Synthesis and Ring-opening of *NH*-aziridine-2-carboxylates, and Preparation of Novel Pyrazolo[3,4-*d*]pyrimidines for Kinase-substrate Identification

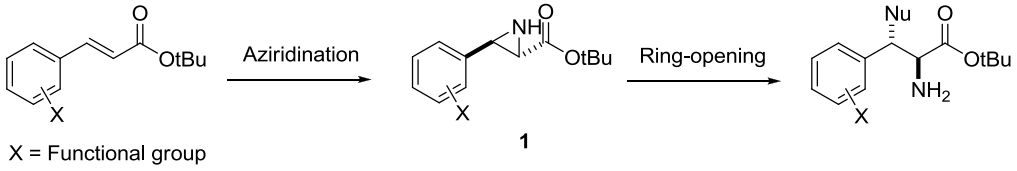
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requirements for the degree of Doctor of Philosophy

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Abstract

1: The ring-opening of aziridine-2-carboxylates dominates their reactivity, providing diverse, biologically relevant compounds. Less is known about the chemistry of *NH*-aziridine-2-carboxylates, owing to multi-step preparation, and lack of *N*-functionality to aid ring-opening. Building on the recent disclosure of an *NH*-aziridination methodology applicable to enones, the substrate scope was expanded to include enoates. Aziridination provided access to *NH*-aziridine-2-carboxylates in a single step from readily available starting materials. Treatment of the resulting aziridine-2-carboxylates with nucleophiles proceeded with high regio- and stereoselectivity, providing access to natural and un-natural amino acid derivatives (**Scheme 1**).



Scheme 1: The synthesis and ring-opening of aziridine-2-carboxylates

2: Identification of kinase protein-substrate sets is crucial to further understand cellular processes, but is challenging with known methodology. Previous study had proposed a new methodology, incorporating two known strategies, bump-hole inhibition and photo-affinity labelling. Novel C3-aryl pyrazolo[3,4-*d*]pyrimidines were designed for the purpose (**Fig. 1**), although preparation of the compounds had proved challenging, with several key steps in the synthesis of analogues low-yielding and lengthy. A new synthetic route was developed, using hydrazone allylation to establish the α-*tert*-amine functionality of the pyrazolo[3,4-*d*]pyrimidines. A late-stage oxidative cleavage was used to re-connect with the original synthetic strategy, to provide access to the C3-hydro analogues. Application of the revised route to the synthesis of the target compounds, using an alternative enol ether for C3-aromatic installation, provided access to two novel pyrazolo[3,4-*d*]pyrimidines for testing.

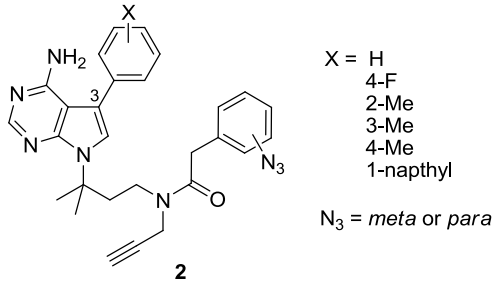


Fig. 1: C3-aryl pyrazolo[3,4-*d*]pyrimidines

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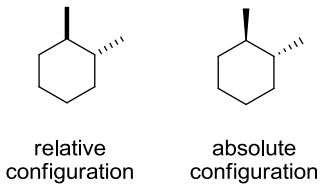
Thanks to Mum and Dad for your hard work and all the opportunities it has given me. Thank you Lizzie for being so supportive and always making me laugh. Finally, thanks to Graham, for always believing in me.

Declaration

I declare that this thesis is my own work, and where this was not the case or help was received, appropriate acknowledgement has been given.

Stereochemical Notation

Throughout this thesis, the pictorial representation of stereochemistry is consistent with the conventions proposed by Maehr.[1] Uniform solid wedges and broken lines represent relative stereochemistry, whilst narrowing of the solid wedge or broken line at one terminus illustrates absolute configuration. Where relative stereochemistry is pictured, the compound has been prepared as a racemate. Conversely, absolute configuration is given where a compound has been prepared as a single enantiomer.



