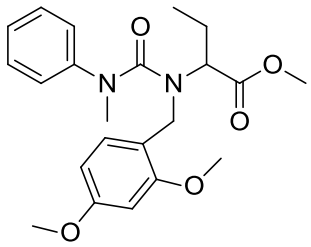
**Methyl 2-((2,4-dimethoxybenzyl)amino)butanoate (612)**



Following general procedure **11**, to a mixture of methyl-DL-α-aminobutyrate hydrochloride (3.00 g, 19.5 mmol), DCM (60.0 mL) and $Et_3N$ (4.08 mL, 29.3 mmol) was added 2,4-dimethoxybenzaldehyde (2.70 g, 16.3 mmol). The reaction was complete after 18 h at room temperature. The crude residue was dissolved in 1:1 DCM:EtOH (15.0 mL:15.0 mL) and $NaBH_4$ (987 mg, 26.08 mmol) added at 0 °C. The reaction was complete after 20 h at room temperature. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc + 1% $Et_3N$) yielded the title compound as a colourless oil (3.37 g, 12.6 mmol, 77%). **612**: $\mathbf{R_f}$ (3:2 Pet.Ether:EtOAc) 0.15; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.12 (1H, d, *J* = 8.0, Ar*H*), 6.46-6.37 (2H, m, Ar*H*), 3.80 (3H, s, OC$H_3$), 3.78 (3H, s, OC$H_3$), 3.70 (1H, d, *J* = 13.2, C$H_A$H$_B$NH), 3.65 (3H, s, O=COC$H_3$), 3.64 (1H, d, *J* = 13.2, CH$_A$$H_B$NH), 3.20 (1H, t, *J* = 6.6, C*H*CH$_2$CH$_3$), 2.05 (1H, br. s, N*H*CH), 1.70-1.63 (2H, m, C$H_2$CH$_3$), 0.90 (3H, t, *J* = 7.4, CH$_2$C$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.7 (*C*=O), 160.1 (Ar*C*OMe), 158.6 (Ar*C*OMe), 130.3 (Ar*C*H), 120.4 (Ar*C*), 103.6 (Ar*C*H), 98.4 (Ar*C*H), 62.0 (N*C*H), 55.3 (O*C*H$_3$), 55.2 (O*C*H$_3$), 51.5 (O=COCH$_3$), 47.1 (N*C*H$_2$), 26.5 (*C*H$_2$CH$_3$), 10.1 (CH$_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3331 (NH), 2950, 2877, 2835 (C-H), 1732 (C=O ester); **MS** (ESI$^+$, MeOH): *m/z* = 268 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{21}NO_4Na$ [M+Na]$^+$ 290.1363, found 290.1358.

*NMR file: $^1$H NMR = 2013-07-11-jpc-3 (10), $^{13}$C NMR = 2013-07-11-jpc-3 (11).*

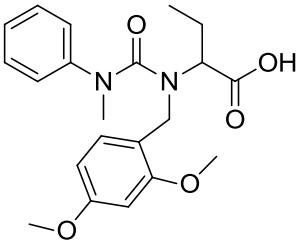
**Methyl 2-(1-(2,4-dimethoxybenzyl)-3-methyl-3-phenylureido)butanoate (613)**



Following general procedure **1c**, *N*-methyl-*N*-phenyl carbamoyl chloride (1.94 g, 11.50 mmol) and DMAP (cat.) were added to a pre-stirred solution of amine **612** (3.37 g, 12.60 mmol) and $Et_3N$ (2.08 mL, 14.95 mmol) in DCE (30.0 mL). The reaction was complete after 16 h. Purification by

flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (3.16 g, 7.89 mmol, 69%). **613: $R_f$** (4:1 Pet.Ether:EtOAc) 0.16; **$^1$H NMR** (300 MHz, $CDCl_3$): $\delta_H$ = 7.33-7.27 (2H, m, Ph*H*), 7.14-7.09 (3H, m, Ph*H*), 7.03 (1H, d, *J* = 8.3, Ar*H*), 6.43-6.38 (2H, m, Ar*H*), 4.16 (1H, d, *J* = 15.9, C$H_A$H$_B$N), 4.08 (1H, t, *J* = 6.9, C*H*CH$_2$CH$_3$), 4.03 (1H, d, *J* = 15.7, CH$_A$$H_B$N), 3.80 (3H, s, OC$H_3$), 3.72 (3H, s, OC$H_3$), 3.67 (3H, s, OC$H_3$), 3.20 (3H, s, NC$H_3$), 2.07-1.93 (1H, m, C$H_A$H$_B$C$H_3$), 1.69-1.55 (1H, m, CH$_A$$H_B$C$H_3$), 0.82 (3H, t, *J* = 7.4, CH$_2$C$H_3$); **$^{13}$C {$^1$H} NMR** (75 MHz, $CDCl_3$): $\delta_C$ = 172.2 (*C*=O), 161.93 (*C*=O), 159.9 (Ar*C*O), 157.9 (Ar*C*O), 146.1 (Ar*C*N), 129.5 (1×OMeAr*C*H), 129.0 (2×Ar*C*H), 124.6 (Ar*C*H), 124.2 (2×Ar*C*H), 118.0 (Ar*C*), 103.5 (OMeAr*C*H), 97.8 (OMeAr*C*H), 61.5 (N*C*H), 55.1 (O*C*H$_3$), 54.9 (O*C*H$_3$), 51.5 (O*C*H$_3$), 44.9 (N*C*H$_2$), 39.6 (N*C*H$_3$), 23.0 (*C*H$_2$CH$_3$), 11.3 (CH$_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2950, 2837 (C-H), 1738 (C=O ester), 1647 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 401 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{28}N_2O_5Na$ [M+Na]$^+$ 423.1896, found 423.1885.
*NMR file: $^1$H NMR = 2013-07-15-jpc-30 (10), $^{13}$C NMR = 2013-07-15-jpc-30 (11).*

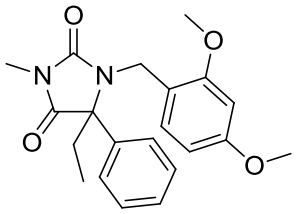
**2-(1-(2,4-Dimethoxybenzyl)-3-methyl-3-phenylureido)butanoic acid (614)**




Following a similar method to general procedure **5**, LiOH (6.00 g, 250.00 mmol, 35.0 eq.) was added to urea acid **613** (2.86 g, 7.14 mmol) in 2:1 THF:$H_2O$ (100 mL: 50.0 mL). The reaction was complete after 22 h at 45 °C. The title compound was yielded as a yellow oil without further purification (2.52 g, 6.52 mmol, 91%). **614**: **$R_f$** (1:1 Pet.Ether:EtOAc) 0.45; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 11.27 (1H, br. s, COO*H*), 7.41-7.37 (2H, m, Ph*H*), 7.23-7.19 (3H, m, Ph*H*), 6.84 (1H, d, *J* = 8.1, Ar*H*), 6.36 (1H, d, *J* = 2.2, Ar*H*), 6.34 (1H, dd, *J* = 8.1, 2.3, Ar*H*), 3.81 (1H, d, *J* = 13.7, C$H_A$H$_B$N), 3.79 (1H, dd, *J* = 9.8, 2.6, C*H*CH$_2$), 3.78 (3H, s, OC$H_3$), 3.75 (3H, s, OC$H_3$), 3.72-3.69 (1H, br. m, CH$_A$$H_B$N), 3.41 (3H, s, NC$H_3$), 2.14-2.03 (1H, m, C$H_A$H$_B$CH$_3$), 1.93-1.81 (1H, m, CH$_A$$H_B$CH$_3$), 0.99 (3H, t, *J* = 7.4, CH$_2$C$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 172.5 (*C*=O), 164.9 (*C*=O), 161.5 (Ar*C*O), 159.1 (Ar*C*O), 145.1 (Ar*C*N), 131.3 (OMeAr*C*H), 129.8 (2×Ar*C*H), 125.9 (Ar*C*H), 124.7 (2×Ar*C*H), 115.7 (Ar*C*), 103.8 (OMeAr*C*H), 98.6 (OMeAr*C*H), 64.1 (N*C*H), 55.4 (O*C*H$_3$), 55.3 (O*C*H$_3$), 49.4(NCH$_2$), 39.6 (N*C*H$_3$), 22.0 (CH*C*H$_2$), 11.5 (CH$_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2965 (OH broad), 2965, 2837, 2836 (C-H), 1731 (C=O acid), 1649 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 387 ([M+H]$^+$, 100%), (ESI$^-$, MeOH): *m/z* = 385 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{26}N_2O_5Na$ [M+Na]$^+$ 409.1739, found 409.1737.
*NMR file: $^1$H NMR = 2014-04-10-jpc-11 (10), 2013-11-22-jpc-45 (11)*

**Synthesis of hydantoin 615:**

**1-(2,4-Dimethoxybenzyl)-5-ethyl-3-methyl-5-phenylimidazolidine-2,4-dione (±615)**

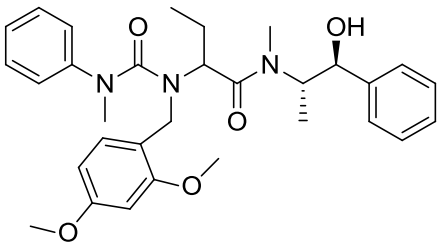


Following a similar procedure to general procedure **6** but the reaction was left overnight, LiCl (33 mg, 0.78 mmol, 3.4 eq.) and THF (1.3 mL) were added to urea acid **614** (89 mg, 0.23 mmol). LDA was prepared with DiPA (0.10 mL, 0.69 mmol), THF (1.0 mL) and *n*BuLi (0.48 mL, 0.69 mmol, 1.43 M in hexanes). Upon addition of LDA the reaction mixture turned yellow and bright orange upon warm up. The reaction was stirred for 21.5 h at room temperature before being quenched with MeOH before acidification. Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (50 mg, 0.14 mmol, 59%). **±615:** $\mathbf{R}_f$ (1:1 Pet.Ether:EtOAc) 0.65;

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **615**

**Synthesis of 616 (from synthesis of 614):**

**2-(1-(2,4-Dimethoxybenzyl)-3-methyl-3-phenylureido)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylbutanamide (616)**



Following general procedure **9**, urea acid **614** (644 mg, 1.67 mmol) was dissolved in DCM (10.0 mL) then HOBt·$H_2O$ (225 mg, 1.67 mmol), EDC·HCl (383 mg, 2.00 mmol) and DiPEA (0.35 mL, 2.00 mmol) were added. Stirred for 20 min at 0 °C and (*S*,*S*)-pseudoephedrine (414 mg, 2.50 mmol) added. The reaction was complete after 69 h at room temperature. Purification by flash column chromatography ($SiO_2$, 6:4-5:5 Pet.Ether:EtOAc) yielded the title compound as a white gum (642 mg, 1.20 mmol, 72%). **616**: $\mathbf{R}_f$ (6:4 Pet.Ether:EtOAc) 0.25;

NMR data is a mixture of diastereomers and rotamers:

Overall: Dia 1, Rot A: Dia 1, Rot B: Dia 2, Rot A: Dia 2, Rot B = 1.0: 0.18: 0.84: 0.45: % 41:7:34:18

Diastereomer 1:

**$^{1}$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.50-7.31 (rot a+b, 4H, m, Ar*H*), 7.29-7.23 (rot a+b, 3H, m, Ar*H*), 7.14-7.03 (rot a, 2H, m, Ar*H*), 7.14-7.03 (rot b, 4H, m, Ar*H*), 6.98-6.93 (rot a, 2H, m, Ar*H*), 6.47-6.39 (rot a+b, 1H, m, Ar*H*), 6.38-6.35 (rot a+b, 1H, m, Ar*H*), 5.61 (rot a, 1H, d, *J* = 8.0, O*H*), 5.17-5.14 (rot b, 1H, br. m, DMBNC*H*$CH_2$), 4.72-4.65 (rot b, 1H, br. m, $CH_3$C*H*CHOH), 4.64-4.59 (2H, m, rot a DMBNC*H*$CH_2$ and rot b CHC*H*OH), 4.57-4.52 (rot a, 2H, m, $CH_3$C*H*CHOH and CHC*H*OH), 4.17 (rot a, 1H, d, *J* = 17.2, NC$H_A$$H_B$), 4.16 (rot b, 1H, d, *J* = 16.6, NC$H_A$$H_B$), 3.91 (rot a 1H, d, *J* = 17.2, NC$H_A$$H_B$), 3.85 (rot b, 1H, d, *J* = 16.7, NC$H_A$$H_B$), 3.79 (rot a+b, 3H, s, $OCH_3$), 3.66 (rot a, 3H, s, $OCH_3$), 3.64 (rot b, 3H, s, $OCH_3$), 3.11 (rot a, 3H, s, NC$H_{3b}$), 3.07 (rot a, 3H, s, NC$H_{3a}$), 2.98 (rot b, 3H, s, NC$H_{3b}$), 2.87 (rot b, 3H, s, NC$H_{3a}$), 1.88-1.67 (2H, m, rot a+b NCHC$H_A$$H_B$ and rot b NCHC$H_A$$H_B$), 1.61-1.53 (rot a, 1H, m, NHCHC$H_A$$H_B$), 1.12 (rot b, 3H, d, *J* = 6.5, C$H_3$CHCHOH), 0.95 (rot a, 3H, d, *J* = 6.1, C$H_3$CHCHOH), 0.78 (rot a, 3H, t, *J* = 7.3, $CHCH_2$C$H_3$), 0.64 (rot b, 3H, t, *J* = 7.2, $CHCH_2$C$H_3$);

Diastereomer 2:

**$^{1}$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.50-7.31 (rot a+b, 4H, m, Ar*H*), 7.29-7.23 (rot a+b, 3H, m, Ar*H*), 7.14-7.03 (rot a+b, 2H, m, Ar*H*), 6.98-6.93 (rot a, 2H, m, Ar*H*), 6.86 (rot b, 2H, d, *J* = 7.6, Ar*H*), 6.47-6.39 (rot a+b, 1H, m, Ar*H*), 6.38-6.35 (rot a+b, 1H, m, Ar*H*), 5.03 (rot a, 1H, dd, *J* = 8.8, 5.8, DMBNC*H*$CH_2$), 4.86-4.84 (rot b, 1H, br. m, DMBNC*H*$CH_2$), 4.76-4.74 (rot b, 1H, br. m, CHC*H*OH),4.72-4.65 (rot a, 1H, br. m, $CH_3$C*H*CHOH), 4.64-4.59 (rot a, m, CHC*H*OH), 4.41 (rot a, 1H, d, *J* = 17.4, NC$H_A$$H_B$), 4.38 (rot b, 1H, br. s, $CH_3$C*H*CHOH), 4.09 (rot b, 1H, d, *J* = 17.2, NC$H_A$$H_B$), 3.91 (rot b, 1H, d, *J* = 17.2, NC$H_A$$H_B$), 3.79 (rot a, 3H, s, $OCH_3$), 3.78 (rot b, 3H, s, $OCH_3$), 3.76 (rot a, 1H, d, *J* = 17.3, NC$H_A$$H_B$), 3.65 (rot b, 3H, s, $OCH_3$), 3.62 (rot a, 3H, s, $OCH_3$), 3.14 (rot b, 3H, s, NC$H_{3a}$), 3.10 (rot a, 3H, s, NC$H_{3b}$), 3.10 (rot b, 3H, s, NC$H_{3b}$), 2.98 (rot a, 3H, s, NC$H_{3a}$), 1.88-1.67 (2H, m, rot a+b NCHC$H_A$$H_B$ and rot a NCHC$H_A$$H_B$), 1.52-1.46 (rot b, 1H, m, NHCHC$H_A$$H_B$), 1.02 (rot b, 3H, d, *J* = 6.9, C$H_3$CHCHOH), 0.97 (rot a, 3H, d, *J* = 6.8, C$H_3$CHCHOH), 0.85 (rot a, 3H, t, *J* = 7.4, $CHCH_2$C$H_3$), 0.78 (rot b, 3H, t, *J* = 7.3, $CHCH_2$C$H_3$);

Not all the rotamers for each carbon were observed and the rotamers could not be assigned:

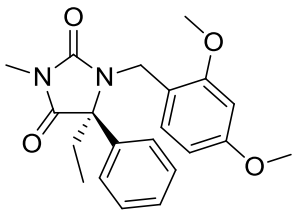
**$^{13}$C {$^{1}$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 173.8 (*C*=$O_a$), 173.2 (*C*=$O_a$), 172.4 (*C*=$O_a$), 163.2 (Ar*C*OMe), 162.8 (Ar*C*OMe), 162.2 (Ar*C*OMe), 159.8 (Ar*C*OMe), 159.7 (Ar*C*OMe), 159.7 (Ar*C*OMe), 157.7 (*C*=$O_b$), 157.7 (*C*=$O_b$), 145.9 (Ar*C*), 145.7 (Ar*C*), 145.2 (Ar*C*), 142.9 (Ar*C*), 142.3 (Ar*C*), 142.0 (Ar*C*), 129.3 (Ar*C*H), 129.3 (Ar*C*H), 129.2 (Ar*C*H), 128.7 (Ar*C*H), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 128.3 (Ar*C*H), 128.1 (Ar*C*H), 127.9 (Ar*C*H), 127.9 (Ar*C*H), 127.8 (Ar*C*H), 127.6 (Ar*C*H). 127.3 (Ar*C*H), 127.2 (Ar*C*H), 127.1 (Ar*C*H), 126.9 (Ar*C*H), 125.1 (Ar*C*H), 125.0 (Ar*C*H), 125.0 (Ar*C*H), 124.5 (Ar*C*H), 124.4 (Ar*C*H), 124.4 (Ar*C*H), 119.5 (Ar*C*), 119.2 (Ar*C*), 119.1 (Ar*C*), 103.7 (Ar*C*H), 103.7 (Ar*C*H), 103.6 (Ar*C*H), 98.2 (Ar*C*H), 98.2

(Ar*C*H), 76.1 (CH*C*HOH), 76.0 (CH*C*HOH), 58.8 ($CH_3$*C*HCHOH), 58.5 ($CH_3$*C*HCHOH) 58.0 (DMBN*C*HCH$_3$), 58.0 (DMBN*C*HCH$_3$), 57.6 (DMBN*C*HCH$_3$), 55.5 (O*C*H$_3$), 55.5 (O*C*H$_3$), 55.4 (DMBN*C*HCH$_3$), 55.2 (O*C*H$_3$), 55.1 (O*C*H$_3$), 55.0 (O*C*H$_3$), 55.0 (O*C*H$_3$), 43.5 (N*C*H$_2$), 42.9 (N*C*H$_2$), 39.9 (N*C*H$_{3a}$), 39.7 (N*C*H$_{3a}$), 39.5 (N*C*H$_{3a}$), 32.1 (N*C*H$_{3b}$), 27.1 (N*C*H$_{3b}$), 24.2 (CH*C*H$_2$CH$_3$), 23.3 (CH*C*H$_2$CH$_3$), 23.2 (CH*C*H$_2$CH$_3$), 16.6 (*C*H$_3$CHCHOH), 14.7 (*C*H$_3$CHCHOH), 14.6 (*C*H$_3$CHCHOH), 11.1 (CHCH$_2$*C*H$_3$), 10.8 (CHCH$_2$*C*H$_3$), 10.5 (CHCH$_2$*C*H$_3$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3393 (OH broad), 2966, 2935, 2876 (C-H), 1615 (C=O amide), 1593 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 556 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{31}H_{39}N_3O_5Na$ [M+Na]$^+$ 556.2782, found 556.2777.
*NMR file: $^1$H NMR = 2014-12-06-jpc-39 (10) 500a, $^{13}$C NMR = 2014-12-06-jpc-39 (11) 500a.*

**Synthesis of hydantoin 615:**

**(*S*)-1-(2,4-Dimethoxybenzyl)-5-ethyl-3-methyl-5-phenylimidazolidine-2,4-dione (615)**



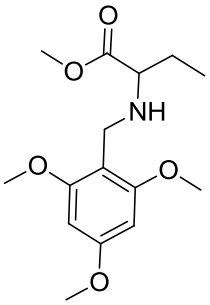
Following a similar method to general procedure **6**, LiCl (84 mg, 1.98 mmol, 10.3 eq.) and THF (1.00 mL) were added to urea pseudo **616** (103 mg, 0.19 mmol). LDA (4.5 eq.) was prepared with DiPA (0.12 mL, 0.87 mmol, 4.5 eq.), THF (0.90 mL) and *n*BuLi (0.61 mL, 0.87 mmol, 1.43 M in hexanes, 4.5 eq.). Upon addition of LDA the reaction mixture turned yellow and upon warm up the reaction turned orange/brown. After 3 h at room temperature the reaction was cooled to –78 °C and quenched with MeOH, stirred for 10 min before warming to room temperature and adding a saturated aqueous $NH_4Cl$ solution. The aqueous was extracted with EtOAc (×3) and the combined organic layer was washed with water (×2), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash column chromatography ($SiO_2$, 4:1 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (23 mg, 0.06 mmol, 32%). **615: R$_f$** (1:1 Pet.Ether:EtOAc) 0.65; $[\alpha]_D^{21}$ = +49.4 (*c* = 0.8 in $CHCl_3$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.29-7.25 (4H, m, Ph*H*), 7.17-7.15 (2H, m, Ph*H* + Ar*H*), 6.38 (1H, dd, *J* = 8.4, 2.4, Ar*H*), 6.21 (1H, d, *J* = 2.4, Ar*H*), 4.55 (1H, d, *J* = 14.9, C*H$_A$*H$_B$NH), 4.18 (1H, d, *J* = 14.9, CH$_A$*H$_B$*NH), 3.76 (3H, s, OC*H$_3$*), 3.56 (3H, s, OC*H$_3$*), 3.10 (3H, s, NC*H$_3$*), 2.40 (1H, dq, *J* = 14.4, 7.2, C*H$_A$*H$_B$CH$_3$), 2.04 (1H, dq, *J* = 14.4, 7.3, CH$_A$*H$_B$*CH$_3$), 0.63 (3H, t, *J* = 7.3, CH$_2$C*H$_3$*); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.9 (*C*=O), 160.7 (Ar*C*OMe), 158.1 (Ar*C*OMe), 157.7 (*C*=O), 136.8 (Ar*C*), 132.3 (Ar*C*H), 128.7 (2×Ar*C*H), 128.5 (Ar*C*H), 126.5 (2×Ar*C*H), 117.6 (Ar*C*), 104.3 (Ar*C*H), 98.0 (Ar*C*H), 71.8 (N*C*C=O), 55.5 (O*C*H$_3$), 54.9 (O*C*H$_3$), 37.8 (N*C*H$_2$), 25.1 (N*C*H$_3$ + *C*H$_2$CH$_3$), 7.6 (CH$_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2926,

2853 (C-H), 1767 (C=O amide), 1703 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 369 ($[M+H]^+$, 100%), 391 ($[M+Na]^+$, 50%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{21}H_{25}N_2O_4$ $[M+H]^+$ 369.1809, found 369.1813; **HPLC**: *er* 7:93, Chiralcel OD-H, Hexane:IPA = 95:5, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 13.1 (minor), 14.3 (major) min.

*NMR file: $^1$H NMR = 2013-10-09-jpc-11 (10), $^{13}$C NMR = 2014-02-14-jpc-38 (11).*

**Synthesis of 2,4,6-TMB 619:**

**Methyl 2-((2,4,6-trimethoxybenzyl)amino)butanoate (619)**

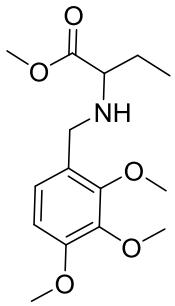


Methyl-DL-α-aminobutyrate hydrochloride (2.00 g, 13.02 mmol, 1.1 eq.) was dissolved in anhydrous MeOH (53.0 mL). To this solution was added 2,4,6-trimethyoxybenzaldehyde (2.32 g, 11.84 mmol, 1.0 eq.) and anhydrous NaOAc (1.94 g, 23.68 mmol, 2.0 eq.). The reaction mixture was stirred for 10 min before sodium triacetoxyborohydride (5.02 g, 23.68 mmol, 2.0 eq.) was added. The reaction was complete after 20 h at room temperature. The solvent was removed *in vacuo* and the residue diluted with DCM (40.0 mL) and quenched with aqueous saturated $NaHCO_3$ (160 mL). The DCM was removed and the aqueous layer was extracted with $Et_2O$ (×2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc + 1% $Et_3N$) yielded the title compound as a pale yellow oil (3.02 g, 10.15 mmol, 86%). **619**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc) 0.18; **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 6.09 (2H, s, Ar*H*), 3.81-3.78 (2H, m, C$H_2$N), 3.80 (9H, s, 3×OC$H_3$), 3.60 (3H, s, O=COC$H_3$), 3.19 (1H, t, *J* = 6.6, C*H*$CH_2CH_3$), 1.69-1.64 (2H, m, C$H_2CH_3$), 0.88 (3H, t, *J* = 7.5, $CH_2CH_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.7 (*C*=O), 160.4 (Ar*C*OMe), 159.4 (2×Ar*C*OMe), 108.5 (Ar*C*), 90.3 (2×Ar*C*H), 61.8 (N*C*H), 55.6 (2×O*C*$H_3$), 55.3 (O*C*$H_3$), 51.3 (O=COC$H_3$), 39.8 (N*C*$H_2$), 26.5 (*C*$H_2CH_3$), 10.0 ($CH_2CH_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3345 (NH), 2941, 2838 (C-H), 1732 (C=O ester); **MS** ($ESI^+$, MeOH): *m/z* = 298 ($[M+H]^+$, 100%), 320 ($[M+Na]^+$, 80%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{15}H_{24}NO_5$ $[M+H]^+$ 298.1649, found 298.1642.

*NMR file: $^1$H NMR = 2013-11-01-jpc-1 (20), $^{13}$C NMR = 2013-11-08-jpc-29 (11).*

**Synthesis of 624:**

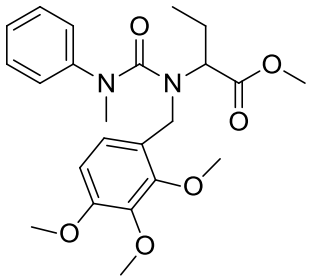
**Methyl 2-((2,3,4-trimethoxybenzyl)amino)butanoate (622)**



Methyl-DL-α-aminobutyrate hydrochloride (1.00 g, 6.51 mmol, 1.0 eq.) was dissolved in anhydrous MeOH (29.0 mL). To this solution was added 2,3,4-trimethyoxybenzaldehyde (1.28 g, 6.51 mmol, 1.0 eq.) and anhydrous NaOAc (1.07 g, 13.02 mmol, 2.0 eq.). The reaction mixture was stirred for 10 min before sodium triacetoxyborohydride (2.76 g, 13.02 mmol, 2.0 eq.) was added. The reaction was complete after 23 h at room temperature. The solvent was removed *in vacuo* and the residue diluted with DCM (20.0 mL) and quenched with aqueous saturated $NaHCO_3$ (80.0 mL). The DCM was removed and the aqueous layer was extracted with $Et_2O$ (×2). The combined organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc + 1% $Et_3N$) yielded the title compound as a colourless oil (1.35 g, 4.54 mmol, 70%). **622**: $\mathbf{R_f}$ (7:3 Pet.Ether:EtOAc + 1% $Et_3N$) 0.23; **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 6.92 (1H, d, *J* = 8.5, Ar*H*), 6.58 (1H, d, *J* = 8.5, Ar*H*), 3.87 (3H, s, OC$H_3$), 3.83 (3H, s, OC$H_3$), 3.80 (3H, s, OC$H_3$), 3.69 (1H, d, *J* = 12.8, C$H_A$H$_B$NH ), 3.66 (3H, s, O=COC$H_3$), 3.57 (1H, d, *J* = 12.8, CH$_A$$H_B$NH), 3.19 (1H, t, *J* = 6.5, C*H*CH$_2$CH$_3$), 2.00 (1H, br. s, N*H*CH), 1.70-1.58 (2H, m, C$H_2$CH$_3$), 0.89 (3H, t, *J* = 7.5, CH$_2$C$H_3$); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 175.6 (*C*=O), 152.9 (Ar*C*OMe), 152.0 (Ar*C*OMe), 142.0 (Ar*C*OMe), 125.6 (Ar*C*H), 124.0 (Ar*C*), 106.8 (Ar*C*H), 62.1 (N*C*H), 60.9 (O*C*H$_3$), 60.6 (O*C*H$_3$), 55.8 (O*C*H$_3$), 51.4 (O=COCH$_3$), 47.0 (N*C*H$_2$), 26.4 (*C*H$_2$CH$_3$), 10.0 (CH$_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3335 (NH), 2937, 2877, 2836 (C-H), 1732 (C=O ester); **MS** (ESI$^+$, MeOH): *m/z* = 298 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{15}H_{23}NO_5Na$ [M+Na]$^+$ 320.1474, found 320.1458.

*NMR file: $^1$H NMR = 2013-10-21-jpc-24 (20), $^{13}$C NMR = 2013-10-21-jpc-24 (21).*

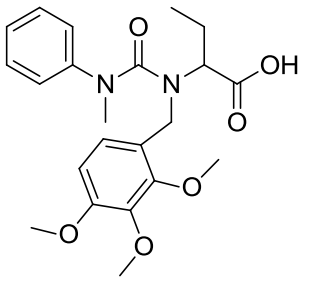
**Methyl 2-(3-methyl-3-phenyl-1-(2,3,4-trimethoxybenzyl)ureido)butanoate (623)**



Following general procedure **1c**, *N*-methyl-*N*-phenyl carbamoyl chloride (449 mg, 2.65 mmol) and DMAP (cat.) were added to a pre-stirred solution of amine **622** (865 mg, 2.91 mmol) and $Et_3N$ (0.48 mL, 3.44 mmol) in DCE (7.0 mL). The reaction was complete after 19 h. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (743 mg, 1.73 mmol, 65%). **623:** $\mathbf{R_f}$ (7:3 Pet.Ether:EtOAc) 0.37; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.32-7.28 (2H, m, Ph*H*), 7.16-7.09 (3H, m, Ph*H*), 6.81 (1H, d, *J* = 8.6, Ar*H*), 6.57 (1H, d, *J* = 8.6, Ar*H*), 4.20 (1H, d, *J* = 16.1, C$H_A$$H_B$N), 4.09 (1H, d, *J* = 16.1, C$H_A$$H_B$N), 4.05 (1H, t, *J* = 7.0, C*H*$CH_2CH_3$), 3.84 (3H, s, OC$H_3$), 3.83 (3H, s, OC$H_3$), 3.78 (3H, s, OC$H_3$), 3.65 (3H, s, OC$H_3$), 3.20 (3H, s, NC$H_3$), 2.03-1.93 (1H, m, C$H_A$$H_B$C$H_3$), 1.65-1.55 (1H, m, C$H_A$$H_B$C$H_3$), 0.79 (3H, t, *J* = 7.4, $CH_2$C$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 172.4 (*C*=O), 161.2 (*C*=O), 152.9 (Ar*C*O), 151.5 (Ar*C*O), 146.4 (Ar*C*O), 141.8 (Ar*C*N), 129.5 (2×Ar*C*H), 125.1 (Ar*C*H), 124.7 (2×Ar*C*H), 123.6 (Ar*C*), 123.2 (OMeAr*C*H), 106.7 (OMeAr*C*H), 61.9 (N*C*H), 60.8 (O$CH_3$), 60.7 (O$CH_3$), 56.0 (O$CH_3$), 51.9 (O$CH_3$), 45.2 (N$CH_2$), 40.2 (N$CH_3$), 23.4 ($CH_2CH_3$), 11.7 ($CH_2CH_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2939, 2877, 2837 (C-H), 1738 (C=O ester), 1650 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 431 ([M+H]$^+$, 100%), 453 ([M+Na]$^+$, 90%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{31}N_2O_6$ [M+H]$^+$ 431.2177, found 431.2178.

