Lithiation Chemistry Of Vinyl Ureas

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

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School of Chemistry

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ABSTRACT

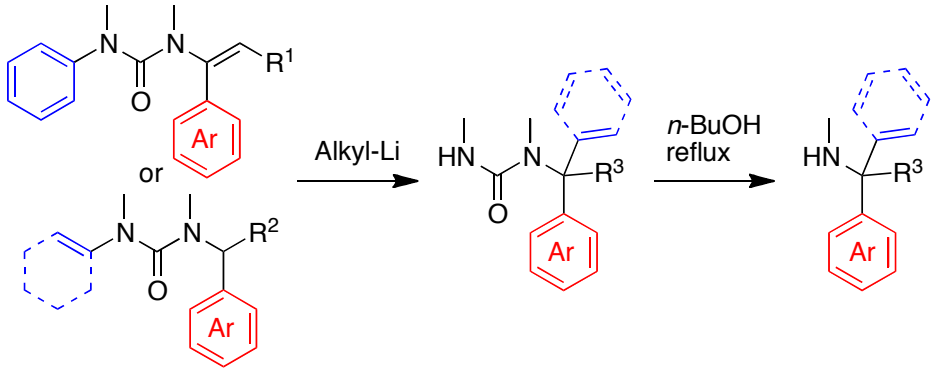
Lithiation Chemistry of Vinyl Ureas

A submission for the degree of Doctor of Philosophy at The University of Manchester,

Julien Lefranc, 2011

The construction of tertiary alkylamines is a synthetic challenge exacerbated by the poor electrophilicity of imines. Due to the presence of this kind of building block in a large number of bioactive molecules, the development of new strategies to synthesise the quaternary carbon centre is essential.

This thesis describes the work carried out on the rearrangement of lithiated vinyl ureas in order to form α-tertiary amines.



The first part presents how vinyl ureas were synthesised, using the reaction between an imine and an aryl isocyanate. The development of one-pot process allows the synthesis of a range of ureas in large scale.

These vinyl ureas present unusual reactivity: the electron-rich double bond can undergo *syn* umpolung carbolithiation followed by retentive aryl migration in order to generate highly substituted amines after cleavage of the urea. The complete mechanism is investigated to understand fully the diastereoselective pathway of the reaction.

In the next part, the rearrangement of lithiated ureas is extended to the N to C vinyl transfer. Different vinyl migrating group are investigated and α-tertiary amines have been synthesised in high yields and enantiomerically pure form using this new rearrangement. The mechanistic insights of the reaction are also studied and a retentive mechanism will be identified. Finally, N to C vinyl transfer is applied toward the synthesis of *Erythrina* alkaloids.

DECLARATION

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Finally I would like to thank my family and friends for their help and very kind support during my three years in England.

ABBREVIATIONS

(−)-spart.	(−)-Sparteine
°C	Degree Celsius
Å	Angstrom
Ac	Acetate
Boc	*Tert*-butoxycarbonyl
Bu	Butyl
Calcd.	Calculated
Cat.	Catalyst
cm	Centimetres
COSY	Correlation Spectroscopy
d.e.	Diastereomeric excess
d.r.	Diastereomeric ratio
Da.	Daltons
DCM	Dichloromethane
δ	Chemical shift
DEPT	Distortionless Enhancement by Polarization Transfer
DIBAL	Diisobutyl Aluminium Hydride
DMPU	1,3-Dimethyltetrahydropyrimidin-2(1*H*)-one
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
e.e.	Enantiomeric excess
e.r.	Enantiomeric ratio
elem. anal.	Elemental analysis
Eq.	Equivalent
Et	Ethyl
g	Gram
h	Hour
HPLC	High Pressure Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
i-Pr	Isopropyl
I.R.	Infra Red spectroscopy
J	Coupling constant

LDA	Lithium Diisopropyl Amide
LRMS	Low-Resolution Mass Spectrometry
M	Molarity
m.p.	Melting Point
Me	Methyl
MHz	Mega Hertz
µm	Micrometer
mL	Millilitre
mm	Millimetre
mmol	millimole
M.S.	Molecular Sieves
µw	Microwave
N	Normality
NBS	N-Bromosuccinimide
n	normal
n.m.	Nanometre
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser effect
PE	Petroleum Ether
Ph	Phenyl
PMP	*para*-Methoxy phenyl
R_f	Retention Factor
s	Secondary
t	Tertiary
Temp.	Temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
Tol.	Toluene
UV	Ultra Violet
ν_{max}	Wave number
w	Weight

“They didn’t know it was impossible,
so they did it.”
Mark Twain

INTRODUCTION

Nitrogen-containing compounds are present in many natural products and biologically active molecules (Figure 1). For these compounds the nitrogen atom is known to play an important role in the biological effect. Moreover, compounds bearing α-quaternary α-amino acid units have very interesting biological properties such as enzyme inhibitors[1] or agonists at glutamate receptors.[2]

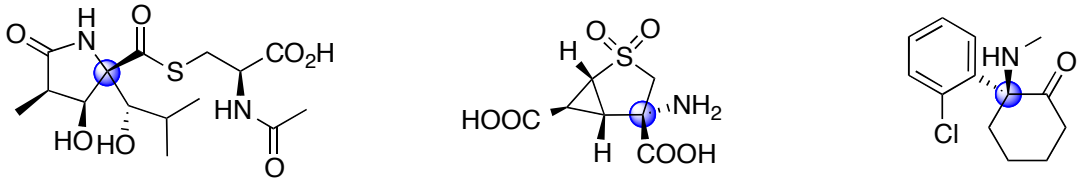
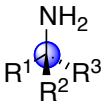


Figure 1: Biologically active molecules containing α-tertiary amines.

Nevertheless, only a few synthetic methods are available today to synthesise α-tertiary amines **1** (Figure 2).



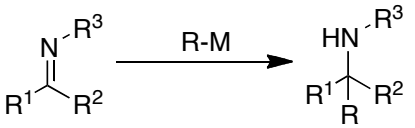
1

Figure 2: α-Tertiary amine.

1. Synthesis of α-tertiary amines

1.1. Addition of organometallic compounds to C-N bonds

The most convenient way to synthesise α-tertiary amines is the 1,2 addition of organometallic reagents to ketimines **2** (Scheme 1).[3-5]



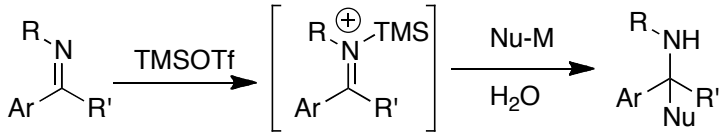
2 **3**

Scheme 1: Organometallic addition to ketimines.

Unfortunately, due to the poor electrophilicity of the carbon of the ketimine **2**, the addition of organometallics to imines can present competitive reactions such as enolisation,[6] creating limitation to this approach.

1.1.1. Activation of the imine

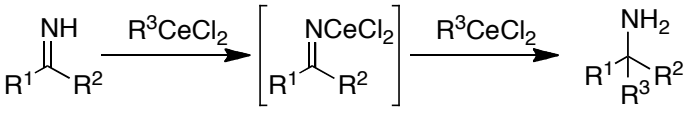
In order to improve the electrophilicity and the reactivity of the carbon centre of the imine, many additives have been tested. One of the first examples has been published by Brook[7] who used trimethylsilyl triflate to improve the addition of Grignard reagents to the imine **4** (Scheme 2). In this case, the proposed mechanism involves the formation of an activated iminium salt **5** which reacts more readily with the nucleophile to form amine **6**. The main drawback of this methodology is its limitation to non-enolisable ketimines.



4 **5** **6**

Scheme 2: Addition of Grignard reagents to ketimines in the presence of TMS.

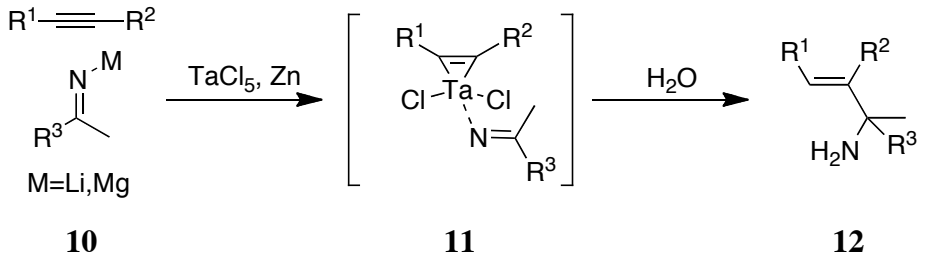
Another possibility to activate the imines is coordination with metals. Many examples have been reported on aldimines but only a few have been presented for ketimines. Du Pont Merck Pharmaceutical Company uses an organocerium reagent with *N*-unsubstituted ketimines to obtain the desired α-tertiary amine **9** (Scheme 3).[8] In this methodology, the ketimine **7** reacted with the organocerium reagent to form the *N*-metalloimine **8** which reacted with a second organocerium to afford the α-tertiary amine **9** after hydrolysis.



7 **8** **9**

Scheme 3: Addition of organocerium regaents to ketimines **7**.

Another approach uses a tantalum chloride to attach an alkyne to the metalo-methylketoimine **10** (generated from the corresponding nitrile) (Scheme 4). This reaction proceeds via the formation of the tantalum-alkyne complex **11** which can then transfer the alkene to form the corresponding amine **12**. [9]

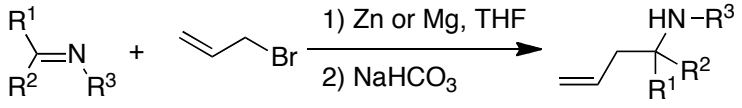


10 **11** **12**

Scheme 4: Reaction of tantalum-alkyne with ketoimines **10**.

1.1.2. Influence of the organometallic reagent

The choice of the organometallic reagent also plays a very important role in these additions. As shown before,[8] organocerium reagents can be used as nucleophiles. Allylic organometallic reagents have also been described as efficient nucleophiles.[10] These reagents are generally more reactive than 'unstabilised' organometallic reagents in the addition to imines. An interesting example has been reported in the Barbier-type reaction of allylbromide to ketimines **13,** with the desired amines **14** being obtained in very good yields (Scheme 5).[10]



13 **14**

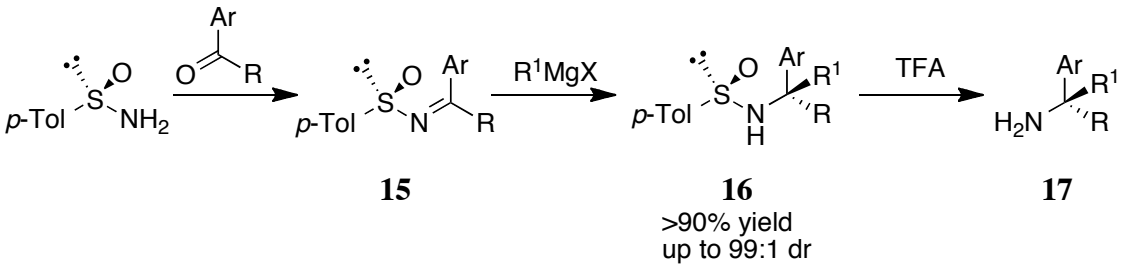
Scheme 5: Barbier-type reaction with allylbromide.

Because of the competitive deprotonation α to the imine, this methodology is used to synthesise amines starting from aldehydes and less often from ketones.

1.1.3. Enantioselective addition to ketimines

Asymmetric synthesis of quaternary centres is a great challenge in organic synthesis. However, despite the prevalence of amine functionality in natural and pharmaceutical products, few methods have been reported for the enantiomeric synthesis of α-tertiary

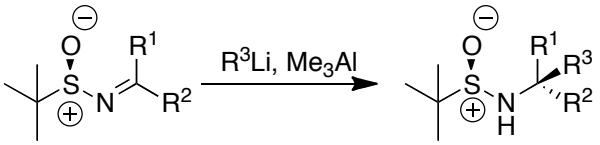
amines. In the example below (Scheme 6), the chiral sulfinyl imine **15**, derived from chiral *p*-toluenesulfinamide, leads to the chiral amine **17** in good yield and with good diastereoselectivity.[11] The Grignard reagent attacks the electrophilic carbon from the less hindered face (opposite to the oxygen) and treatment of sulfinamine **16** with TFA forms the desired deprotected amine **17**.



Scheme 6: Asymmetric addition of Grignard reagent to *p*-toluenesulfinyl imines.

Unfortunately, this reaction is successful only with allylmagnesium and benzyl-magnesium halides. More basic nucleophiles such as *n*-BuLi lead to the deprotonation on the α position of the imine.

In 1999, Ellman *et al*. overcame the problem using $AlMe_3$ to activate the *t*-butyl sulfinyl imine **18** toward the addition of organolithiums (Scheme 7).[12-14] The stereochemistry of the new chiral centre can be rationalised by a six-membered-ring transition state (Figure 3).



Scheme 7: Addition of organolithiums to *t*-butanesulfinyl ketimines.

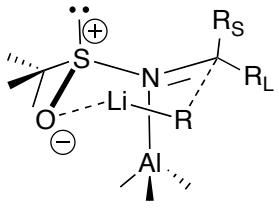
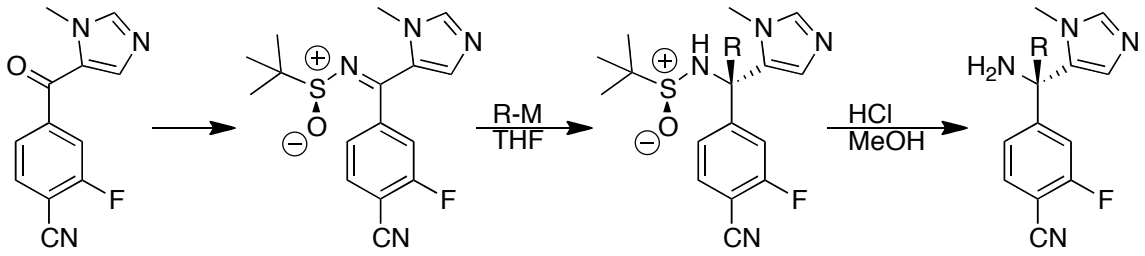


Figure 3: Transition state for the addition to *t*-butanesulfinyl ketimines.

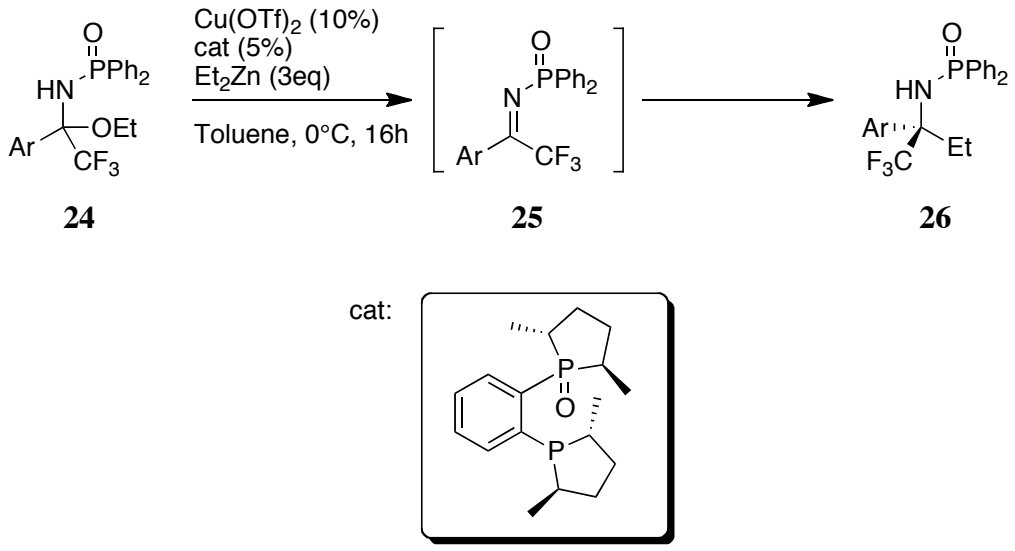
This method is very efficient and has been used to synthesise biologically active compounds such as the ras farnesyl transferase inhibitor **23** (Scheme 8)[15] and can be used with different organometallic reagents.



20 **21** **22** **23**

Scheme 8: Synthesis of ras farnesyl transferase inhibitor derivatives **23**.

Another possible way to synthesise chiral α-tertiary amines is copper-catalysed C-C bond formation.[16] The first example of the use of a copper catalyst has been reported to synthesise α-trifluoromethyl tertiary amines **26** in very high enantiomeric excess (91-99% *e.e.*).[17] In this work, the stable hemiaminal **24** was converted to the trifluoromethyl ketimine **25** using a chiral copper catalyst and diethyl zinc (Scheme 9).



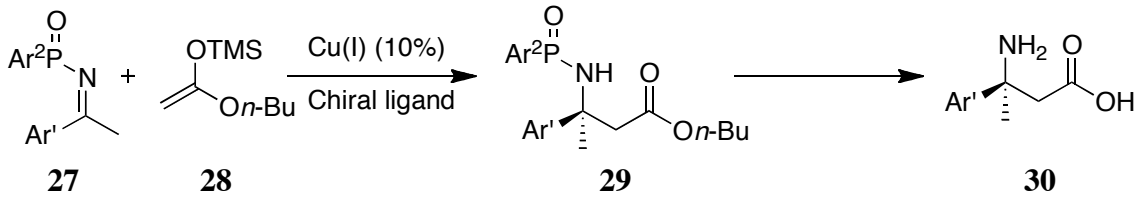
24 **25** **26**

Scheme 9: Copper-catalysed addition of Et_2Zn to trifluoromethyl ketimines **25**.

However this reaction is limited to aromatic ketimines and alkylzinc reagents. In 2006, the scope of the reaction has been extended and a catalytic enantioselective allylation of ketimines has been performed, in the presence of a copper catalyst, this time using allyl boronic esters.[18] As before, the method is successful with aromatic ketimines but not aliphatic ones.

1.1.4. Mannich-Type reactions

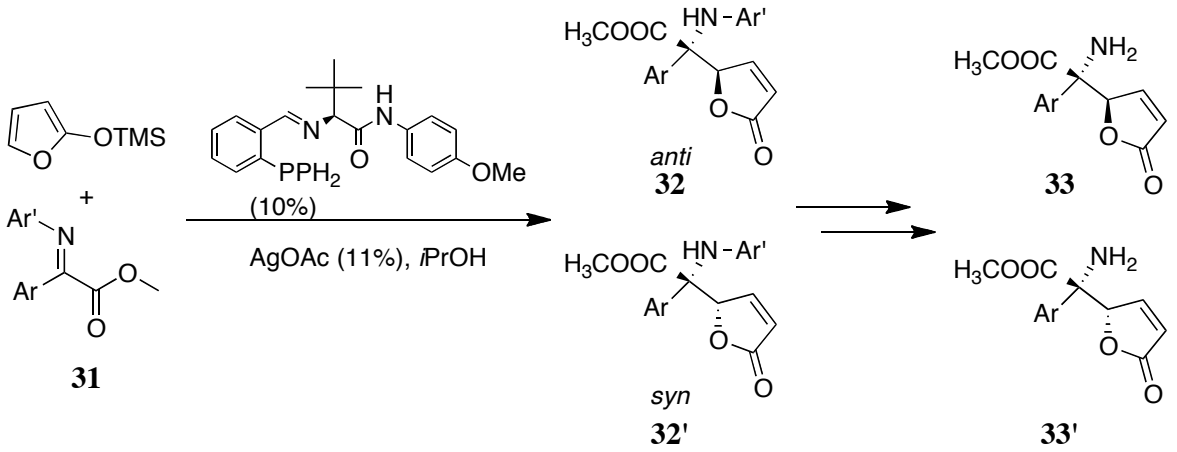
The Mannich reaction is an alternative for the synthesis of α-tertiary amines. The first asymmetric version of this reaction has been reported using copper catalysis.[19] In this example, a methyl ketimine **27** reacted with a silyl enolate **28** to produce the β-amino acid **30** after hydrolysis of **29** (Scheme 10). This method is very efficiently used for the synthesis of β-amino acids however with the limitation of using a methyl ketimine.



27 **28** **29** **30**

Scheme 10: Mannich-type reaction to synthesise β-amino acids **30**.

Recently, Hoveyda and Snapper investigated the same approach starting from α-ketimine esters **31** using a vinylogous Mannich reaction.[20] They have reported an enantioselective version of the reaction catalysed by a chiral silver catalyst (Scheme 11). The desired products **32** and **32'** are obtained in good yield, with very good *syn*/*anti* selectivity and are easily converted to the corresponding amines **33** and **33'**. A similar approach has been reported more recently using copper catalysis.[21]

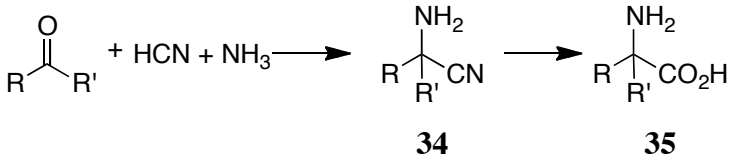


31 **32** **32'** **33** **33'**

Scheme 11: Vinylogous silver-catalysed Mannich reaction.

1.2. Strecker reaction

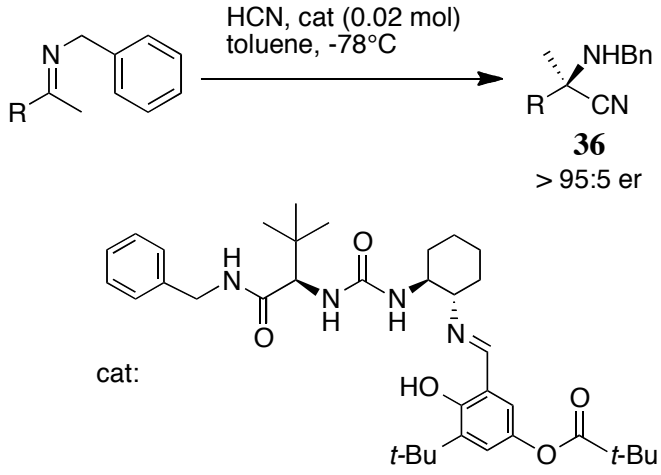
In 1850, Strecker reported one of the first syntheses of amino acids.[22] The Strecker reaction is a multicomponent reaction involving a ketone (or an aldehyde), hydrogen cyanide and ammonia (Scheme 12). The reaction proceeds with the *in situ* formation of the ketimine followed by attack of cyanide to form the α-aminonitrile **34** which upon hydrolysis gives the amino acid **35**.



34 **35**

Scheme 12: The Strecker reaction.

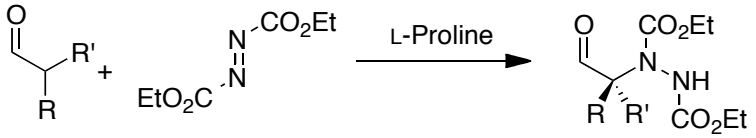
Despite the early report of this reaction, the first asymmetric version of the Strecker synthesis, to synthesise α-tertiary amines, was only reported in 2000.[23, 24] Jacobsen *et al.* have reported an organocatalytic approach to synthesise quaternary α-aminonitriles **36** (Scheme 13). In the following years, other catalysts were used to perform asymmetric Strecker reactions such as biphenols,[25, 26] chiral phosphates,[27] chiral titanium complexes,[28] gadolinium complexes,[29-31] and chiral *N*,*N*'-dioxides.[32, 33]



Scheme 13: Jacobsen's catalytic enantioselective Strecker reaction.

1.3. Amination reactions

Another means of obtaining α-tertiary amines is the amination reaction. One of the first examples of an enantioselective amination reaction uses proline as a catalyst.[34] In this example (Scheme 14), α,α-disubstituted aldehydes **37** react with DEAD to give the product **38**. In this case, the reaction was organocatalysed by L-proline.



37 **38**

Scheme 14: Amination reaction of α,α-disubstituted aldehydes **37**.

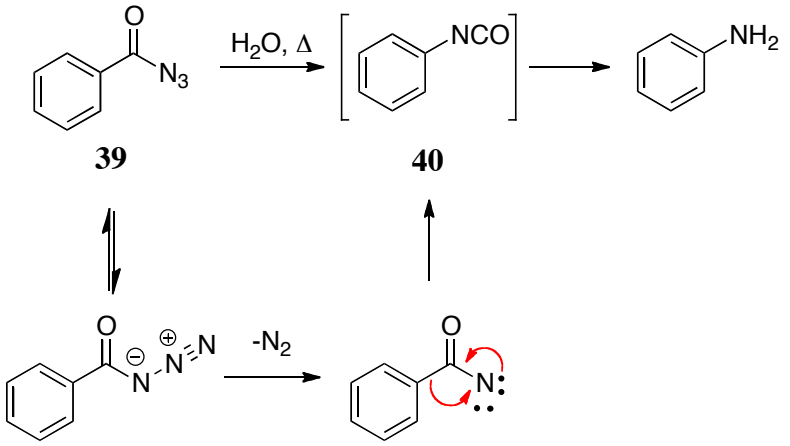
The same approach is used in the synthesis of cyclic amino acids using copper triflate in the presence of chiral bis-oxazolines.[35]

1.4. Rearrangements

An alternative to the synthesis of α-tertiary amines is using rearrangement of a readily prepared starting material. The next section will present the main rearrangements generating α-tertiary amines. For a complete overview of these rearrangements, a review has been published by the group.[36]

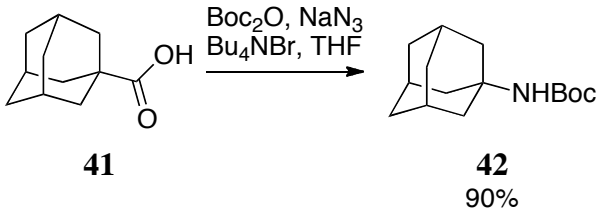
1.4.1. Curtius rearrangement

In 1890, Curtius observed the decomposition of acyl azide **39** to generate aniline after hydrolysis of the intermediate isocyanate **40** (Scheme 15).[37-39] The Curtius rearrangement now provides a valuable and commonly used way to synthesise amines from the corresponding acid.



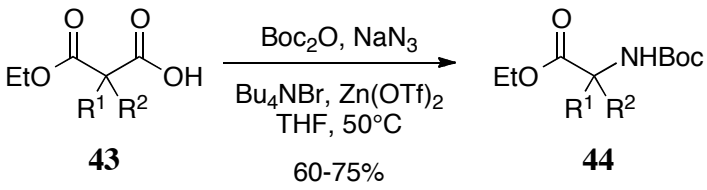
Scheme 15: Curtius rearrangement.

In 2005, Lebel and coworkers published a one-pot method for the synthesis of Boc-protected amines from carboxylic acids using the Curtius rearrangement.[40] In this example, treatment of the acid **41** with a mixture of Boc_2O and sodium azide in the presence of a phase-transfer catalyst, at room temperature, produces the acyl azide. The desired carbamate **42** was generated by increasing the temperature to 80°C (Scheme 16).



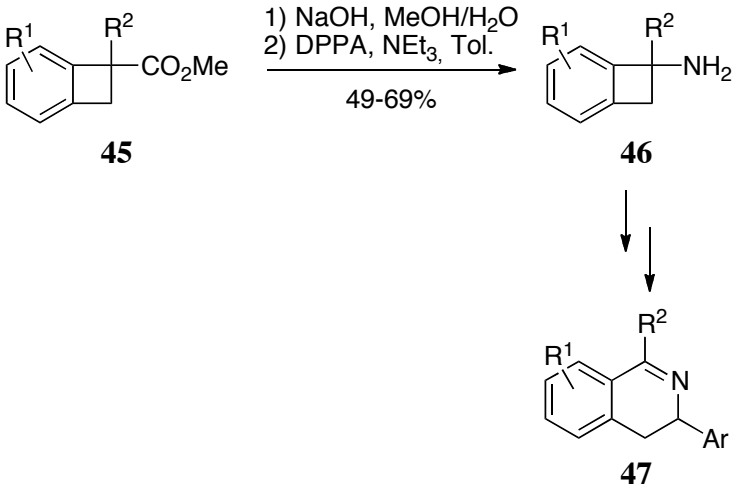
Scheme 16: Synthesis of Boc-protected amines **42** using Curtius rearrangement.

When the reaction has been carried out at 40°C, only traces of **42** have been observed. This problem has been solved using zinc triflate as an additive (3.3 mol%), which resulted in complete conversion. Malonate derivatives **43** can also be used as substrates for such rearrangement, the corresponding amino acid derivatives **44** are obtained in good yields (Scheme 17).



Scheme 17: Curtius rearrangement in the presence of zinc-triflate.

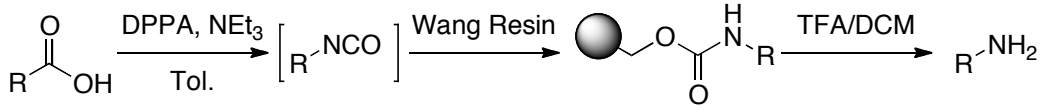
The Curtius rearrangement can also be performed on strained substrates such as cyclopropenes[41] or cyclobutane derivates.[42] In 2009, Baudoin and coworkers reported a synthesis of 3,4-dihydroisoquinolines **47** using a Curtius rearrangement of benzocyclobutenes **45** to generate the corresponding amine **46** (Scheme 18).[43] The acyl-azides in this example are generated using diphenylphosphoryl azide (DPPA), a safer alternative to sodium azide.



45 **46** **47**

Scheme 18: Synthesis of dihydroisoquinolines **47**.

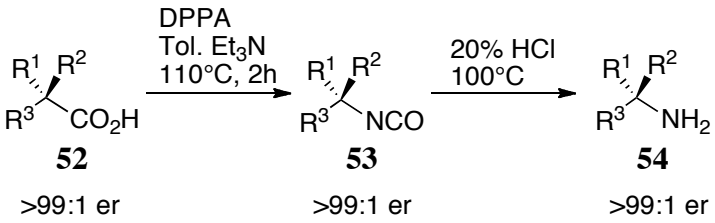
Sunami and coworkers reported an efficient method for solid phase synthesis of amines.[44] Carboxylic acid **48** has been converted to the corresponding isocyanate **49** which can be trapped with Wang resin to generate the carbamate **50**. The cleavage of the resin using TFA leads to the desired amine **51** (Scheme 19).



48 **49** **50** **51**
(57-95%)

Scheme 19: Curtius rearrangement and reaction with Wang resin.

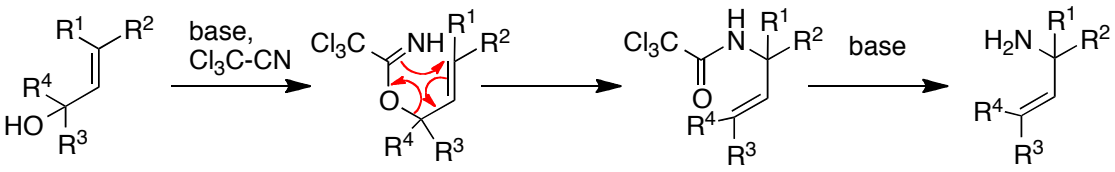
In 2005, the first synthesis of chiral α-tertiary amines using the Curtius rearrangement was reported.[45] The treatment of the enantiopure carboxylic acid **52** with DPPA generates the corresponding isocyanate **53** which can be hydrolysed to the corresponding amine **54** (Scheme 20). The desired amines are obtained with complete chirality transfer.



Scheme 20: Curtius rearrangement of enantiopure carboxylic acid **52**.

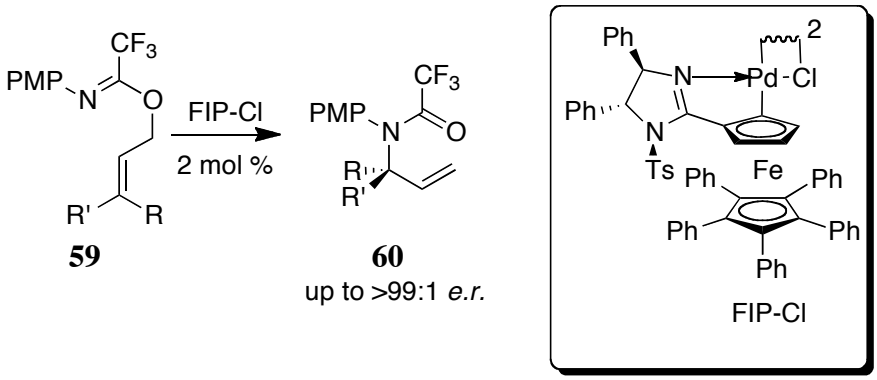
1.4.2. Overman rearrangement

In 1980, Overman reported a rearrangement of allylic trichloroacetimidate.[46] This reaction, also known as the aza-Claisen rearrangement, is a [3,3] sigmatropic rearrangement of trichloroacetimidate **56,** generated from allylic alcohol **55** (Scheme 21). The first step is the formation of an allylic trichloroacetimidate ester **56** which rearranges after heating to give **57**. The removal of the trichloroacetimidate group occures under basic conditions and leads to the free amine **58**.



Scheme 21: Overman rearrangement.

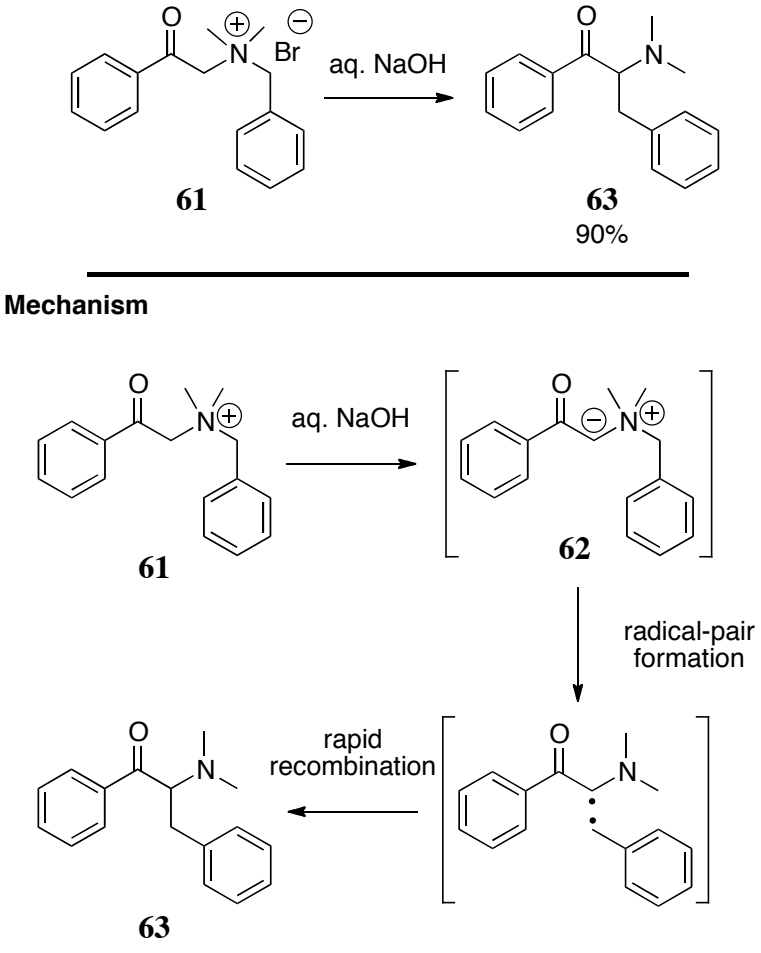
In 2007, the use of a planar-chiral ferrocenyl imidazoline palladacycle catalyst (FIP-X) to synthesise α-tertiary amines enantioselectively, using the Overman rearrangement, was reported (Scheme 22).[47] The desired products **60** were obtained with very good selectivity.



Scheme 22: Overman rearrangement catalysed by FIP-Cl.

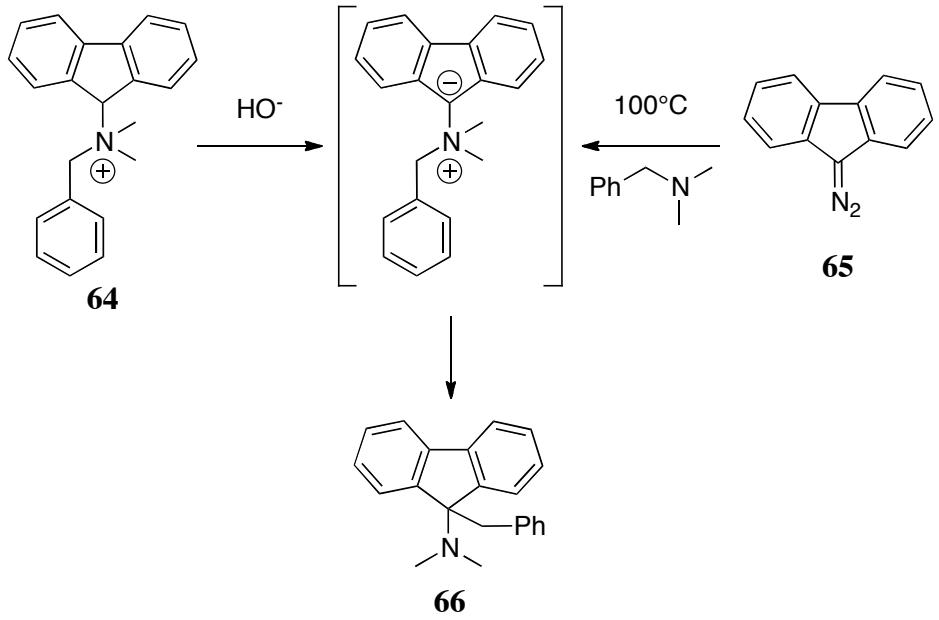
1.4.3. Stevens rearrangement

In 1928, Stevens and co-workers observed a [1,2]-shift of ammonium ylides during their work on quaternary ammonium salts as protecting groups for amines (Scheme 23).[48-57] Treatment of **61** with a solution of sodium hydroxide leads to rearranged compound **63** in excellent yield. In his early studies, Stevens demonstrated the intramolecular character of this reaction and proposed an ionic mechanism involving the formation of a zwitterionic intermediate **62** which rapidly dissociates to form the amine **63** (Scheme 23).[49] In 1932, Stevens and Thomson hypothesised an alternative mechanism involving a radical pathway,[54] evidence for which was found later.[58-62] The mechanism proceeds via homolytic cleavage of the C-N bond to generate a stable radical. Rapid recombination forms the rearranged product **63**. In the same study, Stevens reported the first example of the rearrangement of an allyl group, which later came to be referred to as the Stevens [2-3]-shift. [54]



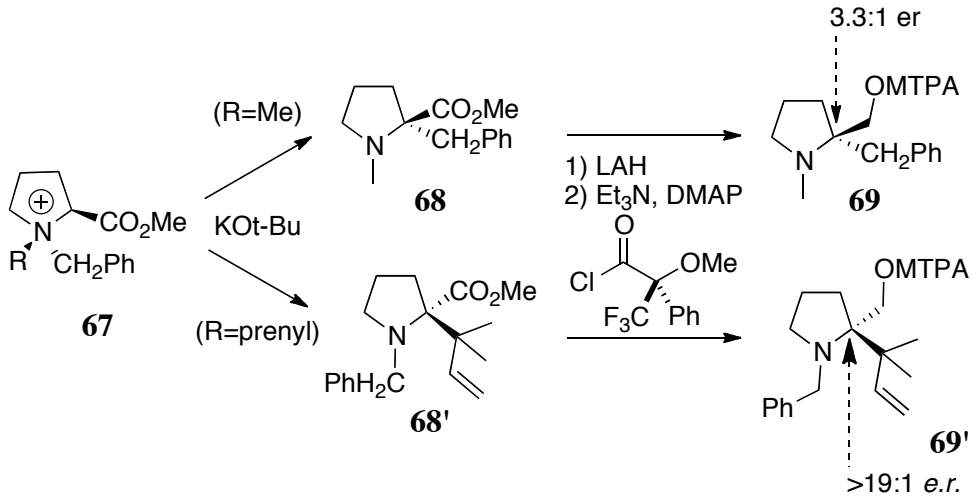
Scheme 23: Stevens rearrangement.

In 1952, the first synthesis of an α-tertiary amine **66** using fluorenyl derivatives **64** has been reported (Scheme 24).[63] In all the previous examples, the treatment of the quaternary ammonium salt with a strong base is necessary to form the ylides that can perform the desired rearrangement. Unfortunately, side reactions, like Hoffman degradation, can be observed during these reactions. Later, another method to generate ylides starting from carbenes precursor **65** has been also presented (Scheme 24).[63]



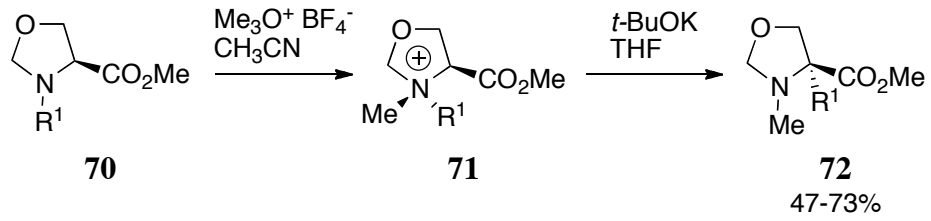
Scheme 24: Synthesis of α-tertiary amine **66** using Stevens rearrangement.

Many years later, in 1999, West and co-workers investigated chirality transfer from nitrogen to carbon in the Stevens rearrangement using cyclic ammonium salts (Scheme 25).[64] This methodology is based on a new approach of chirality transfer, using a temporarily chiral nitrogen atom to transfer selectively only one of the *N*-substituents in a suprafacial migration. Compound **67** is treated with potassium *tert*-butoxide to generate the desired ylide which undergoes [1,2] or [2,3]-shift depending on the R group. The resulting α-tertiary amines **68** are obtained with good selectivity. The relative stereochemistry of the final product **69** was confirmed by X-ray crystallography.



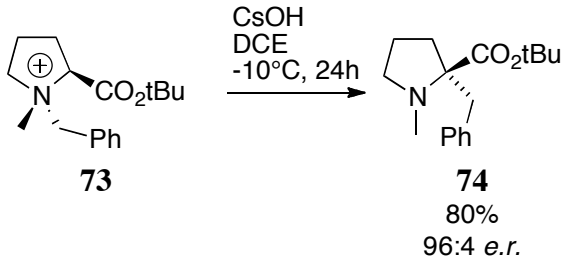
Scheme 25: Chirality transfer in Stevens rearrangement.

This method has been extended to oxazolidines **70** (Scheme 26) and proline derivatives.



Scheme 26: Synthesis of oxazolidines using Stevens rearrangement.

Tayama and coworkers reported the highly enantioselective rearrangement of a proline-derived ammonium salt **73** (Scheme 27).[65] In order to perform the Stevens rearrangement with high enantioselectivity, different biphasic conditions have been investigated. It is shown that the treatment of *t*-butyl ester **73** with solid CsOH in dichloroethane forms the desired amine **74** in 80% yield and 96:4 *e.r.* Variation of the aromatic group of the ammonium salt increases the selectivity up to 99:1 *e.r.*

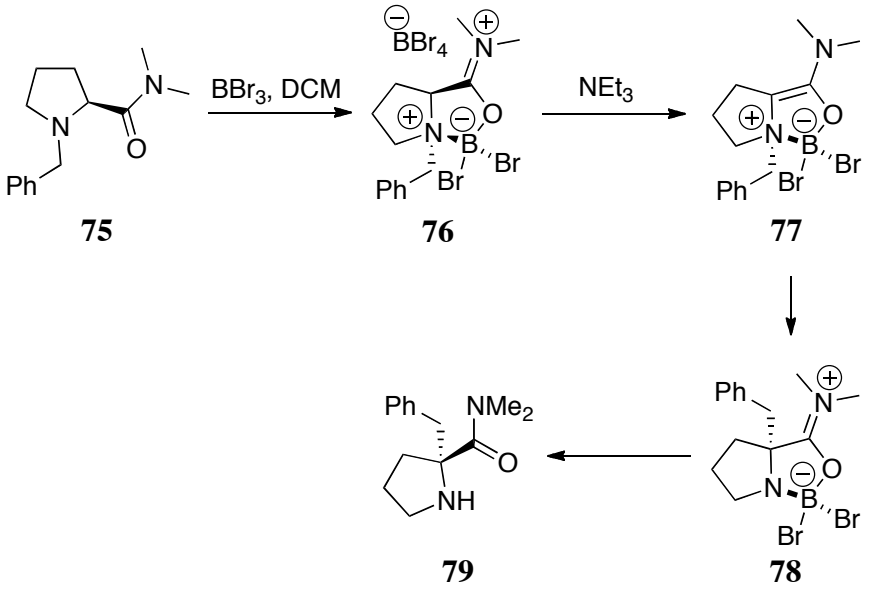


Scheme 27: Stevens rearrangement in heterogeneous conditions.

In 2009, the first example of enantioselective Lewis-acid mediated [1,2] Stevens rearrangement of proline derivatives was reported.[66] In this work, the Stevens

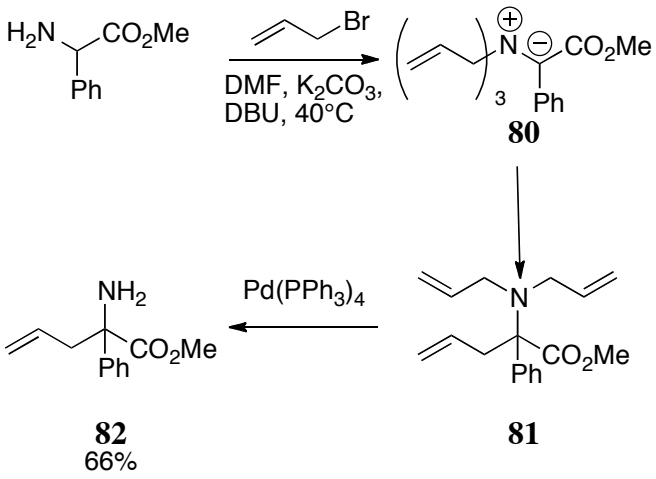
rearrangement proceeds with a complete C to N to C chirality transfer (Scheme 28). The desired free amine **79** is obtained in moderate to good yields.

The proposed mechanism involves the formation of **76** followeb by migration to the carbon α to nitrogen with high chirality transfer. Addition of NEt_3 promotes the formation of **77** which can recombined after homolysis to form the desired amine **79** (after hydrolysis) (Scheme 28).



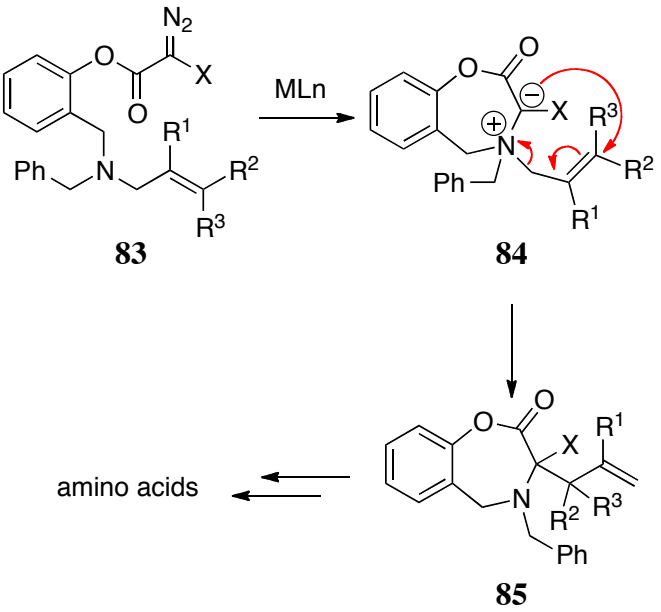
Scheme 28: Enantioselective Lewis-acid mediated Stevens rearrangement.

Coldham *et al.* developed a simple method for the synthesis of glycine derivatives based on a [2-3]-Stevens rearrangement (Scheme 29).[67] Glycine methyl ester is reacted with allyl bromide to form a quaternary ammonium ylide **80** which directly rearranges to the corresponding α-tertiary amine **81**. Amine **81** is then deprotected by treatment with palladium(0) to form the amino acid derivative **82**. Substituted simple α-amino esters have also been investigated.



Scheme 29: Synthesis of glycine derivatives.

In 2002, Clark *et al.* proposed a synthesis of α-substituted and α,α-disubstituted amino acids using the rearrangement of ammonium ylides **84**.[68] In this work, the ylides are generated from the metal carbenes (Scheme 30) – more successfully using copper catalysts tested.

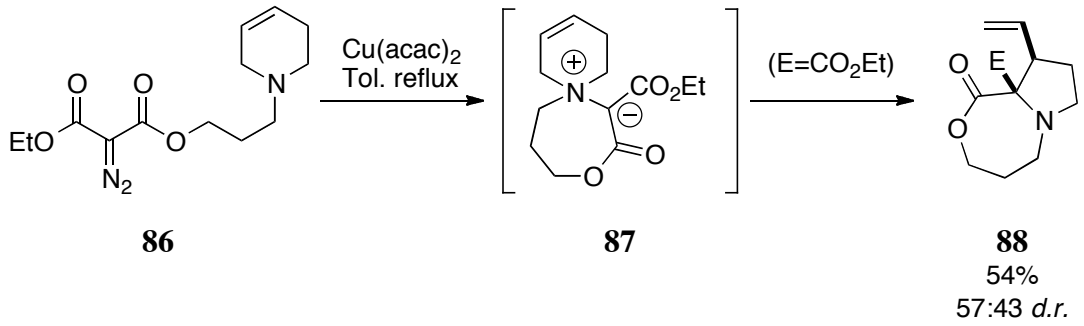


Scheme 30: Amino acid synthesis using a metal-carbene to initiate the Stevens rearrangement.

In all the examples presented, the copper catalysts are more efficient than the rhodium catalysts. This methodology has been extended to the [2,3]-Stevens rearrangement and is used for the synthesis of amino acid derivatives.

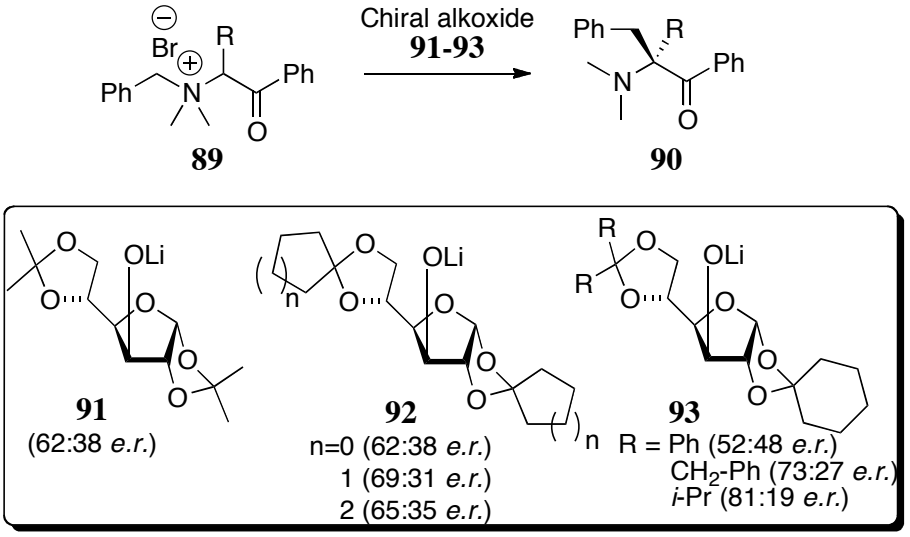
The rearrangement of spiro ylides using the [2,3]-Stevens rearrangement has also been reported (Scheme 31).[69] Compound **86** is treated with $Cu(acac)_2$ in toluene to generate the

intermediate ylide **87** which rearranges to form the desired amine **88** in 54% yield (with a *cis*:*trans* selectivity of 57:43). The synthesis of a pyrrolazepine is achieved using the same methodology.



Scheme 31:Stevens rearrangement of spiro ylides.

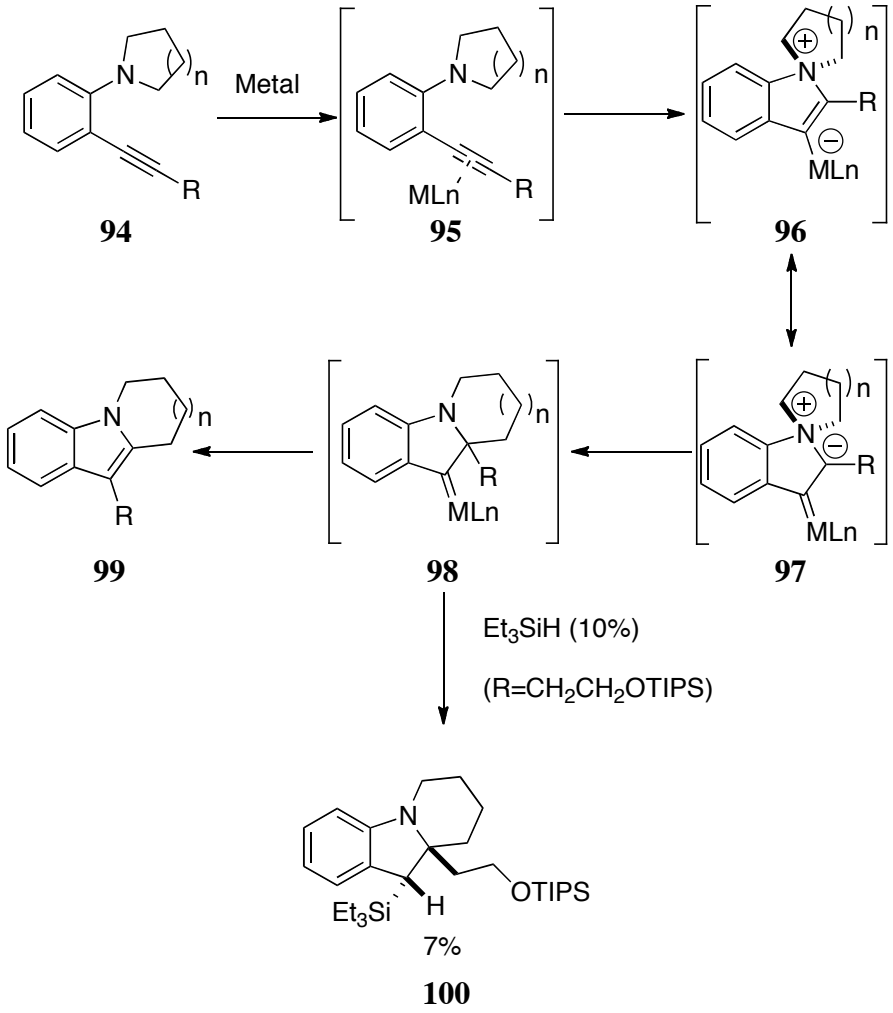
An original enantioselective method to perform a [1,2] Stevens rearrangement has been reported by Tomooka and co-workers,[70] using sugar-derived alkoxides as chiral promoters for this transformation. The treatment of the ammonium salt **89** in the presence of a chiral alkoxide led to the formation of the enantiomerically enriched α-tertiary amine **90** (up to 80:20 *e.r.*) (Scheme 32).



Scheme 32: Enantioselective Stevens rearrangement using chiral alkoxides.

In 2008, Iwasawa *et al.* reported a tandem [1,2] Stevens-1,2 alkyl migration of metal-containing ammonium ylides (Scheme 33).[71] In the presence of a metal, the alkyne π-complex **95** is generated and the corresponding metal-containing ammonium ylide **97** was formed. **97** underwent a [1,2] Stevens rearrangement followed by alkyl migration to generate the *N*-fused tricyclic indole **99**. Different metallic complexes are also investigated

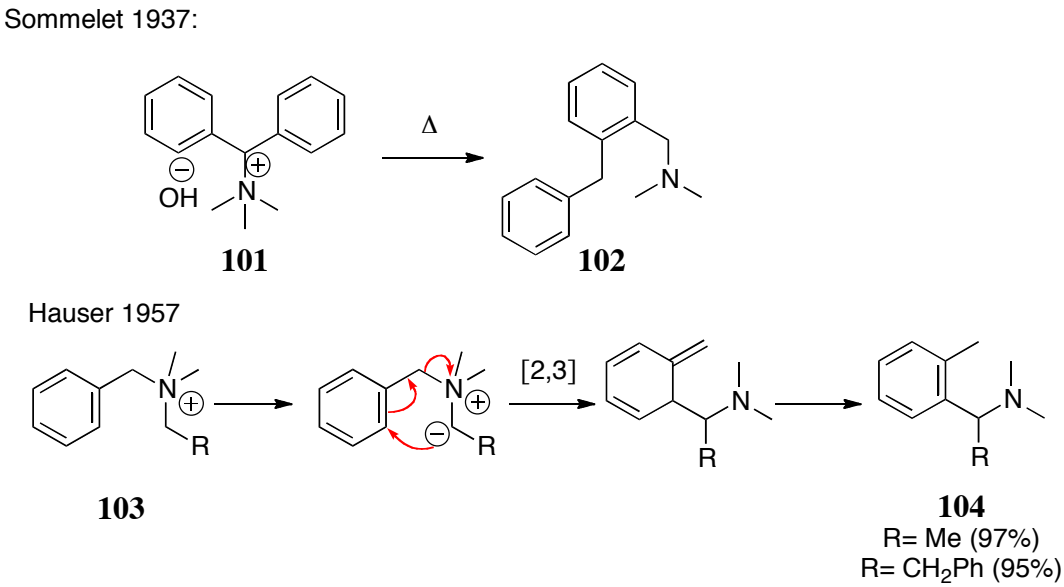
with only $W(CO)_6$ providing the desired product. They also demonstrate that the photoirradiation is crucial for the generation of the unsaturated tungsten species. The carbene intermediate **98** has been trapped using 10% Et_3SiH, allowing the α-tertiary amine **100** to be isolated in 7% yield (Scheme 33).



Scheme 33: Tandem [1,2] Stevens-type rearrangement/1,2 alkyl migration

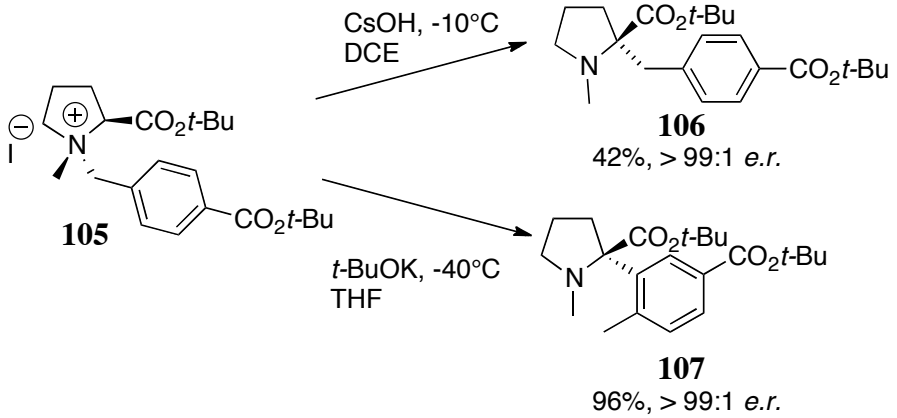
1.4.4. Sommelet-Hauser Rearrangement

In 1937, Sommelet observed that the decomposition of the quaternary ammonium salt **101** leads to the formation of the rearranged amine **102** (Scheme 34).[72] In 1957, Hauser investigated the rearrangement of the benzyltrimethylammonium ion **103**.[73] Hauser also proposed a possible mechanism for this rearrangement involving the deprotonation of the quaternary ammonium salt followed by 2,3 sigmatropic rearrangement (Scheme 34).[74] At the same time, Hauser performed the synthesis of hexamethylbenzene using successive rearrangements.



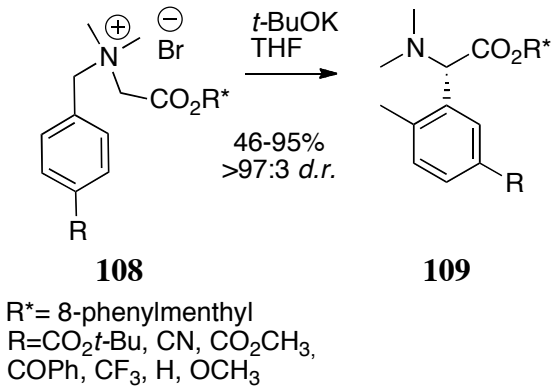
Scheme 34: Sommelet-Hauser rearrangement.

Following their work on the Stevens rearrangement, Tayama and coworkers reported a unique example of the Sommelet-Hauser rearrangement in which no [1,2] Stevens rearrangement was detected (Scheme 35).[75] The treatment of the ammonium iodide **105** with solid CsOH in DCE at -10 °C leads to the formation of the rearranged amine **106** (product of [1,2] Stevens rearrangement). The treatment of the same amine with *t*BuOK at -40 °C in THF leads to the Sommelet-Hauser product **107**.



Scheme 35: Stevens rearrangement vs Sommelet-Hauser rearrangement.

Tayama also reported an asymmetric version of the Sommelet-Hauser rearrangement (Scheme 36).[76] Ammonium salts **108** had been treated with *t*-BuOK to generate the α-tertiary amine **109** in moderate to very good yields and very good diastereoselectivity. *Meta* and *ortho* substituted compounds also give α-tertiary amines in good yields.

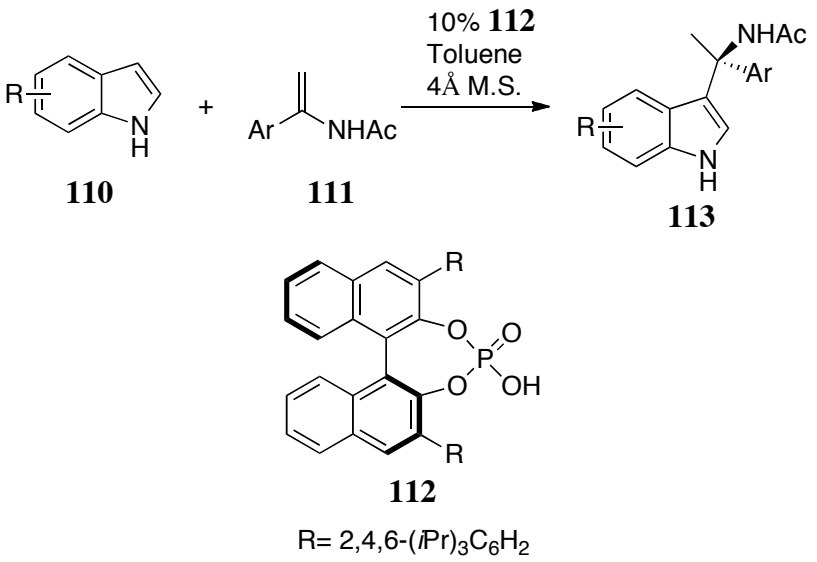


Scheme 36: Diastereoselective Sommelet-Hauser rearrangement.

1.5. Other Methods

1.5.1. Enantioselective Friedel-Crafts reaction

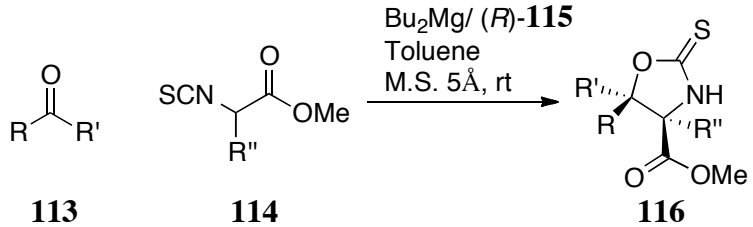
Another possibility to build a quaternary centre bearing a nitrogen atom is the Friedel-Crafts reaction using enamides.[77] The reaction of indoles **110** with enamides **111** in the presence of a chiral Brønsted acid **112** leads to the formation of the quaternary centre in high yields (> 97%) and good *e.r.*s (up to 97:3) (Scheme 37).



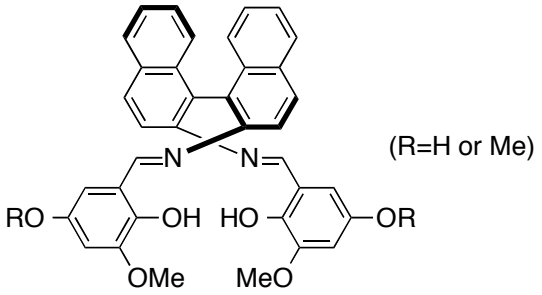
Scheme 37: Enantioselective Friedel-Crafts reaction.

1.5.2. Asymmetric aldol condensation

In 2009, Shibasaki and coworkers reported an asymmetric aldol reaction between ketones **113** and α-isothiocyanato esters **114** (Scheme 38).[78] In this report, the formation of a cyclic thiocarbamate **116** was catalysed by a chiral Schiff-base **115**. The transformation was achieved in high yield and very good diastereo- and enantioselectivity.



113 **114** **116**

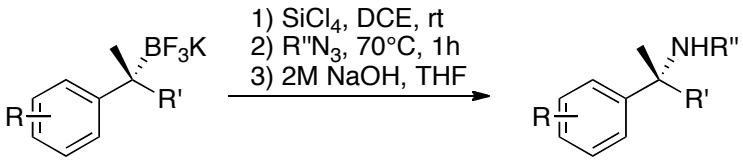


115

Scheme 38: Asymmetric aldol reaction.

1.5.3. Chiral boronic esters

More recently, Aggarwal and co-workers reported the synthesis of enantiopure α-tertiary amines **118** from chiral trifluoroborates.[79] The treatment of trifluoroborates **117** with azides leads to the formation of the corresponding amine **118** with retention of configuration and complete chirality transfer (Scheme 39).



117 **118**

Scheme 39: Synthesis of α-tertiary amines using boronic esters

In 2007, it has been discovered in the Clayden group that α-tertiary amines can be synthesised using the rearrangement of lithiated ureas. Before presenting this work, some background in organolithium chemistry is necessary.

2. Organolithium chemistry

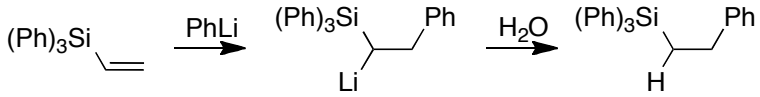
Organolithium compounds are amongst the most versatile reagents in all fields of chemistry. Due to the polarisation of the carbon-lithium bond, organolithium compounds may be used as highly reactive nucleophiles as well as strong bases. Organolithiums are often schematically depicted as monomeric species, however the structure of these compounds is much more complicated.[80, 81]

In the following part, the carbolithiation reaction has been chosen to illustrate the properties of organolithium reagents.

1.1. Carbolithiations

The formation of a C-C bond by the reaction of an organolithium reagent with a C=C double bond is known as carbolithiation.

In 1952, Cason and Brooks presented one of the first examples of carbolithiation,[82] discovered during their work on the synthesis of triphenylvinylsilane. During the synthesis of the silylated compound **119** they identified a new compound **120**. They hypothesised the formation of **120** by reaction of phenyllithium with the double bond of the silane (Scheme 40).



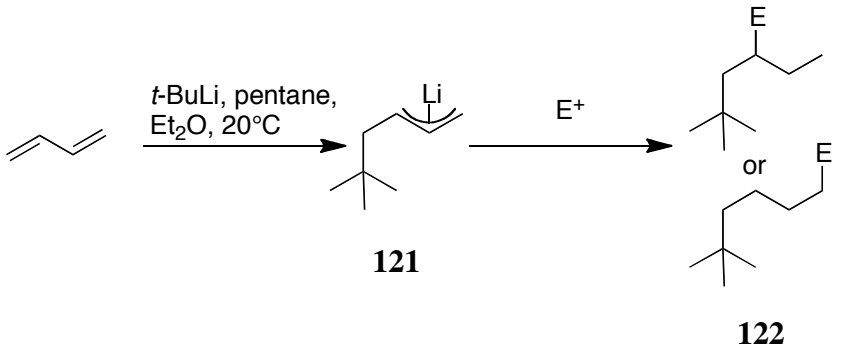
119 **120**

Scheme 40: Carbolithiation of triphenylvinylsilane.

In order to confirm this hypothesis, the triphenylvinylsilane has been treated with *n*-butyllithium and the analaogous compound was obtained in good yield. The same reaction can be carried out with different alkenes and organolithiums.[83-86]

One of the earliest descriptions of the use of carbolithiation chemistry is the addition to an unactivated double bond.[87] In this reaction, the organolithium compound is used as a polymerisation precursor. With unactivated double bonds, the addition product is a new organolithium, which was able to react with another double bond.

The carbolithiation of non-functionalised alkenes has also been extended to dienic systems and triple bonds. Butadiene can react with *t*-BuLi at 20°C to give the allyllithium intermediate **121** (Scheme 41),[88] which can be quenched with a suitable electrophile.

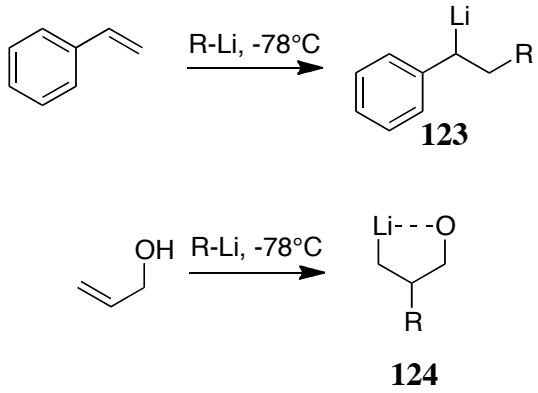


121

122

Scheme 41: Carbolithiation of butadiene.

Carbolithiation reactions require the final organolithium to be stabilised by conjugation or coordination in order to avoid polymerisation (Scheme 42).[89-93] Benzylic organolithiums **123** as well as coordinated species such as **124** are the most common stable compounds.

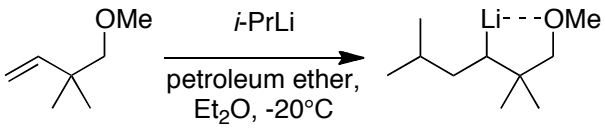


123

124

Scheme 42: Stabilised organolithiums

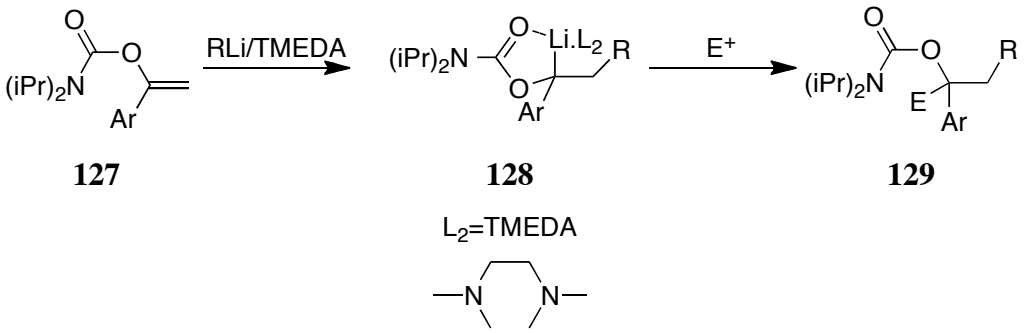
In the example below, the chelation of the lithium with the oxygen atom of **125** occurs preferentially forming a five-membered ring and providing the desired stabilisation (Scheme 43).



125 **126**

Scheme 43: Five-membered ring chelation.

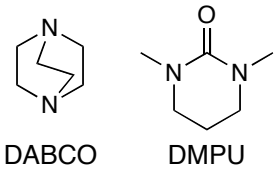
TMEDA has also been used as a ligand in carbolithiation reactions in order to coordinate and to stabilise the intermediate lithium species **128**, with the aim of avoiding competitive polymerisation (Scheme 44).[94, 95]



127 **128** **129**

Scheme 44: Stabilisation of vinylcarbamates using TMEDA.

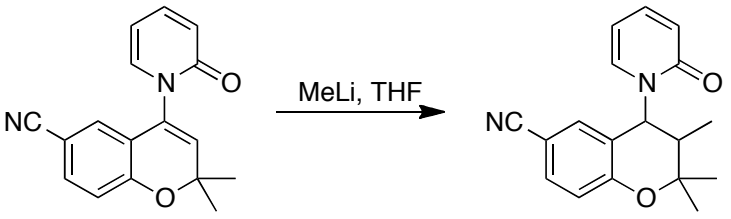
Other ligands such as DMPU or DABCO can also be used to stabilise and increase the reactivity of the organolithium reagent (Figure 4).



DABCO DMPU

Figure 4: Structure of DABCO and DMPU.

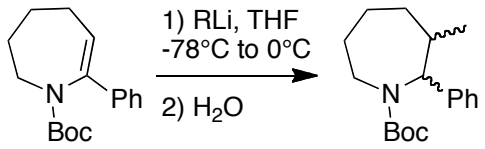
Very few examples of carbolithiations of trisubstituted double bonds had been reported. Merck presented the first example in 1991,[96] during the synthesis of benzopyran derivatives. In this work, chromene **130** is treated with MeLi leading to the corresponding carbolithiated compound **131** (Scheme 45).



130 **131**

Scheme 45: Carbolithiation of chromene **130**.

More recently, Coudert reported the carbolithiation of the electron-rich double bond of ene-carbamates **132** without any diastereoselectivity. (Scheme 46).[97]

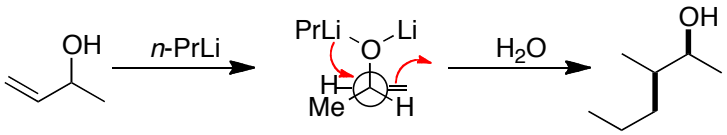


132 **133**

Scheme 46: Carbolithiation of ene-carbamates.

2.1. Stereoselective carbolithiations

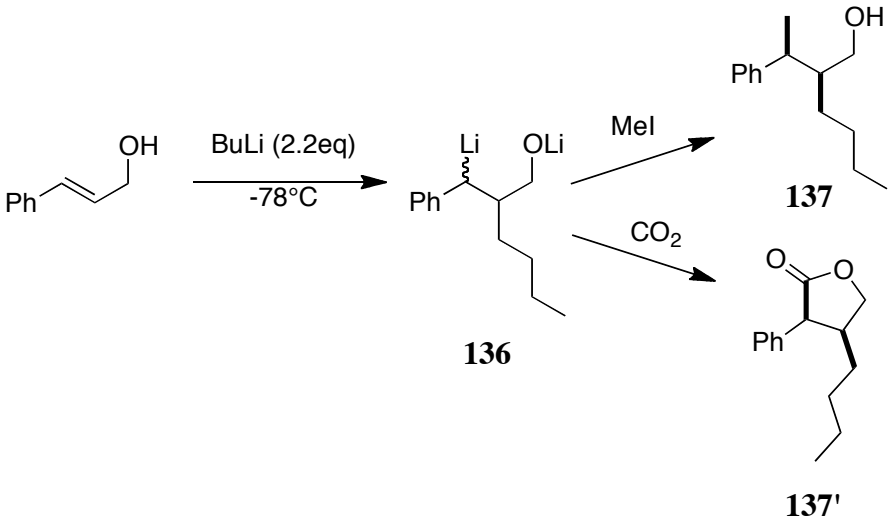
The coordination of the lithium atom is a very important parameter for the stereoselectivity of the reaction. As shown before, the chelation of the lithium in a five-membered ring would be favoured. When the oxygen is on a stereogenic centre, the addition becomes diastereoselective. The stereochemistry can be predicted by transition state **134** and only the *syn* product **135** is obtained with very high diastereoselectivity (Scheme 47).[98]



134 **135**
>98%

Scheme 47: Diastereoselective carbolithiation of vinylalcohol.