Contents

Abbreviations **7**

1. Synthesis and Ring-opening of *NH*-aziridine-2-carboxylates **10**

1.1 Introduction **11**

1.1.1 Synthetic methods to aziridine-2-carboxylates ***12***

1.1.1.1 Cyclisation processes *13*

1.1.1.2 Addition processes *16*

1.1.2 NH-aziridines via addition to electron-poor alkenes ***25***

1.2 Project aims **29**

1.3 Results and Discussion **30**

1.3.1 Optimising the enoate aziridination ***30***

1.3.1.1 Reagent synthesis *30*

1.3.1.2 The catalytic cycle *32*

1.3.1.3 Towards a homogeneous aziridination *33*

1.3.1.4 Investigating reagent stoichiometry *36*

1.3.1.5 The effect of concentration *37*

1.3.1.6 Alternative tertiary amines *38*

1.3.1.7 The effect of water *39*

1.3.1.8 Scaling-up the aziridination *40*

1.3.1.9 Investigating reagent and product stability *42*

1.3.1.10 An alternative aminating agent *44*

1.3.2 Probing the substrate scope ***50***

1.3.2.1 Alternative esters *50*

1.3.2.2 Conjugated oxazoles *54*

1.3.2.3 Furfuracrylates *55*

1.3.2.4 tert-Butyl cinnamates *58*

1.3.2.5 Dienoates *64*

1.3.2.6 Towards 'pleurocybellaziridine' *66*

1.3.3 Summary of the enoate aziridination ***67***

1.3.4 The ring-opening of aziridine-2-carboxylates ***70***

1.3.4.1 Ring-opening with indole *72*

1.3.4.2 Ring-opening with hydrogen *78*

1.3.4.3 Ring-opening with chloride *79*

1.3.4.4 Ring-opening with oxygen-based nucleophiles *81*

1.4 Conclusions **86**

2. Novel Pyrazolo[3,4-*d*]pyrimidines for Kinase-substrate Identification **88**

2.1 Introduction **89**

2.1.1 A novel method for kinase protein-substrate identification ***89***

2.1.2 Synthesis of C3-unfunctionalised pyrazolo[3,4-d]pyrimidines ***92***

2.2 Project aims **93**

2.3 Results and discussion **94**

2.3.1 Synthesis of pyrazolo[3,4,d]pyrimidine 123 ..... ***94***

2.3.1.1 Strategies to N-tert-alkyl pyrazolo[3,4-d]pyrimidines *95*

2.3.1.2 An alternative synthesis of an α-tert-alkyl hydrazine *96*

2.3.1.3 Towards a common aldehyde *104*

2.3.1.4 Rejoining the first generation strategy *107*

2.3.2 Summary of the second generation synthesis ***109***

2.3.3 C3-functionalisation of pyrazole 159 ..... ***110***

2.3.3.1 CH-activation *110*

2.3.3.2 Nucleophilic addition *113*

2.3.3.3 Metallation *114*

2.3.3.4 An alternative enol ether *119*

2.4 Conclusions **123**

3. Experimental **127**

3.1 General procedures **128**

3.2 Experimental details **129**

4. Appendix **175**

5. References **180**

Abbreviations

Ac	acetyl
ADP	adenosine diphosphate
aq.	aqueous
Ar	aryl
atm	atmospheres
ATP	adenosine triphosphate
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
Bz	benzoyl
cat.	catalytic/catalyst
Cbz	benzyloxycarbonyl
CI	chemical ionisation MS
d	doublet/day(s)
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzilydeneacetone
de	diastereomeric excess
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Dpp	diphenylphosphinyl
dr	diastereomeric ratio
EDG	electron donating group
ee	enantiomeric excess
EI	electron impact MS
eq./equiv.	molar equivalent(s)
ES	electrospray MS
er	enantiomeric ratio
Et	ethyl
EWG	electron withdrawing group
h	hour(s)
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry

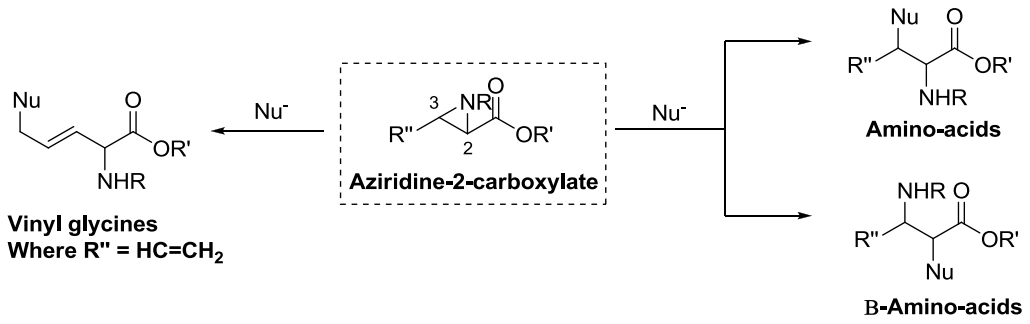
Hz	Hertz
IPA	isopropyl alcohol
^{i}Pr	isopropyl
IR	infra-red
J	coupling constant
LG	leaving group
lit.	literature
m	*meta*
m	multiplet
M	molar
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
ML_n	metal-ligand complex
min	minute(s)
mp	melting point
MS	mass spectrum/mass spectrometry/molecular sieves
MSH	*O*-mesitylenesulfonyl hydroxylamine
m/z	mass/charge ratio
N-	amino-
NBS	*N*-bromosuccinimide
^{n}Bu	*normal*-butyl
NMR	nuclear magnetic resonance
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methylpyrrolidine
Ns	4-nitrobenzenesulfonyl
o	ortho
p	para
petrol	petroleum ether (40-60 °C)
Ph	phenyl
ppm	part(s) per million
Pr	propyl
PTC	phase transfer catalyst
q	quartet
R	alkyl group
R*f*	retention factor
R.S.M.	recovered starting material

r.t.	room temperature
s	second(s), singlet
sec	secondary
t	triplet
T	temperature
TBAB	tetra-*N*-butylammonium bromide
^{t}Bu	*tert*-butyl
Tf	triflyl/trifluromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
Ts	tosyl/*p*-toluenesulfonyl
UV	ultra-violet
X	undefined substituent
Y	undefined substituent

1. Synthesis and Ring-opening of *NH*-aziridine-2-carboxylates

1.1 Introduction

The aziridine-2-carboxylate, of the general structure shown (**Scheme 2**), is an important architecture for the synthetic chemist. Further to being an interesting target in its own right, the motif is highly susceptible to nucleophilic ring-opening chemistry.[2, 3] Accordingly, access to a diverse array of compounds from this common intermediate is possible, depending on the regio- and stereoselectivity of nucleophilic addition. Although the same is true of the aziridine motif in general, ring-opening of aziridine-2-carboxylates can lead to structures of particular biological importance (**Scheme 2**). By way of example, nucleophilic attack at C3 leads to amino acid derivatives,[4, 5] whilst opposing regioselectivity yields β-amino acids.[6] Conjugate nucleophilic addition to a vinyl aziridine-2-carboxylate could provide access to the vinyl glycine motif. Diastereomers of all these products can arise, often dependent on the mechanism of nucleophilic attack.[7]



Scheme 2: Biologically important ring-opening products

The high propensity of aziridine-2-carboxylates, and also aziridines, to undergo ring-opening, can be attributed to the electrophilicity of the carbon atoms of the aziridine; indeed, several structural features of the motif contribute to this. Firstly, the three membered heterocycle is highly strained and a thermodynamic advantage is achieved on ring-opening. The internal bond angles are constrained to 60° instead of the preferred 109.5°, and unfavourable eclipsing interactions exist between the aziridine substituents. This ring-strain causes an increase in the *p*-character and thus weakening of the CN aziridine bonds, and in turn, an increase in *s*-character of the nitrogen lone-pair.[8] Accordingly, the aziridine nitrogen is less basic than analogous larger-ring or acyclic aliphatic amines, so nucleophilic chemistry is less common.[9]

N-substitution of an aziridine also affects the electrophilicity of the motif, with aziridines classified as activated or non-activated, dependent upon this substitution.[10] Activated aziridines bear *N*-substitution that is able to stabilise negative charge build-up at nitrogen during ring-opening (**Fig. 2**).[9] The electron-withdrawing nature of such a substituent also further polarises the aziridine CN bonds. Both result in the increased electrophilicity of the carbon atoms. Non-activated aziridines generally require

initial activation with Lewis or Brønsted acid. Examples of non-activated aziridines include *N*-alkyl and *N*-unfunctionalised (*NH*) aziridines (**Fig. 2**).