*NMR file: $^1$H NMR = 2013-11-22-jpc-46 (10), $^{13}$C NMR = 2013-11-22-jpc-46 (11).*

**2-(3-Methyl-3-phenyl-1-(2,3,4-trimethoxybenzyl)ureido)butanoic acid (624)**



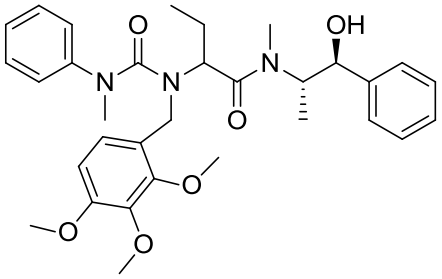
Following a similar method to general procedure **5**, LiOH (597 mg, 24.9 mmol, 16.7 eq.) was added to urea **623** (641mg, 1.49 mmol) in 2:1 THF:$H_2O$ (20.0 mL: 10.0 mL). The reaction was complete after 22 h at 45 °C. The title compound was yielded as a colourless oil without further purification (569 mg, 1.37 mmol, 92%). **624**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc) 0.19; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 12.93 (1H, br. s, O*H*), 7.40-7.37 (2H, m, Ph*H*), 7.23-7.19 (3H, m, Ph*H*), 6.65 (1H, d,

*J* = 8.5, Ar*H*), 6.49 (1H, d, *J* = 8.5, Ar*H*), 3.98-3.95 (1H, br. m, C$H_A$$H_B$N), 3.73-3.67 (2H, br. m, CH$_A$$H_B$N + C*H*CH$_2$CH$_3$), 3.88 (3H, s, OC$H_3$), 3.81 (3H, s, OC$H_3$), 3.79 (3H, s, OC$H_3$), 3.40 (3H, s, NC$H_3$), 2.17-2.06 (1H, m, C$H_A$H$_B$C$H_3$), 1.92-1.81 (1H, m, CH$_A$$H_B$C$H_3$), 0.98 (3H, t, *J* = 7.4, CH$_2$C$H_3$);**$^{13}$C {$^1$H} NMR** (100 MHz, CDCl$_3$): $\delta_C$ = 172.2 (*C*=O), 164.3 (*C*=O), 154.3 (Ar*C*O), 152.3 (Ar*C*O), 144.9 (Ar*C*O), 141.5 (Ar*C*N), 129.8 (2×Ar*C*H), 126.0 (Ar*C*H), 124.7 (Ar*C*H), 124.6 (2×Ar*C*H), 120.4 (Ar*C*), 106.2 (OMeAr*C*H), 64.3 (N*C*H), 60.6 (O*C*H$_3$), 60.5 (O*C*H$_3$), 55.8 (O*C*H$_3$), 49.3 (N*C*H$_2$), 39.7 (N*C*H$_3$), 22.0 (*C*H$_2$CH$_3$), 11.3 (CH$_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2968 (OH broad), 2968, 2837 (C-H), 1737 (C=O ester), 1645 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 417 ([M+H]$^+$, 100%), 439 ([M+Na]$^+$, 20%), (ESI$^-$, MeOH): *m/z* = 415 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{29}N_2O_6$ [M+H]$^+$ 417.2020, found 417.2022.

*NMR file: $^1$H NMR = 2013-11-08-staff-28 (12), $^{13}$C NMR = 2013-11-07-jpc-8 (22).*

**Synthesis of 625 (from synthesis of 624):**

***N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-(3-methyl-3-phenyl-1-(2,3,4-trimethoxybenzyl)ureido)butanamide (625)**




Following a similar procedure to general procedure **9**, urea acid **624** (496 mg, 1.19 mmol) was dissolved in DCM (6.00 mL) then (*S*,*S*)-pseudoephedrine (296 mg, 1.79 mmol), HOBt·H$_2$O (161 mg, 1.19 mmol), EDC·HCl (274 mg, 1.43 mmol) and DiPEA (0.48 mL, 2.74 mmol, 2.3 eq.) were added and stirred for 15 min at 0 °C. The reaction was complete after 17 h at room temperature. Purification by flash column chromatography (SiO$_2$, 1:1 Pet.Ether:EtOAc) yielded the title compound as a white gum (531 mg, 0.942 mmol, 79%). **625**: **R$_f$** (1:1 Pet.Ether:EtOAc) 0.33;

NMR data is a mixture of diastereomers and rotamers:

Overall: Dia 1, Rot A: Dia 1, Rot B: Dia 2, Rot A: Dia 2, Rot B = 1.0: 0.22: 0.75: 0.44: % 42:9:31:18

Diastereomer 1:

**$^1$H NMR** (500 MHz, CDCl$_3$): $\delta_H$ = 7.50-7.49 (rot b, 3H, m, Ar*H*), 7.44-7.39 (rot a, 3H, m, Ar*H*), 7.37-7.26 (rot a+b, 4H, m, Ar*H*), 7.17-7.11 (rot a+b, 2H, m, Ar*H*), 7.07-6.98 (rot a+b, 1H, m, Ar*H*), 6.81-6.75 (rot a+b, 1H, m, Ar*H*), 6.66-6.57 (rot a+b,1H, m, Ar*H*), 5.49 (rot a, 1H, d, *J* = 8.7, O*H*), 5.16-5.09 (rot b, 1H, m, TMBNC*H*CH$_2$), 4.70-4.66 (rot b, 2H, m, CHC*H*OH and CH$_3$C*H*CHOH),

4.68 (rot a, 1H, dd, $J$ = 9.6, 5.1, TMBNC*H*$CH_2$), 4.64-4.58 (rot a, 1H, m, $CH_3$C*H*CHOH), 4.55 (rot a, 1H, t, $J$ = 9.1, CHC*H*OH), 4.34 (rot b, 1H, d, $J$ = 16.7, NC$H_A$$H_B$), 4.27 (rot a, 1H, d, $J$ = 17.4, NC$H_A$$H_B$), 4.03 (rot a, 1H, d, $J$ = 17.3, NC$H_A$$H_B$), 3.91 (rot b, 1H, d, $J$ = 17.7, NC$H_A$$H_B$), 3.85 (rot a, 6H, s, 2×$OCH_3$), 3.84 (rot b, 6H, s, 2×$OCH_3$), 3.75 (rot b, 3H, s, $OCH_3$), 3.72 (rot a, 3H, s, $OCH_3$), 3.14 (rot a, 3H, s, NC$H_{3a}$), 3.07 (rot a, 3H, s, NC$H_{3b}$), 3.01 (rot b, 3H, s, NC$H_{3a}$), 2.87 (rot b, 3H, s, NC$H_{3b}$), 1.91-1.68 (2H, m, rot a+b NCHC$H_A$$H_B$ and rot b NCHC$H_A$$H_B$), 1.60-1.52 (rot a, 1H, m, NHCHC$H_A$$H_B$), 1.12 (rot b, 3H, br. d, $J$ = 5.6, C$H_3$CHCHOH), 1.04-0.94 (rot a, 3H, m, C$H_3$CHCHOH), 0.80-0.75 (rot a, 3H, m, $CHCH_2$C$H_3$), 0.60 (rot b, 3H, t, $J$ = 7.2, $CHCH_2$C$H_3$);

Diasteromer 2:

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.55-7.54 (rot b, 3H, m, Ar*H*), 7.44-7.39 (rot a, 3H, m, Ar*H*), 7.37-7.26 (rot a+b, 4H, m, Ar*H*), 7.17-7.11 (rot a+b, 2H, m, Ar*H*), 7.07-6.98 (rot a+b, 1H, m, Ar*H*), 6.81-6.75 (rot a+b, 1H, m, Ar*H*), 6.66-6.57 (rot a+b, 1H, m, Ar*H*), 5.16-5.09 (rot a, 1H, m, TMBNC*H*$CH_2$), 4.88-4.86 (rot b, 1H, br. m, TMBNC*H*$CH_2$), 4.77-4.72 (rot b, 1H, br. m, CHC*H*OH), 4.64-4.58 (rot a, 2H, m, CHC*H*OH and $CH_3$C*H*CHOH), 4.48 (rot a, 1H, d, $J$ = 17.7, NC$H_A$$H_B$), 4.43 (rot b, 1H, br. s, $CH_3$C*H*CHOH), 4.22 (rot b, 1H, d, $J$ = 17.2, NC$H_A$$H_B$), 4.04 (rot b, 1H, d, $J$ = 17.1, NC$H_A$$H_B$), 3.91 (rot a, 1H, d, $J$ = 17.7, NC$H_A$$H_B$), 3.85 (rot a, 6H, s, 2×$OCH_3$), 3.83 (rot b, 6H, s, 2×$OCH_3$), 3.73 (rot b, 3H, s, $OCH_3$), 3.65 (rot a, 3H, s, $OCH_3$), 3.14 (rot b, 3H, s, NC$H_{3a}$), 3.12 (6H, s, rot b NC$H_{3b}$ and rot a NC$H_{3a}$), 2.99 (rot a, 3H, s, NC$H_{3b}$), 1.91-1.68 (2H, m, rot a+b NCHC$H_A$$H_B$ and rot a NCHC$H_A$$H_B$), 1.50-1.42 (rot b, 1H, m, NHCHC$H_A$$H_B$), 1.04-0.94 (rot a+b, 3H, m, C$H_3$CHCHOH), 0.87 (rot a, 3H, t, $J$ = 7.4, $CHCH_2$C$H_3$), 0.80-0.75 (rot b, 3H, m, $CHCH_2$C$H_3$);

Not all the rotamers for each carbon were observed and the rotamers could not be assigned:

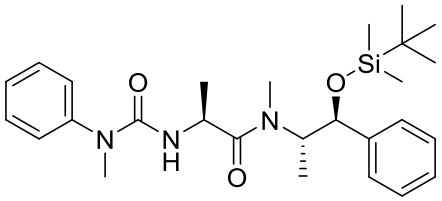
**$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 173.6 (*C*=$O_a$), 172.9 (*C*=$O_a$), 172.3 (*C*=$O_a$), 163.2 (*C*=$O_b$), 162.9 (*C*=$O_b$), 162.3 (*C*=$O_b$), 152.5 (Ar*C*OMe), 152.5 (Ar*C*OMe), 152.3 (Ar*C*OMe), 151.1 (Ar*C*OMe), 151.1 (Ar*C*OMe), 150.9 (Ar*C*OMe), 146.0 (Ar*C*), 145.8 (Ar*C*), 145.1 (Ar*C*), 142.8 (Ar*C*), 142.2 (Ar*C*), 142.0 (Ar*C*), 141.9 (Ar*C*OMe), 141.8 (Ar*C*OMe), 141.6 (Ar*C*OMe) 129.5 (Ar*C*H), 129.5 (Ar*C*H), 129.4 (Ar*C*H), 128.8 (Ar*C*H), 128.7 (Ar*C*H), 128.5 (Ar*C*H), 128.5 (Ar*C*H), 128.4 (Ar*C*H), 127.9 (Ar*C*H), 127.8 (Ar*C*H), 127.3 (Ar*C*H), 127.1 (Ar*C*H). 127.0 (Ar*C*H), 126.8 (Ar*C*H), 125.2 (Ar*C*H), 125.2 (Ar*C*H), 124.9 (Ar*C*), 124.8 (Ar*C*H), 124.6 (Ar*C*), 124.5 (Ar*C*), 124.4 (Ar*C*H), 124.2 (Ar*C*H), 121.8 (Ar*C*H), 121.6 (Ar*C*H), 121.0 (Ar*C*H), 106.9 (Ar*C*H), 106.7 (Ar*C*H), 106.6 (Ar*C*H), 106.4 (Ar*C*H), 76.1 (CH*C*HOH), 76.0 (CH*C*HOH), 75.9 (CH*C*HOH), 75.9 (CH*C*HOH), 60.8 (O*C*$H_3$), 60.8 (O*C*$H_3$), 60.6 (O*C*$H_3$), 60.6 (O*C*$H_3$), 60.6 (O*C*$H_3$), 58.7 ($CH_3$*C*HCHOH), 58.0 (DMBN*C*$HCH_3$) 57.7 (DMBN*C*$HCH_3$), 57.4 ($CH_3$*C*HCHOH), 56.0 (O*C*$H_3$), 56.0 (O*C*$H_3$), 55.5 (DMBN*C*$HCH_3$), 43.5 (N*C*$H_2$), 43.3 (N*C*$H_2$), 42.9 (N*C*$H_2$), 42.1 (N*C*$H_2$), 40.6 (N*C*$H_{3a}$), 40.1 (N*C*$H_{3a}$), 39.9 (N*C*$H_{3a}$), 39.7 (N*C*$H_{3a}$), 31.6 (N*C*$H_{3b}$), 27.6 (N*C*$H_{3b}$),

27.1 (N*C*H$_{3b}$), 24.2 (CH*C*H$_2$CH$_3$), 23.4 (CH*C*H$_2$CH$_3$), 23.3 (CH*C*H$_2$CH$_3$), 23.3 (CH*C*H$_2$CH$_3$), 16.6 (*C*H$_3$CHCHOH), 16.1 (*C*H$_3$CHCHOH), 14.6 (*C*H$_3$CHCHOH), 14.5 (*C*H$_3$CHCHOH), 11.0 (CHCH$_2$*C*H$_3$), 10.8 (CHCH$_2$*C*H$_3$), 10.7 (CHCH$_2$*C*H$_3$), 10.5 (CHCH$_2$*C*H$_3$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3403 (broad NH and OH), 2968, 2936 (C-H), 1627 (C=O amide), 1595 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 564 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{32}H_{41}N_3O_6Na$ [M+Na]$^+$ 586.2893, found 586.2884.
*NMR file: $^1$H NMR = 2014-12-08-jpc-56 (10) 500a, $^{13}$C NMR = 2014-12-08-jpc-56 (11) 500a.*

**Synthesis of 630 (from synthesis of 445):**

**(*S*)-*N*-((1*S*,2*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-1-phenylpropan-2-yl)-*N*-methyl-2-(3-methyl-3-phenylureido)propanamide (630)**




Urea acid **445** (520 mg, 1.41 mmol, 1.0 eq.) was dissolved in DCM (7.00 mL, 0.2 M) and cooled to 0 °C. To this solution was added TBSOTf (0.49 mL, 2.11 mmol, 1.5 eq.) and 2,6-lutidine (0.33 mL, 2.82 mmol, 2.0 eq.) and the resulting mixture stirred for 1 h at 0 °C before warming to room temperature. After 4 h at room temperature the reaction was quenched with a saturated aqueous $NaHCO_3$ solution and stirred for 10 min. The aqueous layer was then extracted with DCM (×3) and the combined organic layer washed with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a pale yellow oil (570 mg, 1.18 mmol, 84%). **630**: **R$_f$** (7:3 Pet.Ether:EtOAc) 0.56; $[\alpha]_D^{20}$ = +75.5 (*c* = 2.2 in $CHCl_3$);

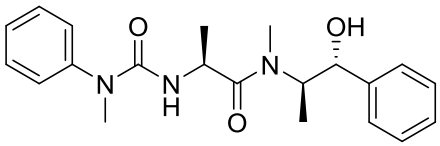
Rotamers in a ratio, Major:Minor, RotA:RotB, 1:0.93, **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.43-7.31 (rot a+b, 4H, m, Ph*H*), 7.29-7.16 (rot a+b, 6H, m, Ph*H*), 5.85 (rot b, 1H, d, *J* = 6.4, N*H*), 5.24 (rot a, 1H, br. d, *J* = 7.1, N*H*), 4.93 (rot a, 1H, quin., *J* = 6.8, NHC*H*CH$_3$), 4.85 (rot b, 1H, br. s, CHC*H*OH), 4.73 (rot b, 1H, br. s, CH$_3$C*H*CHOH), 4.66 (rot b, 1H, quin., *J* = 6.8, NHC*H*CH$_3$), 4.42 (rot a, 1H, d, *J* = 8.3, CHC*H*OH), 3.93 (rot a, 1H, quin., *J* = 7.2, CH$_3$C*H*CHOH), 3.27 (rot b, 3H, s, NC*H*$_3$), 3.22 (rot a, 3H, s, NC*H*$_3$), 2.94 (rot a, 3H, s, NC*H*$_3$), 2.81 (rot b, 3H, s, NC*H*$_3$), 1.24 (rot a, 3H, d, *J* = 6.8, NHCHC*H*$_3$), 1.12 (rot b, 3H, d, *J* = 7.0, C*H*$_3$CHCHOH), 0.96 (rot a, 3H, d, *J* = 6.8, C*H*$_3$CHCHOH), 0.89 (rot a, 9H, s, SiC(C*H*$_3$)$_3$), 0.84 (rot b, 3H, br. d, *J* = 6.2, NHCHC*H*$_3$), 0.79 (rot b, 9H, s, SiC(C*H*$_3$)$_3$), 0.02 (rot a, 3H, s, SiC*H*$_3$), -0.06 (rot b, 3H, s, SiC*H*$_3$), -0.26 (rot a, 3H, s, SiC*H*$_3$), -0.39 (rot b, 3H, s, SiC*H*$_3$);

**$^{13}$C {$^{1}$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.2 (*C*=$O_{maj}$), 173.6 (*C*=$O_{min}$), 156.4 (*C*=$O_{maj}$), 155.9 (*C*=$O_{min}$), 143.6 (Ar*C*$_{min}$), 143.3 (Ar*C*$_{maj}$), 142.1 (Ar*C*$N_{min}$), 141.7 (Ar*C*$N_{maj}$), 130.0 (2×Ar*C*$H_{maj}$), 129.9 (2×Ar*C*$H_{min}$), 128.7 (2×Ar*C*$H_{min}$), 128.2 (Ar*C*$H_{min}$), 128.0 (2×Ar*C*$H_{maj}$), 127.4 (Ar*C*$H_{maj}$), 127.2 (2×Ar*C*$H_{min}$ + Ar*C*$H_{maj}$), 127.1 (2×Ar*C*$H_{maj}$), 127.0 (Ar*C*$H_{min}$), 127.0 (2×Ar*C*$H_{min}$), 126.4 (2×Ar*C*$H_{maj}$), 77.0 (CH*C*HO$H_{min}$), 76.5 (CH*C*HO$H_{maj}$), 58.4 ($CH_3$*C*HCHO$H_{maj+min}$), 47.4 (NH*C*H$CH_{3maj}$), 46.7 (NH*C*H$CH_{3min}$), 37.3 (N*C*$H_{3maj}$), 37.0 (N*C*$H_{3min}$), 27.4 (N*C*$H_{3maj+min}$), 26.0 (SiC(*C*$H_3$)$_{3maj}$), 25.8 (SiC(*C*$H_3$)$_{3min}$), 20.4 (NHCH*C*$H_{3min}$), 19.0 (NHCH*C*$H_{3maj}$), 18.2 (Si*C*$(CH_3)_{3maj}$), 17.9 (Si*C*$(CH_3)_{3min}$), 15.1 (*C*$H_3$CHCHO$H_{min}$), 14.3 (*C*$H_3$CHCHO$H_{maj}$), 4.5 (Si*C*$H_{3maj}$), 4.6 (Si*C*$H_{3min}$), -5.0 (Si*C*$H_{3maj}$), -5.3 (Si*C*$H_{3min}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3402 (NH), 2954, 2929, 2856 (C-H), 1636 (C=O amide), 1596 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 484 ($[M+H]^+$, 100%), 506 ($[M+Na]^+$, 70%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{27}H_{42}N_3O_3Si$ $[M+H]^+$ 484.2990, found 484.2977.
*NMR file: $^{1}$H NMR = 2014-05-06-jpc-42 (10) 400, $^{13}$C NMR = 2014-05-06-jpc-16 (21) 400c.*

**Synthesis of 631 (from synthesis of 445):**

**(*S*)-*N*-((1*R*,2*R*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-(3-methyl-3-phenylureido)propanamide (631)**



Following a similar method to general procedure **9** however (*R*,*R*)-pseudoephedrine was coupled as the chiral auxiliary, urea acid **445** (1.50 g, 6.75 mmol) was dissolved in DCM (35.0 mL) then HOBt·$H_2O$ (912 mg, 6.75 mmol), EDC·HCl (1.55 g, 8.10 mmol) and DiPEA (1.41 mL, 8.10 mmol) were added. Stirred for 20 min at 0 °C and (*R*,*R*)-pseudoephedrine (1.67 g, 10.13 mmol) added. The reaction was complete after 18 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:7-2:8 Pet.Ether:EtOAc) yielded the title compound as a white gum (1.94 g, 5.25 mmol, 78%). **631**: $\mathbf{R_f}$ (3:7 Pet.Ether:EtOAc) 0.13; $[\alpha]_D^{20} = -43.6$ (*c* = 2.6 in $CHCl_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 1:0.33, **$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.46-7.40 (rot a+b, 2H, m, Ph*H*), 7.38-7.26 (rot a+b, 8H, m, Ph*H*), 5.23 (rot b, 1H, br. d, *J* = 8.7, N*H*), 5.20 (rot a, 1H, br. d, *J* = 7.5, N*H*), 4.86 (rot b, 1H, quin., *J* = 6.8, NHC*H*$CH_3$), 4.70 (rot a, 1H, quin., *J* = 6.9, NHC*H*$CH_3$), 4.60 (rot a+b, 1H, br. d, *J* = 7.6, CHC*H*OH), 4.46-4.42 (rot a, 1H, br. m, $CH_3$C*H*CHOH), 4.31 (rot a, 1H, br. s, O*H*), 4.22-4.15 (rot b, 1H, br. m, $CH_3$C*H*CHOH), 3.25 (rot a+b, 3H, s, NC$H_3$), 2.94 (rot a, 3H, s, NC$H_3$), 2.92 (rot b, 3H, s, NC$H_3$), 2.68 (rot b, 1H, br. s, O*H*),

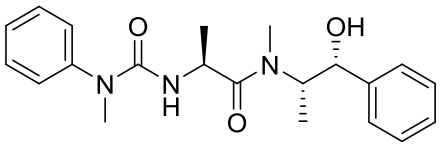
1.34 (rot b, 3H, d, $J$ = 6.8, NHCHC$H_3$), 1.11 (rot a, 3H, d, $J$ = 6.8, NHCHC$H_3$), 1.06 (rot a, 3H, d, $J$ = 6.9, C$H_3$CHCHOH), 1.02 (rot b, 3H, d, $J$ = 6.7, C$H_3$CHCHOH);

**$^{13}$C {$^{1}$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.2 ($C$=O$_{maj}$), 174.3 ($C$=O$_{min}$), 156.8 ($C$=O$_{maj}$), 156.5 ($C$=O$_{min}$), 143.3 (Ar$C_{min}$), 143.1 (Ar$C_{maj}$), 142.0 (Ar$C$N$_{maj}$), 141.4 (Ar$C$N$_{min}$), 130.1 (2×Ar$C$H$_{maj+min}$), 128.9 (2×Ar$C$H$_{min}$), 128.6 (Ar$C$H$_{min}$), 128.4 (2×Ar$C$H$_{maj}$), 127.8 (Ar$C$H$_{maj}$), 127.4 (Ar$C$H$_{maj}$), 127.3 (Ar$C$H$_{min}$), 127.2 (2×Ar$C$H$_{min}$), 127.1 (2×Ar$C$H$_{maj+min}$), 126.7 (2×Ar$C$H$_{maj}$), 75.9 (CH$C$HOH$_{maj}$), 75.5 (CH$C$HOH$_{min}$), 58.7 (CH$_3C$HCHOH$_{min}$), 58.0 (CH$_3C$HCHOH$_{maj}$), 47.3 (NH$C$HCH$_{3maj}$), 46.7 (NH$C$HCH$_{3min}$), 37.3 (N$C$H$_{3min+maj}$), 32.3 (N$C$H$_{3min}$), 27.1 (N$C$H$_{3maj}$), 19.4 (NHCH$C$H$_{3min}$), 18.3 (NHCH$C$H$_{3maj}$), 15.6 ($C$H$_3$CHCHOH$_{min}$), 14.4 ($C$H$_3$CHCHOH$_{maj}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3401 (broad NH + OH), 2980 (C-H), 1624 (C=O amide), 1595 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 370 ([M+H]$^+$, 100%), 408 ([M+K]$^+$, 10%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{28}N_3O_3$ [M+H]$^+$ 370.2125, found 370.2128.
*NMR file: $^{1}$H NMR = 2014-05-02-jpc-9 (10) 400c, $^{13}$C NMR = 2014-05-02-jpc-9 (11) 400c.*

**Synthesis of 633 (from synthesis of 445):**

**(*S*)-*N*-((1*R*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-(3-methyl-3-phenylureido)propanamide (633)**




Following a similar method to general procedure **9** however (1*R*,2*S*)-(-)-ephedrine was coupled as the chiral auxiliary, urea acid **445** (500 mg, 2.25 mmol) was dissolved in DCM (12.0 mL) then HOBt·$H_2O$ (304 mg, 2.25 mmol), EDC·HCl (518 mg, 2.70 mmol) and DiPEA (0.47 mL, 2.70 mmol) were added. Stirred for 15 min at 0 °C and (1*R*,2*S*)-(-)-ephedrine (558 mg, 3.38 mmol) added. The reaction was complete after 16 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:7-2:8 Pet.Ether:EtOAc) yielded the title compound as a white solid (605 mg, 1.64 mmol, 73%). **633**: **R$_f$** (3:7 Pet.Ether:EtOAc) 0.21; **mp**: 152-154 °C; $[\alpha]_D^{20}$ = –29.1 (*c* = 1.8 in $CHCl_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 1:0.25, **$^{1}$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.41-7.32 (rot a+b, 3H, m, Ph$H$), 7.28-7.22 (rot a+b, 7H, m, Ph$H$), 5.27-5.21 (rot a+b, 1H, m, N$H$), 4.85-4.82 (rot b, 1H, br. m, NHC$H$CH$_3$), 4.78-4.75(rot b, 1H, br. m, CHC$H$OH), 4.64-4.60 (rot a, 3H, m, NHC$H$CH$_3$ and CHC$H$OH and CH$_3$C$H$CHOH), 4.08-4.07 (rot b, 1H, br. m, CH$_3$C$H$CHOH), 3.20 (rot a+b, 3H, s, NC$H_3$), 2.76 (rot a, 3H, s, NC$H_3$), 2.63 (rot b, 3H, s, NC$H_3$), 1.28 (rot b, 3H, d, $J$ =

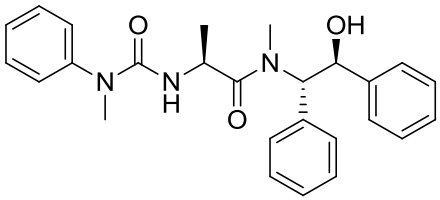
6.7, C*H*$_3$CHCHOH), 1.21-1.20 (rot a, 3H, m, C*H*$_3$CHCHOH), 1.10 (rot b, 3H, d, *J* = 6.7, NHCHC*H*$_3$), 0.85-0.83 (rot a, 3H, m, NHCHC*H*$_3$);

**$^{13}$C {$^{1}$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.3 (*C*=O$_{maj}$), 173.8 (*C*=O$_{min}$), 156.7 (*C*=O$_{min}$), 156.5 (*C*=O$_{maj}$), 143.2 (Ar*C*$_{min}$), 143.1 (Ar*C*$_{maj}$), 141.7 (Ar*C*N$_{maj}$), 141.5 (Ar*C*N$_{min}$), 130.1 (2×Ar*C*H$_{maj}$), 130.0 (2×Ar*C*H$_{min}$), 128.6 (2×Ar*C*H$_{min}$), 128.3 (2×Ar*C*H$_{maj}$), 127.9 (Ar*C*H$_{maj}$), 127.8 (Ar*C*H$_{min}$), 127.3 (Ar*C*H$_{maj}$), 127.2 (Ar*C*H$_{min}$), 127.1 (2×Ar*C*H$_{maj}$), 127.0 (2×Ar*C*H$_{min}$), 126.5 (2×Ar*C*H$_{maj}$), 126.4 (2×Ar*C*H$_{min}$), 77.3 (CH*C*HOH$_{maj}$), 77.0 (CH*C*HOH$_{min}$), 57.6 (CH$_3$*C*HCHOH$_{maj}$), 56.2 (CH$_3$*C*HCHOH$_{min}$), 47.0 (NH*C*HCH$_{3min}$), 46.9 (NH*C*HCH$_{3maj}$), 37.3 (N*C*H$_{3maj}$), 37.2 (N*C*H$_{3min}$), 31.6 (N*C*H$_{3maj}$), 29.1 (N*C*H$_{3min}$), 19.4 (NHCH*C*H$_{3min}$), 18.5 (NHCH*C*H$_{3maj}$), 14.0 (*C*H$_3$CHCHOH$_{maj}$), 12.7 (*C*H$_3$CHCHOH$_{min}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3401 (broad NH + OH), 2980, 2935 (C-H),1624 (C=O amide), 1595 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 370 ([M+H]$^+$, 100%), 392 ([M+Na]$^+$, 100%), 408 ([M+K]$^+$, 50%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{28}N_3O_3$ [M+H]$^+$ 370.2125, found 370.2125.
*NMR file: $^{1}$H NMR = 2015-01-05-jpc-6 (20) 500a, $^{13}$C NMR = 2015-01-05-jpc-6 (21) 500a.*