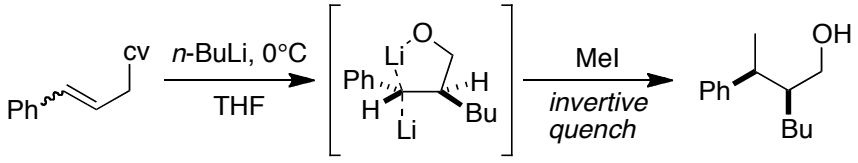
The same *syn* diastereoselectivity arise in the case of cinnamyl alcohol when the quench was performed using methyl iodide or carbon dioxide as electrophiles (Scheme 48).[99, 100]



136 **137** **137'**

Scheme 48: Diastereoselective carbolithiation of cinnamyl alcohol.

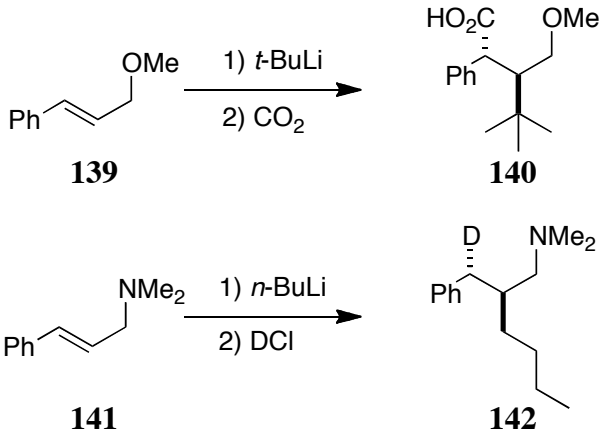
Both isomers of the cinnamyl alcohol form the *syn* diastereoisomer **137** with very good selectivity (98:2 *d.r.*). In this case, the *syn* intermediate **138** seems to be thermodynamically favoured respect to the *anti* (Scheme 49).



138 **137** (98:2 *dr*)

Scheme 49: Proposed transition-state for the *syn* carbolithiation.

The *anti* diastereoselectivity was observed with other derivatives of the cinnamyl alcohol like cinnamyl ether **139** and cinnamyl amine **141** (Scheme 50).[101, 102]

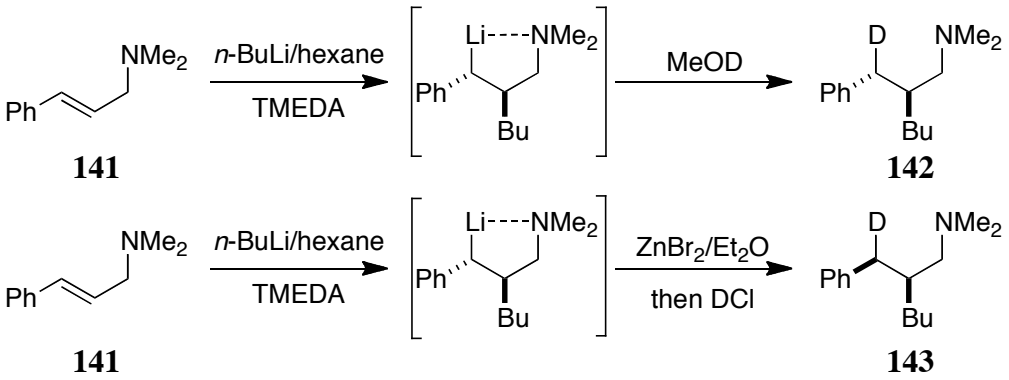


139 **140**

141 **142**

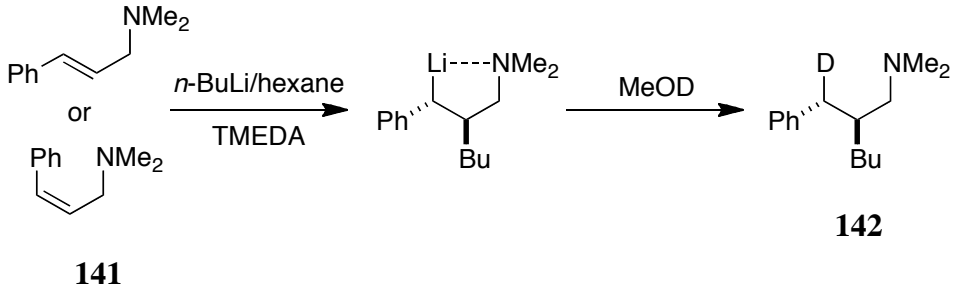
Scheme 50: Carbolithiations of cinnamyl ether **139** and cinnamyl amine **141**.

In the same study, Normant compared the stereochemistry of the lithium intermediate with respect to the zinc intermediate. The exchange between the lithium atom and the zinc atom proceeded with inversion of configuration. So, *syn* product **143** was obtained after exchange and quench with deuterated hydrochloric acid (Scheme 51).



Scheme 51: *Syn* and *anti* selectivity of carbolithiation of cinnamyl amine **141**.

In completing the study of these cinnamyl amines, the stereochemistry of the initial double bond has also been investigated. Starting with the (*Z*) or the (*E*) double bond leads to the same product **142** due to the five-membered ring transition state. In this case, the product **142** was obtained with *anti* stereochemistry (Scheme 52).



Scheme 52: Carbolithiation of (*Z*) and (*E*) cinnamyl amines **141**.

2.2. Enantioselective carbolithiations

An asymmetric version of the carbolithiation has also been reported using chiral ligands in order to discriminate the two faces of the double bond.

2.2.1. (–)-Sparteine

In principle, all the examples of carbolithiations shown before can be extended to enantioselective carbolithiations using a chiral ligand. The most common ligand used for enantioselective carbolithiations is (–)-sparteine (Figure 5): this diamine is used to chelate the lithium.[103]

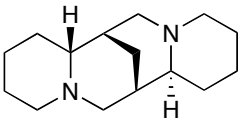
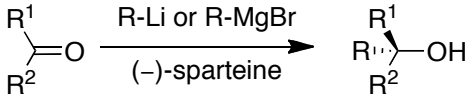


Figure 5: (–)-Sparteine.

The first examples of the use of (–)-sparteine as a chiral ligand to chelate lithium atom has been published in 1971 by Noyori.[104] In this work, (–)-sparteine was used for the addition of a Grignard reagent or an organolithium to a carbonyl to form the corresponding alcohol **144** with low *e.r.* (Scheme 53).

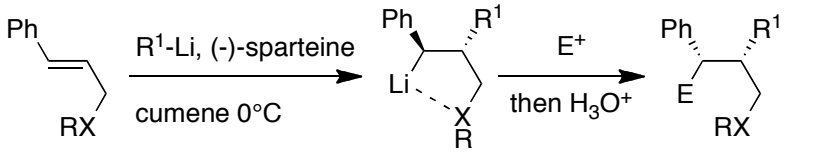


143 **144**

Scheme 53: Enantioselective addition on carbonyl using (–)-sparteine.

Many years later, Beak and Schlosser used this ligand for enantioselective deprotonations with organolithiums.[105-107]

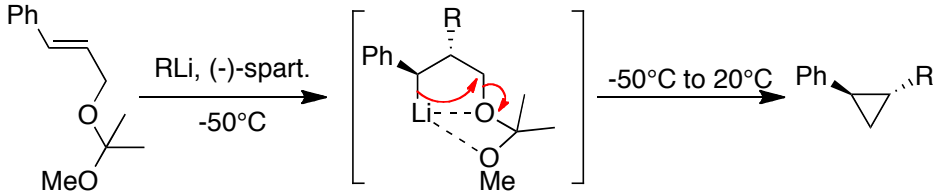
In 1995, Normant described the enantioselective carbolithiation of cinnamyl alcohol and its derivatives **145** using (–)-sparteine (Scheme 54).[108] The carbolithiated compounds **146** has been obtained with good diastereoselectivity.



145 **146**
up to 90:10 *d.r.*

Scheme 54: Enantioselective carbolithiation of cinnamyl derivatives.

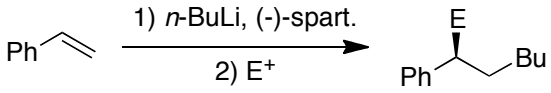
In the case of cinnamyl alcohol, an oxidation of the final alcohol gives the corresponding carboxylic acid in an enantiomerically pure form. The use of protecting groups on the alcohol **147** increased the reactivity and is also used to synthesise more difficult targets such as cyclopropanes **149** (Scheme 55).[109] Here, the temperature is increased from –50°C to 20°C and the organolithium intermediate **148** is able to attack the centre α to the oxygen and yield the cyclised product **149**.



147 **148** **149**

Scheme 55: Synthesis of cyclopropanes derivatives.

(–)-Sparteine can also be used for the carbolithiation of styrene.[110] In this case, the reaction is carried out at very low temperature and the product **150** is formed with good selectivity (Scheme 56).

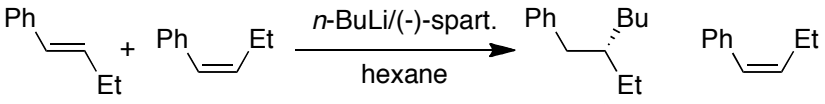


150

Scheme 56: Enantioselective carbolithiation of styrene.

(–)-Sparteine also allows the carbolithiation of substituted alkenes derived from styrene.[111] In this case, only the carbolithiated product is observed and no polymerisation is detected. Additional studies in this case show that (–)-sparteine could also be used in a catalytic amount (10%) but with lower *e.e.s* being obtained (70%).

Normant and coworkers performed a kinetic resolution using the addition of *n*-BuLi on a mixture of the two isomers of β-ethylstyrene (*E*:*Z*=9:1).[111] The carbolithiated product **151** is obtained with 87% yield (89:11 *e.r.*) and the (*Z*)-styrene was recovered in 7% yield (Scheme 57). Both isomers of the styrene can react with the mixture of organolithiums/ (–)-sparteine, but the (*Z*)-isomer reacts more slowly and with a lower enantiomeric excess.



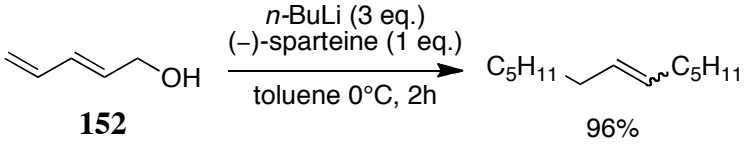
151

9:1 87% 78% *e.e.* 7%

Scheme 57: Kinetic resolution using enantioselective carbolithiation.

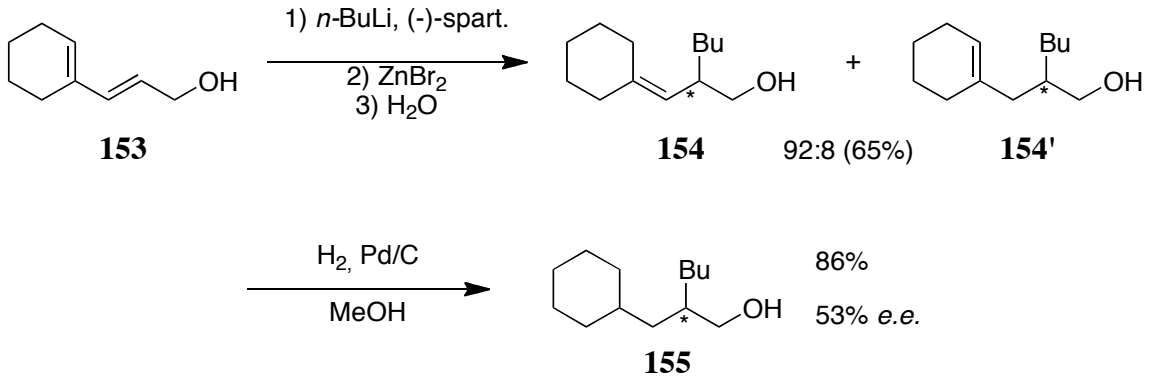
After the studies on cinnamyl alcohols and styrenes, other studies have been performed on conjugated alcohols without the aromatic moiety. Investigations with different dienic systems have been carried out in order to achieve carbolithiation of unactivated double bonds.[112] Unfortunately, the reaction of the dienol **152** in the presence of three equivalents

of *n*-BuLi and one equivalent of (–)-sparteine leads to a mixture of (*Z*) and (*E*) tridec-6-ene (Scheme 58). This product is obtained by the addition of *n*-BuLi to the terminal double bond with elimination of Li_2O to form another diene. This diene reacts with another molecule of *n*-BuLi to form the corresponding lithium intermediate which gives the tridec-6-ene after protonation.



Scheme 58: Carbolithiation of dienic alcohol **152**.

In order to promote addition to the C2 and avoid the reactivity on the C5, double substitution on C4 and C5 has been investigated for the alcohol **153**.[112] In this case the addition occurrs on C2 but the protonation is not regioselective and a mixture of the two alcohols **154** and **154'** is obtained. The hydrogenation of the double bond leads to the product **155** in 53% *e.e.* (Scheme 59).



Scheme 59: Carbolithiation of cyclic dienic alcohol **153**.

2.2.2. Other ligands

Even if (–)-sparteine is the most common chiral ligand in organolithium chemistry, one disadvantage of this compound is the availability of only one isomer. (+)-Sparteine is also a natural product but is less readily available and more difficult to extract than the (–)-isomer (Figure 6).

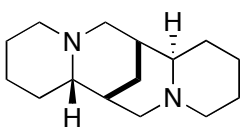
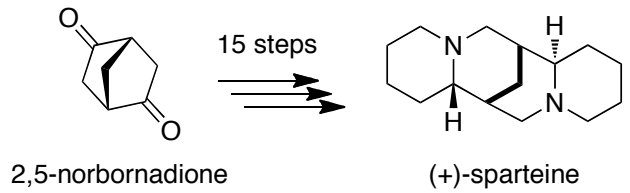


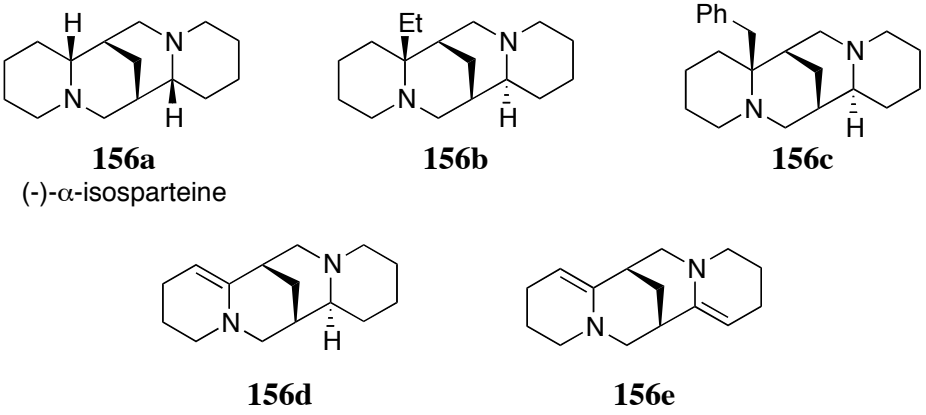
Figure 6: (+)-sparteine

To avoid the problem of the availability of (+)-sparteine, different groups have tried to synthesise this compound. The first asymmetric total synthesis of (+)-sparteine was proposed in 2002 by Aubé and coworkers.[113] This synthesis is accomplished in 15 steps starting from 2,5-norbornadione with a 16% overall yield (Scheme 60). The key steps of the synthesis are two ring-expansion reactions.



Scheme 60: Aubé's enantioselective synthesis of (+)-sparteine.

Much earlier, in 1982, Okamoto *et al.* proposed the synthesis of five (–)-sparteine derivatives (Figure 7) and used them as chiral ligands with Grignard reagents.[114] However, the success of these ligands has been limited.



156a
(-)-α-isosparteine

156b

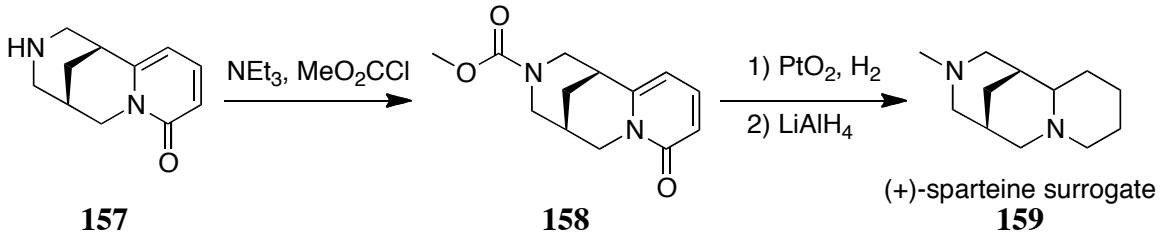
156c

156d

156e

Figure 7: (–)-Sparteine analogues.

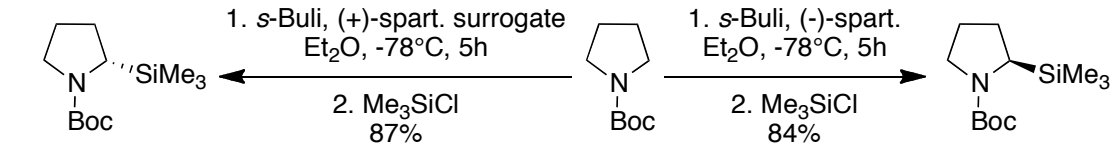
Up to today, the best alternative to (+)-sparteine is the (+)-sparteine surrogate **159** developed by O'Brien.[115,] This ligand can be synthesised in three steps from (–)-cystisine (**157**)(Scheme 61).[116, 117]



157 **158** **159**

Scheme 61: Synthesis of (+)-sparteine surrogate **159**.

In 2002, O'Brien and co-workers reported the first example using (+)-sparteine surrogate for the enantioselective deprotonation of *N*-Boc pyrrolidine (Scheme 62).[115] They have demonstrated that the two enantiomers of the silylated pyrrolidine **160** can be obtained in similar yields and very high enantioselectivity using (–)-sparteine or the surrogate.



(*S*)-160 (95:5 *e.r.*) **(*R*)-160** (95:5 *e.r.*)

Scheme 62: Enantioselective deprotonation of *N*-Boc pyrrolidine.

More recently, the same group reported the first enantioselective deprotonation of *N*-Boc-pyrrolidine in the presence of (+)-sparteine surrogate in THF.[118] For the first time, asymmetric deprotonation using an organolithium was performed in a highly coordinative solvent (THF) while deprotonation using (–)-sparteine has to be done in non-coordinative solvents (toluene, cumene, pentane). This property makes the (+)-sparteine surrogate a better ligand than (–)-sparteine.

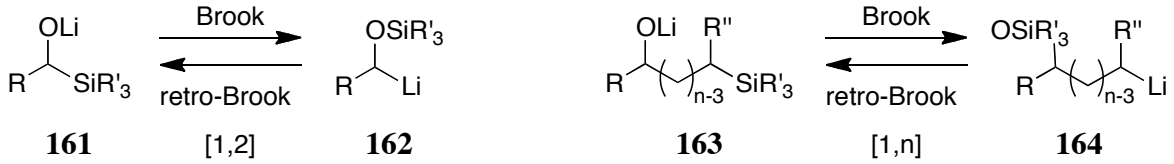
3. Rearrangement involving organolithiums

Different rearrangements involving organolithium reagents have been identified. Besides the common Brook and Wittig rearrangements, other rearrangements involving lithium chemistry have also been reported for the synthesis of hindered amines.

3.1. Brook and Wittig rearrangements

3.1.1. Brook and retro-Brook rearrangement

The Brook rearrangement is an anionic migration of a silicon group from a carbon to an oxygen (Scheme 63).[119] The reverse process is known as the retro-Brook rearrangement. The initial studies have been made on [1,2] migration of the silicon group but today many examples of [1,3] and [1,4] migrations are also known.

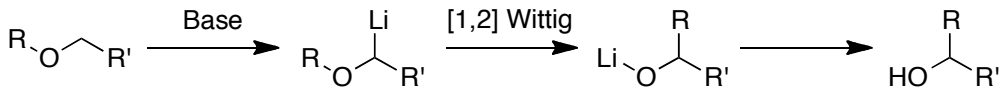


161 [1,2] **162** **163** [1,n] **164**

Scheme 63: [1,2] and [1,n] Brook and retro-Brook rearrangements.

3.1.2. Wittig rearrangements

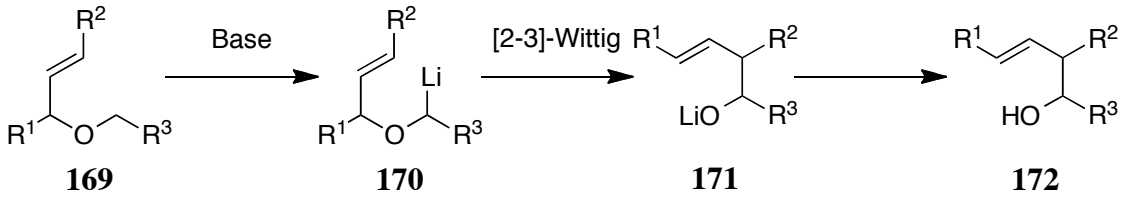
Wittig rearrangement corresponds to a migration of an alkyl group from oxygen to carbon after deprotonation of ether **165** to form alcohol **168**. Originally, this rearrangement was a [1,2] migration (Scheme 64).[120, 121] Mechanistic studies on the reaction have shown the formation of a radical pair.



165 **166** **167** **168**

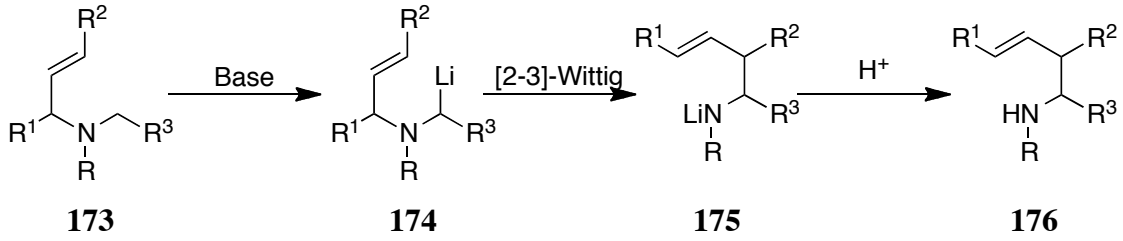
Scheme 64: [1,2] Wittig rearrangement.

Many years later, a vinylogous variant of this rearrangement was observed. This rearrangement is today known as the [2,3] Wittig rearrangement (Scheme 65).[122]



Scheme 65: [2,3] Wittig rearrangement.

The nitrogen analogues of the precedent Wittig rearrangements are known as aza-Wittig rearrangements (Scheme 66). The [1,2] and [2,3] aza-Wittig rearrangements are very common in synthetic chemistry.[123]

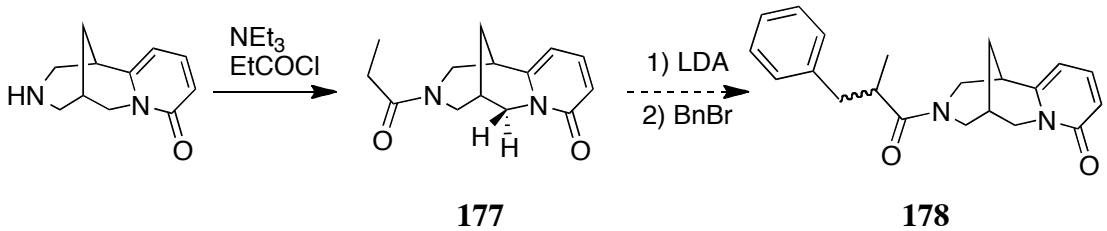


Scheme 66: [2,3] Aza-Wittig rearrangement.

3.2. N-C carbonyl migration

Besides these very common rearrangements in organolithium chemistry other rearrangements involving organolithiums was reported.

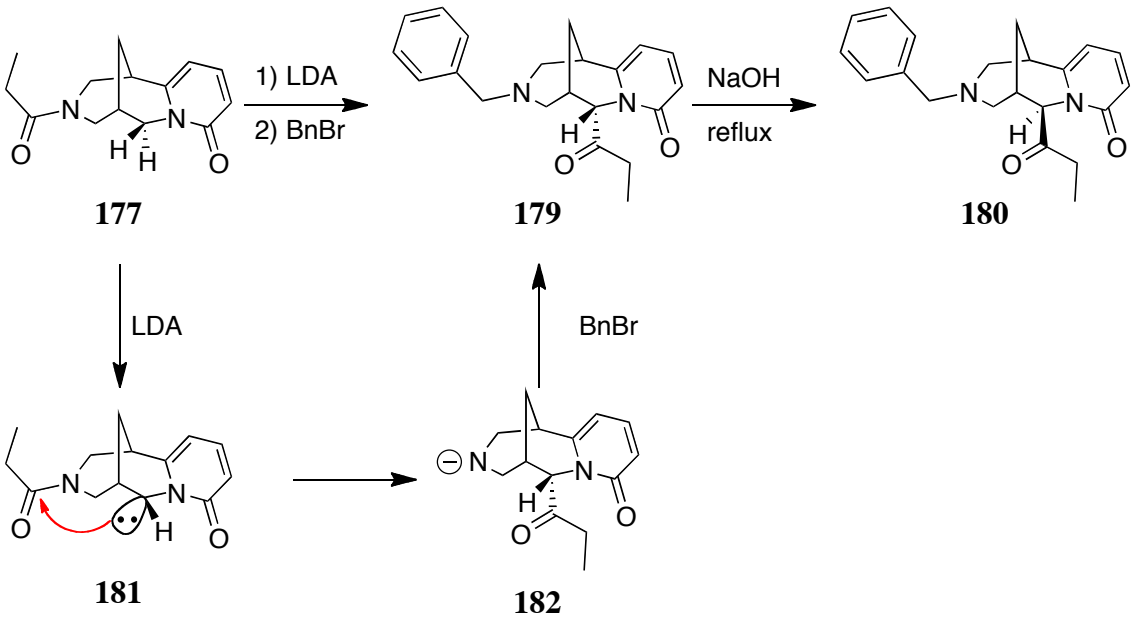
In 2002, Rouden and co-workers presented an unsual N-C acyl migration.[124] To test (–)-cystisine as a chiral inductor, they have tried an enantioselective alkylation of amide enolate (Scheme 67). Unfortunately the expected product **178** has been not observed.



Scheme 67: Enantioselective alkylation of amide enolate.

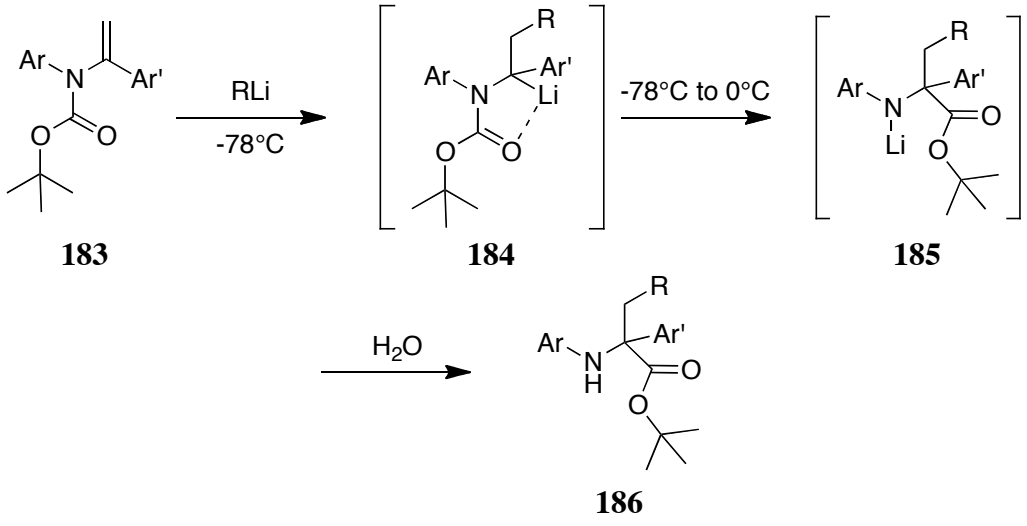
Instead of the anticipated product **178**, compound **179** has been isolated from this reaction with an unexpected N-C acyl migration (Scheme 68). Treatment of **179** in refluxing sodium hydroxide leads to the other epimer **180**. The proposed mechanism involves deprotonation α to nitrogen, followed by an intramolecular cyclisation with the carbonyl to

give the intermediate **181** which rearranges to give the carbanion **182**. This can then react with benzylbromide to form **179**.



Scheme 68: N-C Acyl migration.

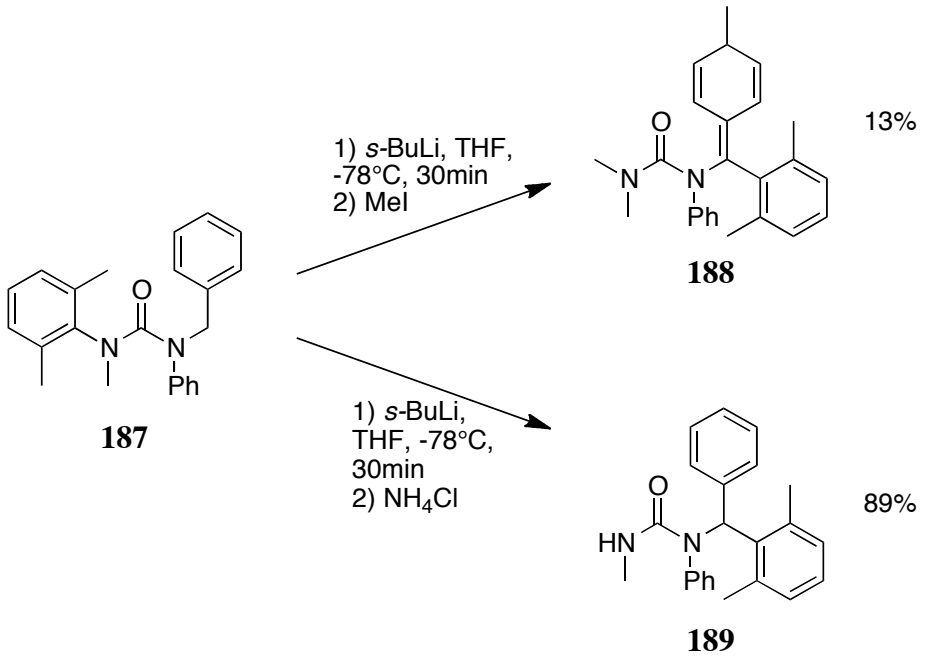
In 2007, a similar rearrangement has been reported.[125] During investigations on carbolithiations of ene-carbamates **183**, a N to C migration of a Boc group had been observed (Scheme 69). The ene-carbamate **183** has been treated with commercially available organolithiums to give the carbolithiated intermediate **184**. Heating the reaction from –78°C to 0°C leads to the migration of the Boc group to give an α-tertiary α-amino ester **186** after quenching.



Scheme 69: Carbolithiation of ene-carbamates **183**.

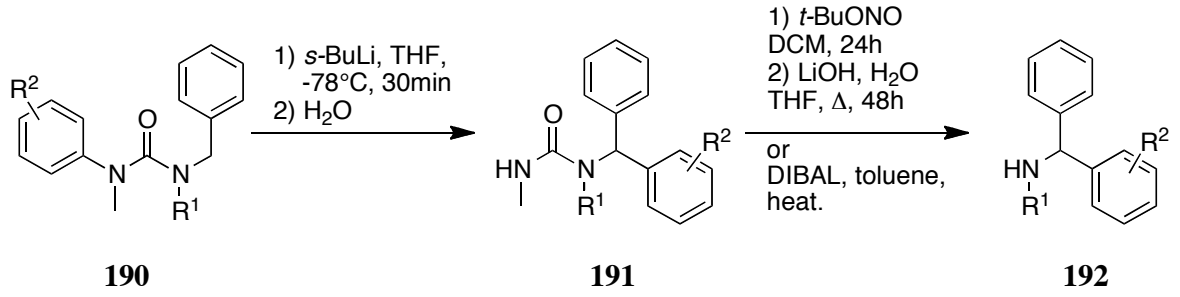
3.3. Rearrangement of ureas

In 2007, Clayden *et al.* reported a rearrangement of lithiated ureas.[126] Treatment of urea **187** with *s*-BuLi followed by quench with MeI, leads to the rearranged product **188** in low yield. However if the final methylation is replaced by an aqueous quench, product **189** is obtained in very good yield (Scheme 70).



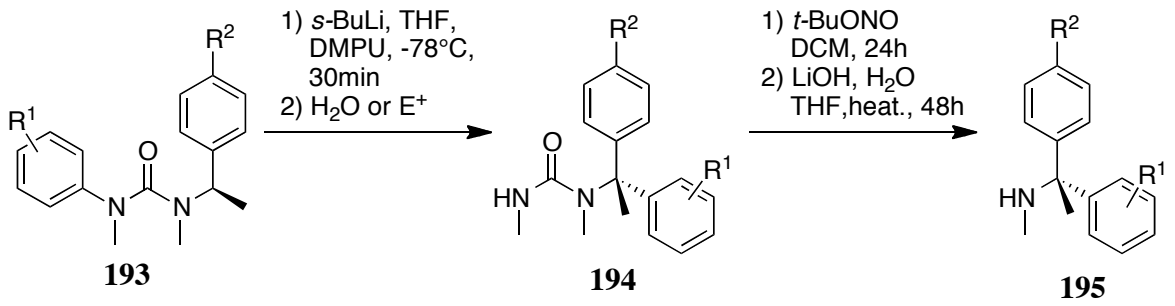
Scheme 70: Rearrangement of lithiated ureas.

This reaction is compatible with other functionalised aryl migrating groups (Scheme 71) and can lead to the desired product **191** and the diarylamines **192** after treatment with DIBAL or hydrolysis of the nitroso derivatives.



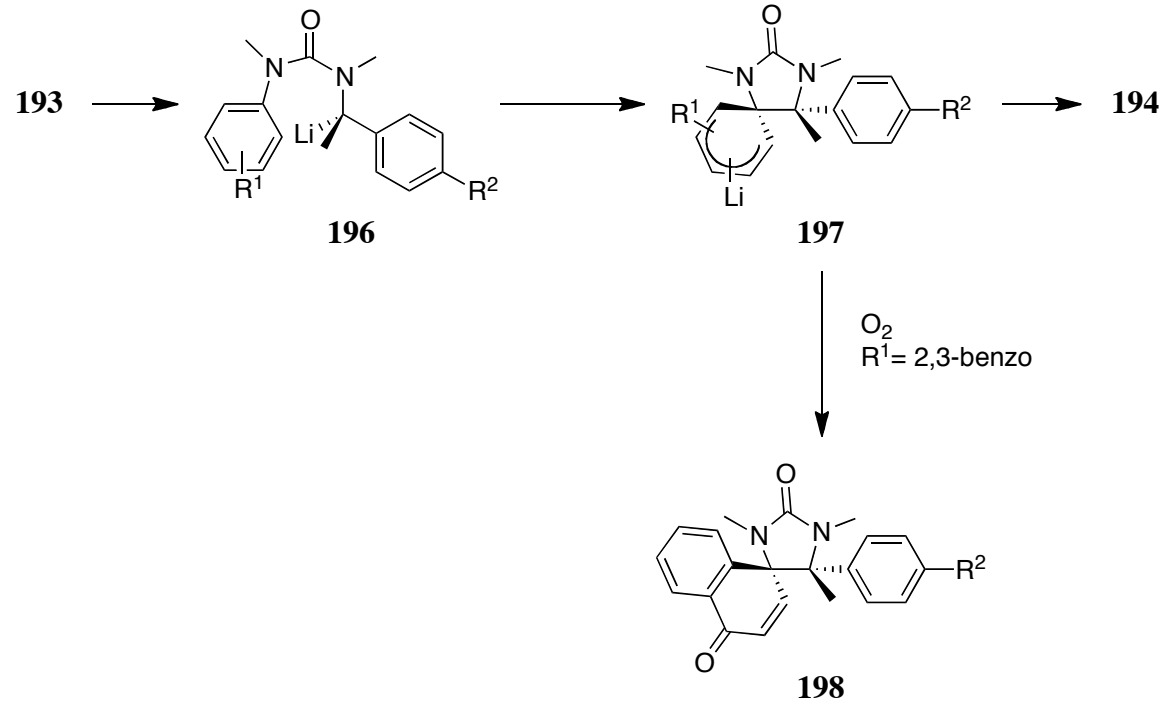
Scheme 71: Synthesis of α-diaryl amines.

A stereospecific version of this rearrangement has also been proposed using methylated ureas **193** to give the corresponding chiral product **194** with complete transfer of chirality and retention of configuration (Scheme 72).



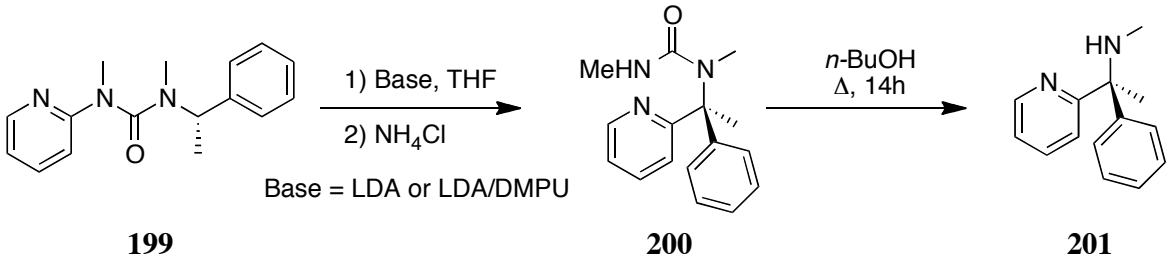
Scheme 72: Stereospecific rearrangement of dimethylated ureas.

It has also been shown that the reaction proceeds with the formation of a dearomatised intermediate **197** which has been trapped by oxidation using oxygen in the case of the naphthyl urea to give the product **198** (Scheme 73).



Scheme 73: Rearrangement of 1-naphthyl urea **193**.

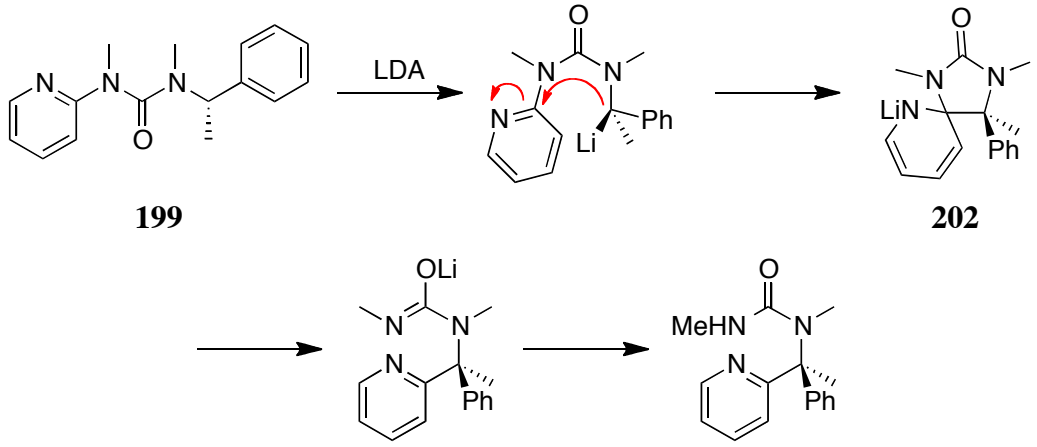
In 2008, the stereospecific rearrangement has been extended to pyridylureas **199** (Scheme 74).[127] The corresponding α-pyridyl chiral amine **201** has been obtained after deprotection of the rearranged product **200** by refluxing in *n*-butanol.



199 **200** **201**

Scheme 74: Stereospecific rearrangement of pyridyl urea.

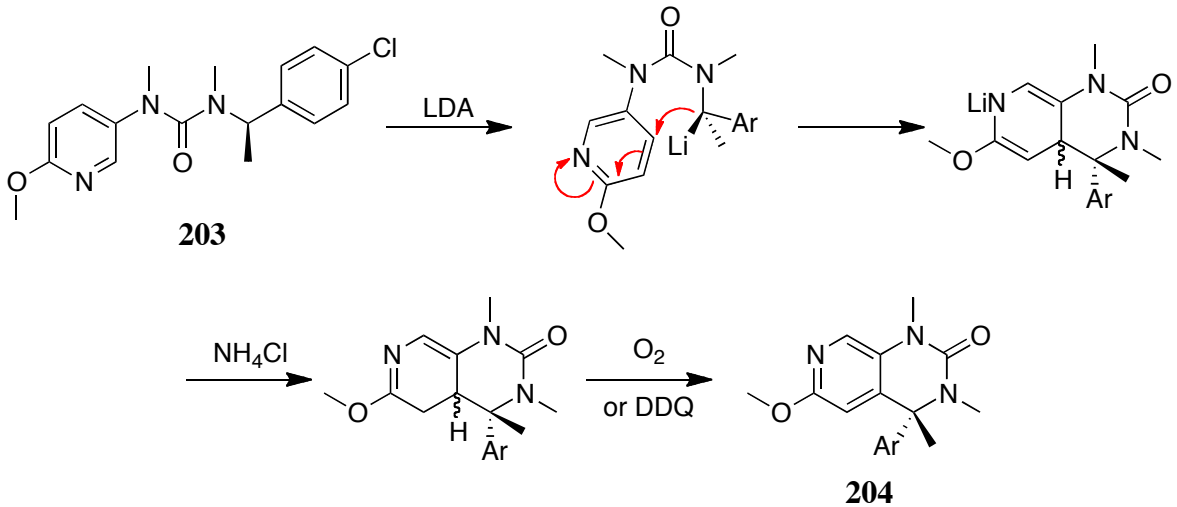
The proposed mechanism also involved a dearomatised intermediate **202** (Scheme 75).



199 **202** **200**

Scheme 75: Proposed mechanism of pyridyl-ureas rearrangement.

With the pyridyl-urea **203**, the cyclic product **204** was obtained (Scheme 76).

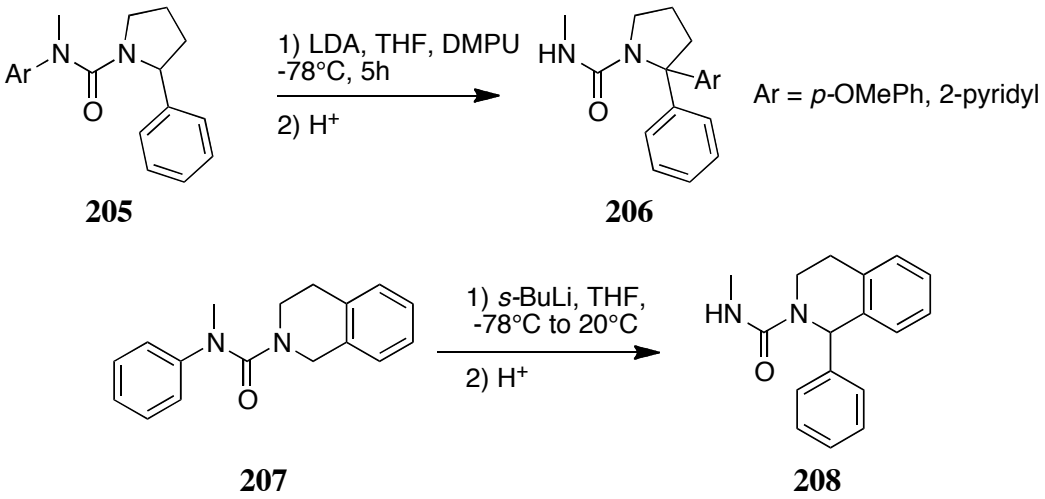


203 **204**

Scheme 76: Synthesis of cyclic ureas **204** via pyridyl-urea rearrangement.

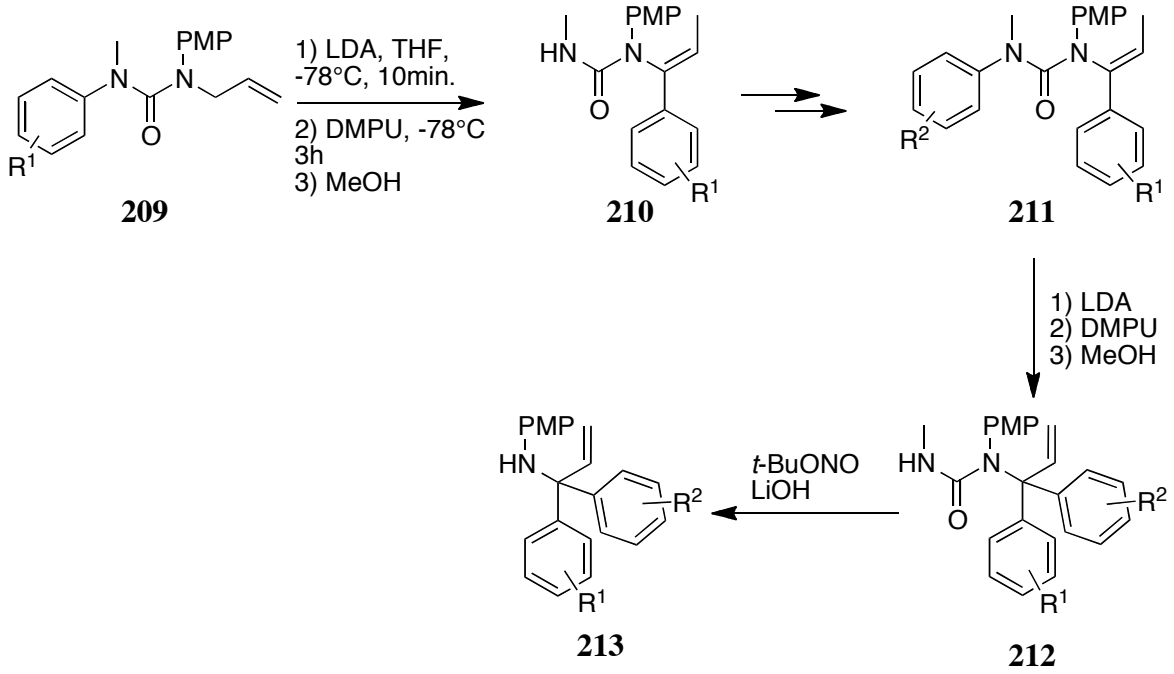
The same approach has been used to obtain cyclic amines **206** and **207** (Scheme 77).[128] In this example, the aryl migration is used on ureas **205** derived from proline and

tetrahydroquinolines **207**. However, attempts to perform this reaction enantioselectively appeared to be unsuccessful.



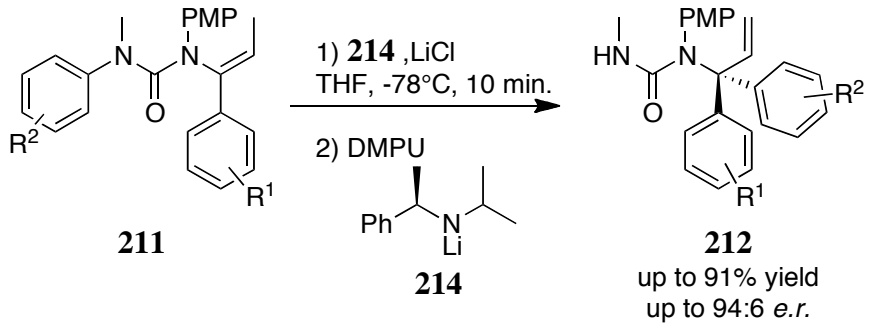
Scheme 77: Rearrangement of cyclic ureas.

Allylic ureas **209** can also be used for this rearrangement leading to the formation of diarylvinyl amines **213** after sequential double aryl migration and deprotection (Scheme 78).[129]



Scheme 78: Sequential double aryl migration.

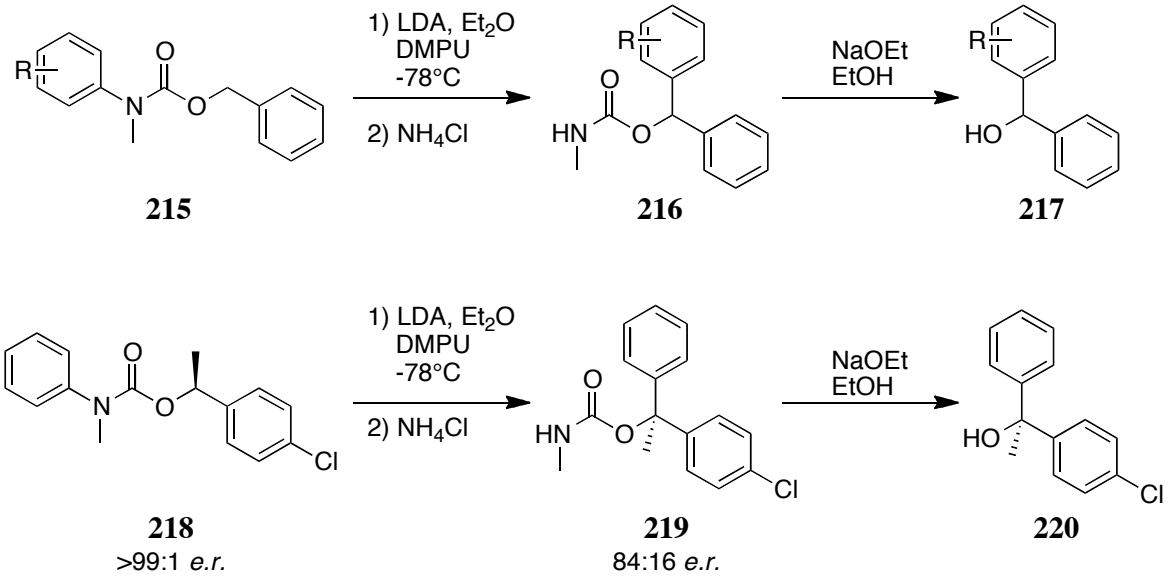
This rearrangement can also be performed enantioselectively using a chiral lithium amide **214** instead of LDA (Scheme 79).



Scheme 79: Enantioselective rearrangement of vinyl ureas **211**.

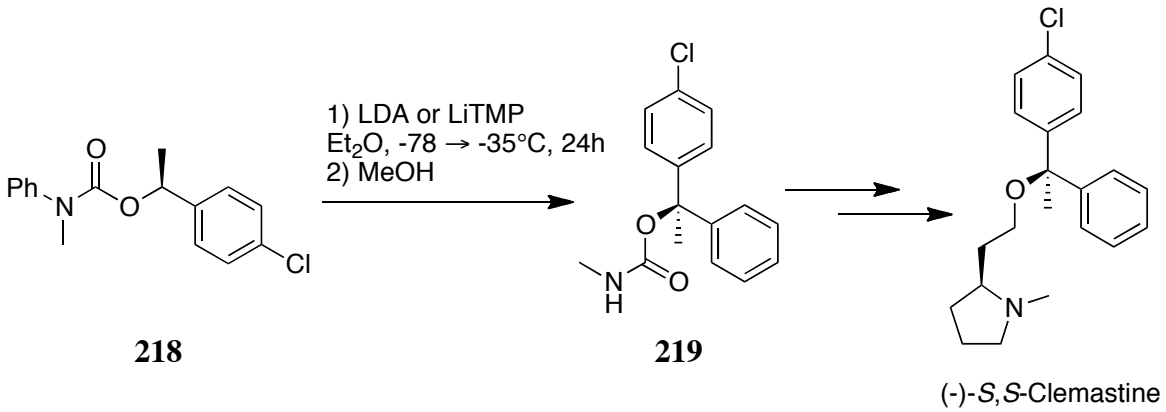
3.3.1. Similar rearrangements

A similar example has been reported in 2009 on carbamates **215** (Scheme 80).[130] The migration of an aromatic group has been observed after deprotonation of carbamate **215**. The rearranged product **216** can be transformed easily to the corresponding alcohol **217**. A stereospecific version of this rearrangement has also been reported starting from chiral carbamate **218** and the final alcohol **220** was obtained with good chirality transfer. In this case, the aryl migration proceeds with an invertive mechanism with a minor loss of enantioselectivity.



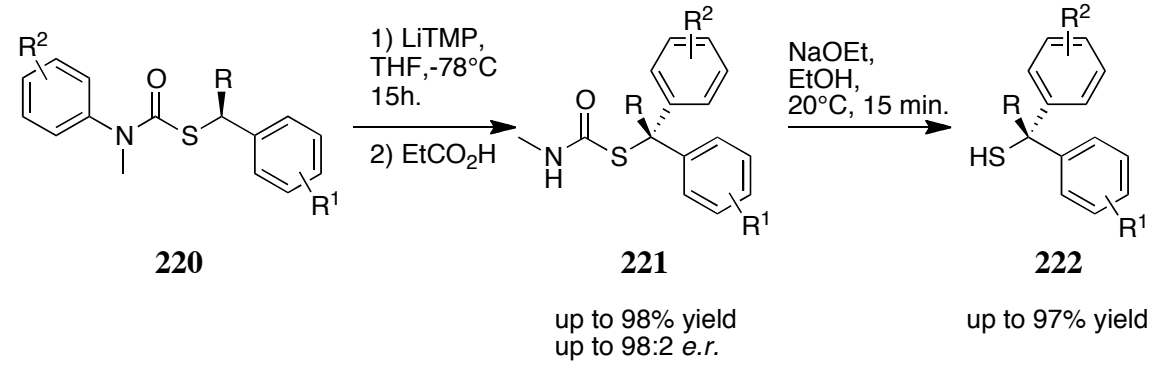
Scheme 80: Rearrangement of carbamates.

This methodology has been recently applied for the first enantioselective synthesis of the potent antihistamine agent (–)-(*S*,*S*)-clemastine (Scheme 81).[131]



Scheme 81: N to C aryl transfer for the synthesis of (–)-*S*,*S*-Clemastine

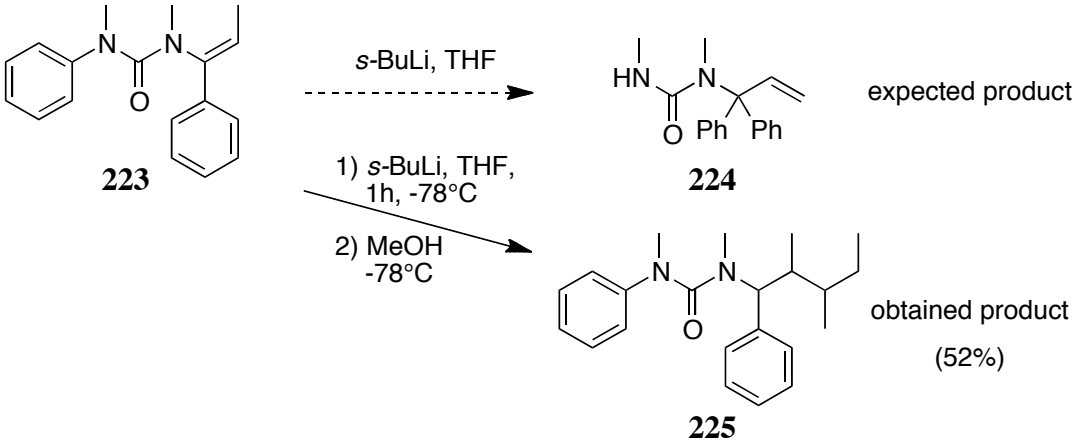
By extension, this methodology has finally been used in the synthesis of tertiary thiols (Scheme 82).[132] The treatment of thiocarbamate **220** with the bulky lithium amide LiTMP leads to the formation of the quaternary thiocarbamate **221** which can be transformed to the corresponding tertiary thiol **222** by reaction with sodium ethoxide in ethanol. The rearrangement is achieved with very good yields and good chirality transfer. X-Ray crystallography confirms the retentive behaviour of the aryl migration in the thiocarbamate series.



Scheme 82: Rearrangement of thiocarbamates **220**.

AIMS OF THE PROJECT

During investigations on the rearrangement of vinyl ureas using allylic deprotonation, an unusual reactivity of urea **223** has been observed* (Scheme 83). Instead of the anticipated rearranged product **224**, treatment of the urea **223** with *s*-BuLi generated the carbolithiated compound **225** in 52% yield. The reactivity of urea **223** is unusual because of the electron-rich character of the double bond.

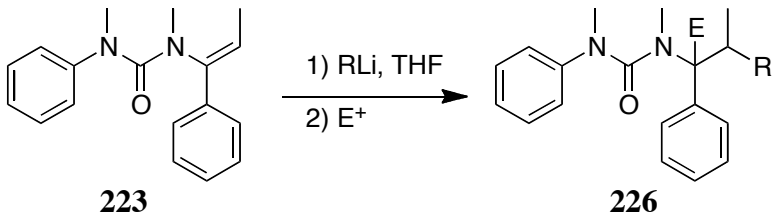


223 **224** **225**

Scheme 83: First example of carbolithiation of the electron-rich urea **223**.

Additional experiments has been performed on urea **223** in order to confirm the reactivity of the substrate. The reaction with *s*-BuLi or *i*-PrLi, using different electrophiles (H or D), leads to the formation of the corresponding carbolithiated compound **226** in moderate yields (Table 1). In all cases, only one diastereomer was observed.

Table 1: Carbolithiation of the electron-rich urea **223**.

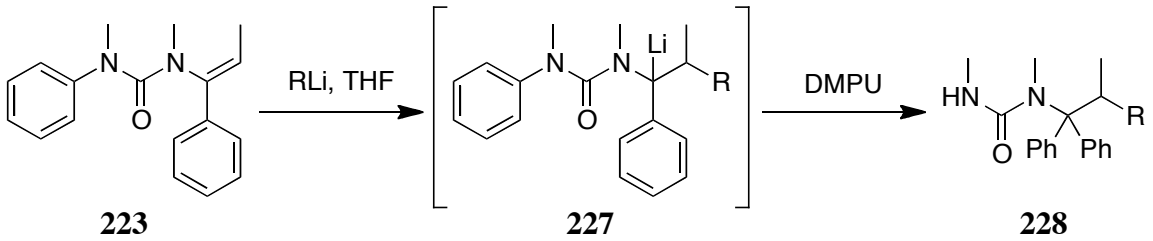


223 **226**

* Daniel J. Tetlow PhD student.

R-Li	E^+	Yield (%)
s-BuLi	MeOD	45
i-PrLi	MeOD	54
i-PrLi	MeOH	58

Addition of DMPU after complete carbolithiation promotes the aryl migration to generate the diaryl urea **228** (Scheme 84).

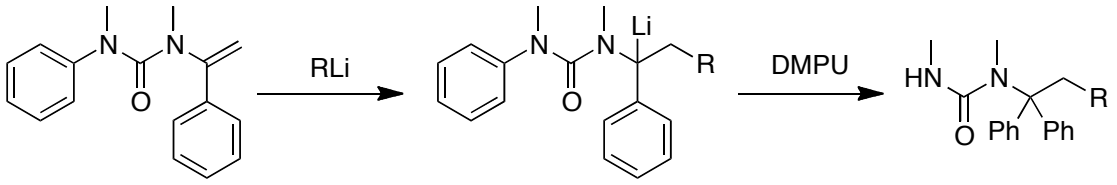


223 **227** **228**

Scheme 84: Tandem carbolithiation/rearrangement of urea **223**.

The initial work on this tandem carbolithiation-aryl migration reaction was performed on the diphenyl urea **229** bearing a *gem* disubstituted double bond* (Table 2).

Table 2: Tandem carbolithiation/rearrangement of diphenyl vinyl urea **229**.

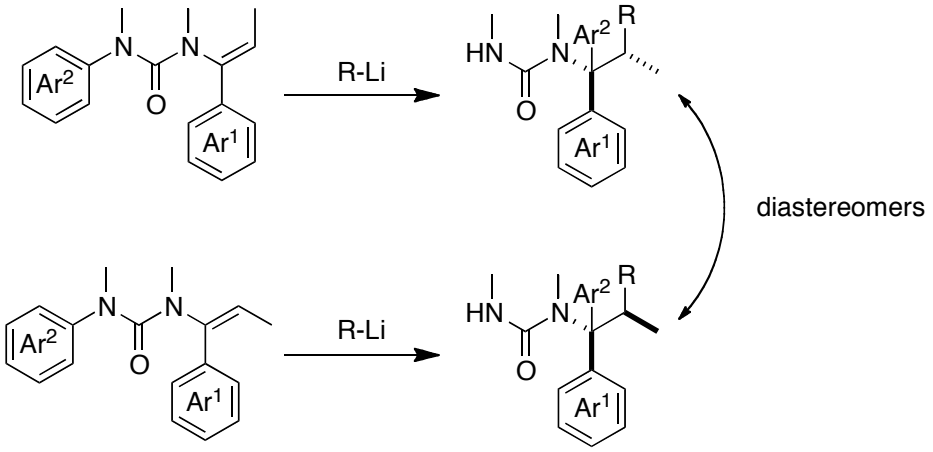


229 **230** **231**

Entry	R	Yield
1	Me	78%
2	*n*-Bu	72%
3	*i*-Pr	74%
4	*s*-Bu	74%
5	Ph	77%

Looking at the results obtained with urea **229**, the proposed work will investigate the tandem reaction on a trisubstituted double bond. Ureas bearing two different aromatic groups will be investigated in order to determine the scope and limitation of the reaction. Moreover, could the use of (*E)* or (*Z)* ureas allow the production of both diasteromers? If the reaction proceed with stereospecificity, (*E*) and (*Z*) ureas should lead to the formation of diastereomers (two new stereogenic centres being created in the reaction) (Scheme 85).

* Dr. Alberto Minassi (visiting researcher)



Scheme 85: Tandem carbolithiation/rearrangement of trisubstitited vinyl ureas.

An enantioselective version of this reaction could also be performed using chiral ligands such as (–)-sparteine or (+)-sparteine surrogate.

In addition, can this unusual carbolithiation of electron rich double bond be extended to other systems to generate highly functionalised amines?

In these reactions, a series of experiments would have to be carried out in order to probe completely the mechanism of the reaction. The stereochemistry of the two steps of the tandem reaction will also be investigated.

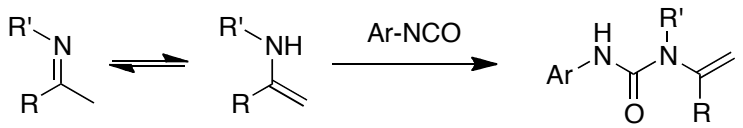
In order to obtain the desired starting materials for the tandem reaction, a simple and efficient synthesis has to be developed, allowing the synthesis of a large range of differently substituted ureas, from readily available starting materials and with a complete control on the stereochemistry of the double bond.

Finally, attempts to extend the N to C aryl transfer to other unsaturated systems will be investigated in order to synthesise α-tertiary amines.

RESULTS AND DISCUSSION

1. Synthesis of vinyl ureas

The main approach for the synthesis of ureas is the reaction between an amine and an isocyanate. To apply this method to the synthesis of vinyl ureas **232**, the reaction of an imine **233**, or the enamine tautomeric form **234**, with an isocyanate will be used.[133-137] This approach will allow the formation of the urea and the double bond in the same step (Scheme 86).

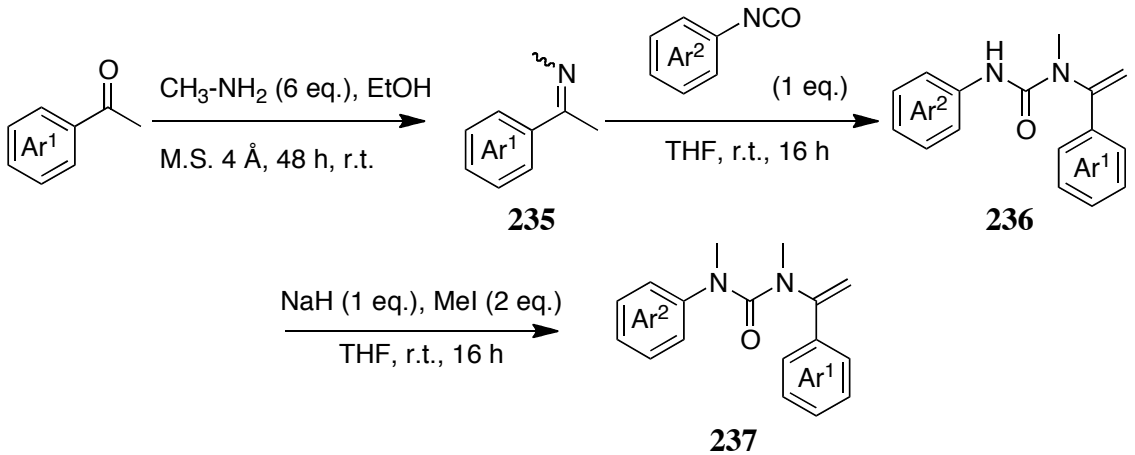


233 **234** **232**

Scheme 86: Reaction of an imine **233** with an isocyanate.

1.1. Synthesis of *gem* disubstituted vinylureas

The synthesis was performed by the reaction of an aryl ketimine **235** with an aryl isocyanate (Scheme 87). The condensation of the acetophenone derivatives with methylamine, for 48 hours at room temperature in presence of molecular sieves, generated the imine **235**, which can react with an aryl isocyanate to form the monomethylated urea **236**. The desired urea **237** was obtained by subsequent methylation using sodium hydride and methyl iodide.



235 **236** **237**

Scheme 87: Synthesis of *gem* disubstituted vinylureas **237**.

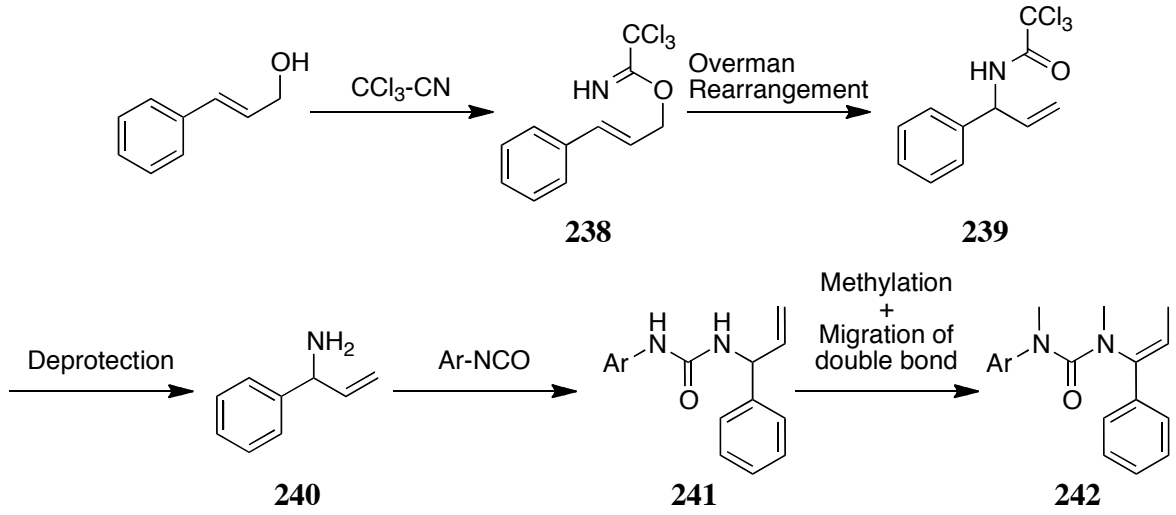
Table 3: Synthesis of non-substituted vinyl ureas **237**.

Ar^1	Ar^2	Yield (%)
Ph	Ph	49
Ph	4-CH_3-C_6H_4	51
Ph	4-OCH_3-C_6H_4	54
Ph	4-Cl- C_6H_4	51
4-Cl-C_6H_4	4-OCH_3-C_6H_4	57

The synthesis was performed in a one-pot process, involving only one chromatography step, in which the dimethylated ureas were obtained in good yields over three steps (Table 3). Similar yields were obtained with electron rich and electron poor aromatic rings.

1.2. Synthesis of trisubstituted vinylureas

A method for the synthesis of trisubstituted vinyl ureas was previously developed in the Clayden group (Scheme 88). This synthesis involved an Overman rearrangement of trichloroacetimidate **238** followed, after deprotection, by reaction with an isocyanate to form the allylic urea **241**. Methylation of the two nitrogens using an excess of base led to the desired product **242** with migration of the double bond. The final product was obtained only as the (*Z*)-isomer probably due to the formation of an allylsodium intermediate in the last step. The high number of steps, the long reaction time and the lack of availability of other cinnamic alcohols, limited the usefulness of this method.

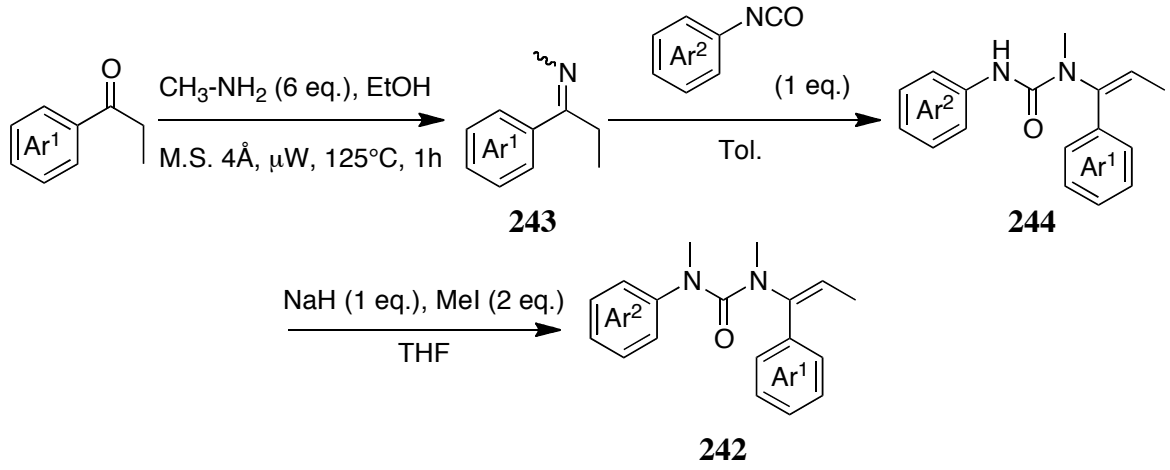


Scheme 88: Synthesis of (*Z*)-vinylureas **242**.

Instead, the reaction between an enamine and an isocyanate was chosen to synthesise the trisubstitued ureas **242** (Scheme 89).

The propiophenone derivative was reacted with methylamine at 50°C for 48h to yield the imine **243** as a mixture with the starting ketone (generally 8:2, determined by NMR). However, the reaction time was dramatically reduced performing the reaction under microwave irradiation at 125°C for an hour (the same ratio was obtained).

The imine **243** was then treated with an arylisocyanate to generate the urea **244**. This reaction, originally performed in THF for 16 hours, appeared to be much cleaner in toluene, however no noticeable increase in the yield was observed. The methylation was performed by treatment of **244** with sodium hydride and methyl iodide to form the desired urea **242**. As before, the synthesis was carried in a one-pot process.



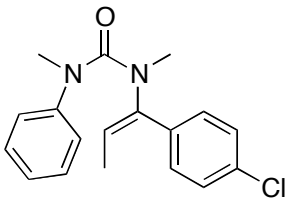
Scheme 89: Synthesis of trisubstituted (*E*)-vinylureas **242**.

The desired ureas were obtained in good yields over three steps (Table 4). The (*E*)-isomer (determined by nOe experiments) was generally obtained in very large excess making this method complementary to the one using the Overman rearrangement.

Only urea **242f**, bearing a 2-OCH_3 substituent, gave a lower (*E*:*Z*) ratio. This was probably due to steric interactions. The yields are lower than the ones reported previously with the acetophenone due to the incomplete formation of the imine **243**. The stereochemistry of urea **242j** was confirmed by X-ray crystallography (Figure 8). In some cases the ureas **244** had been isolated for further studies.

Table 4: Synthesis of trisubstituted vinyl ureas.