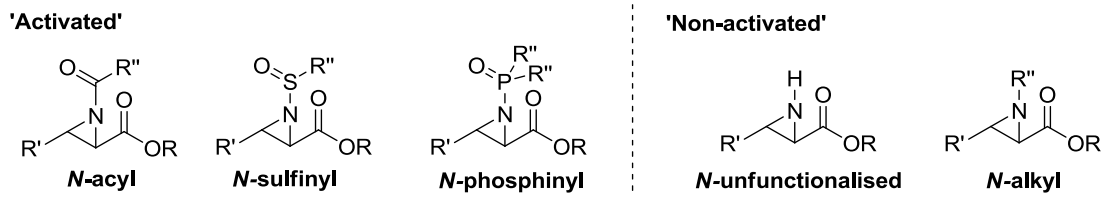


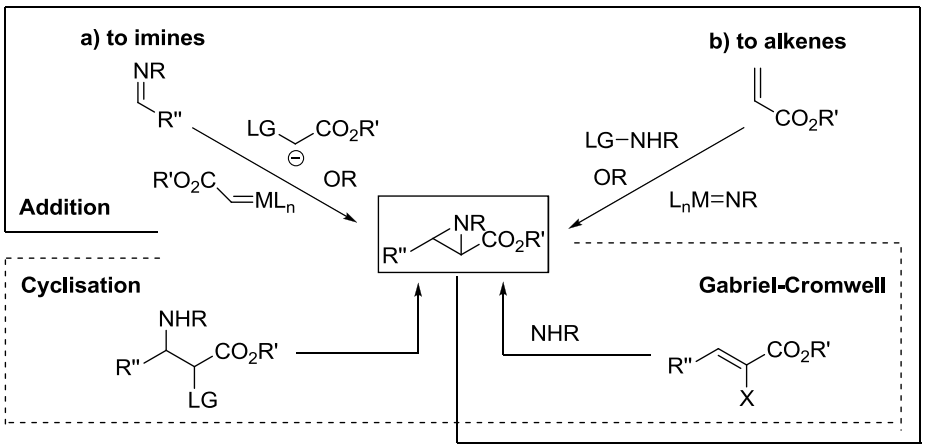
Fig. 2: Examples of *N*-functionality of aziridine-2-carboxylates

The majority of protocols to access aziridine-2-carboxylates yield *N*-functionalised aziridines.[11] Synthetic methods available require protection of the aziridine nitrogen during synthesis (*vide infra)* and the ease of subsequent ring-opening chemistry makes *N*-functionalised aziridines attractive targets. However, a key disadvantage is the usual requirement for *N*-deprotection, either of the aziridine, or of the resulting amine product following ring-opening. This adds a synthetic step, and can be low yielding; in particular, the sensitive nature of the aziridine means that the CN bonds can be cleaved.[12] One solution is to directly synthesise *NH*-aziridine-2-carboxylates, so the problematic deprotection step is not required. Additionally, this would lead to more efficient ring-opening chemistry. However, a limited number of methods to access *NH*-aziridine-2-carboxylates exist. Consequently, little is known about their synthetic use, including their propensity to participate in ring-opening reactions. If successful, ring-opening could provide direct access to a diverse range of biologically important structures from a common aziridine-2-carboxylate.

The review that follows aims to highlight some of the common and very successful methodologies to access aziridine-2-carboxylates. However, the selected examples will also be used to illustrate the lack of applicability of the majority of current methods to the synthesis of *NH*-aziridine-2-carboxylates. Only examples involving synthesis of the aziridine ring are included, rather than functionalisation of a pre-existing aziridine substrate. A full review of the area is not intended, rather a discussion of particularly relevant examples and methods; for a more detailed analysis, the reader is directed towards several reviews.[13-15]

1.1.1 Synthetic methods to aziridine-2-carboxylates

Aziridine syntheses can be grouped into two main classes; addition and cyclisation processes (**Scheme 3**). Addition processes can be further sub-divided into a) addition of carbenoids to imines and b) addition of a nitrene, nitrenoid or nucleophilic nitrogen to alkenes.[15] Ring-contraction, for example of a 1,2,3-triazole with loss of nitrogen, can also lead to aziridine formation, although this class of reactions is not covered in this overview.



Scheme 3: Classical synthetic methods to aziridines

1.1.1.1 Cyclisation processes

Cyclisation processes to form aziridines involve the intramolecular substitution of a β-leaving group by a nitrogen nucleophile. This is the oldest class of aziridine-forming reaction; indeed the first reported synthesis of aziridine by Gabriel in 1888 occurred from the cyclisation of a 1,2-amino alcohol.[16] Synthesis of aziridine-2-carboxylates *via* cyclisation is facile and widely exploited.[11] Common substrates for this chemistry include 1,2-amino- and 1,2-azido alcohols, with displacement of the alcohol functionality usually occurring after activation, for example, with sulfonylation or Mitsunobu chemistry.[17, 18] Substrate synthesis is facile but stepwise, often involving alkene epoxidation and subsequent ring-opening with the required nitrogen nucleophile. 1,2-Haloamines are also frequently used, with the advantage that prior activation of the leaving group is not necessary. Haloamines are commonly derived from the parent amino alcohols (**Fig. 3**).

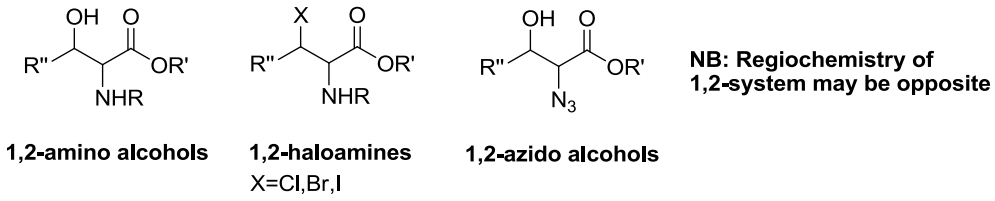
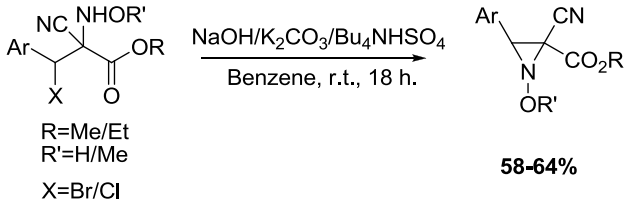