**Synthesis of 635 (from synthesis of 445):** ((*S*,*S*)-pseudoephenamine synthesised with another member of the group according to Myers procedure[209])

**(*S*)-*N*-((1*S*,2*S*)-2-Hydroxy-1,2-diphenylethyl)-*N*-methyl-2-(3-methyl-3-phenylureido)propanamide (635)**




Following a similar method to general procedure **9** however (*S*,*S*)-pseudoephenamine was coupled as the chiral auxiliary, urea acid **445** (326 mg, 1.47 mmol) was dissolved in DCM (10.0 mL) then HOBt·$H_2O$ (198 mg, 1.47 mmol), EDC·HCl (338 mg, 1.76 mmol) and DiPEA (0.31 mL, 1.76 mmol) were added. Stirred for 15 min at 0 °C and (*S*,*S*)- pseudoephenamine (500 mg, 2.20 mmol) added. The reaction was complete after 16 h at room temperature. Purification by flash column chromatography ($SiO_2$, 1:2 Pet.Ether:EtOAc) yielded the title compound as a white solid (465 mg, 1.08 mmol, 73%). **635**: **R$_f$** (1:2 Pet.Ether:EtOAc) 0.33; **mp**: 82-84 °C; $[\alpha]_D^{21}$ = +103.8 (*c* = 1.4 in $CHCl_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 1:0.64, **$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.44-7.38 (rot a+b, 3H, m, Ph*H*), 7.32-7.12 (rot a+b, 12H, m, Ph*H*), 5.65 (rot a, 1H, br. d, *J* = 7.3,

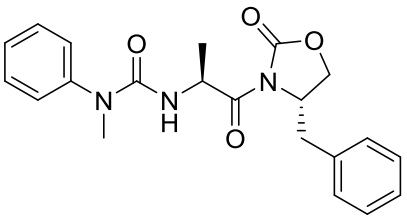
PhC*H*CHOH), 5.55 (rot b, 1H, br. d, *J* = 9.8, PhC*H*CHOH), 5.41 (rot a, 1H, dd, *J* = 6.8, 6.0, PhCHC*H*OH), 5.25 (rot a, 1H, br. d, *J* = 8.8, N*H*), 5.21-5.15 (rot b, 2H, m, PhCHC*H*OH and NHC*H*$CH_3$), 5.08 (rot b, 1H, br. d, *J* = 8.1, O*H*), 4.90 (rot b, 1H, br. d, *J* = 9.6, N*H*), 4.72 (rot a, 1H, quin., *J* = 6.9, NHC*H*$CH_3$), 3.48 (rot a, 1H, br. s, O*H*), 3.25 (rot b, 3H, s, NC$H_3$), 3.23 (rot a, 3H, s, NC$H_3$), 2.96 (rot b, 3H, s, NC$H_3$), 2.94 (rot a, 3H, s, NC$H_3$), 1.22 (rot b, 3H, d, *J* = 6.8, NHCHC$H_3$), 1.06 (rot a, 3H, d, *J* = 6.8, NHCHC$H_3$);

**$^{13}$C {$^{1}$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.0 (*C*=$O_{maj}$), 174.8 (*C*=$O_{min}$), 157.7 (*C*=$O_{min}$), 156.5 (*C*=$O_{maj}$), 143.1 (Ar*C*$_{maj}$), 142.7 (Ar*C*$_{min}$), 142.0 (Ar*C*$N_{min}$), 141.5 (Ar*C*$N_{maj}$), 136.8 (Ar*C*$_{maj}$), 136.5 (Ar*C*$_{min}$), 130.2 (2×Ar*C*$H_{min}$), 130.1 (2×Ar*C*$H_{maj}$), 128.7 (2×Ar*C*$H_{maj}$), 128.6 (3×Ar*C*$H_{maj}$), 128.4 (2×Ar*C*$H_{maj}$), 128.4 (2×Ar*C*$H_{maj}$), 128.1 (Ar*C*$H_{min}$), 127.8 (Ar*C*$H_{maj+min}$), 127.7 (2×Ar*C*$H_{min}$), 127.7 (2×Ar*C*$H_{min}$), 127.4 (2×Ar*C*$H_{min}$), 127.3 (2×Ar*C*$H_{min}$), 127.2 (2×Ar*C*$H_{min}$), 127.1 (2×Ar*C*$H_{maj}$), 126.7 (Ar*C*$H_{maj+min}$), 73.5 (PhCH*C*$HOH_{maj}$), 72.8 (PhCH*C*$HOH_{min}$), 66.2 (Ph*C*$HCHOH_{min}$), 64.6 (Ph*C*$HCHOH_{maj}$), 47.2 (NH*C*$HCH_{3maj}$), 45.8 (NH*C*$HCH_{3min}$), 37.5 (N*C*$H_{3min}$), 37.3 (N*C*$H_{3maj}$), 33.7 (N*C*$H_{3maj}$), 28.6 (N*C*$H_{3min}$), 18.7 (NHCH*C*$H_{3min}$), 18.6 (NHCH*C*$H_{3maj}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3398 (broad NH and OH), 2979, 2933 (C-H), 1629 (C=O amide), 1595 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 432 ($[M+H]^+$, 20%), 454 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{26}H_{29}N_3O_3Na$ $[M+Na]^+$ 454.2101, found 454.2098.
*NMR file: $^{1}$H NMR = 2014-08-06-jpc-53 (10) 400c, $^{13}$C NMR = 2014-08-06-jpc-53 (11) 400c.*

**Synthesis of 639a (from synthesis of 445):**

**3-((*S*)-1-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-1-oxopropan-2-yl)-1-methyl-1-phenylurea (639a)**



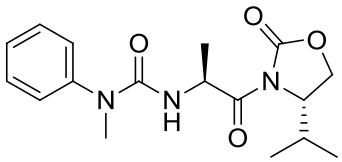
Urea acid **445** (1.00 g, 4.50 mmol, 1.0 eq.) was dissolved in THF (22.0 mL, 0.2 M) and $Et_3N$ (0.75 mL, 5.40 mmol, 1.2 eq.) was added then cooled to –78 °C. Pivaloyl chloride (0.58 mL, 4.73 mmol, 1.05 eq.) was added dropwise over 5 min and stirred at –78 °C for 5 min before warming to room temperature for 3 h (flask a) then cooled back to –78 °C. In a separate flask (flask b) (*S*)-4-benzyl-2-oxazolidinone (957 mg, 5.40 mmol, 1.2 eq.) was dissolved in THF (15.0 mL, 0.3 M) and cooled to –78 °C. To this mixture *n*BuLi (3.46 mL, 4.95 mmol, 1.43 M in hexanes, 1.1 eq.) was added dropwise over 5 min and stirred for 30 min at –78 °C. The solution from flask b was transferred to the main reaction flask (flask a) *via* cannula at –78 °C over 10 min. The reaction mixture was then stirred for 1.5 h at –78 °C before warming to room temperature and stirring for 18 h. The reaction

was quenched with a saturated aqueous $NH_4Cl$ solution and stirred for 15 min before the THF was removed *in vacuo*. The residue was diluted with EtOAc and the aqueous layer extracted with EtOAc (×3). The combined organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography ($SiO_2$, 3:2 Pet.Ether:EtOAc) yielded the title compound as a white gum (1.23 g, 3.22 mmol, 72%). **639a**: **$R_f$** (1:1 Pet.Ether:EtOAc) 0.38; $[\alpha]_D^{20}$ = +99.8 (*c* = 2.1 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.49-7.45 (2H, m, Ph*H*), 7.38-7.26 (8H, m, Ph*H*), 5.54 (1H, quin., *J* = 7.1, NHC*H*$CH_3$), 4.96 (1H, br. d, *J* = 7.8, N*H*), 4.64 (1H, ddt, *J* = 10.2, 6.8, 3.4, NC*H*$CH_2O$), 4.23-4.17 (2H, m, NCHC$H_AH_B$O), 3.37 (1H, dd, *J* = 13.6, 3.2, C$H_A$$H_B$Ph), 3.29 (3H, s, NC$H_3$), 2.83 (1H, dd, *J* =13.5, 9.6, $CH_AH_B$Ph), 1.29 (3H, d, *J* = 7.0, NHCHC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.7 (*C*=O), 156.5 (*C*=O), 152.8 (C=O), 143.2 (Ar*C*N), 135.3 (Ar*C*C), 130.0 (2×Ar*C*H), 129.5 (2×Ar*C*H), 129.0 (2×Ar*C*H), 127.4 (Ar*C*H), 127.3 (Ar*C*H), 127.2 (2×Ar*C*H), 66.4 (NCH*C*$H_2O$), 55.4 (N*C*HCH$_2$O), 49.5 (NH*C*HCH$_3$), 37.6 (*C*$H_2$Ph), 37.3 (N*C*H$_3$), 18.1 (CH*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3429 (NH), 3029, 2929 (C-H), 1776 (C=O carbamate), 1703 (C=O amide), 1657 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 382 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{21}H_{24}N_3O_4$ [M+H]$^+$ 382.1761, found 382.1770.

*NMR file: $^1$H NMR = 2014-05-29-jpc-38 (10) 400c, $^{13}$C NMR = 2014-05-29-jpc-38 (11) 400c.*

**Synthesis of 639b (from synthesis of 445):**

**3-((*S*)-1-((*S*)-4-Isopropyl-2-oxooxazolidin-3-yl)-1-oxopropan-2-yl)-1-methyl-1-phenylurea (639b)**

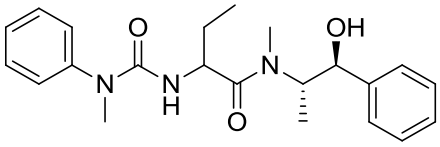


Urea acid **445** (700 mg, 3.15 mmol, 1.0 eq.) was dissolved in THF (16.0 mL, 0.2 M) and $Et_3N$ (0.53 mL, 3.78 mmol, 1.2 eq.) was added then cooled to –78 °C. Pivaloyl chloride (0.41 mL, 3.31 mmol, 1.05 eq.) was added dropwise over 3 min and stirred at –78 °C for 5 min before warming to room temperature for 3 h (flask a) then cooled back to –78 °C. In a separate flask (flask b) (*S*)-(-)-4-*iso*propyl-2-oxazolidinone (488mg, 3.78 mmol, 1.2 eq.) was dissolved in THF (11.0 mL, 0.3 M) and cooled to –78 °C. To this mixture *n*BuLi (2.65 mL, 3.47 mmol, 1.31 M in hexanes, 1.1 eq.) was added dropwise over 5 min and stirred for 30 min at –78 °C. The solution from flask b was transferred to the main reaction flask (flask a) *via* cannula at –78 °C over 45 min and flask b was washed out with THF (4.00 mL). The reaction mixture was then stirred for 1 h at –78 °C before warming to room temperature and stirring for 18 h. The reaction was quenched with a saturated aqueous $NH_4Cl$ solution and stirred for 15 min before the THF was removed *in vacuo*. The resulting mixture was diluted with EtOAc and the aqueous layer extracted with EtOAc (×3). The

combined organic layer was washed with a saturated aqueous $NaHCO_3$ solution and brine then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by two sets of flash column chromatography ($SiO_2$, 3:2 Pet.Ether:EtOAc) yielded the title compound as a pale yellow solid (483 mg, 1.45 mmol, 46%). **639b**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc) 0.51; **mp**: 133-135 °C; $[\alpha]_D^{21}$= +98.5 (*c* = 1.4 in $CHCl_3$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.45-7.42 (2H, m, Ph*H*), 7.32-7.29 (3H, m, Ph*H*), 5.46 (1H, quin., *J* = 7.2, NHC*H*$CH_3$), 4.91 (1H, br. d, *J* = 7.8, N*H*), 4.37 (1H, dt, *J* = 7.3, 3.5, NC*H*$CH_2O$), 4.29-4.22 (2H, m, NCHC*H*$_2$O), 3.25 (3H, s, NC*H*$_3$), 2.46-2.40 (1H, m, NCHC*H*$(CH_3)_2$), 1.26 (3H, d, *J* = 7.0, NHCHC*H*$_3$), 0.93 (3H, d, *J* = 6.9, CH(C*H*$_3$)$_2$), 0.91 (3H, d, *J* = 7.1, CH(C*H*$_3$)$_2$); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.8 (*C*=O), 156.5 (*C*=O), 153.4 (*C*=O), 143.4 (Ar*C*N), 130.1 (2×Ar*C*H), 127.4 (Ar*C*H), 127.3 (2×Ar*C*H), 63.6 (NCH*C*H$_2$O), 58.9 (N*C*HCH$_2$O), 49.6 (NH*C*HCH$_3$), 37.3 (N*C*H$_3$), 28.2 (*C*H$(CH_3)_2$), 18.2 (CH(*C*H$_3$)$_2$), 18.1 (CH*C*H$_3$), 14.5 (CH(*C*H$_3$)$_2$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3429 (NH), 2963, 2877 (C-H), 1778 (C=O carbamate), 1704 (C=O amide), 1661 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 334 ([M+H]$^+$, 30%), 356 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{17}H_{24}N_3O_4$ [M+H]$^+$ 334.1761, found 334.1755.
*NMR file: $^1$H NMR = 2014-06-20-jpc-59 (10) 500a, $^{13}$C NMR = 2014-06-20-jpc-59 (11) 500a.*

**Synthesis of 640 (from synthesis of 458):**

***N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-(3-methyl-3-phenylureido)butanamide (640)**




Following general procedure **9**, urea **458** (1.23 g, 5.21 mmol) was dissolved in DCM (28.0 mL) then HOBt·$H_2O$ (704 mg, 5.21 mmol), EDC·HCl (1.20 g, 6.25 mmol) and DiPEA (1.09 mL, 6.25 mmol) were added. Stirred for 15 min at 0 °C and (*S*,*S*)-pseudoephedrine (1.29 g, 7.82 mmol) added. The reaction was complete after 20 h at room temperature. Purification by flash column chromatography ($SiO_2$, 1:2 Pet.Ether:EtOAc) yielded the title compound as a white gum (1.31 g, 3.42 mmol, 66%). **640**: $\mathbf{R_f}$ (1:2 Pet.Ether:EtOAc) 0.18;

NMR data is a mixture of diastereomers and rotamers:
Overall: Dia 1, Rot A: Dia 1, Rot B: Dia 2, Rot A: Dia 2, Rot B = 1.0: 0.27: 0.82: 0.50: % 39:10:32:19

Diastereomer 1:
**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.45-7.36 (rot a+b, 4H, m, Ph*H*), 7.34-7.24 (rot a+b, 6H, m, Ph*H*), 5.08 (rot b, 1H, br. d, *J* = 8.4, N*H*), 5.02 (rot a, 1H, br. d, *J* = 7.8, N*H*), 4.78-4.73 (rot b, 1H,

m, NHC*H*$CH_2$), 4.64-4.58 (2H, m, rot a NHC*H*$CH_2$ and rot a+b CHC*H*OH), 4.55-4.49 (rot a, 1H, m, $CH_3$C*H*CHOH), 4.26-4.19 (rot b, 1H, m, $CH_3$C*H*CHOH), 3.25 (rot a+b, 3H, s, NC$H_3$), 3.00 (rot a, 3H, s, NC$H_3$), 2.91 (rot b, 3H, s, NC$H_3$), 1.90-1.80 (rot b, 1H, m, NHCHC$H_A$$H_B$), 1.70-1.34 (2H, m, rot a NHCHC$H_A$$H_B$ and rot a+b NHCHC$H_A$$H_B$), 1.06-0.99 (rot a+b, 3H, m, C$H_3$CHCHOH), 0.89-0.80 (rot a+b, 3H, m, CHC$H_2$C$H_3$);

Diastereomer 2:

**$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.51-7.36 (rot a+b, 4H, m, Ph*H*), 7.34-7.24 (rot a+b, 6H, m, Ph*H*), 5.15 (rot b, 1H, br. d, *J* = 8.1, N*H*), 4.98 (rot a, 1H, br. d, *J* = 8.7, N*H*), 4.83 (rot a, 1H, dd, *J* = 15.4, 7.5, NHC*H*$CH_2$), 4.72-4.67 (rot b, 1H, m, NHC*H*$CH_2$), 4.64-4.58 (rot b, 1H, m, CHC*H*OH), 4.55-4.49 (rot b, 1H, m, $CH_3$C*H*CHOH), 4.45 (rot a, 1H, d, *J* = 9.6, CHC*H*OH), 4.42-4.34 (rot a, 1H, m, $CH_3$C*H*CHOH), 3.26 (rot a, 3H, s, NC$H_3$), 3.26 (rot b, 3H, s, NC$H_3$), 2.96 (rot b, 3H, s, NC$H_3$), 2.95 (rot a, 3H, s, NC$H_3$), 1.70-1.34 (rot a+b, 2H, m, NHCHC$H_A$$H_B$ and NHCHC$H_A$$H_B$), 1.06-0.99 (rot a+b, 3H, m, C$H_3$CHCHOH), 0.89-0.80 (rot a+b, 3H, m, CHC$H_2$C$H_3$);

Not all the rotamers for each carbon were observed and the rotamers could not be assigned:

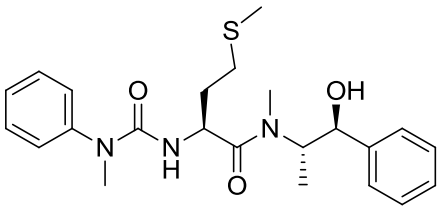
**$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.9 (*C*=$O_a$), 174.4 (*C*=$O_a$), 174.1 (*C*=$O_a$), 173.7 (*C*=$O_a$), 158.0 (*C*=$O_b$), 157.3 (*C*=$O_b$), 157.0 (*C*=$O_b$), 156.9 (*C*=$O_b$), 143.3 (Ar*C*), 143.3 (Ar*C*), 143.2 (Ar*C*), 142.8 (Ar*C*), 142.7 (Ar*C*), 142.1 (Ar*C*), 141.9 (Ar*C*), 141.4 (Ar*C*), 130.2 (Ar*C*H), 130.1 (Ar*C*H), 130.1 (Ar*C*H), 128.9 (Ar*C*H), 128.8 (Ar*C*H), 128.7 (Ar*C*H), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 128.0 (Ar*C*H), 128.0 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 127.5 (Ar*C*H), 127.4 (Ar*C*H), 127.4 (Ar*C*H), 127.2 (Ar*C*H), 127.2 (Ar*C*H), 127.2 (Ar*C*H), 127.2 (Ar*C*H), 127.1 (Ar*C*H), 126.8 (Ar*C*H), 126.6 (Ar*C*H), 76.1 (CH*C*HOH), 75.9 (CH*C*HOH), 75.9 (CH*C*HOH), 75.6 (CH*C*HOH), 58.7 ($CH_3$*C*HCHOH), 58.0 ($CH_3$*C*HCHOH), 52.5 (NH*C*H$CH_2$), 52.3 (NH*C*H$CH_2$), 51.9 (NH*C*H$CH_2$), 51.5 (NH*C*H$CH_2$), 37.6 (N*C*$H_{3a}$), 37.4 (N*C*$H_{3a}$), 37.3 (N*C*$H_{3a}$), 32.1 (N*C*$H_{3b}$), 27.0 (N*C*$H_{3b}$), 26.2 (*C*$H_2$$CH_3$), 26.1 (*C*$H_2$$CH_3$), 26.0 (*C*$H_2$$CH_3$), 25.6 (*C*$H_2$$CH_3$), 16.2 (*C*$H_3$CHCHOH), 15.7 (*C*$H_3$CHCHOH), 14.6 (*C*$H_3$CHCHOH), 14.3 (*C*$H_3$CHCHOH), 10.6 ($CH_2$*C*$H_3$), 10.1 ($CH_2$*C*$H_3$), 9.9 ($CH_2$*C*$H_3$), 9.7($CH_2$*C*$H_3$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3398 (broad NH and OH), 2968, 2934 (C-H), 1629 (C=O amide), 1596 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 384 ([M+H]$^+$, 100%), 406 ([M+Na]$^+$, 20%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{29}N_3O_3Na$ [M+Na]$^+$ 406.2101, found 406.2116.

*NMR file: $^1$H NMR = 2014-03-11-jpc-34 (10) 400c, $^{13}$C NMR = 2014-03-11-jpc-34 (11) 400c.*

**Synthesis of 641 (from synthesis of 461):**

**(*S*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-N-methyl-2-(3-methyl-3-phenylureido)-4-(methylthio)butanamide (641)**



Following general procedure **9**, urea acid **461** (1.33 g, 4.72 mmol) was dissolved in DCM (25.0 mL) then HOBt·$H_2O$ (638 mg, 4.72 mmol), EDC·HCl (1.09 g, 5.66 mmol) and DiPEA (0.99 mL, 5.66 mmol) were added. Stirred for 15 min at 0 °C and (*S*,*S*)-pseudoephedrine (1.17 g, 7.07 mmol) added. The reaction was complete after 19 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:6-3:7 Pet.Ether:EtOAc) yielded the title compound as a white solid (1.47 g, 3.42 mmol, 72%). **641**: $\mathbf{R}_f$ (7:3 Pet.Ether:EtOAc) 0.28; **mp**: 52-54 °C; $[\alpha]_D^{21}$= +63.1 (*c* = 1.4 in $CHCl_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 1.75:1.25, **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.54-7.52 (rot a+b, 1H, m, Ph*H*), 7.47-7.39 (rot a+b, 3H, m, Ph*H*), 7.35-7.27 (rot a+b, 6H, m, Ph*H*), 5.24-5.18 (2H, m, rot b N*H* + rot a NHC*H*$CH_2$), 5.12 (rot a, 1H, br. d, *J* = 8.6, N*H*), 4.89 (rot b, 1H, td, *J* = 8.2, 4.4, NHC*H*$CH_2$), 4.77 (rot a, 1H, d, *J* = 8.4, CHC*H*OH), 4.65-4.60 (rot b, 1H, br. m, $CH_3$C*H*CHOH), 4.48-4.42 (2H, m, rot a $CH_3$C*H*CHOH + rot b CHC*H*OH), 3.27 (rot a, 3H, s, NC*H*$_3$), 3.26 (rot b, 3H, s, NC*H*$_3$), 3.02 (rot b, 3H, s, NC*H*$_3$), 2.94 (rot a, 3H, s, NC*H*$_3$), 2.50-2.37 (rot a+b, 2H, m, $CH_2$C*H*$_2$S), 2.06 (rot b, 3H, s, SC*H*$_3$), 2.03 (rot a, 3H, s, SC*H*$_3$), 1.89-1.80 (rot a, 1H, m, C*H*$_A$$H_B$$CH_2$S), 1.79-1.70 (rot a+b, 1H, m, $CH_A$*H*$_B$$CH_2$S), 1.62-1.53 (rot b, 1H, m, C*H*$_A$$H_B$$CH_2$S), 1.06 (rot b, 3H, d, *J* = 6.6, C*H*$_3$CHCHOH), 1.02 (rot a, 3H, d, *J* = 6.0, C*H*$_3$CHCHOH);

**$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 173.6 (*C*=$O_{maj}$), 173.5 (*C*=$O_{min}$), 157.9 (*C*=$O_{maj}$), 156.9 (*C*=$O_{min}$), 143.0 (Ar*C*$_{min}$), 142.7 (Ar*C*$_{maj}$), 142.3 (Ar*C*$N_{maj}$), 142.0 (Ar*C*$N_{min}$), 130.1 (2×Ar*C*$H_{maj}$), 130.0 (2×Ar*C*$H_{min}$), 128.7 (2×Ar*C*$H_{maj}$), 128.4 (2×Ar*C*$H_{min}$), 128.0 (Ar*C*$H_{maj}$), 127.9 (Ar*C*$H_{min}$), 127.6 (Ar*C*$H_{maj}$), 127.4 (Ar*C*$H_{min}$), 127.2 (2×Ar*C*$H_{maj}$), 127.2 (2×Ar*C*$H_{min}$), 127.1 (2×Ar*C*$H_{maj}$), 126.5 (2×Ar*C*$H_{min}$), 75.8 (CH*C*HO$H_{min+maj}$), 58.4 ($CH_3$*C*HCHO$H_{maj}$), 56.5 ($CH_3$*C*HCHO$H_{min}$), 50.3 (NH*C*H$CH_{2min}$), 49.0 (NH*C*H$CH_{2maj}$), 37.5 (N*C*$H_{3maj}$), 37.3 (N*C*$H_{3min}$), 32.5 (S$CH_2$*C*$H_{2min}$), 32.2 (S$CH_2$*C*$H_{2maj}$), 31.3(N*C*$H_{3min}$), 30.4 (S*C*$H_{2maj}$), 30.1 (S*C*$H_{2min}$), 27.0 (N*C*$H_{3maj}$), 16.2 (*C*$H_3$CHCHO$H_{maj}$), 15.6 (S*C*$H_{3min}$), 15.4 (S*C*$H_{3maj}$), 14.2 (*C*$H_3$CHCHO$H_{min}$);

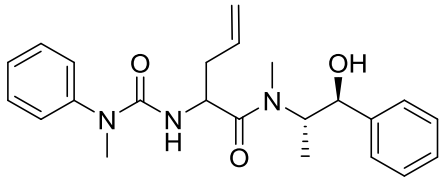
**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3390 (broad NH and OH), 2967, 2916 (C-H), 1632 (C=O amide), 1595 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 430 ([M+H]$^+$, 100%), 452 ([M+Na]$^+$, 50%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{32}N_3O_3S$ [M+H]$^+$ 430.2159, found 430.2161.

*NMR file: $^1$H NMR = 2014-03-14-jpc-50 (10), $^{13}$C NMR = 2014-03-14-jpc-50 (11).*

**Synthesis of 649:**

**(*S*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-(3-methyl-3-phenylureido)pent-4-enamide (648)**

(from urea acid **642** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)**(b)**




Following general procedure **9**, urea acid **642** (1.18 g, 4.75 mmol) was dissolved in DCM (20.0 mL) then HOBt·$H_2O$ (642 mg, 4.75 mmol), EDC·HCl (1.09 g, 5.70 mmol) and DiPEA (0.99 mL, 5.70 mmol) were added. Stirred for 25 min at 0 °C and (*S*,*S*)-pseudoephedrine (1.18 g, 7.13 mmol) added. The reaction was complete after 17 h at room temperature. Purification by flash column chromatography ($SiO_2$, 1:2 Pet.Ether:EtOAc) yielded the title compound as a white gum (1.50 g, 3.79 mmol, 80%). **648**: **$R_f$** (1:2 Pet.Ether:EtOAc) 0.26;

NMR data is a mixture of diastereomers and rotamers:

Overall: Dia 1, Rot a: Dia 1, Rot B: Dia 2, Rot A: Dia 2, Rot B = 1.0: 0.33: 0.88: 0.63: % 35:12:31:22

Diastereomer 1:

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.45-7.25 (rot a+b, 10H, m, Ph*H*), 5.79-5.72 (rot b, 1H, m, $CH_2CH$=$CH_2$), 5.70-5.60 (rot a, 1H, m, $CH_2CH$=$CH_2$), 5.06-4.95 (rot a+b, 3H, m, N*H* and $CH_2CH$=C$H_2$), 4.93-4.89 (rot b, 1H, br. m, NHC*H*$CH_2$), 4.74 (rot a, 1H, dd, *J* = 13.7, 7.1, NHC*H*$CH_2$), 4.65-4.50 (2H, br. m, rot a+b CHC*H*OH and rot a $CH_3$C*H*CHOH), , 4.29-4.24 (rot b, 1H, br. m, $CH_3$C*H*CHOH), 4.13 (rot a, 1H, br. s, O*H*), 3.25 (rot a, 3H, s, NC$H_3$), 3.24 (rot b, 3H, s, NC$H_3$), 3.02 (rot a, 3H, s, NC$H_3$), 2.93 (rot b, 3H, s, NC$H_3$), 2.61 (rot b, 1H, br. s, O*H*), 2.55-2.50 (rot b, 1H, m, NHCHC$H_A$H$_B$), 2.40-2.24 (2H, m, rot a, NHCHC$H_A$H$_B$ and rot b NHCHCH$_A$$H_B$), 1.39-1.32 (rot a, 1H, m, NHCHCH$_A$$H_B$), 1.05 (rot b, 3H, br. d, *J* = 6.0, C$H_3$CHCHOH), 1.01 (rot a, 3H, br. d, *J* = 5.7, C$H_3$CHCHOH);

Diastereomer 2:

**$^{1}$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.51-7.25 (rot a+b, 10H, m, Ph*H*), 5.70-5.60 (rot a+b, 1H, m, $CH_2CH$=$CH_2$), 5.14 (rot b, 1H, br. d, *J* = 8.1, N*H*), 5.06-4.95 (4H, m, rot a N*H* and rot a NHC*H*$CH_2$ and rot a+b $CH_2CH$=C$H_2$), 4.85-4.80 (2H, m, rot b NHC*H*$CH_2$ and rot a O*H*), 4.65-4.50 (rot b, 2H, br. m, CHC*H*OH and $CH_3$C*H*CHOH), 4.48-4.45 (rot a 1H, m, CHC*H*OH), 4.38-4.32 (rot a, 1H, m, $CH_3$C*H*CHOH), 3.42 (rot b, 1H, br. s, O*H*), 3.27 (rot a, 3H, s, NC$H_3$), 3.26 (rot b, 3H, s, NC$H_3$), 2.99 (rot b, 3H, s, NC$H_3$), 2.94 (rot a, 3H, s, NC$H_3$), 2.40-2.24 (2H, m, rot a+b, NHCHC$H_A$$H_B$ and rot a NHCHC$H_A$$H_B$), 1.39-1.32 (rot b, 1H, m, NHCHC$H_A$$H_B$), 1.06 (rot b, 3H, br. d, *J* = 6.8, C$H_3$CHCHOH), 0.99 (rot a, 3H, br. d, *J* = 6.0, C$H_3$CHCHOH);

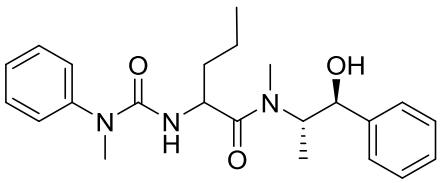
Not all the rotamers for each carbon were observed and the rotamers could not be assigned:

**$^{13}$C {$^{1}$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.1 (*C*=$O_a$), 173.7 (*C*=$O_a$), 173.3 (*C*=$O_a$), 173.0 (*C*=$O_a$), 157.7 (*C*=$O_b$), 157.0 (*C*=$O_b$), 156.7 (*C*=$O_b$), 156.6 (*C*=$O_b$), 143.2 (Ar*C*), 143.1 (Ar*C*), 143.0 (Ar*C*), 142.7 (Ar*C*), 142.5 (Ar*C*), 142.0 (Ar*C*), 141.9 (Ar*C*), 141.5 (Ar*C*), 134.2 ($CH_2$*C*H=$CH_2$), 133.2 ($CH_2$*C*H=$CH_2$), 133.1 ($CH_2$*C*H=$CH_2$), 133.0 ($CH_2$*C*H=$CH_2$), 130.1 (Ar*C*H), 130.1 (Ar*C*H), 130.0 (Ar*C*H), 128.9 (Ar*C*H), 128.8 (Ar*C*H), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 128.5 (Ar*C*H), 128.0 (Ar*C*H), 128.0 (Ar*C*H), 127.9 (Ar*C*H), 127.6 (Ar*C*H), 127.5 (Ar*C*H), 127.4 (Ar*C*H), 127.4 (Ar*C*H), 127.3 (Ar*C*H), 127.2 (Ar*C*H), 127.2 (Ar*C*H), 127.2 (Ar*C*H), 127.1 (Ar*C*H), 127.1 (Ar*C*H), 126.9 (Ar*C*H), 126.6 (Ar*C*H), 118.7 ($CH_2CH$=*C*$H_2$), 118.6 ($CH_2CH$=*C*$H_2$), 118.5 ($CH_2CH$=*C*$H_2$), 118.0 ($CH_2CH$=*C*$H_2$), 76.0 (CH*C*HOH), 75.9 (CH*C*HOH), 75.8 (CH*C*HOH), 75.6 (CH*C*HOH), 58.7 ($CH_3$*C*HCHOH), 58.0 ($CH_3$*C*HCHOH), 50.8 (NH*C*H$CH_2$), 50.7 (NH*C*H$CH_2$), 50.1 (NH*C*H$CH_2$), 49.9 (NH*C*H$CH_2$), 37.5 (N*C*$H_{3a}$), 37.3 (N*C*$H_{3a}$), 37.3 (N*C*$H_{3a}$), 37.2 ($CH$*C*$H_2CH$=$CH_2$), 36.7 ($CH$*C*$H_2CH$=$CH_2$), 31.8 (N*C*$H_{3b}$), 31.6 (N*C*$H_{3b}$), 27.2 (N*C*$H_{3b}$), 27.0 (N*C*$H_{3b}$), 16.2 (*C*$H_3$CHCHOH), 15.7 (*C*$H_3$CHCHOH), 14.6 (*C*$H_3$CHCHOH), 14.3 (*C*$H_3$CHCHOH);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3402 (broad NH and OH), 2978, 2937 (C-H), 1626 (C=O amide), 1595 (C=C) 1494 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 396 ($[M+H]^+$, 100%), ($ESI^-$, MeOH): *m/z* = 394 ($[M–H]^-$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{23}H_{30}N_3O_3$ $[M+H]^+$ 396.2287, found 396.2292.