Ar^1	Ar^2	Urea 242	Yield	Urea 244	Yield	(*E*):(*Z*)
Ph	3-OCH_3-C_6H_4	**(*E*)-242a**	40%	-	-	94:6
Ph	4-OCH_3-C_6H_4	**(*E*)- 242b**	40%	**(*E*)-244b**	40%	95:5
Ph	4-F-C_6H_4	**(*E*)- 242c**	34%	-	-	94:6
Ph	4-Cl-C_6H_4	**(*E*)- 242d**	20%	-	-	92:8
Ph	4-CH_3-C_6H_4	**(*E*)- 242e**	40%	-	-	96:4
Ph	2-OCH_3-C_6H_4	**(*E*)- 242f**	37%	-	-	85:15
Ph	2-Me-C_6H_4	**(*E*)- 242g**	39%	**(*E*)-244g**	42%	91:9
Ph	1-naphthyl	**(*E*)- 242h**	35%	-	-	93:7
4-OCH_3-C_6H_4	Ph	**(*E*)- 242i**	55%	-	-	90:10
4-Cl-C_6H_4	Ph	**(*E*)- 242j**	53%	-	-	95:5
4-CH_3-C_6H_4	Ph	**(*E*)- 242k**	45%	-	-	92:8
4-F-C_6H_4	Ph	**(*E*)- 242l**	46%	**(*E*)-244l**	50%	95:5
4-Cl-C_6H_4	4-OCH_3-C_6H_4	**(*E*)- 242m**	38%	**(*E*)-244m**	40%	92:8



(*E*)-242j

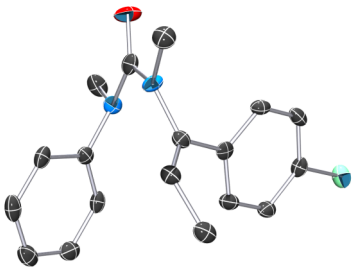
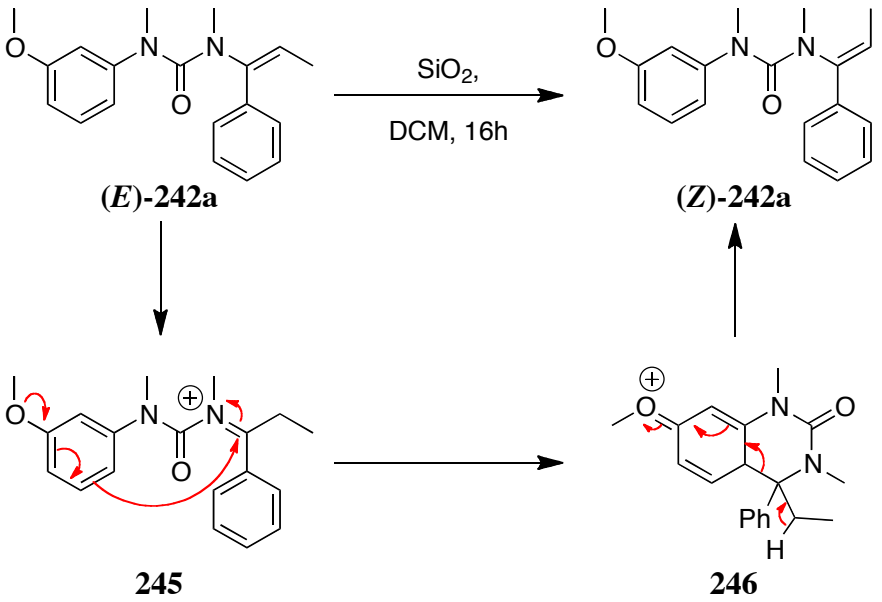


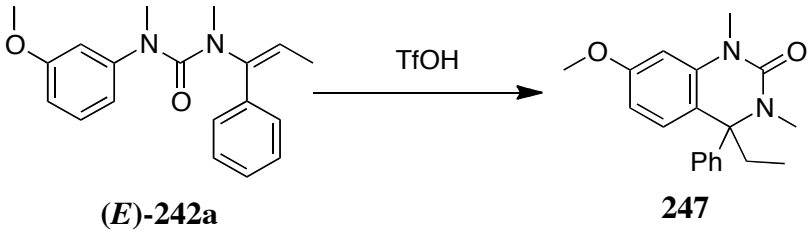
Figure 8: X-ray crystal structure of urea **(*E*)-242j**.

All the compounds were stable to isomerisation of the double bond in the reaction conditions except urea **(*E*)-242a** (bearing a 3-OCH_3 substituent). In contact with silica, this urea isomerised. Treatment with silica in DCM for 16h led to the complete isomerisation of the double bond (Scheme 90). A possible explanation is the formation of iminium **245** which can perform an intramolecular Friedel-Crafts acylation to form the cyclic compound **246** that generates the (*Z*)-isomer after ring opening and rearomatisation.



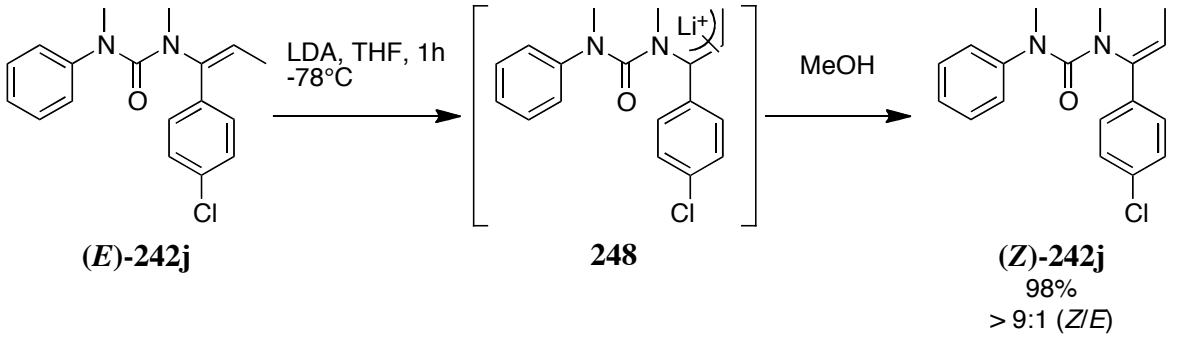
Scheme 90: Isomerisation of urea **(*E*)-242a**.

This hypothesis was supported when urea **(*E*)-242a** was treated with the strong triflic acid (Scheme 91). In this case, the cyclic urea **247** was isolated in 87%.



Scheme 91: Reaction of **(*E*)-242a** with triflic acid.

However, for the other ureas, another approach had to be used to isomerise the double bond. It is known that allyllithium species prefer to adopt a *Z* conformation. Because of this behaviour, urea **(*E*)-242j** was treated with LDA in order to generate the allyllithium intermediate **248**. Quench with methanol led to the desired isomer **(*Z*)-242j** in good yield and selectivity (*Z*/*E*: 9/1) (Scheme 92).



Scheme 92: Isomerisation of (*E*) double bond.

The stereochemistry of **(*Z*)-242j** was also confirmed by nOe experiment and Xray crystallography (Figure 9).

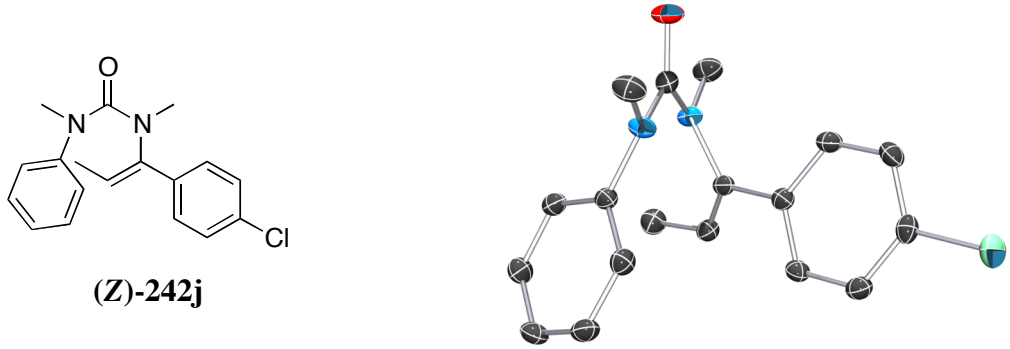
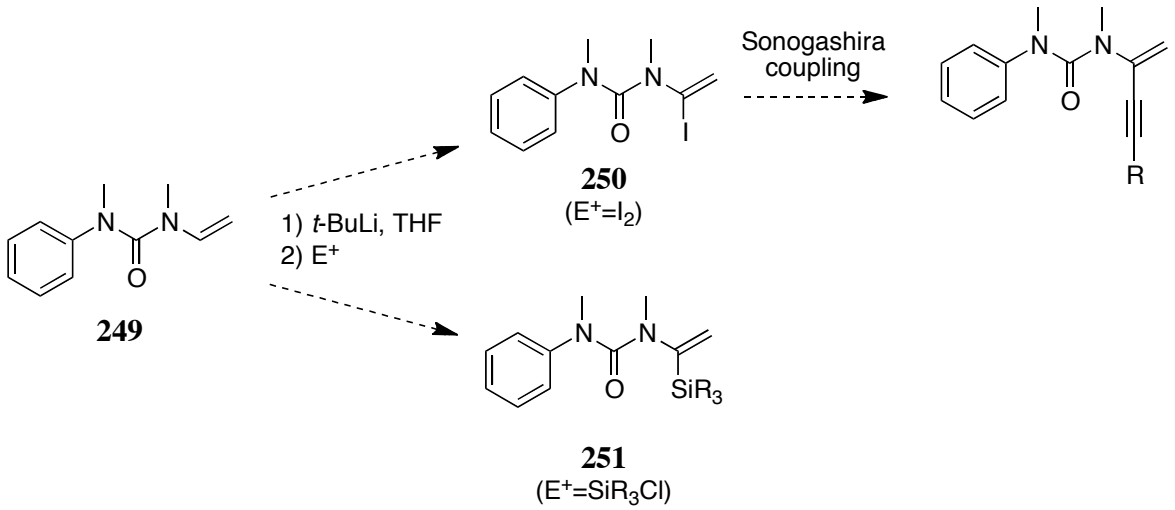


Figure 9: X-ray crystal structure of urea **(*Z*)-242j**.

1.3. Synthesis of other vinyl ureas

To increase the complexity and the applicability of the vinyl ureas toward lithiation chemistry, attempts to synthesise compounds bearing stabilising groups other than phenyl were performed (Scheme 93). The initial idea was to synthesis the non-substituted vinyl-urea **249**. In a second step, lithiation of the sp^2 carbon using *t*-BuLi followed by quench using the appropriate electrophile should allow the access to a larger range of starting materials. A quench using I_2 would allow the synthesis of urea **250**, an ideal precursor for palladium cross-coupling. Another possibility would be to use silicon as an electrophile to form ureas **251** where the stabilisation of the negative charge can be achieved using the silicon atom. In all these compounds, the lithiated intermediate could be stabilised.

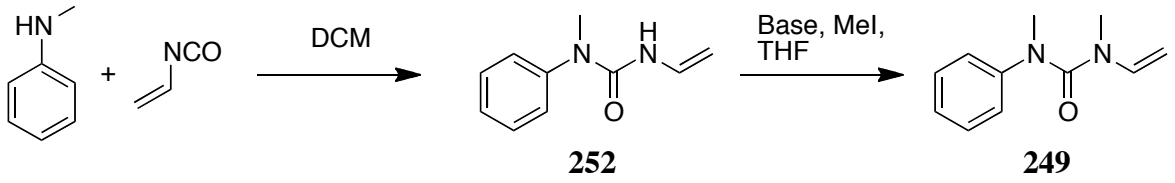


Scheme 93: Synthesis of more functionalised vinyl ureas.

The synthesis of urea **249** started from the coupling of *N*-Methylaniline with vinyl isocyanate. The monomethylated urea **252** was obtained in quantitative yield after one hour in dichloromethane (Scheme 94).

The methylation of the remaining nitrogen appeared to be more problematic than expected. Treatment of urea **252** with different bases followed by addition of a methylating agent (MeI of MeOTf) always led to decomposition of the starting material (Table 5).

The decomposition of **252** was avoided by premixing the urea with MeI at 0°C before the addition of NaH. After an hour the reaction was complete.



Scheme 94: Synthesis of urea **249**.

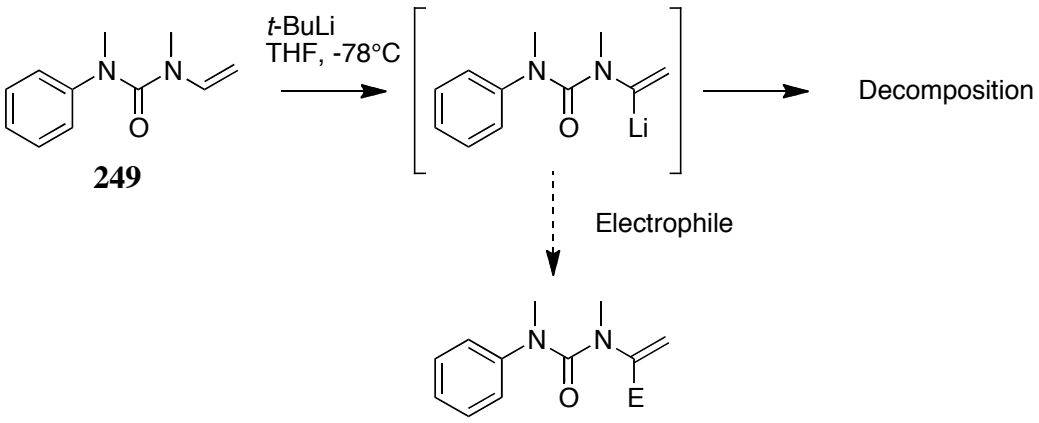
Table 5: Methylation conditions for urea **249**.

Base	Methylated agent
NaH	MeI
NaH[a]	MeI
NaOH	MeI
i-Pr_2Net	MeI
NaH	MeOTf

[a]: reaction performed in DMF

With urea **249** in hand, the lithiation reaction, using different electrophiles, was performed (Table 6). In every case, decomposition of urea **249** was observed. Because of the poor stability of **249** the synthesis was not further investigated.

Table 6: Lithiation of urea **249**.



249

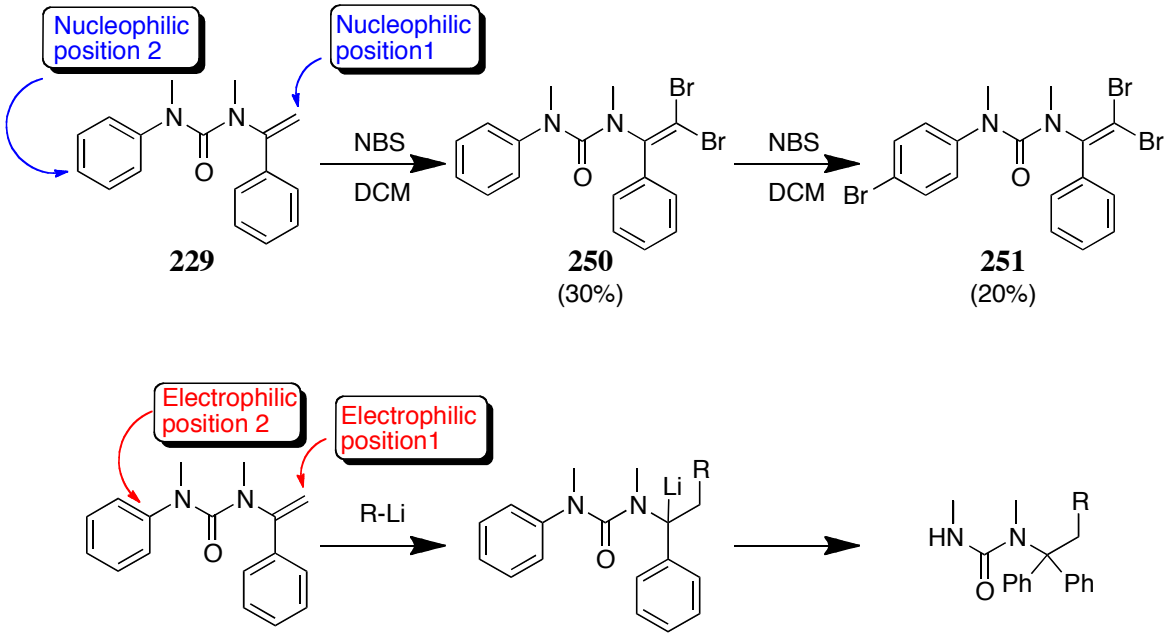
Electrophile	Conclusion
TMSCl	Decomposition
TIPSCl	Decomposition
TBDMSCl	Decomposition
I_2	Decomposition

1.4. Nucleophiles and electrophiles

Because of the structural similarity between vinyl ureas and enamides, it was wondered if the two classes of compounds presented similar reactivities towards electrophiles.

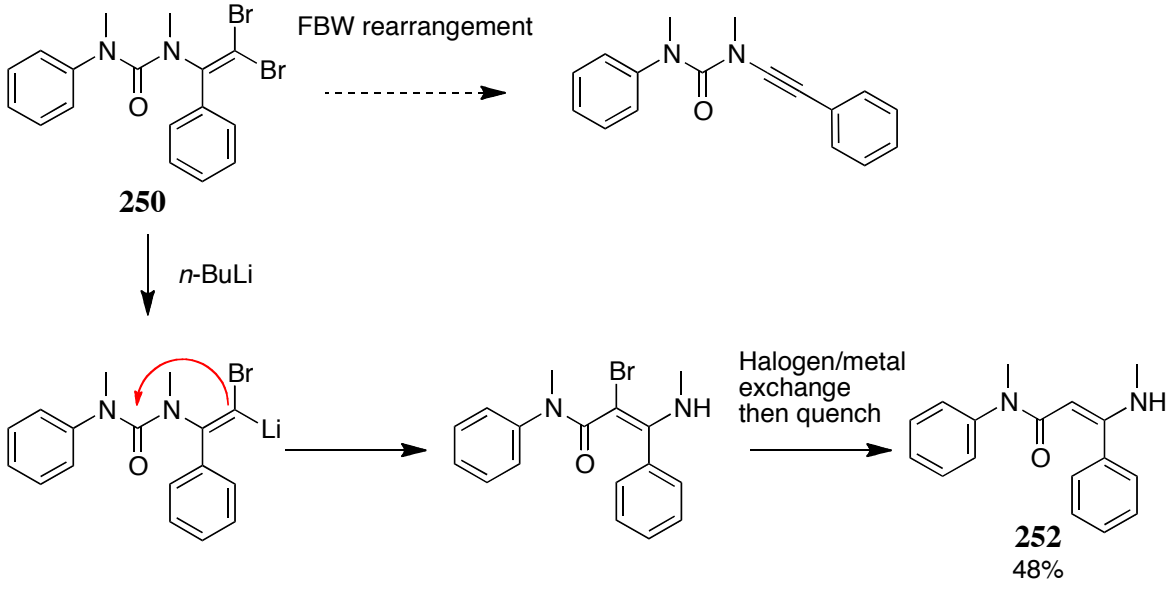
Treatment of urea **229** with 2 equivalents of NBS resulted in the *gem*-dibromination of the terminal position of the double bond to form **250** (Scheme 95). Excess of NBS led to the formation of the tribrominated compound **251** where an extra bromine was installed in *para* position on the aromatic ring bearing the urea susbtituent.

So, if this reactivity is compared to the tandem reaction carbolithiation-rearrangement introduced previously, the nucleophilic positions highlighted by the bromination reaction are the same as the electrophilic positions involved in the tandem reaction. The reaction between an organolithium reagent and a vinyl urea highlights a very unusual umpolung reactivity.



Scheme 95: Double reactivity of vinyl ureas.

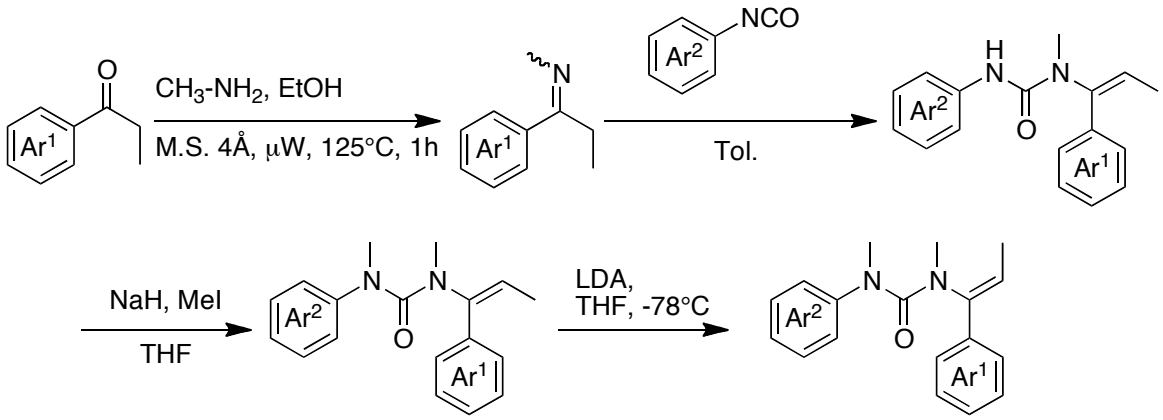
Dibrominated double bonds bearing an aromatic ring are common starting materials to perform a Fritsch–Buttenberg–Wiechell rearrangement. In this transformation, the dibromoalkene is converted to the corresponding alkyne with aryl transfer. This rearrangement was attempted in order to synthesise the corresponding propargyl urea. Urea **250** was treated with 2 equivalents of *n*-BuLi. Unfortunately, the desired product was not formed and compound **252** was isolated instead in 70% yield as a single geometrical isomer (*E* stereochemistry assumed), corresponding to an acyl shift (Scheme 96).



Scheme 96: Rearrangement of di-brominated urea **250**.

1.5. Summary

To summarise, a large range of vinyl ureas were synthesised trapping an enamine, tautomeric form of an imine, with an aromatic isocyanate. This synthesis was developed in a one-pot process, limiting the need for purification, and can be carried out on multigram scale (up to 3 grams). Modifications can be introduced at every stage and allowed the preparation of diversely functionalised vinyl ureas (Scheme 97). All the examples were obtained in good yields (over three steps) and with a very large excess of the (*E*)-stereoisomer. Treatment with LDA converts the (*E*)-isomer to the (*Z*) in quantitative yield. With this efficient synthesis of starting material it is possible to investigate their unusual reactivity toward alkyllithium nucleophiles in order to synthesise highly functionalised amines.

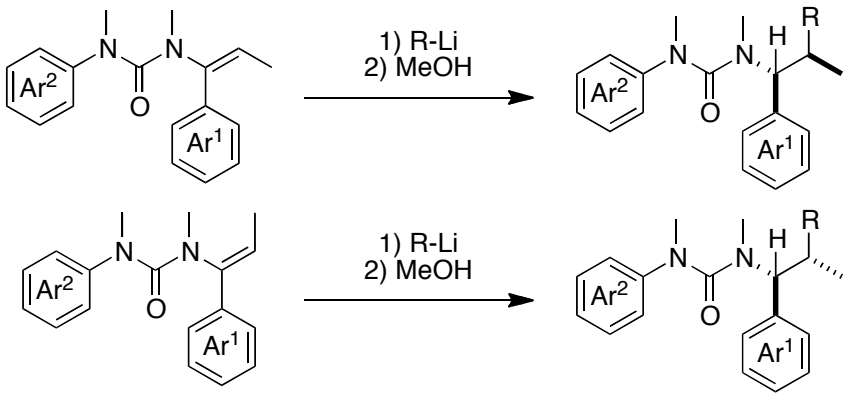


Scheme 97: Synthesis of (*E*) and (*Z*)-vinyl ureas.

2. Tandem carbolithiation-aryl migration

2.1. Umpolung carbolithiation

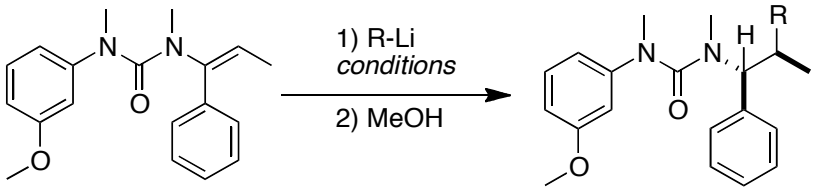
Before investigating the behaviour of the tandem reaction, the unusual umpolung carbolithiation step was studied (Scheme 98). Ureas bearing different aromatic rings were reacted with a range of organolithium reagents to determine the scope of the reaction and its limits. As reported in the literature, the carbolithiation reaction is a *syn* stereospecific process. Therefore, *Z* and *E* ureas should give access to the two diastereomers of the product.



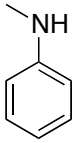
Scheme 98: Carbolithiation of ureas.

The urea **(*E*)-242a** was the first starting material investigated with different nucleophiles under different reaction conditions (solvent, temperature, concentration) (Table 7).

Table 7: Carbolithiation of urea **(*E*)-242a**.



(*E*)-242a **253**

Entry	R-Li	Eq	Solvent	Time	Temp.	Product	Yield
1	MeLi	2	THF	1	−78°C		39%
2	*n*-BuLi	2	THF	1	−78°C	**253a**	20%
3	*n*-BuLi	2	Et_2O	1	−78°C	**253a**	34%
4	*n*-BuLi	2	Et_2O	2	−78°C	**253a**	32%
5	*n*-BuLi	2	Et_2O	1	−40°C	**253a**	85%
6	*n*-BuLi	2	Toluene	1	−78°C	**253a**	0%
7	*i*-PrLi	2	THF	1	−78°C	**253b**	37%
8	*i*-PrLi	2	Et_2O	1	−78°C	**253b**	53%
9	*i*-PrLi	2	Et_2O	3	−78°C	**253b**	46%
10	*i*-PrLi	2	Et_2O	1	−60°C	**253b**	42%
11	*i*-PrLi	2.5	Et_2O	1	−78°C	**253b**	35%
12	*i*-PrLi	2	Toluene	1	−78°C	**253b**	55%
13	*i*-PrLi	2	Toluene	1	−60°C	**253b**	35%
14	*i*-PrLi	2	Toluene	1	−40°C	**253b**	83%
15	*t*-BuLi	2	THF	1	−78°C	**253c**	49%
16	*t*-BuLi	3	THF	1	−78°C	**253c**	60%
17	*t*-BuLi	2	Et_2O	1	−78°C	**253c**	19%
18	*t*-BuLi	2	Toluene	1	−78°C	**253c**	53%
19	*t*-BuLi	2	Toluene	2	−78°C	**253c**	55%
20	*t*-BuLi	2	Toluene	1	−40°C	**253c**	72%
21	PhLi	2	THF	2	−78°C	-	0%
22	vinylLi	2	THF	2	−78°C	-	0%
23	Ethyl-Vinyl-Ether-Li	2	THF	2	−78°C	-	0%

Primary organolithiums were investigated. Treatment of (*E*)-**242a** with MeLi led to the formation of *N*-methylaniline (entry 1) which resulted from the attack of the alkyllithium on to the carbonyl.

n-BuLi however was able to react with the double bond to form the desired carbolithiated compound **253a** as a single diastereomer (entries 2-6). The addition of *n*-BuLi was only

possible in coordinative solvents, THF or Et_2O. The desired compound was obtained in low to very good yields. The best result was obtained when the reaction was performed at –40°C in Et_2O for 1h (entry 5). When the reaction was performed in toluene, only starting material was recovered (entry 6). This is probably due to the poor dissociation of *n*-BuLi in this non-coordinative solvent.

i-PrLi was chosen as secondary organolithium and the desired product **253b** was formed in moderate to good yields, again as a single diastereomer (entries 7-14). In this case, the highest yield was obtained when the reaction was performed at -40°C in toluene (83%, entry 14). *s*-BuLi was not investigated at this stage because of the presence of an additional stereogenic centre.

t-BuLi (entries 15-20) was then used to determine the behaviour of tertiary organolithiums in this carbolithiation. The product **253c** was formed in low to good yields as a single diastereomer. For this alkylithium, the best result was obtained when the urea was reacted for 1h in toluene at –40°C.

Aryllithiums such as phenyllithium (entry 21) did not react and the starting material was recovered even in THF. Other sp^2 organolithium reagents also failed to react (entry 22-23).

Further examples of this umpolung carbolithiation were performed using other ureas. All the reactions were carried out at –40°C in toluene for 1h (Table 8).

Aminolithiation were also attempted using lithiumdibenzylamide without success (entry 8)

Table 8: Carbolithiation of vinyl ureas **242**.

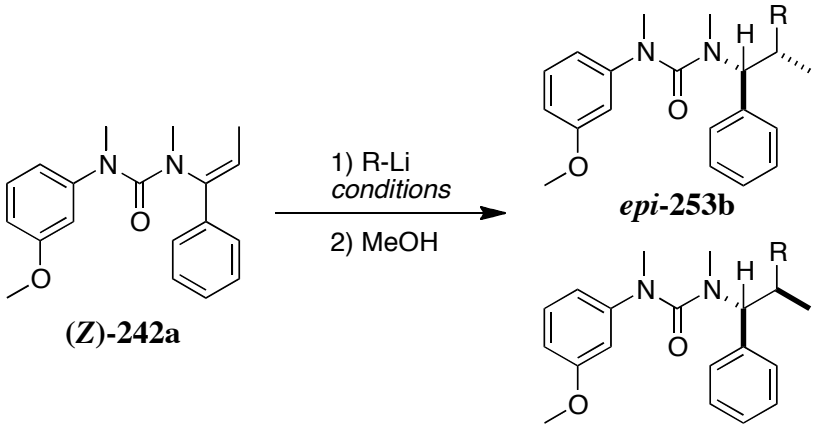
Entry	Urea	Ar^1	Ar^2	R-Li	Product	Yield
1	**(*E*)-242b**	Ph	4-OCH_3-C_6H_4	*n*-BuLi	**254a**	85%
2	**(*E*)-242b**	Ph	4-OCH_3-C_6H_4	*i*-PrLi	**254b**	85%
3	**(*Z*)-242b**	Ph	4-OCH_3-C_6H_4	*i*-PrLi	***epi*-254b**	80%
4	**(*E*)-242j**	4-Cl-C_6H_4	Ph	*i*-PrLi	**255**	80%
5	**(*Z*)-242j**	4-Cl-C_6H_4	Ph	*i*-PrLi	***epi*-255**	81%
6	**(*E*)-242l**	4-F-C_6H_4	Ph	*s*-BuLi	**256**	70%
7	**(*E*)-242k**	4-CH_3-C_6H_4	Ph	*t*-BuLi	**257**	63%
8	**(*E*)-242j**	4-Cl-C_6H_4	Ph	$(CH_2Ph)_2NLi$	**-**	-

In each case, the desired carbolithiated product was obtained in good to excellent yields always as a single diastereoisomer. The reaction of *Z* and *E* ureas led to the formation of the two different diastereoisomers in similar yields (entries 2-5). These results allowed us to conclude that the reaction was completely stereospecific and only the stereochemistry of

the starting urea influences the stereochemistry of the product. These results allow the conclusion that the carbolithiated intermediate is configurationally stable on the reaction time-scale.

A surprising result was obtained when the reaction of urea **(*Z*)-242a** was treated with *i*-PrLi (Table 9). The expected carbolithiated compound ***epi*-253b** was never observed. A screening of different conditions had been carried out to form the desired compound but the *E* and *Z* isomers always led to the formation of the same compound. Treatment of **(*Z*)-242a** with less than 2 equivalents of *i*-PrLi (entries 8 and 9) led to the formation of the **(*E*)-242a** urea as a main product on NMR of the crude mixture.

Table 9: Carbolithiation of urea **(*Z*)-242a**.

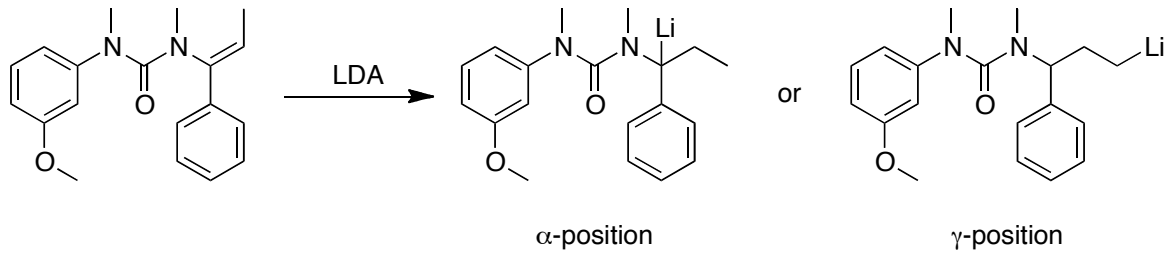


Entry	Eq. of *i*-PrLi	Solvent	Temp.	Product*
1	2	Et_2O	–78°C	**253b**
2	2[a]	Et_2O	–78°C	**253b**
3	2[b]	Et_2O	–78°C	**253b**
4	2[c]	Et_2O	–78°C	**253b**
5	2	Toluene	–78°C	**253b**
6	2[d]	Toluene	–78°C	**253b**
7	2	THF	–78°C	**253b**
8	1	Toluene	–78°C	**(*E*)-242a**
9	0.5	Toluene	–78°C	**(*E*)-242a**

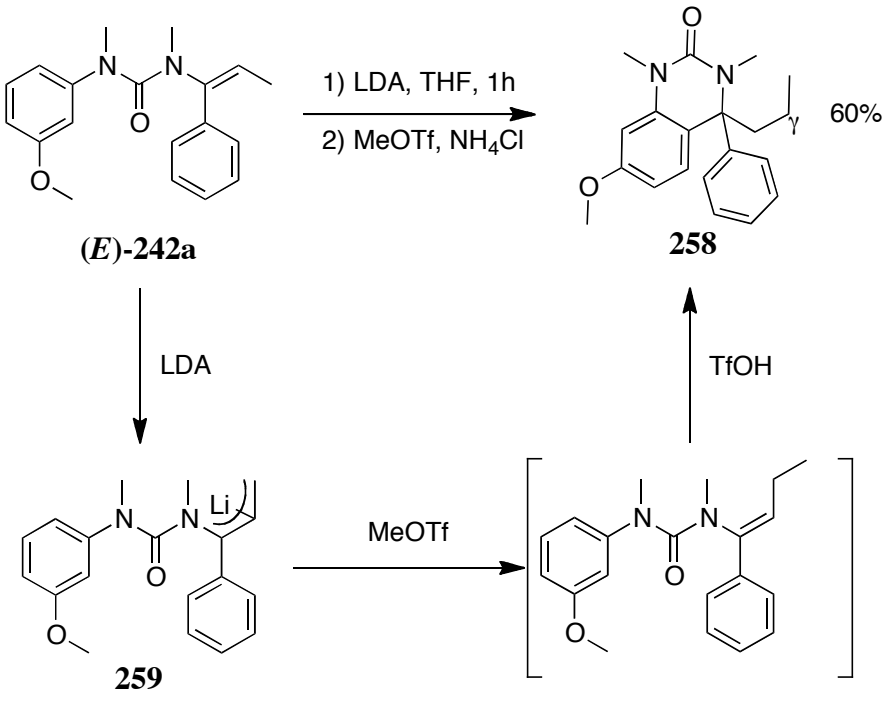
* analysis of the crude mixture by NMR

[a] addition of 1eq LiBr; [b]very slow addition; [c]reverse addition; [d]higher concentration

In order to understand why both isomers **(*Z*)-242a** and **(*E*)-242a** led to the same product, deprotonation of urea **(*E*)-242a** with LDA followed by a quench with methyltriflate was carried out to determine the position of the lithium in the intermediate (Scheme 99).
Instead of the desired methylated product (α or γ), the cyclic urea **258** was obtained with a methylation in the γ position (Scheme 100).



Scheme 99: α or γ-methylation.



Scheme 100: Deprotonation of **(*E*)-242a**.

A possible explanation for this product is the formation of an allylic system followed by a γ methylation with methyl triflate. The cyclisation can be explained by an intramolecular Friedel-Crafts reaction due to the presence of triflic acid in a small amount after methylation of the allyllithium intermediate **259**. This result also highlights the possibility of isomerisation of the double bond. It is possible to hypothesise that this isomerisation can happen before the carbolithiation is performed.

To summarise, the carbolithiation reaction was successful when performed with *n*-BuLi, *i*-PrLi, *s*-BuLi and *t*-BuLi. The best yields were obtained when the reaction was carried out at –40°C in toluene (or Et_2O for *n*-BuLi). The reaction appeared to be diastereoselective for all the substrates investigated except ***(Z)*-242a**. The reaction didn't seem to be dependent of the substituents present on the aromatic rings.

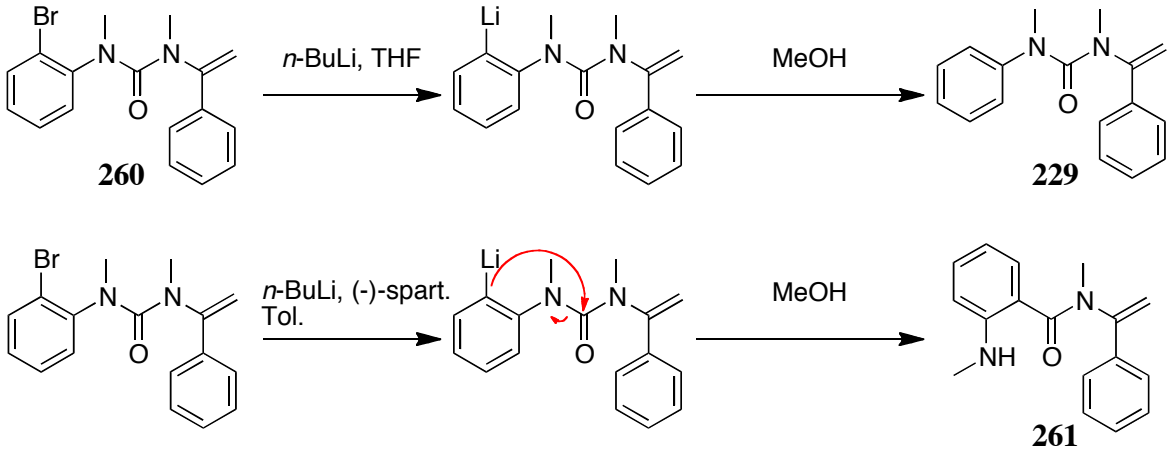
Moreover, *i*-PrLi gave good results and a clean reaction so became the organolithium of choice during further investigations.

2.2. Intramolecular carbolithiation

Ureas bearing a terminal double bond proved to be reactive towards phenyllithium.* In order to investigate the feasibility of an intramolecular carbolithiation, urea **260** bearing an *ortho*-bromo substituent was synthesised following the procedure presented before.

Treatment of urea **260** with *n*-BuLi in THF at –78°C followed by quench using methanol led to the quantitative formation of the dehalogenated urea **229** (Scheme 101).

When the reaction was performed in a non-coordinative solvent (toluene) in the presence of a coordinative ligand, in this case (–)-sparteine, the enamide **261** corresponding to the acyl transfer was formed.

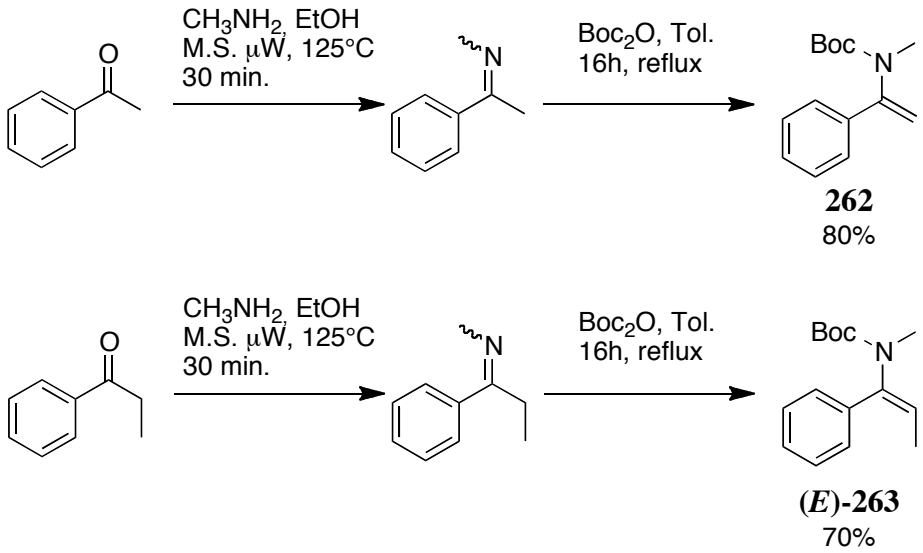


Scheme 101: Attempts on intramolecular carbolithiation.

* Prof. Dr. Alberto Minassi and Dr. Morgan Donnard, University of Manchester.

2.3. Extension of the umpolung carbolithiation: investigations of *N*-Boc vinyl-carbamates

In order to extend the scope of the previous umpolung carbolithiation, investigation of *N*-Boc protected vinyl-carbamates **262** and **263** were investigated (Scheme 102). The synthesis of these substrates was performed by reaction of the corresponding imines with Boc anhydride. The stereochemistry of **(*E*)-263** was determined by nOe experiments and confirmed by X-ray crystallography (Figure 10).



Scheme 102: Synthesis of vinylcarbamates **262** and **263**.

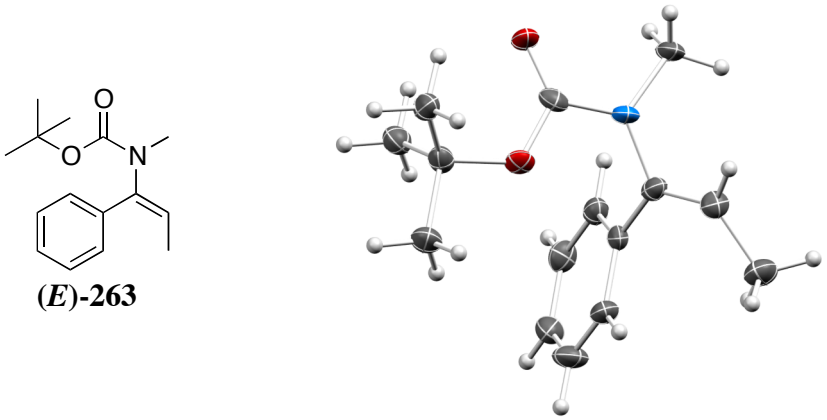
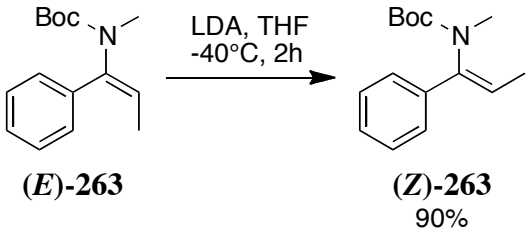


Figure 10: X-ray crystal structure of **(*E*)-263**.

The isomerisation of **(*E*)-263** to **(*Z*)-263** was performed by deprotonation using LDA followed by quench with methanol (Scheme 103). The carbamate **(*Z*)-263** was obtained in a very high yield.

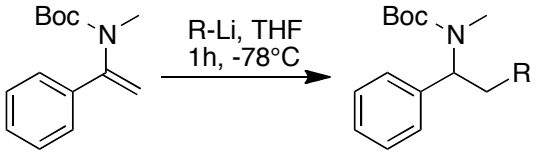


(*E*)-263 **(*Z*)-263** 90%

Scheme 103: Isomerisation of carbamate **(*E*)-263**.

The carbolithiation was first investigated on the non-substituted carbamates **262** (Table 10). The reaction of primary, secondary and tertiary alkyllithium reagents led to the formation of the desired compounds **264** in moderate to good yields. The conversion was complete after 1h in THF at -78°C.

Table 10: Carbolithiation of carbamate **262**.

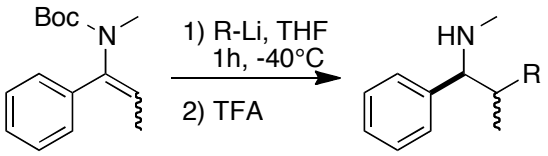


262 **264**

Entry	R-Li	Compound	Yield
1	*n*-BuLi	**264a**	64%
2	*i*-PrLi	**264b**	61%
3	*t*-BuLi	**264c**	80%

The carbolithiation of the vinylcarbamates **263** was then investigated (Table 11). The carbamate was reacted in a one-pot process with an alkyllithium, followed by deprotection using TFA in order to simplify the analysis of the diastereospecificity (carbolithiated compounds appear as rotamers in the NMR spectra).

Table 11: Carbolithiation of carbamate **263**.



263 **265**

Entry	Carbamate	R-Li	Compound	Yield	*d.r.*
1	**(*E*)-263**	*n*-BuLi	**265a**	70%	>95:5
2	**(*E*)-263**	*i*-PrLi	**265b**	80%	>95:5
3	**(*E*)-263**	*t*-BuLi	**265c**	81%	>95:5
4	**(*Z*)-263**[a]	*i*-PrLi	***epi*-265b**	50%	2:8

[a] reaction performed in Tol. for 24h.

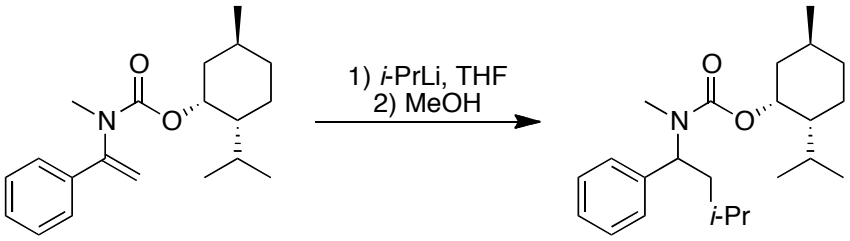
The reaction with **(*E*)-263** was successful with *n*-BuLi, *i*-PrLi and *t*-BuLi and the corresponding amines were obtained in high yields over two steps (entries 1-3). In each case only one diastereomer of the amine was observed.

However, the (*Z*)-isomer presented a different reactivity. Carbolithiation of **(*Z*)-263** to form the compound ***epi*-265b** had to be carried out in toluene for 24h at –40°C. The desired compound was obtained in 50% yield after deprotection but unfortunately as a 8:2 mixture of diastereoisomers. Epimerisation at the lithiated centre might have happened because of the long reaction time.

Increase of the temperature to 0°C (for an hour) after an hour at –78°C led to the formation of a 1:1 mixture of diastereomers **265b** and ***epi*-265b**. No Boc-migration was observed.[125]

The reaction was also performed using (–)-sparteine in cumene in order to attempt an enantioselective carbolithiation. Unfortunately, only an *e.r.* of 6:4 was obtained.

An alternative to the enantioselective carbolithiation was to use a chiral auxiliary attached to the nitrogen. Menthylcarbamate **266** was synthesised and treated with *i*-PrLi. The desired carbolithiated product was isolated in a 1:1 mixture of diastereomers (Scheme 104).



266 1:1 *d.r.* **267**

Scheme 104: Carbolithiation of menthylcarbamate **266**.

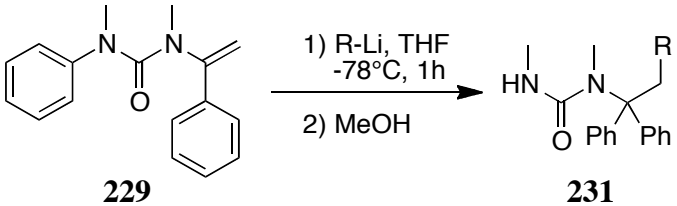
To summarise, carbolithiation of vinyl carbamates was achieved in a similar fashion. When the reaction was performed on trisubstituted vinyl carbamates, diastereoselectivity was observed, however because the (*Z*)-isomer presented slow reactivity, partial epimerisation was observed on the time-scale of the reaction. A one-pot process was developed to form rapidly highly substituted amines. No remarkable enantioselectivity was observed using a chiral ligand or a chiral auxiliary.

2.4. Tandem reaction: carbolithiation/aryl migration

After investigations on the carbolithiation reaction, the tandem alkylation/arylation process was investigated. Previous studies in the group[*], on compounds bearing a terminal double bond, had shown that the treatment of urea **229** with a range of organolithium reagents, in THF at –78°C for an hour, followed by quench with methanol led to the formation of the rearranged products **231** in a good yield (Table 12). The tandem reaction proved to be successful with primary, secondary and aromatic organolithium reagents. However, in the case of *t*-BuLi, only the product corresponding to the carbolithiation was isolated (77% yield) probably due to the steric hindrance of the *t*-butyl group.

[*] Prof. Dr. Alberto Minassi (visiting researcher).

Table 12: Carbolithiation rearrangement of urea **229**.



229 **231**

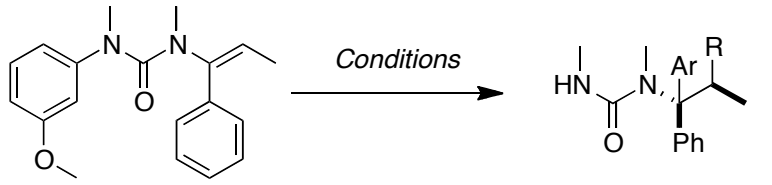
Entry	R-Li	Yield
1	*n*-BuLi	72%
2	CH_3Li	78%
3	*i*-PrLi	74%
4	*s*-BuLi	74%
5	PhLi	77%

We wondered if the same reaction could be performed on trisubstituted ureas. Therefore urea **(*E*)-242a** was investigated under different reaction conditions (Table 13).

Urea **(*E*)-242a** was treated with organolithium reagents (2 equivalents) using different solvents and at different temperatures. In all cases, the addition of DMPU was necessary to observe the rearranged product. Such as HMPA,[138] DMPU is a strong ligand use in lithium chemistry in order to enhance the nucleophilic property of carbanions: coordination to the lithium atom lead to the formation of a 'naked' carbanion. Therefore the nucleophilic centre is more reactive.

After the results obtained for the carbolithiation, only *n*-BuLi, *i*-PrLi and *t*-BuLi were investigated in this study. The reaction with *n*-BuLi was only possible in coordinative solvents such as THF or Et_2O (entries 1-3) with unreacted starting material being recovered when the reaction was performed in toluene (entry 2). The highest yield was obtained in Et_2O at –40°C for 2.5 hours and warmed up to room temperature for 16 hours after addition of DMPU (entry 3). A similar result was observed with *i*-PrLi in toluene (entry 7 and 8). In these two cases, DMPU was added after complete consumption of the starting material (by TLC). However, the rearrangement was never complete and the carbolithiated product was always observed (yield not recorded-conclusion based on analysis of the NMR of the crude mixture). The reaction with *t*-BuLi however led only to the formation of the carbolithiated product and no rearrangement was observed, again probably because of high steric hindrance (entries 9-10).

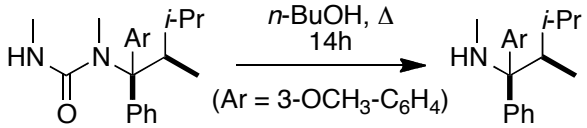
Table 13: Tandem carbolithiation/rearrangement of urea **(*E*)-242a**.



(*E*)-242a **268** (Ar = 3-OCH_3-C_6H_4)

Entry	R-Li	Solvent	Time (before+after DMPU)	Temp.	Product	Yield
1	*n*-BuLi	THF	1h+3h	–78°C	**268a**	35%
2	*n*-BuLi	Toluene	1h+3h	–78°C	**268a**	-
3	*n*-BuLi	Et_2O	2h30+16h	–40°C → r.t.	**268a**	65%
4	*i*-PrLi	THF	1h+1h	–78°C	**268b**	20%
5	*i*-PrLi	THF	1h+3h	–78°C	**268b**	55%
6	*i*-PrLi	Et_2O	1h+3h	–78°C	**268b**	55%
7	*i*-PrLi	Toluene	1h+3h	–78°C	**268b**	55%
8	*i*-PrLi	Toluene	2h+16h	–40°C → r.t.	**268b**	60%
9	*t*-BuLi	THF	1h+3h	–78°C	**253c**	50%
10	*t*-BuLi	Et_2O	1h+3h	–78°C	**253c**	30%

Due to the instability of the rearranged products and the difficulty of characterisation (presence of rotamers), cleavage of the urea to form the amine was investigated (Scheme 105). The urea **268b** was heated in *n*-butanol and the desired amine **269** was obtained in 70% yield.

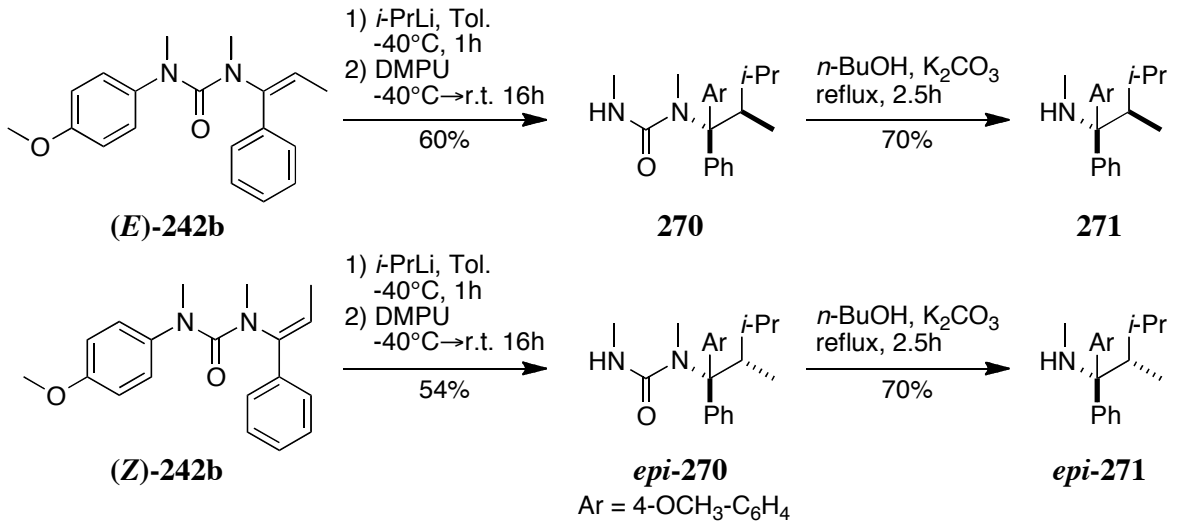


268b 70% **269**

Scheme 105: Deprotection of **268b**.

The diastereoselectivity of the reaction was further investigated using the two isomers of urea **242b** (Scheme 106). For this urea, the reaction was diastereospecific. The reaction was performed at –40°C in toluene for 1 hour followed by addition of DMPU and increase of the temperature to room temperature over 16 hours. The two isomers presented similar

reactivities. The rearranged ureas, as well as the deprotected amines, were obtained in similar yields for both (*E*) and (*Z*) starting materials.

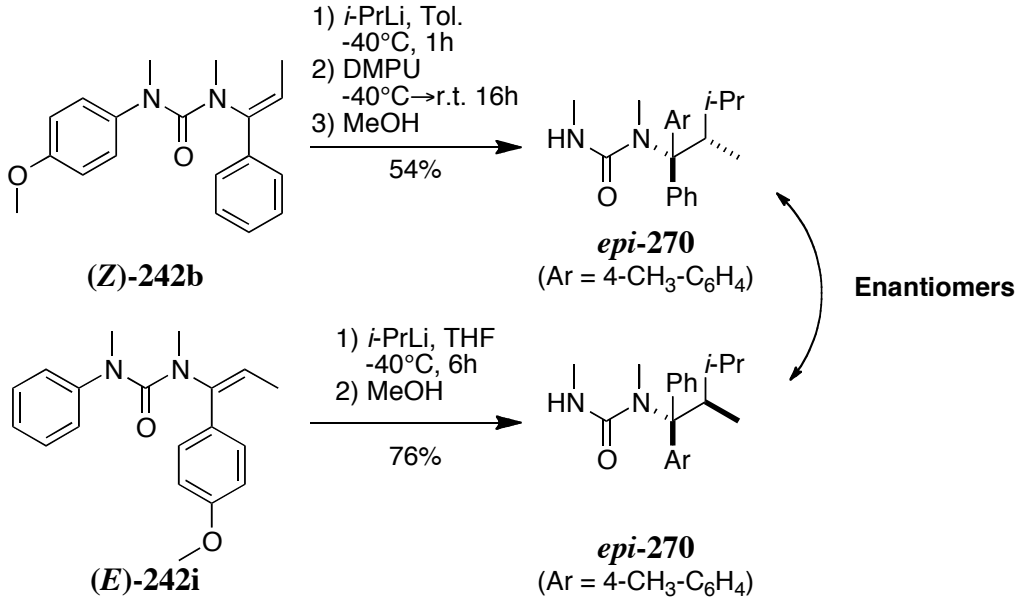


Scheme 106: Carbolithiation/rearrangement/deprotection of **(*E*)** and **(*Z*)-242b**.

If the reaction is stereoselective, ureas bearing opposite stereochemistry of the double bond and same aromatic ring but in different positions, should lead to the same rearranged product.

This was observed when urea **(*E*)-242i** was treated with *i*-PrLi: compound ***epi*-271** was formed in 76% yield (Scheme 107).

This experiment highlighted that the migration of a phenyl ring was faster than the migration of substituted aromatic rings and complete conversion was performed in THF in 6 hours. It is important to notice that the phenyl migration does not need DMPU.



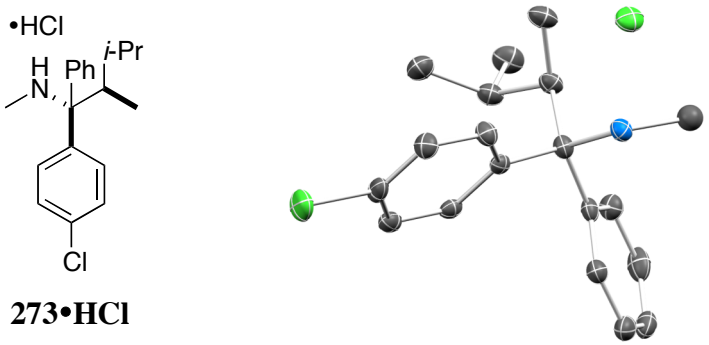
Scheme 107: Carbolithiation/rearrangement of ureas **(*Z*)-242b** and **(*E*)-242i**.

This reaction has been extended to other trisubstituted ureas and the desired rearranged ureas and amines were obtained in good yields (Table 14). The reaction was tolerant of different substituents on the aromatic ring and the reaction of (*E*) and (*Z*) starting material led to the formation of diastereoisomers (entries 2 and 3).

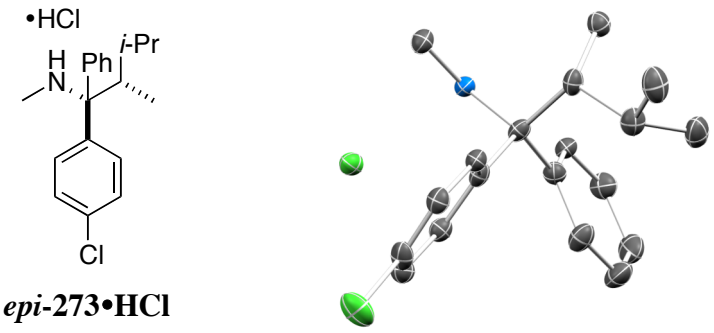
Table 14: Carbolithiation/rearrangement and deprotection of ureas **242**.

Entry	Urea	R-Li	Yield urea	Urea	Yield amine	Amine
1	**(*E*)-242i**	*i*-PrLi	76%	***epi*-270**	70%	***epi*-271**
2	**(*E*)-242j**	*i*-PrLi	81%	**272**	66%	**273**
3	**(*Z*)-242j**	*i*-PrLi	75%	***epi*-272**	67%	***epi*-273**
4	**(*E*)-242j**	*n*-BuLi	70%	**274**	73%	**275**
5	**(*E*)-242k**	*i*-PrLi	69%	**276**	75%	**277**
6	**(*E*)-242l**	*i*-PrLi	60%	**278**	70%	**279**

For compounds **273** and ***epi*-273**, the relative stereochemistry was confirmed by X-ray cristallography of the hydrochloride salt of the deprotected amine (Figure 11).



273•HCl

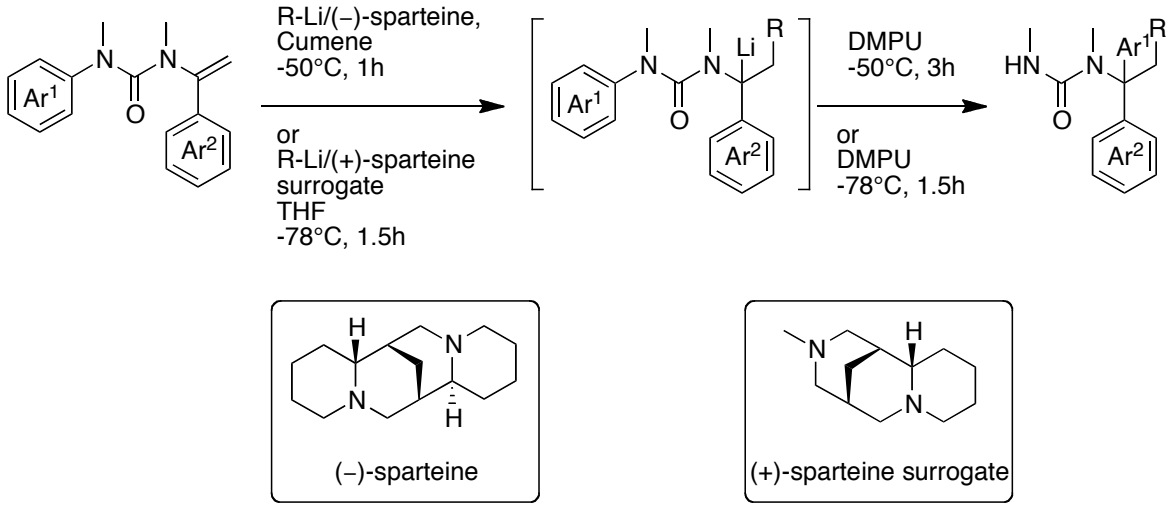


***epi*-273•HCl**

Figure 11: X-ray crystal structures of **273•HCl** and ***epi*-273•HCl**.

2.5. Enantioselective reaction

Previous studies in the group had shown that the enantioselective carbolithiation of vinyl ureas was possible using (–)-sparteine as a ligand (Scheme 108)[*1]. The best results were obtained when the reaction was carried out at -50°C in cumene. The urea was added slowly to a mixture of organolithium/(–)-sparteine. After 1 hour, the carbolithiation was complete and DMPU was added to promote the rearrangement. The other enantiomer was obtained using the (+)-sparteine surrogate. With this ligand, the reaction was performed in THF at –78°C for 1.5 hours followed by addition of DMPU. This is the first example of carbolithiation reaction using the (+)-sparteine surrogate.



Scheme 108: Enantioselective carbolithiation of vinyl ureas.

The enantioselective reaction was carried out using different starting material and organolithium reagents (Table 15).

Table 15: Enantioselective carbolithiations.

Ar^1	Ar^2	R-Li	Ligand	Yield	e.r.
Ph	4-Cl-C_6H_4	*n*-BuLi	(-)-spart.	75%	88:12
Ph	4-Cl-C_6H_4	*i*-PrLi	(-)-spart.	86%	92:8
Ph	4-Cl-C_6H_4	PhLi	(-)-spart.	74%	50:50
Ph	4-OCH_3-C_6H_4	*i*-PrLi	(-)-spart.	76%	89:11
4-Cl-C_6H_4	Ph	*i*-PrLi	(-)-spart.	78%	90:10

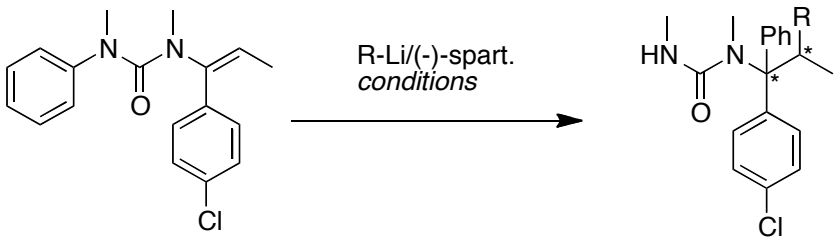
[*] Prof. Dr. A. Minassi, Dr. M. Donnard and M. B. Tait

4-OCH_3-C_6H_4	Ph	*i*-PrLi	(-)-spart.	72%	78:22
Ph	2-F-C_6H_4	*i*-PrLi	(+)-surr.	69%*	8:92
Ph	2-F-C_6H_4	*n*-BuLi	(+)-surr.	61%*	50:50

*: Ethyl group present on the nitrogen bearing the migrating group (instead of methyl)

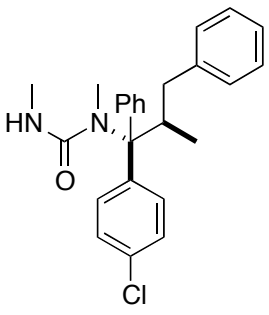
Based on the conditions reported previously, the enantioselective carbolithiation of urea **(*E*)-242j** was attempted (Table 16). This transformation would allow the creation of two chiral centres in a single reaction step.

Table 16: Attempts on enantioselective carbolithiation of urea **(*E*)-242j**



(*E*)-242j **272**

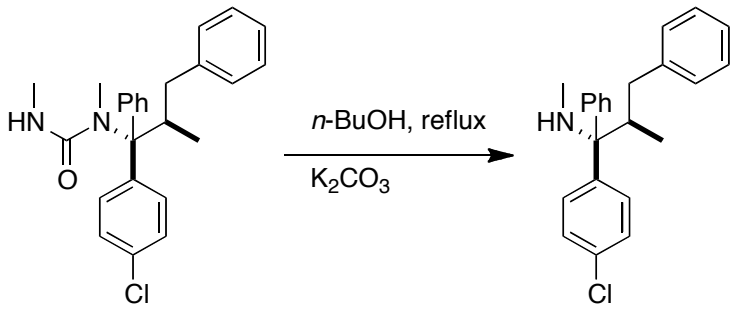
Entry	R-Li	(–)-spart.	Solvent	Temp.	Conclusion
1	*i*-PrLi	0 eq.	Cumene	–50°C	**255** (78%)
2	*i*-PrLi	1 eq.	Cumene	–50°C	**272** (racemic)
3	*i*-PrLi	2 eq.	Cumene	–50°C	**272** (racemic)
4	*i*-PrLi	2 eq.	Cumene	–78°C	**272** (racemic)
5	*i*-PrLi[a]	2 eq.	Cumene	–50°C	**272** (racemic)
6	*n*-BuLi	2 eq.	Cumene	–50°C	No reaction
7	*n*-BuLi	2 eq.	Et_2O	–50°C	**272** (racemic)
8	*n*-BuLi	2 eq.	Et_2O	–78°C	No reaction
9[d]	*i*-PrLi[a]	2 eq.	Cumene	–40°C[c]	***Z*/*E*-242j**
10	*s*-BuLi	2 eq.	Toluene	–50°C	
11	*i*-PrLi	2 eq.	Toluene	–40°C	
12	*i*-PrLi	2 eq.	Toluene	–40°C[b]	
13	*i*-PrLi[a]	2 eq.	Toluene	–65°C	



280

[a] Addition of DMPU for 1h; [b] 2.5h; [c] 2h; [d] freshly distilled (–)-sparteine

Treatment of urea **(*E*)-242j** with 2 equivalents of *i*-PrLi in cumene in the absence of (–)-sparteine led to the formation of the carbolithiated product **255** in good yield (entry 1). When urea **(*E*)-242j** was reacted under the same reaction conditions adding 1 or 2 equivalents of (–)-sparteine (entries 2 and 3), the desired rearranged product was obtained but always as a racemic mixture. The addition of (–)-sparteine in these reactions increased dramatically the speed of the rearrangement and the carbolithiated product **255** was only observed in very small quantities (maximum 10%). When the temperature was decreased to −78°C, the same result was obtained (entry 4). The addition of DMPU for one hour to force the rearrangement also led to a racemic mixture (entry 5). The reaction was then carried out using *n*-BuLi. However, no reaction was observed in cumene (entry 6). When the reaction was performed in Et_2O, racemic product was obtained at −50°C (entry 7) and no reaction was observed at −78°C (entry 8). The next attempt at an enantioselective reaction with (–)-sparteine was carried out with freshly distilled (–)-sparteine (it is known to complex CO_2 and need to be distilled on regular basis).[139] The reaction with freshly distilled ligand led to a completely different result (entry 9). In this case no carbolithiation was observed and the starting material was recovered, but as a 1:1 mixture of (*E*) and (*Z*) isomers. This was only possible by deprotonation of the starting material in the allylic position. An explanation can be the increase of the basicity of the organolithium reagent. The chiral ligand coordinates the lithium atom and increases the distance with the "carbanion" increasing the reactivity of the organolithium.[140, 141] However, because the difference between basicity and nucleophilicity is really small with organolithium reagents, in these conditions, the organolithium reagent became more basic than nucleophilic. Therefore, deprotonation of the starting material can be achieved. When the reaction was performed in toluene (entries 10-13) only the product **280** was observed corresponding to the carbolithiation with benzyllithium. This was possible by benzylic deprotonation of the toluene. When the reaction was performed at -65°C (entry 13) compound **280** was obtained in 65% isolated yield and was easily converted to the corresponding amine **281** (Scheme 109). In all cases the product was obtained in racemic form, (−)-sparteine having no effect on the reaction.

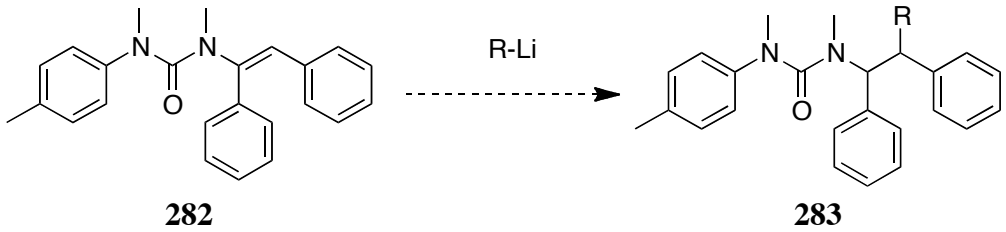


280 **281**

Scheme 109: Deprotection of the rearranged urea **280**.

In conclusion, the reaction was successful with a range of alkyllithium reagents and with ureas bearing different substitutents on the aromatic rings. The diastereoselectivity of the reaction had been highlighted for a trisubstituted double bond. Unfortunately, the enantioselective version of the tandem reaction investigated previously in the group couldn't be extended to a trisubstituted double bond because of the acidity of protons of the vinylic methylene group.

We tried to overcome the problem using urea **282** bearing a phenyl in the terminal position of the double bond however, this urea was unreactive toward organolithiums (Scheme 110).



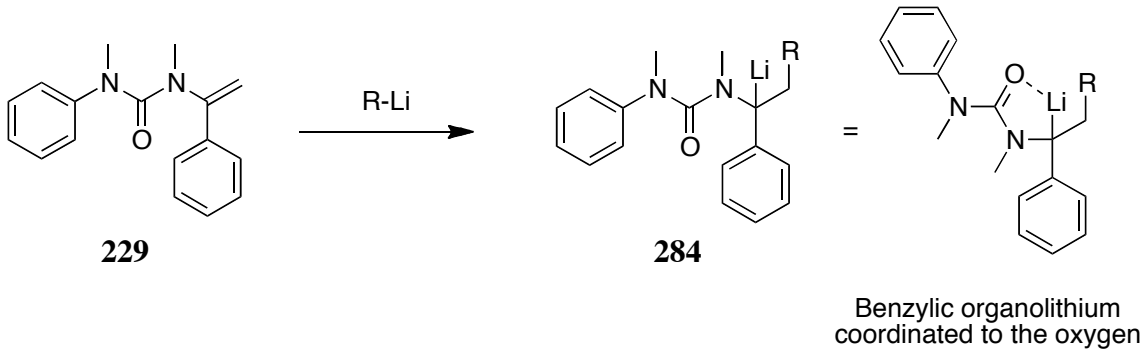
282 **283**

Scheme 110: Carbolithiation of urea **282**.

2.6. Mechanistic investigations

In order to understand completely this new reaction, the mechanism was investigated in detail. The first aspect of the mechanism investigated was the lithiated intermediate **284** after carbolithiation (Scheme 111). When the carbolithiation is performed, the intermediate **284** was formed and appeared to be configurationally stable on the timescale of the reaction. This stability can be explained by the representation below showing that the lithiated intermediate is benzylic and can form a five-membered ring with coordination to the oxygen of the urea.[142]

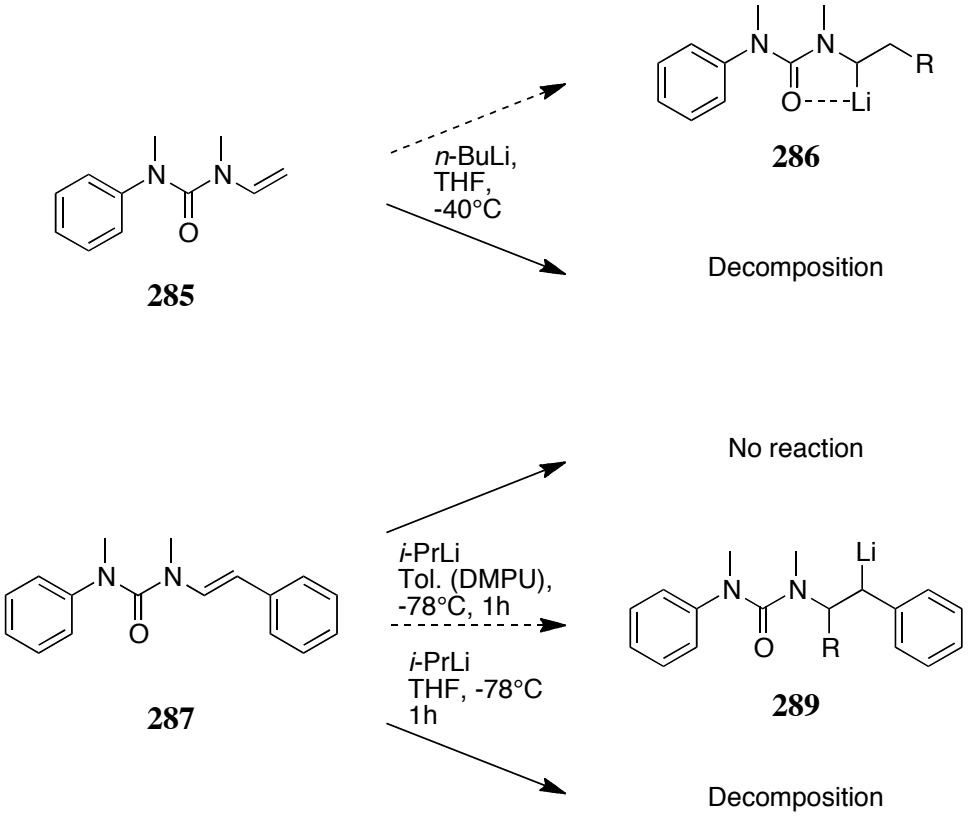
In order to understand if this stability was due to the combination of the two properties or only one of them, new starting materials were investigated.



Scheme 111: Stability of the organolithium intermediate.

Urea **285** was used to determine the influence of the five-membered ring coordination in the absence of phenyl ring. Unfortunately, treatment with *i*-PrLi in THF at -78°C led only to decomposition of the starting urea.

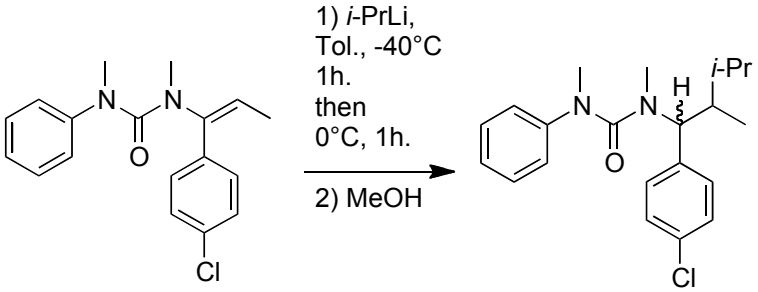
Urea **287** was synthesised to illustrate the benzylic stabilisation and analyse if it was possible to switch the carbolithiation from the β carbon to the α carbon. When urea **287** was reacted with *i*-PrLi in toluene, only starting material was recovered. When the same reaction was performed in THF, decomposition of the starting material was observed.



Scheme 112: Investigations on the stability of the lithiated intermediate.