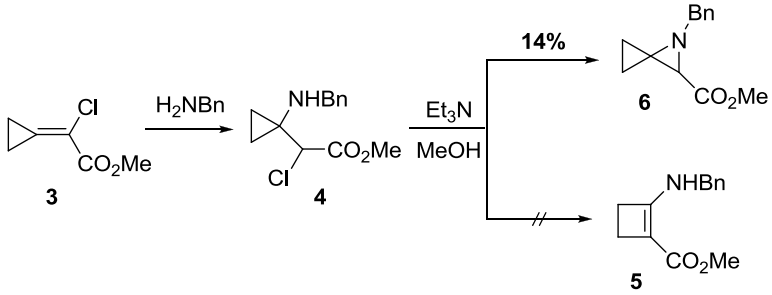
Fig. 3: Common substrates for cyclisation chemistry

β-Halogen-displacement methodology was used by Boukhris to synthesise a range of *N*-alkoxy aziridine-2-carboxylates. The aziridines were isolated in good yields from the displacement of chloride and bromide by *N*-alkoxy amines (**Scheme 4**).[19]



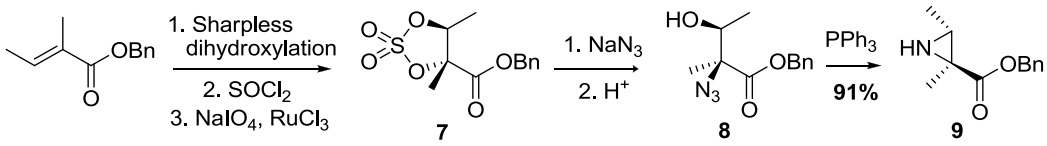
Scheme 4: Boukhris' *N*-alkoxy aziridines

Secondary amines are common intramolecular nucleophiles, leading to *N*-functionalised aziridines. Electron-rich secondary amines assist cyclisation by increasing the nucleophilicity of the nitrogen through inductive effects. An electron-withdrawing group on the amine increases the acidity of the amine proton, facilitating removal in aziridine formation.[9] The interesting azaspiropentane **6** was synthesised following cyclisation of *N*-benzylated chloroamine **4**. The reactive acrylate **3** was prepared and used as a solution in THF, whereupon addition of benzylamine provided the unstable chloroamine **4**. Cyclobutene **5** was the intended target, but on treatment of this compound with triethylamine, the spiro-aziridine **6** proved to be the only isolable product, in 14% yield (**Scheme 5**).[20]



Scheme 5: Azaspiropentane synthesis

However, primary amines are also suitable nucleophiles, leading directly to *NH*-aziridine-2-carboxylates.[17, 18] These products can also be accessed from β-azido alcohols. Staudinger chemistry reveals the primary amine nucleophile, which then displaces the alkoxy group. This reactivity was exploited by Goodman *et al.* to access *tri*-substituted *NH*-aziridine-2-carboxylates from the ring-opening of a cyclic sulfate. The starting sulfate **7** was synthesised using Sharpless dihydroxylation of benzyl tiglate, followed by reaction with thionyl chloride and oxidation. Nucleophilic substitution with azide occurred with complete inversion at the α-stereocentre, and treatment with acid yielded the required 1,2-azido alcohol **8** as a single enantiomer. PPh_3 mediated ring-closure provided the *trans*-aziridine **9** in 91% yield (**Scheme 6**).[21]

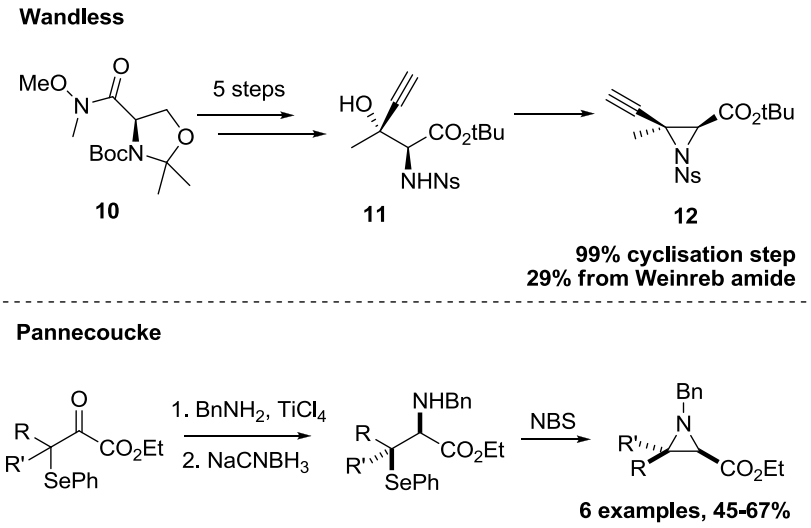


Scheme 6: Ring-closure of a chiral azido-alcohol

As shown, one advantage of cyclisation methodology is that the precursors are often accessible in enatiomerically pure form.[22] The stereochemistry of the aziridine product is set in the cyclisation step, owing to the *anti*- relationship between the nitrogen nucleophile and leaving group necessary for the intramolecular substitution. Enantioenriched amino and azido alcohols in particular are accessed using established chemistry, for example enantioselective epoxidation of an α-β-unsaturated ester followed by ring-opening with azide or the required amine.

A further example of asymmetric aziridine synthesis occurs in Wandless' synthesis of the natural product phomopsin. The interesting 3-alkynyl aziridine-2-carboxylate **12** was obtained from the cyclisation of the corresponding 1,2-amino alcohol **11**, which itself could be prepared in five steps from chiral Weinreb amide **10**. The cyclisation step proceeded in 99% yield, and aziridine **12** was isolated in 29% overall yield in 6 steps from the Weinreb amide (**Scheme 7**).[23]

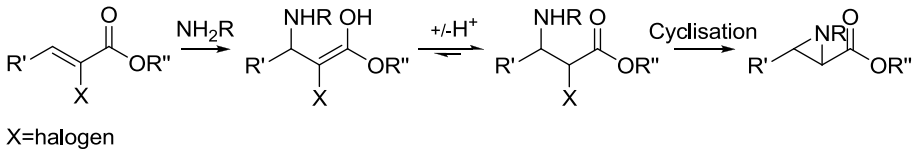
Pannecoucke was able to determine the diastereoselectivity of a prior reduction step, on accessing *cis*-aziridines using cyclisation methodology (**Scheme 7**). 1,2-Amino selenyl compounds were prepared as single diastereomers by ^{1}H NMR following reduction of α-seleno-imines. Cyclisation afforded *cis*-aziridines exclusively, allowing the configuration of the 1,2-amino selenyl esters to be determined as *syn* (**Scheme 7**). 1,2-Amino selenyl esters with the opposite regiochemistry were synthesised using an alternative route, and successfully subject to cyclisation.[24]