*NMR file: $^{1}$H NMR = 2014-10-27-jpc-33 (10) 500a, $^{13}$C NMR = 2014-10-27-jpc-33 (11) 500a.*

**(*S*)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-(3-methyl-3-phenylureido)pentanamide (649)**



Urea pseudo **648** (644 mg, 1.62 mmol, 1.0 eq.) was dissolved in MeOH (16.5 mL, 0.1 M) and nitrogen was bubbled through the solution before 10% palladium on carbon (116 mg, 18% by weight) was added and the reaction was placed under an atmosphere of hydrogen through use of a balloon. The reaction was left stirring for 25 h at room temperature before being filtered over celite, washed through with MeOH and DCM and concentrated *in vacuo*. Purification by flash column chromatography ($SiO_2$, 3:7 Pet.Ether:EtOAc) yielded the title compound as a white gum (573 mg, 1.44 mmol, 89%). **649**: $\mathbf{R_f}$ (3:7 Pet.Ether:EtOAc) 0.33;

NMR data is a mixture of diastereomers and rotamers:
Overall: Dia 1, Rot A: Dia 1, Rot B: dia 2, Rot A: Dia 2, Rot B = 1.0: 0.30: 0.90: 0.60: % 36:11:32:21

Diastereomer 1:
**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.47-7.41 (rot a+b, 3H, m, Ph*H*), 7.39-7.25 (rot a+b, 7H, m, Ph*H*), 5.06-5.02 (rot a+b 1H, m, N*H*), 4.83 (rot b, 1H, td, *J* = 8.6, 3.8, NHC*H*$CH_2$), 4.70-4.66 (rot a, 1H, m, NHC*H*$CH_2$), 4.65-4.57 (1H, m, rot a+b CHC*H*OH), 4.52 (rot a, 1H, br. s, $CH_3$C*H*CHOH), 4.41-4.35 (rot b, 1H, m, O*H*), 4.27-4.20 (rot b, 1H, m, $CH_3$C*H*CHOH), 3.67 (rot a, 1H, br. s, O*H*), 3.25 (rot a, 3H, s, NC$H_3$), 3.25 (rot b, 3H, s, NC$H_3$), 3.00 (rot a, 3H, s, NC$H_3$), 2.93 (rot b, 3H, s, NC$H_3$), 1.78-1.72 (rot b, 1H, m, NHCHC$H_A$$H_B$), 1.59-1.41 (2H, m, rot a NHCHC$H_A$$H_B$ and rot b NHCHC$H_A$$H_B$), 1.39-1.32 (rot a, 1H, m, NHCHC$H_A$$H_B$), 1.32-1.21 (rot a+b, 2H, m, $CHCH_2$C$H_2$$CH_3$), 1.09-1.01 (rot a+b, 3H, m, C$H_3$CHCHOH), 0.93 (rot b, 3H, t, *J* = 7.3, $CH_2CH_2$C$H_3$), 0.88 (rot a, 3H, t, *J* = 7.3, $CH_2CH_2$C$H_3$);

Diastereomer 2:
**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.52-7.41 (rot a+b, 3H, m, Ph*H*), 7.39-7.25 (rot a+b, 7H, m, Ph*H*), 5.14 (rot b, 1H, br. d, *J* = 8.3, N*H*), 5.06-5.02 (rot a, 1H, m, N*H*), 4.95-4.91 (rot a, 1H, m, NHC*H*$CH_2$ and O*H*), 4.77-4.73 (rot b, 1H, m, NHC*H*$CH_2$), 4.65-4.57 (rot b, 2H, m, CHC*H*OH and $CH_3$C*H*CHOH), 4.49-4.45 (rot a, 1H, m, CHC*H*OH), 4.41-4.35 (rot a, 1H, m, $CH_3$C*H*CHOH), 3.28 (rot a, 3H, s, NC$H_3$), 3.26 (rot b, 3H, s, NC$H_3$), 3.03 (rot b, 1H, br. s, O*H*), 2.98 (rot b, 3H, s, NC$H_3$), 2.95 (rot a, 3H, s, NC$H_3$), 1.59-1.41 (2H, m, rot a+b NHCHC$H_A$$H_B$ and rot a

NHCHCH$_A$*H$_B$*), 1.39-1.32 (rot b, 1H, m, NHCHCH$_A$*H$_B$*), 1.32-1.21 (rot a+b, 2H, m, CHCH$_2$C*H$_2$*CH$_3$), 1.09-1.01 (rot a+b, 3H, m, C*H$_3$*CHCHOH), 0.88 (rot a+b, 3H, t, *J* = 7.3, CH$_2$CH$_2$C*H$_3$*);

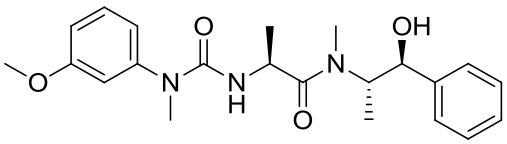
Not all the rotamers for each carbon were observed and the rotamers could not be assigned:
**$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.9 (*C*=O$_a$), 174.5 (*C*=O$_a$), 174.1 (*C*=O$_a$), 173.8 (*C*=O$_a$), 157.9 (*C*=O$_b$), 157.2 (*C*=O$_b$), 156.9 (*C*=O$_b$), 156.8 (*C*=O$_b$), 143.3 (Ar*C*), 143.2 (Ar*C*), 143.1 (Ar*C*), 142.8 (Ar*C*), 142.6 (Ar*C*), 142.1 (Ar*C*), 141.9 (Ar*C*), 141.7 (Ar*C*), 130.1 (Ar*C*H), 130.0 (Ar*C*H), 130.0 (Ar*C*H), 128.7 (Ar*C*H), 128.4 (Ar*C*H), 128.3 (Ar*C*H), 127.9 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 127.5 (Ar*C*H), 127.3 (Ar*C*H), 127.2 (Ar*C*H), 127.1 (Ar*C*H), 127.1 (Ar*C*H), 127.1 (Ar*C*H), 127.0 (Ar*C*H), 126.7 (Ar*C*H), 126.5 (Ar*C*H), 75.9 (CH*C*HOH), 75.8 (CH*C*HOH), 75.7 (CH*C*HOH), 75.5 (CH*C*HOH), 58.6 (CH$_3$*C*HCHOH), 57.9 (CH$_3$*C*HCHOH), 51.0 (NH*C*HCH$_2$), 50.8 (NH*C*HCH$_2$), 50.3 (NH*C*HCH$_2$), 49.9 (NH*C*HCH$_2$), 37.4 (N*C*H$_{3a}$), 37.3 (N*C*H$_{3a}$), 37.3 (N*C*H$_{3a}$), 35.0 (*C*H$_2$CH$_2$CH$_3$), 35.0 (*C*H$_2$CH$_2$CH$_3$), 34.9 (*C*H$_2$CH$_2$CH$_3$), 34.7 (*C*H$_2$CH$_2$CH$_3$), 32.1 (N*C*H$_{3b}$), 31.8 (N*C*H$_{3b}$), 27.2 (N*C*H$_{3b}$), 26.9 (N*C*H$_{3b}$), 19.1 (CH$_2$*C*H$_2$CH$_3$), 18.8 (CH$_2$*C*H$_2$CH), 18.7 (CH$_2$*C*H$_2$CH), 18.6 (CH$_2$*C*H$_2$CH), 16.1 (*C*H$_3$CHCHOH), 15.6 (*C*H$_3$CHCHOH), 14.5 (*C*H$_3$CHCHOH), 14.2 (*C*H$_3$CHCHOH), 13.9 (CH$_2$*C*H$_3$), 13.9 (CH$_2$*C*H$_3$), 13.9 (CH$_2$*C*H$_3$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3397 (broad NH and OH), 2959, 2933, 2872 (C-H), 1626 (C=O amide), 1595 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 398 ([M+H]$^+$, 100%), (ESI$^-$, MeOH): *m/z* = 396 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{32}N_3O_3$ [M+H]$^+$ 398.2444, found 398.2451.
*NMR file: $^1$H NMR = 2015-01-06-jpc-13 (20) 500a, $^{13}$C NMR = 2015-01-06-jpc-13 (21) 500a.*

**Synthesis of 650:**

**(*S*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-2-(3-(3-methoxyphenyl)-3-methylureido)-*N*-methylpropanamide (650)**

(from urea acid **643** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)[(b)]




Following a similar method to general procedure **9**, urea acid **643** (540 mg, 2.14 mmol) was dissolved in DCM (11.0 mL) then HOBt·H$_2$O (289 mg, 2.14 mmol), EDC·HCl (493 mg, 2.57 mmol) and DiPEA (0.45 mL, 2.57 mmol) were added. Stirred for 15 min at 0 °C and (*S*,*S*)-pseudoephedrine (460 mg, 2.78 mmol, 1.3 eq.) added. The reaction was complete after 69 h at room temperature. Purification by flash column chromatography ($SiO_2$, 1:2-1:4 Pet.Ether:EtOAc)

yielded the title compound as a white solid (619 mg, 1.55 mmol, 72%). **650**: $\mathbf{R_f}$ (1:2 Pet.Ether:EtOAc) 0.14; **mp**: 54-56 °C; $[\alpha]_D^{21}$ = +109.0 (*c* = 1.3 in $CHCl_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 1:0.83, **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.49-7.47 (rot a+b, 1H, m, Ar*H*), 7.41-7.38 (rot a+b, 1H, m, Ar*H*), 7.36-7.26 (rot a+b, 4H, m, Ar*H*), 6.92-6.81 (rot a+b, 3H, m, Ar*H*), 5.39 (rot b, 1H, br. d, *J* = 7.7, N*H*), 5.22 (rot a, 1H, br. d, *J* = 7.9, N*H*), 5.01 (rot a, 1H, quin., *J* = 7.0, NHC*H*$CH_3$), 4.75 (rot b, 1H, quin., *J* = 7.0, NHC*H*$CH_3$), 4.63 (rot b, 1H, d, *J* = 7.9, CHC*H*OH), 4.56-4.53 (rot b, 1H, br. m, $CH_3$C*H*CHOH), 4.49 (rot a, 1H, d, *J* = 9.4, CHC*H*OH), 4.27 (rot a, 1H, dq, *J* = 9.3, 6.7, $CH_3$C*H*CHOH), 3.83 (rot a, 3H, s, OC*H*$_3$), 3.83 (rot b, 3H, s, OC*H*$_3$), 3.26 (rot a, 3H, s, NC*H*$_3$), 3.25 (rot b, 3H, s, NC*H*$_3$), 2.95 (rot b, 3H, s, NC*H*$_3$), 2.94 (rot a, 3H, s, NC*H*$_3$), 1.20 (rot a, 3H, d, *J* = 6.9, NHCHC*H*$_3$), 1.17 (rot b, 3H, d, *J* = 6.9, NHCHC*H*$_3$), 1.06 (rot b, 3H, d, *J* = 6.9, C*H*$_3$CHCHOH), 1.01 (rot a, 3H, d, *J* = 6.7, C*H*$_3$CHCHOH);

**$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 175.0 (*C*=O$_{min}$), 174.7 (*C*=O$_{maj}$), 160.9 (Ar*C*OMe$_{maj}$), 160.8 (Ar*C*OMe$_{min}$), 157.6 (*C*=O$_{maj}$), 156.5 (*C*=O$_{min}$), 144.4 (Ar*C*$_{min}$), 144.1 (Ar*C*$_{maj}$), 142.3 (Ar*C*N$_{maj}$), 142.1 (Ar*C*N$_{min}$), 130.8 (Ar*C*H$_{maj}$), 130.7 (Ar*C*H$_{min}$), 128.8 (2×Ar*C*H$_{maj}$), 128.5 (2×Ar*C*H$_{min}$), 128.1 (Ar*C*H$_{maj}$), 128.0 (Ar*C*H$_{min}$), 127.1 (2×Ar*C*H$_{maj}$), 126.5 (2×Ar*C*H$_{min}$), 119.2 (Ar*C*H$_{maj}$), 119.2 (Ar*C*H$_{min}$), 113.4 (Ar*C*H$_{maj}$), 113.0 (Ar*C*H$_{min}$), 112.8 (Ar*C*H$_{min}$), 112.7 (Ar*C*H$_{maj}$), 76.1 (CH*C*HOH$_{min}$), 75.8 (CH*C*HOH$_{maj}$), 58.6 ($CH_3$*C*HCHOH$_{maj}$), 57.4 ($CH_3$*C*HCHOH$_{min}$), 55.5 (O*C*H$_{3maj}$), 55.5 (O*C*H$_{3min}$), 47.3 (NH*C*HCH$_{3min}$), 46.1 (NH*C*HCH$_{3maj}$), 37.4 (N*C*H$_{3maj}$), 37.2 (N*C*H$_{3min}$), 31.9 (N*C*H$_{3min}$), 27.1 (N*C*H$_{3maj}$), 18.8 (NHCH*C*H$_{3min}$), 18.6 (NHCH*C*H$_{3maj}$), 16.1 (*C*H$_3$CHCHOH$_{maj}$), 14.2 (*C*H$_3$CHCHOH$_{min}$);

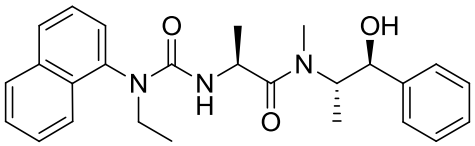
**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3394 (broad NH and OH), 2977, 2936 (C-H), 1628 (C=O amide), 1599 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 400 ([M+H]$^+$, 100%), 422 ([M+Na]$^+$, 50%), (ESI$^-$, MeOH): *m/z* = 398 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{30}N_3O_4$ [M+H]$^+$ 400.2236, found 400.2227.

*NMR file: $^1$H NMR = 2015-01-05-jpc-9 (30) 500a, $^{13}$C NMR = 2015-01-05-jpc-9 (31) 500a, 2D experiments 2014-10-27-jpc-34 (13,14) 500a.*

**Synthesis of 651:**

**(*S*)-2-(3-Ethyl-3-(naphthalen-1-yl)ureido)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropanamide (651)**

(from urea acid **644** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)[(b)]



Following a similar method to general procedure **9**, urea acid **644** (920 mg, 3.22 mmol) was dissolved in DCM (17.0 mL) then HOBt·$H_2O$ (434 mg, 3.22 mmol), EDC·HCl (740 mg, 3.86 mmol) and DiPEA (0.67 mL, 3.86 mmol) were added. Stirred for 15 min at 0 °C and (*S*,*S*)-pseudoephedrine (691 mg, 4.18 mmol, 1.3 eq.) added. The reaction was complete after 63 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:6-3:7 Pet.Ether:EtOAc) yielded the title compound as a white solid (1.15 g, 2.65 mmol, 82%). **651**: $\mathbf{R_f}$ (1:2 Pet.Ether:EtOAc) 0.28; **mp**: 82-84 °C; $[\alpha]_D^{21}$= +78.0 (*c* = 1.4 in $CHCl_3$);

$^1$H NMR in $CDCl_3$ at standard temperature was very complex due to rotamers from the pseudoephedrine and rotamers from the napthyl ring (rotamers in ratio: 1.0:0.6:0.45:0.4). High temperature $^1$H NMR in DMSO-$d_6$ at 392 K resulted in coalescence of rotamers. **$^1$H NMR** (500 MHz, DMSO-$d_6$, 392 K): $\delta_H$ = 8.01-7.98 (1H, m, Ar*H*), 7.95 (1H, d, *J* = 8.3, Ar*H*), 7.84-7.82 (1H, m, Ar*H*), 7.59-7.55 (3H, m, Ar*H*), 7.44 (1H, dd, J = 7.2, 1.1, Ar*H*), 7.38-7.18 (5H, m, Ar*H*), 5.08 (1H, br. s, N*H*), 4.85 (1H, br. s, $CH_3$C*H*CHOH), 4.68 (1H, br. s, NHC*H*$CH_3$), 4.55 (1H, dd, *J* = 7.6, 4.7, CHC*H*OH), 3.83-3.66 (2H, m, NC$H_2$$CH_3$), 2.83 (3H, s, NC$H_3$), 2.80 (1H, br. s, O*H*), 1.08 (3H, t, *J* = 7.1, $NCH_2CH_3$), 0.99 (3H, br. s, NHCHC$H_3$), 0.93 (3H, br. d, *J* = 6.7, $CH_3$CHCHOH);

Not all the carbon signals could be seen at 392 K in DMSO-$d_6$ therefore the carbon in $CDCl_3$ has been assigned for the rotamers that are seen:

**$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 175.0 (*C*=Oa), 174.8 (*C*=Oa), 174.5 (*C*=Oa), 158.0 (*C*=Ob), 156.8 (*C*=Ob), 142.4 (Ar*Ca*), 142.1 (Ar*Ca*), 142.0 (Ar*Ca*), 137.2 (Ar*Cb*), 136.9 (Ar*Cb*), 136.9 (Ar*Cb*), 135.2 (Ar*Cc*), 135.2 (Ar*Cc*), 135.1 (Ar*Cc*), 131.1 (Ar*Cd*), 131.1 (Ar*Cd*), 130.9 (Ar*Cd*), 129.1 (Ar*C*H), 129.0 (Ar*C*H), 128.8 (Ar*C*H), 128.8 (Ar*C*H), 128.7 (Ar*C*H), 128.6 (Ar*C*H), 128.5 (Ar*C*H), 128.1 (Ar*C*H), 128.0 (Ar*C*H), 127.9 (Ar*C*H), 127.7 (Ar*C*H), 127.6 (Ar*C*H), 127.6 (Ar*C*H), 127.4 (Ar*C*H), 127.3 (Ar*C*H), 127.2 (Ar*C*H), 127.2 (Ar*C*H), 127.1 (Ar*C*H), 127.1 (Ar*C*H), 126.8 (Ar*C*H), 126.8 (Ar*C*H), 126.7 (Ar*C*H), 126.6 (Ar*C*H), 126.5 (Ar*C*H), 126.4 (Ar*C*H), 126.2 (Ar*C*H), 125.9 (Ar*C*H), 125.8 (Ar*C*H), 123.3 (Ar*C*H), 123.1 (Ar*C*H), 123.0

(Ar*C*H), 76.1 (CH*C*HOH), 76.1 (CH*C*HOH), 76.0 (CH*C*HOH), 58.7 ($CH_3$*C*HCHOH), 57.6 ($CH_3$*C*HCHOH), 47.3 (NH*C*HCH$_3$), 47.1 (NH*C*HCH$_3$), 46.0 (NH*C*HCH$_3$), 45.9 (NH*C*HCH$_3$), 44.5 (N*C*H$_2$), 44.2 (N*C*H$_2$), 44.2 (N*C*H$_2$), 31.9 (N*C*H$_3$), 27.1 (N*C*H$_3$), 27.1 (N*C*H$_3$), 18.7 (NHCH*C*H$_3$), 18.7 (NHCH*C*H$_3$), 18.5 (NHCH*C*H$_3$), 18.4 (NHCH*C*H$_3$), 16.2 (*C*H$_3$CHCHOH), 14.3 (NCH$_2$*C*H$_3$), 14.2 (NCH$_2$*C*H$_3$), 14.1 (NCH$_2$*C*H$_3$), 14.1 (NCH$_2$*C*H$_3$);

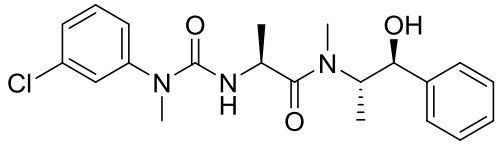
**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3394 (broad NH and OH), 2976, 2932 (C-H), 1622 (C=O amide), 1596 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 434 ([M+H]$^+$, 100%), 456 ([M+Na]$^+$, 40%), (ESI$^-$, MeOH): *m/z* = 432 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{26}H_{32}N_3O_3$ [M+H]$^+$ 434.2444, found 434.2440.

*NMR file:CDCl$_3$: $^1$H NMR = 2015-01-20-jpc-19 (20) 500a, $^{13}$C NMR = 2015-01-20-jpc-19 (21) 500a, DMSO-d$_6$ at 392 K: $^1$H NMR = 2015-01-20-staff-37 (10) 500a, $^{13}$C NMR = 2015-01-20-staff-37 (14) 500a*

**Synthesis of 652:**

**(*S*)-2-(3-(3-Chlorophenyl)-3-methylureido)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylpropanamide (652)**

(from urea acid **645** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)[(b)]




Following a similar method to general procedure **9**, urea acid **645** (1.15 g, 4.48 mmol) was dissolved in DCM (22.0 mL) then HOBt·H$_2$O (636 mg, 4.71 mmol, 1.05 eq.), EDC·HCl (1.03 g, 5.38 mmol) and DiPEA (0.94 mL, 5.38 mmol) were added. Stirred for 15 min at 0 °C and (*S*,*S*)-pseudoephedrine (888 mg, 5.38 mmol, 1.2 eq.) added. The reaction was complete after 17 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:7-2:8 Pet.Ether:EtOAc) yielded the title compound as a white solid (1.36 g, 3.37 mmol, 75%). **652**: **R$_f$** (3:7 Pet.Ether:EtOAc) 0.25; **mp**: 64-66 °C; $[\alpha]_D^{21}$ = +112.6 (*c* = 1.1 in $CHCl_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 1:0.97, **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.47-7.45 (rot a+b, 1H, m, Ar*H*), 7.41-7.18 (rot a+b, 8H, m, Ar*H*), 5.37 (rot b, 1H, br. d, *J* = 7.6, N*H*), 5.20 (rot a, 1H, br. d, *J* = 7.7, N*H*), 5.00 (rot a, 1H, quin., *J* = 7.0, NHC*H*CH$_3$), 4.73 (rot b, 1H, quin., *J* = 6.9, NHC*H*CH$_3$), 4.64-4.57 (2H, m, rot b CHC*H*OH and rot a O*H*), 4.52-4.48 (rot b, 1H, m, CH$_3$C*H*CHOH), 4.39 (rot a, 1H, d, *J* = 6.8, CHC*H*OH), 4.21 (rot a, 1H, dq, *J* = 9.2, 6.8,

$CH_3CHCHOH$), 3.35 (rot b, 1H, br. s, O*H*), 3.25 (rot a, 3H, s, NC$H_3$), 3.24 (rot b, 3H, s, NC$H_3$), 2.94 (rot b, 3H, s, NC$H_3$), 2.93 (rot a, 3H, s, NC$H_3$), 1.22 (rot a, 3H, d, *J* = 6.9, NHCHC$H_3$), 1.17 (rot b, 3H, d, *J* = 6.8, NHCHC$H_3$), 1.06 (rot b, 3H, d, *J* = 6.6, C$H_3$CHCHOH), 1.01 (rot a, 3H, d, *J* = 6.7, C$H_3$CHCHOH);

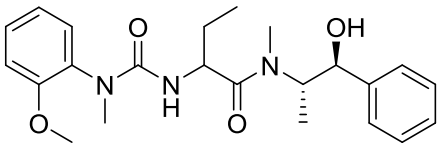
**$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.7 (*C*=$O_{min}$), 174.5 (*C*=$O_{maj}$), 157.1 (*C*=$O_{maj}$), 156.1 (*C*=$O_{min}$), 144.5 (Ar*C*$_{min}$), 144.2 (Ar*C*$_{maj}$), 142.1 (Ar*C*$N_{maj}$), 142.0 (Ar*C*$N_{min}$), 135.4 (Ar*C*$Cl_{min}$), 135.3 (Ar*C*$Cl_{maj}$), 131.0 (Ar*C*$H_{min}$), 130.9 (Ar*C*$H_{maj}$), 128.8 (2×Ar*C*$H_{maj}$), 128.6 (2×Ar*C*$H_{min}$), 128.2 (Ar*C*$H_{maj}$), 128.0 (Ar*C*$H_{min}$), 127.6 (Ar*C*$H_{maj}$), 127.4 (Ar*C*$H_{min}$), 127.3 (Ar*C*$H_{maj}$), 127.3 (Ar*C*$H_{min}$), 127.1 (2×Ar*C*$H_{maj}$), 126.5 (2×Ar*C*$H_{min}$), 125.4 (Ar*C*$H_{maj}$), 125.3 (Ar*C*$H_{min}$), 76.0 (CH*C*$HOH_{min}$), 75.7 (CH*C*$HOH_{maj}$), 58.6 ($CH_3$*C*$HCHOH_{maj+min}$), 47.4 (NH*C*$HCH_{3maj}$), 46.4 (NH*C*$HCH_{3min}$), 37.4 (N*C*$H_{3min}$), 37.2 (N*C*$H_{3maj}$), 31.6 (N*C*$H_{3min}$), 27.1 (N*C*$H_{3maj}$), 18.8 (NHCH*C*$H_{3maj}$), 18.7 (NHCH*C*$H_{3min}$), 16.0 (*C*$H_3$CHCH$OH_{maj}$), 14.2 (*C*$H_3$CHCH$OH_{min}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3392 (broad NH and OH), 3029, 2979, 2934 (C-H), 1627 (C=O amide), 1591 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 404 ($[M+H]^+$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{21}H_{26}N_3O_3{}^{35}ClNa$ $[M+Na]^+$ 426.1560, found 426.1552.
*NMR file: $^1$H NMR = 2014-12-11-jpc-55 (10) 400a, $^{13}$C NMR = 2014-12-11-jpc-55 (11) 400a.*

**Synthesis of 653:**

**(*S*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-2-(3-(2-methoxyphenyl)-3-methylureido)-*N*-methylbutanamide (653)**

(from urea acid **488** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)[(b)]




Following general procedure **9**, urea acid **488** (893 mg, 3.35 mmol) was dissolved in DCM (22.0 mL) then HOBt·$H_2O$ (453 mg, 3.35 mmol), EDC·HCl (771 mg, 4.02 mmol) and DiPEA (0.70 mL, 4.02 mmol) were added. Stirred for 20 min at 0 °C and (*S*,*S*)-pseudoephedrine (831 mg, 5.03 mmol) added. The reaction was complete after 17 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:6-3:7 Pet.Ether:EtOAc) yielded the title compound as a white solid (1.10 g, 2.66 mmol, 79%). **653**: $\mathbf{R}_f$ (1:2 Pet.Ether:EtOAc) 0.19; **mp**: 59-61 °C;

NMR data is a mixture of diastereomers and rotamers:

Overall: Dia 1, Rot A: Dia 1, Rot B: Dia 2, Rot A: Dia 2, Rot B = 1.0: 0.30: 0.75: 0.53: % 39:12:29:20

Diastereomer 1:

**$^{1}$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.42-7.22 (rot a+b, 7H, m, Ar*H*), 7.02-6.97 (rot a+b, 2H, m, Ar*H*), 4.94-4.89 (rot a+b, 1H, m, N*H*), 4.76-4.69 (rot b, 1H, m, NHC*H*$CH_2$), 4.65 (rot a, 1H, dd, *J* = 13.7, 7.5, NHC*H*$CH_2$), 4.62-4.59 (rot a+b, 1H, m, CHC*H*OH), 4.56-4.40 (rot a, 1H, m, $CH_3$C*H*CHOH), 4.32-4.24 (rot b, 1H, m, $CH_3$C*H*CHOH), 3.85 (rot a, 3H, s, OC$H_3$), 3.81 (rot b, 3H, s, OC$H_3$), 3.16 (rot a, 3H, s, NC$H_3$), 3.15 (rot b, 3H, s, NC$H_3$), 2.97 (rot a, 3H, s, NC$H_3$), 2.90 (rot b, 3H, s, NC$H_3$), 1.81-1.73 (rot b, 1H, m, NHCHC$H_A$$H_B$), 1.67-1.44 (2H, m, rot a NHCHC$H_A$$H_B$ and rot b NHCHC$H_A$$H_B$), 1.41-1.32 (rot a, 1H, m, NHCHC$H_A$$H_B$), 1.07-0.99 (rot a+b, 3H, m, C$H_3$CHCHOH), 0.85-0.80 (rot a+b, 3H, m, CHC$H_2$C$H_3$);