These experiments seemed to confirm the necessity of having both benzylic and oxygen-coordinated intermediate. However further experiments should be carried out to obtain a definitive answer.

As shown before, when the urea **(*E*)-242j** is reacted in toluene at –40°C and quenched by methanol at this temperature, the desired carbolithiated product was obtained as a single diastereomer: no epimerisation of the lithiated centre was observed. However when the reaction is performed at –40°C and warmed up to 0°C, a 1:1 mixture of diastereomers was obtained instead (Scheme 113). This result highlights the configurationnal stability of the intermediate at low temperature but not at 0°C.



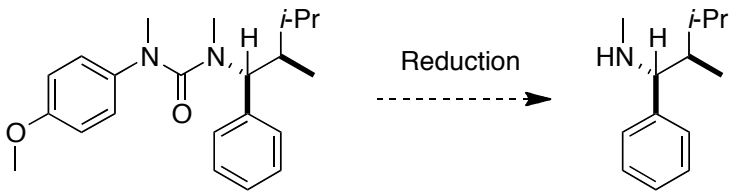
(*E*)-242j **255:*epi*-255 (1:1)**

Scheme 113: Influence of the temperature on the lithiated intermediate.

The next step in the investigation of the mechanism is the determination of the stereochemistry of the reaction.

The X-ray structure obtained for α-tertiary amines **273•HCl** and ***epi*-273•HCl** (Figure 11) seemed to indicate that the tandem reaction takes place via *syn* carbolithiation followed by retentive migration. However the stereochemistry of the carbolithiation step had to be confirmed. *Anti* carbolithiation followed by invertive aryl migration cannot be excluded at this stage. All carbolithiated compounds were obtained as oils. To improve the crystallinity, reactions to cleave the urea to form the corresponding amine were first attempted (Table 17). When the compound **254b** was treated with DIBAL at 0°C or room temperature (entry 1 and 2), only starting material was recovered. The reaction with MeLi, in order to attack the carbonyl (as observed before), did not provide any desired product either.

Table 17: Reduction of urea **254b**.

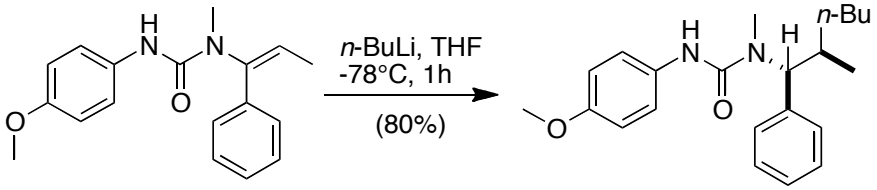


254b **290**

Entry	Conditions	Conclusions
1	DIBAL 0°C, THF	no reaction
2	DIBAL r.t., THF	no reaction
3	MeLi, –18°C, THF	no reaction

Because of the poor reactivity of the tetrasubstituted ureas, other substrates were investigated in order to deprotect afterwards.

It had been observed that urea **(*E*)-244b**, bearing a free NH, when treated with 3 equivalents of *n*-BuLi, led to the formation of carbolithiated urea **291** in high yield and only one diastereomer (Scheme 114). With these ureas, no rearrangement was ever observed.



(*E*)-244b **291**

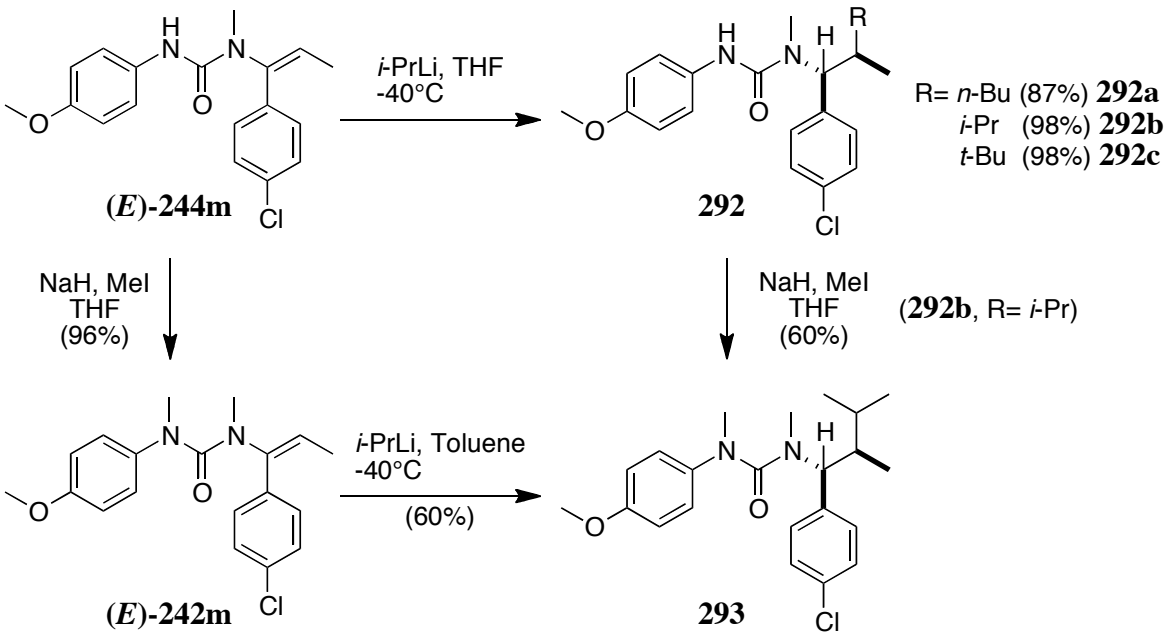
Scheme 114: Carbolithiation of urea **(*E*)-244b**.

In order to obtain an easily cleavable urea, the carbolithiation was attempted on urea **(*E*)-244m** bearing a 4-chloro substituent (Scheme 115). Treatment with 3 equivalents of organolithium reagent led to the formation of the corresponding ureas **292** in very good yields with primary, secondary and tertiary organolithium reagents always as a single diastereomer.

The methylation of the monomethylated urea **292b** led to the formation of **293** which can also be obtained from the fully methylated urea **(*E*)-242m**.

Because the two pathways form the same product **293**, we can conclude that the carbolithiation step of ureas **(*E*)-242m** and **(*E*)-244m** proceed with the same stereochemistry.

The relative stereochemistry of compound **292b** was determined by X-ray crystallography (Figure 12) confirming the *syn* addition of the organolithium reagent across the double bond.



Scheme 115: Determination of the relative stereochemistry of the carbolithiation.

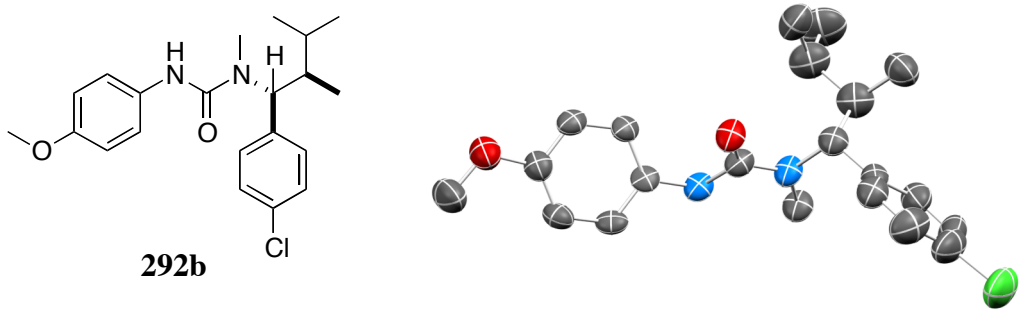
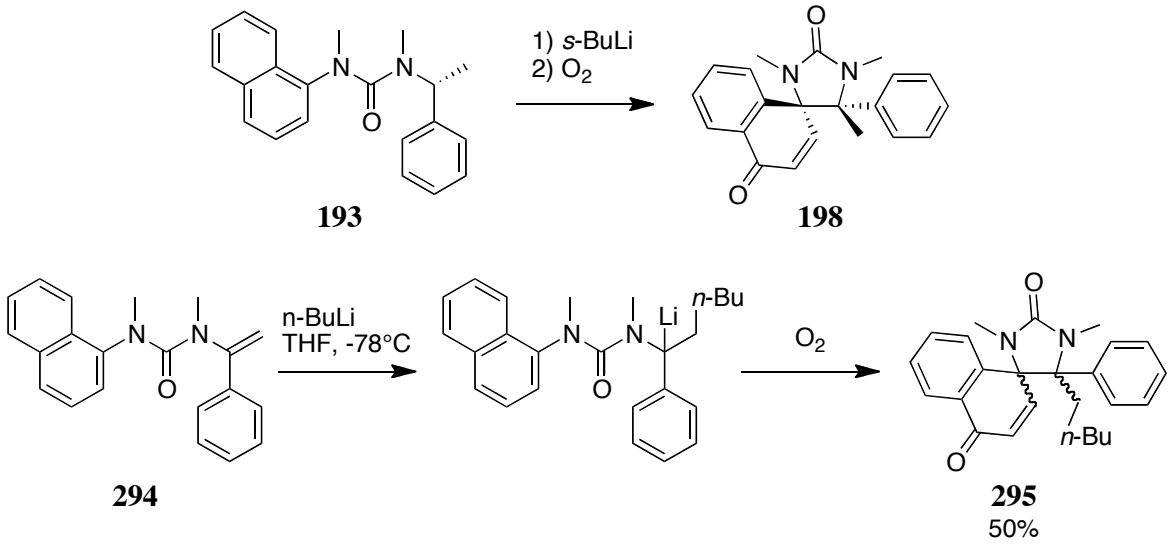


Figure 12: X-ray crystal structure of **292b**.

The last part of the mechanism that was investigated was the intermediate for the aryl transfer (Scheme 116). It has been reported that during the rearrangement of a urea **193** bearing a 1-naphthyl migrating group, a cyclic compound **198** can be isolated after oxidation.[126] We wondered if the same approach be used in the tandem carbolithiation/aryl

migration. In order to attempt the trapping of the cyclic intermediate **295** the vinyl urea **294** was reacted with *n*-BuLi at −78°C in THF. After an hour, the reaction was quenched with oxygen. The desired product was isolated in 50% yield as a mixture of diastereomers.



Scheme 116: Oxidation of the dearomatised intermediate.

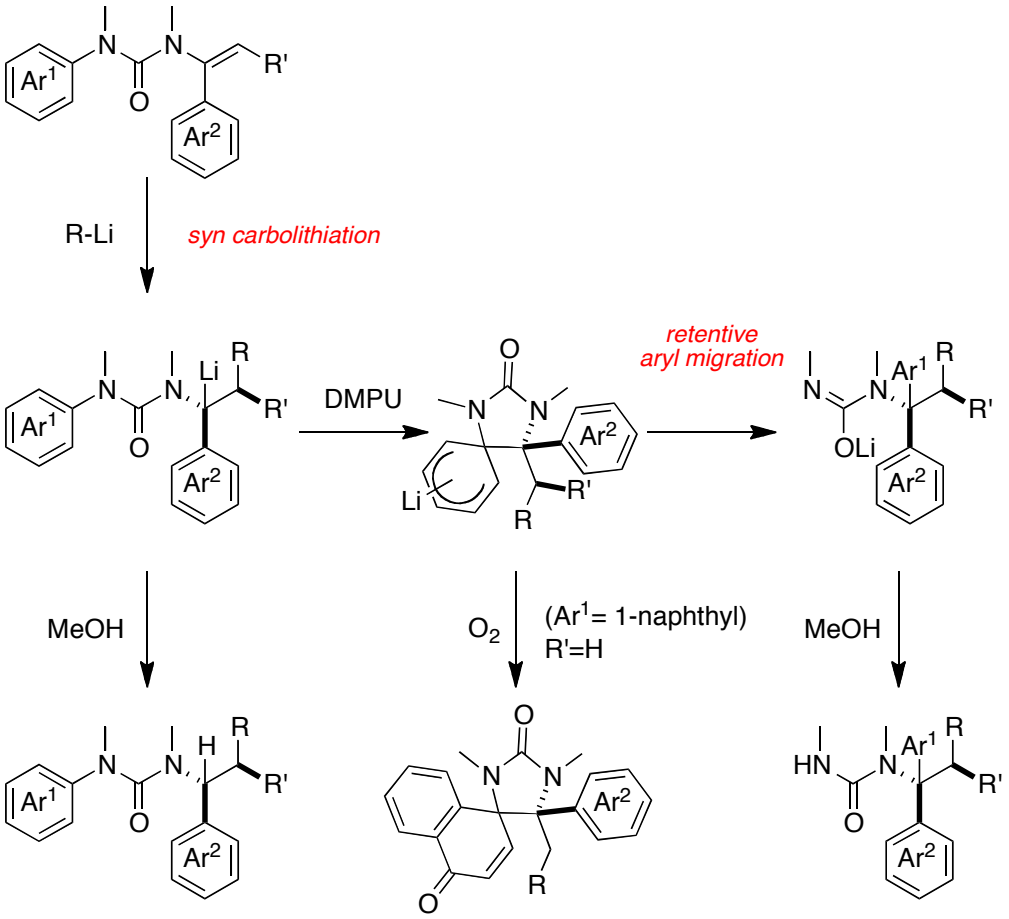
2.7. Summary

In conclusion, new reactions had been developed in order to synthesise hindered ureas and amines. Vinyl ureas and vinyl carbamates can undergo umpolung carbolithiation of the electron-rich double bond in order to synthesise highly substituted protected amines. This reaction was performed with a range of primary, secondary and tertiary alkyllithium reagents and different substitutions on the aromatic rings were tolerated. Introduction of substituents on the double bond proved that the reaction is performed with complete diastereoselectivity: both isomers of the double bond leading to two different diastereoisomers. [143, 144]

When this umpolung carbolithiation of vinyl ureas was coupled with [1,4]-aryl transfer, highly substituted α-tertiary ureas were synthesised in good yields. This tandem reaction also proceeded with complete diastereoselectivity. Deprotection of these ureas by refluxing *n*-butanol led to the corresponding amines always in good yields.

An asymmetric version of this tandem reaction was developed in the group and the highest *e.r.* reported for an intermolecular carbolithiation were obtained. The extension of this method to trisubstituted vinyl ureas failed to give the desired enantioselective reaction, as the complexation of (−)-sparteine with alkyllithium reagents led to deprotonation of the starting material instead of carbolithiation.

The complete mechanism of the tandem carbolithiation/aryl migration reaction had been proved by analysing the different X-ray structures obtained (Scheme 117). In the first step, *syn* carbolithiation is performed across the double bond. Addition of DMPU promote the retentive aryl migration, via the formation of a cyclic five-membered ring intermediate which can be isolated after oxidation when the migrating group is 1-naphthyl.



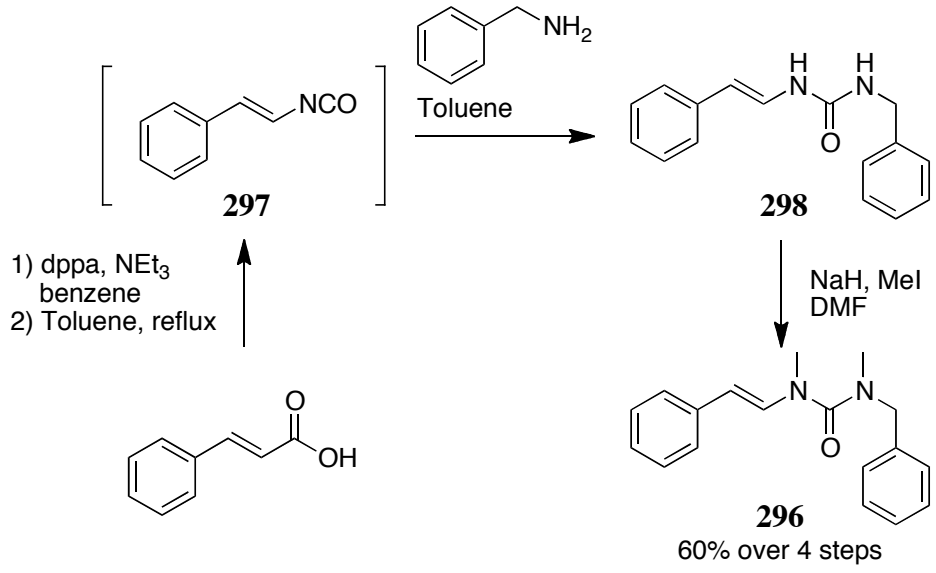
Scheme 117: Tandem carbolithiation/aryl migration

3. N to C vinyl migration

3.1. Preliminary studies

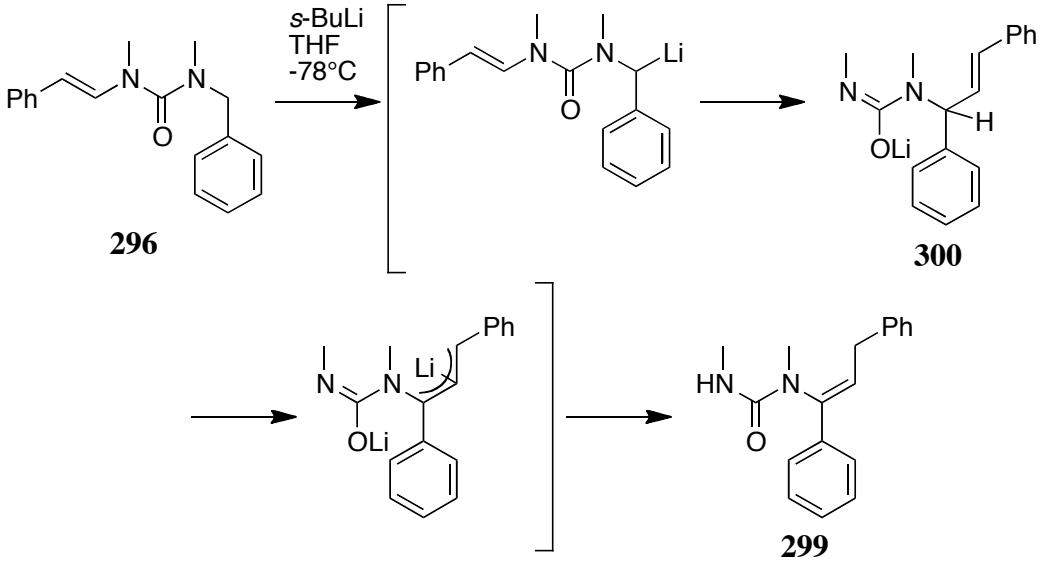
In order to extend the scope of the reaction, new migrating groups were investigated. To simplify these studies, the benzylic intermediates were generated by deprotonation instead of carbolithiation.

After investigating the scope of the aryl migration, new migrating groups bearing similar properties to the aromatic rings were studied. The first and obvious migrating group investigated was a styrene moiety. Benzylic urea **296**, bearing a styrene group was synthesised from the reaction between benzyl amine and styrene isocyanate **297** (Scheme 118). Styrene isocyanate, not commercially available, was generated via a Curtius rearrangement starting from cinnamic acid and diphenylphosphoryl azide (dppa). The choice of using dppa instead of the traditional acyl chloride-sodium azide sequence was for safety reasons. Isocyanate **297** was generated by refluxing the acyl azide in toluene with subsequent reaction with benzylamine leading to the formation of urea **298**. Ureas such as **298**, bearing two NH, appeared to be insoluble in most organic solvents. Therefore simple filtration of the reaction mixture provided the desired urea in high purity. Urea **298** was then solubilsed in DMF and reacted with sodium hydride and methyl iodide to form the desired product **296** in 60% yield over four steps after filtration on silica (to remove the mineral oil). This sequence appeared to be easily scalable and the reaction could be performed on a gram-scale.



Scheme 118: Synthesis of benzylic urea substituted with a styrene.

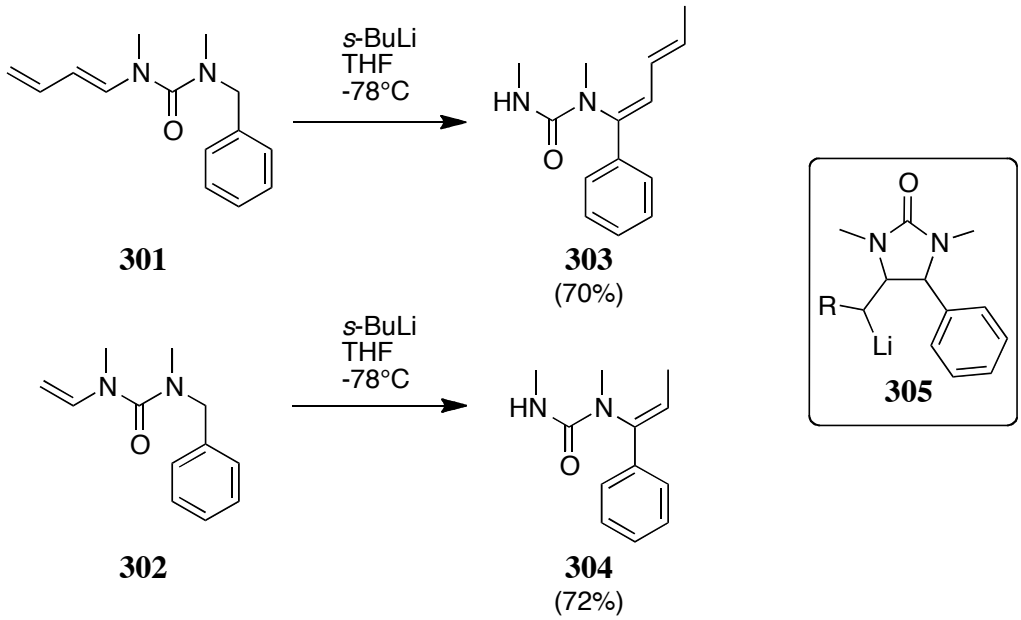
With urea **296** in hand, rearrangement was attempted (Scheme 119). Treatment of **296** with two equivalents of *s*-BuLi in THF at –78°C led to the rearranged product **299** in good yield (as a single geometrical isomer of the double bond). The migration of the double bond, to form vinyl urea **299** can be explained by deprotonation of the benzylic proton of urea **300** by the second equivalent of base. Decreasing the number of equivalents of base to one led to the same result but lower a yield was observed. The migration of the double bond cannot be avoided because the benzylic proton of urea **300** is more acidic than for urea **296**. Therefore, once generated, **300** will be deprotonated before the starting material **296**.



296 **300** **299**

Scheme 119: Rearrangement of urea **296**.

After this promising result, urea **301** bearing a diene and **302** substituted with a vinyl group were synthesised and investigated (Scheme 120). Urea **301** was synthesised like **296** via Curtius rearrangement while **302** was synthesised using commercially available vinyl isocyanate. Treatment of ureas **301** and **302** with *s*-BuLi in THF at –78°C led to the formation of the desired rearranged products in high yields.



Scheme 120: Rearrangement of ureas **301** and **302**.

The formation of rearranged ureas **303** and **304** can be explained by the formation of cyclic intermediate **305**. In these two cases, the cyclic intermediate can be stabilised by the presence of the R group (R = Ph and R = vinyl for **303**). However the rearrangement of urea **302** was more surprising because of the non-stabilised intermediate **305** (in this case R = H). In these two cases, the migration of the double bond was also observed.

The stability of the intermediate will be discussed later with the help of computational chemistry.

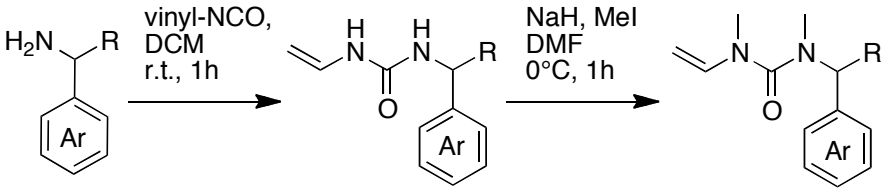
With these very promising preliminary results, we wondered if the migration of vinyl group could be used for synthesise α-tertiary amines.

3.2. Synthesis of α-tertiary amines via N to C vinyl shift

3.2.1. Vinyl transfer

Because of the commercial availability of vinylisocyanate, initial investigations for N to C transfer of vinyl systems were performed on substituted benzylureas bearing a vinyl group. The synthesis of these starting materials was performed in a one-pot process. Desired benzyl amines **306** were reacted with vinyl isocyanate forming urea **307a-f**. While the reaction with benzylamine was performed in toluene, reaction with α-substituted benzylamines had to be carried out in DCM (no reaction was observed in toluene). Methylation of **307** to form **308** was carried out in DMF with sodium hydride and methyl

iodide at 0°C for an hour. During the methylation step, ureas appeared to be unstable in basic conditions. To avoid decomposition, methyl iodide had to be introduced in the reaction mixture prior to the base. This synthesis was used to produce a range of ureas starting from racemic or enantiopure α-substituted benzylamines. The desired ureas were obtained in low to excellent yields after simple filtration on silica gel to remove mineral oil from the sodium hydride (Scheme 121, Table 18).

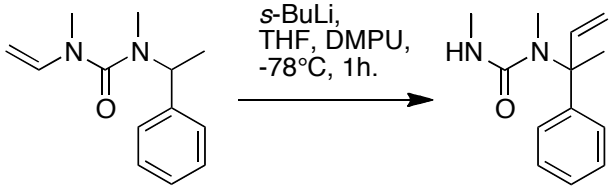


306 **307** **308**

Scheme 121: Synthesis of benzylic vinyl ureas.

Two reasons were identified for the low yields of some products. First, some of the ureas were soluble in pentane (used in the filtration step), so it was difficult to separate them from the mineral oil. A possible means of avoiding this problem was to use pure sodium hydride but this alternative was not explored for safety reasons. The second reason was the instability of ureas **308**. Loss of the double bond can happen easily on such substrates. However no real explanation was found because of the seemingly random behaviour of this degradation.

The first attempted vinyl migration was carried out using **308a** (Scheme 122). Treatment of **308a** under the conditions presented before (THF, –78°C, 1 hour) returned starting material unreacted. Benzylic deprotonation seemed to take place (mixture turned deep orange) but no migration was observed. The same reaction was attempted in the presence of DMPU (10% vol.) and this time complete conversion of the starting material was obtained and the desired urea **309a** was obtained in 63% yield.

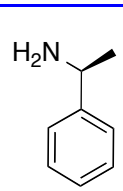
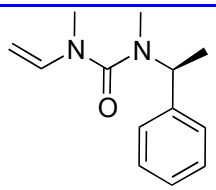
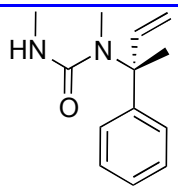
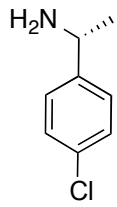
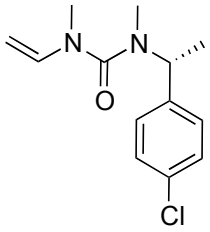
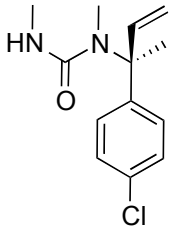
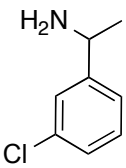
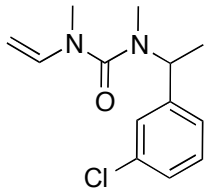
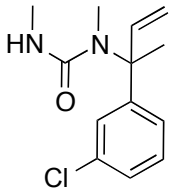


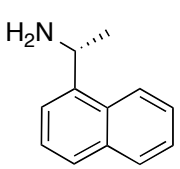
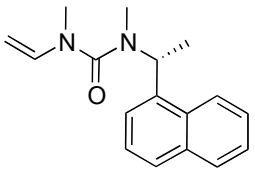
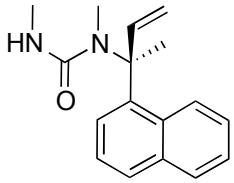
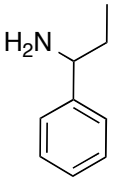
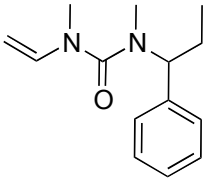
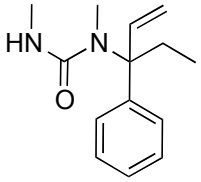
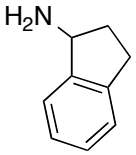
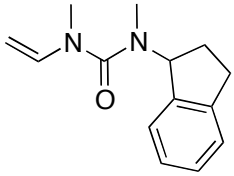
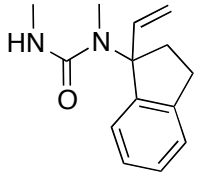
308a **309a** (63%)

Scheme 122: Rearrangement of vinyl urea **308a**.

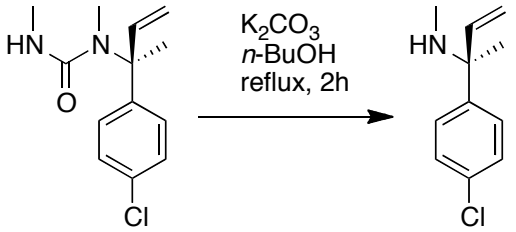
Identical conditions were used for a range of substrates (Table 18). Rearrangement of enantiopure ureas led to the formation of the desired α-tertiary urea with complete transfer of chirality (entry 1). Subtitutents could be introduced on the aromatic ring without changing the reactivity: urea **(*R*)-308b** substituted with a chlorine in the *para*-position led to the rearranged product **(*S*)-309b** in very high yield (entry 2). *Meta*-substituents can also be introduced on the aromatic ring (entry 3 and 4). The use of (*R*) or (*S*) starting material does not influence the reactivity and both enantiomers were synthesised in similar yields (entries 3 and 4). These results confirmed the enantiospecificity of the vinyl migration. When the aromatic ring was naphthyl, only traces of the desired product **309d** were observed and mainly decomposition was obtained. Diversity could also be introduced on the alkyl chain in benzylic position without influencing the yield and selectivity of the reaction (entries 6 and 7). Even cyclic susbtitutens such as **308f** could undergo vinyl migration to form the corresponding urea **309f** in moderate yield.

Table 18: Synthesis and rearrangement of ureas bearing a vinyl migrating group.

Entry	Amines 306	Ureas 308	Yield	Urea 309	Yield(*e.r.*)
1	 **(*S*)-306a**	 **(*S*)-308a**	55%	 **(*R*)-309a**	50% (>99:1)
2	 **(*R*)-306b**	 **(*R*)-308b**	90%	 **(*S*)-309b**	90% (>99:1)
3	 **(*R*)-306c** **(*S*)-306c**	 **(*R*)-308c** **(*S*)-308c**	50% (*R*) 50% (*S*)	 **(*S*)-309c** **(*R*)-309c**	67% (>99:1) 73% (>99:1)

4	 **(*R*)-306d**	 **(*R*)-308d**	85%	 **(*S*)-309d**	traces
5	 **(*R*)-306e** **(*S*)-306e**	 **(*R*)-308e** **(*S*)-308e**	30% (*R*) 27% (*S*)	 **(*S*)-309e** **(*R*)-309e**	54% (99:1) 43% (>99:1)
6	 ***rac*-306f**	 ***rac*-308f**	54%	 ***rac*-309f**	45%

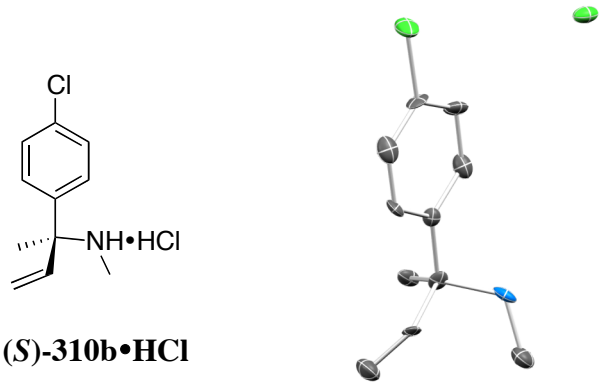
Deprotection of the α-tertiary urea **309b** can be achieved by refluxing the compound in *n*-BuOH for two hours in the presence of K_2CO_3. Treatment of **(*S*)-309b** under these conditions led to the deprotected amine **(*S*)-310b** in 81% yield (Scheme 123).



(*S*)-309b **(*S*)-310b** (81%)

Scheme 123: Deprotection of vinyl α-tertiary urea **(*S*)-309b**.

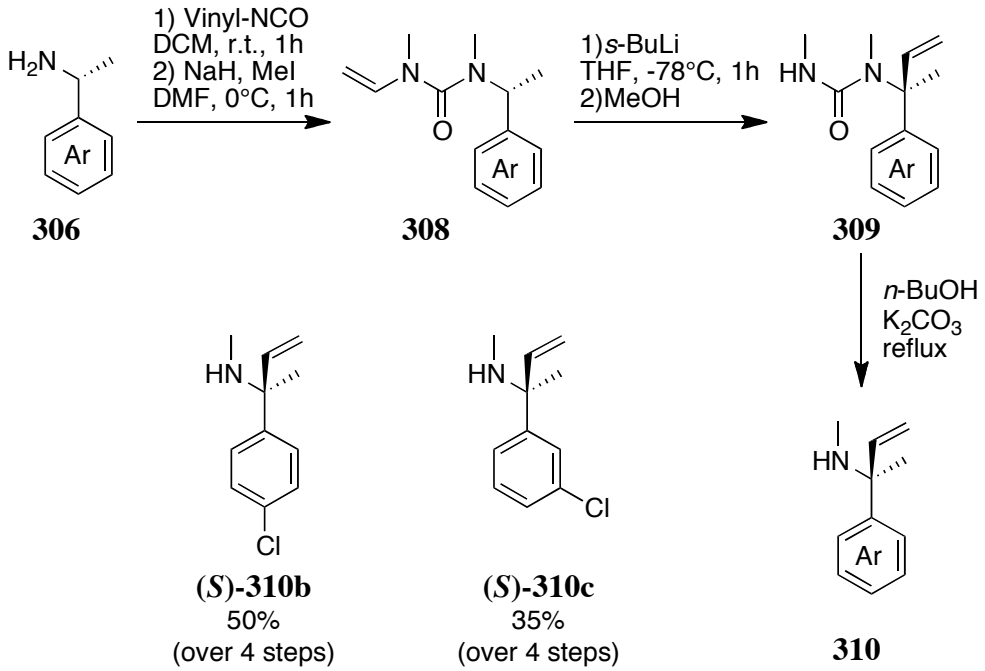
Treatment of **(*S*)-310b** with HCl in methanol formed the corresponding crystalline salt, which allowed absolute stereochemistry to be assigned using X-ray crystallography (Figure 13). Therefore it is possible to conclude that the rearrangement proceeded with retention of configuration: the vinyl group is in the same position as the benzylic proton was before rearrangement.



(*S*)-310b•HCl

Figure 13: X-ray crystal structure of **(*S*)-310b**.

Because every step of the sequence proceeded very cleanly, it was possible to develop a one-pot procedure (Scheme 124). Formation of the urea **308** followed by sequential vinyl migration and deprotection of urea **309** lead to the desired vinylated urea **310**. Synthesis of amines **(*S*)-310b** and **(*S*)-310c** was achieved using this method in 50% and 35% yield over 4 steps respectively, which corresponds to an average yield of respectively 88% and 75% per step. Both amines were obtained in enantiopure form. Overall these transformations could be seen as a four-step sequence for the vinylation of amines.



306 **308** **309**

(*S*)-310b
50%
(over 4 steps)

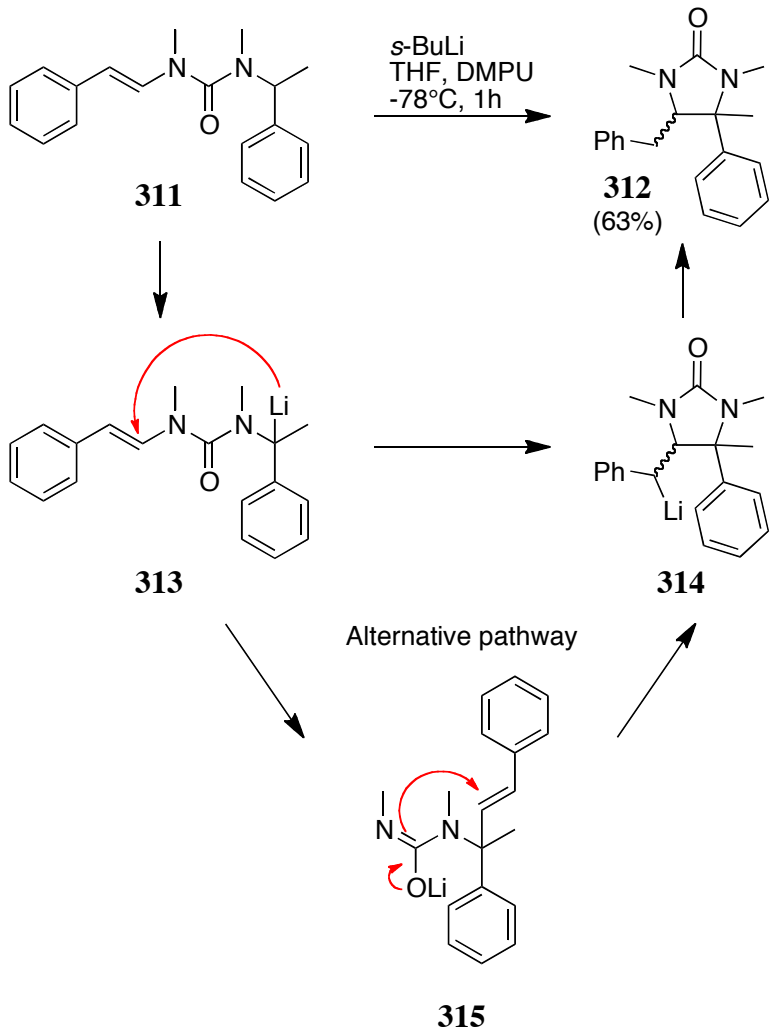
(*S*)-310c
35%
(over 4 steps)

310

Scheme 124: One pot vinylation of amines.

3.2.2. Extension of the vinyl transfer

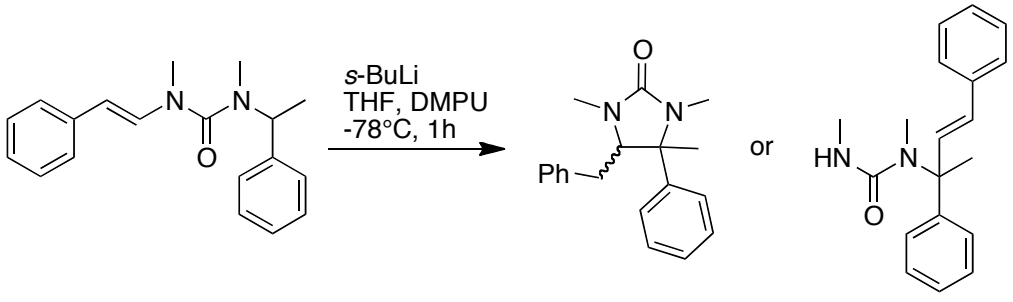
After the good results obtained for the vinyl migration, other vinyl groups were investigated. The first choice was the styrene. Under the conditions presented previously, rearrangement of urea **311** took place however cyclic urea **312** was obtained as a mixture of diastereomers (Scheme 125). Two different pathways could explain the formation of the cyclic product **312**. In the first pathway, the nucleophilic carbon of the carbolithiated intermediate **313** attacks the electrophilic carbon of the styrene to form the cyclic intermediate **314** which doesn't open and lead to the formation of urea **312** after protonation. After cyclisation, the lithiated intermediate **314** formed is benzylic. The presence of a mixture of diastereomers could be explained by a non-selective attack of the intermediate **313**. The other pathway involves a cyclisation after rearrangement. The same lithiated intermediate **313** could form the rearranged urea **315** which can the cyclise, without selectivity, to form the intermediate **314**.



Scheme 125: Rearrangement of urea **311**.

A screening of conditions changing solvent, temperature and additive was carried out to determine the influence of the reaction conditions on the cyclisation (Table 19). Treatment of **311** in THF in absence of DMPU (entry 1) showed poor conversion to the cyclic product **312**, no rearranged product was observed. Because the use of THF seemed to lead to the cyclic compound, reactions in less coordinative solvents were attempted. Diethyl ether returned unreacted starting material at –78°C (entry 2). Increasing the temperature to –40°C slightly increased the conversion and traces of the desired product, non-cyclic urea **316** could be observed (entry 3). However, longer reaction times increased the quantity of side products (entry 4). When the reaction was performed at 0°C (entry 5), the conversion was complete but only a small amount of product could be detected by ^{1}H NMR. A 1:1 mixture of diethyl ether/THF at –40°C for thirty minutes showed complete conversion to the cyclic product **312** (entry 6). Toluene was the next solvent investigated because of its lower coordinativity compare to diethyl ether. When the reaction was carried out at –78°C or at – 40°C (entries 7 and 8), only starting material was recovered. However a quench with deuterated methanol revealed complete deuteration after one hour at –40°C, highlighting full deprotonation of **311**. Increase of the reaction time at –40°C also returned the starting material (entry 9). Addition of DMPU failed to avoid the cyclisation (entry 10). The use of a mixture toluene:THF (entries 11 and 12) mainly decomposed the starting material, with only traces of the desired product observed. Finally, the use of MTBE as a solvent showed poor conversion after four hours and no traces of product were observed.
Signals, that could be assigned to the non-cyclic product, were observed in solvent systems less coordinative than THF, however attempts to isolate the desired compound failed because of the very small quantity present in the reaction mixtures. The reaction pathway cannot be determined with certainty for this example.

Table 19: Attempt to avoid the formation of cyclic urea **312**.

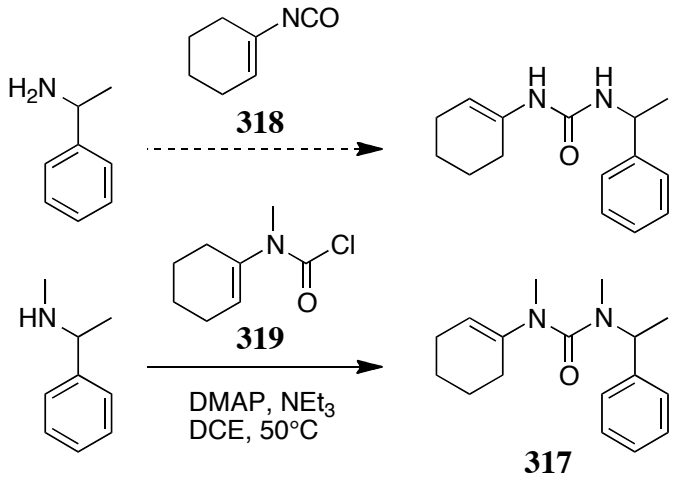


311 **312** **316**

Entry	Solvent	Temp.	Additive	Time	Conclusion (NMR of the crude mixture)
1	THF	–78°C	-	1h	Poor conversion mainly **312**
2	Et_2O	–78°C	-	1h	**311**
3	Et_2O	–40°C	-	1h	low conversion non cyclic product
4	Et_2O	–40°C	-	6h	low conversion traces **316**
5	Et_2O	0°C	-	1h	extra impurity complete conversion mainly decomposition
6	Et_2O	–40°C	THF (1:1)	0.5h	complete conversion mainly **312**
7	Toluene	–78°C	-	1h	**311**
8	Toluene	–40°C	-	1h	**311** (fully deuterated)
9	Toluene	–40°C	-	3h	**311**
10	Toluene	–40°C	DMPU	1h+3h	**311**
11	Toluene	–40°C	THF (1:1)	1h	traces of non-cyclic product **316**
12	Toluene	–40°C	THF (10%)	4h	decomposition
13	MTBE	–40°C	-	3h	poor conversion extra impurity

To extend further the scope of the reaction, the synthesis of cyclic urea **317** was attempted (Scheme 126). Attempts to react cyclohexenyl isocyanate **318**, synthesised from the corresponding acid, with benzylamine were unsuccessful and only decomposition was

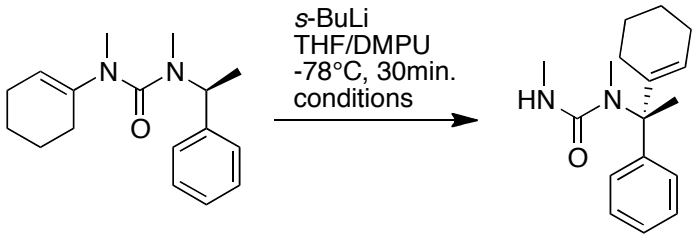
observed. This problem was overcome using the carbamoylchloride **319** and coupling it with the desired amine in DCE using DMAP.



Scheme 126: Synthesis of cyclohexenyl urea **317**.

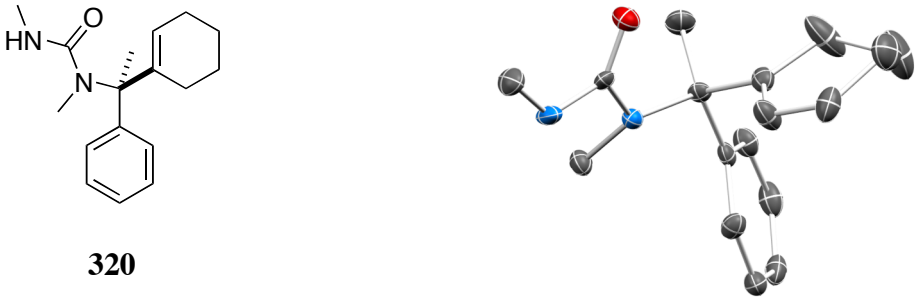
Rearrangement of **317** appeared to be faster than the corresponding vinyl migration: the reaction was complete after twenty minutes (instead of one hour). Enantiospecific migration of cyclohexene was also attempted starting from **(*S*)-317** (Table 20). Standard conditions (entry 1) led to urea **(*R*)-320** but with 90:10 *e.r.* only. This erosion of enantiopurity could be explained by a lower stability of the lithiated intermediate. In order to reduce this effect, dilution of the reaction mixture (entry 2) and reduction of the amount of DMPU (entry 3) were investigated. In both cases, an increase of the *e.r.* was observed but still without complete transfer of chirality.

Table 20: Cyclohexene migration.



(*S*)-317 **(*R*)-320**

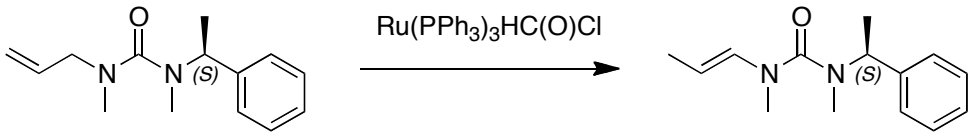
Entry	Conditions	Yield	*e.r.*
1	THF/DMPU:10/1 (*c*=0.1M)	62%	90:10
2	THF/DMPU:10/1 (*c*=0.05M)	65%	93:7
3	THF/DMPU:20/1 (*c*=0.05M)	64%	95:5
4	THF/1eq. DMPU (*c*=0.1M)	-	-



320

Figure 14: X-Ray crystal structure of **320**.

The scope was extended further using urea **(*S*)-322**. The allyl urea **(*S*)-321** was synthesised initially, followed by isomerisation of the double bond using a ruthenium hydride catalyst (Scheme 127). [145]

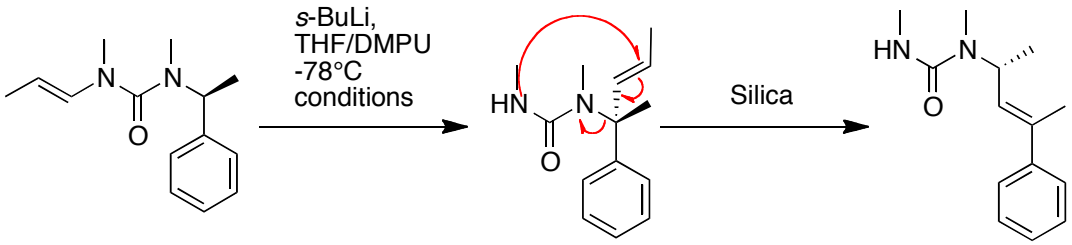


(*S*)-321 **(*S*)-322**

Scheme 127: Synthesis of urea **(*S*)-322**.

Treatment of urea **(*S*)-322** with *s*-BuLi led to complete conversion to the desired rearranged product **(*R*)-323** (Table 21). Unfortunately, in contact with silica, **(*R*)-323** performed a [3,3] sigmatropic rearrangement to form urea **(*R*)-324**. **(*R*)-324** was obtained with incomplete transfer of chirality (*e.r.*: 85:15), allowing the conclusion of a concerted mechanism. As shown before, the *e.r.* was increased by increasing the dilution and decreasing the amount of DMPU. The stereochemistry of the double bond hasn't been confirmed.

Table 21: Rearrangement of urea **(*S*)-322**.

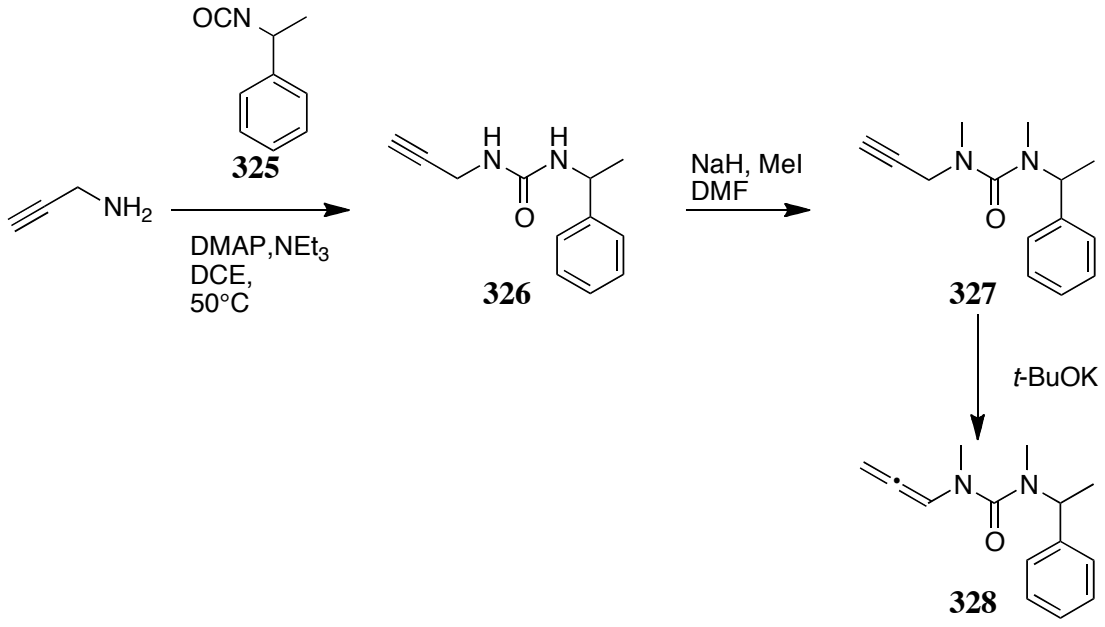


(*S*)-322 | **(*R*)-323** *(not isolated)* | **(*R*)-324** 60%

Entry	Conditions	*e.r.* (*R*)-323	*e.r* (*R*)-324
1	THF/DMPU: 10/1 (*c*=0.1M)	93:7	-
2	THF/DMPU: 10/1 (*c*=0.05M)	95:5	85:15
3	THF/DMPU: 20/1 (*c*=0.05M)	99:1	-

3.2.3. Extension of the vinyl migration

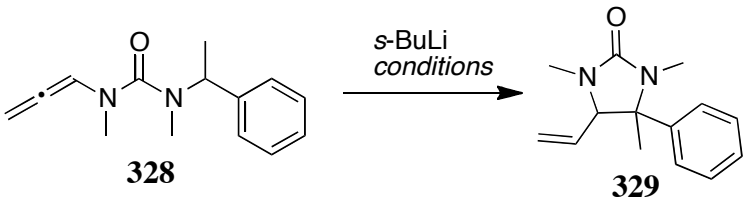
In order to complete this study on the migration of vinyl groups, the synthesis of urea **328**, substituted with an allene, was carried out. Treatment of propargylamine with isocyanate **325** led to the formation of urea **326** in quantitative yield. Methylation followed by deprotonation with *t*-BuOK formed the desired urea **328**. However, because of the decomposition of **328** the rearrangement was performed in a one-pot process starting from **327** (Scheme 128).



Scheme 128: Synthesis of urea **328**.

Treatment of allenic urea **328** with *s*-BuLi, led to the formation of cyclic urea **329** as a single diastereomer. In order to avoid cyclisation, different conditions were tested but none of them were successful and urea **329** was observed in every case with complete conversion (Table 22). When the reaction was carried out in THF in presence or absence of DMPU (entries 1-3), only the cyclic urea was observed. The reaction appeared to be slower when performed in a 1:1 mixture of THF and DMPU and urea **328** was still present in the crude mixture after one hour (entry 3). Addition of LiCl to the reaction mixture also led to the formation of the cyclic compound (entry 4). Increase of the temperature after one hour, in order to open the cyclic urea, also failed in forming the open form. Finally the use of Et_2O lead to complete decomposition of the starting material (entry 6).

Table 22: Formation of urea **329**.



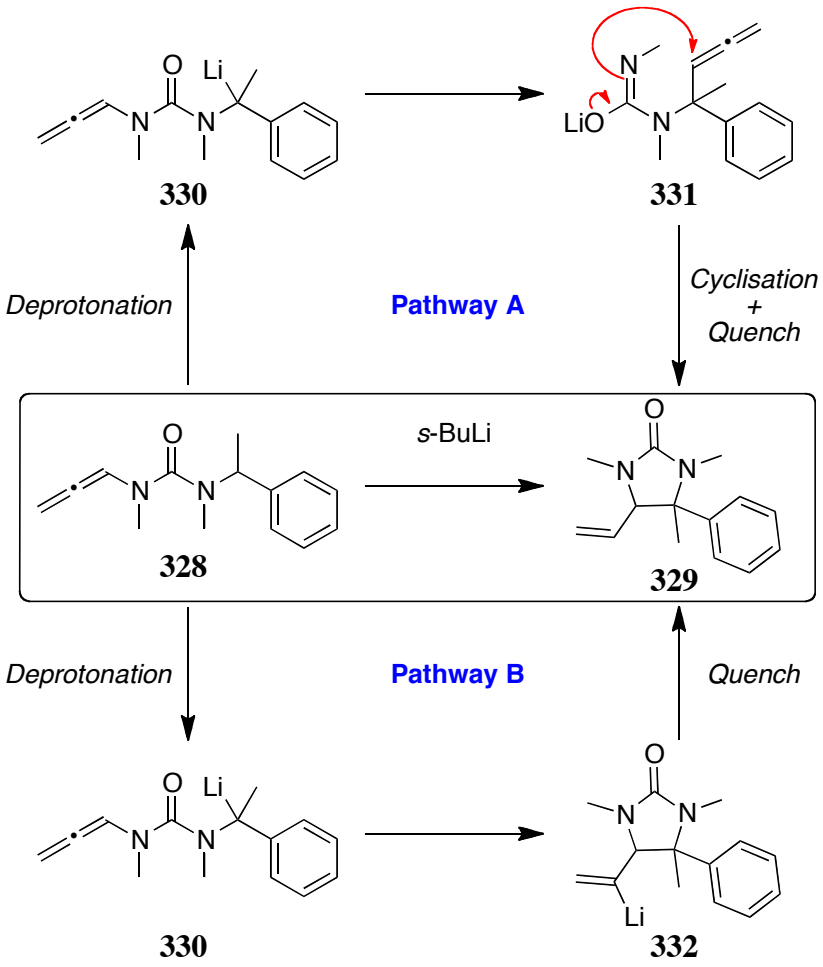
328 **329**

Entry	Condtions	Conclusion
1	THF/DMPU (10/1), –78°C, 1h	**329** (60%)
2	THF, –78°C, 1h	**329** (complete conversion)
3	THF/DMPU (1:1), –78°C, 1h	**328**:**329** (1:1)
4	THF, LiCl, –78°C, 1h	**329**
5	THF, –78°C, 1h then r.t., 1h	**329**
6	Et_2O, –78°C, 1h	decomposition

Two explanations could be proposed for the formation of urea **329** (Scheme 129). The first step of the reaction is the deprotonation of the benzylic proton to form the lithiated intermediate **330**. At this stage, two different pathways could be proposed. In the first case (pathway A), the lithiated intermediate **330** rearranges to form the α-tertiary urea **331** which can then cyclise to form urea **329** after protonation. This pathway is similar to the proposed mechanism for migration of the styrene (Scheme 125).

In the second case (pathway B), the same lithiated intermediate **330** attack the carbon of the allene to form the cyclic intermediate **332** bearing and sp^2-hybridised organolithium. Such organolithiums are known to be more stable than the sp^3-hybridised analogues. Therefore the system stayed blocked in the cyclic form. Protonation leads to the formation

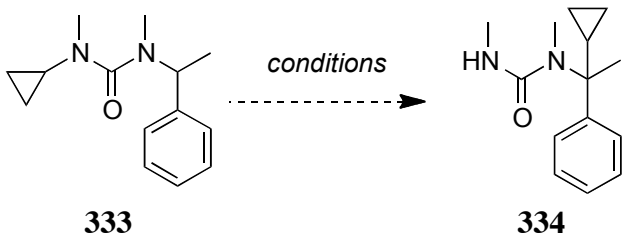
of **329**. As for the migration of the styrene, the pathway cannot be assigned unambiguously for this example. However, the absence of diastereomeric mixture tends to favour the second pathway.



Scheme 129: Possible mechanism pathways for the formation of urea **329**.

Because of the similar properties of sp^2 hybridized carbons and carbons in a cyclopropyl ring, the migration of a cyclopropyl ring was investigated. Urea **333** was synthesised and reacted under different conditions (Table 23). In each case the starting material was recovered completely unreacted.

Table 23: Cyclopropyl migration.



Entry	Conditions	Conclusion
1	*s*-BuLi, THF/DMPU 10:1 –78°C, 1h	**333** recovered
2	*s*-BuLi, THF/DMPU 10:1 0°C, 1h	**333** recovered
3	*s*-BuLi, THF, LiCl –78°C, 1h	**333** recovered

A possibility to increase the reactivity of urea **333** would be to add substituents, such as phenyl, on the cyclopropyl ring but this hypothesis was not investigated.

3.3. Mechanistic investigations

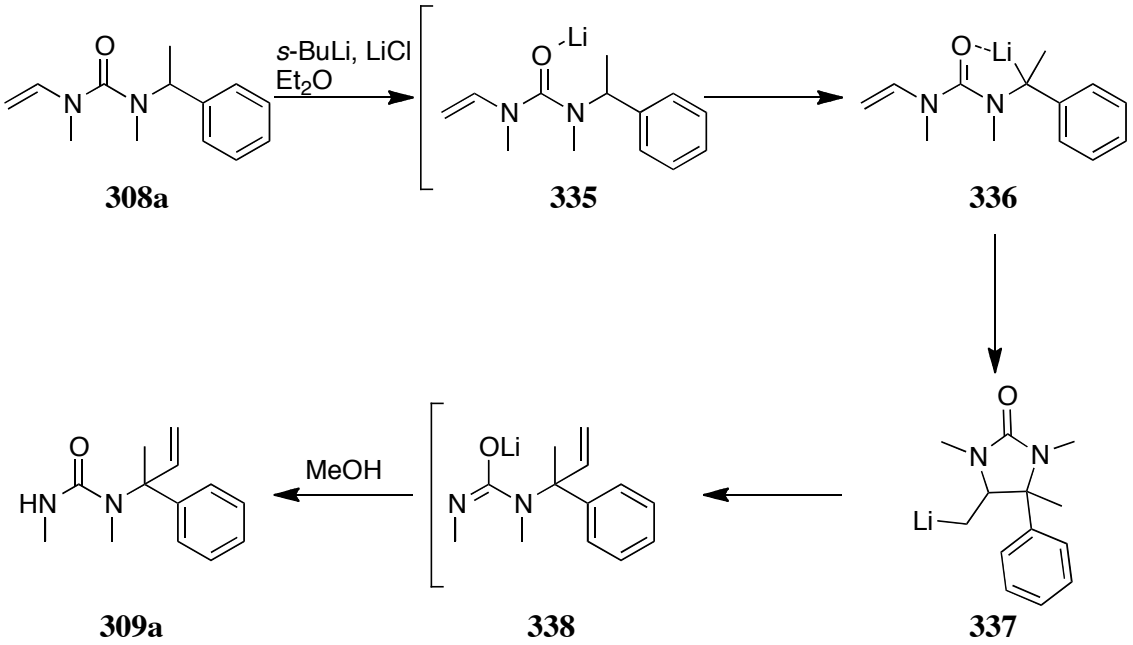
The mechanism of the unusual vinyl migration was investigated in detail to understand how the reaction proceeds. To do so, two different techniques were used. Firstly measurements using *in-situ* IR were carried out and secondly computational calculations were performed.

3.3.1. *In-situ* IR experiments*

In-situ IR experiments were used to analyse the variation of the absorption for the stretching of the C=O bond to determine the mechanism of the transformation. However, because of the presence of a second carbonyl group due to the use of DMPU in the reaction conditions, therefore new conditions had to be developed. Similar results were obtained when the reaction was performed in Et_2O in the presence of LiCl. Under these conditions, the rearrangement appeared to be slower than in THF.

The hypothetical mechanism involves the deprotonation of urea **308a** in the benzylic position to generate intermediate **336**. This deprotonation might involve a prior coordination between the alkylithium reagent and the carbonyl group of starting material (**335**). The next step involves a nucleophilic attack to the vinylic carbon via the cyclic intermediate **337** to form the rearranged urea **338** which leads to the desired product **309a** after quench with methanol (Scheme 130).

* Experiments performed by Anne Fournier (PhD student).



Scheme 130: Postulated mechanism for the vinyl migration.

In order to identify without any doubt species involved in the reaction pathway, the first experiment consisted in the treatment of the final product **309a** with *s*-BuLi to observe **338** (Figure 15). After complete addition of *s*-BuLi, there is appearance of a peak at 1571 cm^{-1} which returned the starting material after quench. This signal can the be assigned to be deprotonated urea **338**.

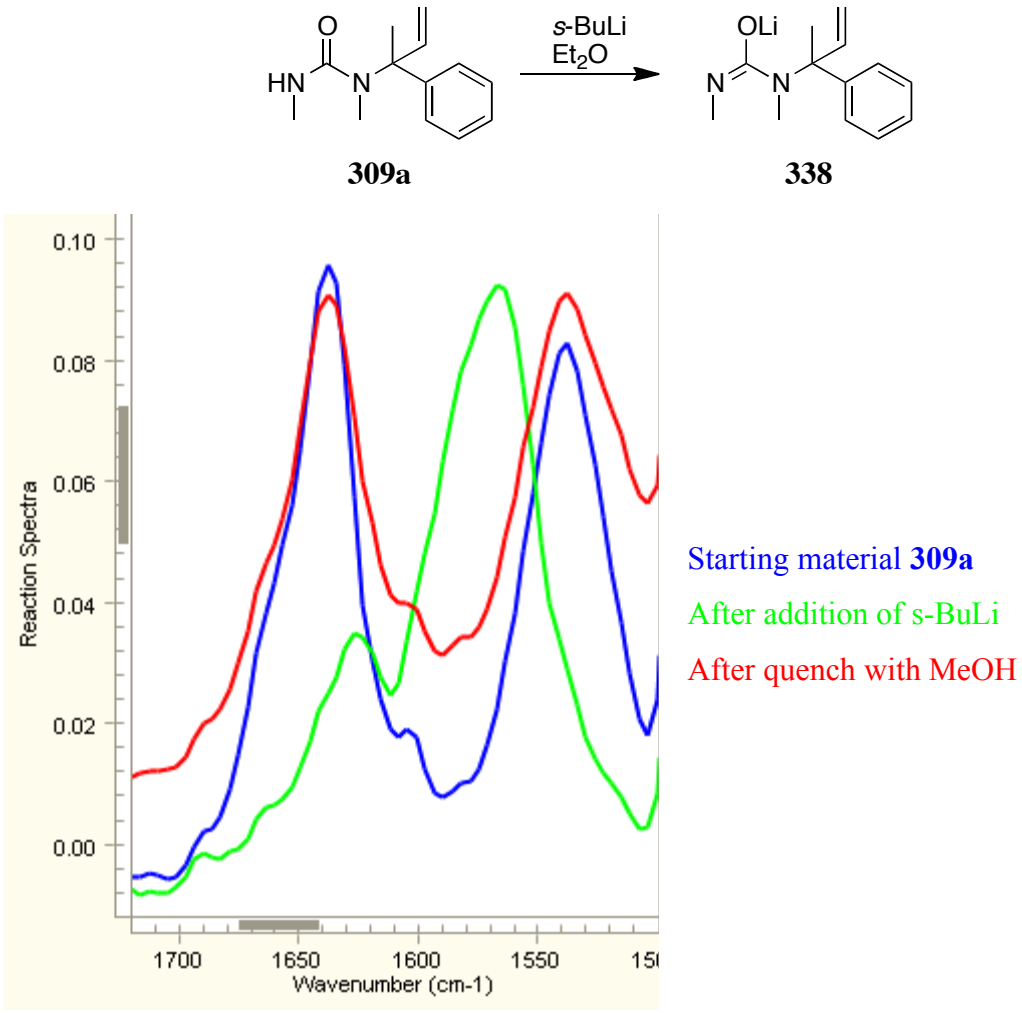


Figure 15: *In-situ* IR for deprotonation of urea **309a**.

In the second experiment, urea **308a** was reacted with one equivalent of *s*-BuLi. Spectra were recorded before addition, after addition of 0.6 equivalents of base and finally after complete addition. The first important observation is the complete disappearance of the carbonyl signal after addition of a substoichiometric amount of base. Two new peaks are observed on the green plot: 1646 and 1608 cm^{-1}. The peak at 1608 cm^{-1} is still present after complete addition of base along with a peak at 1593 cm^{-1}. Therefore, it is possible to hypothesise that the two peaks 1608 and 1593 cm^{-1} correspond to the deprotonated urea **336** while the peak at 1646 cm^{-1} could be assigned to a prelithiated intermediate **335**. Because of the complete absence of signal of urea **308a** after addition of only 0.6 equivalent of base, it can be postulated that the prelithiated intermediate **336** cannot be present as a monomeric form. The reaction was performed at –78°C and under these reaction conditions no rearrangement was observed. In the next experiment, the reaction was warmed up to –15°C after complete addition of base.

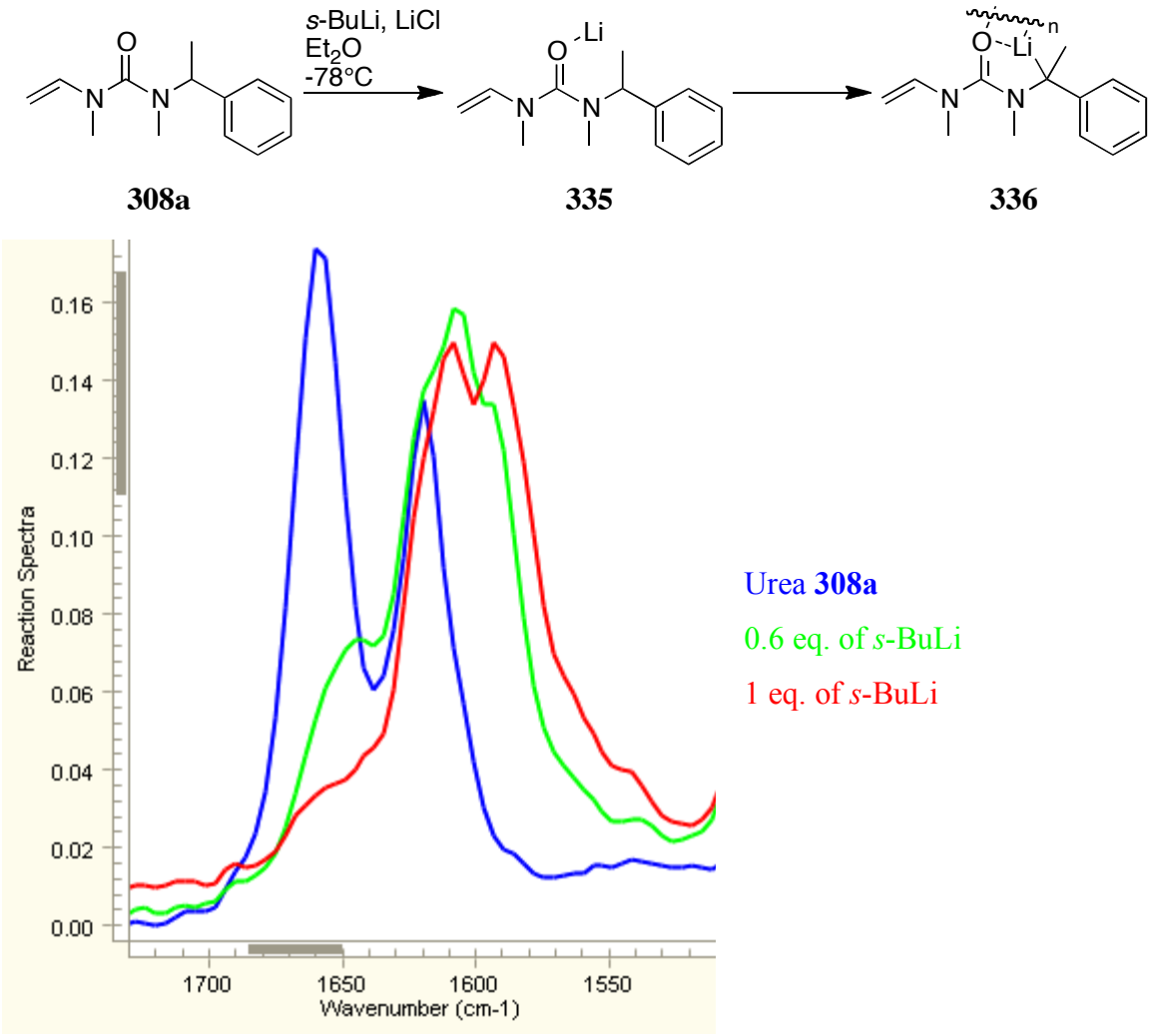
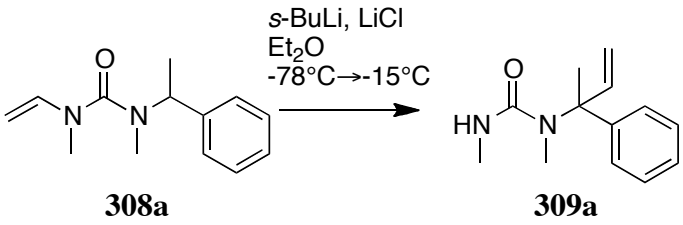


Figure 16: *Insitu* IR for deprotonation of urea **308a**.

In the last experiment, five spectra were recorded in order to observe the different intermediates on the reaction pathway.

When urea **308a** was treated with 1.1 equivalents of base, two peaks appeared (green spectrum) which can be assigned to the deprotonated urea **336**. When the temperature was increased to –15°C, slow disappearance of these two peaks was observed, with a new peak appearing at 1578 cm^{-1} which can be assigned to the rearranged product **338** (in accordance with the peak observed in the first experiment). Finally a quench with methanol led to the apperance of the signals corresponding to the rearranged urea **309a**, along with the signals of the starting material (the reaction did not go to completion).



308a **309a**

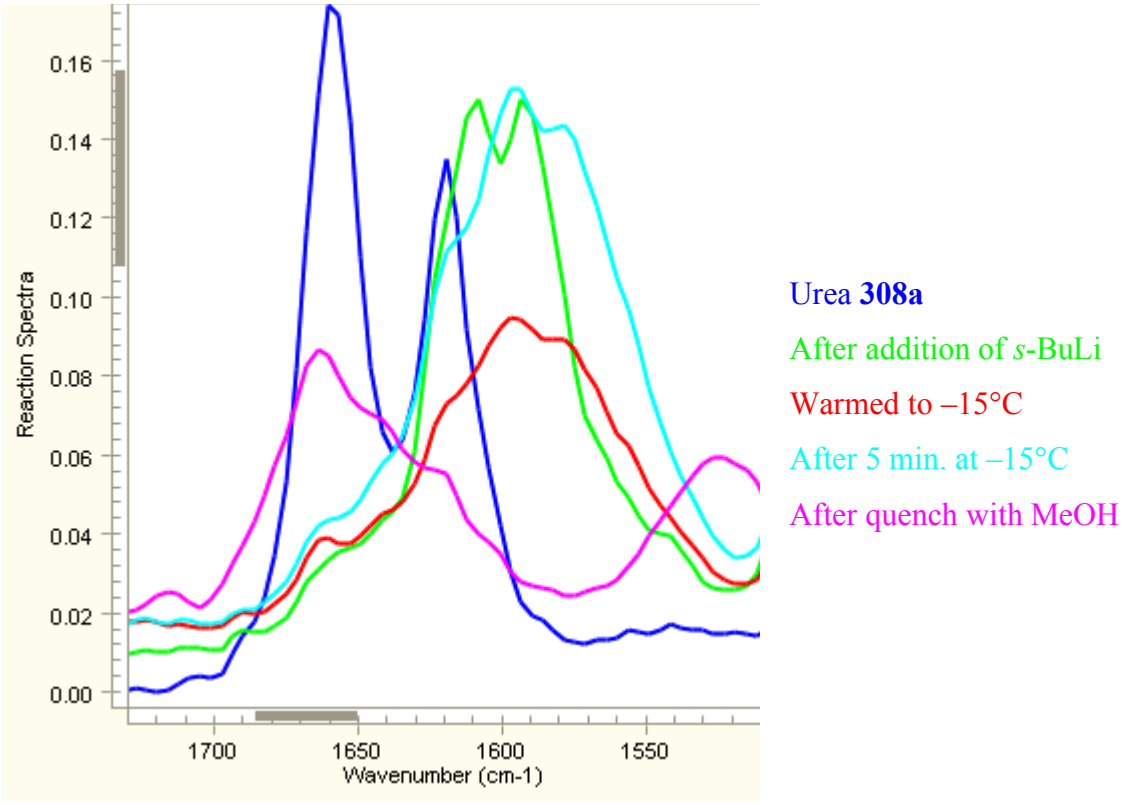


Figure 17: *Insitu* IR for rearrangement of vinyl urea **308a**.

These experiments allowed us to conclude that intermediates **335**, **336** and **338** are involved in the reaction. The postulated cyclic intermediate **337** was not observed.