Scheme 7: Stereoselective syntheses of aziridine-2-carboxylates

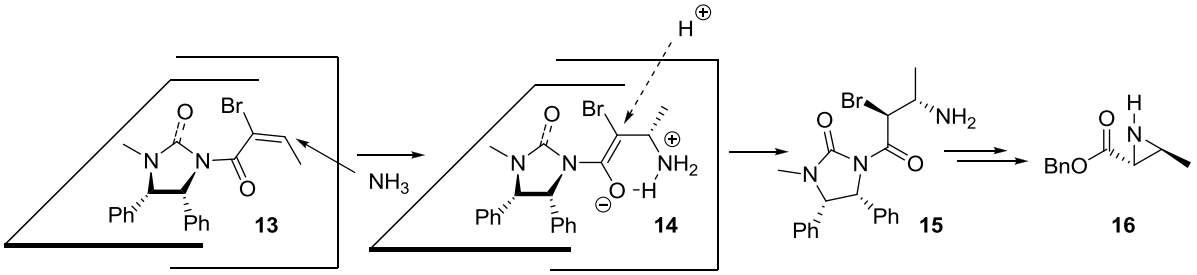
The Gabriel-Cromwell reaction

A well established reaction to synthesise aziridine-2-carboxylates that is a combination of both cyclisation and addition processes is the Gabriel-Cromwell reaction (**Scheme 8**). This involves the addition of a nitrogen nucleophile to an α-halo enoate to establish a 2-haloamine motif. Tautomerisation and cyclisation then occur to provide the aziridine-2-carboxylate.



Scheme 8: Gabriel-Cromwell reaction

NH-Aziridine-2-carboxylates are synthesised with Gabriel-Cromwell chemistry, on using ammonia as the nitrogen nucleophile. Cardillo and co-workers were able to access *trans-NH*-aziridines in good yields and high er (>9:1) on treating an auxiliary-derived chiral enamide with ammonia in DMSO (**Scheme 9**). A mechanism to support the origin of asymmetry was suggested. Initial attack of ammonia occurs on the top face of α-bromo enamide **13**, although the authors make no comment on the preferred conformation of the enamide prior to addition. Subsequent formation of hydrogen-bonded enolate **14** is suggested, which is favoured in the aprotic polar solvent. Protonation to provide α-bromo β-amino amide **15** occurs preferentially from the less hindered bottom face, setting up the required stereochemistry for ring-closure to the *trans*-aziridine. Cleavage of the auxiliary of **15** with lithium benzyloxide provides the benzyl-ester *NH*-aziridine-2-carboxylate **16** (**Scheme 9**).[25]



Scheme 9: Origin of stereoselectivity in Cardillo's Gabriel-Cromwell aziridine synthesis

Cyclisation processes allow access to aziridine-2-carboxylates bearing diverse substitution at carbon and nitrogen. Aziridines can be accessed as single enantiomers, following the use of readily accessed chiral substrates. The main disadvantage is that syntheses of aziridine-2-carboxylates by this method requires multiple steps when the overall route from readily available starting materials is considered. Thus, the chemistry is time consuming and usually occurs in low overall yield. Direct addition methodologies are now more desirable, with the aim of providing aziridine-2-carboxylates in a single step from readily available substrates.

1.1.1.2 Addition processes

Addition to imines

The addition of a carbenoid to an imine is a widely exploited methodology for the direct synthesis of aziridine-2-carboxylates. Carbenoids can be considered as carbene equivalents that display tempered

reactivity. Examples include carbanions bearing an *ipso*-leaving group, and metallo-carbenoids, commonly depicted as species bearing a metal-carbon double bond (**Fig. 4**).

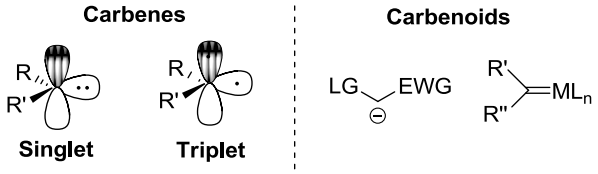
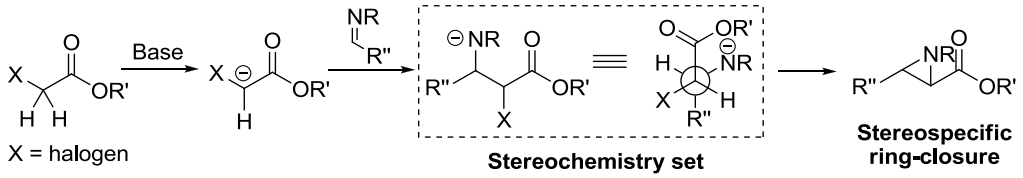


Fig. 4: Comparing carbenes and carbenoids

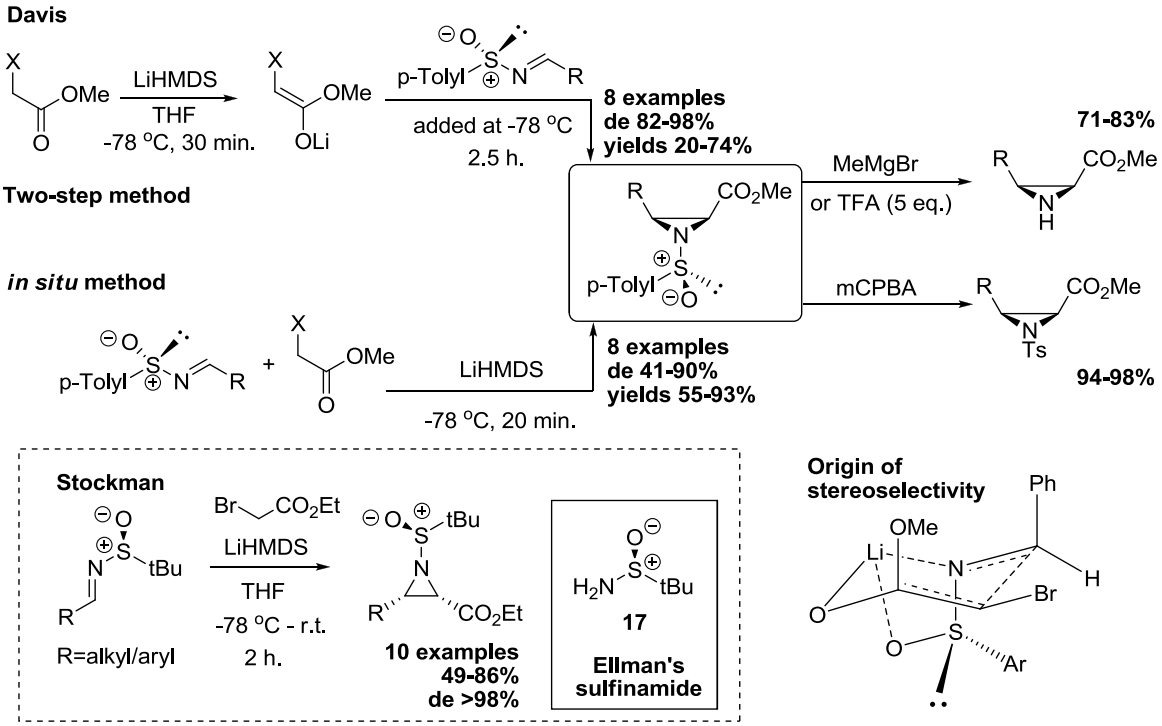
The aza-Darzens reaction provides a good example of this chemistry (**Scheme 10**). Deprotonation of an α-halo-acetate with strong base generates a carbenoid intermediate, which undergoes addition to an imine. Ring-closure furnishes an aziridine-2-carboxylate. Nucleophilic addition of the carbanion is irreversible, so the geometry of the aziridine product is set at this step, proceeding through the lowest energy transition state. Ring-closure is stereospecific, owing to the required *anti*- relationship between the amide anion and halide leaving group for intramolecular nucleophilic substitution.