**$^{1}$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.54-7.22 (rot a+b, 7H, m, Ar*H*), 7.02-6.97 (rot a+b, 2H, m, Ar*H*), 5.03 (rot b, 1H, br. d, *J* = 8.2, N*H*), 4.94-4.89 (rot a, 1H, m, N*H*), 4.89-4.83 (rot a, 1H, m, NHC*H*$CH_2$), 4.76-4.69 (rot b, 1H, m, NHC*H*$CH_2$), 4.62-4.59 (rot b, 1H, m, CHC*H*OH), 4.56-4.40 (2H, m, rot a+b $CH_3$C*H*CHOH and rot a CHC*H*OH), 3.84 (rot a, 3H, s, OC$H_3$), 3.83 (rot b, 3H, s, OC$H_3$), 3.17 (rot a, 3H, s, NC$H_3$), 3.17 (rot b, 3H, s, NC$H_3$), 2.94 (rot a+b, 3H, s, NC$H_3$), 1.67-1.44 (2H, m, rot a+b NHCHC$H_A$$H_B$ and rot a NHCHC$H_A$$H_B$), 1.41-1.32 (rot b, 1H, m, NHCHC$H_A$$H_B$), 1.07-0.99 (rot a+b, 3H, m, C$H_3$CHCHOH), 0.85-0.80 (rot a+b, 3H, m, CHC$H_2$C$H_3$);

Not all the rotamers for each carbon were observed and the rotamers could not be assigned:

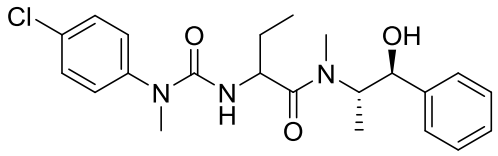
**$^{13}$C {$^{1}$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.9 (*C*=$O_a$), 174.3 (*C*=$O_a$), 173.9 (*C*=$O_a$), 173.5 (*C*=$O_a$), 158.4 (*C*=$O_b$), 157.6 (*C*=$O_b$), 157.3 (*C*=$O_b$), 157.2 (*C*=$O_b$), 155.8 (Ar*C*OMe), 155.7 (Ar*C*OMe), 155.6 (Ar*C*OMe), 142.7 (Ar*C*), 142.2 (Ar*C*), 142.0 (Ar*C*), 141.7 (Ar*C*), 131.1 (Ar*C*), 131.1 (Ar*C*), 131.0 (Ar*C*), 130.7 (Ar*C*), 129.9 (Ar*C*H), 129.8 (Ar*C*H), 129.8 (Ar*C*H), 129.7 (Ar*C*H), 129.6 (Ar*C*H), 129.5 (Ar*C*H), 129.4 (Ar*C*H), 128.7 (Ar*C*H), 128.7 (Ar*C*H), 128.4 (Ar*C*H), 128.3 (Ar*C*H), 127.9 (Ar*C*H), 127.8 (Ar*C*H), 127.7 (Ar*C*H), 127.1 (Ar*C*H), 127.1 (Ar*C*H), 126.6 (Ar*C*H), 126.5 (Ar*C*H), 121.5 (Ar*C*H), 121.4 (Ar*C*H), 112.5 (Ar*C*H), 76.0 (CH*C*HOH), 75.8 (CH*C*HOH), 75.8 (CH*C*HOH), 75.6 (CH*C*HOH), 58.5 ($CH_3$*C*HCHOH), 57.6 ($CH_3$*C*HCHOH), 55.6 (O*C*$H_3$), 55.6 (O*C*$H_3$), 55.5 (O*C*$H_3$), 55.5 (O*C*$H_3$), 52.2 (NH*C*HC$H_2$), 51.9 (NH*C*HC$H_2$), 51.5 (NH*C*HC$H_2$), 51.2 (NH*C*HC$H_2$), 36.3 (N*C*$H_{3a}$), 36.2 (N*C*$H_{3a}$), 36.1 (N*C*$H_{3a}$), 32.1 (N*C*$H_{3b}$), 27.2 (N*C*$H_{3b}$), 26.8 (N*C*$H_{3b}$), 26.2 (*C*$H_2$$CH_3$), 26.1 (*C*$H_2$$CH_3$), 26.0 (*C*$H_2$$CH_3$), 25.8 (*C*$H_2$$CH_3$), 16.1 (*C*$H_3$CHCHOH), 15.6 (*C*$H_3$CHCHOH), 14.5 (*C*$H_3$CHCHOH), 14.2 (*C*$H_3$CHCHOH), 10.3 ($CH_2$*C*$H_3$), 9.8 ($CH_2$*C*$H_3$), 9.6 ($CH_2$*C*$H_3$), 9.4 ($CH_2$*C*$H_3$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3396 (broad NH and OH), 2967, 2934, 2875 (C-H), 1626 (C=O amide), 1598 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 414 ([M+H]$^+$, 100%), (ESI$^-$, MeOH): *m/z* = 412 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{32}N_3O_4$ [M+H]$^+$ 414.2393, found 414.2400.
*NMR file: $^1$H NMR = 2015-01-06-jpc-12 (10) 500a, $^{13}$C NMR = 2015-01-06-jpc-12 (21) 500a.*

**Synthesis of 654:**

**(*S*)-2-(3-(4-Chlorophenyl)-3-methylureido)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methylbutanamide (654)**

(from urea acid **646** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)[(b)]




Following a similar method to general procedure **9**, urea acid **646** (1.02 g, 3.77 mmol) was dissolved in DCM (20.0 mL) then HOBt·$H_2O$ (509 mg, 3.77 mmol), EDC·HCl (867 mg, 4.52 mmol) and DiPEA (0.79 mL, 4.52 mmol) were added. Stirred for 40 min at 0 °C and (*S*,*S*)-pseudoephedrine (684 mg, 4.14 mmol, 1.1 eq.) added. The reaction was complete after 17 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:6-3:7 Pet.Ether:EtOAc) yielded the title compound as a white solid (1.10 g, 2.63 mmol, 70%). **654**: **$R_f$** (1:2 Pet.Ether:EtOAc) 0.18; **mp**: 60-62 °C;

NMR data is a mixture of diastereomers and rotamers:
Overall: Dia 1, Rot A: Dia 1, Rot B: Dia 2, Rot A: Dia 2, Rot B = 1.0: 0.29: 0.91: 0.66: % 35:10:32:23

Diastereomer 1:

**$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.33-7.24 (rot a+b, 6H, m, Ar*H*), 7.20-7.14 (rot a+b, 3H, m, Ar*H*), 5.05 (rot b, 1H, br. d, *J* = 8.0, N*H*), 4.98 (rot a, 1H, br. d, *J* = 7.8, N*H*), 4.69-4.59 (1H, m, rot b NHC*H*$CH_2$), 4.57-4.41 (3H, m, rot a NHC*H*$CH_2$ and rot a+b CHC*H*OH and rot a $CH_3$C*H*CHOH), 4.12-4.06 (rot b, 2H, m, $CH_3$C*H*CHOH and O*H*), 3.33 (rot a,1H, br. s, O*H*), 3.14 (rot a+b, 3H, s, NC*H*$_3$), 2.92 (rot a, 3H, s, NC*H*$_3$), 2.84 (rot b, 3H, s, NC*H*$_3$), 1.59-1.41 (rot b, 2H, m, NHCHC*H*$_2$), 1.36-1.27 (rot a, 2H, m, NHCHC*H*$_2$), 0.98-0.92 (rot a+b, 3H, m, C*H*$_3$CHCHOH), 0.82-0.73 (rot a+b, 3H, m, $CHCH_2$C*H*$_3$);

Diastereomer 2:

**$^{1}$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.41-7.24 (rot a+b, 6H, m, Ar*H*), 7.20-7.14 (rot a+b, 3H, m, Ar*H*), 5.10 (rot b, 1H, br. d, *J* = 8.0, N*H*), 4.95 (rot a, 1H, br. d, *J* = 8.3, N*H*), 4.76 (rot a, 1H, dd, *J* = 15.1, 7.3, NHC*H*$CH_2$), 4.69-4.59 (2H, m, rot b NHC*H*$CH_2$ and rot a O*H*), 4.57-4.41 (rot b, 2H, m, CHC*H*OH and $CH_3$C*H*CHOH), 4.38-4.37 (rot a, 1H, br. m, CHC*H*OH), 4.28-4.22 (rot a, 1H, m, $CH_3$C*H*CHOH), 3.16 (rot a, 3H, s, NC$H_3$), 3.15 (rot b, 3H, s, NC$H_3$), 2.89 (rot b, 3H, s, NC$H_3$), 2.86 (rot a, 3H, s, NC$H_3$), 2.68 (rot b,1H, br. s, O*H*), 1.59-1.41 (rot a+b, 2H, m, NHCHC$H_2$), 0.98-0.92 (rot a+b, 3H, m, C$H_3$CHCHOH), 0.82-0.73 (rot a+b, 3H, m, $CHCH_2$C$H_3$);

Not all the rotamers for each carbon were observed and the rotamers could not be assigned:

**$^{13}$C {$^{1}$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.7 (*C*=$O_a$), 174.1 (*C*=$O_a$), 173.9 (*C*=$O_a$), 173.5 (*C*=$O_a$), 157.7 (*C*=$O_b$), 157.0 (*C*=$O_b$), 156.7 (*C*=$O_b$), 156.7 (*C*=$O_b$), 143.4 (Ar*C*), 142.0 (Ar*C*), 141.9 (Ar*C*), 141.9 (Ar*C*), 141.8 (Ar*C*), 141.8 (Ar*C*), 141.5 (Ar*C*), 141.4 (Ar*C*), 133.2 (Ar*C*Cl), 132.9 (Ar*C*Cl), 132.9 (Ar*C*Cl), 132.8 (Ar*C*Cl), 130.3 (Ar*C*H), 130.2 (Ar*C*H), 130.2 (Ar*C*H), 128.9 (Ar*C*H), 128.8 (Ar*C*H), 128.5 (Ar*C*H), 128.5 (Ar*C*H), 128.4 (Ar*C*H), 128.4 (Ar*C*H), 128.0 (Ar*C*H), 128.0 (Ar*C*H), 127.8 (Ar*C*H), 127.1 (Ar*C*H), 127.1 (Ar*C*H), 126.8 (Ar*C*H), 126.6 (Ar*C*H), 76.0 (CH*C*HOH), 75.8 (CH*C*HOH), 75.8 (CH*C*HOH), 75.5 (CH*C*HOH), 58.7 ($CH_3$*C*HCHOH), 58.1 ($CH_3$*C*HCHOH), 57.2 ($CH_3$*C*HCHOH), 52.5 (NH*C*H$CH_2$), 52.3 (NH*C*H$CH_2$), 52.0 (NH*C*H$CH_2$), 51.7 (NH*C*H$CH_2$), 37.5 (N*C*$H_{3a}$), 37.3 (N*C*$H_{3a}$), 37.3 (N*C*$H_{3a}$), 37.3 (N*C*$H_{3a}$), 31.8 (N*C*$H_{3b}$), 27.0 (N*C*$H_{3b}$), 26.1 (*C*$H_2CH_3$), 26.1 (*C*$H_2CH_3$), 25.8 (*C*$H_2CH_3$), 25.6 (*C*$H_2CH_3$), 16.1 (*C*$H_3$CHCHOH), 15.7 (*C*$H_3$CHCHOH), 14.6 (*C*$H_3$CHCHOH), 14.3 (*C*$H_3$CHCHOH), 10.4 ($CH_2$*C*$H_3$), 10.0 ($CH_2$*C*$H_3$), 9.8 ($CH_2$*C*$H_3$), 9.7($CH_2$*C*$H_3$);

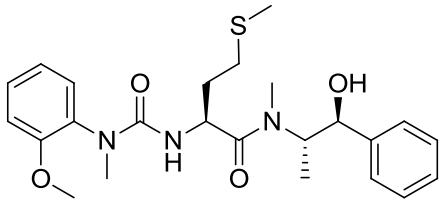
**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3391 (broad NH and OH), 2968, 2934 (C-H), 1626 (C=O amide), 1593 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 418 ([M+H]$^+$, 100%), 440 ([M+Na]$^+$, 30%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{22}H_{28}N_3O_3{}^{35}ClNa$ [M+Na]$^+$ 440.1717, found 440.1712.

*NMR file: $^{1}$H NMR = 2015-01-05-jpc-12 (20) 500a, $^{13}$C NMR = 2015-01-05-jpc-12 (21) 500a, other spectra 2014-09-25-jpc-13 (13,14) 400c*

**Synthesis of 655:**

**(*S*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-2-(3-(2-methoxyphenyl)-3-methylureido)-*N*-methyl-4-(methylthio)butanamide (655)**

(from urea acid **489** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)[(b)]



Following general procedure **9**, urea acid **489** (722 mg, 2.31 mmol) was dissolved in DCM (15.0 mL) then HOBt·$H_2O$ (312 mg, 2.31 mmol), EDC·HCl (532 mg, 2.77 mmol) and DiPEA (0.48 mL, 2.77 mmol) were added. Stirred for 20 min at 0 °C and (*S*,*S*)-pseudoephedrine (573 mg, 3.47 mmol) added. The reaction was complete after 65 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:6-3:7 Pet.Ether:EtOAc) yielded the title compound as a white gum (805 mg, 1.75 mmol, 76%). **655**: $\mathbf{R}_f$ (1:2 Pet.Ether:EtOAc) 0.34; $[\alpha]_D^{21}$= +49.1 (*c* = 1.1 in $CHCl_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 1.0:0.71, **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.53-7.52 (rot a+b, 1H, m, Ar*H*), 7.40-7.37 (rot a+b, 1H, m, Ar*H*), 7.33-7.21 (rot a+b, 5H, m, Ar*H*), 7.00-6.97 (rot a+b, 2H, m, Ar*H*), 5.18 (rot a, 1H, dd, *J* = 14.8, 7.9, NHC*H*$CH_2$), 5.05 (rot b, 1H, br. d, *J* = 8.2, N*H*), 4.96 (rot a, 1H, br. d, *J* = 8.6, N*H*), 4.90-4.86 (rot b, 1H, m, NHC*H*$CH_2$), 4.59 (rot b, 1H, d, *J* = 7.7, CHC*H*OH), 4.55 (rot b, 1H, br. s, $CH_3$C*H*CHOH), 4.51-4.45 (rot a, 1H, m, $CH_3$C*H*CHOH), 4.41 (rot a, 1H, d, *J* = 9.6, CHC*H*OH), 3.83 (rot a, 3H, s, OC$H_3$), 3.82 (rot b, 3H, s, OC$H_3$), 3.15 (rot a+b, 3H, s, NC$H_3$), 2.98 (rot b, 3H, s, NC$H_3$), 2.92 (rot a, 3H, s, NC$H_3$), 2.49-2.35 (rot a+b, 2H, m, $CH_2$C$H_2$S), 2.04 (rot b, 3H, s, SC$H_3$), 2.00 (rot a, 3H, s, SC$H_3$), 1.85-1.77 (rot a+b, 1H, m, C$H_A$$H_B$$CH_2$S), 1.74-1.69 (rot a, 1H, m, $CH_A$$H_B$$CH_2$S), 1.60-1.53 (rot b, 1H, m, $CH_A$$H_B$$CH_2$S), 1.03 (rot b, 3H, d, *J* = 6.6, C$H_3$CHCHOH), 0.99 (rot a, 3H, d, *J* = 6.5, C$H_3$CHCHOH);

**$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 173.8 (*C*=$O_{maj}$), 173.6 (*C*=$O_{min}$), 158.5 (*C*=$O_{min}$), 157.3 (*C*=$O_{maj}$), 155.7 (Ar*C*$OMe_{min}$), 155.6 (Ar*C*$OMe_{maj}$), 142.5 (Ar$C_{maj}$), 142.0 (Ar$C_{min}$), 131.0 (Ar*C*$N_{min}$), 130.7 (Ar*C*$N_{maj}$), 129.9 (Ar*C*$H_{min}$), 129.7 (2×Ar*C*$H_{maj}$), 129.6 (Ar*C*$H_{min}$), 128.8 (2×Ar*C*$H_{maj}$), 128.5 (2×Ar*C*$H_{min}$), 128.0 (Ar*C*$H_{maj}$), 128.0 (Ar*C*$H_{min}$), 127.2 (2×Ar*C*$H_{maj}$), 126.5 (2×Ar*C*$H_{min}$), 121.6 (Ar*C*$H_{maj+min}$), 112.6 (Ar*C*$H_{maj+min}$), 76.1 (CH*C*$HOH_{min}$), 75.9 (CH*C*$HOH_{maj}$), 58.4 ($CH_3$*C*$HCHOH_{maj+min}$), 55.7 (O*C*$H_{3min}$), 55.6 (O*C*$H_{3maj}$), 50.2 (NH*C*$HCH_{2maj}$), 48.7

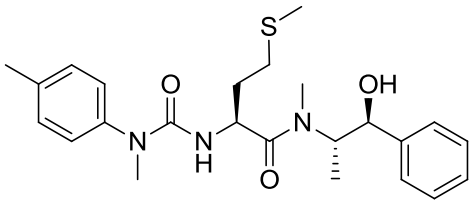
(NH*C*HCH$_{2min}$), 36.5 (N*C*H$_{3maj}$), 36.3 (N*C*H$_{3min}$), 32.9 (SCH$_2$*C*H$_{2min}$), 32.5 (SCH$_2$*C*H$_{2maj}$), 31.6 (N*C*H$_{3min}$), 30.4 (S*C*H$_{2maj}$), 30.0 (S*C*H$_{2min}$), 26.9 (N*C*H$_{3maj}$), 16.3 (*C*H$_3$CHCHOH$_{maj}$), 15.6 (S*C*H$_{3min}$), 15.4 (S*C*H$_{3maj}$), 14.2 (*C*H$_3$CHCHOH$_{min}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3395 (broad NH and OH), 2967, 2916 (C-H), 1626 (C=O amide), 1497 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 460 ([M+H]$^+$, 100%), 482 ([M+Na]$^+$, 20%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{24}H_{34}N_3O_4S$ [M+H]$^+$ 460.2270, found 460.2267.
*NMR file: $^1$H NMR = 2015-01-05-jpc-24 (10) 500a, $^{13}$C NMR = 2014-07-29-jpc-26 (11) 500a.*

**Synthesis of 656:**

**(*S*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-(3-methyl-3-(p-tolyl)ureido)-4-(methylthio)butanamide (656)**

(from urea acid **486** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)**(b)**




Following general procedure **9**, urea acid **486** (823 mg, 2.78 mmol) was dissolved in DCM (18.0 mL) then HOBt·H$_2$O (376 mg, 2.78 mmol), EDC·HCl (639 mg, 3.33 mmol) and DiPEA (0.58 mL, 3.33 mmol) were added. Stirred for 20 min at 0 °C and (*S*,*S*)-pseudoephedrine (688 mg, 4.17 mmol) added. The reaction was complete after 17 h at room temperature. Purification by flash column chromatography (SiO$_2$, 4:6-3:7 Pet.Ether:EtOAc) yielded the title compound as a pale yellow gum (885 mg, 1.99 mmol, 72%). **656**: **R$_f$** (1:2 Pet.Ether:EtOAc) 0.31; $[\alpha]_D^{21}$= +60.9 (*c* = 1.1 in CHCl$_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 1.0:0.65, **$^1$H NMR** (400 MHz, CDCl$_3$): $\delta_H$ = 7.52-7.50 (rot a+b, 1H, m, Ar*H*), 7.41-7.37 (rot a+b, 1H, m, Ar*H*), 7.31-7.13 (rot a+b, 7H, m, Ar*H*), 5.20-5.15 (2H, m, rot b N*H* + rot a NHC*H*CH$_2$), 5.04 (rot a, 1H, br. d, *J* = 8.7, N*H*), 4.91-4.86 (rot b, 1H, br. m, NHC*H*CH$_2$), 4.74 (rot a, 1H, d, *J* = 8.2, CHC*H*OH), 4.60 (2H, br. s, rot b CH$_3$C*H*CHOH + rot b O*H*), 4.50-4.40 (2H, m, rot a CH$_3$C*H*CHOH + rot b CHC*H*OH), 3.22 (rot a+b, 3H, s, NC*H$_3$*), 3.16 (rot a, 1H, br. s, O*H*), 3.01 (rot b, 3H, s, NC*H$_3$*), 2.93 (rot a, 3H, s, NC*H$_3$*), 2.48-2.37 (rot a+b, 2H, m, CH$_2$C*H$_2$*S), 2.37 (rot a+b, 3H, s, CC*H$_3$*), 2.05 (rot b, 3H, s, SC*H$_3$*), 2.01 (rot a, 3H, s, SC*H$_3$*), 1.87-1.79 (rot a+b, 1H, m, C*H$_A$*H$_B$CH$_2$S), 1.79-1.71 (rot a, 1H, m, CH$_A$*H$_B$*CH$_2$S), 1.66-1.57 (rot b, 1H, m, CH$_A$*H$_B$*CH$_2$S), 1.04 (rot b, 3H, d, *J* = 6.2, C*H$_3$*CHCHOH), 1.00 (rot a, 3H, d, *J* = 5.9, C*H$_3$*CHCHOH);

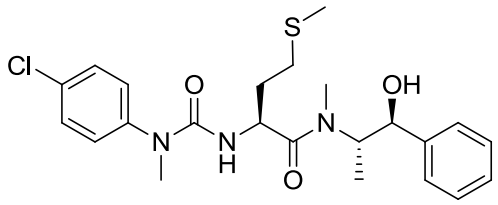
**$^{13}$C {$^{1}$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 173.7 (*C*=$O_{maj+min}$), 158.1 (*C*=$O_{maj}$), 157.0 (*C*=$O_{min}$), 142.4 (Ar*C*$_{maj}$), 142.0 (Ar*C*$_{min}$), 140.3 (Ar*C*$N_{min}$), 139.9 (Ar*C*$N_{maj}$), 137.7 (Ar*C*$C_{maj}$), 137.4 (Ar*C*$C_{min}$), 130.8 (2×Ar*C*$H_{maj}$), 130.7 (2×Ar*C*$H_{min}$), 128.8 (2×Ar*C*$H_{maj}$), 128.5 (2×Ar*C*$H_{min}$), 128.0 (Ar*C*$H_{maj}$), 127.9 (Ar*C*$H_{min}$), 127.1 (2×Ar*C*$H_{maj}$), 127.0 (2×Ar*C*$H_{maj+min}$), 126.5 (2×Ar*C*$H_{min}$), 75.9 (CH*C*$HOH_{min}$), 75.9 (CH*C*$HOH_{maj}$), 58.5 ($CH_3$*C*$HCHOH_{maj}$), 56.6 ($CH_3$*C*$HCHOH_{min}$), 50.3 (NH*C*$HCH_{2min}$), 48.9 (NH*C*$HCH_{2maj}$), 37.6 (N*C*$H_{3maj}$), 37.4 (N*C*$H_{3min}$), 32.6 ($SCH_2$*C*$H_{2min}$), 32.2 ($SCH_2$*C*$H_{2maj}$), 31.4 (N*C*$H_{3min}$), 30.5 (S*C*$H_{2maj}$), 30.1 (S*C*$H_{2min}$), 27.0 (N*C*$H_{3maj}$), 21.1 (C*C*$H_{3maj+min}$), 16.3 (*C*$H_3$CHCHOH$_{maj}$), 15.7 (S*C*$H_{3min}$), 15.4 (S*C*$H_{3maj}$), 14.2 (*C*$H_3$CHCHOH$_{min}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3390 (broad NH and OH), 2971, 2917 (C-H), 1628 (C=O amide), 1511 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 444 ($[M+H]^+$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{24}H_{33}N_3O_3SNa$ $[M+Na]^+$ 466.2140, found 466.2122.
*NMR file: $^{1}$H NMR = 2014-11-05-jpc-7 (10) 400c, $^{13}$C NMR = 2014-08-29-jpc-18 (11) 400c.*

**Synthesis of 657:**

**(*S*)-2-(3-(4-Chlorophenyl)-3-methylureido)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*-methyl-4-(methylthio)butanamide (657)**

(from urea acid **647** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)[(b)]




Following a similar method to general procedure **9**, urea acid **647** (1.11 g, 3.50 mmol) was dissolved in DCM (20.0 mL) then HOBt·$H_2O$ (472 mg, 3.50 mmol), EDC·HCl (805 mg, 4.20 mmol) and DiPEA (0.73 mL, 4.20 mmol) were added. Stirred for 15 min at 0 °C and (*S*,*S*)-pseudoephedrine (636 mg, 3.85 mmol, 1.1 eq.) added. The reaction was complete after 17 h at room temperature. Purification by flash column chromatography ($SiO_2$, 4:6-4:7 Pet.Ether:EtOAc) yielded the title compound as a white solid (1.26 g, 2.72 mmol, 78%). **657**: $\mathbf{R_f}$ (1:2 Pet.Ether:EtOAc) 0.24; **mp**: 60-62 °C; $[\alpha]_D^{21}$= +73.9 (*c* = 1.0 in $CHCl_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 1.0:0.71, **$^{1}$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.49-7.47 (rot a+b, 1H, m, Ar*H*), 7.39-7.35 (rot a+b, 3H, m, Ar*H*), 7.31-7.18 (rot a+b, 5H, m, Ar*H*), 5.23-5.15 (2H, m, rot a NHC*H*$CH_2$ and rot b N*H*), 5.09 (rot a, 1H, br. d, *J* = 8.5, N*H*), 4.86 (rot b, 1H, td, *J* = 8.1, 4.3, NHC*H*$CH_2$), 4.65-4.56 (2H, m, rot b $CH_3$C*H*CHOH and rot a O*H*), 4.52 (rot a,

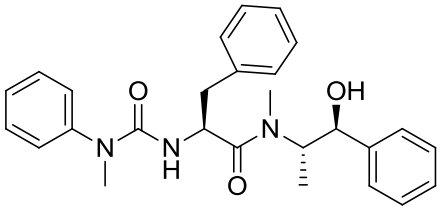
1H, br. d, *J* = 7.9, CHC*H*OH), 4.44-4.35 (2H, m, rot a $CH_3C$*H*CHOH and rot b CHC*H*OH), 3.21 (rot a, 3H, s, NC$H_3$), 3.20 (rot b, 3H, s, NC$H_3$), 3.13 (rot b, 1H, br. s, O*H*), 2.99 (rot b, 3H, s, NC$H_3$), 2.91 (rot a, 3H, s, NC$H_3$), 2.49-2.35 (rot a+b, 2H, m, $CH_2CH_2S$), 2.03 (rot b, 3H, s, SC$H_3$), 2.00 (rot a, 3H, s, SC$H_3$), 1.85-1.69 (2H, m, rot a+b $CH_AH_BCH_2S$ and rot a $CH_AH_BCH_2S$), 1.62-1.53 (rot b, 1H, m, $CH_AH_BCH_2S$), 1.02 (rot b, 3H, d, *J* = 6.6, $CH_3$CHCHOH), 0.98 (rot a, 3H, d, *J* = 5.7, $CH_3$CHCHOH);

**$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 173.6 (*C*=$O_{maj}$), 173.6 (*C*=$O_{min}$), 157.8 (*C*=$O_{min}$), 156.7 (*C*=$O_{maj}$), 142.2 (Ar*C*$_{maj}$), 141.9 (Ar*C*$_{min}$), 141.7 (Ar*C*$N_{min}$), 141.3 (Ar*C*$N_{maj}$), 133.3 (Ar*C*$Cl_{maj}$), 133.1 (Ar*C*$Cl_{min}$), 130.4 (2×Ar*C*$H_{maj}$), 130.3 (2×Ar*C*$H_{min}$), 128.8 (2×Ar*C*$H_{maj}$), 128.6 (2×Ar*C*$H_{maj+min}$), 128.5 (2×Ar*C*$H_{min}$), 128.1 (Ar*C*$H_{maj}$), 128.1 (Ar*C*$H_{min}$), 127.2 (2×Ar*C*$H_{maj}$), 126.6 (2×Ar*C*$H_{min}$), 76.0 (CH*C*$HOH_{min}$), 75.9 (CH*C*$HOH_{maj}$), 58.5 ($CH_3$*C*$HCHOH_{maj}$), 56.6 ($CH_3$*C*$HCHOH_{min}$), 50.5 (NH*C*$HCH_{2min}$), 49.2 (NH*C*$HCH_{2maj}$), 37.6 (N*C*$H_{3maj}$), 37.4 (N*C*$H_{3min}$), 32.5 ($SCH_2$*C*$H_{2min}$), 32.2 ($SCH_2$*C*$H_{2maj}$), 31.3 (N*C*$H_{3min}$), 30.5 (S*C*$H_{2maj}$), 30.2 (S*C*$H_{2min}$), 27.1 (N*C*$H_{3maj}$), 16.2 (*C*$H_3$CHCH$OH_{maj}$), 15.8 (S*C*$H_{3min}$), 15.5 (S*C*$H_{3maj}$), 14.2 (*C*$H_3$CHCH$OH_{min}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3393 (broad NH and OH), 2973, 2916 (C-H), 1627 (C=O amide), 1593 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 464 ([M+H]$^+$, 70%), 486 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{23}H_{30}N_3O_3{}^{35}ClSNa$ [M+Na]$^+$ 486.1594, found 486.1610.
*NMR file: $^1$H NMR = 2014-09-29-jpc-8 (22) 400c, $^{13}$C NMR = 2014-09-29-jpc-8 (23) 400c.*

**<u>Synthesis of 658 (from synthesis of 462):</u>**

**(*S*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-*N*-methyl-2-(3-methyl-3-phenylureido)-3-phenylpropanamide (658)**