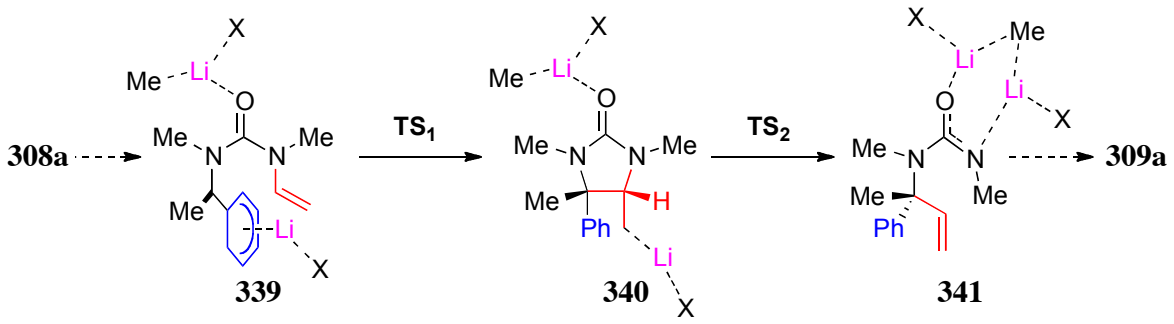
3.3.2. Molecular modelling*

In order to understand more the mechanism, computational calculations were performed. The calculations focused on the nucleophilic attack of the carbanion and the opening of the cyclic transition state (B3LYP/6-311+G(2d,2p)).

The model system includes the deprotonated urea, an additional methyllithium to simplify the calculations) coordinated to the carbonyl and two molecules of THF or DMPU (to

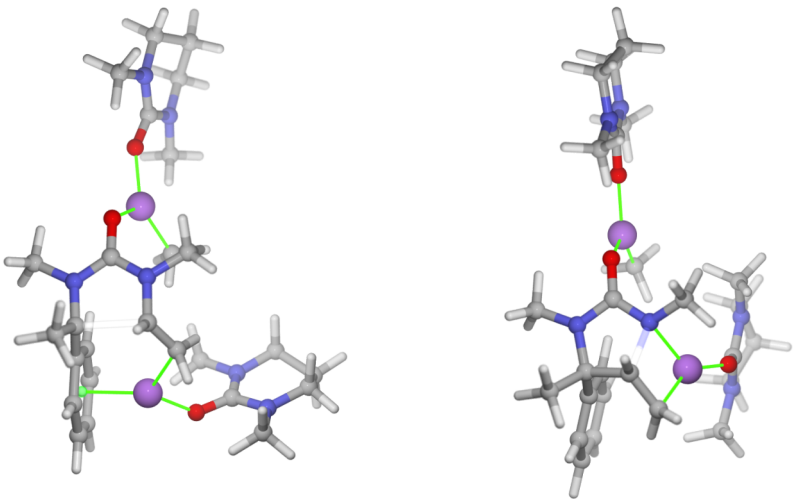
* Work done by Dr. Tommaso Marcelli (visiting researcher).

coordinate each lithium atom) (Scheme 131). The studies were performed starting from the carbanion formed after deprotonation (the deprotonation step was not studied).



Scheme 131: Mechanistic model for the vinyl migration (X=THF or DMPU).

The first step of the reaction involves the attack of the carbanion **339** on the vinylic carbon to form the cyclic intermediate **340** via the first transition state (Figure 18). Interestingly, after optimisation, the lithium atom in structure **339** appeared to be coordinated to the π system of the aromatic ring and not the carbon of the carbanion. During the formation of the C-C bond, the lithium cation moved to the terminal position of the olefin in order to stabilise the negative charge (with THF or DMPU). The optimisation showed a *syn* relationship between the H and the methyl group in the cyclic compound **340**. The opening of the 5-membered ring intermediate **340** leads to the formation of the urea **341** via a second transition state **TS_2**. After opening, the two lithium atoms present in the model are coordinated to the same carbanion.



TS_1 **TS_2**

Figure 18: Calculated transition states.

In the two pathways (DMPU or THF) **340** appeared to be a minimum in energy (Figure 19). The barrier in energy between the cyclic intermediate and the $\mathbf{TS_2}$ is only about 5kcal/mol making the trapping of the intermediate extremely difficult. Attempts to trap experimentally this intermediate with electrophiles were unsuccessful.

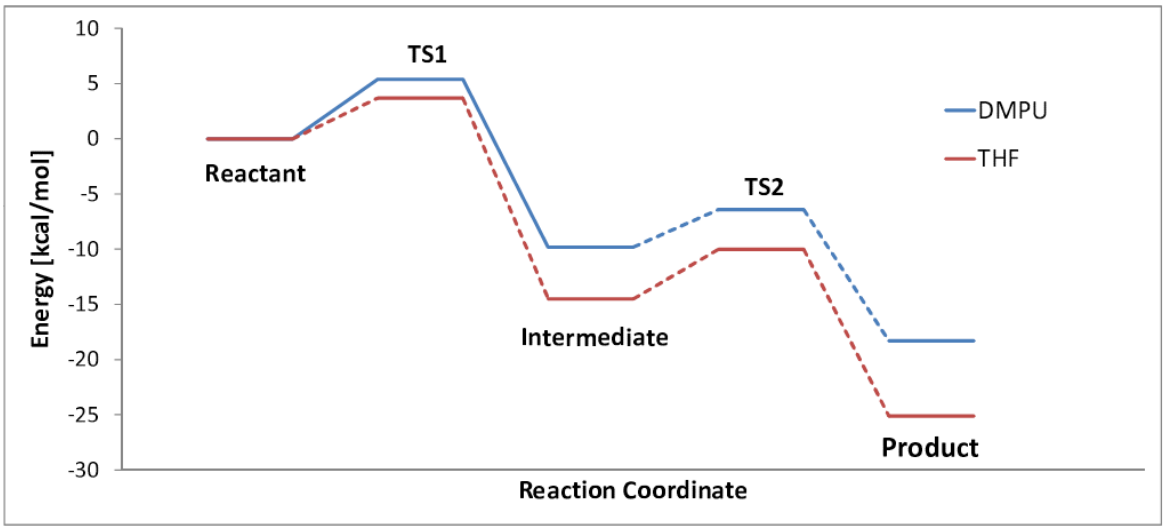


Figure 19: Calculated potential energy profile.

3.4. Application of the vinyl migration: toward the synthesis of (±)-erythrinane and (±)-homoerythrinane

3.4.1. Introduction

Erythrinanes are a large class of alkaloids isolated from *Erythrina* plants.[146] These alkaloids are known to exhibit a range of pharmacological properties such as hypertensive, sedative, anticonvulsive etc. Structurally, these alkaloids contained a tetracyclic core and an α-tertiary amine (Figure 20).[147-152]

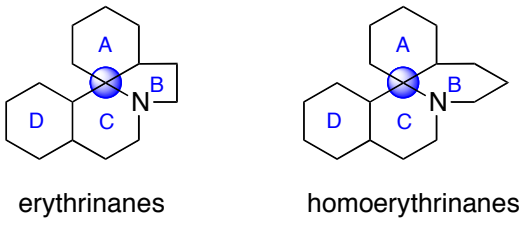


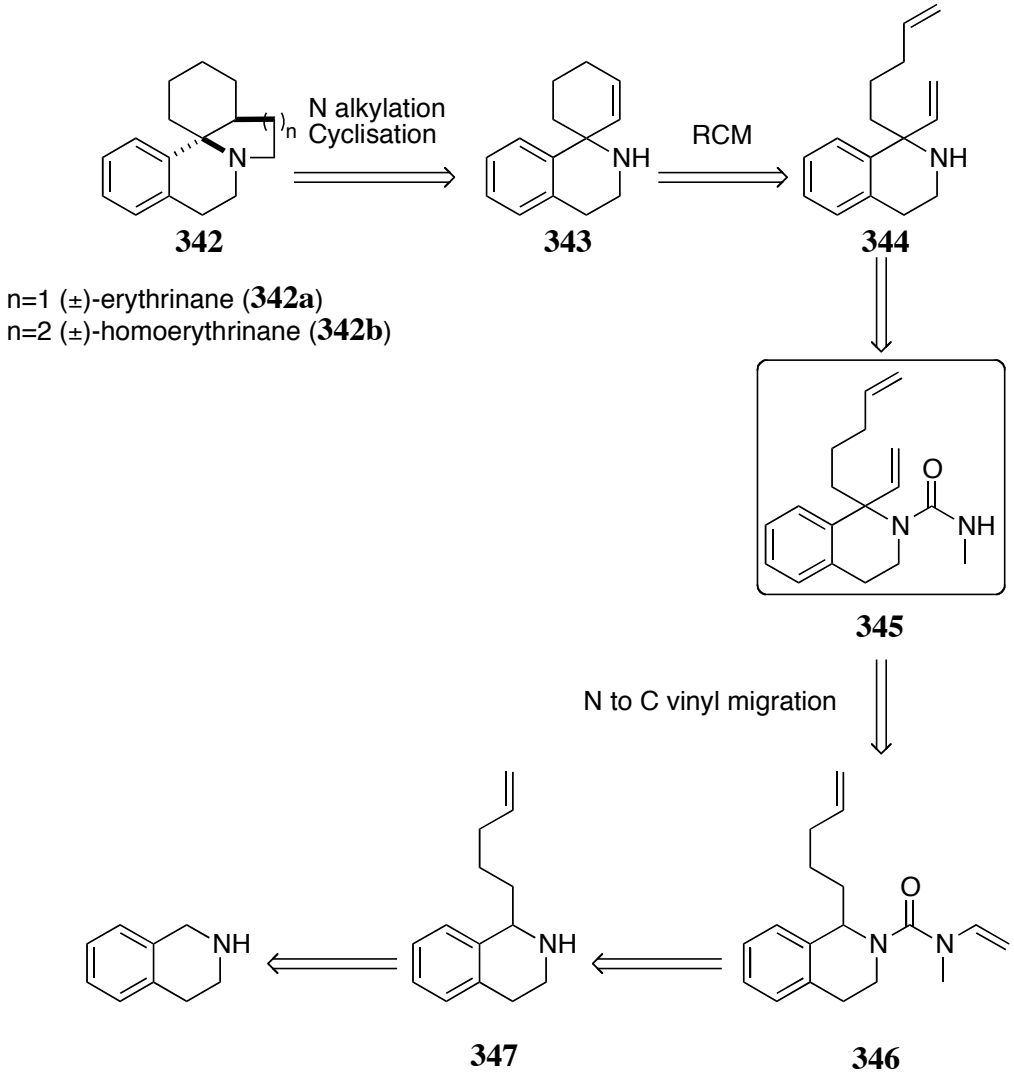
Figure 20: Erythrina alkaloids.

A formal synthesis of (±)-erythrinane and (±)-homoerythrinane could be investigated using N to C vinyl transfer to construct the α-tertiary amine.

3.4.2. Retrosynthesis

The key intermediate of the proposed synthesis is the α-tertiary urea **345** (Scheme 132). The compound can be synthesised by N to C transfer of a vinyl group starting from urea **346**. **346** will be synthesised starting from the commercially available tetra-hydroisoquinoline.

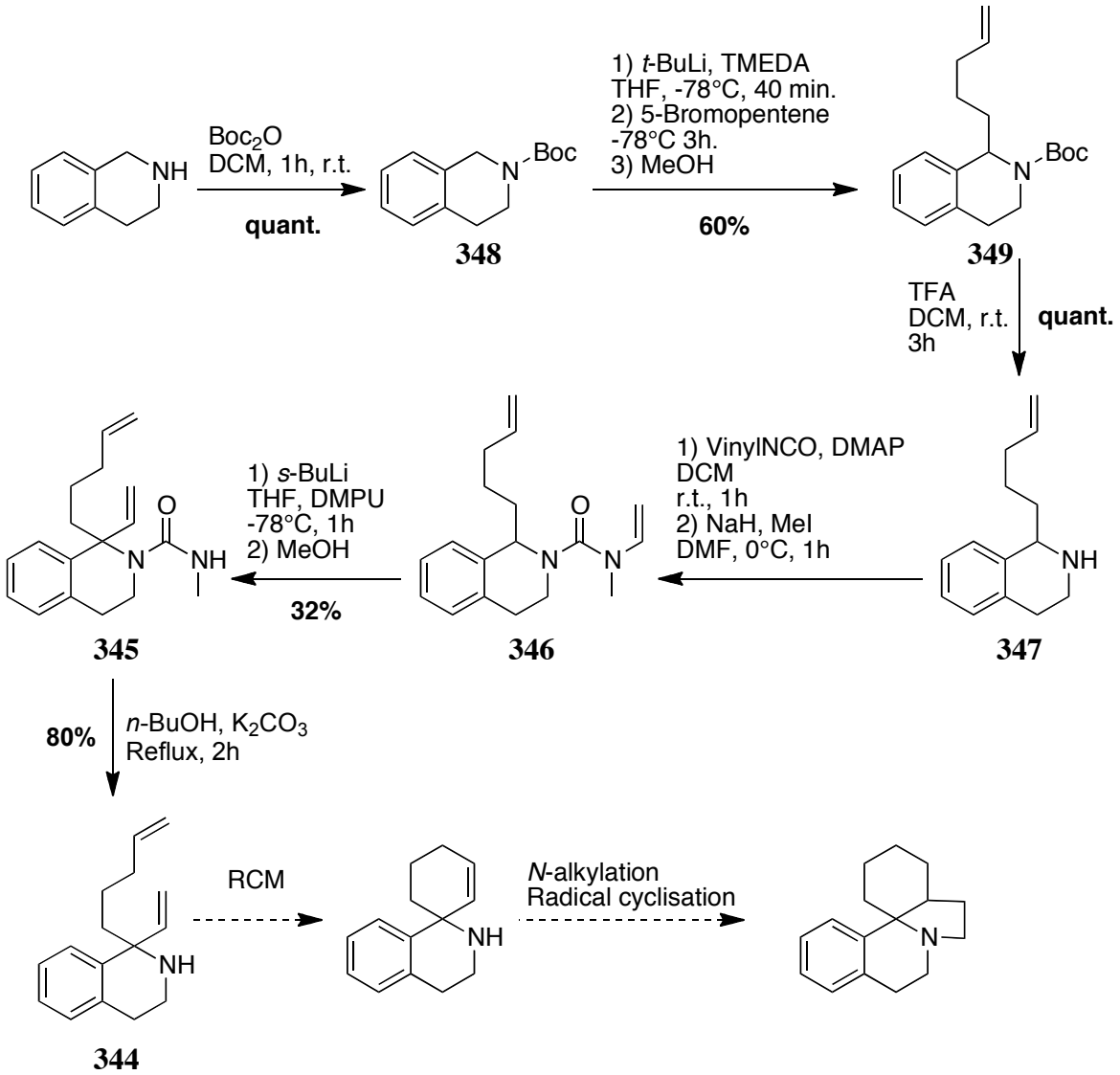
With urea **345** in hand, deprotection followed by ring closure metathesis should provide the tricyclic amine **343**. Amine **343** can be therefore used as a common precursor for both (±)-erythrinane and (±)-homoerythrinane. *N*-alkylation of **343** followed by cyclisation should lead to the desired natural procducts.



Scheme 132: Retrosynthetic approach for the synthesis of erythrinane **342a** and homoerythrinane **342b**.

3.4.3. Synthesis

The first step on the synthesis involved the protection of tetrahydroisoquinoline using Boc anhydride (Scheme 133). The reaction was performed in CH_2Cl_2 for an hour at room temperature.[153] The desired protected amine **348** was obtained in quantitative yield. The side-chain was installed by treatment of **348** with *t*-BuLi in THF in presence of TMEDA. After stirring the reaction at –78°C for 30 minutes, the reaction was quenched with 5-bromo-1-pentene to form **349** in 60% yield.



Scheme 133: Toward the synthesis of erythrinane.

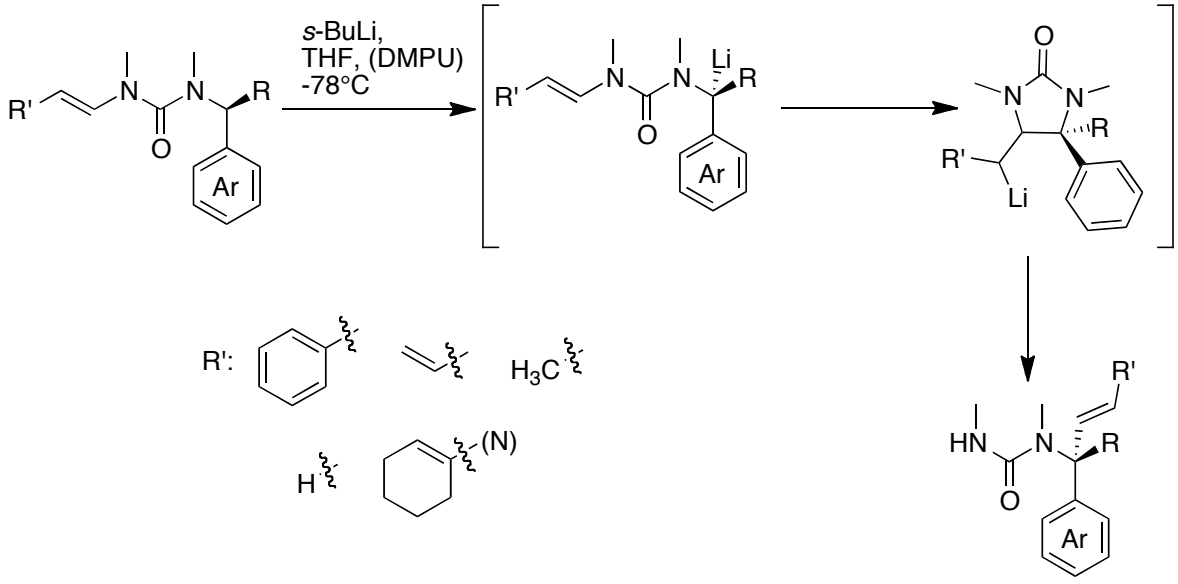
Quantitative Boc deprotection using TFA generated amine **347**. Amine **347** was treated with vinyl isocyanate, in the presence of DMAP, and then methylated under standard

conditions to afford urea **346**. With urea **346** in hand, vinyl migration could be performed. Treatment of **346** with *s*-BuLi in a mixture THF/DMPU formed the desired product **345** in only 32% yield, with low yield attributed to purification difficulties. Rearranged urea **345** can be easily deprotected by refluxing it in *n*-butanol for 2 hours, the desired α-tertiary amine **344** was obtained in 80% yield.

Completion of the synthesis will involve a ring closure metathesis, followed by *N*-alkylation and radical cyclisation. Alkylation using dibromoethane or dibromopropane should allow the formation of erythrinane of homoerythrinane respectively.

3.5. Summary

To conclude, a new N to C vinyl migration involving lithiated benzylic ureas was discovered. The migration of different vinyl groups was successfully investigated on benzylic and substituted benzylic ureas. Five new migrating groups were highlighted and a enantiospecific version of the reaction was developed (Scheme 134).

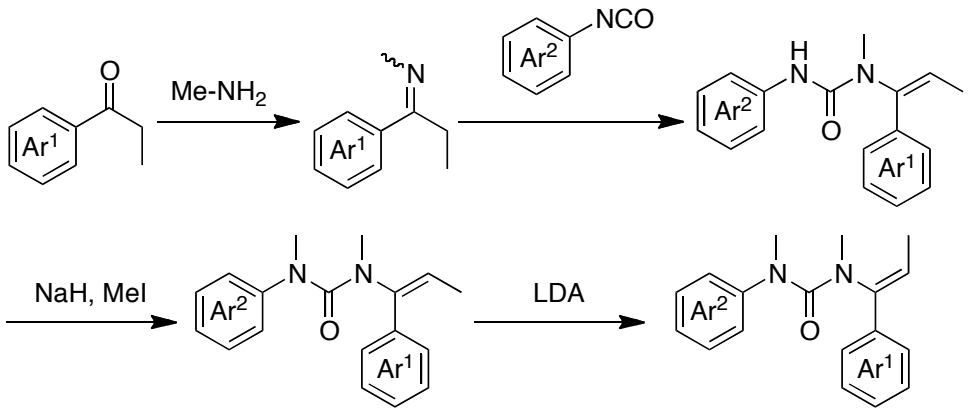


Scheme 134: N to C vinyl migration.

Computational calculations as well as *in-situ* IR experiments provided evidence of the mechanistic pathway of the reaction. This new rearrangement is currently being applied to the synthesis of *Erythrina alkaloids*.

CONCLUSION

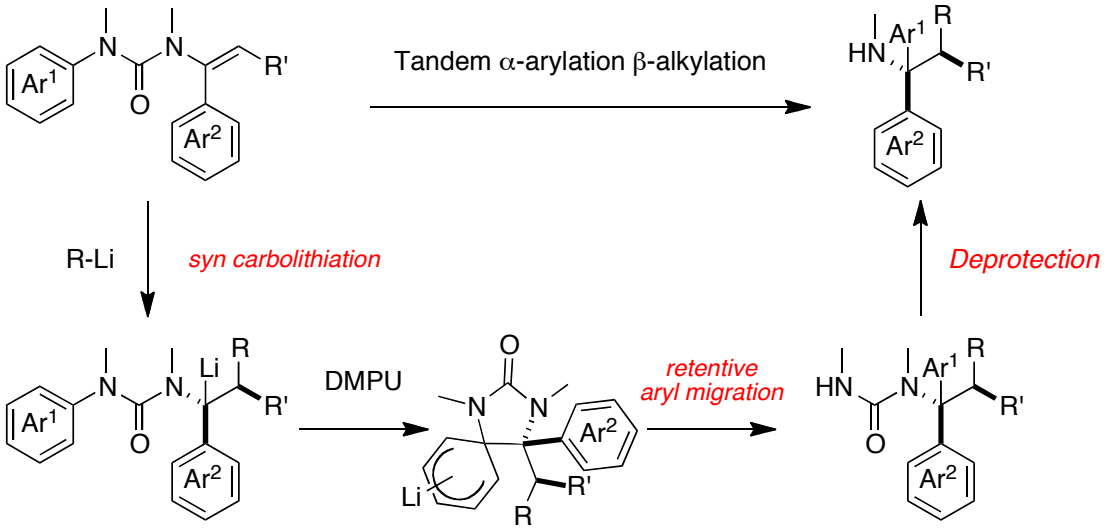
In conclusion, the synthesis of vinyl ureas was developed by reacting an enamine tautomer of the corresponding imine, with the required isocyanate (Scheme 135). This synthesis was carried out in a one-pot process in order to reduce the number of purifications and appeared to be reliable on multigram scale. A large range of substituted vinyl ureas was synthesised with excellent control on the stereochemistry of the double bond: the (*E*)-isomer was generally obtained in large excess. The (*Z*)-isomer could be obtained from the (*E*) by deprotonation using LDA.



Scheme 135: Synthesis of vinyl ureas.

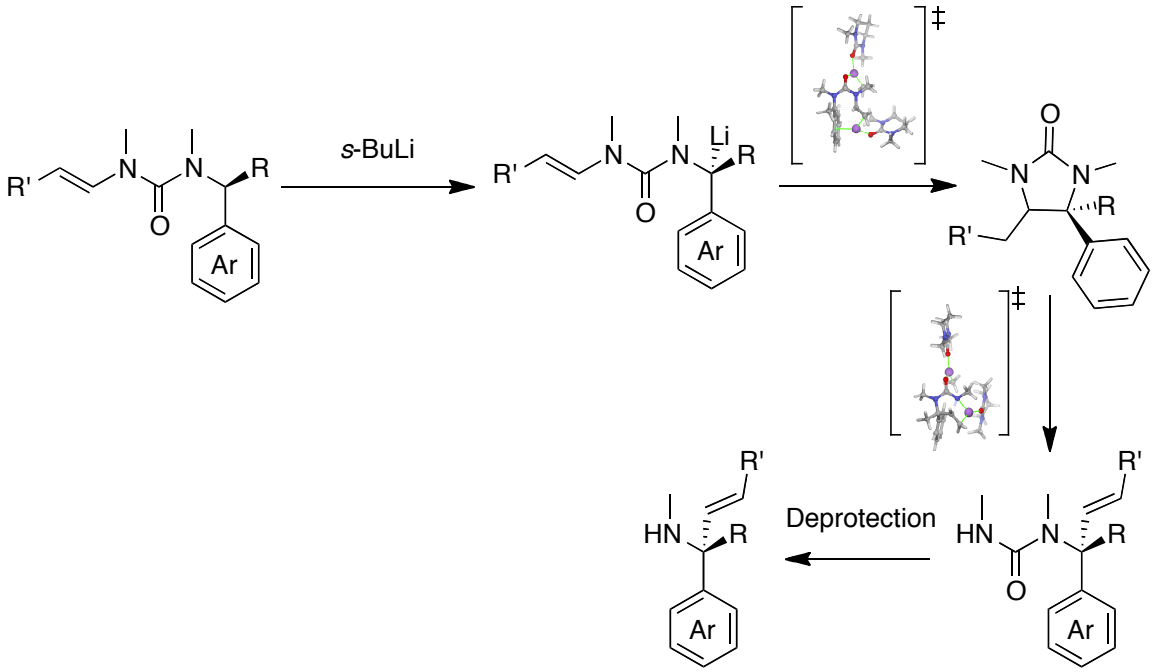
These vinyl ureas were then used for the synthesis of highly substituted α-tertiary amines (Scheme 136). It had been demonstrated that vinyl ureas could undergo umpolung carbolithiation of the electron-rich double bond, followed by N to C aryl migration. The carbolithiation was performed with a range of alkyllithium reagents and proved to allow the migration of both, electron rich and electron deficient aromatic rings. Deprotection of the rearranged ureas under mild conditions led to the formation of the corresponding α-tertiary amines. The tandem reaction was diastereospecific: both isomers of the double bond led to different diastereomers.

The complete mechanism of the reaction was studied and *syn* carbolithiation followed by retentive aryl migration were confirmed. However, the extension to the enantioselective version of the tandem reaction using (–)-sparteine or (+)-sparteine surrogate was not successful.



Scheme 136: Tandem carbolithiation-aryl migration.

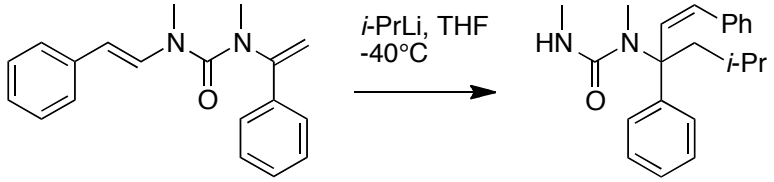
Finally, the scope of the N to C aryl transfer was widened to vinyl groups (Scheme 137). Five new migrating groups were identified and enantiopure α-tertiary amines were synthesised using this methodology. The complete mechanism was investigated using *in-situ* IR experiments as well as computational calculations. This methodology was then applied toward the synthesis of *Erythrina* alkaloids.



Scheme 137: N to C vinyl migration.

FUTURE WORK

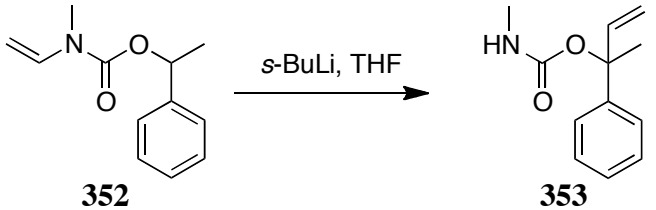
Extension of the vinyl migration to the tandem carbolithiation-migration will also be studied. Preliminary studies, for urea **350**, have shown that the reaction proceeds in moderate yield to form the rearranged urea **351** with complete selectivity between the two double bonds present in the molecule (Scheme 138). In this case, the migration of a styrene proceeded without any cyclic product being observed (probably due to steric hinderance of the *i*-propyl group).



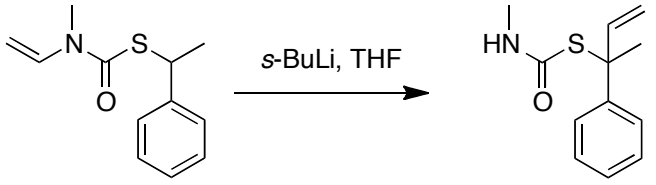
350 **351**
50%
(unoptimised)

Scheme 138: Tandem carbolithiation/styrene migration.

The vinyl migration is currently applied in the group for the rearrangement of carbamates **352** and thiocarbamates **354** (Scheme 139).



352 **353**

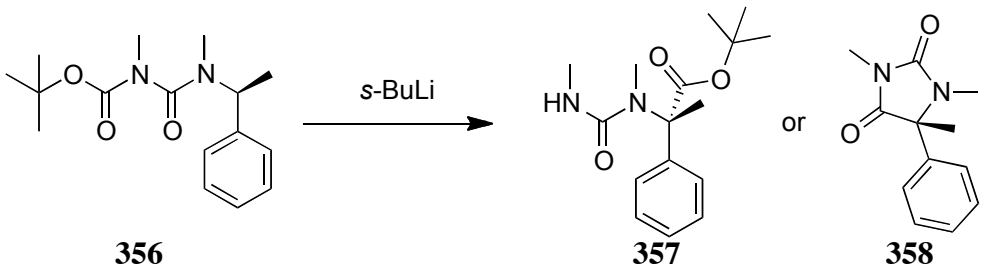


354 **355**

Scheme 139: Vinyl migration of carbamates and thiocarbamates.

The next stage of the work will be to extend the rearrangement of lithiated ureas. After the good results obtained for the migration of a sp^2 hybridized carbon, the migration of sp^2 carbons attached to heteroatoms should be investigated (Scheme 140). A possibility will be the migration of a Boc group in order to generate protected amino acids **357** in

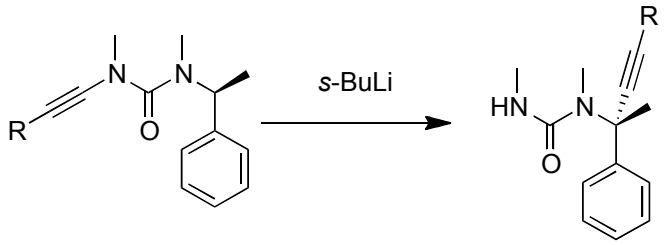
enantiomerically pure form from readily available chiral starting materials. However, the risk of forming the hydantoin **358** is present.



356 **357** **358**

Scheme 140: N to C Boc migration.

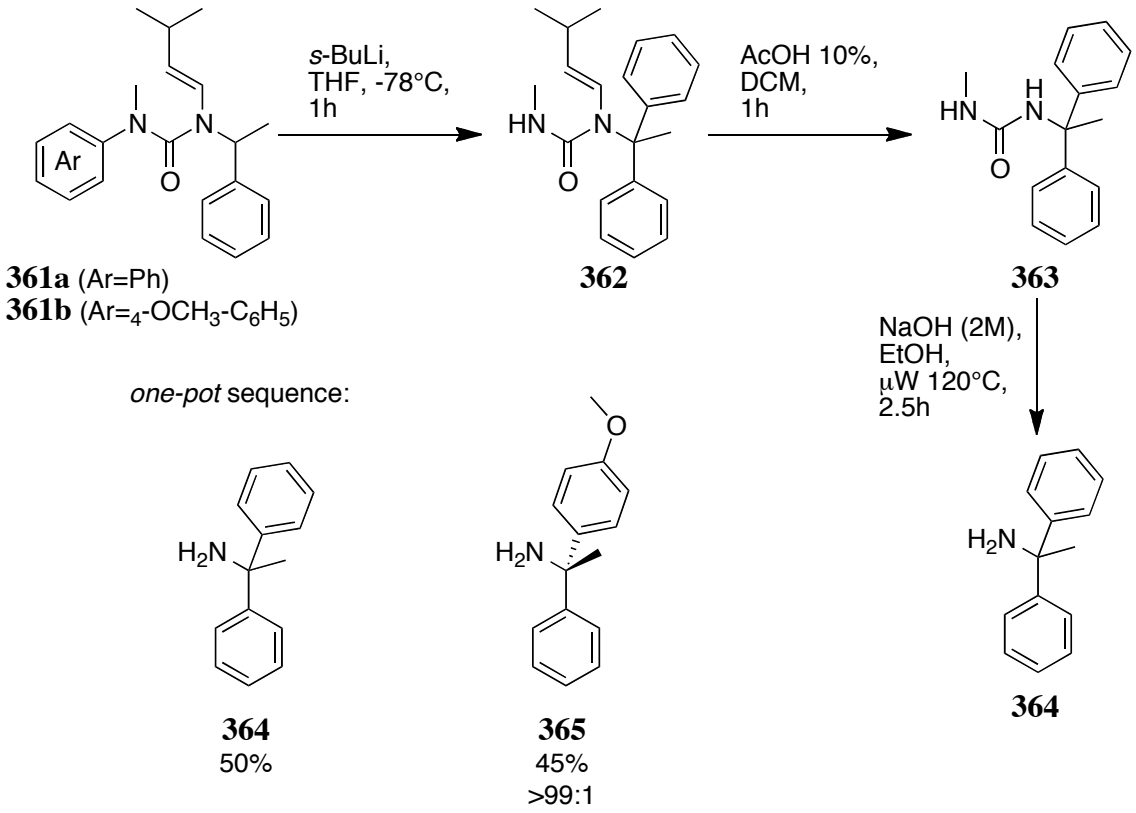
A long held aim is the investigation of *sp* hybridized migrating groups (Scheme 141). Several attempts to synthesise the alkyne starting material **359** were unsuccessful.



359 **360**

Scheme 141: N to C propargyl transfer.

A new protecting group is currently under investigation in the group allows the synthesis of free amines (instead of *N*-methyl amines). Initial investigations have indicated that rearrangement of urea **361a** followed by sequential double deprotection allowed the formation of amine **364** (Scheme 142).



Scheme 142: Synthesis of NH_2 amines.

These reactions can also be performed in a one-pot process and in high yield. The synthesis of enantiopure amines was also found to be compatible with the new protecting group and enantiopure urea **(*S*)-361b** led to the formation of **365** in 45% yield over three steps. The application of this protecting group will be investigated for the enantiospecific vinyl transfer.

EXPERIMENTAL DATA

1. General information

NMR spectra were recorded on a Bruker Ultrashield 300, 400 or 500 MHz spectrometer. The chemical shifts (δ) are reported in ppm downfield of trimethylsilane and coupling constants (J) reported in Hertz and rounded to 0.1 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sep), multitiplet (m), broad (br), or a combination of these. Solvents were used as internal standards when assigning NMR spectra (δ H: $CDCl_3$ 7.26 ppm, MeOD 3.31 ppm; δ C: $CDCl_3$ 77.0 ppm, MeOD 49.0 ppm, C_6D_6 128.1 ppm).

Low and high-resolution mass spectra were recorded by staff at the University of Manchester. EI and CI spectra were recorded on a Micromass Trio 2000; ES and APCI spectra were recorded on a Micromass Platform II; high-resolution mass spectra (HRMS, EI and ES) were recorded on a Thermo Finnigan MAT95XP mass spectrometer.

Infrared spectra were recorded on a Perkin Elmer Spectrum RX I FTIR spectrometer as a film on a sodium chloride plate. Absorptions reported are sharp and strong, only absorption maxima of interest are reported.

Melting points (m.p.) were determined on a Gallenkamp apparatus and are uncorrected.

Optical rotations $[\alpha]^T_D$ were measured with a Perkin-Elmer 341 Polarimeter using a cell with a pathlength of 1 dm. Concentrations (c) are given in grams per 100 mL.

Enantiomeric ratio were determined using HPLC on Hewlett Packard system coupled with UV detector at 254 and 214nm.

Thin layer chromatography (TLC) was performed using commercially available pre-coated plates (Macherey- Nagel alugram Sil G/UV254) and visualised with UV light at 254 nm or phosphomolybdic acid dip (5 % in ethanol). Flash chromatography was carried out using Fluorochem Davisil 40-63u 60 Å.

Tetrahydrofuran (THF) was distilled under nitrogen from sodium using benzophenone as indicator. Dichloromethane and toluene were obtained by distillation from calcium hydride under nitrogen or obtained from Solvent Purification System. DMPU and cumene were distilled under reduced pressure from calcium hydride and stored over molecular sieves. Petrol refers to the fraction of light petroleum ether boiling between 40-65 °C. All other solvents and commercially obtained reagents were used as received or purified using standard procedures.

n-Butyl lithium was used as a solution in hexanes (2.5M), *i*-propyl lithium as a solution in pentane (0.7M), *s*-butyl lithium as a solution in cyclohexane/hexane (92/8) (1.3M), *t*-butyl lithium as a solution in pentane (1.7M) and phenyl lithium as a solution in n-butylether (2.0M). All the above organolithium solutions were titrated prior to use against a solution of benzyl benzamide. Cooling baths used are acetone/dry ice for –78°C and acetonitrile/dry ice for –40°C.

All experiments were performed in anhydrous conditions under an atmosphere of argon, unless otherwise noted in the experimental text. The glassware was flame-dried and standard techniques were employed in handling air-sensitive materials.

2. General Procedures

General procedure 1: *One-pot sequence for the synthesis of trisubstituted vinyl ureas*

The desired ketone (1 eq.) was added to a solution of methylamine (8M in EtOH, 6 eq.) in the presence of molecular sieves (1:1 w/w) and heated in a microwave for 1h at 125°C. The crude mixture was filtered through Celite® and concentrated under vacuum.

The obtained imine was solubilised in toluene (0.5M) and treated with the desired isocyanate (1 eq.) for 16h at r.t. The solvent was removed and the product was solubilised in THF. The reaction mixture was cooled at 0°C and treated with sodium hydride (2 eq., 60% in mineral oil). After 30 min. at 0°C, methyliodide (2 eq.) was added slowly and the reaction was stirred for 24h at r.t.

The reaction was diluted with Et_2O and quenched slowly with water. The crude mixture was extracted with ethyl actetate, dried ($MgSO_4$) and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (PE/EtOAc: 8/2, 1% NEt_3).

General procedure 2: *Synthesis of monomethylated ureas*

The ketone (1 eq.) was added to a solution of methylamine (8M in EtOH, 4 eq.) in the presence of molecular sieves (1:1 w/w). The mixture was heated under microwave irradiation for 1h at 125°C (or alternatively at 50°C for 48h). The crude mixture was filtered through Celite and concentrated under vacuum. The obtained imine was solubilised in toluene (0.5M) and treated with the desired isocyanate (1 eq.), then stirred for 16h at r.t. The solvent was evaporated and the crude was purified on silica gel (PE/EtOAc: 8/2+1% NEt_3).

General procedure 3: *Carbolithiation of dimethylated ureas*

To a solution of urea in dry solvent (0.1M) cooled at the desired temperature, the organolithium reagent (2 eq.) was added slowly. After 1h, the reaction was quenched slowly with MeOH and sat. NH_4Cl. The crude was extracted with EtOAc, dried with MgSO4, concentrated under reduced pressure and purified by chromatography on silicagel (PE/EtOAc: 9/1).

General procedure 4: *Carbolithiation of vinyl carbamates*

To a solution of carbamate in dry THF (0.1M), cooled at -78°C, the desired organolithium reagent (2 eq.) was added slowly. After 1h at -78°C, the reaction was quenched by slow addition of MeOH. The mixture was extracted with EtOAc and washed with sat. NH_4Cl.

The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (PE/CH_2Cl_2: 1/1).

General procedure 5: *One-pot process carbolithiation-deprotection of vinyl carbamates*

The desired carbamate was solubilised in dry THF and the mixture was cooled to -40°C. Isopropyllithium was added slowly and the reaction was stirred for 1h at -40°C. The reaction was quenched by slow addition of MeOH. The solvent was removed under reduced pressure and the crude was solubilised in TFA. The reaction was stirred for 1h at r.t. The reaction mixture was diluted in CH_2Cl_2 and washed with aq. $NaHCO_3$ (1M). The organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure

General procedure 6: *Carbolithiation/rearrangement of vinyl ureas*

Condition A: *Migration of substituted phenyl ring*

To a solution of urea in dry solvent (0.1M) cooled at -40°C, the desired organolithium reagent (2 eq.) was added slowly. After 1h, DMPU was added to obtain a (1/4 v/v DMPU/solv). The reaction was slowly warmed to r.t. and stirred for 16h. The reaction was quenched with MeOH and sat. NH_4Cl. The crude was extracted with a mixture 1:1 PE/Et_2O, dried with $MgSO_4$, concentrated under reduced pressure and purified by chromatography on silica gel (PE/EtOAc:7/3+1% Et_3N) to afford the corresponding rearranged product.

Condition B: *Migration of phenyl ring*

To a solution of urea in dry THF (0.3M) cooled at -40°C, the desired organolithium reagent (2 eq.) was added slowly. After 3-6h (cf. desired product description), the reaction was quenched with MeOH and NH_4Cl. The crude was extracted with EtOAc, dried with $MgSO_4$, concentrated under reduced pressure and purified by chromatography on silicagel (PE/EtOAc: 7/3+1% Et_3N) to afford the corresponding rearranged product.

General procedure 7: *Deprotection of rearranged ureas*

The urea was solubilised in *n*-BuOH (0.03M) and K_2CO_3 was added (1 eq. w/w). The solution was refluxed for 2.5h. The reaction mixture was washed with H_2O, extracted with EtOAc, dried with $MgSO_4$ and concentrated under reduced pressure. The desired product was obtained by purification on silica gel (PE/EtOAc: 9/1+1% NEt_3).

General procedure 8: *Carbolithiation of monomethylated ureas*

To a solution of urea in dry THF (0.1M) cooled at -40°C, the desired organolithium reagent (3 eq.) was added slowly. After 1h, the reaction was quenched slowly with MeOH and NH_4Cl. The crude was extracted with EtOAc, dried with $MgSO_4$, concentrated under reduced pressure. The product was obtained without further purification.

General procedure 9: *Synthesis of vinyl ureas using vinyl isocyanate*

The desired amine was solubilised in dry CH_2Cl_2 (1M) under inert atmosphere and cooled to 0°C. Vinylisocyanate (1 eq.) was added very slowly and the reaction was stirred for 1h at 0°C. The white solid was filtered and solubilised in dry DMF (0.3M) under inert atmosphere. Methyliodide (3 eq.) was added to the solution and the reaction mixture was cooled to 0°C and stirred for 30min. Sodium hydride (2.1 eq., 60% in mineral oil) was added very slowly and the reaction was stirred 1h at the same temperature. The reaction mixture was diluted with Et_2O and quench very carefully with H_2O. The reaction mixture was washed with H_2O. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was filtered through silica (first using pentane then EtOAc) to remove the grease. The desired ureas were generally used without further purification. In some cases, chromatography on silica gel (PE/EtOAc: 9/1+1%NEt_3) was performed.

General procedure 10: *Rearrangement of non-substituted benzylureas*

The desired urea was solubilised in THF (0.1M) and the reaction mixture was cooled to -78°C. *s*-BuLi (2 eq.) was added slowly and the reaction was stirred at -78°C for 1h. The reaction was quenched by slow addition of MeOH. The reaction was warmed up to r.t. and diluted with EtOAc. The organic phase was washed with H_2O, dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash chromatography (PE/EtOAc : 6/4→ 1/1).

General procedure 11: *Rearrangement of substituted benzylureas*

The desired urea was solubilised in THF (0.1M) and DMPU (10/1 v/v. THF/DMPU). The reaction mixture was cooled to -78°C. *s*-BuLi (2 eq.) was added slowly and the reaction was stirred at -78°C for 1h. The reaction was quenched by slow addition of MeOH. The reaction was warmed up to r.t. and diluted with Et_2O. The organic phase was washed with H_2O, dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash chromatography.

General procedure 12: *One-pot sequence for the synthesis of amines*

Vinylisocyanate was added very slowly to a solution of the desired amine in CH_2Cl_2 (1M) at r.t. The reaction was stirred for 1h and then filtered to obtain the ureas as a white solid. This solid was solubilised in DMF (0.3M) and methyliodide was added (3 eq.). The reaction was cooled to 0°C and sodium hydride (2.1 eq., 60% in mineral oil) was added very slowly. After 1h at 0°C, the reaction was diluted with Et_2O and quenched very carefully with water. The reaction mixture was washed 3 times with H_2O and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was then solubilised in dry THF under inert atmosphere (0.1M) and DMPU (10% vol.). After cooling the reaction to -78°C, *s*-BuLi (2 eq.) was added very slowly. The reaction was stirred at this temperature for 1h and quenched slowly with MeOH. The reaction mixture was diluted with Et_2O and washed with H_2O. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure.

The crude mixture was finally solubilised in *n*-BuOH in the presence of K_2CO_3 (1:1 w:w). The reaction was refluxed for 1h. Once the reaction cooled, the mixture was washed with H_2O and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude was purified by silica gel chromatography.

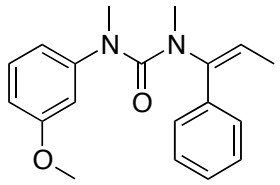
General procedure 13: *one-pot sequence for the synthesis of NH_2 amines*

The desired urea (1 eq.) was solubilised in dry THF (0.05M) and the reaction was cooled to −78°C. *s*-BuLi (2 eq.) was then added and the reaction was stirred for 1h at -78°C. The reaction was quenched with MeOH, washed with H_2O and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude urea was solubilised in CH_2Cl_2 (0.1M) in presence of a 10% aqueous solution of acetic acid (1/1 v/v. compared to CH_2Cl_2). The reaction was stirred for 1h at r.t. The crude mixture was extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was solubilised in EtOH (0.03M) and treated with 2M NaOH (1/1 v/v. compared to EtOH). The reaction was heated to 130°C under microwave irradiation for 2.5h. The reaction mixture was washed with brine and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The desired amine was obtained after purification by flash chromatography on silica gel.

3. Characterisation

3.1. Synthesis of vinyl ureas

1-(3-Methoxyphenyl)-1,3-dimethyl-3-[(*E*)-1-phenylprop-1-enyl]urea **(*E*)-242a**:



The urea was synthesised following the general procedure 1 starting from 2.00g (14.9mmol) of propiophenone. The desired product was obtained in 40% yield (1.85g) as a yellow oil.

R*f*: 0.2 (PE/EtOAc:8/2).

IR υ_{max} (film)/cm^{-1}: 2931, 2357, 1661, 1652 and 1599.

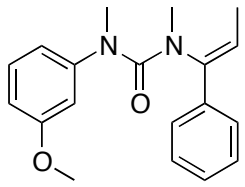
^{1}H NMR (400 MHz in $CDCl_3$): δ 7.24-7.32 (m, 3H, 3xAr*H*), 7.16 (t, 1H, *J*=8Hz, Ar*H*), 7.08-7.05 (m, 2H, 2xAr*H*), 6.63 (ddd, *J*=8.0, 2.0 and 0.8Hz, 1H, Ar*H*), 6.52 (ddd, *J*=8.0, 2.0 and 0.8Hz, 1H, Ar*H*), 6.44 (t, *J*=2.0Hz, 1H, Ar*H*), 5.33 (q, *J*=7.6Hz, 1H, C=C*H*-CH_3), 3.77 (s, 3H, O-C*H*$_3$), 3.14 (s, 3H, N-C*H*$_3$), 2.95 (s, 3H, N-C*H*$_3$) and 1.59 (d, *J*=7.6Hz, 3H, C=CH-C*H*$_3$).

^{13}C NMR (100 MHz in $CDCl_3$): δ 161.0 (C=O), 159.8 (C_{ar}-OCH_3), 146.6 (C_{ar}), 142.5 (*C*=CH), 136.7 (C_{ar}), 129.1 (CH_{ar}), 128.2 (2xCH_{ar}), 127.8 (2xCH_{ar}), 127.6 (CH_{ar}), 120.7 (C=*C*H), 117.2 (CH_{ar}), 110.6 (CH_{ar}), 109.8 (CH_{ar}), 55.3 (O-CH_3), 39.7 (N-CH_3), 38.4 (N-CH_3) and 14.4 (C=CH-*C*H_3).

HRMS (ES): *m/z* calcd for $C_{19}H_{22}N_2O_2Na$ 333.1573 found 333.1582 $(M+Na)^+$.

nOe: irridiation at 5.33 ppm (C*H*=C) enhanced peak at 3.14 ppm (N-C*H*$_3$) from 0.61%.

1-(3-Methoxyphenyl)-1,3-dimethyl-3-[(*Z*)-1-phenylprop-1-enyl]urea **(*Z*)-242a**:



Urea **(*E*)-242a** (100mg, 0.32mmol) was solubilised in CH_2Cl_2 (10mL) in the presence of silica (0.1g). The reaction mixture was stirred for 16h and filtered. The solvent was removed under reduce pressure. The desired compound was obtained in quantitative yield (100mg) as an oil.

R*f*: 0.2 (PE/EtOAc:8/2).

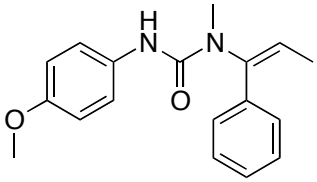
IR υ_{max} (film)/cm^{-1}: 1660 and 1594.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29-7.21 (m, 3H, 3xAr*H*), 7.10-7.05 (m, 3H, 3xAr*H*), 6.61 (ddd, *J*=8.3, 3.5 and 0.8Hz, 1H, Ar*H*), 6.41 (ddd, *J*=7.8, 2.0 and 0.8Hz, 1H, Ar*H*), 6.29 (t, *J*=2.3Hz, 1H, Ar*H*), 5.33 (q, *J*=7.1Hz, 1H, C=C*H*-CH_3), 3.72 (s, 3H, O-C*H*$_3$), 3.20 (s, 3H, N-C*H*$_3$), 2.95 (s, 3H, N-C*H*$_3$) and 1.52 (d, *J*=7.1Hz, 3H, C=CH-C*H*$_3$).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.0 (C=O), 159.6 (C_{ar}-OCH_3), 146.4 (C_{ar}), 142.7 (*C*=CH), 138.8 (C_{ar}), 129.1 (CH_{ar}), 128.1 (2xCH_{ar}), 127.4 (2xCH_{ar}), 125.0 (CH_{ar}), 120.3 (C=*C*H), 117.8 (CH_{ar}), 111.0 (CH_{ar}), 110.8 (CH_{ar}), 55.2 (O-CH_3), 39.4 (N-CH_3), 38.5 (N-CH_3) and 14.4 (C=CH-*C*H_3).

HRMS (ES): calcd for $C_{19}H_{23}N_2O_2$ 311.1754 found 311.1754 $(M+H)^+$.

3-(4-Methoxyphenyl)-1-methyl-1-[(*E*)-1-phenylprop-1-enyl]urea **(*E*)-244b**:



The urea was synthesised following the general procedure 2 starting from 1.00g (7.45mmol) of propiophenone. The desired compound was obtained in 40% (0.88g) as an oil.

R_f: 0.2 (PE/EtOAc:8/2).

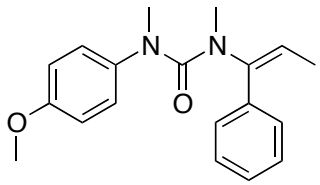
IR υ_{max} (film)/cm^{-1}: 3407, 3326, 2933, 2830, 1664, 1591 and 1508.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33-7.20 (m, 5H, 5xAr*H*), 7.12-7.09 (m, 2H, 2xAr*H*), 6.70-6.66 (m, 2H, 2xAr*H*), 6.47 (br. s, 1H, N*H*), 6.17 (q, *J*=6.9 Hz, 1H, C*H*=C), 3.63 (d, *J*=0.5 Hz, 3H, O-CH_3), 2.96 (s, 3H, N-CH_3) and 1.76 (d, *J*=6.9 Hz, 3H, CH_3-CH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.6 (O-CH_3), 154.7 (C=O), 140.8 (C_{ar}), 135.8 (C_{ar}), 128.9 (2xCH_{ar}), 128.44 (CH_{ar}), 125.4 (2xCH_{ar}), 124.4 (*C*H=C), 121.47 (2xCH_{ar}), 121.40 (2xCH_{ar}), 114.0 (*C*=CH), 55.4 (O-CH_3), 34.0 (N-CH_3) and 13.6 (*C*H_3-CH).

HRMS (ES): *m/z* calcd for $C_{18}H_{21}N_2O_2$ 297.1590 found 297.1598 $(M+H)^+$.

1-(4-methoxyphenyl)-1,3-dimethyl-3-[(*E*)-1-phenylprop-1-enyl]urea **(*E*)-242b**:



The urea was synthesised following the general procedure 1 starting from 2.00g (14.9mmol) of propiophenone. The desired product was obtained in 50% yield (2.00g) as a yellow oil.

R_f: 0.2 (PE/EtOAc:8/2).

IR υ_{max} (film)/cm^{-1}: 2931, 2356, 1661, 1652, 1645, 1634 and 1511.

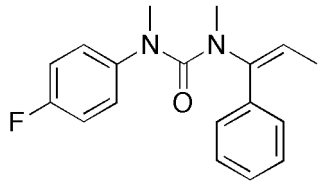
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22-7.30 (m, 3H, 3xAr*H*), 7.04 (d, *J*=6.0Hz, 2H, 2xAr*H*), 6.85 (d, *J*=7.4Hz, 2H, 2xAr*H*), 6.79 (d, *J*=7.6Hz, 2H, 2xAr*H*), 5.32 (q, *J*=5.8Hz, 1H, C=C*H*-CH_3), 3.79 (s, 3H, O-CH_3), 3.06 (s, 3H, N-CH_3), 2.99 (s, 3H, N-CH_3) and 1.60 (d, *J*=5.8Hz, 3H, C=CH-CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.2 (C=O), 156.8 (O-CH_3), 142.7(*C*=CH), 138.5 (C_{ar}), 136.4 (C_{ar}), 128.2 (2xCH_{ar}), 127.6 (2xCH_{ar}), 127.4 (CH_{ar}), 126.7 (2xCH_{ar}), 119.9 (C=*C*H), 113.8 (2xCH_{ar}), 55.3 (O-CH_3), 39.4 (N-CH_3), 39.1 (N-CH_3) and 14.2 (C=CH-*C*H_3).

HRMS (ES): *m/z* calcd for $C_{19}H_{22}N_2O_2Na$ 333.1573 found 333.1567 $(M+Na)^+$.

nOe: irridiation at 5.32 ppm (C*H*=C) enhanced peak at 3.06 ppm (N-CH_3) from 0.59%.

1-(4-Fluorophenyl)-1,3-dimethyl-3-[(*E*)-1-phenylprop-1-enyl]urea **(*E*)-242c**:



The urea was synthesised following the general procedure 1 starting from 2.00g (14.9mmol) of propiophenone. The desired product was obtained in 34% yield (1.50g) as an oil.

R_f: 0.2 (PE/EtOAc:8/2).

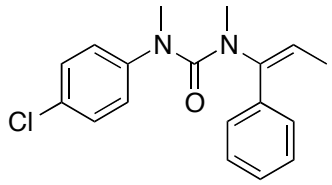
IR υ_{max} (film)/cm^{-1}: 3054, 2933, 1652 and 1505.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23-7.31 (m, 3H, 3xAr*H*), 7.05 (dd, *J*=6.4 and 1.2Hz, 2H, 2xAr*H*), 6.97 (t, *J*=8.0Hz, 2H, 2xAr*H*), 6.90-6.87 (m, 2H, 2xAr*H*), 5.32 (q, *J*=7.6Hz, 1H, C=C*H*-CH_3), 3.16 (s, 3H, N-CH_3), 2.97 (s, 3H, N-CH_3) and 1.62 (d, *J*=7.6Hz, 3H, C=CH-CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1 (C=O), 159.7 (d, J_F=242.3Hz, C-F), 142.6 (*C*=CH), 141.5 (d, J_F=2.8Hz, C_{ar}), 136.5 (C_{ar}), 128.0 (2xCH_{ar}), 127.8 (2xCH_{ar}), 127.6 (CH_{ar}), 126.6 (d, J_F=8.2Hz, 2xCH_{ar}), 120.6 (C=*C*H), 115.2 (d, J_F=22.4Hz, 2xCH_{ar}), 39.8 (N-CH_3), 38.8 (N-CH_3) and 14.3 (C=CH-*C*H_3).

HRMS (ES): *m/z* calcd for $C_{18}H_{19}N_2OFNa$ 321.1374 found 321.1371$(M+Na)^+$.

1-(4-Chlorophenyl)-1,3-dimethyl-3-[(*E*)-1-phenylprop-1-enyl]urea **(*E*)-242d**:



The urea was synthesised following the general procedure 1 starting from 2.00g (14.9mmol) of propiophenone. The desired product was obtained in 20% yield (0.94g) as a pale yellow oil.

R_f: 0.2 (PE/EtOAc:8/2).

IR υ_{max} (film)/cm^{-1}: 2930 and 1668.

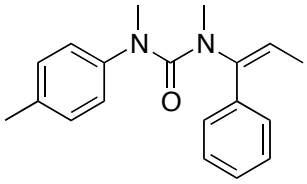
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22-7.30 (m, 3H, 3xAr*H*), 7.17 (d, *J*=6.8Hz, 2H, 2xAr*H*), 6.99 (d, *J*=5.6Hz, 2H, 2xAr*H*), 6.76 (d, *J*=6.8Hz, 2H, 2xAr*H*), 5.27 (q, *J*=6.4Hz, 1H, C=C*H*-CH_3), 3.17 (s, 3H, N-CH_3), 2.85 (s, 3H, N-CH_3) and 1.56 (d, *J*=6.4Hz, 3H, C=CH-CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.7 (C=O), 143.8 (*C*=CH), 143.5 (C_{ar}), 136.6 (C_{ar}-Cl), 129.4 (C_{ar}), 128.5 (2xCH_{ar}), 127.9 (2xCH_{ar}), 127.9 (2xCH_{ar}), 127.7 (CH_{ar}), 125.6 (2xCH_{ar}), 120.9 (C=*C*H), 40.1 (N-CH_3), 38.1 (N-CH_3) and 14.3 (C=CH-*C*H_3).

HRMS (ES): *m/z* calcd for $C_{18}H_{19}N_2OClNa$ 337.1078 found 337.1072 $(M+Na)^+$.

1,3-Dimethyl-1-[(*E*)-1-phenylprop-1-enyl]-3-(*p*-tolyl)urea **(*E*)-242e**:

The urea was synthesised following the general procedure 1 starting from 2.00g (14.9mmol) of propiophenone. The desired product was obtained in 40% yield (1.75g) as a colourless oil.



R_f: 0.2 (PE/EtOAc:8/2).

IR υ_{max} (film)/cm^{-1}: 2922, 1661 and 1514.

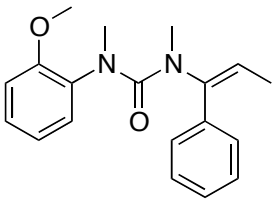
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15-7.30 (m, 3H, 3xAr*H*), 7.06-7-04 (m, 4H, 4xAr*H*), 6.81 (d, *J*=8.0Hz, 2H, 2xAr*H*), 5.30 (q, *J*=7.4Hz, 1H, C=C*H*-CH_3), 3.09 (s, 3H, N-CH_3), 2.97 (s, 3H, N-CH_3), 2.31 (s, 3H, Ar-CH_3) and 1.57 (d, *J*=7.4Hz, 3H, C=CH-CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.3 (C=O), 143.0 (*C*=CH), 136.7 (C_{ar}-CH_3) 134.3 (C_{ar}), 129.2 (2xCH_{ar}), 129.0 (C_{ar}), 128.3 (2xCH_{ar}), 128.2 (CH_{ar}), 127.7 (2xCH_{ar}), 125.1 (2xCH_{ar}), 120.2 (C=*C*H), 39.6 (N-CH_3), 38.8 (N-CH_3), 20.9 (C_{ar}-*C*H_3) and 14.3 (C=CH-*C*H_3).

HRMS (ES): *m/z* calcd for $C_{19}H_{22}N_2ONa$ 317.1624 found 317.1628 $(M+Na)^+$.

1-(2-Methoxyphenyl)-1,3-dimethyl-3-[(*E*)-1-phenylprop-1-enyl]urea **(*E*)-242f**:

The urea was synthesised following the general procedure 1 starting from 1.00g (7.45mmol) of propiophenone. The desired compound was obtained in 37% (0.85g) as a colourless oil.



R_f: 0.2 (PE/EtOAc:8/2).

IR υ_{max} (film)/cm^{-1}: 2935, 1655, 1596 and 1502.

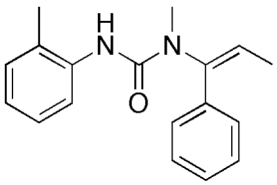
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26-6.83 (m, 9H, 9xAr*H*), 5.37 (q, *J*=7.5Hz, 1H, C=C*H*-CH_3), 3.81 (s, 3H, O-CH_3), 3.04 (s, 3H, N-CH_3), 2.87 (s, 3H, N-CH_3) and 1.58 (d, *J*=7.5Hz, 3H, C=CH-CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.8 (C=O), 154.7 (C_{ar}-OCH_3), 142.6 (*C*=CH), 136.2 (C_{ar}), 134.1 (C_{ar}), 128.8 (CH_{ar}), 128.7 (2xCH_{ar}), 127.6 (2xCH_{ar}), 127.4 (CH_{ar}), 127.2 (CH_{ar}), 120.5 (CH_{ar}), 119.1 (C=*C*H), 111.4 (CH_{ar}), 55.4 (O-CH_3), 38.4 (N-CH_3), 38.3 (N-CH_3) and 14.3 (C=CH-*C*H_3).

HRMS (ES): *m/z* calcd for $C_{19}H_{22}N_2O_2Na$ 333.1573 found 333.1581 $(M+Na)^+$.

1-Methyl-3-(*o*-tolyl)-1-[(E)-1-phenylprop-1-enyl]urea **(*E*)-244g**:

The urea was synthesised following the general procedure 2 starting from 1.00g (7.45mmol) of propiophenone. The desired compound was obtained in 42% (0.88g) as an oil.



R_f: 0.2 (PE/EtOAc:8/2).

IR υ_{max} (film)/cm^{-1}: 3434, 1681, 1651, 1588 and 1524.

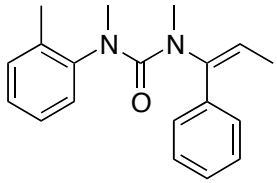
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.84 (d, *J*=8.1Hz, 1H, Ar*H*), 7.27-7.19 (m, 4H, 4xAr*H*), 7.06-703 (m, 1H, Ar*H*), 6.94 (d, *J*=6.9Hz, 1H, Ar*H*), 6.81-6.78 (m, 2H, 2xAr*H*), 5.92 (q, *J*=7.5Hz, 1H, C=C*H*-CH_3), 2.91 (s, 3H, N-CH_3), 1.87 (s, 3H, C-CH_3) and 1.82 (d, *J*=7.5Hz, 3H, CH-CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 154.7 (C=O), 141.4 (*C*=CH), 137.2 (C_{ar}-CH_3), 134.7 (C_{ar}), 130.0 (CH_{ar}), 128.7 (2xCH_{ar}), 128.7 (2xCH_{ar}), 128.6 (CH_{ar}), 126.8 (CH_{ar}), 126.6 (C_{ar}), 125.5 (C=*C*H), 123.0 (CH_{ar}), 120.9 (CH_{ar}), 35.3 (N-CH_3), 17.5 (C_{ar}-CH_3), and 14.5 (C=CH-*C*H_3).

HRMS (ES): *m/z* calcd for $C_{18}H_{20}N_2ONa$ 303.1468 found 303.1465$(M+Na)^+$.

1,3-Dimethyl-1-(*o*-tolyl)-3-[(*E*)-1-phenylprop-1-enyl]urea **(*E*)-242g**:

The urea was synthesised following the general procedure 1 starting from 1.00g (7.45mmol) of propiophenone. The desired compound was obtained in 39% yield (0.85g) as an oil.



R_f: 0.2 (PE/EtOAc:8/2).

IR υ_{max} (film)/cm^{-1}: 2926, 1658 and 1600.

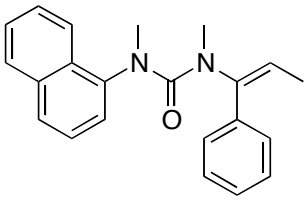
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.26-7.16 (m, 4H, 4xAr*H*), 7.11-7.05 (m, 2H, 2xAr*H*), 6.90-6.84 (m, 3H, 3xAr*H*), 5.34 (q, *J*=7.2Hz, 1H, C=C*H*-CH_3), 3.07 (s, 3H, N-CH_3), 2.88 (s, 3H, N-CH_3), 2.15 (s, 3H, Ar-CH_3) and 1.60 (d, 3H, *J*=7.2Hz, C=CH-CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.9 (C=O), 144.2 (C_{ar}), 143.1 (*C*=CH), 136.1 (C_{ar}-CH_3), 135.3 (C_{ar}), 131.0 (CH_{ar}), 128.6 (2xCH_{ar}), 128.4 (CH_{ar}), 127.8 (2xCH_{ar}), 127.5 (CH_{ar}), 126.6 (CH_{ar}), 126.5 (CH_{ar}) 119.6 (C=*C*H), 38.8 (N-CH_3), 38.7 (N-CH_3), 17.7 (C_{ar}-CH_3) and 14.4 (C=CH-*C*H_3).

HRMS (ES): *m/z* calcd for $C_{19}H_{22}N_2ONa$ 317.1624 found 317.1630 $(M+Na)^+$.

1,3-Dimethyl-1-(1-naphthyl)-3-[(*E*)-1-phenylprop-1-enyl]urea **(*E*)-242h**:

The urea was synthesised following the general procedure 1 starting from 1.00g (7.45mmol) of propiophenone. The desired compound was obtained in 35% (0.86g) as an orange oil.



R_f: 0.2 (PE/EtOAc:8/2).

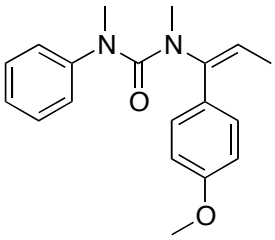
IR υ_{max} (film)/cm^{-1}: 1651 and 1595.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85-7.73 (m, 2H, 2xAr*H*), 7.64 (d, *J*=8.4Hz, 1H, Ar*H*), 7.49-7.46 (m, 2H, 2xAr*H*), 7.31 (dd, *J*=8.0 and 7.6Hz, 1H, Ar*H*), 7.18-7.08 (m, 4H, 4xAr*H*), 6.75-6.70 (m, 2H, Ar*H*), 5.15 (q, *J*=7.6Hz, 1H, C=C*H*-CH_3), 3.27 (s, 3H, N-CH_3), 2.87 (s, 3H, N-CH_3) and 1.34 (d, J=7.6Hz, 3H, C=CH-CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.2 (C=O), 142.2 (C_{ar}), 142.0 (*C*=CH), 135.6 (C_{ar}), 134.6 (C_{ar}), 130.2(C_{ar}), 128.5 (CH_{ar}), 128.4 (2xCH_{ar}), 127.6 (CH_{ar}), 127.3 (2xCH_{ar}), 126.8 (CH_{ar}), 126.4 (CH_{ar}), 126.0 (CH_{ar}), 125.4 (CH_{ar}), 125.1 (CH_{ar}), 123.0 (CH_{ar}), 121.2 (C=*C*H), 40.1 (N-CH_3), 39.0 (N-CH_3) and 14.3 (C=CH-*C*H_3).

HRMS (ES) m/z calcd for $C_{22}H_{23}N_2O$ 331.1805 found 331.1812 $(M+H)^+$.

1-[(*E*)-1-(4-Methoxyphenyl)prop-1-enyl]-1,3-dimethyl-3-phenyl-urea **(*E*)-242i**:



The urea has been synthesised following the general procedure 1 starting from 2.00g (12.2mmol) of *p*-methoxypropiophenone. The desired product was obtained in 55% yield (2.10g) as a yellow oil.

R_f: 0.3 (PE/EtOAc:7/3).

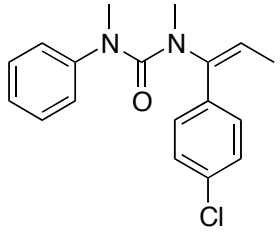
IR υ_{max} (film)/cm^{-1}: 2935, 1661, 1652,1645, 1634, 1596, 1584 and 1511.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-6.77 (m, 9H, 9xAr*H*), 5.19 (q, *J*=7.6Hz 1H, C=C*H*-CH_3), 3,80 (s, 3H, O-CH_3), 3.10 (s, 3H, N-CH_3), 2.98 (s, 3H, N-CH_3) and 1.52 (d, *J*=7.6Hz 3H, C=CH-CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.1 (C=O), 158.8 (C_{ar}-OCH_3), 145.5 (C_{ar}), 142.2 (*C*=CH), 129.5 (2xCH_{ar}), 129.1 (C_{ar}) 128.5 (2xCH_{ar}), 125.0 (2xCH_{ar}), 124.5 (CH_{ar}), 119.3 (C=*C*H), 113.1 (2xCH_{ar}), 55.2 (O-CH_3), 39.6 (N-CH_3), 38.6 (N-CH_3) and 14.2 (C=CH-*C*H_3).

HRMS (ES): calcd for $C_{19}H_{23}N_2O_2$ 311.1754 found 311.1747 $(M+H)^+$.

1-[(*E*)-1-(4-Chlorophenyl)prop-1-enyl]-1,3-dimethyl-3-phenyl-urea **(*E*)-242j**:



The urea was synthesised following the general procedure 1 starting from 2.00g (11.9mmol) of *p*-chloropropiophenone. The desired product was obtained in 53% yield (2.00g) as a white solid. The urea is then recrystalised in petroleum ether.

R_f: 0.3 (PE/EtOAc:7/3).

m.p.: 59-61°C (PE).

IR υ_{max} (film)/cm^{-1}: 2930, 1662 and 1596.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 4H, 4xAr*H*), 7.10 (tt, *J*= 7.2 and 1.2Hz, 1H, Ar*H*), 6.97-6.91 (m, 4H, 4xAr*H*), 5.31 (q, *J*=7.4Hz, 1H, C=C*H*-CH_3), 3.13 (s, 3H, N-CH_3), 3.00 (s, 3H, N-CH_3) and 1.54 (d, J=7.4Hz, 3H, C=CH-CH_3).

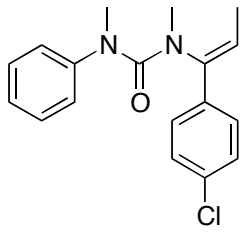
^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.9 (C=O), 145.3 (C_{ar}), 141.1 (C=*C*H), 135.1 (C_{ar}), 133.1 (C_{ar}-Cl), 129.5 (2xCH_{ar}), 128.6 (2xCH_{ar}), 128.0 (2xCH_{ar}), 125.0 (2xCH_{ar}), 124.7 (CH_{ar}), 121.1 (C=*C*H), 39.6 (N-CH_3), 38.7 (N-CH_3) and 14.2 (C=CH-*C*H_3).

HRMS (ES): calcd for $C_{18}H_{19}N_2OClNa$ 337.1078 found 337.1080 $(M+Na)^+$.

Elem. anal.: calcd: C 68.67, H 6.08, N 8.90 found: C 68.79, H 6.07, N 8.71.

nOe: irridiation at 5.31 ppm (C*H*=C) enhanced peak at 3.13 ppm (N-CH_3) from 0.59%.

1-[(*Z*)-1-(4-Chlorophenyl)prop-1-enyl]-1,3-dimethyl-3-phenyl-urea **(*Z*)-242j**:



The urea **(*E*)-242j** (0.500g, 1.6mmol, 1eq) was solubilised in dry THF (30mL). The reaction mixture was cooled to -78 °C. A freshly prepared solution of LDA (2eq) was added drowpwise. The reaction was stirred for 1 hour and then quenched slowly with MeOH. The reaction mixture was washed with NH_4Cl and extracted with EtOAc, dried with $MgSO_4$, concentrated under reduce pressure and purified by flash chromatography (SiO_2, PE/EtOAc: 9/1+1% Et_3N). The desired product is obtained in 98% yield (0.49g) as a pale yellow solid.

R_f: 0.3 (PE/EtOAc:7/3).

m.p.: 83-84°C (PE).

IR υ_{max} (film)/cm^{-1}: 2908, 1661, 1638 and 1596.

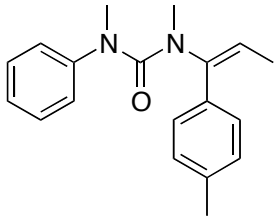
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.18 (m, 4H, 4xAr*H*), 7.10-7.07 (m, 1H, Ar*H*), 6.99-6.96 (m, 2H, 2xAr*H*), 6.82-6.80 (m, 2H, 2xAr*H*), 5.26 (q, *J*= 7.2Hz, 1H, C=C*H*-CH_3), 3.19 (s, 3H, N-CH_3), 3.00 (s, 3H, N-CH_3) and 1.50 (d, *J*=7.2Hz, 3H, C=CH-CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.8 (C=O), 145.0 (C_{ar}), 141.8 (C=*C*H), 137.3 (C_{ar}), 132.9 (C_{ar}-Cl), 128.5 (2xCH_{ar}), 128.2 (2xCH_{ar}), 126.2 (2xCH_{ar}), 125.2 (2xCH_{ar}), 125.1 (CH_{ar}), 120.7 (C=*C*H), 39.5 (N-CH_3), 38.4 (N-CH_3) and 14.5 (C=CH-*C*H_3).

HRMS (ES): calcd for $C_{18}H_{19}N_2OClNa$ 337.1078 found 337.1083 $(M+Na)^+$.

nOe: irridiation at 1.50 ppm (CH_3-CH=C) enhanced peak at 3.19 ppm (N-CH_3) from 0.82%.

1,3-Dimethyl-1-phenyl-3-[(*E*)-1-(*p*-tolyl)prop-1-enyl]urea **(*E*)-242k**:



The urea was synthesised following the general procedure 1 starting from 2.00g (6.75mmol) of *p*-methylpropiophenone. The desired product was obtained in 45% yield (1.80g) as a colourless oil.

R_f: 0.3 (PE/EtOAc:7/3).

IR υ_{max} (film)/cm^{-1}: 2934, 1661 and 1597.

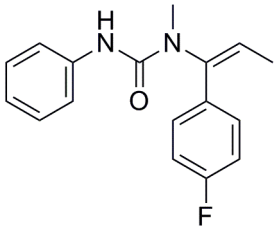
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-6.90 (m, 9H, 9xAr*H*), 5.23 (q, *J*=7.2Hz, 1H, C=C*H*-CH_3), 3.10 (s, 3H, N-C*H*$_3$), 2.97 (s, 3H, N-C*H*$_3$), 2.33 (s, 3H, Ar-C*H*$_3$) and 1.53 (d, *J*=7.2Hz, 3H, C=CH-C*H*$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.1 (C=O), 145.6 (C_{ar}), 142.5 (*C*=CH), 137.3 (C_{ar}-CH_3), 133.8 (C_{ar}), 128.5 (2xCH_{ar}), 128.4 (2xCH_{ar}), 128.1 (2xCH_{ar}), 125.0 (2xCH_{ar}), 124.4 (CH_{ar}), 119.9 (C=*C*H), 39.6 (N-CH_3), 38.6 (N-CH_3), 21.2 (C_{ar}-*C*H_3) and 14.2 (C=CH-*C*H_3).