Scheme 10: The aza-Darzens reaction

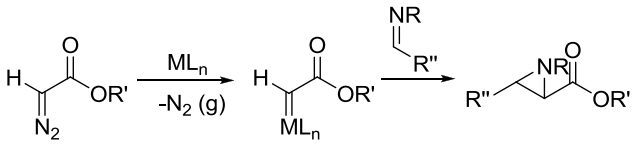
Asymmetric induction in the aza-Darzens reaction has been realised through using chiral alkyl and aryl sulfinimines by Davis (**Scheme 11**). Lithiation of methyl α-bromoacetate at -78 °C, followed by reaction with the chiral sulfinimines afforded *N*-sulfinyl aziridine-2-carboxylates with excellent *cis*-diastereoselectivity (de 82-98%). However, isolated yields of some aziridines were poor, rationalised as being due to the suspected instability and self dimerisation of the lithium enolate of methyl α-bromoacetate. As a result, an *in situ* trapping method was developed, whereby the sulfinimine and α-halo enolate were mixed prior to treatment with LiHMDS (**Scheme 11**). This method provided aziridines in increased yields, but poorer diastereoselectivity (de 41-90%). Stereocontrol is proposed to arise from a chair-like transition state, with co-ordination of the imine nitrogen, acrylate oxygen and sulfinyl oxygen with the lithium (**Scheme 11**). Co-ordination of the sulfinyl oxygen in the chair transition state accounts for the excellent diastereoselectivity observed with respect to the auxiliary. Oxidation of the *N*-sulfinyl aziridines with *m*CPBA provided the corresponding *N*-tosyl aziridines in excellent yields, which were subjected to ring-opening chemistry. Additionally, cleavage of the *N*-sulfinyl group was possible in good yields, providing access to *NH*-aziridine-2-carboxylates.[26, 27] The aziridination and ring-opening methodology was applied towards the synthesis of the antibiotic (+)-thiamphenicol. An intermediate in the route could be accessed in 49% yield over three steps, starting from an enantiopure sulfoxide.[28]

Extension of Davis' methodology was reported by Stockman *et al.* (**Scheme 11**). Chiral imines derived from Ellman's *tert*-butanesulfinamide **17**,[29] were reacted with lithiated α-bromoethylacetate, to give the corresponding aziridines in moderate to good yields (49-86%), and excellent de's (>98%, *c.f.* 41-90% in Davis' *in situ* method). The reaction was *cis*-selective (>90:10) in accordance with Davis' findings, but a slight drop in diastereoselectivity was observed for electron-poor substrates and heteroaromatics. *N-tert*-Butylsulfiniyl ketimine substrates displayed poorer reactivity but gave 2,2,3-trisubstituted aziridines, with excellent de's (>96%) observed for ketimines bearing aromatic functionality at carbon.[30]



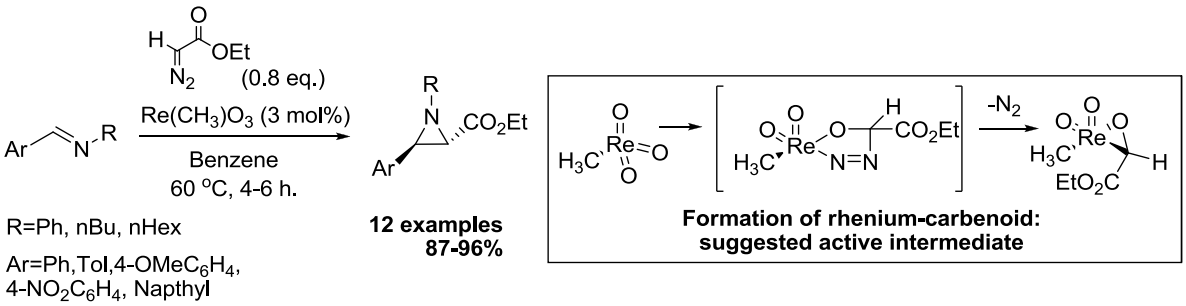
Scheme 11: Aza-Darzens chemistry to *N*-sulfinyl aziridine-2-carboxylates

α-Diazoacetates are commonly used as metallo-carbenoid precursors in aza-Darzens-like chemistry (**Scheme 12**). Carbenoid formation is driven by loss of nitrogen from the starting material, promoted by heat, light or the metal catalyst.