Following general procedure **9**, urea acid **462** (178 mg, 0.60 mmol) was dissolved in DCM (4.00 mL) then HOBt·$H_2O$ (81 mg, 0.60 mmol), EDC·HCl (137 mg, 0.72 mmol) and DiPEA (0.12 mL, 0.72 mmol) were added. Stirred for 20 min at 0 °C and (*S*,*S*)-pseudoephedrine (148 mg, 0.90 mmol) added. The reaction was complete after 23 h at room temperature. Purification by flash column chromatography ($SiO_2$, 1:1-1:2 Pet.Ether:EtOAc) yielded the title compound as a white solid (200 mg, 0.45 mmol, 75%). **658**: $\mathbf{R}_f$ (1:1 Pet.Ether:EtOAc) 0.13; **mp**: 71-73°C; $[\alpha]_D^{21}$= +90.6 (*c* = 1.0 in $CHCl_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 1:0.36, **$^{1}$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.46-7.42 (rot a+b, 3H, m, Ph*H*), 7.40-7.15 (rot a+b, 11H, m, Ph*H*), 7.10-7.09 (rot a+b, 1H, m, Ph*H*), 5.16-5.10 (2H, m, rot a N*H* and rot b NHC*H*$CH_2$Ph), 5.05 (rot b, 1H, br. d, *J* = 8.2, N*H*), 4.98-4.94 (rot a, 1H, m, NHC*H*$CH_2$Ph), 4.61 (rot b, 1H, d, *J* = 7.9, CHC*H*OH), 4.32 (2H, br. d, *J* = 9.4, rot a CHC*H*OH and rot b $CH_3$C*H*CHOH), 4.11 (rot a, 1H, dq, *J* = 9.5, 6.5, $CH_3$C*H*CHOH), 3.27 (rot a, 3H, s, NC$H_3$), 3.24 (rot b, 3H, s, NC$H_3$), 2.92-2.78 (rot a+b, 2H, m, C$H_2$Ph), 2.84 (rot a, 3H, s, NC$H_3$), 2.76 (rot b, 3H, s, NC$H_3$), 1.03 (rot b, 3H, d, *J* = 6.9, C$H_3$CHCHOH), 0.32 (rot a, 3H, d, *J* = 6.6, C$H_3$CHCHOH);

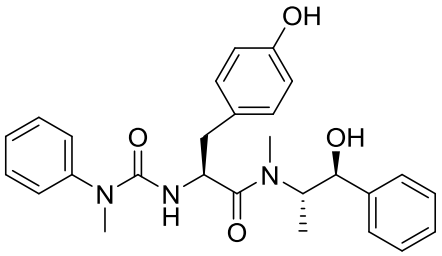
**$^{13}$C {$^{1}$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.0 (*C*=$O_{min}$), 173.1 (*C*=$O_{maj}$), 157.8 (*C*=$O_{maj}$), 156.6 (*C*=$O_{min}$), 143.0 (Ar*C*$_{min}$), 142.8 (Ar*C*$_{maj}$), 142.6 (Ar*C*$N_{maj}$), 141.9 (Ar*C*$N_{min}$), 136.7 (Ar*C*$_{maj+min}$), 130.2 (2×Ar*C*$H_{maj}$), 130.1 (2×Ar*C*$H_{min}$), 129.5 (2×Ar*C*$H_{min}$), 129.3 (2×Ar*C*$H_{maj}$), 128.7 (2×Ar*C*$H_{maj}$), 128.7 (2×Ar*C*$H_{maj}$), 128.6 (2×Ar*C*$H_{min}$), 128.5 (2×Ar*C*$H_{min}$), 127.9 (Ar*C*$H_{min}$), 127.9 (Ar*C*$H_{maj}$), 127.7 (Ar*C*$H_{maj}$), 127.5 (Ar*C*$H_{min}$), 127.2 (2×Ar*C*$H_{maj}$), 127.2 (2×Ar*C*$H_{min}$), 127.1 (2×Ar*C*$H_{maj}$), 127.0 (2×Ar*C*$H_{min}$), 127.0 (Ar*C*$H_{maj}$), 126.6 (Ar*C*$H_{min}$), 75.9 (CH*C*$HOH_{maj+min}$), 58.8 ($CH_3$*C*$HCHOH_{maj+min}$), 52.4 (NH*C*$HCH_2Ph_{min}$), 51.7 (NH*C*$HCH_2Ph_{maj}$), 39.4 (*C*$H_2Ph_{maj}$), 39.1 (*C*$H_2Ph_{min}$), 37.5 (N*C*$H_{3maj}$), 37.3 (N*C*$H_{3min}$), 26.8 (N*C*$H_{3maj+min}$), 15.1 (*C*$H_3$CHCHO$H_{maj}$), 14.2 (*C*$H_3$CHCHO$H_{min}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3395 (broad NH and OH), 2974, 2934 (C-H), 1628 (C=O amide), 1595 (C=O urea); **MS** ($ESI^+$, MeOH): *m/z* = 446 ($[M+H]^+$, 100%), 468 ($[M+Na]^+$, 50%), ($ESI^-$, MeOH): *m/z* = 444 ($[M–H]^-$, 100%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{27}H_{32}N_3O_3$ $[M+H]^+$ 446.2444, found 446.2422.

*NMR file: $^{1}$H NMR = 2015-01-05-jpc-11 (10) 500a, $^{13}$C NMR = 2015-01-05-jpc-11 (21) 500a.*

**<u>Synthesis of 659 (from synthesis of 476):</u>**

**(*S*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-3-(4-hydroxyphenyl)-*N*-methyl-2-(3-methyl-3-phenylureido)propanamide (659)**




Following general procedure **9**, urea acid **476** (1.23 g, 3.91 mmol) was dissolved in DCM (21.0 mL) then HOBt·$H_2O$ (529 mg, 3.91 mmol), EDC·HCl (900 mg, 4.70 mmol) and DiPEA (0.82 mL, 4.70 mmol) were added. Stirred for 20 min at 0 °C and (*S*,*S*)-pseudoephedrine (970 mg, 5.87

mmol) added. The reaction was complete after 65 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:7-2:8 Pet.Ether:EtOAc) yielded the title compound as a white solid (468 mg, 1.01 mmol, 26%). **659**: $\mathbf{R_f}$ (1:4 Pet.Ether:EtOAc) 0.25; **mp**: 98-100 °C; $[\alpha]_D^{21}$= +73.9 (*c* = 1.3 in $CHCl_3$);

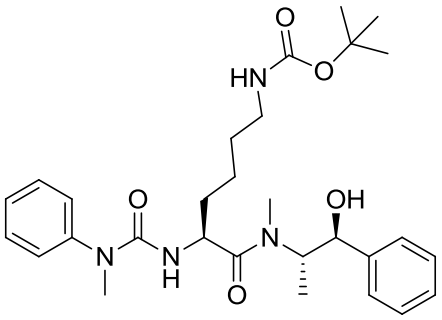
Rotamers in a ratio, Major:Minor, RotA:RotB, 1:0.50, **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.76 (rot a+b, 1H, br. s, O*H*), 7.43-7.25 (rot a+b, 8H, m, Ph*H*), 7.22-7.18 (rot a+b, 2H, m, Ph*H*), 6.93 (rot b, 2H, d, *J* = 8.4, OHAr*H*), 6.88 (rot a, 2H, d, *J* = 8.4, OHAr*H*), 6.65 (rot a+b, 2H, d, *J* = 8.4, OHAr*H*), 5.17 (rot a, 1H, br. d, *J* = 8.1, N*H*), 5.11 (rot b, 1H, br. d, *J* = 7.9, N*H*), 5.10-5.06 (rot a, 1H, m, NHC*H*$CH_2$Ar), 4.91 (rot b, 1H, dd, *J* = 14.6, 7.4, NHC*H*$CH_2$Ar), 4.55 (rot b, 1H, d, *J* = 8.3, CHC*H*OH), 4.44-4.37 (rot b, 1H, br. m, $CH_3$C*H*CHOH), 4.33 (rot a, 1H, br. d, *J* = 9.5, CHC*H*OH), 4.14 (rot a, 1H, dq, *J* = 9.3, 6.8, $CH_3$C*H*CHOH), 3.22 (rot a, 3H, s, NC$H_3$), 3.22 (rot b, 3H, s, NC$H_3$), 2.83 (rot a, 3H, s, NC$H_3$), 2.81-2.77 (rot a+b, 1H, m, C$H_A$$H_B$Ar), 2.76 (rot b, 3H, s, NC$H_3$), 2.72-2.66 (rot a+b, 1H, m, $CH_A$$H_B$Ar), 0.97 (rot b, 3H, d, *J* = 6.9, C$H_3$CHCHOH), 0.41 (rot a, 3H, d, *J* = 6.6, C$H_3$CHCHOH);

**$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.2 (*C*=$O_{min}$), 173.6 (*C*=$O_{maj}$), 157.7 (*C*=$O_{maj}$), 156.9 (*C*=$O_{min}$), 155.9 (Ar*C*$OH_{maj+min}$), 142.8 (Ar*C*$_{min}$), 142.5 (Ar*C*$_{maj}$), 142.4 (Ar*C*$N_{maj}$), 141.8 (Ar*C*$N_{min}$), 130.5 (2×Ar*C*$H_{min}$), 130.3 (2×Ar*C*$H_{maj}$), 130.2 (2×Ar*C*$H_{maj}$), 130.2 (2×Ar*C*$H_{min}$), 128.8 (2×Ar*C*$H_{maj}$), 128.5 (2×Ar*C*$H_{min}$), 128.0 (Ar*C*$H_{min}$), 128.0 (Ar*C*$H_{maj}$), 127.8 (Ar*C*$H_{maj}$), 127.7 (Ar*C*$H_{min}$), 127.3 (Ar*C*$_{maj}$), 127.2 (2×Ar*C*$H_{maj+min}$), 127.2 (Ar*C*$_{min}$), 127.1 (2×Ar*C*$H_{maj}$), 126.7 (2×Ar*C*$H_{min}$), 115.7 (2×Ar*C*$H_{maj}$), 115.6 (2×Ar*C*$H_{min}$), 75.8 (CH*C*$HOH_{maj+min}$), 58.9 ($CH_3$*C*$HCHOH_{maj+min}$), 52.7 (NH*C*$HCH_2Ph_{min}$), 52.0 (NH*C*$HCH_2Ph_{maj}$), 38.5 (*C*$H_2Ph_{maj}$), 38.2 (*C*$H_2Ph_{min}$), 37.5 (N*C*$H_{3maj}$), 37.4 (N*C*$H_{3min}$), 27.1 (N*C*$H_{3maj+min}$), 15.3 (*C*$H_3$CHCHOH$_{maj}$), 14.3 (*C*$H_3$CHCHOH$_{min}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3309 (broad NH and OH), 3029, 2939 (C-H), 1627 (C=O amide), 1594 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 462 ([M+H]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{27}H_{31}N_3O_4Na$ [M+Na]$^+$ 484.2212, found 484.2208.
*NMR file: $^1$H NMR = 2015-01-06-jpc-11 (10) 500a, $^{13}$C NMR = 2015-01-06-jpc-11 (21) 500a.*

**Synthesis of 660 (from synthesis of 475):**

***tert*-Butyl ((*S*)-6-(((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)(methyl)amino)-5-(3-methyl-3-phenylureido)-6-oxohexyl)carbamate (660)**



Following general procedure **9**, urea acid **475** (923 mg, 2.43 mmol) was dissolved in DCM (12.0 mL) then HOBt·$H_2O$ (326 mg, 2.43 mmol), EDC·HCl (560 mg, 2.92 mmol) and DiPEA (0.51 mL, 2.92 mmol) were added. Stirred for 20 min at 0 °C and (*S*,*S*)-pseudoephedrine (603 mg, 3.65 mmol) added. The reaction was complete after 65 h at room temperature. Purification by flash column chromatography ($SiO_2$, 3:7-2:8 Pet.Ether:EtOAc) yielded the title compound as a white solid (916 mg, 1.74 mmol, 72%). **660**: $\mathbf{R}_f$ (1:4 Pet.Ether:EtOAc) 0.28; **mp**: 60-62 °C; $[\alpha]_D^{21}$ = +56.5 (*c* = 1.3 in $CHCl_3$);

Rotamers in a ratio, Major:Minor, RotA:RotB, 1.0:0.82, **$^1$H NMR** (400 MHz, $CDCl_3$):, $\delta_H$ = 7.51-7.38 (rot a+b, 4H, m, Ph*H*), 7.33-7.27 (rot a+b, 6H, m, Ph*H*), 5.25 (rot b, 1H, br. d, *J* = 7.9, N*H*), 5.02 (rot a, 1H, br. d, *J* = 8.4, N*H*), 4.91 (rot a, 1H, dd, *J* = 15.1, 7.5, NHC*H*$CH_2$), 4.84-4.74 (3H, m, rot b NHC*H*$CH_2$ and rot b BocN*H* and rot a O*H*), 4.70-4.62 (rot b, 1H, br. m, $CH_3$C*H*CHOH), 4.60-4.54 (2H, m, rot b CHC*H*OH and rot a BocN*H*), 4.45 (rot a, 1H, t, *J* = 9.2, CHC*H*OH), 4.38-4.31 (rot a, 1H, m, $CH_3$C*H*CHOH), 3.37 (rot b, 1H, br. s, O*H*), 3.27 (rot a+b, 3H, s, NC*H*$_3$), 3.11-2.99 (rot a+b, 2H, m, C*H*$_2$NHBoc), 2.99 (rot b, 3H, s, NC*H*$_3$), 2.94 (rot a, 3H, s, NC*H*$_3$), 1.60-1.39 (rot a+b, 4H, m, HCC*H*$_2$($CH_2$)$_3$NH and C*H*$_2$$CH_2$NH), 1.41 (rot a, 9H, s, OC(C*H*$_3$)$_3$), 1.39 (rot b, 9H, s, OC(C*H*$_3$)$_3$), 1.33-1.20 (rot a+b, 2H, m, HCC$H_2$C*H*$_2$($CH_2$)$_2$NH), 1.01 (rot a+b, 3H, d, *J* = 6.5, C*H*$_3$CHCHOH);

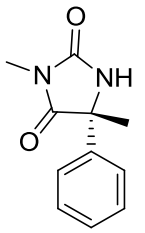
**$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.0 (*C*=O$_{min}$), 174.0 (*C*=O$_{maj}$), 157.9 (*C*=O$_{maj}$), 156.9 (*C*=O$_{min}$), 156.1 (*C*=O$_{min}$), 156.0 (*C*=O$_{maj}$), 143.1 (Ar*C*$_{min}$), 142.7 (Ar*C*$_{maj}$), 142.5 (Ar*C*N$_{maj}$), 142.0 (Ar*C*N$_{min}$), 130.2 (2×Ar*C*H$_{maj}$), 130.1 (2×Ar*C*H$_{min}$), 128.8 (2×Ar*C*H$_{maj}$), 128.6 (2×Ar*C*H$_{min}$), 128.0 (Ar*C*H$_{maj+min}$), 127.7 (Ar*C*H$_{maj}$), 127.5 (Ar*C*H$_{min}$), 127.2 (2×Ar*C*H$_{maj}$), 127.2 (2×Ar*C*H$_{min}$), 127.1 (2×Ar*C*H$_{maj}$), 126.7 (2×Ar*C*H$_{min}$), 79.2 (*C*(CH$_3$)$_{3maj}$), 79.1 (*C*(CH$_3$)$_{3min}$), 75.9 (CH*C*HOH$_{min}$), 75.9 (CH*C*HOH$_{maj}$), 58.6 (CH$_3$*C*HCHOH$_{maj}$), 56.5 (CH$_3$*C*HCHOH$_{min}$), 50.8 (NH*C*HCH$_{2min}$), 50.0 (NH*C*HCH$_{2maj}$), 40.2 (*C*H$_2$NHBoc$_{maj}$), 40.1 (*C*H$_2$NHBoc$_{min}$), 37.6 (N*C*H$_{3maj}$), 37.3 (N*C*H$_{3min}$), 32.6 (HC*C*H$_2$($CH_2$)$_3$NH$_{maj}$), 32.4 (HC*C*H$_2$($CH_2$)$_3$NH$_{min}$), 31.3 (N*C*H$_{3min}$), 29.8 (*C*H$_2$$CH_2$NH$_{maj}$), 29.3

($CH_2CH_2NH_{min}$), 28.5 ($C(CH_3)_{3maj+min}$), 27.0 ($NCH_{3maj}$), 23.1 ($HCCH_2CH_2(CH_2)_2NH_{maj}$), 22.0 ($HCCH_2CH_2(CH_2)_2NH_{min}$), 16.2 ($CH_3CHCHOH_{maj}$), 14.3 ($CH_3CHCHOH_{min}$);

**IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3349 (broad NH and OH), 2975, 2934 (C-H), 1694 (C=O carbamate), 1627 (C=O amide), 1596 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 527 ([M+H]$^+$, 100%), 549 ([M+Na]$^+$, 70%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{29}H_{42}N_4O_5Na$ [M+Na]$^+$ 549.3053, found 549.3056.
*NMR file: $^1$H NMR = 2014-08-06-jpc-51 (10) 400c, $^{13}$C NMR = 2014-08-06-jpc-51 (11) 400c.*

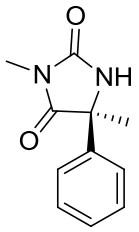
**Synthesis of enantiomerically enriched hydantoins:**

**(*R*)-3,5-Dimethyl-5-phenylimidazolidine-2,4-dione (446)**[226]




Following general procedure **12**, a stock solution of LDA was prepared with THF (2.80 mL), DiPA (0.46 mL, 3.31 mmol) and *n*BuLi (2.16 mL, 3.27 mmol, 1.51 M in hexanes). The urea pseudoephedrine **546** (151 mg, 0.41 mmol) in THF (2.70 mL) was added to cooled LDA (1.36 mL, 0.82 mmol) from the stock solution and the reaction mixture turned yellow. TMSCl (0.11 mL, 0.86 mmol) was added and the reaction mixture became colourless. Further LDA (1.36 mL, 0.82 mmol) from the stock solution was added and the reaction mixture went yellow again. Upon warming to room temperature the yellow colour was very bright. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a white solid (69 mg, 0.34 mmol, 83%). **446**: **R$_f$** (1:1 Pet.Ether:EtOAc) 0.35; **mp**: 125-127 °C; $[\alpha]_D^{21}$= –85.3 (*c* = 1.1 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.52-7.51 (2H, m, Ph*H*), 7.41-7.32 (3H, m, Ph*H*), 6.43 (1H, br. s, N*H*), 3.02 (3H, s, $NCH_3$), 1.84 (3H, s, $CCH_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.4 (*C*=O), 157.0 (*C*=O), 138.7 (Ar*C*), 129.0 (2×Ar*C*H), 128.7 (Ar*C*H), 125.3 (2×Ar*C*H), 63.9 ($CCH_3$), 25.8 ($CCH_3$), 25.0 ($NCH_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3263 (NH), 2983, 2941 (C-H), 1780 (C=O amide), 1707 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 205 ([M+H]$^+$, 20%), 227 ([M+Na]$^+$, 100%), (ESI$^-$, MeOH): *m/z* = 203 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{13}N_2O_2$ [M+H]$^+$ 205.0977, found 205.0967; **HPLC**: *er* 92:8, Chiralcel OD-H, Hexane:IPA = 70:30, flow = 1.0 mL/min, λ = 210 nm, $t_R$ = 6.1 (major), 8.3 (minor) min.
*NMR file: $^1$H NMR = 2014-12-16-jpc-31 (10), $^{13}$C NMR = 2014-02-11-jpc-23 (12).*

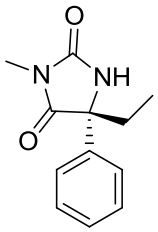
**(*S*)-3,5-Dimethyl-5-phenylimidazolidine-2,4-dione (ent-446)**[226]



To a flame dried flask was added LiCl (87 mg, 2.04 mmol, 7.2 eq.) and a solution of LDA prepared with THF (1.00 mL), DiPA (0.16 mL, 1.13 mmol, 4.0 eq.) cooled to 0 °C and *n*BuLi (0.79 mL, 1.13 mmol, 1.43 M in hexanes, 4.0 eq.) added and stirred for 20 min. The solution was cooled to –78 °C and TMSCl (0.07 mL, 0.56 mmol, 2.0 eq.) was added and stirred for 5 min before the (*R*,*R*) pseudoephedrine **631** (104 mg, 0.28 mmol, 1.0 eq.) in THF (1.80 mL) was added. The reaction was stirred at –78 °C for 30 min before warming to room temperature and leaving 16 h. The reaction mixture went from bright yellow to cloudy. The reaction was quenched with an aqueous saturated $NH_4Cl$ solution and acidified with 1.0 M HCl. After a 45 min stir the aqueous layer was extracted with EtOAc (×3) and the combined organic layer washed once with water and once with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography ($SiO_2$, 8:2-7:3 Pet.Ether:EtOAc) yielded the title compound as a white solid (41 mg, 0.20 mmol, 71%). **ent-446**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc) 0.38; **mp**: 122-126 °C; $[\alpha]_D^{21}$= +73.5 (*c* = 0.8 in $CHCl_3$); **HPLC**: *er* 10:90, Chiralcel OD-H, Hexane:IPA = 70:30, flow = 1.0 mL/min, $\lambda$ = 210 nm, $t_R$ = 6.1 (minor), 8.3 (major) min

**$^1$H NMR**, **$^{13}$C NMR**, **IR**, **MS** and **HRMS** data with compound **446**

**(*R*)-5-Ethyl-3-methyl-5-phenylimidazolidine-2,4-dione (21)**[221,227]

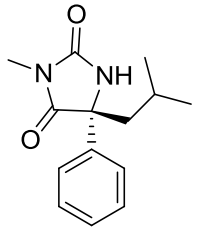


Following general procedure **12**, a stock solution of LDA was prepared with THF (2.00 mL), DiPA (0.36 mL, 2.58 mmol) and *n*BuLi (1.68 mL, 2.55 mmol, 1.51 M in hexanes). The urea pseudoephedrine **640** (122 mg, 0.32 mmol) in THF (2.20 mL) was added to cooled LDA (1.01 mL, 0.64 mmol) from the stock solution and the reaction mixture turned pale yellow. TMSCl (0.09 mL, 0.67 mmol) was added and the reaction mixture became colourless. Further LDA (1.01 mL, 0.64 mmol) from the stock solution was added and the reaction mixture went yellow again. Upon warming to room temperature the yellow colour was bright and got lighter over time. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a

white solid (40 mg, 0.18 mmol, 58%). **21**: $\mathbf{R}_f$ (7:3 Pet.Ether:EtOAc) 0.32; **mp**: 123-125 °C; $[\alpha]_D^{21}$ = –71.4 (*c* = 0.14 in EtOH);[xxxii] **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.58-7.56 (2H, m, Ph*H*), 7.50 (1H, br. s, N*H*), 7.40-7.30 (3H, m, Ph*H*), 3.00 (3H, s, NC$H_3$), 2.23 (1H, dq, *J* = 14.6, 7.3, C$H_A$H$_B$CH$_3$), 2.12 (1H, dq, *J* = 14.7, 7.4, CH$_A$$H_B$CH$_3$), 0.90 (3H, t, *J* = 7.4, CH$_2$CH$_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.1 (*C*=O), 158.0 (*C*=O), 137.9 (Ar*C*), 128.9 (2×Ar*C*H), 128.4 (Ar*C*H), 125.5 (2×Ar*C*H), 68.1 (*C*CH$_2$), 32.3 (*C*H$_2$CH$_3$), 24.8 (N*C*H$_3$), 8.2 (CH$_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3289 (NH), 2972, 2938, 2880 (C-H), 1775 (C=O amide), 1700 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 219 ([M+H]$^+$, 100%), 241 ([M+Na]$^+$, 70%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{15}N_2O_2$ [M+H]$^+$ 219.1134, found 219.1130; **HPLC**: *er* 91:9, ChiralPak® AD-H, Hexane:IPA = 95:5, flow = 1.0 mL/min, λ = 210 nm, $t_R$ = 11.0 (major), 13.2 (minor) min.

*NMR file: $^1$H NMR = 2014-03-13-jpc-43 (10), $^{13}$C NMR = 2014-03-13-jpc-43 (12).*

**(*R*)-5-*iso*Butyl-3-methyl-5-phenylimidazolidine-2,4-dione (464)**



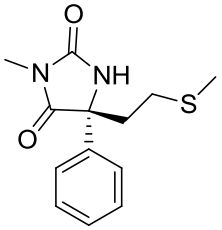

Following general procedure **12**, a stock solution of LDA was prepared with THF (2.60 mL), DiPA (0.44 mL, 3.11 mmol) and *n*BuLi (2.03 mL, 3.07 mmol, 1.51 M in hexanes). The urea pseudoephedrine **548**(158 mg, 0.38 mmol) in THF (2.50mL) was added to cooled LDA (1.27 mL, 0.77 mmol) from the stock solution and the reaction mixture turned yellow. TMSCl (0.10 mL, 0.81 mmol) was added and the reaction mixture became colourless. Further LDA (1.27 mL, 0.77 mmol) from the stock solution was added and the reaction mixture went yellow again. Upon warming to room temperature the yellow colour was bright and got darker and more orange over time. The reaction was left for 26 h. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a white solid (43 mg, 0.18 mmol, 46%). **464**: $\mathbf{R}_f$ (1:1 Pet.Ether:EtOAc) 0.50; **mp**: 130-132 °C; $[\alpha]_D^{21}$ = –60.2 (*c* = 1.0 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.71 (1H, br. s, N*H*), 7.60-7.58 (2H, m, Ph*H*), 7.39-7.29 (3H, m, Ph*H*), 2.99 (3H, s, NC$H_3$), 2.14 (1H, dd, *J* = 14.5, 5.7, CC$H_A$H$_B$CH), 2.07 (1H, dd, *J* = 14.5, 7.1, CCH$_A$$H_B$CH), 1.73-1.64 (1H, m, CH$_2$C*H*(CH$_3$)$_2$), 0.89 (3H, d, *J* = 6.6, CH(C$H_3$)$_2$), 0.85 (3H, d, *J* = 6.7, CH(C$H_3$)$_2$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.4 (*C*=O), 157.8 (*C*=O), 138.7 (Ar*C*), 128.8 (2×Ar*C*H), 128.3 (Ar*C*H), 125.4 (2×Ar*C*H), 67.4 (*C*CH$_2$), 47.5 (C*C*H$_2$), 24.9 (C*C*H$_2$), 24.8 (N*C*H$_3$), 24.2 (CH(*C*H$_3$)$_2$), 23.2 (CH(*C*H$_3$)$_2$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3278 (NH), 2957, 2871 (C-H), 1773 (C=O amide), 1704 (C=O urea); **MS** (ESI$^+$, MeOH): *m/z* = 269 ([M+Na]$^+$, 30%), 301 ([M+Na+MeOH]$^+$,

[xxxii] Also run in $CHCl_3$ as a higher concentration could be achieved $[\alpha]_D^{21}$ = –102.5 (*c* = 1.3 in $CHCl_3$)

100%), (ESI⁻, MeOH): *m/z* = 245 ([M–H]⁻, 100%); **HRMS** (ESI⁺): *m/z* calcd for $C_{14}H_{18}N_2O_2Na$ $[M+Na]^+$ 269.1266, found 269.1255; **HPLC**: *er* 80:20, Chiralcel OD-H, Hexane:IPA = 70:30, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 4.3 (major), 4.9 (minor) min.

*NMR file: [1]H NMR = 2014-01-23-jpc-33 (30), [13]C NMR = 2014-01-23-jpc-33 (31).*

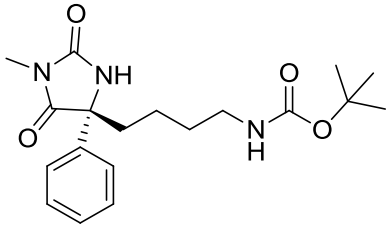
**(*R*)-3-Methyl-5-(2-(methylthio)ethyl)-5-phenylimidazolidine-2,4-dione (465)**




Following general procedure **12**, a stock solution of LDA was prepared with THF (2.40 mL), DiPA (0.42 mL, 3.02 mmol) and *n*BuLi (1.98 mL, 2.98 mmol, 1.51 M in hexanes). The urea pseudoephedrine **641** (160 mg, 0.37 mmol) in THF (2.50 mL) was added to cooled LDA (1.20 mL, 0.75 mmol) from the stock solution and the reaction mixture turned yellow. TMSCl (0.10 mL, 0.78 mmol) was added and the reaction mixture became colourless. Further LDA (1.20 mL, 0.75 mmol) from the stock solution was added and the reaction mixture went yellow again. Upon warming to room temperature the yellow colour was bright and darker over time. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a white solid (69 mg, 0.26 mmol, 70%).**465:** $\mathbf{R_f}$ (7:3 Pet.Ether:EtOAc) 0.36; **mp**: 133-135 °C; $[\alpha]_D^{21}$ = –54.2 (*c* = 1.0 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.58-7.56 (2H, m, Ph*H*), 7.42-7.32 (3H, m, Ph*H*), 7.31 (1H, br. s, N*H*), 3.00 (3H, s, NC$H_3$), 2.52-2.34 (4H, m, C$H_2$C$H_2$S), 2.06 (3H, s, SC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.6 (*C*=O), 157.3 (*C*=O), 138.0 (Ar*C*), 129.0 (2×Ar*C*H), 128.7 (Ar*C*H), 125.5 (2×Ar*C*H), 67.2 (*C*$CH_2$), 37.5 (*C*$H_2$), 28.9 (*C*$H_2$), 25.0 (N*C*$H_3$), 15.5 (S*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3290 (NH), 2916 (C-H), 1775 (C=O amide), 1703 (C=O urea); **MS** (ESI⁺, MeOH): *m/z* = 287 ([M+Na]⁺, 100%), (ESI⁻, MeOH): *m/z* = 263 ([M–H]⁻, 100%); **HRMS** (ESI⁺): *m/z* calcd for $C_{13}H_{16}N_2O_2SNa$ $[M+Na]^+$ 287.0830, found 287.0838; **HPLC**: *er* 93:7, ChiralPak® AD-H, Hexane:IPA = 95:5, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 17.7 (major), 20.0 (minor) min.