HRMS (ES): calcd for $C_{19}H_{22}N_2ONa$ 317.1624 found 317.1633 $(M+Na)^+$.

nOe: irridiation at 1.53 ppm (C*H*$_3$-CH=C) enhanced peak at 3.10 ppm (N-C*H*$_3$) from 0.91%.

1-[(*E*)-1-(4-Fluorophenyl)prop-1-enyl]-1-methyl-3-phenyl-urea **(*E*)-244l**:



The urea was synthesised following the general procedure starting from 1.00g (6.57mmol) of *p*-fluoropropiophenone. The desired product was obtained in 50% yield (0.94g) as a colourless oil.

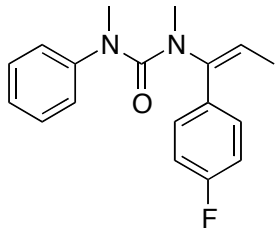
IR υ_{max} (film)/cm^{-1}: 3424, 1667, 1593, 1523, and 1508.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.16 (m, 6H, 6xAr*H*), 7.06-6.88 (m, 4H, 3xAr*H* and N*H*), 5.92 (q, *J*=7.5Hz, 1H, C=C*H*-CH_3), 2.94 (s, 3H, N-C*H*$_3$) and 1.86 (d, *J*=7.5Hz, 3H, C=CH-C*H*$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.6 (d, J_F=247.7Hz, C_{ar}-F), 154.6 (C=O), 140.3 (*C*=CH), 138.9 (C_{ar}), 130.8 (d, J_F=3.7Hz, C_{ar}), 130.5 (d, J_F=8.3Hz, 2xCH_{ar}), 128.9 (2xCH_{ar}), 125.5 (C=*C*H), 122.9 (CH_{ar}), 119.2 (2xCH_{ar}), 115.7 (d, J_F=21.5Hz, 2xCH_{ar}), 35.2 (N-CH_3), 15.6 (C=CH-*C*H_3);

HRMS (ES): calcd for $C_{17}H_{18}N_2OF$ 285.1398 found 285.1396 $(M+H)^+$.

1-[(*E*)-1-(4-Fluorophenyl)prop-1-enyl]-1,3-dimethyl-3-phenyl-urea **(*E*)-242l**:



The urea was synthesised following the general procedure 1 starting from 1.00g (6.57mmol) of *p*-fluoropropiophenone. The desired product was obtained in 46% yield (0.90g) as a colourless oil.

R_f: 0.3 (PE/EtOAc:7/3).

IR υ_{max} (film)/cm^{-1}: 3040, 2935 and 1661

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.22 (m, 2H, 2xAr*H*), 7.08-7.05 (m, 1H, Ar*H*), 6,96-6.94 (m, 4H, 4xAr*H*), 6.90-6.88 (m, 2H, 2xAr*H*), 5.25 (q, *J*=7.4Hz, 1H, C=C*H*-CH_3), 3.09 (s, 3H, N-CH_3), 2.96 (s, 3H, N-CH_3) and 1.50 (d, *J*=7.4Hz, 3H, C=CH-CH_3);

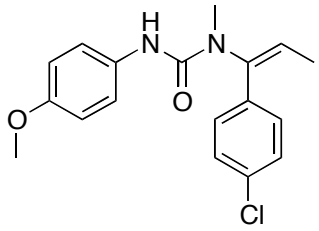
^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.8 (d, J_F=245.6Hz, C_{ar}-F), 160.9 (C=O), 145.2 (C_{ar}), 141.5 (*C*=CH), 132.6 (d, J_F=3.6Hz, C_{ar}) 129.9 (d, J_F=7.6Hz, 2xCH_{ar}), 128.5 (2xCH_{ar}), 124.9 (2xCH_{ar}), 124.6 (CH_{ar}), 120.3 (C=*C*H), 114.6 (d, J_F=21.1Hz, 2xCH_{ar}), 39.5 (N-CH_3), 38.5 (N-CH_3) and 14.1 (C=CH-*C*H_3).

HRMS (ES): calcd for $C_{18}H_{19}N_2OFNa$ 321.1374 found 321.1379 $(M+Na)^+$.

Elem. anal.: calcd: C 72.46, H 6.42, N 9.39 found: C 72.42, H 6.28, N 9.34.

nOe: irridiation at 5.92 ppm (C*H*=C) enhanced peak at 3.09 ppm (N-CH_3) from 0.53%.

1-[(*E*)-1-(4-Chlorophenyl)prop-1-enyl]-3-(4-methoxyphenyl)-1-methyl-urea **(*E*)-244m**:



The urea was synthesised following the general procedure 2 starting from 2.00g (11.9mmol) of *p*-chloropropiophenone. The desired product was obtained in 40% yield (1.6g) as a white solid after recrystallisation in petroleum ether.

R_f: 0.3 (PE/EtOAc:7/3).

m.p.: 120-122°C (PE).

IR υ_{max} (powder)/cm^{-1}: 3317, 1653, 1592 and 1521.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 4H, 4xAr*H*), 7.24-7.20 (m, 2H, 2xAr*H*), 6.82-6.79 (m, 3H, 2xAr*H* + NH), 6.01 (q, *J*=7.4Hz, 1H, C=C*H*-CH_3), 3.76 (s, 3H, O-CH_3), 2.99 (s, 3H, N-CH_3) and 1.93 (d, *J*=7.4Hz, 3H, C=CH-CH_3).

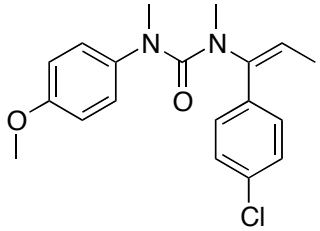
^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.6 (C_{ar}-OCH_3), 145.9 (C=O), 140.1 (*C*=CH), 134.3 (C_{ar}), 133.3 (C_{ar}-Cl), 131.8, 129.9 (2xCH_{ar}), 128.8 (2xCH_{ar}), 126.0 (C=*C*H), 121.5 (2xCH_{ar}), 114.0 (2xCH_{ar}), 55.1 (O-CH_3), 35.2 (N-CH_3) and 14.6 (C=CH-*C*H_3).

HMRS (ES): calcd for $C_{18}H_{20}ClN_2O_2$ 331.1135 found 331.1139 $(M+H)^+$.

Elem. anal.: calcd: C 65.35, H 5.79, N 8.47 found: C 65.33, H 5.47, N 8.46.

nOe: irradiation at 2.99 ppm (N-CH_3) enhanced peak at 6.01 ppm (CH=CH_3) from 0.83%.

1-[(*E*)-1-(4-Chlorophenyl)prop-1-enyl]-3-(4-methoxyphenyl)-1,3-dimethyl-urea **(*E*)-242m**



The urea was synthesised following the general procedure 1 starting from 2.00g (11.9mmol) of *p*-chloropropiophenone. The desired product was obtained in 38% yield (1.55g) as a colourless oil.

R_f: 0.3 (PE/EtOAc:7/3).

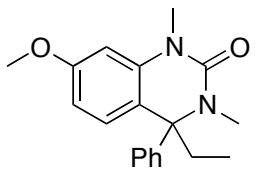
IR υ_{max} (film)/cm^{-1}: 2932, 1655 and 1511.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (dt, *J*=8.5 and 2.1Hz, 2H, 2xAr*H*), 6.93 (dt, *J*=8.5 and 2.1Hz, 2H, 2xAr*H*), 6.84-6.80 (m, 4H, 4xAr*H*), 5.31 (q, *J*=7.5Hz, 1H, C=C*H*-CH_3), 3.77 (s, 3H, O-C*H*$_3$), 3.01 (s, 3H, N-C*H*$_3$), 2.98 (s, 3H, N-C*H*$_3$) and 1.56 (d, 3H, *J*=7.5Hz, C=CH-C*H*$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.3 (C=O), 157.0 (C_{ar}-OCH_3), 141.9 (*C*=CH), 138.5 (C_{ar}), 135.0 (C_{ar}), 133.2 (C_{ar}-Cl), 129.7 (2xCH_{ar}), 127.9 (2xCH_{ar}), 126.9 (2xCH_{ar}), 120.6 (C=*C*H), 114.0 (2xCH_{ar}), 55.5 (O-CH_3), 39.4 (N-CH_3), 39.3 (N-CH_3) and 14.3 (C=CH-*C*H_3).

HRMS (ES): calcd for $C_{19}H_{22}N_2O_2Cl$ 345.1365 found 345.1365 $(M+H)^+$.

7-Methoxy-1,3-dimethyl-4-ethyl-4-phenyl-quinazolin-2-one **247**:



Urea **(*E*)-242a** (115mg, 0.37mmol) was solubilised in CH_2Cl_2 (7mL). Triflic acid was added slowly and the reaction was stirred at room temperature for 1h. The reaction was diluted with water. The crude was extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated under vacuum. The crude was purified by silica gel chromatography (PE/EtOAc:7/3) and the product was isolated in 87% yield (0.1g) as an oil.

R_f: 0.3 (PE/EtOAc:7/3).

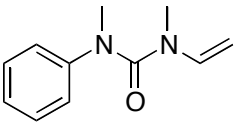
IR *υ*max (film)/cm^{-1}: 2966, 2936, 1651 and 1615.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.17 (m, 5H, 5xAr*H*), 6.49-6.91 (m, 3H, 3xAr*H*), 3.75 (s, 3H, O-C*H*$_3$), 3.39 (s, 3H, N-C*H*$_3$), 2.64 (s, 3H, N-C*H*$_3$), 2.35 (m, 1H, C-C*H*$_2$-CH_3), 2.15 (m, 1H, C-C*H*$_2$-CH_3) and 0.82 (t, *J*=7.2Hz, 3H, C-CH_2-C*H*$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 159.2 (C=O), 154.1 (C_{ar}-OCH_3), 146.7 (C_{ar}), 139.4 (C_{ar}), 128.8 (CH_{ar}), 128.4 (2xCH_{ar}), 127.3 (2xCH_{ar}), 127.1 (CH_{ar}), 118.3 (C_{ar}), 106.1 (CH_{ar}), 98.7 (CH_{ar}), 67.7 (C), 55.2 (O-CH_3), 31.5 (*C*H_2-CH_3), 30.8 (N-CH_3), 30.1 (N-CH_3) and 7.6 (CH_2-*C*H_3).

HRMS (ES): calcd for $C_{19}H_{22}N_2O_2Na$ 311.1755 found 311.1753 $(M+Na)^+$.

1,3-Dimethyl-1-phenyl-3-vinyl-urea **249**:



N-Methylaniline (200mg, 1.87mmol) was solubilised in dry THF (0.4M). Vinyl isocyanate (1 eq.) was added really slowly and stirred at room temperature for 24 hours. The solvent was evaporated under reduce pressure. The crude solid was dissolved in THF and cooled to 0°C. Methyliodide (2 eq.) was added to the solution and the reaction was stirred for 15 minutes. Sodium hydride (1 eq., 60% in mineral oil) was then added very slowly and the reaction was stirred for a further hour at 0°C. The reaction mixture was then diluted with Et_2O and vey carefully quenched with H_2O. The mixture was extracted with Et_2O and washed with H_2O. The organic phase was dried ($MgSO_4$) and the solvent was evaporated under reduce pressure. The crude mixture was purified by filtration on silica gel (to remove the oil). The desired urea was obtained in 70% yield (247mg) as a pale yellow oil.

R_f: 0.3 (PE/EtOAc:8/2)**.**

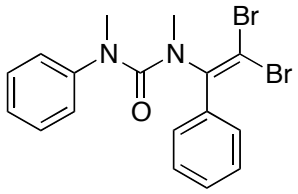
IR υ_{max} (film)/cm^{-1}: 3443, 3378, 2919, 1661, 1652 and 1596.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 2H, 2xAr*H*), 7.13 (tt, *J*=5.7 and 1.2 Hz, 1H, Ar*H*), 7.05-7.02 (m, 2H, 2xAr*H*), 6.92 (dd, *J*=15.8 and 9.2Hz, 1H, C*H*=CH_2), 4.06 (dd, *J*=15.8 and 1.2Hz, 1H, CH=CH_{cis}H), 4.01 (dd, *J*=9.2 and 1.2Hz, 1H, C=CH_{trans}H), 3.28 (s, 3H, N-CH_3) and 2.74 (s, 3H, N-CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) : δ 159.5 (C=O), 145.9 (C_{ar}), 135.8 (*C*H=CH_2), 129.6 (2xCH_{ar}), 125.0 (CH_{ar}), 124.2 (2xCH_{ar}), 89.8 (CH=*C*H_2), 39.7 (N-CH_3) and 32.6 (N-CH_3).

HRMS (ES): calcd for $C_{11}H_{14}N_2ONa$ 213.0997 found 213.0998 $(M+Na)^+$.

1-(2,2-Dibromo-1-phenyl-vinyl)-1,3-dimethyl-3-phenyl-urea **250**:



Urea **229** (180mg, 0.67mmol) was treated with NBS (1.8 eq.) in CH_2Cl_2 (18mL). The reaction was stirred overnight and the quenched with NEt_3 (4 eq.). The reaction mixture was washed with $NaHCO_3$ (sat.), brine and water. The solvent was removed under reduce pressure and the crude was purified by flash chromatography (PE/EtOAc:8/2). The desired compound was obtained in 30% yield (86mg) as a yellow oil.

R_f: 0.4 (CH_2Cl_2).

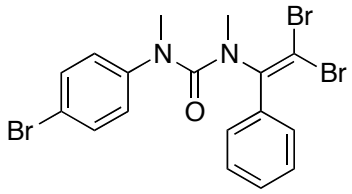
IR υ_{max} (film)/cm^{-1}: 1650 and 1594.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.15 (m, 8H, 8xAr*H*), 6.93 (m, 2H, 2xAr*H*), 3.18 (s, 3H, N-C*H*$_3$) and 3.00 (s, 3H, N-C*H*$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.5 (C=O), 145.6 (C_{ar}), 144.3 (*C*=CBr_2), 136.2 (C_{ar}), 129.1 (CH_{ar}), 129.1 (2xCH_{ar}), 128.9 (2xCH_{ar}), 127.9 (2xCH_{ar}), 125.7 (CH_{ar}), 125.4 (2xCH_{ar}), 89.4 (C=*C*Br_2), 39.5 (N-CH_3) and 38.2 (N-CH_3).

HRMS (ES): calcd for $C_{17}H_{17}Br_2N_2O$ 422.9702 found 422.9698 $(M+H)^+$.

1-(4-Bromophenyl)-3-(2,2-dibromo-1-phenyl-vinyl)-1,3-dimethyl-urea **251**:



The urea **229** (50.0mg, 0.19mmol) was treated with NBS (3 eq.) in CH_2Cl_2 (5mL). The reaction was stirred overnight and the quenches with NEt_3 (4 eq.). The reaction mixture was washed with $NaHCO_3$ (sat.), brine and water. The solvent was removed under reduce pressure and the crude was purified by flash chromatography (PE/EtOAc:8/2). The desired compound was obtained in 20% yield (20mg) as a yellow oil.

R_f: 0.4 (CH_2Cl_2).

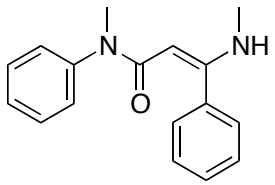
IR υ_{max} (film)/cm^{-1}: 1655.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.22 (m, 7H, 7xAr*H*), 6.77-6.74 (m, 2H, 2xAr*H*), 3.23 (s, 3H, N-C*H*$_3$) and 2.95 (s, 3H, N-C*H*$_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.3 (C=O), 145.4 (C_{ar}), 143.3 (*C*=CBr_2), 136.2 (C_{ar}), 132.0 (2xCH_{ar}), 129.3 (CH_{ar}), 128.7 (2xCH_{ar}), 128.1 (2xCH_{ar}), 126.5 (2xCH_{ar}), 118.6 (C_{ar}-Br), 89.9 (C=*C*Br_2), 39.1 (N-CH_3) and 38.4 (N-CH_3).

HRMS (ES): calcd for $C_{17}H_{16}Br_3N_2O$ 500.8807 found 500.8807 $(M+H)^+$.

(*E*)-*N*-methyl-3-methylamino-*N*,3-diphenyl-prop-2-enamide **252**:



Urea **250** (50.0mg, 0.12mmol) was solubilised in dry toluene (0.02M) and the reaction mixture was cooled to -20°C. *n*-BuLi (3.5 eq.) was then added slowly and the reaction was stirred at -20°C for 2 hours. The reaction was quenched with MeOH and the crude was washed with H_2O and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated under reduce pressure. The crude mixture was purified by flash chromatography on silica gel (PE/EtOAc:7/3) and the desired product was obtained in 48% yield as an oil (6:4 mixture of isomers).

R_f: 0.1 (PE/EtOAc: 7/3).

IR υ_{max} (film)/cm^{-1}: 3430, 2931, 1650, 1611 and 1573.

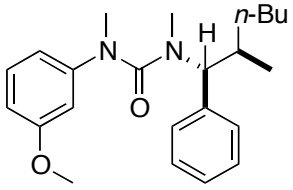
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (br s, 1H, NH), 7.40-7.38 (m, 1H, Ar*H* (major isomer)), 7.30-714 (m, 18H Ar*H* (8H from major isomer and 10H from minor isomer), 7.07-7.04 (m, 1H, Ar*H* (major isomer)), 4.34 (s, 1H, C=C*H*-C (major isomer)), 4.31 ((s, 1H, C=C*H*-C (minor isomer)), 3.25 (s, 3H, N-CH_3) (major isomer)), 3.22 (s, 3H, N-CH_3) (minor isomer)), 2.66 (d, *J*=5.2Hz, 3H, NH-CH_3 (major isomer)) and 2.66 (d, *J*=5.2Hz, 3H, NH-CH_3 (minor isomer))

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5 (C=O, major isomer), 170.3 (C=O, minor isomer), 163.7 (*C*=CH, minor isomer), 163.2 (*C*=CH, major isomer), 145.0 (C_{ar}, major isomer), 144.1 (C_{ar}, minor isomer), 136.7 (C_{ar}, major isomer), 136.5 (C_{ar}, minor isomer), 132.3 (CH_{ar}, both isomer), 129.2 (2xCH_{ar}, major isomer), 129.1 (2xCH_{ar}, minor isomer), 128.8 (2xCH_{ar}, minor isomer), 128.6 (CH_{ar}, minor isomer)**,** 128.2 (2xCH_{ar}, minor isomer), 128.1 (2xCH_{ar}, major isomer), 127.9 (2xCH_{ar}, major isomer), 127.8 (2xCH_{ar}, minor isomer), 127.4 (2xCH_{ar}, major isomer), 126.5 (CH_{ar}, major isomer), 86.1 (C=*C*H, major isomer), 85.6 (C=*C*H, minor isomer), 36.6 (N-CH_3, major isomer), 36.5 (N-CH_3, minor isomer) and 31.2 (NH-CH_3 both isomers).

HRMS (ES): calcd for $C_{17}H_{19}N_2O$ 267.1492 found 267.1497 $(M+H)^+$.

3.2. Tandem carbolithiation-aryl migration

1-(3-Methoxyphenyl)-1,3-dimethyl-3-[(1*R**,2*R**)-2-methyl-1-phenyl-hexyl]urea **253a**:



The compound was synthesised following the general procedure 3 in Et_2O for 1.5h starting from 78mg (0.25mmol) of urea. The desired product was obtained in 85% yield (70mg) as a yellow oil.

R_f: 0.5 (PE/EtOAc:8/2).

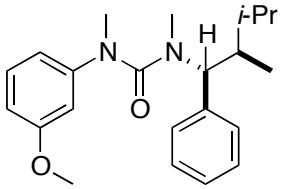
IR υ_{max} (film)/cm^{-1}: 2928, 1644 and 1597.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.30 (m, 4H, 4xAr*H*), 7.25-7.22 (m, 1H, Ar*H*), 7.08 (t, *J*=8.0Hz, 1H, Ar*H*), 6.59 (dd, *J*=8.5Hz and 2.5Hz, 1H, Ar*H*), 6.49 (dd, *J*=8.0 and 2.0Hz, 1H, Ar*H*), 6.41 (t, *J*=2.0Hz, 1H, Ar*H*), 5.14 (d, *J*=11.5Hz, 1H, C*H*-N), 3.56 (s, 3H, O-CH_3), 3.17 (s, 3H, N-CH_3), 2.36 (s, 3H, N-CH_3), 2.12 (m, 1H, CH_3-CH-CH_2), 1.36 (m, 3H, CH-CH_2-CH_2), 1.19 (m, 3H, C*H*-$(CH_2)_2$-CH_2-CH_3), 0.93 (t, *J*=7.0Hz, 3H, CH-CH_3) and 0.75 (d, *J*=7.0Hz, 3H, CH_2-CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4 (C=O), 162.0 (C_{ar}-OCH_3), 148.2 (C_{ar}), 139.2 (C_{ar}), 129.8(CH_{ar}), 128.7 (2xCH_{ar}), 128.3 (2xCH_{ar}), 127.2 (CH_{ar}), 116.3 (CH_{ar}), 110.0 (CH_{ar}), 109.5 (CH_{ar}), 64.4 (CH-N), 55.1 (O-CH_3), 40.3 (N-CH_3), 32.5 (*C*H-CH_3), 32.2 (*C*H_2-CH), 30.7 (N-CH_3), 29.3 (*C*H_2-CH_2-CH_3), 23.0 (*C*H_2-CH_3), 17.1 (*C*H_3-CH) and 14.2 (*C*H_3-CH_2).

HRMS (ES): *m/z* calcd for $C_{23}H_{33}N_2O_2$ 369.2537 found 369.2547 $(M+H)^+$.

1-[(1*R**,2*R**)-2,3-Dimethyl-1-phenyl-butyl]-3-(3-methoxyphenyl)-1,3-dimethyl-urea **253b**



The compound was synthesised following the general procedure 3 in toluene for 1.5h starting from 80mg (0.26mmol) of urea. The desired product was obtained in 83% yield (76mg) as a yellow oil.

R_f: 0.5 (PE/EtOAc:8/2).

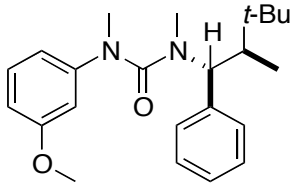
IR υ_{max} (film)/cm^{-1}: 2959, 1645 and 1597.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, *J*=7.5Hz, 2H, 2xAr*H*), 7.31 (t, *J*=7.5Hz, 2H, 2xAr*H*), 7.27 (d, *J*=7.0Hz, 1H, Ar*H*), 7.08 (t, *J*=8.Hz, 1H, Ar*H*), 6.60 (dd, *J*=8.0 and 2.5Hz, 1H, Ar*H*), 6.46 (d, *J*=7.5 Hz, 1H, Ar*H*), 6.40 (t, *J*=2.5Hz, 1H, Ar*H*), 5.31 (d, *J*=11.5Hz, 1H, C*H*-N), 3.58 (s, 3H, O-CH_3), 3.15 (s, 3H, N-CH_3), 2.34 (s, 3H, N-CH_3), 2.14 (m, 1H, CH-C*H*-CH_3), 1.80 (dsept, *J*=2.0 and 7.0Hz, 1H, C*H*-$(CH_3)_2$), 0.97 (d, *J*=6,5Hz, 6H, $(CH_3)_2$-CH) and 0.61 (d, *J*=7.0Hz, 3H, CH_3-CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.8 (C=O), 160.4 (C_{ar}-OCH_3), 148.3 (C_{ar}), 139.2 (C_{ar}), 129.9 (CH_{ar}), 128.8 (2xCH_{ar}), 128.2 (2xCH_{ar}), 127.2 (CH_{ar}), 116.3 (CH_{ar}), 110.1 (CH_{ar}), 109.4 (CH_{ar}), 61.9 (CH-N), 55.1 (O-CH_3), 40.4 (N-CH_3), 37.0 (*C*H-CH_3), 30.6 (N-CH_3), 26.7 (*C*H-$(CH_3)_2$), 21.9 (CH-(*C*H_3)$_2$), 15.2 (CH-(*C*H_3)$_2$) and 10.5 (*C*H_3-CH).

HRMS (ES): *m/z* calcd for $C_{22}H_{30}N_2O_2Na$ 377.2199 found 377.2207 $(M+Na)^+$.

1-(3-Methoxyphenyl)-1,3-dimethyl-3-[(1*R**,2*R**)-2,3,3-trimethyl-1-phenylbutyl]urea **253c**



The compound was synthesised following the general procedure 3 in toluene for 1h starting from 54mg (0.17mmol) of urea. The desired product is obtained in 60% yield (38mg) as a yellow oil.

R$_f$: 0.5 (PE/EtOAc:8/2).

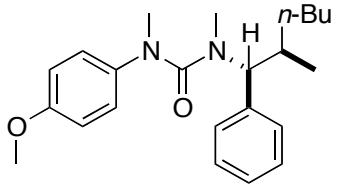
IR υ_{max} (film)/cm^{-1}: 2958, 1644 and 1597.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.26 (m, 5H, 5xAr*H*), 6.95 (t, *J*=8.0Hz, 1H, Ar*H*), 6.54 (dd, *J*=7.5 and 1.5Hz, 1H, Ar*H*), 6.27-6.24 (m, 2H, Ar*H*), 5.56 (d, *J*=10.0Hz, 1H, C*H*-N), 3.52 (s, 3H, O-CH_3), 3.18 (s, 3H, N-CH_3), 2.44 (s, 3H, N-CH_3), 2.17 (m, 1H, C-C*H*-CH_3), 1.10, (s, 9H, 3x(CH_3)-C) and 0.69 (d, *J*=6.5Hz, 3H, CH_3-CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.1 (C=O), 160.3 (C_{ar}-OCH_3), 147.9 (C_{ar}), 140.2 (C_{ar}), 129.7 (CH_{ar}), 128.3 (2xCH_{ar}), 128.2 (2xCH_{ar}), 126.8 (CH_{ar}), 115.8 (CH_{ar}), 110.1 (CH_{ar}), 108.8 (CH_{ar}), 62.3 (CH-N), 55.0 (O-CH_3), 40.6 (N-CH_3), 40.3 (*C*H-C), 38.9 (N-CH_3), 32.5 (C_q), 28.3 (3x*C*H_3-C) and 15.0 (*C*H_3-CH).

HRMS (ES): *m/z* calcd for $C_{23}H_{33}N_2O_2$ 369.2537 found 369.2527 $(M+H)^+$.

1-(4-Methoxyphenyl)-1,3-dimethyl-3-[(1*R**,2*R**)-2-methyl-1-phenyl-hexyl]urea **245a**:



The compound was prepared following the procedure 3 starting from 86mg (0.28mmol) of urea and obtained in 60% yield (60mg) as a colourless oil.

R$_f$: 0.5 (PE/EtOAc:8/2).

IR υ_{max} (film)/cm^{-1}: 2957, 2931, 1651, 1644and 1510.

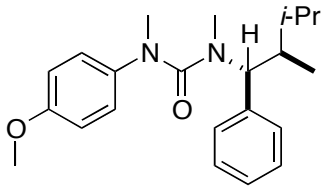
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.17 (m, 5H, 5xAr*H*), 6.79 (dt, *J*=8.8Hz and 2.5Hz, 2H, 2xAr*H*), 6.66 (dt *J*=8.8Hz and 2.5Hz, 2H, 2xAr*H*), 5.02 (d, *J*=12.0Hz, 1H, C*H*-N), 3.70 (s, 3H, O-CH_3), 3.05 (s, 3H, N-CH_3), 2.21 (s, 3H, N-CH_3), 2.04 (m, 1H, C*H*-CH_3), 1.20 (m, 6H, 3xCH_2), 0.88 (t, *J*=7.6Hz, 3H, CH_3-CH) and 0.70 (d, *J*=6.4Hz, 3H, CH_3-CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6 (C=O), 156.6 (C_{ar}-OCH_3), 140.1 (C_{ar}), 139.2 (C_{ar}), 128.6 (2xCH_{ar}), 128.1 (2xCH_{ar}), 127.1 (CH_{ar}), 126.1 (2xCH_{ar}), 114.4 (2xCH_{ar}), 64.3 (CH-N), 55.3 (O-CH_3), 41.0 (N-CH_3), 32.6 (*C*H-CH_3), 32.1 (*C*H_2-CH), 30.7 (N-CH_3), 29.2 (*C*H_2-CH_2-CH_3), 23.1 (*C*H_2-CH_3), 17.1 (*C*H_3-CH) and 14.2 (*C*H_3-CH_2).

HRMS (ES) *m/z* calcd for $C_{23}H_{33}N_2O_2$ 369.2537 found 369.2536 $(M+H)^+$.

1-[(1*R**,2*R**)-2,3-Dimethyl-1-phenyl-butyl]-3-(4-methoxyphenyl)-1,3-dimethyl-urea

254b:



The compound was synthesised following the general procedure 3 in toluene for 1h30 starting from 47mg (0.15mmol) of urea. The desired product was obtained in 85% yield (46mg) as a yellow oil.

R_f: 0.5 (PE/EtOAc:8/2).

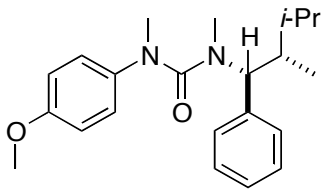
IR υ_{max} (film)/cm^{-1}: 2960, 1641 and 1511.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, *J*=8.0Hz, 2H, 2xAr*H*), 7.31 (t, *J*=7.0Hz, 2H, 2xAr*H*), 7.28-7.24 (m, 1H, Ar*H*), 6.80 (dt, *J*=9.0 and 3.0Hz, 2H, 2xAr*H*), 6.72 (dt, *J*=9.0 and 3.0Hz, 2H, 2xAr*H*), 5.23 (d, *J*=11.5Hz, 1H, C*H*-N), 3.77 (s, 3H, O-CH_3), 3.09 (s, 3H, N-CH_3), 2.26 (s, 3H, N-CH_3), 2.10 (m, 1H, C*H*-CH_3), 1.74 (dsept, *J*=2.5 and 7Hz, 1H, C*H*-$(CH_3)_2$), 0.94 (d, *J*=7.0Hz, 3H, (CH_3)$_2$-CH), 0.93 (d, *J*=7.0Hz, 3H, (CH_3)$_2$-CH) and 0.61 (d, *J*=7.0Hz, 3H, CH_3-CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.5 (C=O), 158.7 (C_{ar}-OCH_3), 140.3 (C_{ar}), 139.3 (C_{ar}), 128.8 (2xCH_{ar}), 128.1 (2xCH_{ar}), 127.1 (CH_{ar}), 126.1 (2xCH_{ar}), 114.4 (2xCH_{ar}), 62.0 (CH-N), 55.4 (O-CH_3), 41.0 (N-CH_3), 36.9 (*C*H-CH_3), 30.7 (N-CH_3), 26.6 (*C*H-$(CH_3)_2$), 21.8 (CH-(*C*H_3)$_2$), 15.3 (CH-(*C*H_3)$_2$) and 10.5 (*C*H_3-CH).

HRMS (ES): *m/z* calcd for $C_{22}H_{31}N_2O_2$ 355.2380 found 355.2388 $(M+H)^+$.

1-[(1*R**,2*S**)-2,3-Dimethyl-1-phenyl-butyl]-3-(4-methoxyphenyl)-1,3-dimethyl-urea ***epi*-**



254b:

The compound was synthesised following the general procedure in toluene for 1h30 starting from 40mg (0.13mmol) of urea. The desired product was obtained in 85% yield (40mg) as a yellow oil.

R_f: 0.5 (PE/EtOAc:8/2).

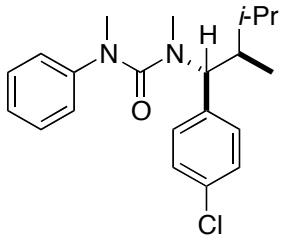
IR υ_{max} (film)/cm^{-1}: 2960, 1643 and 1511.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22-7.30 (m, 5H, 5xAr*H*), 6.81 (dt, *J*=9.0 and 2.5Hz, 2H, 2xAr*H*), 6.69 (dt, *J*=9.0 and 2.5Hz, 2H, 2xAr*H*), 5.22 (d, *J*=12.0Hz, 1H, C*H*-N), 3.73 (s, 3H, O-CH_3), 3.08 (s, 3H, N-CH_3), 2.24 (s, 3H, N-CH_3), 2.09 (m, 1H, CH_3-C*H*-CH), 1.46 (dsept, *J*=2.5 and 7.0Hz, 1H, C*H*-$(CH_3)_2$), 0.84 (d, *J*=7.0Hz, 3H, (CH_3)$_2$-CH), 0.78 (d, *J*=7.5Hz, 3H, CH_3-CH) and 0.68 (d, *J*=7.0Hz, 3H, (CH_3)$_2$-CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 162.8 (C=O), 156.7 (C_{ar}-OCH_3), 140.2 (C_{ar}), 138.7 (C_{ar}), 128.6 (2xCH_{ar}), 128.2 (2xCH_{ar}), 127.2 (CH_{ar}), 126.2 (2xCH_{ar}), 114.4 (2xCH_{ar}), 62.4 (CH-N), 55.4 (O-CH_3), 41.0 (N-CH_3), 37.0 (*C*H-CH_3), 30.5 (N-CH_3) 27.3 (*C*H-$(CH_3)_2$), 22.0 (CH-(*C*H_3)$_2$), 14.8 (CH-(*C*H_3)$_2$) and 9.7 (*C*H_3-CH).

HRMS (ES): *m/z* calcd for $C_{22}H_{31}N_2O_2$ 355.2380 found 355.2372 $(M+H)^+$.

1-[(1*R**,2*R**)-1-(4-Chlorophenyl)-2,3-dimethyl-butyl]-1,3-dimethyl-3-phenyl-urea **255**:



The compound was synthesised following the general procedure 3 starting from 108mg (0.34mmol) of urea. The desired product was obtained in 81% yield (100mg) as a yellow oil.

R_f: 0.5 (PE/EtOAc:8/2).

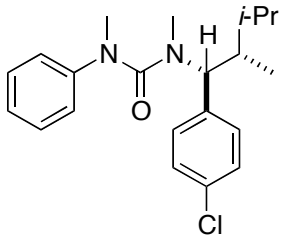
IR υ_{max} (film)/cm^{-1}: 2958, 1632 and 1594.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.15 (m, 6H, 6xAr*H*), 7.05 (tt, *J*=8.7 and 1.2Hz, 1H, Ar*H*), 6.87-6.83 (m, 2H, 2xAr*H*), 5.18 (d, *J*=12.0Hz, 1H, C*H*-N), 3.11 (s, 3H, N-CH_3), 2.23 (s, 3H, N-CH_3), 2.03 (m, 1H, CH-C*H*-CH_3), 1.71 (dsept, *J*=2.4 and 6.9Hz, 1H, C*H*-$(CH_3)_2$), 0.92 (d, *J*=6.9Hz, 6H, CH-(CH_3)$_2$) and 0.56 (d, *J*=6.6Hz, 3H, CH_3-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2 (C=O), 147.1 (C_{ar}), 137.8 (C_{ar}-Cl), 132.9 (C_{ar}), 130.1 (2xCH_{ar}), 129.3 (2xCH_{ar}), 128.3 (2xCH_{ar}), 124.7 (CH_{ar}), 124.3 (2xCH_{ar}), 61.4 (CH-N), 40.5 (N-CH_3), 37.1 (*C*H-CH_3), 30.6 (N-CH_3), 26.6 (*C*H-$(CH_3)_2$), 21.7 (CH-(*C*H_3)$_2$), 15.2 (CH-(*C*H_3)$_2$) and 10.4 (*C*H_3-CH).

HRMS (ES): *m/z* calcd for $C_{21}H_{28}N_2OCl$ 359.1885 found 359.1899 $(M+H)^+$.

1-[(1*R**,2*S**)-1-(4-chlorophenyl)-2,3-dimethyl-butyl]-1,3-dimethyl-3-phenyl-urea ***epi*-255**:



The compound was synthesised following the general procedure 3 starting from 100mg (0.32mmol) of urea. The desired product was obtained in 80% yield (90mg) as a yellow oil.

R_f: 0.5 (PE/EtOAc:8/2).

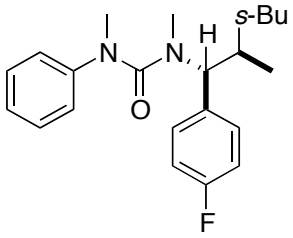
IR υ_{max} (film)/cm^{-1}: 2958, 1637 and 1594.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.18 (m, 6H, 6x Ar*H*), 7.06 (tt, *J*=7.5 and 1.2Hz, 1H, Ar*H*), 6.92-6.88 (m, 2H, 2xAr*H*), 5.19 (d, *J*=12Hz, 1H, C*H*-N), 3.14 (s, 3H, N-CH_3), 2.26 (s, 3H, N-CH_3), 2.05 (m, 1H, C*H*-CH_3), 1.42 (dsept, *J*=2.4 and 6.9Hz, 1H, C*H*-$(CH_3)_2$), 0.85 (d, *J*=6.9Hz, 3H, CH-(CH_3)$_2$), 0.80 (d, *J*=6.9Hz, 3H, CH_3-CH) and 0.68 (d, *J*=6.9Hz, 3H, CH-(CH_3)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5 (C=O), 147.0 (C_{ar}), 137.2 (C_{ar}-Cl), 133.0 (C_{ar}), 130.0 (2xCH_{ar}), 129.3 (2xCH_{ar}), 128.4 (2xCH_{ar}), 124.6 (CH_{ar}), 124.4 (2xCH_{ar}), 61.8 (CH-N), 40.4 (N-CH_3), 37.3 (*C*H-CH_3), 30.5 (N-CH_3), 27.3 (*C*H-$(CH_3)_2$), 21.9 (CH-(*C*H_3)$_2$), 14.7 (CH-(*C*H_3)$_2$) and 9.6 (*C*H_3-CH).

HRMS (ES): *m/z* calcd for $C_{21}H_{27}N_2OClNa$ 381.1704 found 381.1692 $(M+Na)^+$.

1-[(1*R**,2*R**)-1-(4-Fluorophenyl)-2,3-dimethyl-pentyl]-1,3-dimethyl-3-phenyl-urea **256**:



The compound was synthesised following the general procedure 3 starting from 113mg (0.38mmol) of urea. The desired product was obtained in 70% yield (100mg) as a colourless oil. (Mixture of diastereomers 2:1)

R_f: 0.5 (PE/EtOAc:8/2).

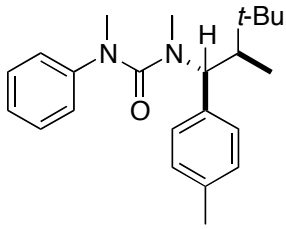
IR υ_{max} (film)/cm^{-1}: 3062, 3038, 2963, 2929, 2876, 2242, 1651 and 1644.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-6.90 (m, 18H, 9xAr*H* from both dia.), 5.32 (d, *J*=12.0Hz, 1H, C*H*-N from major dia.), 5.31 (d, *J*=12.0Hz, 1H, C*H*-N from minor dia.), 3.18 (s, 3H, N-CH_3, from major dia.) and 3.17 (s, 3H, N-CH_3, from minor dia.), 2.33 (s, 3H, N-CH_3 from minor dia.), 2.28 (s, 3H, N-CH_3 from major dia.), 2.18 (m, 2H, C*H*-CH_3 from both dia.), 1.77-1.69 (m, 1H, CH_2-CH_3 from minor dia.) 1.49-1.28 (m, 4H, CH_3-C*H*-CH_2-CH_3 from major dia. and CH_3-C*H*-CH_2 from minor dia.), 1.04-0.92 (m, 14H, 2xCH_3 from both dia. and CH_2-CH_3 from minor dia.), 0.62 (d, *J*=6.6Hz, 3H, CH_3-CH from minor dia.) and 0.61 (d, *J*=6.6Hz, 3H, CH_3-CH from major dia.).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1 (C=O from major dia.), 162.0 (C=O from minor dia), 161.9 (d, J_F=243.7Hz, C_{ar}-F from major dia.), 161.8 (d, J_F= 243.9Hz, C_{ar}-F from minor dia.), 147.1 (C_{ar} from major dia.), 147.0 (C_{ar} from minor dia.), 135.1 (J_F=3.5Hz, C_{ar} from both dia.), 130.4 (d, J_F=7.7Hz, 2xCH_{ar} from major dia.), 130.2 (d, J_F=8.2Hz 2xCH_{ar} from minor dia.), 129.3 (2xCH_{ar} from minor dia.), 129.2 (2xCH_{ar} from major dia.), 124.6 (2xCH_{ar} from minor dia.), 124.5 (2xCH_{ar} from major dia.), 124.4 (CH_{ar} from minor dia.), 124.0 (CH_{ar} from major dia.) 114.9 (d, J_F=20.9Hz 2xCH_{ar} from major dia.), 114.9 (d, J_F=21.7Hz 2xCH_{ar} from minor dia.), 61.0 (CH-N from minor dia.), 60.8 (CH-N from major dia.), 40.5 (N-CH_3 from major dia.), 40.4 (N-CH_3 from minor dia.), 38.2 (*C*H-CH_3 from minor dia.), 35.3 (*C*H-CH_3 from major dia.), 33.9 (CH_3-*C*H-CH_2 from major dia.), 33.6 (CH_3-*C*H-CH_2 from minor dia.), 30.6 (N-CH_3 from minor dia.), 30.5 (N-CH_3 from major dia.), 28.5 (*C*H_2-CH_3 from major dia.), 21.9 (CH_2 from minor dia.), 18.1 (CH_3 from major dia.), 13.0 (CH_3 from major dia.), 12.5 (CH_3 from minor dia.), 12.5 (CH_3 from minor dia.), 11.2 (CH_3 from minor dia.) and 10.7 (CH_3 from major dia.).

HRMS (ES): 357.2337 for $C_{22}H_{29}N_2OF$ ($M+H^+$) found 357.2340.

1,3-Dimethyl-1-phenyl-3-[(1*R**,2*R**)-2,3,3-trimethyl-1-(*p*-tolyl)butyl]urea **257**:



The compound was synthesised following the general procedure 3 starting from 80mg (0.27mmol) of urea. The desired product was obtained in 63% yield (63mg) as a colourless oil.

R_f: 0.5 (PE/EtOAc:8/2).

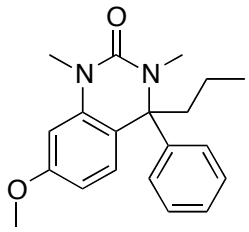
IR υ_{max} (film)/cm^{-1}: 2965, 1642 and 1596.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (s, 4H, 4xAr*H*), 7.03-6.93 (m, 3H, 3xAr*H*), 6.64-6.60 (m, 2H, 2xAr*H*), 5.43 (d, *J*=9.6Hz, 1H, C*H*-N), 3.12 (s, 3H, N-CH_3), 2.35 (s, 3H, C_{ar}-CH_3), 2.29 (s, 3H, N-CH_3), 2.09 (dq, *J*=9.6 and 6.9Hz, 1H, C*H*-CH_3), 1.04 (s, 9H, (CH_3)$_3$C) and 0.67 (d, *J*=6.9Hz, 3H, CH_3-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4 (C=O), 146.6 (C_{ar}), 137.1 (C_{ar}), 136.2 (*C*ar-CH_3), 129.0 (2xCH_{ar}), 128.7 (2xCH_{ar}), 128.3 (2xCH_{ar}), 123.9 (CH_{ar}), 123.5 (2xCH_{ar}), 62.3 (CH-N), 40.5 (*C*H-CH_3), 40.2 (N-CH_3), 33.9 (*C*-(CH_3)$_3$), 32.6 (N-CH_3), 28.2 (3x(*C*H_3)-C), 21.0 (C_{ar}-*C*H_3) and 12.9 (*C*H_3-CH).

HRMS (ES): calcd for $C_{23}H_{32}N_2O$ 375.2407 found 375.2410 $(M+Na)^+$.

7-Methoxy-1,3-dimethyl-4-phenyl-4-propyl-quinazolin-2-one **258**:



The urea **(*E*)-242a** (50mg, 0.16mmol) was solubilised in 3mL of THF and cooled to -78°C. LDA (2 eq.) was added slowly and the reaction stirred at this temperature for 1h. The reaction was quenched by addition of methyltriflate (5 eq.) and the reaction was stirred for 30 minutes. The reaction was diluted with methanol and the crude was extracted with ethyl acetate, dried ($MgSO_4$) and concentrated under vacuum. The crude was purified by silica gel chromatography (PE/EtOAc : 9/1) and the product was isolated in 45% yield (24mg) as an oil.

R_f: 0.19 (PE/EtOAc:8/2).

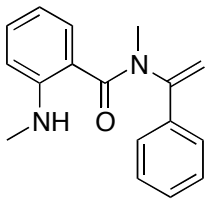
IR υ_{max} (film)/cm^{-1}: 2957, 2872, 1652, 1656 and 1615.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (m, 2H, 2xAr*H*), 7.34 (t, *J*=8Hz, 2H, 2xAr*H*), 7.27-7.24 (m, 1H, Ar*H*), 6.49 (d, *J*=8.5Hz, 1H, Ar*H*), 6.35 (m, 2H, 2xAr*H*), 3.77 (s, 3H, O-CH_3), 3.40 (s, 3H, N-CH_3), 2.65 (s, 3H, N-CH_3), 2.35 (td, *J*=13.0 and 3.5Hz, 1H, CH_2-CH_2-CH_3), 2.10 (td, 1H, *J*=13.0 and 3.5Hz, CH_2-CH_2-CH_3), 1.32 (m, 1H, CH_2-CH_2-CH_3), 1.12 (m, 1H, CH_2-CH_2-CH_3) and 0.92 (t, 3H, *J*=5.5 Hz, CH_2-CH_2-CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1 (C=O), 154.0 (*C*$_{ar}$-OCH_3), 146.7 (C_{ar}), 139.1 (C_{ar}), 128.7 (CH_{ar}), 128.3 (2xCH_{ar}), 127.3 (2xCH_{ar}), 127.1 (CH_{ar}), 118.8 (C_{ar}), 106.0 (CH_{ar}), 98.7 (CH_{ar}), 67.2 (C_q), 55.2 (O-CH_3), 41.3 (N-CH_3), 30.9 (N-CH_3), 30.1 (*C*H_2-CH_2-CH_3), 16.5 (CH_2-*C*H_2-CH_3) and 14.1 (*C*H_3-CH_2-CH_2).

HRMS (ES): *m/z* calcd for $C_{20}H_{24}N_2O_2Na$ 347.1730 found 347.1729 $(M+Na)^+$.

N-Methyl-2-methylamino-*N*-(1-phenylvinyl)benzamide **261**:



Enamide **261** was synthesised following the general procedure 6b (using 2 eq. of (−)-sparteine) starting from 75mg (0.22mmol) of urea **260** and isolated in 52% yield (30mg) as an oil.

R_f: 0.25 (PE/EtOAc: 8/2).

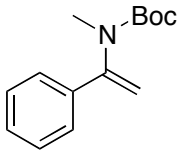
IR υ_{max} (film)/cm^{-1}: 3385, 1628, 1574 and 1511.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.21 (m, 5H, 5xAr*H*), 7.11 (dd, *J*=1.0 and 7.5Hz, 1H, Ar*H*), 7.07 (dt, *J*=1.5 and 7.0Hz, 1H, Ar*H*), 6.45 (d, *J*=8.0Hz, 1H, Ar*H*), 6.36 (t, *J*=7.5Hz, 1H, Ar*H*), 5.61 (br s, 1H, N*H*), 5.23 (s, 1H, C=CH_2), 4.89 (s, 1H, C=CH_2), 3.20 (s, 3H, N-CH_3) and 2.72 (s, 3H, N-CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6 (C=O), 149.6 (C_{ar}-NCH_3), 148.6 (C=CH_2), 136.5 (C_{ar}), 131.1 (CH_{ar}), 128.5 (3xCH_{ar}), 127.9 (CH_{ar}), 125.9 (2xCH_{ar}), 119.0 (C_{ar}), 114.7 (CH_{ar}), 110.1 (C=CH$_2$ and CH_{ar}), 36.5 (N-CH_3) and 30.0 (N-CH_3).

HRMS (ES): *m/z* calcd for $C_{17}H_{18}N_2ONa$ 289.1311 found 289.1318 $(M+Na)^+$.

tert-Butyl *N*-methyl-*N*-(1-phenylvinyl)carbamates **262**:



Acetophenone (2.00g, 16.6mmol, 1 eq.) was treated with a solution of methylamine (8M in EtOH, 4 eq.) in the presence of M.S. 4Å. The reaction was strirred for 48h at room temperature (alternatively 0.5h in a microwave at 125°C). The crude is filtered through Celite®. The solvent was removed under vacuum. The crude was solubilised in toluene and Boc_2O was added (1 eq.) to the reaction mixture. The reaction was stirred 16h refluxing. The crude was washed with H_2O, the organic phases combined and dried with $MgSO_4$ and solvent was removed under reduce pressure. The desired compound was obtained without further purification in 80% yield (3.10g) as an oil.

R_f: 0.5 (PE/EtOAc: 8/2).

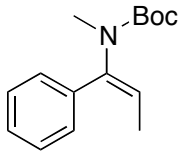
IR υ_{max} (film)/cm^{-1}: 2976, 1807, 1755, 1697 and 1625.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H, 5xAr*H*), 5.27 (s, 1H, C=CH_2), 5.05 (s, 1H, C=CH_2), 3.22 (s, 3H, N-CH_3) and 1.20 (s, 9H, C-(CH_3)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6 (C=O), 149.3 (C=CH_2), 138.9 (C_{ar}), 128.2 (2xCH_{ar}), 127.9 (CH_{ar}), 125.5 (2xCH_{ar}), 107.9 (C=CH$_2$), 80.0 (C-(CH_3)$_3$), 37.4 (N-CH_3) and 27.9 (3x(CH$_3$)-C).

HRMS (ES): calcd for $C_{14}H_{19}NO_2Na$ 256.1305 found 256.1308 $(M+Na)^+$.

tert-Butyl *N*-methyl-*N*-[(*E*)-1-phenylprop-1-enyl]carbamates **(*E*)-263**:



Propiophenone (2.00g, 14.9 mmol, 1 eq.) was treated with a solution of methylamine (8M in EtOH, 4 eq.) in the presence of M.S. 4Å. The reaction was strirred for 1h under microwave irradiation (125°C). The crude was filtered through Celite®. The solvent was removed under vacuum and the crude solubilised in toluene. Boc_2O (1 eq.) was added to the reaction mixture and the reaction was stirred 16h refluxing. The crude was washed with H_2O, the organic phases were combined and dried ($MgSO_4$) and the solvent was removed under reduce pressure. The desired compound was obtained after distillation under reduced pressure in 70% yield (2.58g) as a white solid. The stereochemistry is confirmed by nOe experiments and X-ray structure.

m.p.: 20°C (PE).

R_f: 0.5 (PE/EtOAc: 8/2).

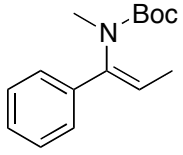
IR υ_{max} (film)/cm^{-1}: 2977 and 1686.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.23 (m, 5H, 5xAr*H*), 5.65 (q, *J*=7.0Hz, 1H, C=C*H*), 3.12 (s, 3H, N-CH_3), 1.77 (d, J=7.0Hz, 3H, CH_3-CH) and 1.22 (br s, 9H, 3xC-CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2 (C=O), 141.5 (*C*=CH), 128.4 (2xCH_{ar}), 127.9 (2xCH_{ar}), 127.3 (CH_{ar}), 120.7 (C=*C*H), 79.7 (*C*-$(CH_3)_3$), 37.6 (N-CH_3), 28.1 (3x(*C*H_3)-C) and 14.0 (*C*H_3-CH).

HRMS (ES): calcd for $C_{15}H_{21}NO_2Na$ 270.1465 found 270.1468 $(M+Na)^+$.

Tert-butyl *N*-methyl-*N*-[(*Z*)-1-phenylprop-1-enyl]carbamates **(*Z*)-263**:



Carbamate **(*E*)-263** (100mg, 0.40mmol) was solubilised in dry THF and cooled to -40°C. LDA (2 eq.) was added slowly and the reaction was stirred for 2h at this temperature. The reaction was quenched slowly with methanol and the mixture washed with NH_4Cl and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude was purified by flash chromatography and the desired compound was obtained in 90% yield (colourless oil).

R_f: 0.5 (PE/EtOAc : 8/2)

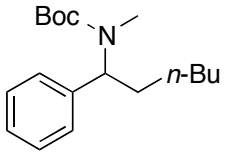
IR υ_{max} (film)/cm^{-1}: 2975, 1703 and 1699.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.19 (m, 5H, 5xAr*H*), 5.84 (q, *J*=7.2Hz, 1H, C=C*H*-CH_3), 2.97 (s, 3H, N-CH_3), 1.71 (d, *J*=7.2Hz, 3H, CH_3-CH) and 1.27 (br s, 9H, 3x(CH_3)-C).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3 (C=O), 141.1 (*C*=CH), 138.1 (C_{ar}), 128.3 (2xCH_{ar}), 127.3 (CH_{ar}), 125.2 (2xCH_{ar}), 120.9 (C=*C*H), 79.5 (*C*-$(CH_3)_3$), 35.2 (N-CH_3), 28.2 (3x(*C*H_3)-C) and 13.6 (*C*H_3-CH).

HRMS (ES): calcd 270.1465 for $C_{15}H_{21}NO_2Na$ $(M+Na^+)$ found 270.1473.

tert-Butyl *N*-methyl-*N*-(1-phenylpentyl)carbamates **264a**:



The compound has been synthesised following the general procedure 4 starting from 50mg (0.21mmol) of vinyl carbamate. The desired product was obtained in 61% yield (40mg) as a colourless oil.

The NMR analysis shows the presence of two rotamers.

R_f: 0.7 (PE/EtOAc: 8/2).

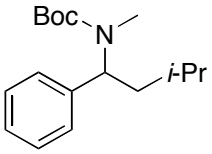
IR υ_{max} (film)/cm^{-1}: 3361, 2929 and 1676.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.21 (m, 10H, 10xAr*H* from both rotamers), 5.37 (br s, 1H, C*H*-N from 1st rotamer), 5.23 (br s, 1H, C*H*-N from 2nd rotamer), 2.55 (br s, 6H, N-CH_3 from both rotamers), 1.87 (br s, 4H, CH_2-CH from both rotamers), 1.49 (s, 18H, 3x(CH_3)-C from both rotamers), 1.37-1.34(m, 12H, CH_2-CH_2-CH_2 from both rotamers) and 0.90 (br t, *J*=6.6Hz, 6H, CH_3-CH_2 from both rotamers).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2 (C=O), 140.9 (C_{ar}), 128.3 (2xCH_{ar}), 127.4 (CH_{ar}), 127.0 (2xCH_{ar}), 79.4 (*C*-$(CH_3)_3$), 57.0 (CH-N), 31.6 (CH-CH_2-*C*H_2), 30.0 (*C*H_2-CH), 28.5 (3x(*C*H_3)-C), 28.0 (N-CH_3), 26.0 (CH_2-*C*H_2-CH_2), 22.6 (*C*H_2-CH_3) and 14.0 (*C*H_3-CH_2).

HRMS (ES): calcd for $C_{18}H_{29}NO_2Na$ 314.2091 found 314.2094 $(M+Na)^+$.

tert-Butyl *N*-methyl-*N*-(3-methyl-1-phenyl-butyl)carbamates **264b**:



The compound has been synthesised following the general procedure 4 starting from 40mg (0.17mmol) of carbamate. The desired product was obtained in 61% yield (29mg) as a colourless oil.

The NMR analysis shows the presence of two rotamers.

R_f: 0.7 (PE/EtOAc: 8/2).

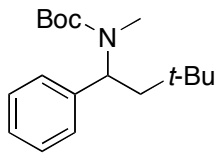
IR υ_{max} (film)/cm^{-1}: 2955 and 1686.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.23 (m, 10H, 10xAr*H* from both rotamers), 5.50 (br s, 1H, C*H*-N from 1st rotamer), 5.34 (br s, 1H, C*H*-N from 2nd rotamer), 2.55 (s, 6H, N-CH_3 from both rotamers), 1.83 (br s, 2H, C*H*-$(CH_3)_2$, from both rotamers), 1.62-1.60 (m, 4H, CH-CH_2, from both rotamers), 1.50 (s, 18H, 3x(CH_3)-C, from both rotamers), 1.00 (d, *J*=6.3Hz, 6H, CH_3-CH, from both rotamers) and 0.98 (d, *J*=6.3Hz, 6H, CH_3-CH, from both rotamers).

^{13}C NMR (75 MHz, $CDCl_3$): δ 156.1 (C=O), 141.0 (C_{ar}), 128.3 (2xCH_{ar}), 127.4 (CH_{ar}), 127.1 (2xCH_{ar}), 79.5 (*C*-$(CH_3)_3$), 55.5 (CH-N), 39.2 (CH-*C*H_2), 28.5 (N-CH_3), 28.0 (3x(*C*H_3)-C), 24.8 (*C*H-$(CH_3)_2$), 23.5 (CH-*C*H_3) and 21.9 (CH-*C*H_3).

HRMS (ES): calcd for $C_{17}H_{27}NO_2Na$ 300.1934 found 300.1936 $(M+Na)^+$.

tert-Butyl *N*-(3,3-dimethyl-1-phenyl-butyl)-*N*-methyl-carbamate **264c**:



The compound has been synthesised following the general procedure 4 starting from 50mg (0.21mmol) of carbamate. The desired product was obtained in 80% yield (50mg) as a colourless oil.

The NMR analysis shows the presence of two rotamers.

R_f: 0.7 (PE/EtOAc: 8/2).

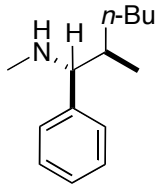
IR υ_{max} (film)/cm^{-1}: 2955, 2357 and 1676.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.18 (m, 10H, 10xAr*H* from both rotamers), 5.57 (br s, 1H, C*H*-N from 1st rotamer), 5.41 (br s, 1H, C*H*-N from 2nd rotamer) 2.52 (s, 6H, N-CH_3, from both rotamers), 1.85 (dd, *J*= 14.4and 9.9Hz, 2H, CH-CH_2, from both rotamers), 1.71 (dd, *J*=14.4 and 3.9Hz, 2H, CH-CH_2, from both rotamers), 1.48 (br s, 18H, 3x(CH_3)-C, from both rotamers) and 0.94 (s, 18H, 3x(CH_3)-C, from both rotamers).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3 (C=O), 142.1 (C_{ar}), 128.3 (2xCH_{ar}), 127.4 (2xCH_{ar}), 127.0 (CH_{ar}), 79.6 (*C*-$(CH_3)_3$), 79.4 (O-*C*-$(CH_3)_3$), 54.9 (CH-N from 2nd rotamer), 53.8 (CH-N from 1st rotamer), 42.8 (*C*H_2-CH), 30.6 (3xCH-C-*C*H_3), 29.7 (3xO-C-*C*H_3) and 28.6 (N-CH_3).

HRMS (ES): calcd for $C_{18}H_{29}NO_2Na$ 314.2091 found 314.2099 $(M+Na)^+$.

(1*R**,2*R**)-*N*,2-Dimethyl-1-phenyl-hexan-1-amine **265a**:



The compound was prepared following the general procedure 5 starting from 104mg (0.42mmol) of carbamate. The desired product was obtained in 70% yield (60mg) as an oil after flash chromatography (PE/DCM: 1/1).

R_f: 0.4 (PE/DCM: 1/1).

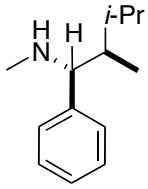
IR υ_{max} (film)/cm^{-1}: 2975, 1703 and 1699.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.20 (m, 5H, 5xAr*H*), 3.32 (d, *J*=6.6Hz, 1H, C*H*-N), 2.25 (s, 3H, N-CH_3), 1.74 (m, 1H, C*H*-CH_3), 1.52 (m, 1H, CH-CH_2), 1.29 (m, 5H, CH_2-CH_2-CH_3 and N*H*), 1.06 (m, 1H, CH-CH_2), 0.90 (t, *J*=6.9Hz, 3H, CH_3-CH_2) and 0.74 (d, *J*=6.6Hz, 3H, CH_3-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.3 (C_{ar}), 128.1 (2xCH_{ar}), 127.9 (2xCH_{ar}), 126.6 (CH_{ar}), 70.4 (CH-N), 39.0 (*C*H-CH_3), 34.9 (N-CH_3), 33.3 (*C*H_2-CH), 29.4 (*C*H_2-CH_2-CH_3), 23.0 (*C*H_2-CH_3), 16.0 (*C*H_3-CH) and 14.1 (*C*H_3-CH_2).

HRMS (ES): calcd for $C_{14}H_{24}N$ 206.1904 found 206.1902 $(M+H)^+$.

(1*R**,2*R**)-*N*,2,3-Trimethyl-1-phenyl-butan-1-amine **265b**:



The compound was prepared following the general procedure 5 starting from 97mg (0.39mmol) of carbamate. The desired product was obtained in 80% yield (60mg) as an oil.

R_f: 0.4 (PE:DCM: 1/1).

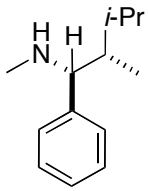
IR υ_{max} (film)/cm^{-1}: 2960, 2872 and 1682.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.22 (m, 5H, 5xAr*H*), 3.34 (d, *J*=9Hz, 1H, C*H*-N), 2.95 (br s, 1H, N*H*), 2.21 (s, 3H, N-CH_3), 2.04 (m, 1H, C*H*-$(CH_3)_2$), 1.68 (m, 1H, C*H*-CH_3), 0.97 (d, *J*=6.6Hz, 3H, CH-(CH_3)$_2$), 0.82 (d, *J*=6.9Hz, 3H, CH-(CH_3)$_2$) and 0.53 (d, J=6.9Hz, 3H, CH-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.2 (C_{ar}), 128.2 (2xCH_{ar}), 128.1 (2xCH_{ar}), 127.0 (CH_{ar}), 68.3 (CH-N), 44.1 (*C*H-CH_3), 34.3 (N-CH_3), 27.6 (*C*H-$(CH_3)_2$), 21.8 (CH-(*C*H_3)$_2$), 16.0 (CH-(*C*H_3)$_2$) and 10.8 (CH-*C*H_3).

HRMS (ES): calcd for $C_{13}H_{22}N$ 192.1747 found 192.1740 $(M+H)^+$.

(1*R**,2*S**)-*N*,2,3-Trimethyl-1-phenyl-butan-1-amine ***epi*-265c**:



The carbamate **(*Z*)-263** (98mg, 0.40mmol) was solubilised in dry toluene and the mixture was cooled to –40°C. Isopropyllithium was added slowly and the reaction was stirred for 24h at –40°C. The reaction was quenched by slow addition of methanol. The solvent was removed under reduced pressure and the crude solubilised in TFA. The reaction was stirred for 1h at r.t. The reaction mixture was diluted in DCM and washed with $NaHCO_3$ (1M). The organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The desired compound was obtained in 50% yield (40mg) as an oil.

8:2 mixture of 2 diastereomers.

Only the main diastereomer described

R_f: 0.4 (PE:DCM: 1/1).

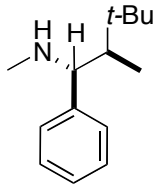
IR υ_{max} (film)/cm^{-1}: 3024, 2958, 2872 and 2790.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.22 (m, 5H, 5xAr*H*), 3.38 (d, *J*=7.8Hz, 1H, C*H*-N), 2.21 (s, 3H, N-CH_3), 1.56 (m, 1H, C*H*-$(CH_3)_2$), 1.44 (m, 1H, C*H*-CH_3), 0.92 (d, *J*=6.9Hz, 3H, CH-(CH_3)$_2$), 0.88 (d, *J*=6.9Hz, 3H, CH-(CH_3)$_2$), 0.77 (d, *J*=6.9Hz, 3H, CH-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6 (C_{ar}), 128.1 (2xCH_{ar}), 127.7 (2xCH_{ar}), 126.6 (CH_{ar}), 68.4 (CH-N), 45.3 *C*H-CH_3), 34.7 (N-CH_3), 28.7 (*C*H-$(CH_3)_2$), 21.8 (CH-(*C*H_3)$_2$), 17.1 (CH-*C*H_3) and 10.6 (CH-(*C*H_3)$_2$).

HRMS (ES): calcd for $C_{13}H_{22}N$ 192.1747 found 192.1743 $(M+H)^+$.

(1*R**,2*R**)-*N*,2,3,3-Tetramethyl-1-phenyl-butan-1-amine **265d**:



The compound was prepared following the general procedure 5 starting from 103mg (0.42mmol) of carbamate. The desired product was obtained in 81% yield (70mg) as an oil.

R_f: 0.4 (PE:DCM: 1/1).

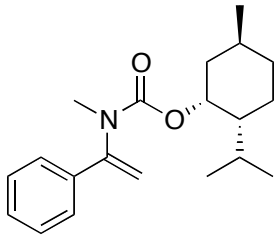
IR υ_{max} (film)/cm^{-1}: 2960, 2868 and 1676.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.03 (m, 5H, 5xAr*H*), 3.70 (d, *J*=4.4Hz, 1H, C*H*-N), 3.33 (br s, 1H, NH), 2.17 (s, 3H, N-CH_3), 1.64 (dq, *J*=4.4 and 7.2Hz, 1H, C*H*-CH_3), 0.81 (s, 9H (3x(CH_3)-C) and 0.79 (d, *J*=7.2Hz, 3H, CH-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3 (C_{ar}), 129.1 (2xCH_{ar}), 127.9 (2xCH_{ar}), 127.0 (CH_{ar}), 66.4 (CH-N), 48.5 (*C*H-CH_3), 34.1 (*C*-$(CH_3)_3$), 33.5 (N-CH_3), 28.3 (3x(*C*H_3)-C) and 11.3 (CH_3-CH).

HRMS (ES): calcd for $C_{14}H_{24}N$ 206.1903 found 206.1900 $(M+H)^+$.

[(1*R*,2*R*,5*S*)-2-Isopropyl-5-methyl-cyclohexyl] *N*-methyl-*N*-(1-phenylvinyl)carbamate **266**:



Acetophenone (2.00g, 16.6mmol, 1 eq.) was treated with a solution of methylamine (8M in EtOH, 4 eq.) in the presence of M.S. 4Å. The reaction was strirred for 0.5h under microwave irradiation at 125°C. The crude was filtered through Celite®. The solvent was removed under vacuum. The crude was solubilised in toluene and menthylchloroformate was added (1 eq.) to the reaction mixture. The reaction was stirred 16h refluxing. The crude was washed with H_2O, the organic phases combined and dried with $MgSO_4$ and solvent was removed under reduced pressure. The desired compound was obtained as a white solid without further purification in 70% yield (3.8g) as a white solid.

R_f: 0.5 (PE/EtOAc: 8/2).

IR υ_{max} (powder)/cm^{-1}: 2954, 2867, 2247, 1688 and 1628.

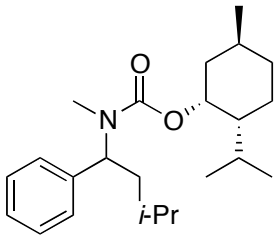
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5H, 5xAr*H*), 5.40 (s, 1H, C=CH_2), 5.12 (s, 1H, C=CH_2), 4.44 (dt, *J*=4.5 and 10.8Hz, 1H, C*H*-O), 3.22 (s, 3H, N-CH_3), 2.01-1.94 (m, 1H, CH_2-CH-O), 1.63-1.51 (m, 2H, CH_2-CH-CH-O and CH_2-CH-CH_3), 1.47-1.34 (m, 2H, C*H*-$(CH_3)_2$ and C*H*-CH_3), 1.11-1.04 (m, 1H, C*H*-CH-$(CH_3)_2$), 0.94 (dq, *J*=4.2 and 12.6Hz, 1H, CH_2-CH-CH-O), 0.84 (d, *J*=6.6Hz, 3H, CH-(CH_3)$_2$), 0.80-0.73 (m, 1H, CH_2-CH-CH_3), 0.69 (br d, *J*=6.9Hz, 4H, (CH_3-CH) and CH_2-CH-O) and 0.65 (d, *J*=6.9Hz, 3H, (CH-CH_3)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5 (C=O), 148.6 (*C*=CH_2), 138.0 (C_{ar}), 128.4 (2xCH_{ar}), 128.2 (CH_{ar}), 125.5 (2xCH_{ar}), 109.6 (C=CH_2), 75.6 (CH-O), 49.2 (*C*H-CH-$(CH_3)_2$), 41.0 (*C*H_2-CH-O), 37.6 (N-CH_3), 34.2 (*C*H_2-CH-CH_3), 31.3 (*C*H-$(CH_3)_2$), 25.7 (*C*H-CH_3), 23.2 (*C*H_2-CH-CH-O), 22.0 (CH-(*C*H_3)$_2$), 20.8 (*C*H_3-CH) and 16.1 (CH-(*C*H_3)$_2$).

HRMS (ES): calcd for $C_{20}H_{29}N_2ONa$ 316.2271 found 316.2271$(M+Na)^+$.

Elem. anal.: calcd: C 76.15, H 9.27, N 4.44 found: C 76.14, H 9.24, N 4.42.

[(2R,5S)-2-Isopropyl-5-methyl-cyclohexyl]N-methyl-N-(3-methyl-1-phenyl-butyl)carbamate **267**:



The desired carbamates was synthesised following the general procedure 4 starting from 52mg (0.16mmol) of carbamate **266** in 60% yield as an oil.

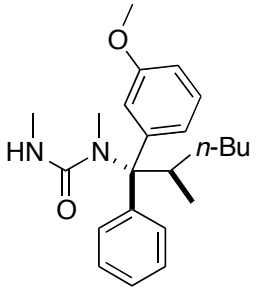
The presence of two diastereomers make the assignment difficult.

$\mathbf{R}_f$: 0.5 (PE/EtOAc: 7/3).

^{1}H NMR (400 MHz, DMSO-d^6, 383.1K): δ 7.25- 7.13 (m, 10H, 10xAr*H* for both dia.), 5.21 (t, *J*=5.6Hz, 1H, C*H*-N one dia.), 5.18 (t, *J*=6Hz, 1H, C*H*-N one dia.), 4.46 (dt, *J*=4.4 and 10.8Hz, 2H, C*H*-O both dia.), 2.81 (s, 6H, N-CH_3 both dia.), 1.88-1.71 (m, 6H), 1.65-1.25 (m, 14H), 1.25-1.03 (m, 4H), 0.87 (d, *J*=6.8Hz, 12H, 2xCH-(CH_3)$_2$ both dia.), 0.81-0.76 (m, 12H, 2xCH-(CH_3)$_2$ both dia.) and 0.67 (d, *J*=6.8Hz, 6H, 3xCH_3-CH both dia.).

^{13}C NMR (100 MHz, DMSO-d^6, 383.1K): δ 155.2, 140.3, 140.2, 127.7, 127.7, 126.5, 126.4, 126.4, 74.1, 55.4, 55.3, 46.7, 40.8, 40.8, 39.5, 38.7, 38.6, 33.5, 33.4, 30.4, 27.9, 27.8, 25.8, 25.7, 24.3, 24.2, 23.2, 23.1, 22.3, 22.1, 21.4, 21.2, 21.1, 19.88, 19.8, 16.0 and 15.9.

1-[(1*R**,2*R**)-1-(3-Methoxyphenyl)-2-methyl-1-phenyl-hexyl]-1,3-dimethyl-urea **268a**:

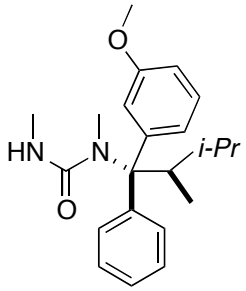


The product was synthesised following the procedure 6 (conditions a) starting from 84mg (0.27mmol) of urea in Et_2O. The desired product was obtained in 65% yield (65mg) as a colourless oil.

(Due to the instability of the product, only ^{1}H NMR analysis had been done).

^{1}H NMR (400 MHz, CD_3OD): δ 7.29-7.07 (m, 8H, 8xAr*H*), 6.83 (dd, *J*=8.4 and 2.4Hz, 1H, Ar*H*), 3.74 (s, 3H, O-CH_3), 3.59 (br s, 1H, C*H*-CH_3), 2.77 (s, 3H, N-CH_3), 2.57 (s, 3H, N-CH_3), 1.54-1.16 (m, 6H, 3xCH_2) and 0.84 (m, 6H, 2xCH_3).

1-[(1*R**,2*R**)-1-(3-Methoxyphenyl)-2,3-dimethyl-1-phenyl-butyl]-1,3-dimethyl-urea **268b**:

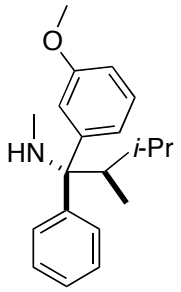


The product was synthesised following the general procedure 6 described (conditions a) from 220mg (0.71mmol) of the urea in toluene. The desired product was obtained in 60% yield (150mg) as a clear yellow oil.

(Due to the instability of the product, only ^{1}H NMR analysis had been done).

^{1}H NMR (400 MHz, CD_3OD): δ 7.53-7.23 (m, 8H, 8xAr*H*), 7.02 (ddd, 1H, *J*=8.0, 2.4 and 0.8Hz, Ar*H*), 6.12 (br d, *J*=4.0Hz, 1H, N*H*), 3.93 (s, 3H, O-C*H*$_3$), 3.73 (br s, 1H, C*H*-CH_3) 2.85 (s, 3H, N-C*H*$_3$), 2.67 (d, *J*=4.0Hz, 3H, N-C*H*$_3$), 1.95 (m, 1H, C*H*-$(CH_3)_2$), 1.15 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$), 0.91 (d, *J*=7.2Hz, 3H, CH-C*H*$_3$) and -0.08 (d, *J*=7.2Hz, 3H, CH-(C*H*$_3$)$_2$).

(1*R**,2*S**)-1-(3-Methoxyphenyl)-*N*,2,3-trimethyl-1-phenyl-butan-1-amine **269**:



The amine was synthesised following the general procedure 7 starting from 120mg (0.34mmol) of urea. The desired compound was obtained in 69% yield (41mg) as an oil.

R$_f$: 0.2 (PE/EtOAc :7/3).