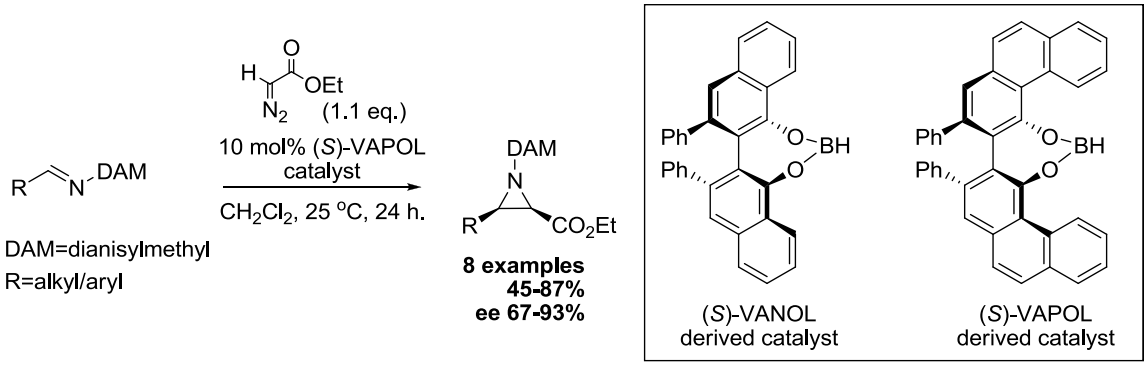
Scheme 12: α-Diazoacetates in aza-Darzens-like chemistry

An early publication in this field from Espenson *et al.* used catalytic methylrhenium trioxide to generate the carbenoid derived from ethyldiazoacetate. Addition to aryl imines provided *trans*-aziridine-2-carboxylates in yields of 87-96%, with variation of the aryl imine. A rhenium-carbenoid was tentatively suggested as the active species (**Scheme 13**).[31]



Scheme 13: $Re(CH_3)O_3$ catalysed aziridine formation

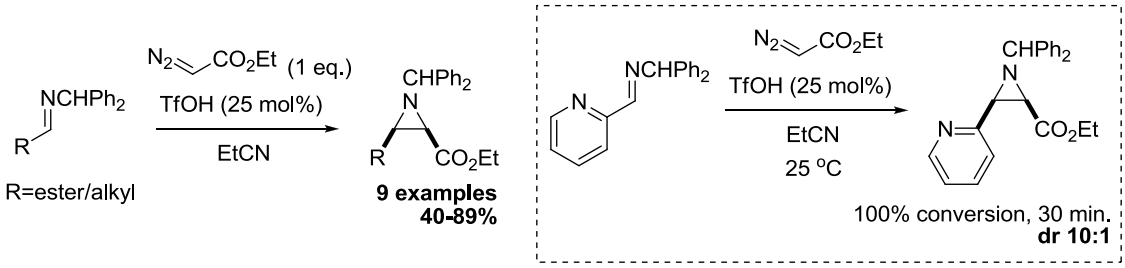
Detailed research into this reaction has led to the publication of seminal work from Wulff *et al.* An enantioselective protocol employing boronate VAPOL-derived catalysts provided *cis*-aziridine-2-carboxylates in good yield (**Scheme 14**).[32] Subsequent investigation revealed that VANOL-derived catalysts were also suitable for the transformation.[33] Initially *N*-benzhydryl protection was found to be necessary for good levels of enantiocontrol, but hydrogenolytic removal in the presence of Pearlman's catalyst led to ring-opening of aryl-substituted aziridines. Although this presented a simple synthesis of enantioenriched amino acid derivatives, *NH*-aziridines were the desired targets. Substitution of *N*-benzhydryl with the acid labile *N*-dianisylmethyl (DAM) in the methodology provided access to *NH*-aziridine-2-carboxylates on protecting-group cleavage, with no ring-opening observed.[34]



Scheme 14: Wulff's asymmetric synthesis of *N*-DAM aziridines

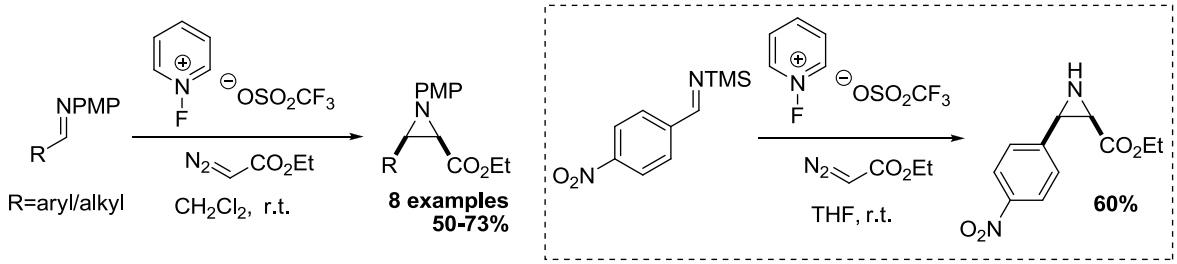
Following Wulff's Lewis acid-mediated protocol, an attractive Brønsted acid-catalysed methodology was described by Johnston *et al.* to access aziridine-2-carboxylates. The authors highlight the relative ease of catalyst removal using a basic wash, in comparison to column chromatography required for removal of the VANOL- and VAPOL-derived Lewis acids. However, a limitation of the procedure is lack of asymmetric induction, in contrast with Wulff's methodology. Initial optimisation found that Brønsted acids with low pK_a's provided decreased reaction times, and that polar solvents were the optimum media for aziridination. Addition of ethyldiazoacetate to a range of *N*-benzhydryl aldimines in the presence of TfOH in CH_3CH_2CN, provided good yields of aziridine-2-carboxylates in high *cis*-diastereoselectivity (**Scheme 15**). Yields and diastereoselectivity were found to decrease with more electron-rich aliphatic aldimine substrates. Further experimentation revealed that the electron-poor 2-

pyridyl-substituted aldimine underwent complete conversion to the corresponding aziridine in 30 min. in excellent *cis*-diastereoselectivity (**Scheme 15**). Chelation of the proton between the imine and pyridine nitrogen atoms was suggested to rationalise the increased reaction rate.[35]



Scheme 15: Brønsted acid-catalysed aza-Darzens reaction

Fluoronium salts have also been used as catalysts in aza-Darzens-like chemistry by Bew *et al.* Eight *N*-PMP aziridines were synthesised in good yields from aromatic and aliphatic aldimines (**Scheme 16**). The aziridination was *cis*-selective, although diastereoselectivity was moderate for three substrates. The fluoronium ion was the presumed catalyst, activating the aldimine substrate to nucleophilic attack, in an analogous manner to Brønsted acid-catalysis. Indeed, a control experiment in the absence of a fluoronium salt produced no aziridine. *N*-fluoropyridinium triflate was found to be the optimum fluoronium source for aziridination; other fluoropyridinium catalysts tested provided decreased yields of aziridine. One example of an *N*-TMS aldimine undergoing aziridination was described, providing direct access to an *NH*-aziridine following cleavage of the *N*-TMS group on chromatographic purification on silica (**Scheme 16**).[36]