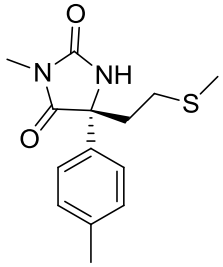
*NMR file: [1]H NMR = 2014-01-27-jpc-20 (12), [13]C NMR = 2014-01-27-jpc-20 (11).*

**(*R*)-*tert*-Butyl (4-(1-methyl-2,5-dioxo-4-phenylimidazolidin-4-yl)butyl)carbamate (478)**



Following a similar method to general procedure **12**, a stock solution of LDA was prepared with THF (2.60 mL), DiPA (0.54 mL, 3.84 mmol, 10.1 eq.) and *n*BuLi (2.46 mL, 3.80 mmol, 1.54 M in hexanes, 10.0 eq.). The urea pseudoephedrine **660** (200 mg, 0.38 mmol) in THF (2.50 mL) was added to cooled LDA (1.68 mL, 1.14 mmol, 3.0 eq.) from the stock solution and the reaction mixture turned yellow. TMSCl (0.15 mL, 1.18 mmol, 3.1 eq.) was added and the reaction mixture became colourless. Further LDA (1.12 mL, 0.76 mmol, 2.0 eq.) from the stock solution was added and the reaction mixture went yellow again. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (67 mg, 0.19 mmol, 49%). **478**: **$R_f$** (1:4 Pet.Ether:EtOAc) 0.71; $[\alpha]_D^{21}$= –57.0 (*c* = 1.6 in $CHCl_3$); **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.57-7.55 (2H, m, Ph*H*), 7.39-7.30 (3H, m, Ph*H*), 7.21 (1H, br. s, N*H*), 4.61 (1H, br.s, BocN*H*), 3.08-3.06 (2H, m, C$H_2$NH), 3.00 (3H, s, NC$H_3$), 2.14 (2H, t, *J* =8.3, CC$H_2$($CH_2$)$_3$NH), 1.53-1.44 (2H, m, C$H_2$$CH_2$NH), 1.42 (9H, s, OC(C$H_3$)$_3$), 1.33-1.21 (2H, m, $CCH_2CH_2$($CH_2$)$_2$NH); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.1 (*C*=O), 157.6 (*C*=O), 156.3 (*C*=O), 138.1 (Ar*C*), 128.9 (2×Ar*C*H), 128.4 (Ar*C*H), 125.5 (2×Ar*C*H), 79.5 (*C*($CH_3$)$_3$), 67.4 (*C*$CH_2$), 39.8 (*C*$H_2$NH), 38.4 (C*C*$H_2$($CH_2$)$_3$NH), 29.8 (*C*$H_2$$CH_2$NH), 28.5 (C(*C*$H_3$)$_3$), 24.9 (N*C*$H_3$), 20.8 ($CCH_2$*C*$H_2$($CH_2$)$_2$NH); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3296 (broad NH), 2932(C-H), 1773 (C=O), 1707 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 384 ([M+Na]$^+$, 100%), (ESI$^-$, MeOH): *m/z* = 360 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{19}H_{27}N_3O_4Na$ [M+Na]$^+$ 384.1899, found 384.1894; **HPLC**: *er* 92:8, Chiralcel OD-H, Hexane:IPA = 70:30, flow = 1.0 mL/min, λ = 210 nm, $t_R$ = 14.3 (major), 16.4 (minor) min.
*NMR file: $^1$H NMR = 2014-12-04-jpc-28 (10) 400c, $^{13}$C NMR = 2014-12-04-jpc-28 (11) 400c.*

**(*R*)-3-Methyl-5-(2-(methylthio)ethyl)-5-(*p*-tolyl)imidazolidine-2,4-dione (487)**

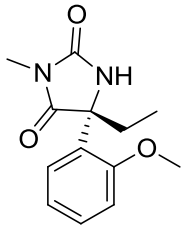


Following general procedure **12**, a stock solution of LDA was prepared with THF (2.40 mL), DiPA (0.40 mL, 2.79 mmol) and *n*BuLi (1.82 mL, 2.76 mmol, 1.51 M in hexanes). The urea pseudoephedrine **656** (153 mg, 0.35 mmol) in THF (2.30 mL) was added to cooled LDA (1.16 mL,

0.69 mmol) from the stock solution and the reaction mixture turned yellow. TMSCl (0.09 mL, 0.73 mmol) was added and the reaction mixture became colourless. Further LDA (1.16 mL, 0.69 mmol) from the stock solution was added and the reaction mixture went yellow again. Upon warming to room temperature the yellow colour was bright and became light orange. The reaction was left for 16.5 h. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (46 mg, 0.17 mmol, 48%). **487**: $\mathbf{R_f}$ (1:1 Pet.Ether:EtOAc) 0.51; $[\alpha]_D^{21}$ = –43.9 (*c* = 1.4 in $CHCl_3$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.45 (1H, br. s, N*H*), 7.43 (2H, d, *J* = 8.3, Ar*H*), 7.19 (2H, d, *J* = 8.0, Ar*H*), 2.99 (3H, s, NC$H_3$), 2.51-2.35 (4H, m, C$H_2$C$H_2$S), 2.34 (3H, s, CC$H_3$), 2.06 (3H, s, SC$H_3$); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.8 (*C*=O), 157.5 (*C*=O), 138.5 (Ar*C*), 134.2 (Ar*C*), 129.7 (2×Ar*C*H), 125.3 (2×Ar*C*H), 67.0 (*C*$CH_2$), 37.6 (*C*$H_2$), 28.8 (*C*$H_2$), 24.9 (N*C*$H_3$), 21.1 (C*C*$H_3$), 15.5 (S*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3280 (broad NH), 2917 (C-H), 1775 (C=O), 1707 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 279 ([M+H]$^+$, 50%), 301 ([M+Na]$^+$, 100%), 317 ([M+K]$^+$, 20%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{18}N_2O_2SNa$ [M+Na]$^+$ 301.0987, found 301.0987; **HPLC**: *er* 90:10, ChiralPak® AD-H, Hexane:IPA = 95:5, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 16.6 (major), 18.6 (minor) min.

*NMR file: $^1$H NMR = 2014-08-05-jpc-20 (10) 500a, $^{13}$C NMR = 2014-08-05-jpc-20 (11) 500a.*

**(*R*)-5-(3-Methoxyphenyl)-3,5-dimethylimidazolidine-2,4-dione (490)**

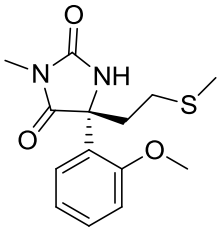



Following general procedure **12**, a stock solution of LDA was prepared with THF (2.4 mL), DiPA (0.42 mL, 3.01 mmol) and *n*BuLi (1.98 mL, 2.98 mmol, 1.51 M in hexanes). The urea pseudoephedrine **653** (154 mg, 0.37 mmol) in THF (2.5 mL) was added to cooled LDA (1.20 mL, 0.75 mmol) from the stock solution and the reaction mixture turned pale yellow. TMSCl (0.10 mL, 0.78 mmol) was added and the reaction mixture became colourless. Further LDA (1.20 mL, 0.75 mmol) from the stock solution was added and the reaction mixture went yellow again. Upon warming to room temperature the yellow colour was bright. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (51 mg, 0.21 mmol, 55%). **490**: $\mathbf{R_f}$ (7:3 Pet.Ether:EtOAc) 0.25; **mp**: 116-118 °C; $[\alpha]_D^{21}$ = +162.7 (*c* = 1.2 in $CHCl_3$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.59 (1H, d, *J* = 7.7, Ar*H*), 7.30 (1H, t, *J* = 7.9, Ar*H*), 6.96-6.92 (2H, m, Ar*H*), 6.46 (1H, br. s, N*H*), 3.87 (3H, s, OC$H_3$), 3.05 (3H, s, NC$H_3$), 2.17 (1H, dq, *J* = 14.8, 7.4, C$H_A$H$_B$CH$_3$), 2.07 (1H, dq, *J* = 14.5, 7.3, CH$_A$$H_B$CH$_3$), 0.88 (3H, t, *J* = 7.4, CH$_2$C$H_3$); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 174.7 (*C*=O), 157.0 (*C*=O), 156.7 (Ar*C*OMe),

129.7 (Ar*C*H), 126.4 (Ar*C*H), 126.1 (Ar*C*), 121.1 (Ar*C*H), 111.7 (Ar*C*H), 67.2 (*C*$CH_2$), 55.7 (O*C*$H_3$), 30.6 (*C*$H_2$$CH_3$), 24.6 (N*C*$H_3$), 8.3 ($CH_2$*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3297 (broad NH), 2972, 2938 (C-H), 1766 (C=O), 1701 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 249 ([M+H]$^+$, 100%), 271 ([M+Na]$^+$, 40%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{16}N_2O_3Na$ [M+Na]$^+$ 271.1059, found 271.1072; **HPLC**: *er* 88:12, Chiralcel OD-H, Hexane:IPA = 90:10, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 9.8 (major), 13.9 (minor) min.

*NMR file: $^1$H NMR = 2014-11-03-jpc-56 (10) 500a, $^{13}$C NMR = 2014-11-03-jpc-49 (11) 500a.*

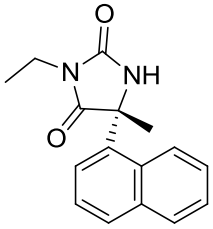
**(*R*)-5-(2-Methoxyphenyl)-3-methyl-5-(2-(methylthio)ethyl)imidazolidine-2,4-dione (491)**




Following general procedure **12**, a stock solution of LDA was prepared with THF (2.80 mL), DiPA (0.47 mL, 3.35 mmol) and *n*BuLi (2.20 mL, 3.31 mmol, 1.51 M in hexanes). The urea pseudoephedrine **655** (190 mg, 0.41 mmol) in THF (2.70 mL) was added to cooled LDA (1.37 mL, 0.83 mmol) from the stock solution and the reaction mixture turned pale yellow. TMSCl (0.11 mL, 0.87 mmol) was added and the reaction mixture became colourless. Further LDA (1.37 mL, 0.83 mmol) from the stock solution was added and the reaction mixture went yellow again. Upon warming to room temperature the yellow colour was bright. The reaction was left for 4 h. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a white solid (79 mg, 0.27 mmol, 65%). **491**: **$R_f$** (1:1 Pet.Ether:EtOAc) 0.38; **mp**: 125-127 °C; $[\alpha]_D^{21}$= +135.8 (*c* = 1.1 in $CHCl_3$), **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.56 (1H, d, *J* = 7.1, Ar*H*), 7.34-7.30 (1H, m, Ar*H*), 6.97-6.93 (2H, m, Ar*H*), 6.59 (1H, br. s, N*H*), 3.89 (3H, s, OC$H_3$), 3.06 (3H, s, NC$H_3$), 2.63-2.56 (1H, m, CC$H_A$$H_B$$CH_2$S), 2.42-2.25 (3H, m, $CH_2$C$H_2$S + $CCH_A$$H_B$$CH_2$S), 2.06 (3H, s, SC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.1 (*C*=O), 156.7 (*C*=O), 156.6 (Ar*C*OMe), 130.0 (Ar*C*H), 126.3 (Ar*C*H), 125.3 (Ar*C*), 121.2 (Ar*C*H), 111.7 (Ar*C*H), 66.3 (*C*$CH_2$), 55.7 (O*C*$H_3$), 36.8 (S*C*$H_2$), 28.6 (S$CH_2$*C*$H_2$), 24.8 (N*C*$H_3$), 15.6 (S*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3297 (broad NH), 2917 (C-H), 1771 (C=O), 1708 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 295 ([M+H]$^+$, 80%), 317 ([M+Na]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{14}H_{18}N_2O_3SNa$ [M+Na]$^+$ 317.0936, found 317.0939; **HPLC**: *er* 90:10, ChiralPak® AD-H, Hexane:IPA = 90:10, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 15.4 (major), 18.5 (minor) min.

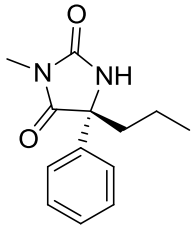
*NMR file: $^1$H NMR = 2014-09-04-jpc-43 (10) 400c, $^{13}$C NMR = 2014-09-04-jpc-43 (11) 400c.*

**(*R*)-3-Ethyl-5-methyl-5-(naphthalen-1-yl)imidazolidine-2,4-dione (507)**



Following general procedure **12**, a stock solution of LDA was prepared with THF (2.40 mL), DiPA (0.42 mL, 3.03 mmol) and *n*BuLi (1.98 mL, 2.99 mmol, 1.51 M in hexanes). The urea pseudoephedrine **651** (162 mg, 0.37 mmol) in THF (2.50 mL) was added to cooled LDA (1.20 mL, 0.75 mmol) from the stock solution and the reaction mixture turned yellow/orange. TMSCl (0.10 mL, 0.79 mmol) was added and the reaction mixture became colourless. Further LDA (1.20 mL, 0.75 mmol) from the stock solution was added and the reaction mixture went yellow again. Upon warming to room temperature the yellow colour was bright and got darker over time. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a colourless oil which upon standing became a white solid (73 mg, 0.27 mmol, 73%). **507**: $\mathbf{R_f}$ (7:3 Pet.Ether:EtOAc) 0.25; **mp**: 121-123 °C; $[\alpha]_D^{21}$= +88.0 (*c* = 1.3 in $CHCl_3$); **$^1$H NMR** (400 MHz, MeOD): $\delta_H$ = 7.92-7.88 (2H, m, Ar*H*), 7.81-7.79 (1H, m, Ar*H*), 7.74 (1H, d, *J* = 7.0, Ar*H*), 7.49-7.45 (3H, m, Ar*H*), 3.69 (2H, q, *J* = 7.2, NC$H_2$CH$_3$), 1.99 (3H, s, CC$H_3$), 1.30 (3H, t, *J* = 7.2, NCH$_2$C$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 175.8 (*C*=O), 156.6 (*C*=O), 135.0 (Ar*C*), 133.1 (Ar*C*), 130.5 (Ar*C*), 130.4 (Ar*C*H), 130.0 (Ar*C*H), 126.9 (Ar*C*H), 125.9 (Ar*C*H), 125.2 (Ar*C*H), 125.1 (Ar*C*H), 123.8 (Ar*C*H), 64.6 (*C*CH$_3$), 34.1 (*C*H$_2$CH$_3$), 26.7 (NCH$_3$), 13.4 (CH$_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3288 (broad NH), 2977, 2937 (C-H), 1774 (C=O), 1704 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 291 ([M+Na]$^+$, 20%), (ESI$^-$, MeOH): *m/z* = 267 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{16}H_{16}N_2O_2Na$ [M+Na]$^+$ 291.1109, found 291.1118; **HPLC**: *er* 84:16, ChiralPak® AD-H, Hexane:IPA = 90:10, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 9.9 (major), 16.0 (minor) min.
*NMR file: $^1$H NMR = 2014-10-13-jpc-34 (21) 400c, $^{13}$C NMR = 2014-10-29-jpc-26 (21) 400c.*

**(*R*)-3-Methyl-5-phenyl-5-propylimidazolidine-2,4-dione (661)**

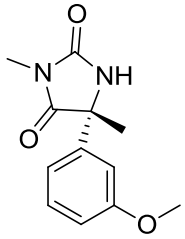


Following general procedure **12**, a stock solution of LDA was prepared with THF (3.20 mL), DiPA (0.52 mL, 3.71 mmol) and *n*BuLi (2.42 mL, 3.67 mmol, 1.51 M in hexanes). The urea pseudoephedrine **649** (182 mg, 0.46 mmol) in THF (3.00 mL) was added to cooled LDA (1.54 mL, 0.92 mmol) from the stock solution and the reaction mixture turned yellow. TMSCl (0.12 mL, 0.96

mmol) was added and the reaction mixture became colourless. Further LDA (1.54 mL, 0.92 mmol) from the stock solution was added and the reaction mixture went yellow again. Upon warming to room temperature the yellow colour was bright and got darker over time. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a white solid (75 mg, 0.32 mmol, 71%). **661**: $\mathbf{R}_f$ (1:1 Pet.Ether:EtOAc) 0.50; **mp**:131-133 °C; $[\alpha]_D^{21} = -94.5$ (*c* = 1.9 in $CHCl_3$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.57-7.55 (2H, m, Ph*H*), 7.39-7.36 (2H, m, Ph*H*), 7.34-7.31 (1H, m, Ph*H*), 7.07 (1H, br. s, N*H*), 3.00 (3H, s, NC$H_3$), 2.18-2.04 (2H, m, C$H_2$CH$_2$CH$_3$), 1.35-1.20 (2H, m, CH$_2$C$H_2$CH$_3$), 0.93 (3H, t, *J* = 7.3, CH$_2$CH$_2$C$H_3$); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 175.1 (*C*=O), 157.7 (*C*=O), 138.1 (Ar*C*), 128.9 (2×Ar*C*H), 128.4 (Ar*C*H), 125.5 (2×Ar*C*H), 67.6 (*C*CH$_2$), 41.3 (*C*H$_2$CH$_2$CH$_3$), 24.8 (NCH$_3$), 17.3 (CH$_2$*C*H$_2$CH$_3$), 14.0 (CH$_2$CH$_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3284 (broad NH), 2960, 2874 (C-H), 1773 (C=O), 1705 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 233 ([M+H]$^+$, 100%), 255 ([M+Na]$^+$, 40%), (ESI$^-$, MeOH): *m/z* = 231 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{13}H_{16}N_2O_2Na$ [M+Na]$^+$ 255.1109, found 255.1098; **HPLC**: *er* 92:8 Chiralcel OD-H, Hexane:IPA = 90:10, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 7.5 (major), 9.7 (minor) min.

*NMR file: $^1$H NMR = 2014-11-03-jpc-12 (10) 500a, $^{13}$C NMR = 2014-11-03-jpc-12 (21) 500a.*

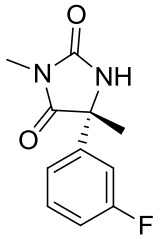
**(*R*)-5-(3-Methoxyphenyl)-3,5-dimethylimidazolidine-2,4-dione (662)**




Following general procedure **12**, a stock solution of LDA was prepared with THF (3.40 mL), DiPA (0.58 mL, 4.10 mmol) and *n*BuLi (2.68 mL, 4.05 mmol, 1.51 M in hexanes). The urea pseudoephedrine **650** (202 mg, 0.51 mmol) in THF (3.40 mL) was added to cooled LDA (1.67 mL, 1.01 mmol) from the stock solution and the reaction mixture turned yellow. TMSCl (0.14 mL, 1.06 mmol) was added and the reaction mixture became colourless. Further LDA (1.67 mL, 1.01 mmol) from the stock solution was added and the reaction mixture went yellow again. Upon warming to room temperature the yellow colour was bright and got darker over time. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a colourless oil (80 mg, 0.34 mmol, 68%). **662**: $\mathbf{R}_f$ (1:1 Pet.Ether:EtOAc) 0.44; $[\alpha]_D^{21} = -66.0$ (*c* = 1.2 in $CHCl_3$); **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.30 (1H, t, *J* = 8.0, Ar*H*), 7.08 (1H, ddd, *J* = 7.8, 2.0, 1.0, Ar*H*), 7.06-7.05 (1H, m, Ar*H*), 6.87 (1H, ddd, *J* = 8.2, 2.0, 1.0, Ar*H*), 6.25 (1H, br. s, N*H*), 3.81 (3H, s, OC$H_3$), 3.02 (3H, s, NC$H_3$), 1.82 (3H, s, CC$H_3$); **$^{13}$C {$^1$H} NMR** (125 MHz, $CDCl_3$): $\delta_C$ = 175.4 (*C*=O), 160.0 (Ar*C*OMe), 157.2 (*C*=O), 140.4 (Ar*C*), 130.0 (Ar*C*H), 117.6 (Ar*C*H), 113.7 (Ar*C*H),

111.6 (Ar*C*H), 63.9 (*C*$CH_3$), 55.5 (O*C*$H_3$), 25.9 (C*C*$H_3$), 25.0 (N*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3286 (broad NH), 2941, 2836 (C-H), 1779 (C=O), 1708 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 235 ([M+H]$^+$, 100%), 257 ([M+Na]$^+$, 50%), (ESI$^-$, MeOH): *m/z* = 233 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{12}H_{14}N_2O_3Na$ [M+Na]$^+$ 257.0902, found 257.0900; **HPLC**: *er* 93:7, Chiralcel OD-H, Hexane:IPA = 90:10, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 19.2 (major), 21.2 (minor) min.
*NMR file: $^1$H NMR = 2014-10-13-jpc-2 (10) 500a, $^{13}$C NMR = 2014-11-03-jpc-48 (11) 500a.*

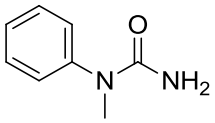
**(R)-5-(3-Fluorophenyl)-3,5-dimethylimidazolidine-2,4-dione (663)**
(from urea pseudoephedrine **681** (pg324) that was synthesised by another group member using the same procedures described above for its analogues)**(b)**




Following general procedure **12**, a stock solution of LDA was prepared with THF (2.40 mL), DiPA (0.42 mL, 3.03 mmol) and *n*BuLi (1.98 mL, 2.99 mmol, 1.51 M in hexanes). The urea pseudoephedrine **681** (145 mg, 0.37 mmol) in THF (2.50 mL) was added to cooled LDA (1.20 mL, 0.75 mmol) from the stock solution and the reaction mixture turned bright yellow. TMSCl (0.10 mL, 0.79 mmol) was added and the reaction mixture became colourless. Further LDA (1.20 mL, 0.75 mmol) from the stock solution was added and the reaction mixture went yellow again. Upon warming to room temperature the yellow colour was bright and turned bright orange over time. Purification by flash column chromatography ($SiO_2$, 7:3 Pet.Ether:EtOAc) yielded the title compound as a white solid (37 mg, 0.17 mmol, 45%). **663**: $\mathbf{R}_f$ (7:3 Pet.Ether:EtOAc) 0.30; **mp**: 197-199 °C; **$^1$H NMR** (500 MHz, $CDCl_3$): $\delta_H$ = 7.37 (1H, td, *J* = 8.0, 5.8, Ar*H*), 7.31-7.29 (1H, m, Ar*H*), 7.27-7.24 (1H, m, Ar*H*), 7.04 (1H, tdd, *J* = 8.3, 2.5, 1.0, Ar*H*), 6.25 (1H, br. s, N*H*), 3.03 (3H, s, NC$H_3$), 1.83 (3H, s, CC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 174.9 (*C*=O), 163.1 (d, $^1J_{C\text{-}F}$ = 247.2, Ar*C*F), 156.8 (*C*=O), 141.3 (d, $^3J_{C\text{-}F}$ = 7.1, Ar*C*C), 130.6 (d, $^3J_{C\text{-}F}$ = 8.3, Ar*C*H), 121.0 (d, $^4J_{C\text{-}F}$ = 3.1, Ar*C*H), 115.7 (d, $^2J_{C\text{-}F}$ = 21.1, Ar*C*H), 113.0 (d, $^2J_{C\text{-}F}$ = 23.5, Ar*C*H), 63.6 (*C*$CH_3$), 25.9 (C*C*$H_3$), 25.1 (N*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3252 (NH), 2989, 2957 (C-H), 1786 (C=O), 1688 (C=O); **MS** (ESI$^-$, MeOH): *m/z* = 221 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{12}N_2O_2F$ [M+H]$^+$ 223.0883, found 223.0879. **HPLC:** *er* 55:45, ChiralPak® AD-H, Hexane:IPA = 95:5, flow = 1.0 mL/min, λ = 230 nm, $t_R$ = 10.5 (major), 11.7 (minor) min.
*NMR file: $^1$H NMR* = 2014-08-15-jpc-14 (10) 500a, *$^{13}$C NMR* = 2014-11-27-jpc-6 (11) *400c.*

**Synthesis of proposed impurity 666:**

**1-Methyl-1-phenylurea (666)**[235]

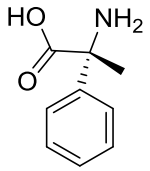


*N*-methyl-*N*-phenylcarbamoyl chloride (250 mg, 1.48 mmol, 1.0 eq.) was dissolved in DCM (5.00 mL) and $Et_3N$ (0.27 mL, 1.92 mmol, 1.3 eq.) added followed by 35% $NH_3$ solution (1.50 mL). The reaction was stirred vigorously for 1.5 h and TLC analysis showed there was still starting material therefore further 35% aqueous $NH_3$ solution (1.00 mL) was added. The reaction was complete after a further 47 h. The reaction was diluted with DCM and 1.0 M HCl added, the DCM was separated from the aqueous layer and washed with brine (×2) before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. The title compound was yielded as a purple solid without further purification (190 mg, 1.27 mmol, 86%). **666**: $\mathbf{R_f}$ (5:95 MeOH:DCM) 0.21; **mp**: 81-83 °C; **$^1$H NMR** (400 MHz, $CDCl_3$): $\delta_H$ = 7.44-7.41 (2H, m, Ph*H*), 7.33-7.28 (3H, m, Ph*H*), 4.39 (2H, br. s, N$H_2$), 3.27 (3H, s, NC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, $CDCl_3$): $\delta_C$ = 157.8 (*C*=O), 143.8 (Ar*C*), 130.2 (2×Ar*C*H), 127.7 (Ar*C*H), 127.2 (2×Ar*C*H), 37.3 (N*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3415 (NH), 2978, 2930 (C-H), 1637 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 151 ([M+H]$^+$, 100%), 173 ([M+Na]$^+$, 50%); **HRMS** (ESI$^+$): *m/z* calcd for $C_8H_{10}N_2ONa$ [M+Na]$^+$ 173.0691, found 173.0689. Matches literature data.

*NMR file: $^1$H NMR = 2014-10-17-jpc-55(10) 400c, $^{13}$C NMR = 2014-10-17-jpc-55(11) 400c.*

**Synthesis of 510:**

**(*R*)-2-Amino-2-phenylpropanoic acid (508)**[228]

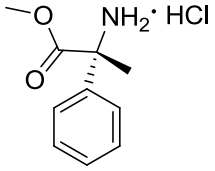


Following general procedure **13**, 4.0 M NaOH solution (1.00 mL) was added to hydantoin **446** (35 mg, 0.17 mmol) and heated to reflux for 65 h. Purification with dowex ion exchange resin yielded the title compound as a white solid (26 mg, 0.16 mmol, 92%). **508**: $\mathbf{R_f}$ (1:9 MeOH:DCM) 0.06; **mp**: >296 °C; **$^1$H NMR** (400 MHz, MeOD): $\delta_H$ = 7.58-7.56 (2H, m, Ph*H*), 7.42-7.32 (3H, m, Ph*H*), 1.86 (3H, s, CC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, MeOD): $\delta_C$ = 175.7 (*C*=O), 140.8 (Ar*C*), 129.8 (2×Ar*C*H), 129.5 (Ar*C*H), 127.1 (2×Ar*C*H), 64.0 (*C*CH$_3$), 22.8 (C*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3062 (OH), 2978 (C-H), 1615 ($NH_3^+$), 1593 ($^-$OC=O); **MS** (ESI$^+$, MeOH): *m/z* = 166 ([M+H]$^+$, 100%), 188 ([M+Na]$^+$, 75%);

**HRMS** (ESI$^+$): *m/z* calcd for $C_9H_{12}NO_2$ [M+H]$^+$ 166.0868, found 166.0869. Matches literature data.

*NMR file: $^1$H NMR = 2014-12-04-jpc-20 (10) 400c, $^{13}$C NMR = 2014-12-01-jpc-46 (10) 400c.*

**(*R*)-Methyl 2-amino-2-phenylpropanoate hydrochloride (510)**[216]

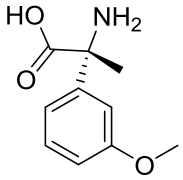


Following general procedure **14**, quaternary amino acid **508** (19 mg, 0.12 mmol) was dissolved in MeOH (10.0 mL), cooled to 0 °C and thionyl chloride (0.50 mL) added. The reaction was complete after 36 h at reflux. The title compound was yielded as a white solid (25 mg, 0.12 mmol, >99%). **510**: $\mathbf{R_f}$ (1:9 MeOH:DCM) 0.24; **mp**: 168-169 °C; $[\alpha]_D^{21} = -46.4$ (*c* = 0.5 in MeOH); **$^1$H NMR** (400 MHz, MeOD): $\delta_H$ = 7.52-7.47 (5H, m, Ph*H*), 3.84 (3H, s, OC$H_3$), 2.00 (3H, s, CC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, MeOD): $\delta_C$ = 172.2 (*C*=O), 137.0 (Ar*C*), 130.9 (Ar*C*H), 130.5 (2×Ar*C*H), 126.8 (2×Ar*C*H), 62.8 (*C*$CH_3$), 54.4 (O*C*$H_3$), 22.1 (C*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2987, 2920 (C-H), 2751 (O-C), 1753 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 180 ([M–Cl]$^+$, 50%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{10}H_{14}NO_2$ [M–Cl]$^+$ 180.1025, found 180.1031. Matches literature data.

*NMR file: $^1$H NMR = 2014-12-03-jpc-13 (10) 400c, $^{13}$C NMR = 2014-12-04-jpc-21 (10) 400c.*

**Synthesis of 670:**

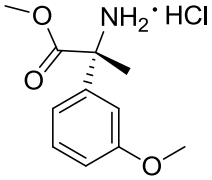
**(*R*)-2-Amino-2-(3-methoxyphenyl)propanoic acid (667)**



Following general procedure **13**, 4.0 M NaOH solution (1.50 mL) was added to hydantoin **662** (65 mg, 0.28 mmol) and heated to reflux for 40 h. Purification with dowex ion exchange resin yielded the title compound as a white solid (54 mg, 0.28 mmol, >99%). **667**: $\mathbf{R_f}$ (1:9 MeOH:DCM) 0.06; **mp**: 249-251 °C; **$^1$H NMR** (400 MHz, MeOD): $\delta_H$ = 7.33-7.29 (1H, m, Ph*H*), 7.14-7.13 (2H, m, Ph*H*), 6.92-6.90 (1H, m, Ph*H*), 3.81 (3H, s, OC$H_3$), 1.84 (3H, s, CC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, MeOD): $\delta_C$ = 176.1 (*C*=O), 161.4 (Ar*C*OMe), 142.7 (Ar*C*C), 130.7 (Ar*C*H), 119.1 (Ar*C*H), 114.7 (Ar*C*H), 113.0 (Ar*C*H), 63.9 (*C*$CH_3$), 55.7 (O*C*$H_3$), 23.2 (C*C*$H_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2991 (OH), 2942 (C-H), 1615 ($NH_3^+$), 1602 ($^-$OC=O); **MS** (ESI$^+$, MeOH): *m/z* = 218 ([M+Na]$^+$, 100%), (ESI$^-$, MeOH): *m/z* = 194 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{10}H_{14}NO_3$ [M+H]$^+$ 196.0974, found 196.0967.