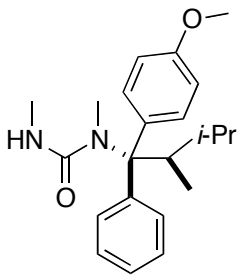
IR υ_{max} (film)/cm^{-1}: 2953, 2871, 2832, 1598 and 1580.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.13 (m, 6H, 6xAr*H*), 7.00 (t, *J*=2.4Hz, 1H, Ar*H*), 6.95 (d, *J*=7.6Hz, 1H, Ar*H*), 6.81 (ddd, *J*=8.4, 2.8 and 1.2Hz, 1H, Ar*H*), 3.80 (s, 3H, O-C*H*$_3$), 2.41 (q, *J*=7.0Hz, 1H, C*H*-CH_3), 2.20 (sept, *J*=6.8Hz, 1H, C*H*-$(CH_3)_2$) 1.94 (s, 3H, N-C*H*$_3$), 1.01 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$), 0.85 (d, *J*=7.0Hz, 3H, C*H*$_3$-CH), -0,09 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8 (*C*$_{ar}$-OCH_3), 145.5 (C_{ar}), 144.1 (C_{ar}), 129.3 (2xCH_{ar}), 128.0 (CH_{ar}), 127.1(2xCH_{ar}), 126.2 (CH_{ar}), 122.2 (CH_{ar}), 115.7 (CH_{ar}), 111.1 (CH_{ar}), 69.8 (C_q), 55.2 (O-CH_3), 41.7 (*C*H-CH_3), 29.4 (N-CH_3), 25.8 (*C*H-$(CH_3)_2$), 24.5 (CH-(*C*H_3)$_2$), 17.1 (*C*H_3-CH) and 9.2 (CH-(*C*H_3)$_2$).

HRMS (ES): calcd for $C_{20}H_{28}NO$ 298.2165 found 298.2177 $(M+H)^+$.

1-[(1*R**,2*R**)-1-(4-Methoxyphenyl)-2,3-dimethyl-1-phenyl-butyl]-1,3-dimethyl-urea **270**:

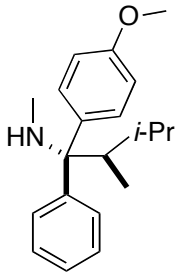


The product was synthesised following the procedure 6 (conditions a) from 55mg (0.18mmol) of the urea in toluene. The desired product was obtained in 60% yield (37mg) as a clear yellow oil.

(Due to the instability of the product, only ^{1}H NMR analysis had been done).

^{1}H NMR (300 MHz, CD_3OD): δ 7.52 (br d, *J*=7.2Hz, 2H, 2xAr*H*), 7.31-7.27 (m, 5H, 5xAr*H*), 6.83 (br d, *J*=9Hz, 2H, 2xAr*H*), 3.78 (s, 4H, O-CH_3 and C*H*-CH_3), 2.78 (s, 3H, N-CH_3), 2.55 (s, 3H, N-CH_3), 1.71 (br s, 1H, C*H*-$(CH_3)_2$), 0.99 (d, *J*=6.9Hz, 3H, CH-(CH_3)$_2$), 0.77 (br d, *J*=6.9Hz, 3H, CH_3-CH) and -0.29 (br d, *J*=6.9Hz, 3H, CH-(CH_3)$_2$).

(1*R**,2*R**)-1-(4-Methoxyphenyl)-*N*,2,3-trimethyl-1-phenyl-butan-1-amine **271**:



The amine was synthesised following the general procedure 7 starting from 60mg (0.17mmol) of urea. The desired compound was obtained in 70% yield (54mg) as an oil.

R_f: 0.2 (PE/EtOAc:7/3).

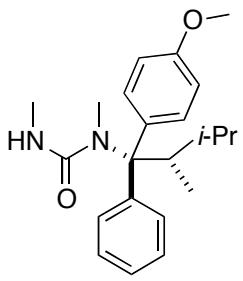
IR υ_{max} (film)/cm^{-1}: 2954, 1609 and 1510.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.22 (m, 7H, 7xAr*H*), 6.80 (d, *J*=9.0Hz, 2H, 2xAr*H*), 3.81 (s, 3H, O-CH_3), 2.39 (q, *J*=6.9Hz, 1H, C*H*-CH_3), 2.16 (sept, *J*=6.9Hz, 1H, C*H*-$(CH_3)_2$), 1.92 (s, 3H, N-CH_3), 0.99 (d, *J*=6.9Hz, 3H, CH-(CH_3)$_2$), 0.84 (d, *J*=6.9Hz, 3H, CH_3-CH) and -0.11 (d, *J*=6.9Hz, 3H, CH-(CH_3)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9 (C_{ar}-OCH_3), 143.9 (C_{ar}), 136.4 (C_{ar}), 130.5 (2xCH_{ar}), 129.4 (2xCH_{ar}), 127.2 (2xCH_{ar}), 126.2 (CH_{ar}), 112.4 (2xCH_{ar}), 69.4 (C_q), 55.2 (O-CH_3), 41.9 (*C*H-CH_3), 29.4 (N-CH_3), 25.8 (*C*H-$(CH_3)_2$), 24.5 (CH-(*C*H_3)$_2$), 17.1 (CH-(*C*H_3)$_2$) and 9.2 (*C*H_3-CH).

HRMS (ES): calcd for $C_{20}H_{28}NO$ 298.2165 found 298.2156 $(M+H)^+$.

1-[(1*R**,2*S**)-1-(4-Methoxyphenyl)-2,3-dimethyl-1-phenyl-butyl]-1,3-dimethyl-urea ***epi*-270**:



The product was synthesised following the general procedure 6 (conditions a) for 3.5 h starting from 101mg (0.33mmol) of the urea **(*Z*)-242b**. The desired product was obtained in 76% yield (85mg) as a clear yellow oil.

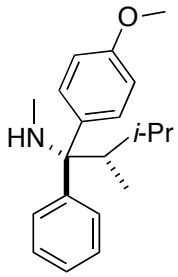
alternatively

The product was synthesised following the general procedure 6 (conditions b) from 50mg (0.16mmol) of the urea **(*E*)-242i** in toluene. The desired product was obtained in 54% yield (31mg) as a clear yellow oil.

(Due to the instability of the product, only ^{1}H NMR analysis had been done).

^{1}H NMR (400 MHz, CD_3OD): δ 7.50-7.09 (m, 7H, 7xAr*H*), 6.89 (d, *J*=8.8Hz, 2H, 2xAr*H*), 3.82 (br s, 1H, C*H*-CH_3), 3.81 (s, 3H, O-C*H*$_3$), 2.70 (s, 3H, N-C*H*$_3$), 2.56 (s, 3H, N-C*H*$_3$), 1.71 (br s, 1H, C*H*-$(CH_3)_2$), 1.00 (d, *J*=6.8 Hz, 3H, CH-(C*H*$_3$)$_2$), 0.79 (d, *J*=7.2 Hz, 3H, C*H*$_3$-CH) and -0.33 (br. d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$).

(1*R**,2*S**)-1-(4-Methoxyphenyl)-*N*,2,3-trimethyl-1-phenyl-butan-1-amine ***epi*-271**:



The amine was synthesised following the general procedure 7 starting from 80mg (0.23mmol) of urea. The desired compound was obtained in 70% yield (71mg) as an oil.

R$_f$: 0.2 (PE/EtOAc:7/3).

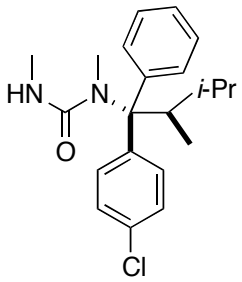
IR υ_{max} (film)/cm^{-1}: 2954, 1608 and 1509.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.18 (m, 7H, 7xAr*H*), 6.88-6.84 (m, 2H, 2xAr*H*), 3.83 (s, 3H, O-C*H*$_3$), 2.39 (q, *J*=7.2Hz, 1H, C*H*-CH_3), 2.18 (sept, *J*=7.0Hz, 1H, C*H*-$(CH_3)_2$), 1.92 (s, 3H, N-C*H*$_3$), 0.99 (d, *J*=7.0Hz, 3H, CH-(C*H*$_3$)$_2$), 0.83 (d, *J*=7.2Hz, 3H, C*H*$_3$-CH) and -0.10 (d, *J*=7.0Hz, 3H, CH-(C*H*$_3$)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0 (*C*$_{ar}$-OCH_3), 144.6 (C_{ar}), 135.5 (C_{ar}), 130.5 (2xCH_{ar}), 129.3 (2xCH_{ar}), 127.1 (2xCH_{ar}), 126.1 (CH_{ar}), 112.5 (2xCH_{ar}), 69.4 (C_q), 55.2 (O-CH_3), 41.9 (*C*H-CH_3), 29.3 (N-CH_3), 25.7 (*C*H-$(CH_3)_2$), 24.5 (CH-(*C*H$_3$)$_2$), 17.1 (CH-(*C*H$_3$)$_2$) and 9.3 (*C*H$_3$-CH).

HRMS (ES): calcd for $C_{20}H_{27}NONa$ 320.1985 found 320.1969 $(M+Na)^+$.

1-[(1*R**,2*R**)-1-(4-Chlorophenyl)-2,3-dimethyl-1-phenyl-butyl]-1,3-dimethyl-urea **272**:

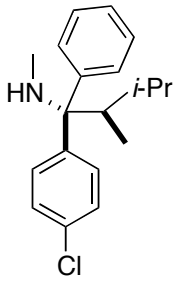


The product was synthesised following the general procedure 6 (conditions b) for 4h starting from 102mg (0.32mmol) of the urea. The desired product was obtained in 81% yield (94mg) as a clear yellow oil.

(Due to the instability of the product, only 1H NMR analysis had been done).

^{1}H NMR (500 MHz, CD_3OD): δ 7.54-7.28 (m, 9H, 9xAr*H*), 3.25 (br s, 1H, C*H*-CH_3), 2.80 (s, 3H, N-C*H*$_3$), 2.56 (s, 3H, N-C*H*$_3$), 1.75 (br s, 1H, C*H*-$(CH_3)_2$), 1.02 (br d, *J*=6.9Hz, 3H, CH-(C*H*$_3$)$_2$), 0.78 (br d, *J*=6.6Hz, 3H, C*H*$_3$-CH) and –0.26 (br d, *J*=6.6Hz, 3H, CH-(C*H*$_3$)$_2$).

(1*R**,2*R**)-1-(4-Chlorophenyl)-*N*,2,3-trimethyl-1-phenyl-butan-1-amine **273**:



The amine was synthesised following the general procedure 7 starting from 75mg (0.21mmol) of urea. The desired compound was obtained in 66% yield (41mg) as an oil. The compound **273**•HCl was obtained by solubilisation of the amine in a solution of HCl 1.25 M in methanol.

R$_f$: 0.2 (PE/EtOAc :7/3).

IR υ_{max} (film)/cm^{-1}: 2954 and 2871.

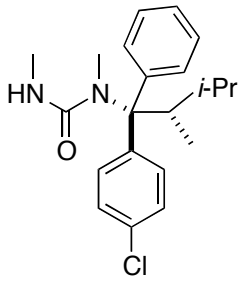
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.23 (m, 9H, 9xAr*H*), 2.39 (q, *J*=7.2Hz, 1H, C*H*-CH_3), 2.16 (sept, *J*=6.8Hz, 1H, C*H*-$(CH_3)_2$), 1.92 (s, 3H, N-C*H*$_3$), 1.00 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$), 0.83 (d, *J*=7.2Hz, 3H, CH-C*H*$_3$) and -0.1 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1 (C_{ar}), 142.8 (C_{ar}), 132.0 (C_{ar}-Cl), 130.8 (2xCH_{ar}), 129.3 (2xCH_{ar}), 127.3 (2xCH_{ar}), 127.2 (2xCH_{ar}), 126.4 (CH_{ar}), 69.5 (C_q), 41.8 (*C*H-CH_3), 29.3 (N-CH_3), 25.7 (*C*H-$(CH_3)_2$), 24.4 (CH-(*C*H_3)$_2$), 17.1 (CH-(*C*H_3)$_2$) and 9.1 (*C*H_3-CH).

HRMS (ES): calcd for $C_{19}H_{25}NCl$ 301.1670 found 301.1664 $(M+H)^+$.

1-[(1*R**,2*S**)-1-(4-Chlorophenyl)-2,3-dimethyl-1-phenyl-butyl]-1,3-dimethyl-urea

***epi*-272**:

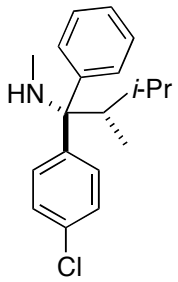


The product was synthesised following the procedure 6 (conditions b) for 3.5 hours starting from 60mg (0.19mmol) of the urea. The desired product was obtained in 73% yield (53mg) as a clear yellow oil.

(Due to the instability of the product, only ^{1}H NMR analysis has been done).

^{1}H NMR (300 MHz, CD_3OD): δ 7.50-7-21 (m, 9H, 9xAr*H*), 3.64 (br s, 1H, C*H*-CH_3), 2.76 (br s, 3H, N-C*H*$_3$), 2.52 (s, 3H, N-C*H*$_3$), 1.67 (br s, 1H, C*H*-$(CH_3)_2$), 0.97 (d, *J*=6.9Hz, 3H, CH-(C*H*$_3$)$_2$), 0.78 (br d, *J*=6.9Hz, 3H, CH-C*H*$_3$) and -0.31 (br d, *J*=6.9Hz, 3H, CH-(C*H*$_3$)$_2$).

(1*R**,2*S**)-1-(4-Chlorophenyl)-*N*,2,3-trimethyl-1-phenyl-butan-1-amine ***epi*-273**:



The amine was synthesised following the general procedure 7 starting from 56mg (0.16mmol) of urea. The desired compound was obtained in 67% yield (30mg) as an oil. The compound **273**.HCl was obtained by solubilisation of the amine in a solution of HCl 1.25 M in methanol.

R$_f$: 0.2 (PE/EtOAc: 7/3).

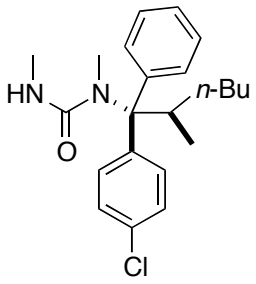
IR υ_{max} (film)/cm^{-1}: 2952 and 2872.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.22 (m, 9H, 9xAr*H*), 2.36 (q, *J*=7.2Hz, 1H, C*H*-CH_3), 2.17 (sept, *J*=6.8Hz, 1H, C*H*-$(CH_3)_2$), 1.88 (s, 3H, N-C*H*$_3$), 0.96 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$), 0.80 (d, *J*=7.2Hz, 3H, C*H*$_3$-CH) and -0.12 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (C_{ar}), 142.0 (C_{ar}), 132.0 (C_{ar}-Cl), 130.9 (2xCH_{ar}), 129.1 (2xCH_{ar}), 127.3 (2xCH_{ar}), 127.3 (2xCH_{ar}), 126.5 (CH_{ar}), 69.5 (C_q), 41.9 (C*H*-CH_3), 29.3 (N-CH_3), 25.5 (*C*H-$(CH_3)_2$), 24.5 (CH-(*C*H$_3$)$_2$), 17.1 (CH-(*C*H$_3$)$_2$) and 9.3 (CH_3-CH).

HRMS (ES): calcd for $C_{19}H_{25}NCl$ 302.1670 found 302.1661 $(M+H)^+$.

1-[(1*R**,2*R**)-1-(4-Chlorophenyl)-2-methyl-1-phenyl-hexyl]-1,3-dimethyl-urea **274**:

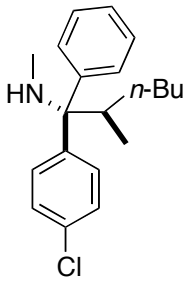


The product was synthesised following the general procedure 6 (conditions b) for 5h starting from 120mg (0.38mmol) of the urea. The desired product was obtained in 70% yield (100mg) as a colourless oil.

(Due to the instability of the product, only ^{1}H NMR analysis has been done).

^{1}H NMR (300 MHz, CD_3OD): δ 7.28 (m, 9H, 9xAr*H*), 3.48 (br s, 1H, C*H*-CH_3), 2.77 (s, 3H, N-C*H*$_3$), 2.56 (s, 3H, N-C*H*$_3$), 1.48 (br s, 1H, CH-CH_2-CH_2), 1.32-1.23 (m, 5H, CH_2-CH_2-CH_2 and N*H*), 0.84-0.63 (m, 6H, 2xC*H*$_3$) and 0.31 (br s, 1H, CH_2-CH).

(1*R**,2*R**)-1-(4-Chlorophenyl)-*N*,2-dimethyl-1-phenyl-hexan-1-amine **275**:



The amine was synthesised following the general procedure 7 starting from 75mg (0.20mmol) of urea. The desired compound was obtained in 76% yield (45mg) as an oil.

R$_f$: 0.2 (PE/EtOAc :7/3).

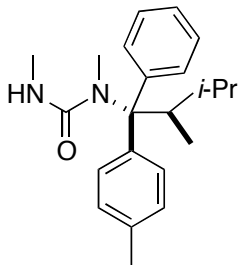
IR υ_{max} (film)/cm^{-1}: 3428, 3302, 3157, 3083, 2956, 2871, 2797 and 1598.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.22 (m, 9H, 9xAr*H*), 2.37 (m, 1H, C*H*-CH_3), 1.93 (s, 3H, N-C*H*$_3$), 1.71 (m, 1H, CH-CH_2-CH_2), 1.40-1.16 (m, 5H, CH_2-CH_2-CH_2 and N*H*), 0.85 (t, *J*=7.2Hz, 3H, C*H*$_3$-CH_2), 0.81 (d, *J*=6.8Hz, 3H, C*H*$_3$-CH) and 0.46 (m, 1H, CH_2-CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4 (C_{ar}), 141.9 (C_{ar}), 132.0 (C_{ar}-Cl), 131.0 (2xCH_{ar}), 129.1 (2xCH_{ar}), 127.3 (2xCH_{ar}), 127.1 (2xCH_{ar}), 126.3 (CH_{ar}), 69.6 (C_q), 36.8 (C*H*-CH_3), 32.1 (*C*H_2-CH), 30.5 (CH_2-*C*H_2-CH_2), 29.2 (N-CH_3), 23.1 (*C*H_2-CH_3), 14.7 (*C*H_3-CH) and 14.2 (*C*H_3-CH_2).

HRMS (ES): calcd for $C_{20}H_{27}N_2OCl$ 316.1827 found 316.1828 $(M+H)^+$.

1-[(1*R**,2*R**)-2,3-Dimethyl-1-phenyl-1-(*p*-tolyl)butyl]-1,3-dimethyl-urea **276**:

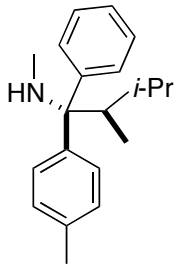


The product was synthesised following the procedure 6 (conditions b) for 4 hours starting from 118mg (0.40mmol) of the urea. The desired product was obtained in 60% yield (81mg) as a clear yellow oil.

(Due to the instability of the product, only ^{1}H NMR analysis had been done).

^{1}H NMR (300 MHz, CD_3OD): δ 7.55-7.08 (m, 9H, 9xAr*H*), 3.73 (br s, 1H, C*H*-CH_3), 2.78 (s, 3H, N-C*H*$_3$), 2.55 (s, 3H, N-C*H*$_3$), 2.32 (s, 3H, C_{ar}-C*H*$_3$), 1.72 (br s, 1H, C*H*-$(CH_3)_2$), 1.00 (d, *J*=6.9Hz, 3H, CH-(C*H*$_3$)$_2$), 0.78 (d, *J*=6.9Hz, 3H, C*H*$_3$-CH) and -0.32 (d, *J*=6.3Hz, 3H, CH-(C*H*$_3$)$_2$).

(1*R**,2*R**)-*N*,2,3-Trimethyl-1-phenyl-1-(*p*-tolyl)butan-1-amine **277**:



The amine was synthesised following the general procedure 7 starting from 40mg (0.12mmol) of urea. The desired compound was obtained in 66% yield (23mg) as an oil.

R$_f$: 0.2 (PE/EtOAc:7/3).

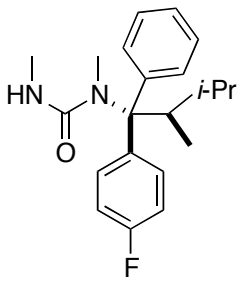
IR υ_{max} (film)/cm^{-1}: 2952 and 1636.

^{1}HNMR (300 MHz, $CDCl_3$): δ 7.40-7.06 (m, 9H, 9xAr*H*), 2.40 (q, *J*=7.0Hz, 1H, C*H*-CH_3), 2.34 (s, 3H, N-C*H*$_3$), 2.20 (sept, *J*=6.8Hz, 1H, C*H*-$(CH_3)_2$), 1.93 (s, 3H, C_{ar}-CH_3), 0,99 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$), 0.84 (d, *J*=7.0Hz, 3H, C*H*$_3$-CH) and -0.12 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6 (C_{ar}), 141.3 (C_{ar}), 135.7 (*C*$_{ar}$-CH_3), 129.5 (2xCH_{ar}), 129.3 (2xCH_{ar}), 127.9 (2xCH_{ar}), 127.1 (2xCH_{ar}), 126.1 (CH_{ar}), 69.6 (C_q), 41.9 (*C*H-CH_3), 29.4 (C_{ar}-*C*H_3), 25.7 (N-CH_3), 24.5 (*C*H-$(CH_3)_2$), 20.9 (CH-(*C*H_3)$_2$), 17.1 (CH-(*C*H_3)$_2$) and 9.3 (*C*H_3-CH).

HRMS (ES): calcd for $C_{20}H_{28}N$ 282.2216 found 282.2217 $(M+H)^+$.

1-[(1*R**,2*R**)-1-(4-Fluorophenyl)-2,3-dimethyl-1-phenyl-butyl]-1,3-dimethyl-urea **278**:

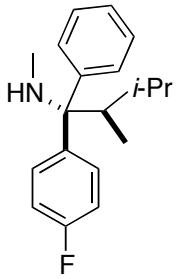


The product was synthesised following the procedure 6 (conditions b) for 4h starting from 100mg (0.33mmol) of the urea. The desired product was obtained in 69% yield (80mg) as a clear yellow oil.

(Due to the instability of the product, only ^{1}H NMR analysis had been done).

^{1}H NMR (300 MHz, CD_3OD): δ 7.53-6.96 (m, 9H, 9xAr*H*), 3.57 (br s, 1H, C*H*-CH_3), 2.79 (s, 3H, N-C*H*$_3$), 2.56 (s, 3H, N-C*H*$_3$), 1.75 (br s, 1H, C*H*-$(CH_3)_2$), 1.01 (d, *J*=6.9Hz, 3H, CH-(C*H*$_3$)$_2$), 0.77 (br d, *J*=6.6Hz, 3H, C*H*$_3$-CH) and -0.28 (br d, *J*=6.9Hz, 3H, CH-(C*H*$_3$)$_2$).

(1*R**,2*R**)-1-(4-Fluorophenyl)-*N*,2,3-trimethyl-1-phenyl-butan-1-amine **279**:



The amine was synthesised following the general procedure 7 starting from 50mg (0.15mmol) of urea. The desired compound was obtained in 75% yield (30mg) as an oil.

R$_f$: 0.2 (PE/EtOAc:7/3).

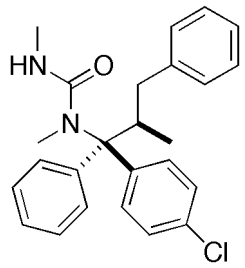
IR υ_{max} (film)/cm^{-1}: 3432, 2956, 1603 and 1506.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.18 (m, 7H, 7xAr*H*), 6.90 (t, *J*=8.5Hz, 2H, 2xAr*H*), 2.34 (q, *J*=7.0Hz, 1H, C*H*-CH_3), 2.08 (sept, *J*=6.8Hz, 1H, C*H*-$(CH_3)_2$), 1.83 (s, 3H, N-C*H*$_3$), 0.94 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$), 0.77 (d, *J*=7.0Hz, 3H, C*H*$_3$-CH) and -0.17 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2 (d, J_F=243.6Hz, C_{ar}-F), 139.9 (d, J_F=3.3Hz, C_{ar}), 131.0 (C_{ar}), 130.9 (d, J_F=7.6Hz, 2xCH_{ar}), 129.3 (2xCH_{ar}), 127.3 (2xCH_{ar}), 126.4 (CH_{ar}), 113.8 (d, J_F=20.5Hz, 2xCH_{ar}), 69.5 (C_q), 41.7 (*C*H-CH_3), 29.3 (N-CH_3) , 25.8 (*C*H-$(CH_3)_2$), 24.4 (CH-(*C*H$_3$)$_2$), 17.0 (CH-(*C*H$_3$)$_2$) and 9.0 (*C*H$_3$-CH).

HRMS (ES): calcd for $C_{19}H_{25}NF$ 286.1966 found 286.1959 $(M+H)^+$.

1-[(1*R**,2*R**)-1-(4-Chlorophenyl)-2-methyl-1,3-diphenyl-propyl]-1,3-dimethyl-urea **280**:

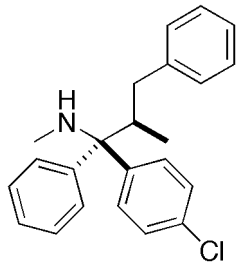


(-)-Sparteine (2 eq.) was solubilised in toluene (0.1M). The mixture was cooled to –40°C and the *i*-PrLi (2 eq.) was added slowly. The mixture was strirred at –40°C for 30 min. The urea **(*E*)-242j** (50mg, 0.16 mmol, 1 eq.) was solubilised in toluene (0.1M) and added really slowly to the organolithium solution (4mL/h). The reaction was quenched at -40°C after 2.5h with MeOH. The reaction mixture was washed with NH_4Cl and extracted with EtOAc. The organic phases were combined and dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude was purified by flash chromatography (PE/EtOAc: 7/3 +1% NEt_3). The compound was isolated as a colourless oil in 50% yield (35mg).

(Due to the instability of the product, only ^{1}H NMR analysis has been done).

^{1}H NMR (300 MHz, CD_3OD): δ 7.46-7.10 (m, 14H, 14xAr*H*), 4.06 (br s, 1H, C*H*-CH_3), 2.82 (s, 3H, N-C*H*$_3$), 2.61 (s, 3H, N-C*H*$_3$), 1.51 (m, 2H, C*H*$_2$-Ph) and 0.56 (br s, 3H, C*H*$_3$-CH).

(1*R**,2*R**)-1-(4-Chlorophenyl)-*N*,2-dimethyl-1,3-diphenyl-propan-1-amine **281**:



The amine was synthesised following the general procedure 7 starting from 30mg of urea. The desired compound was obtained in 65% yield (17mg) as a colourless oil.

R_f: 0.2 (PE/EtOAc: 7/3).

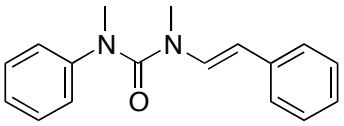
IR υ_{max} (film)/cm^{-1}: 3330, 2247 and 1600.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.07 (m, 14H, 14xAr*H*), 3.28 (d, *J*=13.0Hz, 1H, CH-C*H*$_2$-Ph), 2.65 (m, 1H, C*H*-CH_3), 1.99 (s, 3H, N-C*H*$_3$), 1.55 (dd, *J*=13.0 and 11.5Hz, 1H, CH-C*H*$_2$-Ph) and 0.70 (d, *J*=7.0Hz, 3H, C*H*$_3$-CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 143.0 (C_{ar}), 141.8 (C_{ar}), 141.5 (C_{ar}), 132.3 (C_{ar}-Cl), 131.1 (CH_{ar}), 129.2 (2xCH_{ar}), 129.1 (CH_{ar}), 128.2 (2xCH_{ar}), 127.4 (2xCH_{ar}), 127.3 (2xCH_{ar}), 126.5 (2xCH_{ar}), 125.7 (2xCH_{ar}), 69.5 (C_q), 39.2 (*C*H-CH_3), 38.2 (CH_2-Ph), 29.3 (N-CH_3) and 15.1 (*C*H_3-CH).

HRMS (ES): calcd for $C_{23}H_{24}NCl$ 350.1670 found 350.1657 $(M+H)^+$.

1,3-Dimethyl-1-phenyl-3-[(*E*)-styryl]urea **287**:



Styrene isocyanate was synthesised following the described procedure.*

Trans-cinnamic acid (500mg, 3.37mmol, 1 eq.) was solubilised in benzene (0.7M) and treated with dppa (1 eq.) and triethylamine (1.1 eq.). The reaction was stirred for 4h at room temperature. The reaction was quenched by addition of NH_4Cl and the organic phase was sequentially washed with 1N $KHSO_4$, H_2O, $NaHCO_3$ (sat.) and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure **at 25°C**. The crude mixture was solubilised in toluene (0.3M) and refluxed. After 2h, the reaction mixture was cooled to room temperature and treated with *N*-methylaniline (1 eq.). The reaction was strirred for 16h at room temperature. The solvent was evaporated and the crude mixture was solubilised in THF (0.3M). The reaction was cooled to 0°C and treated with NaH (2 eq.). After 30 min, MeI (3 eq.) was added and the reaction was stirred for 16h. The reaction was then diluted with Et_2O and carefully quenched with H_2O. The reaction mixture was washed with H_2O and extracted wit EtOAc. The organic phase was dried ($MgSO_4$) filtered and concentrated under vacuum. The desired urea was obtained in 35% (325mg) as an oil after purification by flash chromatography (PE/EtOAc: 8/2 +1% NEt_3).

R_f: 0.4 (PE/EtOAc: 7/3).

IR υ_{max} (film)/cm^{-1}: 2932, 1667, 1639 and 1595.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J*=14.5Hz, 1H, C*H*-N), 7.39-7.06 (m, 10H, 10xAr*H*), 5.58 (d, *J*=14.5Hz, 1H), 3.34 (s, 3H, N-CH_3) and 2.90 (s, 3H, N-CH_3).

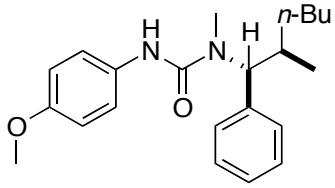
^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4 (C=O), 145.9 (C_{ar}), 137.3 (C_{ar}), 131.0 (CH-N), 129.7 (2xCH_{ar}), 128.5 (2xCH_{ar}), 125.6 (CH_{ar}), 125.3 (CH-Ph), 125.1 (2xCH_{ar}), 124.3 (2xCH_{ar}), 107.5 (CH_{ar}), 39.9 (N-CH_3) and 33.5 (N-CH_3).

HRMS (ES): calcd for $C_{17}H_{19}N_2O$ 267.1492 found 267.1495 $(M+H)^+$.

Elem. anal.: calcd: C 76.66, H 6.81, N 10.52 found: C 76.55, H 6.32, N 10.49.

* Greco, M. N. *et al*. *J. Med. Chem.* **2007,** *50,* 1727-1730.

3-(4-Methoxyphenyl)-1-methyl-1-[(1*R**,2*R**)-2-methyl-1-phenyl-hexyl]urea **291**:



The compound was synthesised following the general procedure 8 starting from 53mg (0.18mmol) of urea. The desired product was obtained in 80% yield (40mg) as a colourless oil.

R_f: 0.6 (PE/EtOAc: 7:3).

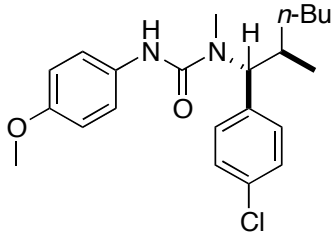
IR υ_{max} (film)/cm^{-1}: 2956, 1633, 1600 and 1513.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.24 (m, 7H, 7xAr*H*), 6.85-6.81 (m, 2H, 2xAr*H*), 6.17 (br s, 1H, N*H*), 5.27 (d, *J*=11.2Hz, 1H, C*H*-N), 3.77 (s, 3H, O-CH_3), 2.76 (s, 3H, N-CH_3), 2.20 (m, 1H, C*H*-CH_3), 1.53-1.21 (m, 6H, CH_2-CH_2-CH_2), 0.93 (t, *J*=6.8Hz, 3H, CH_3-CH_2) and 0.84 (d, *J*=6.4Hz, 3H, CH_3-CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0 (C=O), 155.7 (C_{ar}-OCH_3), 139.7 (C_{ar}), 132.2 (C_{ar}), 128.5 (2xCH_{ar}), 128.4 (2xCH_{ar}), 127.3 (CH_{ar}), 122.1 (2xCH_{ar}), 114.0 (2xCH_{ar}), 62.4 (CH-N), 55.5 (O-CH_3), 32.6 (*C*H_2-CH_2-CH_2), 32.2 (*C*H-CH_3), 29.0 (*C*H_2-CH_2-CH_3), 28.7 (N-CH_3), 23.0 (*C*H_2-CH_2), 17.1 (*C*H_3-CH) and 14.2 (*C*H_3-CH_2).

HRMS (ES): calcd 377.2199 for $C_{22}H_{30}N_2O_2Na$ found 377.2207 $(M+Na)^+$.

1-[(1*R**,2*R**)-1-(4-Chlorophenyl)-2-methyl-hexyl]-3-(4-methoxyphenyl)-1-methyl-urea **292a**:



The compound was synthesised following the general procedure 8 starting from 98mg (0.30mmol) of urea. The desired product was obtained in 87% yield (100mg) as a colourless oil.

R_f: 0.6 (PE/EtOAc: 7:3).

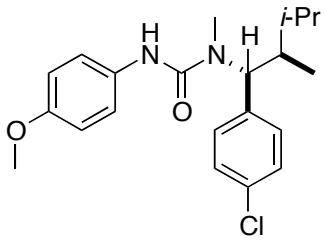
IR υ_{max} (film)/cm^{-1}: 3325, 2956 and 1684.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.22 (m, 6H, 6xAr*H*), 6.77 (d, *J*=8.8Hz, 2H, 2xAr*H*), 6.26 (s, 1H, N*H*), 5.22 (d, *J*=8.8Hz, 1H, C*H*-N), 3.73 (s, 3H, O-CH_3), 2.68 (s, 3H, N-CH_3), 2.12 (m, 1H, C*H*-CH_3), 1.46-1.12 (m, 6H, CH_2-CH_2-CH_2), 0.89 (t, *J*=6.8Hz, 3H, CH_3-CH_2) and 0.78 (d, *J*=6.4Hz, 3H, CH_3-CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.0 (C=O), 155.7 (C_{ar}-OCH_3), 138.2 (C_{ar}), 132.9 (C_{ar}), 132.0 (C_{ar}-Cl), 129.8 (2xCH_{ar}), 128.5 (2xCH_{ar}), 122.3 (2xCH_{ar}), 113.9 (2xCH_{ar}), 61.5 (CH-N), 55.4 (O-CH_3), 32.4 (*C*H_2-CH), 32.0 (*C*H-CH_3), 28.8 (CH_2-*C*H_2-CH_2), 28.6 (N-CH_3), 22.9 (*C*H_2-CH_3), 16.9 (*C*H_3-CH) and 14.1 (*C*H_3-CH_2).

HRMS (ES): calcd 387.1844 for $C_{22}H_{28}N_2O_2Cl$ found 387.1847$(M-H)^-$.

1-[(1*R**,2*R**)-1-(4-Chlorophenyl)-2,3-dimethyl-butyl]-3-(4-methoxyphenyl)-1-methyl-urea **292b**:



The compound was synthesised following the general procedure 8 starting from 99mg (0.30mmol) of urea. The desired product was obtained in 98% yield (110mg) as white solid. The compound was recrystallised from petroleum ether.

R_f: 0.6 (PE/EtOAc: 7:3).

m.p.: 157-158°C (PE).

IR υ_{max} (film)/cm^{-1}: 3361, 1643 and 1511.

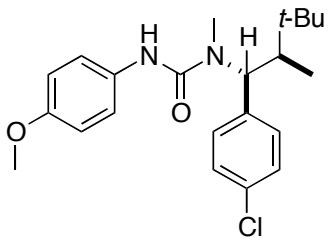
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.30 (m, 4H, 4xAr*H*), 7.28-7.24 (m, 2H, 2xAr*H*), 6.84-6.80 (m, 2H, 2xAr*H*), 5.40 (d, *J*=12.0Hz, 1H, C*H*-N), 3.77 (s, 3H, O-C*H*$_3$), 2.73 (s, 3H, N-C*H*$_3$), 2.15 (m, 1H, C*H*-CH_3), 1.82 (dsept, *J*=6.8 and 2.4Hz, 1H, C*H*-$(CH_3)_2$), 1.01 (d, *J*=6.8 Hz, 3H, CH-(C*H*$_3$)$_2$), 0.88 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$) and 0.67 (d, *J*=6.8Hz, 3H C*H*$_3$-CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7 (C=O), 155.7 (C_{ar}-OCH_3), 138.3 (C_{ar}), 133.0 (C_{ar}), 132.0 (C_{ar}-Cl), 129.8 (2xCH_{ar}), 128.6 (2xCH_{ar}), 122.3 (2xCH_{ar}), 114.0 (2xCH_{ar}), 59.4 (CH-N), 55.5 (O-CH_3), 37.0 (*C*H-CH_3), 28.6 (N-CH_3), 27.1 (*C*H-$(CH_3)_2$), 21.8 (CH-(*C*H$_3$)$_2$), 15.1 (CH-(*C*H$_3$)$_2$) and 10.5 (*C*H$_3$-CH).

HRMS (ES): calcd 373.1688 for $C_{21}H_{26}N_2O_2Cl$ found 373.1689 $(M-H)^-$.

Elem. Anal.: calcd C 67.28, H 7.26 and N 7.47 found C 67.56, H 7.52 and N 7.49.

1-[(1*R**,2*R**)-1-(4-chlorophenyl)-2,3,3-trimethyl-butyl]-3-(4-methoxyphenyl)-1-methyl-urea **292c**:



The compound was synthesised following the general procedure 8 starting from 98mg (0.29mmol) of urea. The desired product was obtained in 98% yield (120mg) as a clear yellow oil.

R_f: 0.6 (PE/EtOAc: 7:3).

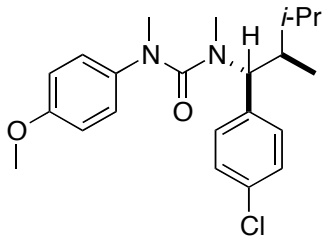
IR υ_{max} (film)/cm^{-1}: 3341, 2953, 2834, 1664, 1534 and 1514.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.22 (m, 6H, 6xAr*H*), 6.80-6.76 (m, 2H, 2xAr*H*), 6.28 (br s, 1H, N*H*), 5.56 (d, *J*=10.8Hz, 1H, C*H*-N), 3.74 (s, 3H, O-C*H*$_3$), 2.68 (s, 3H, N-C*H*$_3$), 2.06 (dq, *J*=10.8 and 6.8Hz, 1H, C*H*-CH_3), 1.02 (s, 9H, 3x(C*H*$_3$)-C) and 0.69 (d, *J*=6.8Hz, 3H, C*H*$_3$-CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6 (C=O), 155.3 (C_{ar}-OCH_3), 139.5 (C_{ar}), 132.4 (C_{ar}), 131.9 (C_{ar}-Cl), 129.5 (2xCH_{ar}), 128.4 (2xCH_{ar}), 122.4 (2xCH_{ar}), 113.8 (2xCH_{ar}), 59.1 (CH-N), 55.4 (O-CH_3), 40.5 (*C*H-CH_3), 33.5 (*C*-$(CH_3)_3$), 30.0 (N-CH_3), 28.3 (3xC-*C*H$_3$) and 14.8 (*C*H$_3$-CH).

HRMS (ES): calcd 387.1844 for $C_{22}H_{28}N_2O_2Cl$ found 387.1844 $(M-H)^-$.

1-[(1*R**,2*R**)-1-(4-Chlorophenyl)-2,3-dimethyl-butyl]-3-(4-methoxyphenyl)-1,3-dimethyl-urea **293**:



The product was prepared following the general procedure 8 starting from 40mg of urea **(*E*)-242m**. The desired compound in obtained in 60% yield (30mg) as an oil.

Alternatively, the compound can be synthesised by treatment of the urea **292** with sodium hydride (2 eq.), in dry THF at 0°C for 30 min, followed by addition of methyl iodide (2 eq.), at r.t. for 24h. The reaction was diluted with Et_2O and quenched with water. The mixture was extracted with EtOAc, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The desired compound was obtained in 60% yield after flash chromatography on silica gel (PE/EtOAc: 9/1).

R_f: 0.6 (PE/EtOAc: 7:3).

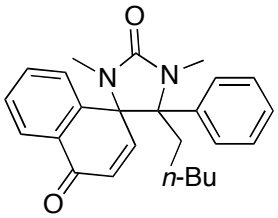
IR υ_{max} (film)/cm^{-1}: 2958, 2361, 1634 and 1509.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.24 (m, 4H, 4xAr*H*), 6.88-6.73 (m, 4H, 4xAr*H*), 5.17 (d, *J*=11.7Hz, 1H, C*H*-N), 3.77 (s, 3H, O-CH_3), 3.07 (s, 3H, N-CH_3), 2.23 (s, 3H, N-CH_3), 2.03 (m, 1H, C*H*-CH_3), 1.71 (dsept, *J*=6.9 and 2.4Hz, 1H, C*H*-$(CH_3)_2$), 0.93 (d, *J*=6.9Hz, 3H, CH-(CH_3)$_2$), 0.92 (d, *J*=6.9Hz, 3H, CH-(CH_3)$_2$) and 0.58 (d, *J*=6.9Hz, 3H, CH_3-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5 (C=O), 156.9 (C_{ar}-OCH_3), 140.1 (C_{ar}), 138.0 (C_{ar}), 132.8 (C_{ar}-Cl), 130.1 (2xCH_{ar}), 128.3 (2xCH_{ar}), 126.2 (2xCH_{ar}), 114.5 (2xCH_{ar}), 61.4 (CH-N), 55.4 (O-CH_3), 41.1 (N-CH_3), 37.1 (*C*H-CH_3), 30.7 (N-CH_3), 26.6 (*C*H-$(CH_3)_2$), 21.8 (CH-(*C*H_3)$_2$), 15.1 (CH-(*C*H_3)$_2$) and 10.4 (CH_3-CH).

HRMS (ES): calcd for $C_{22}H_{29}ClN_2O_2$ 389.1990 found 389.1986 $(M+H)^+$.

1,3-Dimethyl-4-pentyl-4-phenyl-spiro[imidazolidine-5,4'-naphthalene]-1',2-dione **295**:



Urea **294** (50mg, 0.16mmol) was solubilised in dry THF (0.1M) and cooled to −78°C. *n*-BuLi (2 eq.) was then added to the mixture and the reaction was stirred for 1h. The reaction was then put under oxygen atmosphere (balloon) and stirred for 16h increasing slowly the temperature to r.t. The reaction was diluted with EtOAc, extracted with H_2O, dried ($MgSO_4$) and concentrated under reduced pressure. The titled compound was obtained in 56% as an oil yield after flash chromatography on silica gel (PE/EtOAc: 8/2). The compound was isolated as a mixture of diastereoisomer.

R_f: 0.2 (PE/EtOAc: 8/2).

IR υ_{max} (film)/cm^{-1}: 2951, 1706 and 1669.

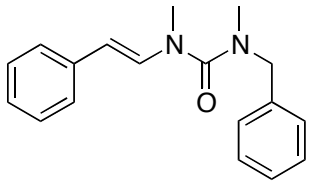
^{1}H NMR (400 MHz, C_6D_6): δ 8.36-8.34 (m, 1H, Ar*H* major dia.), 7.87 (dd, *J*=1.2 and 7.6Hz, 1H, Ar*H* minor dia.), 7.39-7.36 (m, 1H, Ar*H* major dia.), 7.16 (m, 1H, Ar*H* major dia.), 7.07-6.96 (m, 7H, 5xAr*H* major dia. and 2xAr*H* minor dia.), 6.93 (d, *J*=7.2Hz, 1H, Ar*H* minor dia.), 6.81 (dt, *J*=1.6 and 7.6Hz, 2H, 2xAr*H* minor dia.), 6.75-6.71 (m, 2H, Ar*H* major dia. and Ar*H* minor dia.), 6.73 (d, *J*=10.4Hz, 1H, CH=C*H*-C(O) minor dia.), 6.55-6.53 (m, 2H, 2xAr*H* minor dia.), 6.38 (d, *J*=10.4Hz, 1H, C*H*=CH-C(O) minor dia.), 6.05 (d, *J*=10.4Hz, 1H, CH=C*H*-C(O) major dia.), 5.54 (d, *J*=10.4Hz, 1H, C*H*=CH-C(O) major dia), 2.85 (s, 3H, N-CH_3 major dia.), 2.73 (s, 3H, N-CH_3 minor dia.), 2.57 (s, 3H, N-CH_3 minor dia.), 2.45 (s, 3H, N-CH_3 major dia.), 1.97 (ddd, *J*=3.8, 11.6 and 15.6Hz, 1H, C-CH_2 minor dia.), 1.65 (ddd, *J*=3.6, 12.8 and 16.4Hz, 1H, C-CH_2 minor dia.), 1.49-1.41 (m, 2H, C-CH_2 major dia. and C-CH_2-CH_2 minor dia.), 1.30-1.23 (m, 2H, C-CH_2 major dia. and C-CH_2-CH_2 minor dia.), 1.17-0.97 (m, 4H, CH_2-CH_2-C major dia and CH_2-CH_2-CH_3 minor dia.), 0.93-0.83 (m, 5H, CH_3-CH_2 major dia. and CH_2-CH_3 minor dia.), 0.74-0.68 (m, 5H, CH_2-CH_2-CH_3 major dia. and CH_3-CH_2 minor dia.) and 0.62 (t, *J*=7.2Hz, 3H, CH_3 major dia.).

^{13}C NMR (100 MHz, $CDCl_3$): δ 183.9 (CH-*C*=O major dia.), 182.8 (CH-*C*=O minor dia.), 162.0 (N-C=O minor dia.), 161.7 (N-C=O major dia.), 151.0 (C*H*=CH-C(O) major dia.), 147.4 (C*H*=CH-C(O) minor dia.), 140.5 (C_{ar} minor dia.), 139.6 (C_{ar} major dia.), 137.6 (C_{ar} minor dia.), 137.5 (C_{ar} major dia.), 133.4 (*C*H-C(O) minor dia.), 132.9 (C_{ar}), 132.4 (CH_{ar}), 132.1 (C_{ar}), 131.4 (CH_{ar}), 131.0 (*C*H-C(O) major dia.), 128.9 (CH_{ar}), 128.6 (CH_{ar}), 127.9 (CH_{ar}), 127.9 (CH_{ar}), 127.4 (CH_{ar}), 127.3 (CH_{ar}), 127.3 (CH_{ar}), 126.8 (CH_{ar}), 126.4 (CH_{ar}), 74.5 (C_q minor dia), 73.7 (C_q major dia.), 69.0 (C_q minor dia.), 68.5 (C_q major dia.), 36.8 (CH_2 minor dia.), 35.2 (CH_2 major dia.), 32.7 (CH_2 major dia), 32.4 (CH_2 minor dia), 29.5 (CH_3 major dia.), 28.9 (CH_3 minor dia.), 28.1 (CH_3 minor dia.), 27.8 (CH_3 major dia.), 24.6 (CH_2 minor dia.), 24.5 (CH_2 major dia.), 22.4 (CH_2 minor dia.), 22.2 (CH_2 major dia.), 14.1 (CH_3 minor dia.) and 13.8 (CH_3 major dia).

HRMS (ES): calcd for $C_{25}H_{29}N_2O_2$ 389.2224 found 389.2221 $(M+H)^+$.

3.3. N to C vinyl migration

1-Benzyl-1,3-dimethyl-3-[(*E*)-styryl]urea **296**:



A suspension of trans-cinnamic acid (1.00g, 6.70mmol) in dry benzene (0.6M), under inert atmosphere, was stirred in a presence of triethylamine (1eq.) at 0°C. DPPA (1 eq.) was added slowly and the reaction was stirred at room temperature for 3h. The reaction was quenched with saturated NH_4Cl and then washed with 1N $KHSO_4$, H_2O, saturated $NaHCO_3$ and brine. The organic phase was concentrated under reduced pressure **AT ROOM TEMPERATURE**. The acyl azide was solubilised directly in dry toluene (0.6M) and the reaction mixture was reflux for 1h under inert atmosphere. After cooling down the reaction, N-methyl-benzylamine (1 eq.) was added slowly to the isocyanate solution. The reaction was stirred at room temperature for 12h.

The reaction mixture was filtered and the white solid was solubilised in dry DMF (0.3M). Methyliodide (3 eq.) was added and the reaction mixture was cooled to 0°C. After stirring for 30 min., sodium hydride (2.1 eq., 60% in mineral oil) was added really slowly and the reaction was stirred for another hour. The reaction was diluted with Et_2O and carefully quenched with H_2O. The reaction mixture was washed with H_2O. The organic phase was dried ($MgSO_4$) and concentrated under reduce pressure. The crude product was purified by column chromatography (PE/EtOAc :8/2). The desired product **296** was obtained as an oil in 48% overall yield (900mg).

R_f: 0.32 (PE/EtOAc: 7/3).

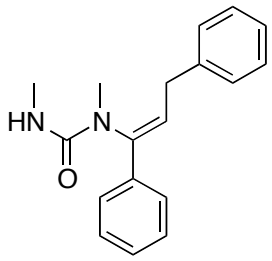
IR υ_{max} (film)/cm^{-1}: 2915, 1634 and 1661.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.09 (m, 11H, 10xAr*H* and Ph-C*H*=CH), 5.74 (d, *J*=14.7Hz, 1H, C*H*-N), 4.48 (s, 2H, CH_2-N), 3.17 (s, 3H, N-CH_3) and 2.86 (s, 3H, N-CH_3).

^{13}C NMR (75MHz, $CDCl_3$): δ 162.1 (C=O), 137.4 (C_{ar}), 137.2 (C_{ar}), 131.9(Ph-*C*H=CH), 128.8 (2xCH_{ar}), 128.6 (2xCH_{ar}), 127.5 (2xCH_{ar}), 127.4 (CH_{ar}), 125.6 (CH_{ar}), 125.0 (2xCH_{ar}), 107.3 (CH-N), 54.6 (CH_2-N), 36.8 (N-CH_3) and 33.7 (N-CH_3).

HRMS: calcd for $C_{18}H_{20}N_2O$ 281.1649 found 281.1650 $(M+H)^+$.

1-[(*Z*)-1,3-Diphenylprop-1-enyl]-1,3-dimethyl-urea **299**:



The rearranged urea **299** was synthesised following the general procedure 10 in 60% yield (0.11mmol) starting from 50mg (0.17mmol) of **296** as an oil. The stereochemistry was confirmed by nOe experiment.

R_f: 0.1 (PE/EtOAc: 7/3).

IR υ_{max} (film)/cm^{-1}: 3444, 3028, 2942, 1652, 1645, 1634 and 1520.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7-30 (m, 8H, 8xAr*H*), 7.25-7.21 (m,

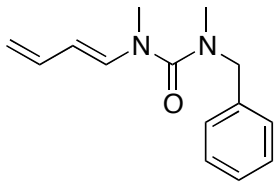
2H, 2xAr*H*), 6.32 (t, *J*=7.2Hz, 1H, C*H*=C), 4.66 (br q, *J*=4.4Hz, 1H, N*H*), 3.58 (br d, *J*=7.2Hz, 1H, CH_2-CH), 3.51 (br d, *J*=7.2Hz, 1H, CH_2-CH), 3.09 (s, 3H, N-CH_3) and 2.72 (d, *J*=4.4Hz, 3H, N-CH_3).

^{13}C NMR (100MHz, $CDCl_3$): δ 157.7 (C=O), 140.0 (C_{ar}), 139.1 (C_{ar}), 135.6 (*C*=CH), 128.9 (2xCH_{ar}), 128.7 (2xCH_{ar}), 128.5 (CH_{ar}), 128.4 (2xCH_{ar}), 127.9 (*C*H=C), 126.4 (CH_{ar}), 125.6 (2xCH_{ar}), 34.6 (N-CH_3), 34.1 (CH_2) and 27.1 (N-CH_3).

HRMS: calcd for $C_{18}H_{20}N_2O$ 281.1649 found 281.1642 $(M+H)^+$.

nOe: irridiation at 6.32 ppm (C*H*=C) enhanced aromatic peaks.

1-Benzyl-3-[(1*E*)-buta-1,3-dienyl]-1,3-dimethyl-urea **301**:



A suspension of 2,4 pentadienoic acid (500mg, 5.00mmol) in dry benzene (0.6M), under inert atmosphere, was stirred in a presence of triethylamine (1 eq.) at 0°C. DPPA (1 eq.) was added slowly and the reaction was stirred at room temperature for 3h. The reaction was quenched with saturated NH_4Cl and then washed with 1N $KHSO_4$, H_2O, saturated $NaHCO_3$ and brine. The organic phase was concentrated under reduce pressure AT ROOM TEMPERATURE. The acyl azide was solubilised directly in dry toluene (0.6M) and the reaction mixture was reflux for 3h under inert atmosphere. After cooling down the reaction, benzylamine (1 eq.) was added slowly to the isocyanate solution. The reaction was stirred at room temperature for 12h.

The reaction mixture was filtered and the white solid was solubilised in dry DMF (0.3M). Methyliodide (3 eq.) was added and the reaction mixture was cooled to 0°C. After stirring for 30 min., sodium hydride (2.1 eq., 60% in mineral oil) was added really slowly and the reaction was stirred for another hour. The reaction was diluted with Et_2O and carefully quenched with H_2O. The reaction mixture was washed with H_2O. The organic phase was dried ($MgSO_4$) and concentrated under reduce pressure. The crude product was filtered through silica (first using pentane then EtOAc) to remove the grease and the desired product **301** was obtained as an oil in 42% overall yield (500mg).

R_f: 0.56 (PE/EtOAc: 7/3).

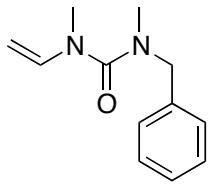
IR υ_{max} (film)/cm^{-1}: 2905, 1661 and 1637.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.25 (m, 5H, 5xAr*H*), 6.80 (d, *J*=14.1Hz, 1H, C*H*-N), 6.23 (dt, *J*=17.0 and 10.5Hz, 1H, CH_2=C*H*-CH), 5.52 (dd, *J*= 10.5 and 14.1Hz, 1H, C*H*=CH-N), 5.25 (dd, *J*=1.6 and 17.0Hz, 1H, C$H_{2(trans)}$=CH), 4.85 (dd, *J*=1.6 and 10.5Hz, 1H, C$H_{2(cis)}$=CH), 4.42 (s, 2H, CH_2-N), 3.06 (s, 3H, N-CH_3) and 2.78 (s, 3H, CH_3).

^{13}C NMR (75MHz, $CDCl_3$): δ 161.9 (C=O), 137.1 (C_{ar}), 135.4 (CH_2=*C*H-CH), 135.1 (CH-N), 128.7 (2xCH_{ar}), 127.7 (2xCH_{ar}), 127.5 (CH_{ar}), 111.9 (*C*H_2=CH), 108.7 (*C*H=CH-N), 54.3 (CH_2-N), 36.7 (N-CH_3) and 33.7 (N-CH_3).

HRMS: calcd for $C_{14}H_{18}N_2O$ 253.1312 found 253.1315 $(M+Na)^+$.

1-Benzyl-1,3-dimethyl-3-vinyl-urea **302**:



The urea **302** was synthesised following the general procedure 9 in 12% yield (118mg) as an oil starting from 200mg (2.90mmol) of vinylisocyanate.

R*f*: 0.6 (PE/EtOAc: 6/4).

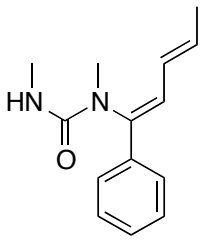
IR υ_{max} (film)/cm^{-1}: 2921, 1654 and 1619.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.25 (m, 5H, 5xAr*H*), 6.76 (dd, *J*=9.0 and 15.6Hz, 1H, C*H*=CH_2), 4.42 (s, 2H, CH_2-N), 4.21 (d, *J*=15.6Hz, 1H, $CH_{2(cis)}$=CH), 4.15 (dd, *J*=0.6 and 9.0Hz, 1H, $CH_{2(trans)}$=CH), 3.02 (s, 3H, N-CH_3) and 2.78 (s, 3H, N-CH_3).

^{13}C NMR (75MHz, $CDCl_3$): δ 162.2 (C=O), 137.3 (C_{ar}), 136.9 (*C*H=CH_2), 128.6 (2xCH_{ar}), 127.7 (2xCH_{ar}), 127.4 (CH_{ar}), 89.3 (*C*H_2=CH), 54.2 (CH_2-N), 36.7 (N-CH_3) and 32.7 (N-CH_3).

HRMS: calcd for $C_{12}H_{16}N_2O$ 227.1155 found 227.1158 $(M+Na)^+$.

1,3-Dimethyl-1-[(1*Z*,3*E*)-1-phenylpenta-1,3-dienyl]urea **303**:



The urea **303** was synthesised following the general procedure 10 in 70% yield (76mg) as an oil starting from 108mg (0.47mmol) of urea **301**.

R*f*: 0.1 (PE/EtOAc: 7/3).

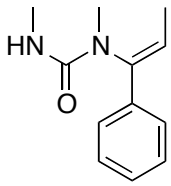
IR υ_{max} (film)/cm^{-1}: 3351, 2932, 1650 and 1523.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.28 (m, 5H, 5xAr*H*), 6.64 (d, *J*=10.7Hz, 1H, C=C*H*), 6.27 (ddq, *J*=15.2, 10.7 and 1.6Hz, 1H, CH-C*H*=CH), 6.03 (ddq, *J*=15.2, 0.8 and 6.8Hz, 1H, CH_3-C*H*=CH), 4.63 (q, *J*=4.4Hz, 1H, N*H*), 3.07 (s, 3H, N-CH_3), 2.74 (d, *J*=4.4Hz, 3H, N-CH_3), 1.86 (dd, *J*=6.8 and 1.6 Hz, 3H, CH_3-CH).

^{13}C NMR (100MHz, $CDCl_3$): δ 157.8 (C=O), 137.0 (C_{ar}), 135.7 (*C*=CH), 134.8 (*C*-CH_3), 128.9 (2xCH_{ar}), 128.3 (CH_{ar}), 127.2 (*C*H=C), 126.5 (*C*H=CH-CH_3), 125.3 (2xCH_{ar}), 34.8 (N-CH_3), 27.5 (N-CH_3) and 18.8 (*C*H_3-CH).

HRMS: calcd for $C_{14}H_{18}N_2O$ 253.1312 found 253.1302 $(M+Na)^+$.

1,3-Dimethyl-1-[(*Z*)-1-phenylprop-1-enyl]urea **304**:



The rearranged **304** urea was synthesised following the general procedure 10 in 70% yield (35mg) as an oil starting from 50mg (0.25mmol) of urea **302**.

R_f: 0.21 (PE/EtOAc: 6/4).

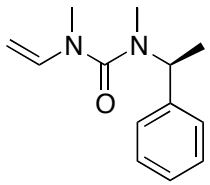
IR υ_{max} (film)/cm^{-1}: 3352, 2958, 1640 and 1524.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.26 (m, 5H, 5xAr*H*), 6.19 (q, *J*=6.9Hz, 1H, C*H*-CH_3), 4.65 (br s, 1H, N*H*), 3.02 (s, 3H, N-CH_3), 2.75 (d, *J*=4.8Hz, 3H, N-CH_3) and 1.79 (d, *J*=6.9Hz, 3H, CH_3-CH).

^{13}C NMR (75MHz, $CDCl_3$): δ 157.6 (C=O), 140.7 (C_{ar}), 136.0 (*C*=CH), 128.8 (2xCH_{ar}), 128.2 (CH_{ar}), 125.3 (2xCH_{ar}), 124.0 (*C*H-CH_3), 34.1 (N-CH_3), 27.5 (N-CH_3) and 13.4 (*C*H_3-CH).

HRMS: calcd for $C_{12}H_{16}N_2O$ 227.1155 found 227.1159 $(M+Na)^+$.

1,3-Dimethyl-1-[(1*S*)-1-phenylethyl]-3-vinyl-urea **(*S*)-308a**:



The urea was synthesised following the general procedure 9 in 55% yield (174mg) as an oil, starting from 100mg (1.50mmol) of vinylisocyanate.

R_f: 0.1 (PE/EtOAc: 9/1).

IR υ_{max} (film)/cm^{-1}: 2972, 1653, 1647, 1628 and 1539.

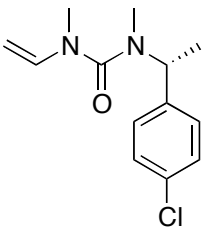
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.24 (m, 5H, 5xAr*H*), 6.72 (dd, *J*=9.0 and 15.4Hz, 1H, C*H*=CH_2), 5.27 (q, *J*=7.4Hz, 1H, C*H*-N), 4.20 (dd, *J*=15.4 and 0.8Hz, 1H, C$H_{2(trans)}$=CH), 4.14 (dd, *J*=9.0 and 0.8Hz, 1H, C$H_{2(cis)}$=CH), 3.02 (s, 3H, N-CH_3), 2.57 (s, 3H, N-CH_3) and 1.58 (d, *J*= 7.4Hz, 3H, CH_3-CH).

^{13}C NMR (75MHz, $CDCl_3$): δ 162.1 (C=O), 140.7 (C_{ar}), 137.1 (*C*H=CH_2), 128.5 (2xCH_{ar}), 127.2 (3xCH_{ar}), 89.0 (CH_2), 54.9 (CH-N), 32.8 (N-CH_3), 31.3 (N-CH_3) and 16.0 (CH_3-CH).

HRMS: calcd for $C_{13}H_{18}N_2O$ 241,1312 found 241,1321 $(M+Na)^+$.

$[\alpha]^{25}_D$: -45.2 (*c*=1 in $CHCl_3$).

1-[(1*R*)-1-(4-Chlorophenyl)ethyl]-1,3-dimethyl-3-vinyl-urea **(*R*)-308b**:



The urea was synthesised following the general procedure 9 in 90% yield (330mg) as an oil starting from 100mg (1.50mmol) of vinylisocyanate.

R_f: 0.2 (PE/EtOAc: 8/2).

IR υ_{max} (film)/cm^{-1}: 2921, 1655 and 1620.

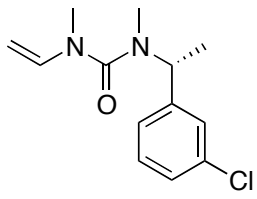
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.25 (m, 4H, 4xAr*H*), 6.69 (dd, *J*= 9.3 and 15.6Hz, 1H, C*H*=CH_2), 5.24 (q, *J*=7.1Hz, 1H, C*H*-N), 4.21 (dd, *J*=0.8 and 15.6Hz, 1H, C$H_{2(cis)}$=CH), 4.16 (dd, *J*= 0.8 and 9.0Hz, 1H, C$H_{2(trans)}$=CH), 3.00 (s, 3H, N-CH_3), 2.56 (s, 3H, N-CH_3) and 1.55 (d, *J*=7.1Hz, 3H, CH_3-CH).

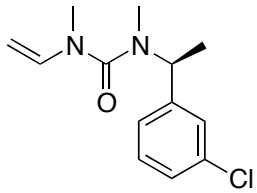
^{13}C NMR (75MHz, $CDCl_3$): δ 162.0 (C=O), 139.3 (C_{ar}), 136.9 (*C*H=CH_2), 133.1 (C_{ar}-Cl), 128.7 (2xCH_{ar}), 128.6 (2xCH_{ar}), 89.3 (CH_2), 54.2 (CH-N), 32.8 (N-CH_3), 31.4 (N-CH_3) and 16.0 (*C*H_3-CH).

HRMS: calcd for $C_{13}H_{17}N_2OCl$ 275.0922 found 275.0933 $(M+Na)^+$.

$[\alpha]^{25}_D$: +75.2 (*c*=1 in $CHCl_3$).

1-[1-(3-Chlorophenyl)ethyl]-1,3-dimethyl-3-vinyl-urea **308c**:





The ureas were synthesised following the general procedure 9 in 50% yield (275mg) as an oil starting from 150mg (2.17mmol) of vinylisocyanate

R_f: 0.25 (DCM).

IR υ_{max} (film)/cm^{-1}: 2976, 1656, 1651, 1620 and 1572.

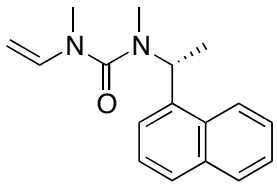
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.21 (m, 4H, 4xAr*H*), 6.71 (dd, *J*=9.0 and 15.6Hz, 1H, C*H*=CH_2), 5.25 (q, *J*=6.9Hz, 1H, C*H*-N), 4.22 (dd, *J*=0.9 and 15.6Hz, 1H, C$H_{2(cis)}$=CH), 4.18 (dd, *J*=0.9 and 9.0Hz, 1H, C$H_{2(trans)}$=CH), 3.01 (s, 3H, N-CH_3), 2.58 (s, 3H, N-CH_3) and 1.55 (d, *J*=6.9Hz, 3H, CH_3-CH).

^{13}C NMR (75MHz, $CDCl_3$): δ 161.9 (C=O), 143.0 (C_{ar}), 136.8 (*C*H=CH_2), 134.4 (C_{ar}-Cl), 129.7 (CH_{ar}),127.4 (CH_{ar}), 127.3 (CH_{ar}), 125.5 (CH_{ar}), 89.3 (CH_2), 54.3 (CH-N), 32.8 (N-CH_3), 31.4 (N-CH_3) and 15.9 (*C*H_3-CH).

HRMS: calcd for $C_{13}H_{17}N_2OCl$ 253.1103 found 253.1105 $(M+H)^+$.

$[\alpha]^{20}_D$: +58.5 (*R*) (*c*=1 in $CHCl_3$) and -65.0 (*S*) (*c*=2 in $CHCl_3$).

1,3-Dimethyl-1-[(1*R*)-1-(1-naphthyl)ethyl]-3-vinyl-urea **(*R*)-308d**:



The urea was synthesised following the general procedure 9 in 85% yield (485mg) as an oil starting from 150mg (2.17mmol) of vinylisocyanate.

R_f: 0.1 (DCM).

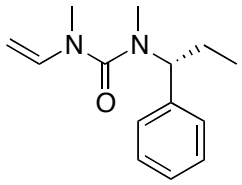
IR υ_{max} (film)/cm^{-1}: 2971, 1651, 1644 and 1634.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90-7-81 (m, 3H, 3xAr*H*), 7.55-7.44 (m, 4H, 4xAr*H*), 6.49 (dd, *J*=9.0 and 15.6Hz, 1H, C*H*=CH_2), 6.00 (q, *J*=6.9Hz, 1H, C*H*-N), 4.13 (dd, *J*=0.8 and 15.6Hz, 1H, C$H_{2(cis)}$=CH), 4.02 (dd, *J*=0.8 and 9.0Hz, 1H, C$H_{2(trans)}$=CH), 2.96 (s, 3H, N-CH_3), 2.40 (s, 3H, N-CH_3) and 1.74 (d, *J*=6.9Hz, 1H, CH_3-CH).

^{13}C NMR (75MHz, $CDCl_3$): δ 161.3 (C=O), 137.1 (*C*H=CH_2), 136.0 (C_{ar}), 133.9 (C_{ar}), 131.8 (C_{ar}), 128.8 (CH_{ar}), 128.5 (CH_{ar}), 126.6 (CH_{ar}), 125.9 (CH_{ar}), 124.9 (CH_{ar}), 124.5 (CH_{ar}), 123.4 (CH_{ar}), 88.6 (CH_2), 51.0 (CH-N), 32.9 (N-CH_3), 31.6 (N-CH_3) and 14.9 (*C*H_3-CH).

HRMS: calcd for $C_{17}H_{20}N_2O$ 291.1468 found 291.1467 $(M+Na)^+$.

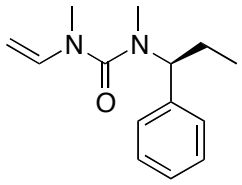
1,3-Dimethyl-1-[1-phenylpropyl]-3-vinyl-urea **308e**:



The ureas were synthesised following the general procedure 1 in 30% yield (100mg, for the *R* enantiomer) and 27% (91mg, for the *S* enantiomer) as oils starting from 100mg (1.45mmol) of vinylisocyanate.

R_f: 0.5 (PE/EtOAc: 7/3).

IR υ_{max} (film)/cm^{-1}: 2930 and 1651.



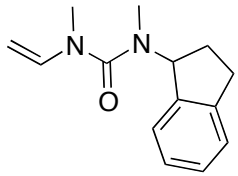
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.27 (m, 5H, 5xAr*H*), 6.69 (dd, *J*=9.0 and 15.5Hz, 1H, C*H*=CH_2), 5.05 (dd, *J*= 6.5 and 9.0Hz, 1H, C*H*-N), 4.18 (d, *J*=15.5Hz, 1H, C$H_{2(cis)}$=CH), 4.11 (dd, *J*=0.5 and 9.0Hz, 1H, C$H_{2(trans)}$=CH), 3.00 (s, 3H, N-CH_3), 2.62(s, 3H, N-CH_3), 2.05 (m, 1H, CH_2-CH_3), 1.95 (m, 1H, CH_2-CH_3) and 0.98 (t, *J*=7.0Hz, 3H, CH_3-CH_2).

^{13}C NMR (125MHz, $CDCl_3$): δ 150.0 (C=O), 139.8 (C_{ar}), 137.2 (*C*H=CH_2), 128.5 (2xCH_{ar}), 127.9 (2xCH_{ar}), 127.4 (2xCH_{ar}), 88.7 (*C*H_2=CH), 61.1 (CH-N), 32.9 (N-CH_3), 31.4 (N-CH_3), 23.4 (*C*H_2-CH_3) and 11.3 (*C*H_3-CH_2).

HRMS: calcd for $C_{14}H_{20}N_2O$ 255.1468 found 255.1472 $(M+Na)^+$.

$[\alpha]^{20}_D$: + 151.0 (*R*) (*c*=1 in $CHCl_3$) and -147.1 (*S*) (*c*=1 in $CHCl_3$).

1-Indan-1-yl-1,3-dimethyl-3-vinyl-urea ***rac*-308f**:



The urea was synthesised following the general procedure 9 in 54% yield (90mg) as an oil starting from 50mg (0.72mmol) of vinylisocyanate.

R_f: 0.4 (PE/EtOAc: 7/3).

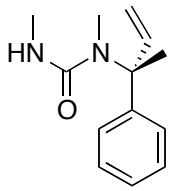
IR υ_{max} (film)/cm^{-1}: 2947, 1653, 1623 and 1534.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-721 (m, 4H, 4xAr*H*), 6.83 (dd, *J*=9.3 and 15.6Hz, 1H, C*H*=CH_2), 5.51 (t, *J*=8.1Hz, 1H, C*H*-N), 4.24 (dd, *J*=0.8 and 15.6Hz, 1H, $CH_{2(cis)}$=CH), 4.19 (dd, *J*=0.8 and 9.3Hz, 1H, $CH_{2(trans)}$=CH), 3.06 (s, 3H, N-CH_3), 2.94 (m, 2H, CH_2-CH_2-CH), 2.57 (s, 3H, N-CH_3), 2.45 (m, 1H, CH_2-CH) and 2.05 (m, 1H, CH_2-CH).

^{13}C NMR (75MHz, $CDCl_3$): δ 162.4 (C=O), 143.5 (C_{ar}), 141.1 (C_{ar}), 137.2 (*C*H=CH_2), 127.8 (CH_{ar}), 126.6 (CH_{ar}), 124.9 (CH_{ar}), 124.3 (CH_{ar}), 89.2 (*C*H_2=CH), 63.3 (CH-N), 32.8 (N-CH_3), 31.5 (N-CH_3), 30.3 (*C*H_2-CH_2-CH) and 28.7 (*C*H_2-CH).

HRMS: calcd for $C_{14}H_{18}N_2O$ 253.1312 found 253.1319 $(M+Na)^+$.

1,3-Dimethyl-1-[(1*R*)-1-methyl-1-phenyl-allyl]urea **(*R*)-309a**:



The urea was synthesised following the general procedure 11 in 52% yield (26mg) as an oil starting from 50mg (0.23mmol) of urea **(*S*)-308a** (*e.r.* : >99 :1).

R_f: 0.1 (PE/EtOAc: 7/3).

IR υ_{max} (film)/cm^{-1}: 3357, 2945, 1635, 1539 and 1534.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7-38-7-22 (m, 5H, 5xAr*H*), 6.31 (dd, *J*= 10.7 and 17.4Hz, 1H, C*H*=CH_2), 5.19 (dd, *J*=0.6 and 10.7Hz, 1H, $CH_{2(trans)}$=CH), 5.10 (dd, *J*=0.6 and 17.4Hz, 1H, $CH_{2(cis)}$=CH), 4.22 (br s, 1H, N*H*), 3.00 (s, 3H, N-CH_3), 2.55 (d, *J*=4.5Hz, 3H, N-CH_3) and 1.72 (s, 3H, C-CH_3).

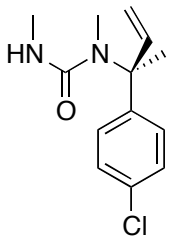
^{13}C NMR (75MHz, $CDCl_3$): δ 159.6 (C=O), 145.7 (C_{ar}), 142.3 (*C*H=CH_2), 128.9 (2xCH_{ar}), 127.2 (CH_{ar}), 125.5 (2xCH_{ar}), 113.4 (*C*H_2=CH), 64.3 (C_q), 32.5 (N-CH_3), 27.4 (N-CH_3) and 25.5 (C-*C*H_3).

HRMS: calcd for $C_{13}H_{18}N_2O$ 241.1312 found 241.1316 $(M+Na)^+$.

$[\alpha]^{20}_D$: -4.6 (*c*=1 in $CHCl_3$).

HPLC: 22.8 min (minor) and 24.4 min (major) (column: (*R*,*R*) Whelk-01; solvent: hexane/IPA: 9/1; 1mL/min).

1-[(1*S*)-1-(4-Chlorophenyl)-1-methyl-allyl]-1,3-dimethyl-urea **(*S*)-309b**:



The urea was synthesised following the general procedure 11 in 90% yield (45mg) as an oil starting from 50mg (0.2mmol) of urea **(R)-308b** (*e.r.* : >99 :1).

R*f*: 0.1 (DCM).

IR υ_{max} (film)/cm^{-1}: 3354, 2985, 2945, 1645 and 1538.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.25 (m, 4H, 4xAr*H*), 6.28 (dd, *J*=10.5 and 17.4Hz, 1H, C*H*=CH_2), 5.19 (dd, *J*=0.6 and 10.5Hz, 1H, C$H_{2(trans)}$=CH), 5.08 (dd, *J*=0.6 and 17.4Hz, 1H, C$H_{2(trans)}$=CH), 4.28 (br s, 1H, N*H*), 2.96 (s, 3H, N-CH_3), 2.60 (d, *J*=4.5Hz, 3H, N-CH_3) and 1.70 (s, 3H, C-CH_3).

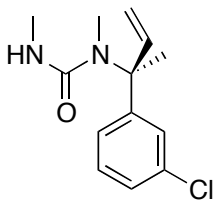
^{13}C NMR (75MHz, $CDCl_3$): δ 159.3 (C=O), 144.6 (C_{ar}), 142.2 (*C*H=CH_2), 132.7 (C_{ar}-Cl), 128.9 (2xCH_{ar}), 126.9 (2xCH_{ar}), 113.6 (*C*H_2=CH), 64.1 (C_q), 32.6 (N-CH_3), 27.4 (N-CH_3) and 25.3 (C-*C*H_3).

HRMS: calcd for $C_{13}H_{17}N_2OCl$ 275.0922 found 275.0921 $(M+Na)^+$.

$[\alpha]^{28}_D$: +22.9 (*c*=1 in $CHCl_3$).

HPLC: 27.1 min (major) and 34.0 min (minor) (column: (*R*,*R*)-Whelk-01; solvent: hexane/IPA: 9/1; 1mL/min).

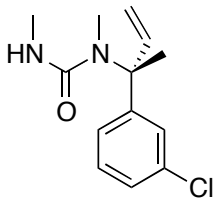
1-[1-(3-Chlorophenyl)-1-methyl-allyl]-1,3-dimethyl-urea **309c**:



Ureas **(*S*)-309c** and **(*R*)-309c** were synthesised following the general procedure 11 in 67% yield (60mg starting from 0.36mmol) and 73% yield (47mg starting from 0.026mmol) as oils.

R*f* 0.1 (DCM).

IR υ_{max} (film)/cm^{-1}: 3357, 2947, 1634 and 1531.



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.19 (m, 4H, 4xAr*H*), 6.28 (dd, *J*=10.7 and 17.4Hz, 1H, C*H*=CH_2), 5.20 (d, *J*=10.7Hz, 1H, C$H_{2(trans)}$=CH), 6.09 (d, *J*=17.4Hz, 1H, C$H_{2(cis)}$=CH), 4.28 (br. s, 1H, N*H*), 2.96 (s, 3H, N-CH_3), 2.61 (d, *J*=4.5Hz, 3H, N-CH_3) and 1.71 (s, 3H, C-CH_3).

^{13}C NMR (75MHz, $CDCl_3$): δ 159.3 (C=O), 148.4 (C_{ar}), 142.0 (*C*H=CH_2), 134.7 (C_{ar}-Cl), 130.0 (CH_{ar}), 127.1 (CH_{ar}), 125.7 (CH_{ar}), 123.6 (CH_{ar}), 113.9 (*C*H_2=CH), 64.3 (C_q), 32.6 (N-CH_3), 27.4 (N-CH_3) and 25.2 (C-*C*H_3).

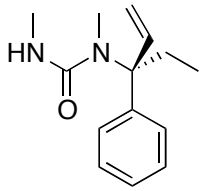
HRMS: calcd for $C_{13}H_{17}N_2OCl$ 275.0922 found 275.0928 $(M+Na)^+$.

$[\alpha]^{20}_D$: –6.8 (*S*) (*c*=1 in $CHCl_3$) and +8.4 (*R*) (*c*=1 in $CHCl_3$).

HPLC: 24.5 min (*S*) and 28.4 min (*R*) (column: (*R*,*R*) Whelk-01; solvent: hexane/IPA: 90/10; 1mL/min).

Elem. Anal.: (*R*) calcd: C 61.78, H 6.78, N 11.08 found: C 61.86, H 6.42, N 10.96.

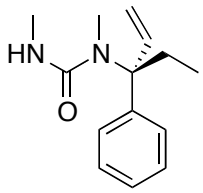
1-(1-Ethyl-1-phenyl-allyl)-1,3-dimethyl-urea **309e**:



The ureas **(*S*)-309e** and **(*R*)-309e** were synthesised following the general procedure 11 in 54% yield (27mg starting from 0.22mmol) and 43% yield (26mg starting from 0.26mmol) as oils.

R_f: 0.1 (DCM).

IR υ_{max} (film)/cm^{-1}: 3352, 2968, 2940, 1634 and 1531.



H NMR (300 MHz, $CDCl_3$): δ 7.36-7.22 (m, 5H, 5xAr*H*), 6.38 (dd, *J*=10.8 and 17.4Hz, 1H, C*H*=CH_2), 5.20 (d, *J*=10.8Hz, 1H, C$H_{2(trans)}$=CH), 4.95 (d, *J*=17.4Hz, 1H, C$H_{2(cis)}$=CH), 4.16 (br s, 1H, N*H*), 3.04 (s, 3H, N-CH_3), 2.54 (d, *J*=4.5Hz, 3H, N-CH_3), 2.29 (m, 1H, CH_2-CH_3), 2.16 (m, 1H, CH_2-CH_3) and 0.82 (t, *J*=7.2Hz, 3H, CH_3-CH_2).

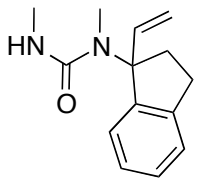
^{13}C NMR (75MHz, $CDCl_3$): δ 159.8 (C=O), 144.5 (C_{ar}), 139.7 (*C*H=CH_2), 128.6 (2xCH_{ar}), 127.1 (CH_{ar}), 126.3 (2xCH_{ar}), 114.2 (*C*H_2=CH), 67.4 (C_q), 33.0 (N-CH_3), 32.3 (*C*H_2-CH_3), 27.4 (N-CH_3) and 9.0 (*C*H_3-CH_2).

HRMS: calcd for $C_{14}H_{20}N_2O$ 255.1468 found 255.1458 $(M+Na)^+$.

$[\alpha]^{20}_D$: +9.2 (*R*) (*c*=1 in $CHCl_3$) and –12.2 (*S*) (*c*=1 in $CHCl_3$).

HPLC: 14.6 min (*R*) and 15.2 min (*S*) (column: chiralpak AD-H; solvent: hexane/IPA: 95/5; 1mL/min).

1,3-Dimethyl-1-(1-vinylindan-1-yl)urea ***rac*-309f**:



The urea was synthesised following the general procedure 11 in 45% yield (32mg) as an oil starting from 70mg (0.30mmol) of urea ***rac*-308f**.

R_f: 0.1 (PE/EtOAc: 7/3).

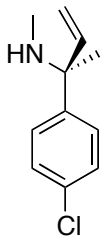
IR υ_{max} (film)/cm^{-1}: 2936, 1636, 1540 and 1533.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.19 (m, 4H, 4xAr*H*), 6.14 (dd, *J*=10.5 and 17.4Hz, 1H, C*H*=CH_2), 5.15 (d, *J*=17.4Hz, 1H, C$H_{2(cis)}$=CH), 5.12 (dd, *J*=10.5 and 0.6 Hz, 1H, C$H_{2(trans)}$=CH), 4.71 (br s, 1H, N*H*), 3.08 (m, 1H, CH_2-C), 2.84 (m, 1H, CH_2-C), 2.74 (d, *J*=4.5Hz, 3H, N-CH_3), 2.73 (s, 3H, N-CH_3) and 2.52 (m, 2H, CH_2-CH_2-C).

^{13}C NMR (75MHz, $CDCl_3$): δ 159.8 (C=O), 144.5 (C_{ar}), 142.8 (*C*H=CH_2), 142.7 (C_{ar}), 128.3 (CH_{ar}), 126.7 (CH_{ar}), 125.4 (CH_{ar}), 125.3 (CH_{ar}), 112.0 (*C*H_2=CH), 73.2 (C_q), 35.4 (CH_2), 33.6 (N-CH_3), 30.3 (CH_2) and 27.5 (N-CH_3).

HRMS: calcd for $C_{14}H_{18}N_2O$ 253.1312 found 253.1318 $(M+Na)^+$.

(2*R*)-2-(4-Chlorophenyl)-*N*-methyl-but-3-en-2-amine **(*S*)-310b**:



The amine was synthesised in 81% yield (31mg) following the general procedure 7 starting from 50mg (0.20mmol) of urea **(*S*)-309b**.

Alternatively

The amine was synthesised following the general procedure 12 starting from 100mg (1.45mmol) of vinylisocyanate and the desired product was obtained in 50% yield (140mg) as an oil.

(Treatment of the amine with 1M HCl in MeOH, for an hour, led to the formation of **(*S*)-310b**•HCl).

R_f: 0.1 (PE/EtOAc : 7/3).

IR υ_{max} (film)/cm^{-1}: 2976 and 1634.

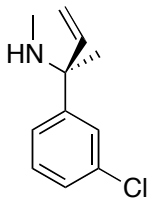
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.36 (m, 2H, 2xAr*H*), 7.30-7.25 (m, 2H, 2xAr*H*), 5.94 (dd, *J*=10.8 and 17.2Hz, 1H, C*H*=CH_2), 5.21 (dd, *J*=1.0 and 10.8Hz, 1H, C$H_{2(trans)}$=CH), 5.16 (dd, *J*=1.0 and 17.2Hz, 1H, C$H_{2(cis)}$=CH), 2.22 (d, *J*=0.3Hz, 3H, N-CH_3), 1.46 (s, 3H, C-CH_3) and 1.40 (br s, 1H, N*H*).

^{13}C NMR (75MHz, $CDCl_3$): δ 144.7 (C_{ar}), 144.2 (*C*H=CH_2), 132.3 (C_{ar}-Cl), 128.2 (2xCH_{ar}), 128.0 (2xCH_{ar}), 113.4 (*C*H_2=CH), 60.4 (C_q), 29.5 (N-CH_3) and 25.2 (C-*C*H_3).

HRMS: calcd for $C_{11}H_{14}ClN$ 196.0888 found 196.0894 $(M+H)^+$.

$[\alpha]^{20}_D$: -4.3 (*c*=1 in $CHCl_3$).

(2*R*)-2-(4-chlorophenyl)-*N*-methyl-but-3-en-2-amine **(*S*)-310c**:



The amine was synthesised following the general procedure 12 starting from 100mg (1.45mmol) of vinylisocyanate and the desired product was obtained in 35% yield (80mg) as an oil.

R_f: 0.1 (PE/EtOAc :7/3).

IR υ_{max} (film)/cm^{-1}: 2976, 2870, 2799, 1636, 1594 and 1570.

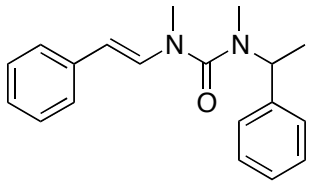
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (t, *J*=2.0Hz, 1H, Ar*H*), 7.32 (dt, *J*=7.6 and 2.0Hz, 1H, Ar*H*), 7.25 (t, *J*=7.6Hz, 1H, Ar*H*), 7.20 (dt, *J*=7.6 and 2.0Hz, 1H, Ar*H*), 5.95 (dd, *J*=10.8 and 17.2Hz, 1H, C*H*=CH_2), 5.22 (dd, *J*=0.9 and 10.8Hz, 1H, C$H_{2(trans)}$=CH), 5.18 (dd, J=0.9 and 17.2Hz, 1H, C$H_{2(cis)}$=CH), 2.94 (s, 3H, N-CH_3) and 1.47 (s, 3H, CH_3).

^{13}C NMR (75MHz, $CDCl_3$): δ 148.4 (C_{ar}), 143.9 (*C*H=CH_2), 134.9 (C_{ar}-Cl), 129.4 (CH_{ar}), 126.9 (CH_{ar}), 126.7 (CH_{ar}), 124.7 (CH_{ar}), 113.6 (*C*H_2=CH), 60.6 (C_q), 29.5 (N-CH_3) and 25.0 (C-*C*H_3).

HRMS: calcd for $C_{11}H_{14}ClN$ 196.0888 found 196.0884 $(M+H)^+$.

$[\alpha]^{20}_D$: -4.3 (*c*=1 in $CHCl_3$).

1,3-Dimethyl-1-(1-phenylethyl)-3-[(*E*)-styryl]urea **311**:



A suspension of cinnamic acid (500mg, 3.35mmol) in dry benzene (0.6M), under inert atmosphere, was stirred in a presence of triethylamine (1 eq.) at 0°C. DPPA (1 eq.) was added slowly and the reaction was trirred at room temperature for 3h. The reaction was quench with saturated NH_4Cl and then washed with 1N $KHSO_4$, H_2O, saturated $NaHCO_3$ and brine.The organic phase was concentrated under reduce pressure AT ROOM TEMPERATURE. The acyl azide was solubilised directly in dry toluene (0.6M) and the reaction mixture was reflux for 3h under inert atmosphere. After cooling down the reaction, α-methylbenzylamine (1 eq.) was added slowly to the isocyanate solution. The reaction was stirred at room temperature for 12h.

The reaction mixture was then filtered and the white solid was solubilised in dry DMF (0.3M). The reaction mixture was cooled to 0°C. After stirring for 30 min., sodium hydride (2.1 eq., 60% in mineral oil) was added really slowly and the reaction was stirred for 30 minutes. Methyliodide (3 eq.) was then added and the reaction was stirred for 16h at room temperature. The reaction was diluted with Et_2O and carefully quench with H_2O. The reaction mixture was washed with H_2O. The organic phase was dried ($MgSO_4$) and concentrated under reduce pressure. The crude product was simply filtered through silica (first using pentane then EtOAc) to remove the grease and the desired product 9 was obtained as an oil in 30% overall yield (300mg) as a white solid.

R_f: 0.3 (PE/EtOAc : 7/3).

M.p.: 81-83 (Et_2O)

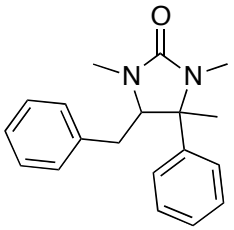
IR υ_{max} (film)/cm^{-1}: 2974, 1656, 1651 and 1634.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-6.99 (m, 11H), 5.64 (d, J=14.4Hz, 1H), 5.19 (q, J= 6.9Hz, 1H), 3.07 (s, 3H), 2.57 (s, 3H) and 1.52 (d, J=6.9Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ 162.1 (C=O), 140.8 (C_{ar}), 137.4 (C_{ar}), 132.0 (CH-Ph), 128.6 (4xCH_{ar}), 127.3 (CH_{ar}), 127.1 (2xCH_{ar}), 125.5 (CH_{ar}), 124.9 (2xCH_{ar}), 106.9 (N-CH), 55.5 (*C*H-CH_3), 33.8 (N-CH_3), 31.3 (N-CH_3) and 16.5 (*C*H_3-CH).

HRMS: calcd for $C_{19}H_{22}N_2O$ 377.1624 found 317.1620 $(M+Na)^+$.

5-Benzyl-1,3,4-trimethyl-4-phenyl-imidazolidin-2-one **312**:



Cyclic urea **312** was synthesised following the general procedure 11 in 64% yield (36mg) as an oil starting from 56mg (0.19mmol) of urea **311**.

Mixture of diasteroisomers 2:1

R_f: 0.2 (DCM).

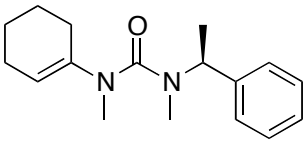
IR υ_{max} (film)/cm^{-1}: 1703, 1698 and 1651.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.10 (m, 16H, 8xAr*H* major dia. and 8xAr*H* minor dia.), 6.98-6.95 (m, 2H, 2xAr*H* major dia.), 6.91-6.88 (m, 2H, 2xArH minor dia.), 3.65-3.58 (m, 2H, C*H*-CH_2 both dia.), 2.91 (t, *J*=6.8Hz, 2H, CH_2-Ph major dia.), 2.64 (s, 3H, N-CH_3, minor dia.), 2.59 (s, 3H, N-CH_3, major dia.), 2.59 (s, 3H, N-CH_3 minor dia.), 2.57 (s, 3H, N-CH_3, major dia.), 2.47 (dd, *J*=6.9 and 14.1Hz, 1H CH_2-CH, minor dia.), 2.26 (dd, *J*=6.9 and 14.4Hz, 1H, CH_2-CH minor dia.), 1.56 (s, 3H, CH_3-C major dia) and 1.54 (s, 3H, CH_3-C minor dia.).

^{13}C NMR (75MHz, $CDCl_3$): 161.4 (C=O), 142.7(C_{ar} major dia.), 139.0 (C_{ar} minor dia.), 138.0 (C_{ar} minor dia.), 137.8 (C_{ar} major dia.), 129.1, 128.8, 128.5, 128.3, 128.3, 128.2, 128.2, 127.8, 127.7, 127.4, 126.4, 126.4, 70.3 (CH major dia.), 69.5 (CH minor dia.), 64.7 (C_q major dia.), 64.2 (C_q minor dia.), 36.7 (CH_2 minor dia.), 34.9 (CH_2 major dia.), 31.1 (N-CH_3 major dia.), 31.0 (N-CH_3 minor dia.), 26.1 (N-CH_3 major dia.), 25.9 (N-CH_3 minor dia.), 24.5 (CH_3-C minor dia.) and 15.2 (CH_3-C major dia.).

HRMS: calcd for $C_{19}H_{22}N_2O$ 295.1805 found 295.1801 $(M+H)^+$.

1-Cyclohexen-1-yl-1,3-dimethyl-3-[(1*S*)-1-phenylethyl]urea **317**:



Cyclohexanone (1.00g, 10.2mmol, 1 eq.) was treated with methylamine (4 eq. 8M in solution in EtOH) in the presence of molecular sieved (1/1 w/w). The reaction mixture was heated at 125°C for 1h under microwave irradiation. The crude mixture was filtered through Celite ® and concentrated under reduce pressure. The crude mixture was solubilised in CH_2Cl_2 (0.4M). Triphosgene (0.5 eq.) was solubilised in CH_2Cl_2 (0.2M) and cooled to 0°C. Pyridine (1 eq.) was added to the solution. After 30 min. at 0°C, the imine solution was added to the phosgene solution and the reaction was stirred for 2h at 0°C. The reaction was quenched with 1N HCl and extracted with EtOAc. The organic phase was dried (MgSO4), filtered and concentrated under reduce pressure to afford the carbamoyl chloride. The crude carbamoyl chloride was dissolved in dry DCE (0.2M) and treated with (S)-N-α-dimethylbenzylamine (1 eq.), triethylamine (1 eq.) and DMAP (0.1 eq.). the reaction mixture was refluxed for 16h. The reaction was quenched by addition of H_2O and extracted with CH_2Cl_2 The organic phase was dried ($MgSO_4$), filtered and concentrated under reduce pressure. The desired compound was obtained after flash chromatography on silica gel in 40% yield (1.02g) as an oil.

R_f: 0.2 (PE/EtOAc:1/1).

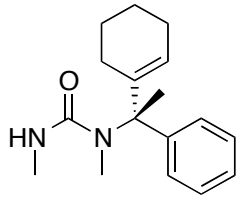
IR υ_{max} (film)/cm^{-1}: 2930, 1636 and 1535.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.23 (m, 5H, 5xAr*H*), 5.49 (q, *J*=7.0Hz, 1H, C*H*-N), 5.35 (t, *J*=3.9Hz, 1H, C*H*=C), 2.90 (s, 3H, N-CH_3), 2.46 (s, 3H, N-CH_3), 2.09 (m, 2H, C-CH_2), 2.03 (m, 2H, CH-CH_2), 1.65 (m, 2H, CH_2), 1.51 (m, 2H, CH_2) and 1.48 (d, *J*=7.0Hz, 3H, CH_3-CH).

^{13}C NMR (125MHz, $CDCl_3$): δ 162.6 (C=O), 141.7 (C_{ar}), 141.5 (*C*=CH), 128.3 (2xCH_{ar}), 127.2 (2xCH_{ar}), 126.9 (CH_{ar}), 119.0 (C*H*=C), 53.7 (*C*H-CH_3), 36.7 (N-CH_3), 30.4 (N-CH_3), 27.0 (CH_2), 24.7 (CH_2), 23.0 (CH_2), 21.9 (CH_2) and 15.9 (*C*H_3-CH).

HRMS: calcd for $C_{17}H_{24}N_2O$ 273.1962 found 273.1962 $(M+H)^+$.

1-[(1*R*)-1-Cyclohexen-1-yl-1-phenyl-ethyl]-1,3-dimethyl-urea **320**:



The urea was synthesised following the general procedure 11 (stirring for 20 minutes instead of 1h) in 64% yield (36mg) as an oil starting from 56mg (0.21mmol) of urea **317** (*e.r.*: 95:5).

R_f: 0.2 (PE/EtOAc: 1/1).

IR υ_{max} (film)/cm^{-1}: 3349, 2930, 1634 and 1532.

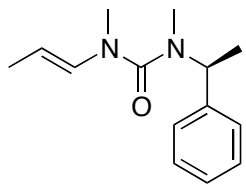
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.22 (m, 5H, 5xAr*H*), 5.43 (m, 1H, C*H*=C), 5.06 (br d, *J*=4.4Hz, 1H, N*H*), 2.90 (s, 3H, N-CH_3), 2.69 (d, *J*=4.4Hz, 3H, N-CH_3), 2.12-1.94 (m, 4H, 2xCH_2), 1.80 (s, 3H, C-CH_3), 1.70 (m, 1H, CH_2-C) and 1.55 (m, 3H, CH_2-C and CH_2).

^{13}C NMR (75MHz, $CDCl_3$): 160.4 (C=O), 143.6 (C_{ar}), 143.1 (C), 128.1 (2xCH_{ar}), 127.5 (2xCH_{ar}), 126.9 (CH_{ar}), 124.8 (*C*H=C), 68.1 (C_q), 33.0 (N-CH_3), 27.5 (N-CH_3), 27.0 (C-*C*H_3), 25.6 (CH_2), 25.5 (CH_2), 23.0 (CH_2) and 22.0 (CH_2).

HRMS: calcd for $C_{17}H_{24}N_2O$ 273.1962 found 273.1963 $(M+H)^+$.

HPLC: 7.7 min (minor) and 8.6 min (major) (column: Chiralpak AD-H; solvent: hexane/IPA: 9/1; 1mL/min).

1,3-Dimethyl-1-[(1*S*)-1-phenylethyl]-3-[(*E*)-prop-1-enyl]urea **(*S*)-321**:



(*S*)-α-methylbenzylamine (300mg, 2.48mmol, 1 eq.) was solubilised in CH_2Cl_2 (1M) and treated with allyl isocyanate (1 eq.). The reaction was stirred for an hour at room temperature. The solvent was the evaporated under reduce pressure and the corresponding urea was recovered as a white solid. The crude product was the dissolved in dry DMF (0.3M) and methyliodide was added (3 eq.). The reaction mixture was cooled to 0°C and stirred for 15min. Sodium hydride (60% in mineral oil, 2.5 eq.) was the added very slowly and the reaction was stirred for an hour at 0°C. The reaction was the diluted with Et_2O and quenched very slowly with water. The reaction mixture was washed with H_2O and the organic phase was dried ($MgSO_4$), filtered and concentrated under reduce pressure to afford the methylated allyl urea. The crude mixture was then dissolved in THF (0.2M) and treated with Carbonylchlorohydridotris(triphenylphosphine)ruthenium(II) (0.1eq). The reaction mixture was refluxed for 16h. The reaction was the cooled to room temperature and concentrated under reduce

pressure. The crude mixture was purified by flash chromatography on silica gel (PE/EtOAc:7/3) and the desired compound was obtained in 47% yield (274mg) as an oil.

R_f: 0.3 (PE/EtOAc: 7/3).

IR υ_{max} (film)/cm^{-1}: 2963, 2936, 1668, 1652, 1634 and 1538.

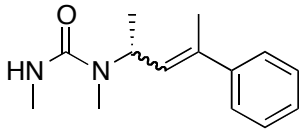
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H, 5xAr*H*), 6.49 (dd, *J*=13.9 and 1.5Hz, 1H, CH=C*H*-N), 5.24 (q, *J*=7.0Hz, 1H, CH_3-C*H*-N), 4.76 (dq, *J*=13.9 and 6.7Hz, 1H, CH=C*H*-CH_3), 2.99 (s, 3H, N-CH_3), 2.55 (s, 3H, N-CH_3), 1.66 (dd, *J*=6.7 and 1.5Hz, 3H, CH_3-CH=CH) and 1.56 (d, *J*=7.0Hz, 3H, CH_3-CH-N).

^{13}C NMR (75MHz, $CDCl_3$): 162.3 (C=O), 141.0 (C_{ar}), 132.1 (CH=*C*H-N), 128.4 (2xCH_{ar}), 127.21 (2xCH_{ar}), 127.10 (CH_{ar}), 101.8 (*C*H=CH-N), 54.9(N-*C*H-CH_3), 33.8 (N-CH_3), 31.2 (N-CH_{ar}), 16.1 (*C*H_3-CH-N) and 15.3 (*C*H_3-CH=CH).

HRMS: calcd for $C_{14}H_{20}N_2O$ 255.1468 found 255.1465 $(M+Na)^+$.

$[\alpha]^{25}_D$: -57.3(*c*=1) in $CHCl_3$.

1,3-dimethyl-1-[(*E*,1*R*)-1-methyl-3-phenyl-but-2-enyl]urea **(*R*)-324**:



The urea was synthesised following the general procedure 11 in 60% yield (36mg) as an oil starting from 56mg (0.21mmol) of urea **(*R*)-321**. The compound rearranged in contact with silica and was obtained with 85:15 *er* (when the crude of the expected product **(*R*)-323** was 95:5 *er*)

The stereochemistry of the double bond wasn't confirmed.

R_f: 0.1 (PE/EtOAc: 9:1+ 1%NEt_3).

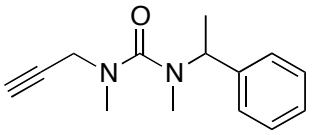
IR υ_{max} (film)/cm^{-1}: 3338, 2962, 1623 and 1539.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70-7.29 (m, 5H, 5xAr*H*), 5.67 (dq, *J*=7.3 and 1.2Hz, 1H, C*H*=C), 5.29 (quint., *J*=7.3Hz, 1H, C*H*-N), 4.30 (br s, 1H, NH), 2.84 (d, *J*=4.7Hz, 3H, N-CH_3), 2.75 (s, 3H, N-CH_3), 2.10 (d, *J* =1.2Hz, 3H, C-CH_3), 1.26 (d, *J*=7.3Hz, 3H, CH_3-CH-N)

^{13}C NMR (75MHz, $CDCl_3$): 158.5 (C=O), 143.2 (C_{ar}), 138.5 (*C*=CH), 128.3 (2xCH_{ar}), 127.9 (*C*H=C), 127.2 (CH_{ar}), 125.8 (2xCH_{ar}), 47.8 (CH-N), 28.4 (N-CH_3), 27.7 (N-CH_3), 19.3(*C*H_3-CH-N) and 16.5 (CH_3-C=CH).

HRMS: calcd for $C_{14}H_{20}N_2O$ 255.1468 found 255.1459 $(M+Na)^+$.

1,3-Dimethyl-1-(1-phenylethyl)-3-prop-2-ynyl-urea **328**:



α-Methylbenzylamine (1.00g, 8.25mmol, 1 eq.) was solubilised in CH_2Cl_2 (0.2M) and cooled to 0°C. Triphosegene (0.5 eq.) was solubilised in CH_2Cl_2 (0.2M), cooled to 0°C and treated with pyridine (1 eq.). After 30min. the solution of amine was added slowly to the phosgene solution and the reaction was stirred for 2h at 0°C. The reaction was quenched with 1N HCl, washed with $NaHCO_3$ (sat.) extracted with CH_2Cl_2. The crude mixture was solubilsed in DCE (0.4M) and treated with propargylamine (1 eq.), triethylamine (1 eq.) and DMAP (0.1 eq.). The reaction mixture was refluxed for 16h. The reaction was quenched by addition of H_2O and extracted with CH_2Cl_2. The crude urea was the solubilised in dry DMF (0.2M) and methyliodide (3 eq.) was added to the mixture. The mixture was cooled to 0°C and stirred for 15 min. Sodium hydride (2.5 eq., 60% in mineral oil) was added really slowly and the reaction was stirred for 1h at 0°C. The reaction was the diluted with Et_2O and quenched carefully with H_2O. The crude was washed with H_2O and extracted with Et_2O. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduce pressure. The desired product **328** was otained by purification by flash chromatography (PE/EtOAc:7/3) in 40% yield as an oil.

R_f: 0.2 (PE/EtOAc).

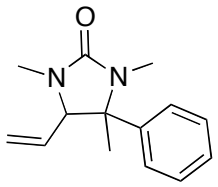
IR υ_{max} (film)/cm^{-1}: 3289, 2974 and 1638.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.18 (m, 5H, 5xAr*H*), 5.21 (q, J=7.0Hz, 1H, C*H*-N), 3.84 (t, J=2.8, 2H, CH_2-N), 2.82 (s, 3H, N-CH_3), 2.51 (d, *J*=0.7Hz, 3H, N-CH_3), 2.18 (td, J=2.8 and 0.9, 1H, C*H*) and 1.48 (dd, *J*=7.0 and 0.7Hz, 3H, CH_3-CH).

^{13}C NMR (75MHz, $CDCl_3$): 164.8(C=O), 141.3 (C_{ar}), 128.5 (2xCH_{ar}), 127.38 (2xCH_{ar}), 127.22 (CH_{ar}), 79.9 (C_q), 72.0 (CH), 54.6 (CH-N), 40.5 (CH_2), 36.7 (N-CH_3), 31.1 (N-CH_3) and 16.3 (*C*H_3-CH).

HRMS: calcd for $C_{14}H_{18}N_2O$ 231.1492 found 231.1494 $(M+H)^+$.

1,3,4-Trimethyl-4-phenyl-5-vinyl-imidazolidin-2-one **329**:



Urea **329** (100mg, 0.46mmol, 1 eq.) was solubised in THF (0.2M) cooled at 0°C and treated with *t*-BuOK (1 eq.) for 1h. The reaction was quenched with H_2O and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduce pressure. The crude was purified by flash chromatography (PE/EtOAc :7:3). The freshly purified allene was directly solubilised in dry THF/DMPU (0.3M, 10/1 ratio) and cooled at -78°C under inert atmosphere. The reaction mixture was treated with *s*-BuLi (2 eq.) and stirred for 1h. The reaction was quenched with MeOH, diluted with Et_2O and washed with H_2O. The organic phases was dried ($MgSO_4$), filtered and concentrated under reduce pressure. The titled cyclic urea was obtained in 60% yield (60mg) as an oil after flash chromatography on silica gel (PE/EtOAc: 8/2).

R_f: 0.3 (PE/EtOAc: 8/2).

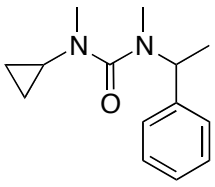
IR υ_{max} (film)/cm^{-1}: 3289, 2974 and 1638.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.29 (m, 5H, 5xAr*H*), 5.74 (ddd, *J*=17.1, 10.2 and 8.6Hz, 1H, C*H*=CH_2), 5.30 (ddd, *J*=10.2, 1.5 and 0.6Hz, 1H, C$H_{2(trans)}$-CH), 5.06 (ddd, J=17.1, 1.5 and 0.8Hz, 1H, C$H_{2(cis)}$=CH), 3.53 (dt, *J*=8.6 and 0.6, 1H, C*H*-N), 2.70 (s, 3H, N-CH_3), 2.65 (s, 3H, N-CH_3) and 1.47 (s, 3H, CH_3-C).

^{13}C NMR (100MHz, $CDCl_3$): 143.0 (C_{ar}), 132.6 (*C*H=CH_2), 128.6 (2xCH_{ar}), 127.5 (CH_{ar}), 126.1 (2xCH_{ar}), 121.4 (*C*H_2=CH), 73.0 (C_q), 29.9 (N-CH_3), 26.5 (N-CH_3) and 16.7 (*C*H_3-C).

HRMS: calcd for $C_{14}H_{18}N_2O$ 231.1492 found 231.1497 $(M+H)^+$.

1-Cyclopropyl-1,3-dimethyl-3-(1-phenylethyl)urea **333**:



Triphosgene (1.40g, 4.72mmol) was solubilised in CH_2Cl_2 and the reaction mixture was cooled to 0°C. Pyridine (1 eq.) was added to the mixture and the reaction was stirred for 15 minutes. α-Methylbenzylamine was then added and the reaction was stirred at 0°C for 2 hours. The reaction was quenched with 1M HCl, extracted with EtOAc and washed with H_2O. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude isocyanate was use without further purification.

The isocyanate (200mg, 1 eq.) was diluted in DCE (0.7M) was treated with NEt_3 (1 eq.), DMAP (0.1 eq.) and cyclopropylamine (1 eq.). The reaction was refluxed for 16 hours. After cooling the reaction to r.t., the crude was washed with H_2O and the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure.

The crude was solubilsed in DMF (0.1M), cooled to 0°C and treated with methyliodide. Sodium hydride (2 eq., 60% in mineral oil) was slowly added and the reaction was stirred for 3 hours at 0°C. The reaction was diluted with Et_2O and quenched slowly with H_2O. The organic phase was washed with H_2O, dried ($MgSO_4$) and concentrated under reduced pressure. The crude was filtrated through silica and the desired compound was obtained in 67% yield as an oil (211 mg).

R_f: 0.4 (PE/EtOAc: 7/3).

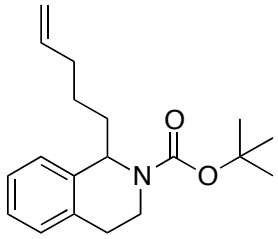
IR υ_{max} (film)/cm^{-1}: 2972, 2936 and 1634.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.14 (m, 5H, 5xAr*H*), 5.30 (q, *J*=7.0Hz, 1H, C*H*-CH_3), 2.76 (s, 3H, N-C*H*$_3$), 2.58-2.50 (m, 1H, C*H*-$(CH_2)_2$), 2.51 (s, 3H, N-C*H*$_3$), 1.45 (d, *J*=7.0Hz, 3H, C*H*$_3$-CH), 0.64-0.59 (m, 2H, C*H*$_2$) and 0.54-0.49 (m, 2H, C*H*$_2$).

^{13}C NMR (75MHz, $CDCl_3$): δ 164.7 (C=O), 141.4 (C_{ar}), 128.2 (2xCH_{ar}), 127.3 (2xCH_{ar}), 126.9 (CH_{ar}), 53.8(C*H*-CH_3), 37.6 (N-CH_3), 32.6 (*C*H-$(CH_2)_2$), 30.4 (N-CH_3), 16.1 (*C*H_3-CH), 8.0 (CH_2) and 7.9 (CH_2).

HRMS: calcd for $C_{14}H_{20}N_2O$ 255.1468 found 255.1468 $(M+Na)^+$.

<u>*tert*-Butyl 1-pent-4-enyl-3,4-dihydro-1*H*-isoquinoline-2-carboxylate **349**:</u>



N-Boc protected tetrahydroisoquinoline (3.57g, 15.3mmol) was solubilised in dry THF (0.2M) under inert atmosphere. TMEDA (2 eq.) was added to the solution and the reaction mixture was cooled to -78°C. *t*-BuLi (2 eq.) was added dropwise and the reaction was stirred for 40 minutes at -78°C. 5-Bromo-1-pentene (3 eq.) was then added and the reaction was stirred for 3 more hours at -78°C. The reaction was slowly quenched with MeOH. The reaction mixture was washed with H_2O and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The desired compound was obtained after flash chromatography (PE/EtOAc: 95/5) as a colourless oil in 46% yield (2.15g).

R$_f$: 0.6 (DCM/EtOAc:95/5).

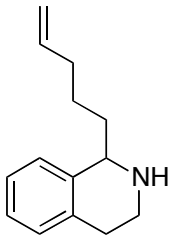
IR υ_{max} (film)/cm^{-1}: 2973, 2931, 2360 and 1692.

^{1}H NMR (300 MHz, DMSO-d_6, 373K): δ 7.33-7.30 (m, 4H, 4xAr*H*), 6.00 (ddt, *J*= 17.1, 10.3 and 6.6 Hz, 1H, C*H*=CH_2), 5.22-5.17 (m, 2H, C*H*$_2$=CH), 5.14 (ddt, *J*=10.4, 2.4 and 1.2Hz, 1H, C*H*-N), 4.12 (dddd, *J*=13.2, 6.0, 4.0 and 0.2Hz, 1H, C*H*$_2$-N), 3.42 (ddd, *J*=5.2, 10.0 and 15.2Hz, 1H, C*H*$_2$-N), 3.04-2.90 (m, 2H, C*H*$_2$-CH_2-N), 2.34-2.23 (m, 2H, C*H*$_2$-CH=CH_2), 2.01-1.85 (m, 2H, C*H*$_2$-CH), 1.70-1.58 (m, 2H, C*H*$_2$-CH_2-CH=CH_2) and 1.63 (s, 9H, 3x(C*H*$_3$)$_3$-C).

^{13}C NMR (75MHz, DMSO-d_6, 373K): δ 153.7 (C=O), 138.0 (*C*H=CH_2), 137.6 (C_{ar}), 133.4 (C_{ar}), 128.1 (CH_{ar}), 126.2 (CH_{ar}), 125.7 (CH_{ar}), 125.2 (CH_{ar}), 113.9 (*C*H_2=CH), 78.3 (*C*-$(CH_3)_3$), 53.5 (CH-N), 37.0 (CH_2-N), 35.3(*C*H_2-CH_2-CH=CH_2), 32.1 (*C*H_2-CH=CH_2), 27.6 (3xCH_3), 27.2 (*C*H_2-CH_2-N) and 24.7 (*C*H_2-CH)

HRMS: calcd 324.1934 for $C_{19}H_{27}NO_2Na$ found 324.1931 $(M+Na)^+$.

1-Pent-4-enyl-1,2,3,4-tetrahydroisoquinoline **347**:



Carbamate **349** (1.55g, 5.14mmol) was solubilised in CH_2Cl_2 (0.7M) and treated with TFA (10 eq.) and stirred for 3h at r.t.. The solvent then removed under reduced pressure and NaOH 1N was added to the crude mixture. The reaction was extracted with TBME and then CH_2Cl_2, dried ($MgSO_4$) and concentrated under reduced pressure. The desired amine was obtained in quantitative yield (1.03g) without further purification as a colourless oil.

R_f: 0.3 (PE/EtOAc: 7/3).

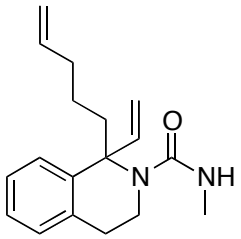
IR υ_{max} (film)/cm^{-1}: 2925, 2854 and 1639.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17-7.06 (m, 4H, 4xAr*H*), 5.83 (ddt, *J*=17.1, 10.2 and 6.7 Hz, 1H, C*H*=CH_2), 5.06-5.00 (m, 1H, CH_2=CH), 4.96 (ddt, *J*=10.2, 2.2 and 1.1Hz, 1H, CH_2=CH), 3.98 (dd, *J*=9.0 and 3.6Hz, 1H, C*H*-N), 3.24 (dt, *J*=12.5 and 5.5Hz, 1H, CH_2-N), 2.99 (ddd, *J*= 12.5, 7.3 and 5.2, 1H, CH_2-N), 2.88-2.69 (m, 2H, CH_2-CH_2-N), 2.17-2.08 (m, 2H, CH_2-CH=CH_2) and 1.91-1.47 (m, 5H, 2xCH_2 and NH).

^{13}C NMR (75MHz, $CDCl_3$): δ 139.7 (C_{ar}), 138.7 (*C*H=CH_2), 135.1 (C_{ar}), 129.2 (CH_{ar}), 126.1 (CH_{ar}), 125.8 (CH_{ar}), 125.7 (CH_{ar}) 114.7 (*C*H_2=CH), 55.6 (CH-N), 41.0 (CH_2-N), 35.9 (CH_2), 33.8 (*C*H_2-CH=CH_2), 30.0 (*C*H_2-CH_2-N) and 25.4 (CH_2).

HRMS: calcd for $C_{14}H_{19}N$ 202.1591 found 202.1594 $(M+H)^+$.

N-Methyl-1-pent-4-enyl-1-vinyl-3,4-dihydroisoquinoline-2-carboxamide **345**:



Amine **347** (100mg, 0.50mmol) was solubilised in DCM (0.2M) and reacted with vinylisocyanate (1 eq.) and DMAP (0.1 eq.), and stirred for 1h at r.t. The solvent was then removed under reduced pressure and the crude urea was solubilised in dry DMF (0.05M). Methyliodide (3 eq.) was added and the reaction was cooled to 0°C. NaH (2 eq., 60% in mineral oil) was then added slowly and the reaction was stirred for 1 hour at 0°C. The reaction was then diluted with Et_2O and quenched slowly with H_2O. The reaction was washed with H_2O and the organic phase dried ($MgSO_4$) and concentrated under reduced pressure. The crude mixture was solubilised in dry THF (0.2M) and DMPU (0.1vol./THF) was added to the reaction mixture. The reaction was cooled to -78°C and treated with *s*-BuLi (2.5eq). The reaction was stirred for 2 hours and then quenched with MeOH. The reaction was diluted with Et_2O and washed with H_2O. The organic phase was dried ($MgSO_4$) and concentrated under reduce pressure. The desired compound was obtained after flash chromatography on silicagel (PE/EtOAc: 1/1) in 32% (45mg) yield as an oil.

R_f: 0.1 (PE/EtOAc: 7/3).

IR υ_{max} (film)/cm^{-1}: 2934, 1636, 1539 and 1534.

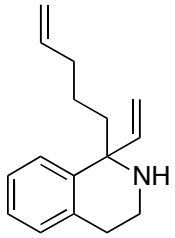
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.09 (m, 4H, 4xAr*H*), 6.08 (dd, *J*=17.7 and 10.7, 1H, CH_2=C*H*-C), 5.65 (ddt, *J*=17.0, 10.3 and 6.7Hz, 1H, CH_2=C*H*-CH_2), 5.35 (dd, *J*=17.7 and 0.5 Hz, 1H, C$H_{2(cis)}$=CH-C), 5.23 (br s, 1H, NH), 5.20 (dd, *J*=10.7 and 0.5Hz, 1H, C$H_{2(trans)}$=CH-C), 4.95-

4.88 (m, 2H, CH_2=CH-CH$_2$), 4.20 (dt, *J*= 12.8 and 4.9Hz, 1H, CH_2-N), 3.48 (dt, *J*=12.8 and 5.9Hz, 1H, CH_2-N), 2.82 (t, *J*=5.9Hz, 2H, CH_2-CH$_2$-N), 2.79 (d, *J*=4.6Hz, 3H, N-CH_3), 2.60 (ddd, *J*=13.7, 12.5 and 4.6Hz, 1H, CH_2-C$_q$), 2.09 (ddd, J=13.7, 12.6 and 4.0 Hz, 1H, CH_2-C$_q$), 2.03-1.88 (m, 2H, CH_2-CH=CH$_2$), 1.47-1.39 (m, 1H, CH_2-CH$_2$-C$_q$) and 1.09-0.98 (m, 1H, CH_2-CH$_2$-C$_q$).

^{13}C NMR (100MHz, CDCl$_3$): δ 159.1 (C=O), 146.5 (CH$_2$=*C*H-C), 138.2 (CH$_2$=*C*H-CH$_2$), 138.1 (C$_{ar}$), 136.6 (C$_{ar}$), 128.4 (CH$_{ar}$), 127.0 (CH$_{ar}$), 126.6 (CH$_{ar}$), 126.2 (CH$_{ar}$), 114.7 (*C*H$_2$=CH-CH$_2$), 112.3 *C*H$_2$=CH-C), 64.1 (C$_q$), 41.5 (CH$_2$-N), 36.0 (CH$_2$-C), 33.7 (CH$_2$-*C*H$_2$-N), 30.6 (CH$_2$), 27.4 (N-CH$_3$) and 22.9 (CH$_2$).

HRMS: calcd for C$_{18}$H$_{24}$N$_2$O 285.1962 found 285.1962 (M+H)$^+$.

1-Pent-4-enyl-1-vinyl-3,4-dihydro-2*H*-isoquinoline **344**:



Amine **344** was prepared following the general procedure 7 starting from 50mg (0.18mmol) of urea **345** and the titled compound was obtained in 80% yield (32mg) as an oil.

R$_f$: 0.1 (PE/EtOAc:8/2).

IR υ_{max} (film)/cm^{-1}: 3078, 2930, 2358 and 1640.

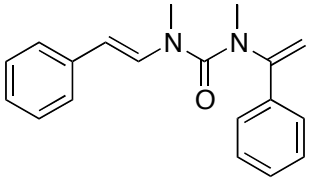
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.15-7.06 (m, 4H, 4xAr*H*), 5.95 (dd, *J*=17.3 and 10.5Hz, 1H, CH$_2$=C*H*-C$_q$), 5.74 (ddt, *J*=17.0, 10.2 and 5.7Hz, 1H, CH$_2$=C*H*-CH$_2$), 5.09 (dd, *J*=10.5 and 1.2Hz, 1H, C$H_{2(trans)}$=CH-C$_q$), 4.99-4.90 (m, 2H, CH_2=CH-CH$_2$), 4.79 (dd, *J*=17.3 and 1.2Hz, 1H, C$H_{2(cis)}$=CH-C$_q$), 3.08-2.99 (m, 2H, CH_2-CH$_2$-N), 2.86 (ddd, *J*=16.1, 9.6 and 6.4Hz, 1H, CH$_2$-CH_2-N), 2.66 (dt, *J*=16.1 and 3.3Hz, 1H, CH$_2$-CH_2-N), 2.01 (q, *J*=7.2Hz, 2H, CH_2-CH=CH$_2$) 1.95 (ddd, *J*=13.7, 12.7 and 5.7Hz, 1H, CH_2-C$_q$), 1.71 (ddd, *J*=13.7, 12.3 and 4.1Hz, 1H, CH_2-C$_q$), 1.50-1.41 (m, 1H, CH_2-CH$_2$-C$_q$) and 1.26-1.14 (m, 1H, CH_2-CH$_2$-C$_q$).

^{13}C NMR (100MHz, CDCl$_3$): δ 145.2 (C-*C*H=CH$_2$), 139.3 (C$_{ar}$), 138.7(CH$_2$-*C*H=CH$_2$), 135.9 (C$_{ar}$), 129.2 (CH$_{ar}$), 127.1 (CH$_{ar}$), 125.8 (CH$_{ar}$), 125.6 (CH$_{ar}$), 114.6 (*C*H$_2$=CH-CH$_2$), 113.7 (*C*H$_2$=CH-C$_q$), 60.4 (C$_q$), 41.1 (CH$_2$-C$_q$), 38.8 (*C*H$_2$-CH$_2$-N), 34.1 (*C*H$_2$-CH=CH$_2$), 30.5 (*C*H$_2$-N) and 22.8 (*C*H$_2$-CH$_2$-C$_q$).

HRMS: calcd for C$_{16}$H$_{21}$N 228.1747 found 228.1754 (M+H)$^+$.

3.4. Future work

1,3-Dimethyl-1-(1-phenylvinyl)-3-[(*E*)-styryl]urea **350**:



A suspension of *trans*-cinnamic acid (1.00g, 6.70mmol) in dry benzene (0.6M) was stirred under inert atmosphere, in presence of triethylamine (1 eq.) at 0°C. DPPA (1 eq.) was added slowly and the reaction was stirred at room temperature for 3h. The reaction was quenched with sat. NH_4Cl and then washed with 1N $KHSO_4$, H_2O, sat. $NaHCO_3$ and brine. The organic phase was concentrated under reduced pressure **AT ROOM TEMPERATURE**. The acyl azide was solubilised directly in dry toluene (0.6M) and the reaction mixture was refluxed for 1h under inert atmosphere.

Acetophenone (1 eq.) was reacted with methylamine (3 eq., 8M in EtOH) with molecular sieves (1/1 w/w) under microwave irradiation for 30 minutes at 125°C. The mixture was filtered through celite® and concentrated under reduced pressure. The crude imine was added slowly to the freshly prepared isocyanate and the reaction was stirred for 16 hours at r.t. The solvent was the removed under reduced pressure and the crude was solubilised in dry THF. The urea was treated with sodium hydride (2 eq.) and methyl iodide (3 eq.) for 16h. at r.t. The desired urea was obtained after purification by recrystallisation from Et_2O (25%, 490mg).

R_f: 0.4 (PE/EtOAc: 7/3).

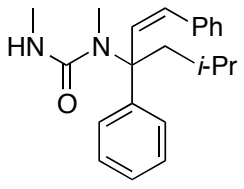
IR υ_{max} (film)/cm^{-1}: 1632.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.35 (m, 3H, 2xAr*H* and Ph-C*H*=CH), 7.27 (m, 3H, 3xAr*H*), 7.12-7.07 (m, 2H, 2xAr*H*), 7.03-6.96 (m, 3H, 3xAr*H*), 5.44 (d, *J*=14.5Hz, 1H, Ph-CH=C*H*), 5.20 (s, 1H, CH_2=C), 4.82 (s, 1H, CH_2=C), 3.06 (s, 3H, N-CH_3) and 2.84 (s, 3H, N-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.8 (C=O), 150.4 (*C*=CH), 137.4 (C_{ar}), 136.8 (C_{ar}), 130.6 (Ph-*C*H=CH), 128.9 (CH_{ar}), 128.7 (2xCH_{ar}), 128.5 (2xCH_{ar}), 125.9 (2xCH_{ar}), 125.6 (CH_{ar}), 125.0 (2xCH_{ar}), 107.8 (Ph-CH=*C*H), 106.4 (*C*H_2=C), 38.4 (N-CH_3) and 32.6 (N-CH_3).

HRMS: calcd for $C_{19}H_{21}N_2O$ 293.1649 found 293.1645 $(M+H)^+$.

1,3-Dimethyl-1-[3-methyl-1-phenyl-1-[(*E*)-styryl]butyl]urea **351**:



Urea **351** was synthesised following the general procedure 6b starting from 50mg (0.17mmol) and isolated in 63% yield (36mg) as an oil.

R_f: 0.2 (PE/EtOAc: 7/3).

IR υ_{max} (film)/cm^{-1}: 2954, 2916, 1620 and 1530.

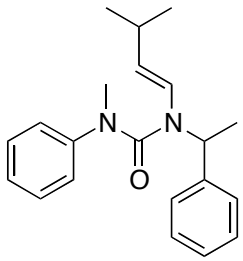
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.27 (m, 10H, 10xAr*H*), 6.44 (d, *J*=9.2Hz, 1H, C-C*H*=CH-Ph), 5.87 (d, *J*=9.2 Hz, 1H, C-CH=C*H*-Ph), 4.37 (br q, *J*=4.4Hz, 1H, N*H*), 2.87 (d, *J*=4.4Hz, 3H, N-CH_3), 2.70 (s, 3H, N-CH_3), 1.56 (m, 1H, C*H*-(CH_3)$_2$), 0.83 (d, *J*=6.6Hz, 3H, CH-(CH_3)$_2$), 0.78

(d, *J*=6.6Hz, 3H, CH-(C*H*$_3$)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.8 (C=O), 144.8 (C_{ar}), 143.0 (C_{ar}), 141.1 (C-*C*H=CH-Ph), 128.5 (2xCH_{ar}), 128.3 (2xCH_{ar}), 127.2 (CH_{ar}), 127.2 (2xCH_{ar}), 127.1 (CH_{ar}), 126.8 (2xCH_{ar}), 126.1 (C-CH=*C*H-Ph), 55.1 (C_q), 39.2 (CH_2), 30.0 (N-CH_3), 27.8 (N-CH_3), 27.0 (*C*H-(CH_3)$_2$), 22.5 (CH-(*C*H$_3$)$_2$) and 22.4 (CH-(*C*H$_3$)$_2$).

HRMS: calcd for $C_{22}H_{29}N_2O$ 337.2275 found 337.2275 $(M+H)^+$.

1-Methyl-3-[(*E*)-3-methylbut-1-enyl]-1-phenyl-3-(1-phenylethyl)urea **361a**:



α-Methylbenzylamine (1.00g, 8.25mmol, 1 eq.) was solubilised in dry DCM (0.4M) in the presence of $MgSO_4$. Isovaleraldehyde (1 eq.) was then added slowly and the reaction was stirred at room temperature. After 2 hours, the reaction was filtered and concentrated under reduced pressure. The crude imine was solubilised in dry THF (0.4M) and treated with phenyl isocyanate (1 eq.). The reaction was stirred for 16 hours at room temperature. The reaction was quenched with H_2O and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude urea was solubilised in dry THF and cooled to 0°C. Sodium hydride (2 eq., 60% in mineral oil) was added followed by addition of methyl iodide (3 eq.). The reaction was stirred for 1 hour at 0°C. The reaction was then diluted with Et_2O and carefully quenched with H_2O. The crude was extracted with Et_2O and the organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Urea **361a** was obtained after purification by flash chromatography on silica gel (PE/EtOAc: 8/2) in 34% (904mg) yield as an oil.

R_f: 0.3 (PE/EtOAc: 8/2).

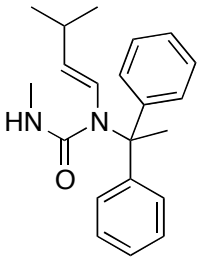
IR υ_{max} (film)/cm^{-1}: 2958, 2869, 1665 and 1596.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.12 (m, 7H, 8xAr*H*), 7.02-6.93 (m, 3H, 3xAr*H*), 5.49 (q, *J*=7.1Hz, 1H, C*H*-CH_3), 5.24 (dd, *J*=14.2 and 1.2Hz, 1H, N-C*H*=CH), 4.66 (dd, *J*=14.2 and 6.8Hz, 1H, N-CH=C*H*), 3.21 (s, 3H, N-C*H*$_3$), 1.77 (m, 1H, C*H*-(CH_3)$_2$), 1.50 (d, *J*=7.1Hz, 3H, C*H*$_3$-CH), 0.55 (t, *J*=6.8Hz, 6H, CH-(C*H*$_3$)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.0 (C=O), 146.3 (C_{ar}), 141.5 (C_{ar}), 129.0 (2xCH_{ar}), 128.9 (N-*C*H=CH), 128.0 (2xCH_{ar}), 127.5 (2xCH_{ar}), 126.8 (CH_{ar}), 125.0 (2xCH_{ar}), 124.6 (CH_{ar}), 124.6 (N-CH=*C*H), 54.6 (*C*H-CH_3), 39.6 (N-CH_3), 29.2 (*C*H-(CH_3)$_2$), 22.3 (CH-(*C*H$_3$)$_2$), 22.3 (CH-(*C*H$_3$)$_2$) and 16.6 (*C*H$_3$-CH).

HRMS: calcd for $C_{21}H_{26}N_2ONa$ 345.1937 found 345.1940 $(M+Na)^+$.

1-(1,1-Diphenylethyl)-3-methyl-1-[(*E*)-3-methylbut-1-enyl]urea **362**:



Urea **361a** (100mg, 0.31mmol) was solubilised in dry THF (0.05M) and the reaction was cooled to −78°C. *s*-BuLi (2 eq.) was then added and the reaction was stirred for 1h at −78°C. The reaction was quenched with MeOH, washed with H_2O and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The desired compound was obtained in 40% yield (40mg) as an oil after flash chromatography (PE/EtOAc: 7/3).

R_f: 0.2 (PE/EtOAc: 7/3).

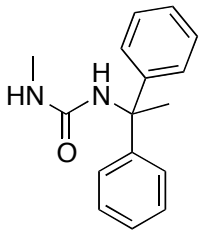
IR υ_{max} (film)/cm^{-1}: 3373, 2956, 1651 and 1505.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.17 (m, 10H, 10xAr*H*), 5.69 (dd, *J*=13.8 and 1.1Hz, 1H, N-C*H*=CH), 5.49 (dd, *J*=13.8 and 7.4Hz, 1H, C*H*=CH-N), 4.96 (br d, *J*=4.6Hz, 1H, N*H*), 2.69 (d, *J*=4.6Hz, 3H, N-CH_3), 2.20-2.17 (m, 1H, C*H*-$(CH_3)_2$)), 2.17 (s, 3H, N-CH_3) and 0.85 (d, *J*=6.7Hz, 6H, CH-(CH_3)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7 (C=O), 146.0 (2xC_{ar}), 140.9 (*C*H=CH-N), 127.7 (4xCH_{ar}), 127.6 (4xCH_{ar}), 127.5 (2xCH_{ar}), 126.3 (N-*C*H=CH), 67.6 (C_q), 30.6 (N-CH_3), 29.1 (*C*H-$(CH_3)_2$), 27.3 (*C*H_3-C) and 22.0 (2xCH-(*C*H_3)$_2$).

HRMS: calcd for $C_{21}H_{27}N_2O$ 345.1938 found 345.1950 $(M+H)^+$.

1-(1,1-Diphenylethyl)-3-methyl-urea **363**:



Urea **362** (30mg, 0.09mmol) was solubilised in CH_2Cl_2 (0.1M) in presence of 10% aqueous solution of acetic acid (1/1 vol. compare to CH_2Cl_2). The reaction was stirred for 1h at r.t. The crude mixture was extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated under reduced pressure. The desired product was purified by recrystallisation from toluene and obtained in 64% yield (15mg) as a white solid.

R_f: 0.1 (PE/EtOAc: 7/3).

M.p.: 149°C (Toluene).

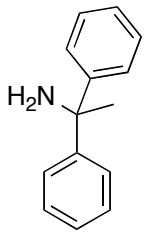
IR υ_{max} (film)/cm^{-1}: 3357, 3292, 2972, 1626 and 1557.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.25 (m, 10H, 10xAr*H*), 5.22 (s, 1H, N*H*), 4.17 (br d, *J*=4.6Hz, 1H, N*H*), 2.60 (d, *J*=4.6Hz, 3H, N-CH_3) and 2.11 (s, 3H, N-CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0 (C=O), 146.1 (2xC_{ar}), 128.5 (4xCH_{ar}), 127.2 (4xCH_{ar}), 126.6 (2xCH_{ar}), 61.4 (C_q), 28.9 (*C*H_3-C) and 27.0 (N-CH_3).

HRMS: calcd for $C_{16}H_{19}N_2O$ 255.1492 found 255.1496 $(M+H)^+$.

1,1-Diphenylethanamine **364**[*] :



Urea **363** (15mg, 0.05mmol) was solubilised in EtOH (0.03M) and treated with 2M NaOH (1/1 vol. compared to EtOH). The reaction was heated to 130°C under microwave irradiation for 2.5 hours. The crude mixture was washed with brine and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The desired amine was obtained in quantitative yield without further purification as an oil.

Alternatively

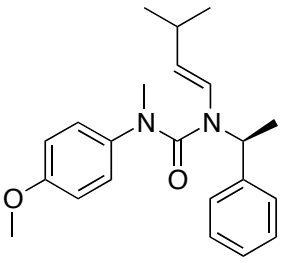
The amine was synthesised following the general procedure 13 in 50% yield over 3 steps, starting from 100mg (0.31mmol) of urea **361a**.

R_f: 0.1 (DCM).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.21 (m, 10H, 10xAr*H*) and 1.85 (s, 3H, C*H*$_3$-CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 149.9 (C_{ar}), 128.1 (4xCH_{ar}), 126.3 (4xCH_{ar}), 126.1 (2xCH_{ar}), 58.4 (C_q) and 31.9 (CH_3).

1-(4-Methoxyphenyl)-1-methyl-3-[(*E*)-3-methylbut-1-enyl]-3-[(1*S*)-1-phenylethyl]urea **361b**:



(*S*)-α-Methylbenzylamine (1.00g, 8.25mmol, 1 eq.) was solubilised in dry DCM (0.4M) in the presence of $MgSO_4$. Isovaleraldehyde (1 eq.) was then added slowly and the reaction was stirred at room temperature. After 2 hours, the reaction was filtered and concentrated under reduced pressure. The crude imine was solubilised in dry THF (0.4M) and treated with 4-methoxyphenyl isocyanate (1 eq.). The reaction was stirred for 16 hours at room temperature. The reaction was quenched with H_2O and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude urea was solubilised in dry THF and cooled to 0°C. Sodium hydride (2 eq., 60% in mineral oil) was added followed by addition of methyl iodide (3 eq.). The reaction was stirred for 1 hour at 0°C. The reaction was then diluted with Et_2O and carefully quenched with H_2O. The crude was extracted with Et_2O and the organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Urea **361b** was obtained after purification by flash chromatography on silica gel (PE/EtOAc: 8/2) in 38% yield (900mg) as an oil.

R_f: 0.3 (PE/EtOAc: 8/2).

IR υ_{max} (film)/cm^{-1}: 2956, 1645 and 1511.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.18 (m, 5H, 5xAr*H*), 6.97-6.92 (m, 2H, 2xAr*H*), 6.81-6.76 (m, 2H, 2xAr*H*), 5.52 (q, *J*=7.1Hz, 1H, C*H*-N), 5.34 (dd, *J*=14.2 and 1.2Hz, 1H, N-C*H*=CH), 4.69 (dd, *J*=14.2 and 7.1Hz, 1H, C*H*=CH-N), 3.76 (s, 3H, O-C*H*$_3$), 3.21 (s, 3H, N-C*H*$_3$), 1.86 (m, 1H,

[*] Synthesis **1982**, *6*, 461-462.

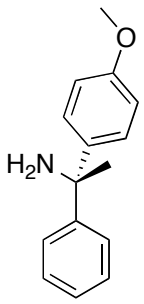
C*H*-(CH_3)$_2$), 1.54 (d, *J*=7.1Hz, 3H, C*H*$_3$-CH), 0.66 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$) and 0.62 (d, *J*=6.8Hz, 3H, CH-(C*H*$_3$)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3 (C=O), 156.9 (C_{ar}-OCH_3), 141.8 (C_{ar}), 139.4 (C_{ar}), 128.3 (*C*H=CH-N), 128.0 (2xCH_{ar}), 127.5 (2xCH_{ar}), 126.8 (2xCH_{ar}), 126.8 (CH_{ar}), 124.9 (N-*C*H=CH), 114.2 (2xCH_{ar}), 55.5 (O-CH_3), 54.7 (*C*H-CH_3), 40.2 (N-CH_3), 29.2 (*C*H-(CH_3)$_2$), 22.4 (CH-(*C*H_3)$_2$), 22.4 (CH-(*C*H_3)$_2$) and 16.7 (*C*H_3-CH).

HRMS: calcd for $C_{22}H_{28}N_2O_2Na$ 375.2043 found 375.2051 $(M+Na)^+$.

$[\alpha]^{20}_D$: 73.6 (*c*=1 in $CHCl_3$).

(1*S*)-1-(4-methoxyphenyl)-1-phenyl-ethanamine **365**:



Amine **365** was synthesised following the general procedure 13 in 45% (*e.r.* >99:1) yield as an oil, starting from 104mg (0.30mmol) of urea **361b**.

R$_f$: 0.1 (DCM).

IR υ_{max} (film)/cm^{-1}: 3293, 2963, 1608, 1582 and 1511.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.16 (m, 7H, 7xAr*H*), 6.84-6.79 (m, 2H, 2xAr*H*), 3.77 (s, 3H, OC*H*$_3$), 1.98 (br s, 2H, N*H*$_2$) and 1.82 (s, 3H, C*H*$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0 (C_{ar}-OCH_3), 150.1 (C_{ar}), 142.1 (C_{ar}), 128.0 (2xCH_{ar}), 127.3 (2xCH_{ar}), 126.2 (CH_{ar}), 126.1 (2xCH_{ar}), 113.4 (2xCH_{ar}), 57.9 (C_q), 55.2 (O-CH_3) and 32.1 (CH_3).

HRMS: calcd for $C_{15}H_{15}O$ 211.1118 found 211.1112 $(M-NH_2)^+$.

$[\alpha]^{20}_D$: -2.8 (*c*=1 in $CHCl_3$).

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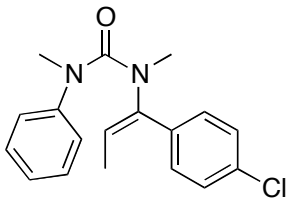
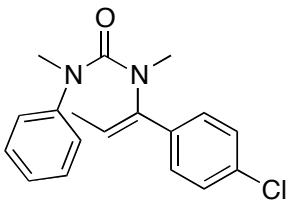
APPENDIX



(*E*)-3.7j

Crystal data and structure refinement for s3323p.

Identification code	s3323p
Empirical formula	C18 H19 Cl N2 O
Formula weight	314.80
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 16.398(3) A alpha = 90 deg.
	b = 7.6279(14) A beta = 99.836(4) deg.
	c = 13.045(2) A gamma = 90 deg.
Volume	1607.8(5) A^3
Z, Calculated density	4, 1.301 Mg/m^3
Absorption coefficient	0.241 mm^-1
F(000)	664
Crystal size	0.20 x 0.18 x 0.15 mm
Theta range for data collection	1.26 to 26.41 deg.
Limiting indices	-16<=h<=20, -9<=k<=9, -15<=l<=16
Reflections collected / unique	9022 / 3287 [R(int) = 0.0870]
Completeness to theta = 25.00	99.8 %
Absorption correction	None
Max. and min. transmission	0.9648 and 0.9534
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3287 / 0 / 202
Goodness-of-fit on F^2	0.859
Final R indices [I>2sigma(I)]	R1 = 0.0581, wR2 = 0.0917
R indices (all data)	R1 = 0.1268, wR2 = 0.1377
Largest diff. peak and hole	0.274 and -0.245 e.A^-3

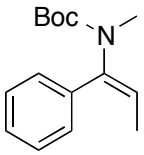


(Z)-3.7j

Crystal data and structure refinement for s3329n.

Identification code	s3329n
Empirical formula	C18 H19 Cl N2 O
Formula weight	314.80
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 7.9594(8) A alpha = 90 deg.
	b = 11.7961(11) A beta = 98.137(2) deg.
	c = 17.4102(16) A gamma = 90 deg.
Volume	1618.2(3) A^3
Z, Calculated density	4, 1.292 Mg/m^3
Absorption coefficient	0.239 mm^-1
F(000)	664
Crystal size	0.35 x 0.30 x 0.25 mm
Theta range for data collection	2.09 to 28.25 deg.
Limiting indices	-6<=h<=10, -15<=k<=15, -22<=l<=19
Reflections collected / unique	9931 / 3770 [R(int) = 0.0451]
Completeness to theta = 25.00	99.8 %
Absorption correction	None
Max. and min. transmission	0.9426 and 0.9209
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3770 / 0 / 202
Goodness-of-fit on F^2	0.889
Final R indices [I>2sigma(I)]	R1 = 0.0398, wR2 = 0.0721
R indices (all data)	R1 = 0.0649, wR2 = 0.0775
Largest diff. peak and hole	0.313 and -0.220 e.A^-3

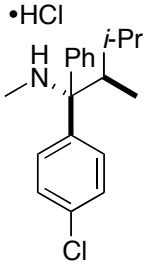
Crystal data and structure refinement for s3386abs.



(*E*)-4.13

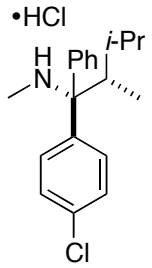
Identification code	s3386abs
Empirical formula	C15 H21 N O2
Formula weight	247.33
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 7.626(4) A alpha = 90 deg. b = 25.042(12) A beta = 116.762(8) deg. c = 8.473(4) A gamma = 90 deg.
Volume	1444.8(12) A^3
Z, Calculated density	4, 1.137 Mg/m^3
Absorption coefficient	0.075 mm^-1
F(000)	536
Crystal size	0.40 x 0.40 x 0.35 mm
Theta range for data collection	2.44 to 25.02 deg.
Limiting indices	-9<=h<=8, -29<=k<=28, -10<=l<=10
Reflections collected / unique	6817 / 2591 [R(int) = 0.0487]
Completeness to theta = 25.02	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.000 and 0.692
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2591 / 1 / 336
Goodness-of-fit on F^2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0456, wR2 = 0.0991
R indices (all data)	R1 = 0.0567, wR2 = 0.1039
Largest diff. peak and hole	0.231 and -0.214 e.A^-3

Crystal data and structure refinement for s3320p.



	Identification code	s3320p
	Empirical formula	C21 H31 Cl2 N O
	Formula weight	384.37
	Temperature	100(2) K
	Wavelength	0.71073 A
4.24•HCl	Crystal system, space group	Triclinic, P-1
Unit cell dimensions		a = 8.1672(10) A alpha = 105.912(2) deg.
		b = 14.7597(17) A beta = 94.878(2) deg.
		c = 18.591(2) A gamma = 94.771(2) deg.
Volume		2134.0(4) A^3
Z, Calculated density		4, 1.196 Mg/m^3
Absorption coefficient		0.313 mm^-1
F(000)		824
Crystal size		0.22 x 0.20 x 0.18 mm
Theta range for data collection		1.44 to 25.03 deg.
Limiting indices		-9<=h<=9, -17<=k<=17, -22<=l<=22
Reflections collected / unique		15451 / 7475 [R(int) = 0.0616]
Completeness to theta = 25.00		99.1 %
Absorption correction		None
Max. and min. transmission		0.9458 and 0.9344
Refinement method		Full-matrix least-squares on F^2
Data / restraints / parameters		7475 / 0 / 433
Goodness-of-fit on F^2		0.941
Final R indices [I>2sigma(I)]		R1 = 0.0678, wR2 = 0.1633
R indices (all data)		R1 = 0.1190, wR2 = 0.1866
Largest diff. peak and hole		0.966 and -0.481 e.A^-3

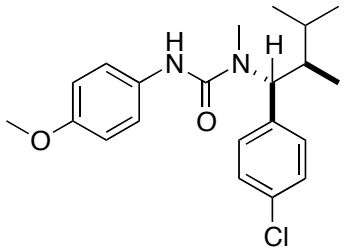
Crystal data and structure refinement for s3341n.



***epi*-4.24•HCl**

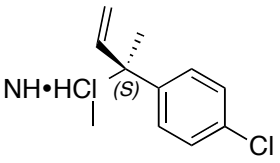
Identification code	s3341n
Empirical formula	C19 H25 Cl2 N
Formula weight	338.30
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 12.3958(15) A alpha = 90 deg. b = 11.9401(14) A beta = 110.557(2) deg. c = 13.0503(16) A gamma = 90 deg.
Volume	1808.5(4) A^3
Z, Calculated density	4, 1.242 Mg/m^3
Absorption coefficient	0.356 mm^-1
F(000)	720
Crystal size	0.29 x 0.25 x 0.20 mm
Theta range for data collection	1.95 to 25.05 deg.
Limiting indices	-14<=h<=14, -14<=k<=14, -15<=l<=15
Reflections collected / unique	12689 / 3199 [R(int) = 0.0710]
Completeness to theta = 25.00	99.9 %
Absorption correction	None
Max. and min. transmission	0.9322 and 0.9038
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3199 / 0 / 203
Goodness-of-fit on F^2	1.066
Final R indices [I>2sigma(I)]	R1 = 0.0629, wR2 = 0.1107
R indices (all data)	R1 = 0.0933, wR2 = 0.1196
Largest diff. peak and hole	0.371 and -0.233 e.A^-3

Crystal data and structure refinement for s3430b.



Identification code	s3430b
Empirical formula	C21 H27 Cl N2 O2
Formula weight	374.90
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, Pbcn
Unit cell dimensions	a = 18.293(2) A alpha = 90 deg.
	b = 22.343(3) A beta = 90 deg.
	c = 9.9739(13) A gamma = 90 deg.
Volume	4076.6(9) A^3
Z, Calculated density	8, 1.222 Mg/m^3
Absorption coefficient	0.204 mm^-1
F(000)	1600
Crystal size	0.50 x 0.30 x 0.20 mm
Theta range for data collection	1.44 to 25.03 deg.
Limiting indices	-21<=h<=21, -26<=k<=26, -11<=l<=11
Reflections collected / unique	27596 / 3613 [R(int) = 0.0878]
Completeness to theta = 25.03	100.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3613 / 490 / 332
Goodness-of-fit on F^2	0.983
Final R indices [I>2sigma(I)]	R1 = 0.0717, wR2 = 0.1855
R indices (all data)	R1 = 0.1360, wR2 = 0.2172
Largest diff. peak and hole	0.324 and -0.283 e.A^-3

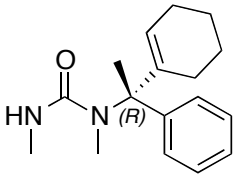
Crystal data and structure refinement for s3533m.



(S)-4.15b•HCl

Identification code	s3533m
Empirical formula	C11 H15 Cl2 N
Formula weight	232.14
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Unit cell dimensions	a = 6.7873(17) A alpha = 90 deg. b = 7.4504(18) A beta = 90 deg. c = 24.010(6) A gamma = 90 deg.
Volume	1214.1(5) A^3
Z, Calculated density	4, 1.270 Mg/m^3
Absorption coefficient	0.498 mm^-1
F(000)	488
Crystal size	0.22 x 0.12 x 0.02 mm
Theta range for data collection	1.70 to 25.04 deg.
Limiting indices	-8<=h<=8, -8<=k<=8, -27<=l<=28
Reflections collected / unique	8678 / 2135 [R(int) = 0.1521]
Completeness to theta = 25.00	100.0 %
Absorption correction	None
Max. and min. transmission	0.9901 and 0.8983
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2135 / 6 / 129
Goodness-of-fit on F^2	0.961
Final R indices [I>2sigma(I)]	R1 = 0.0868, wR2 = 0.0879
R indices (all data)	R1 = 0.1401, wR2 = 0.1014
Absolute structure parameter	0.23(18)
Largest diff. peak and hole	0.377 and -0.466 e.A^-3

Crystal data and structure refinement for s3577m.



(*R*)-4.22

Identification code	s3577m
Empirical formula	C17 H24 N2 O
Formula weight	272.38
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)
Unit cell dimensions	a = 8.5070(13) A alpha = 90 deg.
	b = 14.818(2) A beta = 98.947(3) deg.
	c = 12.1608(18) A gamma = 90 deg.
Volume	1514.2(4) A^3
Z, Calculated density	4, 1.195 Mg/m^3
Absorption coefficient	0.075 mm^-1
F(000)	592
Crystal size	0.40 x 0.25 x 0.20 mm
Theta range for data collection	1.70 to 26.45 deg.
Limiting indices	-10<=h<=7, -18<=k<=18, -14<=l<=15
Reflections collected / unique	8884 / 3225 [R(int) = 0.0469]
Completeness to theta = 26.45	99.1 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3225 / 1 / 375
Goodness-of-fit on F^2	1.033
Final R indices [I>2sigma(I)]	R1 = 0.0524, wR2 = 0.1192
R indices (all data)	R1 = 0.0619, wR2 = 0.1232
Largest diff. peak and hole	0.859 and -0.311 e.A^-3