*NMR file: $^1$H NMR = 2014-12-03-jpc-45 (10) 400c, $^{13}$C NMR = 2014-12-03-jpc-19 (10) 400c.*

**Methyl (*R*)-2-amino-2-(3-methoxyphenyl)propanoate hydrochloride (670)**

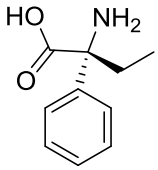


Following general procedure **14**, quaternary amino acid **667** (54 mg, 0.28 mmol) was dissolved in MeOH (10.0 mL), cooled to 0 °C and thionyl chloride (0.50 mL) added. The reaction was complete after 36 h at reflux. The title compound was yielded as a yellow solid (66 mg, 0.27 mmol, 97%). **670**: $\mathbf{R}_f$ (1:9 MeOH:DCM) 0.36; **mp**: 75-77 °C; $[\alpha]_D^{21}$= –45.2 (*c* = 0.5 in MeOH); **$^1$H NMR** (400 MHz, MeOD): $\delta_H$ = 7.44-7.40 (1H, m, Ph*H*), 7.08-7.03 (3H, m, Ph*H*), 3.84 (6H, s, 2×OC$H_3$), 1.98 (3H, s, CC$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, MeOD): $\delta_C$ = 172.1 (*C*=O), 161.8 (Ar*C*OMe), 138.4 (Ar*C*C), 131.7 (Ar*C*H), 118.7 (Ar*C*H), 115.9 (Ar*C*H), 112.9 (Ar*C*H), 62.7 (*C*CH$_3$), 56.0 (OCH$_3$), 54.4 (OCH$_3$), 22.2 (CCH$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3376 (NH), 2838 (C-H), 1745 (C=O); **MS** (ESI$^+$, MeOH): *m/z* = 210 ([M–Cl]$^+$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{11}H_{16}NO_3$ [M-Cl]$^+$ 210.1130, found 210.1128.

*NMR file: $^1$H NMR = 2014-12-11-jpc-34 (10) 400c, $^{13}$C NMR = 2014-12-11-jpc-34 (11) 400c.*

**<u>Synthesis of 671:</u>**.

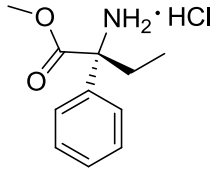
**(*R*)-2-Amino-2-phenylbutanoic acid (668)**[236]



Following general procedure **13**, 4.0 M NaOH solution (1.50 mL) was added to hydantoin **21** (21 mg, 0.10 mmol) and heated to reflux for 96 h. $^1$H NMR analysis showed a mix of the quaternary amino acid and the quaternary amino amide. The residue was redisolved in 4.0 M NaOH solution (5.00 mL) and heated back to reflux for a further 67 h. $^1$H NMR analysis showed the reaction was complete. Purification with dowex ion exchange resin yielded the title compound as a white solid (17 mg, 0.10 mmol, >99%). **668**: $\mathbf{R}_f$ (1:9 MeOH:DCM) 0.06; **mp**: >297 °C; **$^1$H NMR** (400 MHz, MeOD): $\delta_H$ = 7.57-7.55 (2H, m, Ph*H*), 7.40-7.29 (3H, m, Ph*H*), 2.37-2.21 (2H, ABX$_3$ m, C$H_AH_B$CH$_3$), 1.02 (3H, t, *J* = 7.4, CH$_2$C$H_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, D$_2$O): $\delta_C$ = 161.8 (*C*=O), 142.2 (Ar*C*), 128.7 (2×Ar*C*H), 127.7 (Ar*C*H), 125.8 (2×Ar*C*H), 48.8 (*C*CH$_2$), 29.7 (*C*H$_2$CH$_3$), 7.9 (CH$_2$*C*H$_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 3295 (OH/NH$_2$), 3059, 2971 (C-H), 1644 (NH$_3^+$), 1594 ($^-$OC=O); **MS** (ESI$^+$, MeOH): *m/z* = 202 ([M+Na]$^+$, 100%), (ESI$^-$, MeOH): *m/z* = 178 ([M–H]$^-$, 100%); **HRMS** (ESI$^+$): *m/z* calcd for $C_{10}H_{13}NO_2Na$ [M+Na]$^+$ 202.0844, found 202.0854. Matches literature data given.

*NMR file: $^1$H NMR = 2014-12-15-jpc-54 (10) 400c, $^{13}$C NMR = 2014-12-15-jpc-57 (20) 400c.*

**Methyl (*R*)-2-amino-2-phenylbutanoate hydrochloride (671)**

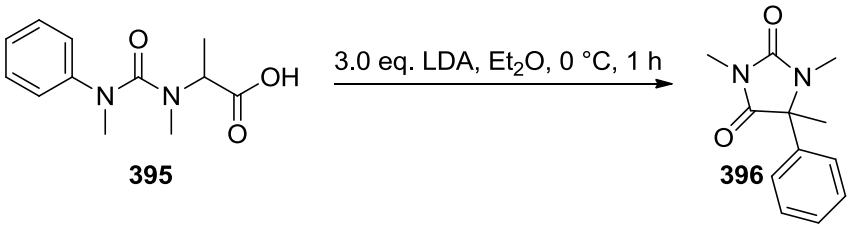



Following general procedure **14**, quaternary amino acid **668** (17 mg, 0.10 mmol) was dissolved in MeOH (10.0 mL), cooled to 0 °C and thionyl chloride (0.80 mL) added. The reaction was complete after 44.5 h at reflux. The title compound was yielded as a white solid (21 mg, 0.09 mmol, 96%). **671**: **$R_f$** (1:9 MeOH:DCM) 0.27; **mp**: 174-176 °C; $[\alpha]_D^{22} = -11.8$ (*c* = 0.5 in MeOH); **$^1$H NMR** (500 MHz, MeOD): $\delta_H$ = 7.52-7.47 (5H, m, Ph*H*), 3.87 (3H, s, $OCH_3$), 2.49-2.40 (2H, $ABX_3$ m, $CH_AH_BCH_3$), 1.05 (3H, t, *J* = 6.9, $CH_2CH_3$); **$^{13}$C {$^1$H} NMR** (100 MHz, MeOD): $\delta_C$ = 171.5 (*C*=O), 136.5 (Ar*C*), 130.8 (Ar*C*H), 130.5 (2×Ar*C*H), 127.0 (2×Ar*C*H), 67.2 (*C*$CH_2$), 54.4 (O*C*$H_3$) 30.1 (*C*$H_2CH_3$), 8.4 ($CH_2CH_3$); **IR (film, cm$^{-1}$)**: $\nu_{max}$ = 2920, 2850 (C-H), 1746 (C=O); **MS** ($ESI^+$, MeOH): *m/z* = 194 ($[M–Cl]^+$, 80%); **HRMS** ($ESI^+$): *m/z* calcd for $C_{11}H_{16}NO_2$ $[M\text{-}Cl]^+$ 194.1181, found 194.1173.

*NMR file: $^1$H NMR = 2015-01-12-jpc-43 (10) 500a, $^{13}$C NMR = 2015-01-09-jpc-11 (10) 400c*

## 3.4 ReactIR Experiments

### 3.4.1 Reaction in $Et_2O$

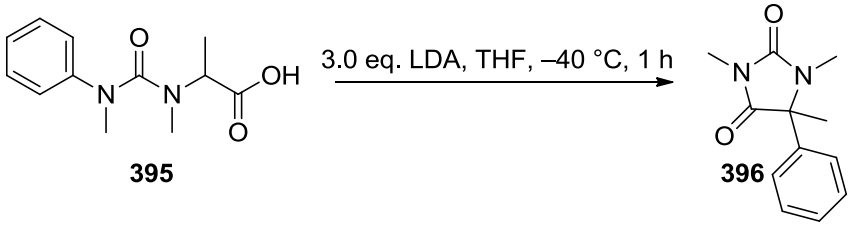



**395** **396**

Anhydrous $Et_2O$ (8.00 mL) was added to a 100 mL three-necked flask equipped with a stirrer bar and ReactIR probe under nitrogen. The solution was cooled to 0 °C using an ice bath, and left to stabilise, after which time an IR solvent background spectrum was taken. Urea acid **395** (250 mg, 1.06 mmol, 1.0 eq.) was added *via* one of the three necks, followed by anhydrous $Et_2O$ (6.00 mL) to wash the substrate into the flask and dissolve the urea acid **395**. The reaction mixture was warmed to room temperature and left to stir for 30 min, whilst all the urea acid **395** dissolved. The reaction mixture was a pale orange solution. In a separate flask LDA was prepared; anhydrous $Et_2O$ (4.00 mL) and DiPA (0.45 mL, 3.18 mmol, 3.0 eq.) were cooled to 0 °C, *n*BuLi (1.38 mL, 3.18 mmol, 2.3 M in hexanes, 3.0 eq.) was added dropwise and stirred for 30 min. The three-necked flask was cooled to 0 °C and an IR reactant background spectrum was taken. The LDA was added dropwise to the reaction mixture over 10 min and the reaction mixture became cloudy. The reaction mixture was left to stir for 1 h at 0 °C and was quenched by a dropwise addition of MeOH. The reaction mixture was allowed to warm to room temperature and the ReactIR probe was removed. The reaction mixture was acidified with 1.0 M HCl and the product was extracted with EtOAc (×3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. NMR analysis of the crude reaction mixture confirmed the presence of hydantoin **396**, along with unreacted **395** (1:3 **395:396**)

Throughout the experiment IR spectra were recorded at varying time intervals. An IR spectrum was initially recorded every min, with **395** in $Et_2O$ at 0 °C. The frequency of recording IR spectra was increased to every 15 seconds during the LDA addition and for 10 min after the addition was complete. The frequency was then reduced to every 45 seconds for the remainder of the 1 h hold at 0 °C and finally the frequency was increased to every 15 seconds during the MeOH quench of the reaction.

### 3.4.2 Reaction in THF



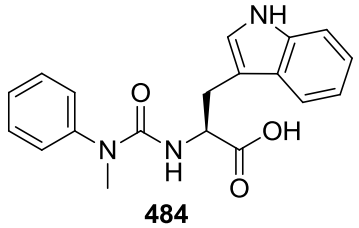

Anhydrous THF (8.00 mL) was added to a 100 mL three-necked flask equipped with a stirrer bar and ReactIR probe under nitrogen. The solution was cooled to –40 °C using a MeCN/dry ice bath and left to stabilise. An IR solvent background spectrum was taken. Urea acid **395** (250 mg, 1.06 mmol, 1.0 eq.) was added through one of the three necks and an IR reactant background spectrum was taken. The reaction mixture was warmed to room temperature to allow the urea acid **395** to dissolve. Once homogeneous the reaction mixture was cooled to –40 °C. In a separate flask LDA was prepared; anhydrous THF (4.00 mL) and DiPA (0.45 mL, 3.18 mmol, 3.0 eq.) were cooled to 0 °C, *n*BuLi (1.38 mL, 3.18 mmol, 2.3 M in hexanes, 3.0 eq.) was added dropwise and the mixture was stirred for 30 min. The LDA was added very slowly dropwise to the reaction mixture over 25 min (1.0 eq. with 5 min wait, 2.0 eq. with 5 min wait and 3.0 eq.). The reaction mixture was left to stir for 1 h at –40 °C and was quenched by a dropwise addition of MeOH. The reaction mixture was allowed to warm to room temperature and the ReactIR probe was removed. The reaction mixture was acidified with 1.0 M HCl and the product extracted with EtOAc (×3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. NMR analysis confirmed the hydantoin **396** was present at the end of the reaction (1:1 **395**:**396**).

Throughout the experiment IR spectra were recorded at varying time intervals. An IR spectrum was recorded every 15 seconds from the start of the experiment until 7 min after the LDA addition was complete. After this time the frequency of recording IR spectra was decreased to every 45 seconds. When the MeOH was added to quench the reaction the frequency was increased to recording spectra every 15 seconds.

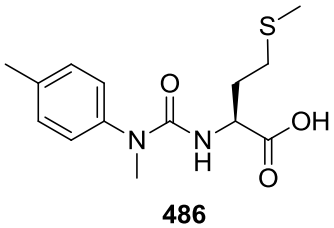
# 4 Appendix

## 4.1 Appendix 1: Compounds Synthesised by Other Group Members[(b)]

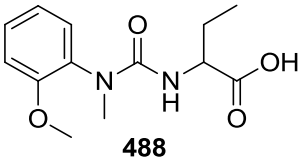
The compounds are referred to in the experimental as starting materials for reactions and were synthesised according to the general procedures as their analogues.



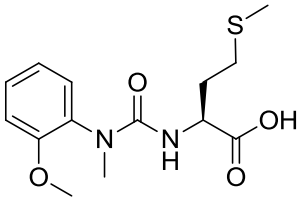

**484**



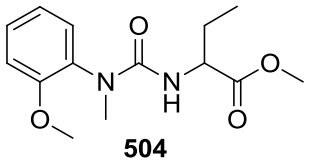

**486**



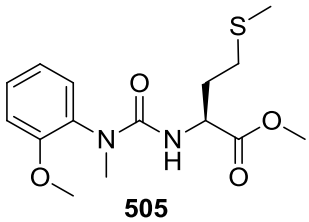

**488**



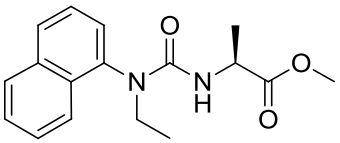

**489**



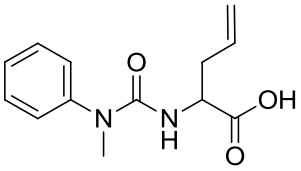

**504**



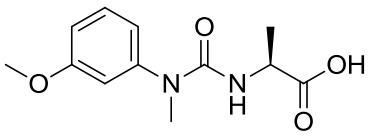

**505**



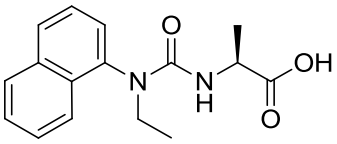

**506**



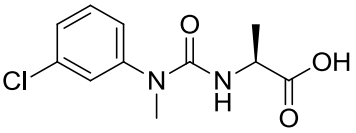

**642**



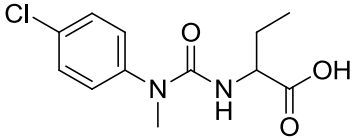

**643**



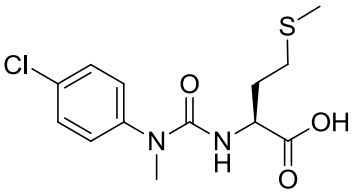

**644**



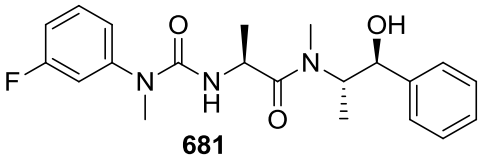

**645**




**646**




**647**



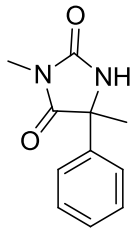

**681**

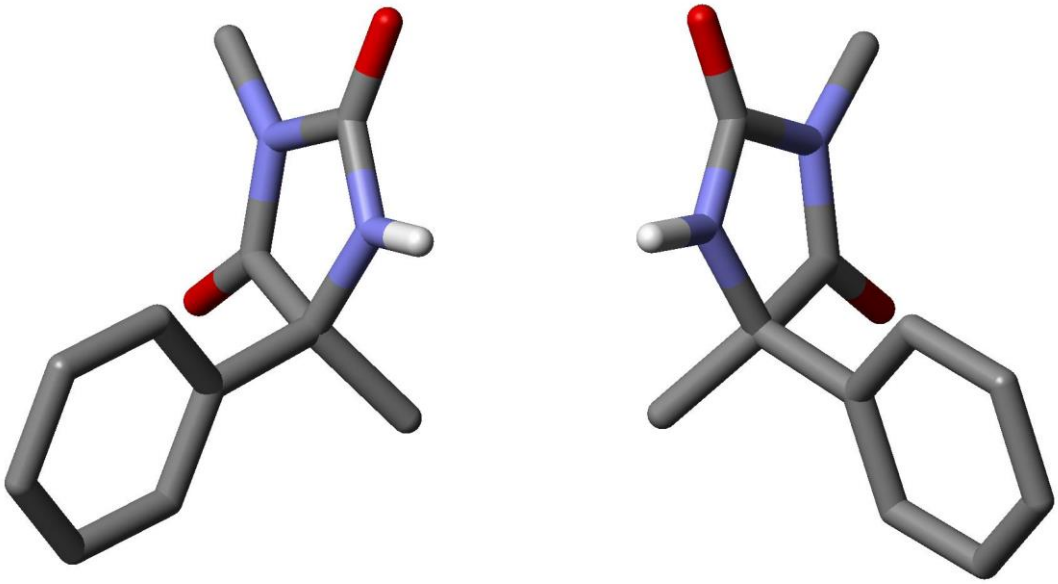
With thanks to Fernando Fernández-Nieto and Mary Okoh

## 4.2 Appendix 2: X-ray Crystal Structure Data

### 4.2.1 X-ray Crystal Structure

Crystal structure and data for the racemate **446** (s4144ma) crystallised using chloroform (CCDC deposition number 1051080)



### 4.2.2 Crystal Data and Structure Refinement

| | | |
|---|---|---|
| Identification code | s4144ma | |
| Empirical formula | C11 H12 N2 O2 | |
| Formula weight | 204.23 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/c | |
| Unit cell dimensions | a = 10.8082(5) Å | a= 90°. |
| | b = 8.2768(4) Å | b= 92.289(2)°. |
| | c = 11.0617(5) Å | g = 90°. |
| Volume | 988.76(8) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.372 $Mg/m^3$ | |
| Absorption coefficient | 0.789 $mm^{-1}$ | |
| F(000) | 432 | |
| Crystal size | 0.25 x 0.17 x 0.06 $mm^3$ | |
| Theta range for data collection | 4.09 to 72.12°. | |
| Index ranges | -13<=h<=12, -10<=k<=10, -13<=l<=13 | |
| Reflections collected | 9673 | |
| Independent reflections | 1947 [R(int) = 0.0297] | |
| Completeness to theta = 67.00° | 99.9 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.9542 and 0.830983 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1947 / 0 / 142 | |
| Goodness-of-fit on $F^2$ | 1.079 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0347, wR2 = 0.0828 | |
| R indices (all data) | R1 = 0.0367, wR2 = 0.0840 | |
| Largest diff. peak and hole | 0.231 and -0.250 $e.Å^{-3}$ | |

### 4.2.3 Atomic Coordinates (x$10^4$)

and Equivalent Isotropic Displacement Parameters ($Å^2$x $10^3$)

U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 2988(1) | 7590(1) | 833(1) | 15(1) |
| C(2) | 3437(1) | 9947(1) | -231(1) | 14(1) |
| C(3) | 3254(1) | 9007(1) | 1699(1) | 14(1) |
| C(4) | 1634(1) | 7084(1) | 962(1) | 16(1) |
| C(5) | 1303(1) | 5910(2) | 1795(1) | 22(1) |
| C(6) | 67(1) | 5507(2) | 1918(1) | 28(1) |
| C(7) | -854(1) | 6277(2) | 1224(1) | 28(1) |
| C(8) | -532(1) | 7448(2) | 404(1) | 27(1) |
| C(9) | 702(1) | 7847(2) | 267(1) | 21(1) |
| C(10) | 3926(1) | 6229(1) | 1048(1) | 18(1) |
| C(11) | 3659(1) | 11963(1) | 1474(1) | 18(1) |
| N(1) | 3177(1) | 8369(1) | -324(1) | 16(1) |
| N(2) | 3424(1) | 10342(1) | 1011(1) | 15(1) |
| O(1) | 3649(1) | 10917(1) | -1025(1) | 20(1) |
| O(2) | 3290(1) | 8955(1) | 2800(1) | 18(1) |

### 4.2.4 Bond Lengths [Å] and Angles [°]

| | |
|---|---|
| C(1)-N(1) | 1.4549(14) |
| C(1)-C(10) | 1.5285(15) |
| C(1)-C(3) | 1.5342(15) |
| C(1)-C(4) | 1.5347(15) |
| C(2)-O(1) | 1.2181(14) |
| C(2)-N(1) | 1.3390(15) |
| C(2)-N(2) | 1.4134(14) |
| C(3)-O(2) | 1.2167(14) |
| C(3)-N(2) | 1.3584(14) |
| C(4)-C(9) | 1.3936(17) |
| C(4)-C(5) | 1.3948(17) |
| C(5)-C(6) | 1.3895(18) |
| C(5)-H(5) | 0.9500 |
| C(6)-C(7) | 1.387(2) |
| C(6)-H(6) | 0.9500 |
| C(7)-C(8) | 1.382(2) |
| C(7)-H(7) | 0.9500 |
| C(8)-C(9) | 1.3888(18) |
| C(8)-H(8) | 0.9500 |
| C(9)-H(9) | 0.9500 |
| C(10)-H(10A) | 0.9800 |
| C(10)-H(10B) | 0.9800 |
| C(10)-H(10C) | 0.9800 |
| C(11)-N(2) | 1.4548(14) |
| C(11)-H(11A) | 0.9800 |
| C(11)-H(11B) | 0.9800 |
| C(11)-H(11C) | 0.9800 |
| N(1)-H(1) | 0.854(17) |

| | |
|---|---|
| N(1)-C(1)-C(10) | 110.35(9) |
| N(1)-C(1)-C(3) | 100.47(9) |
| C(10)-C(1)-C(3) | 111.06(9) |
| N(1)-C(1)-C(4) | 111.79(9) |
| C(10)-C(1)-C(4) | 114.42(9) |
| C(3)-C(1)-C(4) | 107.85(9) |
| O(1)-C(2)-N(1) | 129.22(11) |

| | |
|---|---|
| O(1)-C(2)-N(2) | 123.90(10) |
| N(1)-C(2)-N(2) | 106.88(9) |
| O(2)-C(3)-N(2) | 126.12(10) |
| O(2)-C(3)-C(1) | 126.55(10) |
| N(2)-C(3)-C(1) | 107.32(9) |
| C(9)-C(4)-C(5) | 118.82(11) |
| C(9)-C(4)-C(1) | 119.67(10) |
| C(5)-C(4)-C(1) | 121.47(11) |
| C(6)-C(5)-C(4) | 120.29(12) |
| C(6)-C(5)-H(5) | 119.9 |
| C(4)-C(5)-H(5) | 119.9 |
| C(7)-C(6)-C(5) | 120.47(12) |
| C(7)-C(6)-H(6) | 119.8 |
| C(5)-C(6)-H(6) | 119.8 |
| C(8)-C(7)-C(6) | 119.46(12) |
| C(8)-C(7)-H(7) | 120.3 |
| C(6)-C(7)-H(7) | 120.3 |
| C(7)-C(8)-C(9) | 120.43(13) |
| C(7)-C(8)-H(8) | 119.8 |
| C(9)-C(8)-H(8) | 119.8 |
| C(8)-C(9)-C(4) | 120.53(12) |
| C(8)-C(9)-H(9) | 119.7 |
| C(4)-C(9)-H(9) | 119.7 |
| C(1)-C(10)-H(10A) | 109.5 |
| C(1)-C(10)-H(10B) | 109.5 |
| H(10A)-C(10)-H(10B) | 109.5 |
| C(1)-C(10)-H(10C) | 109.5 |
| H(10A)-C(10)-H(10C) | 109.5 |
| H(10B)-C(10)-H(10C) | 109.5 |
| N(2)-C(11)-H(11A) | 109.5 |
| N(2)-C(11)-H(11B) | 109.5 |
| H(11A)-C(11)-H(11B) | 109.5 |
| N(2)-C(11)-H(11C) | 109.5 |
| H(11A)-C(11)-H(11C) | 109.5 |
| H(11B)-C(11)-H(11C) | 109.5 |
| C(2)-N(1)-C(1) | 113.62(9) |
| C(2)-N(1)-H(1) | 123.3(11) |
| C(1)-N(1)-H(1) | 123.0(11) |

| | |
|---|---|
| C(3)-N(2)-C(2) | 111.32(9) |
| C(3)-N(2)-C(11) | 125.37(9) |
| C(2)-N(2)-C(11) | 123.16(9) |

Symmetry transformations used to generate equivalent atoms:

### 4.2.5 Anisotropic Displacement Parameters ($Å^2 x\ 10^3$)

The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 18(1) | 14(1) | 13(1) | 0(1) | 2(1) | 0(1) |
| C(2) | 12(1) | 18(1) | 13(1) | 0(1) | 2(1) | 0(1) |
| C(3) | 12(1) | 15(1) | 15(1) | 0(1) | 1(1) | 1(1) |
| C(4) | 18(1) | 16(1) | 14(1) | -4(1) | 3(1) | -2(1) |
| C(5) | 24(1) | 24(1) | 17(1) | 0(1) | 2(1) | -3(1) |
| C(6) | 31(1) | 30(1) | 23(1) | -1(1) | 9(1) | -11(1) |
| C(7) | 20(1) | 35(1) | 30(1) | -10(1) | 6(1) | -9(1) |
| C(8) | 19(1) | 31(1) | 31(1) | -4(1) | -2(1) | 0(1) |
| C(9) | 20(1) | 20(1) | 21(1) | 1(1) | 1(1) | -1(1) |
| C(10) | 19(1) | 15(1) | 20(1) | -1(1) | 4(1) | 1(1) |
| C(11) | 21(1) | 14(1) | 19(1) | -2(1) | 1(1) | -2(1) |
| N(1) | 22(1) | 17(1) | 11(1) | -2(1) | 3(1) | -1(1) |
| N(2) | 16(1) | 14(1) | 14(1) | 0(1) | 1(1) | -1(1) |
| O(1) | 26(1) | 21(1) | 15(1) | 4(1) | 3(1) | -4(1) |
| O(2) | 23(1) | 18(1) | 12(1) | 0(1) | 2(1) | -1(1) |

### 4.2.6 Hydrogen Coordinates ($x10^4$)

and Isotropic Displacement Parameters ($Å^2 x\ 10^3$)

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(5) | 1927 | 5384 | 2280 | 26 |
| H(6) | -150 | 4699 | 2482 | 33 |
| H(7) | -1699 | 6001 | 1312 | 34 |
| H(8) | -1160 | 7984 | -70 | 33 |
| H(9) | 914 | 8647 | -305 | 25 |
| H(10A) | 3778 | 5379 | 443 | 27 |
| H(10B) | 3837 | 5779 | 1859 | 27 |
| H(10C) | 4767 | 6656 | 980 | 27 |
| H(11A) | 3482 | 12001 | 2336 | 27 |
| H(11B) | 3124 | 12734 | 1029 | 27 |
| H(11C) | 4528 | 12247 | 1368 | 27 |
| H(1) | 3160(14) | 7855(19) | -995(16) | 22(4) |

### 4.2.7 Torsion Angles [°]

| | |
|---|---|
| N(1)-C(1)-C(3)-O(2) | -175.42(11) |
| C(10)-C(1)-C(3)-O(2) | -58.67(14) |
| C(4)-C(1)-C(3)-O(2) | 67.44(14) |
| N(1)-C(1)-C(3)-N(2) | 5.55(11) |
| C(10)-C(1)-C(3)-N(2) | 122.30(10) |
| C(4)-C(1)-C(3)-N(2) | -111.58(10) |
| N(1)-C(1)-C(4)-C(9) | -22.31(14) |
| C(10)-C(1)-C(4)-C(9) | -148.67(11) |
| C(3)-C(1)-C(4)-C(9) | 87.22(12) |
| N(1)-C(1)-C(4)-C(5) | 160.04(10) |
| C(10)-C(1)-C(4)-C(5) | 33.68(15) |
| C(3)-C(1)-C(4)-C(5) | -90.43(12) |
| C(9)-C(4)-C(5)-C(6) | 0.45(18) |
| C(1)-C(4)-C(5)-C(6) | 178.12(11) |
| C(4)-C(5)-C(6)-C(7) | -0.6(2) |
| C(5)-C(6)-C(7)-C(8) | 0.2(2) |
| C(6)-C(7)-C(8)-C(9) | 0.4(2) |
| C(7)-C(8)-C(9)-C(4) | -0.6(2) |
| C(5)-C(4)-C(9)-C(8) | 0.15(18) |
| C(1)-C(4)-C(9)-C(8) | -177.57(11) |
| O(1)-C(2)-N(1)-C(1) | 179.39(11) |
| N(2)-C(2)-N(1)-C(1) | -0.69(12) |
| C(10)-C(1)-N(1)-C(2) | -120.19(10) |
| C(3)-C(1)-N(1)-C(2) | -2.92(12) |
| C(4)-C(1)-N(1)-C(2) | 111.26(11) |
| O(2)-C(3)-N(2)-C(2) | 174.48(10) |
| C(1)-C(3)-N(2)-C(2) | -6.49(12) |
| O(2)-C(3)-N(2)-C(11) | -1.18(18) |
| C(1)-C(3)-N(2)-C(11) | 177.85(9) |
| O(1)-C(2)-N(2)-C(3) | -175.40(10) |
| N(1)-C(2)-N(2)-C(3) | 4.68(12) |
| O(1)-C(2)-N(2)-C(11) | 0.37(17) |
| N(1)-C(2)-N(2)-C(11) | -179.55(10) |

Symmetry transformations used to generate equivalent atoms:

### 4.2.8 Hydrogen Bonds [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-H(1)...O(2)#1 | 0.854(17) | 2.015(17) | 2.8358(13) | 160.9(15) |

Symmetry transformations used to generate equivalent atoms:
#1 x,-y+3/2,z-1/2

## 4.3 Appendix 3: List of Publications

1. Atkinson, R. C.; Leonard, D. J.; Maury, J.; Castagnolo, D.; Volz, N.; Clayden, J. *Chem. Commun.* **2013**, *49*, 9734.
   Intramolecular Arylation of Amino Acid Enolates

2. Atkinson, R. C.; Fernández-Nieto, F.; Mas Roselló, J.; Clayden, J. *In Press*
   DOI : 10.1002/anie.201502569R1
   Pseudoephedrine-Directed Asymmetric α-Arylation of α-Amino Acid Derivatives

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[10] *Asymmetric Synthesis and Application of α-Amino Acids*; Soloshonok, V. A., Izawa, K., Eds.; ACS Symposium Series 1009; American Chemical Society: Washington, DC, **2009**.

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