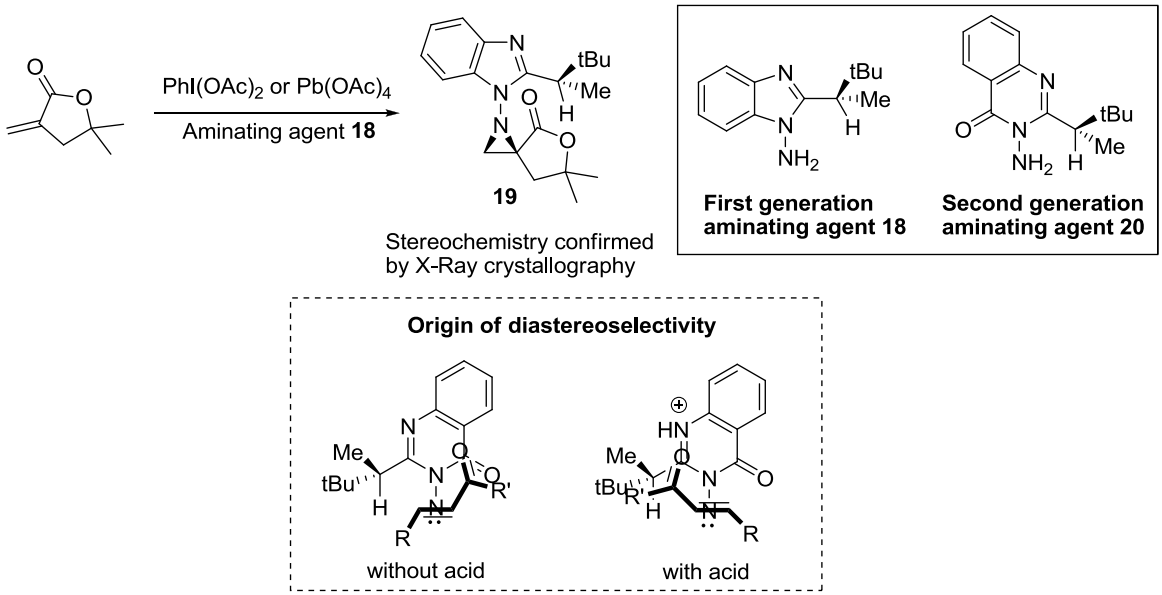
Scheme 16: Fluoronium-catalysed aziridination

The addition of carbenoid reagents to imines is a rapid method to access aziridine-2-carboxylates, in high stereoselectivity if desired. However, the developed chemistry often proceeds under strongly basic or acidic conditions, or in the presence of metal catalysts, which are not appropriate for *NH*-imine substrates. Thus synthesis of *NH*-aziridine-2-carboxylates *via* this method requires a final deprotection step, and cannot be classified as direct with respect to these substrates.

Addition to alkenes

Nitrene and nitrenoid reagents

Initial forays into aziridine-2-carboxylate synthesis from alkene substrates utilised nitrenes. An early communication from Atkinson *et al.* described a chiral alkene aziridination using *N*-aminobenzimidazole **18** (**Scheme 17**). Oxidation of this reagent, followed by treatment with methyl acrylate, provided the *N*-aminated aziridine as a mixture of stereoisomers. α-Methylene-γ-butyrolactone underwent aziridination with an improved steroisomeric ratio, and introduction of a gem-dimethyl group to the α-methylene-γ-butyrolactone substrate saw **19** produced as a single diastereomer. The configuration of the major diastereomer was confirmed by X-Ray crystallography, allowing a transition state model to be suggested.[37] A second-generation aminating agent **20** was developed, using an *N*-aminoquinazolone, which allowed control of aziridine stereochemistry through the presence or absence of an acid catalyst.[38] The group applied the *N*-aminoquinazolone catalyst to a range of α,β-unsaturated esters, isolating aziridine-2-carboxylates in moderate to good yields. Access to either aziridine diastereomer was possible through the presence or lack of TFA (**Scheme 17**).[39] Both aminating agents **18** and **20** were synthesised as racemates. However, a later communication describes the synthesis of a third generation aminoquinazolone as a single enantiomer, for the asymmetric synthesis of aziridine-2-carboxylates.[40]

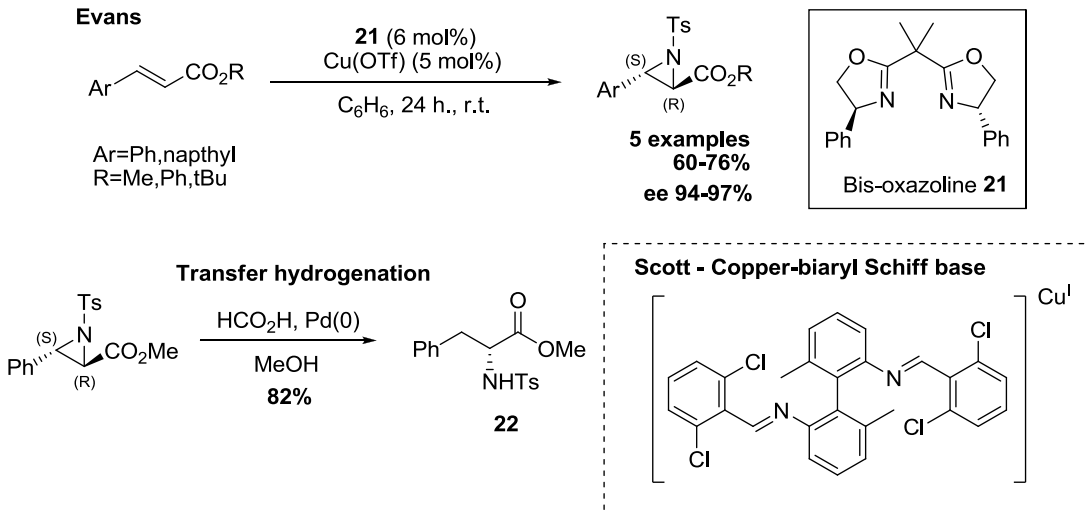


Scheme 17: Nitrene-aziridination methodology

Notwithstanding this elegant chemistry, nitrene methodologies commonly suffer from lack of selectivity and functional group compatibility, due to the harsh conditions required for their generation. Nitrenoid reagents[41, 42] with tempered reactivity were generated from PhI=NTs and iron or manganese catalysis and first used for aziridination by Manusy.[43] The chemistry was subsequently

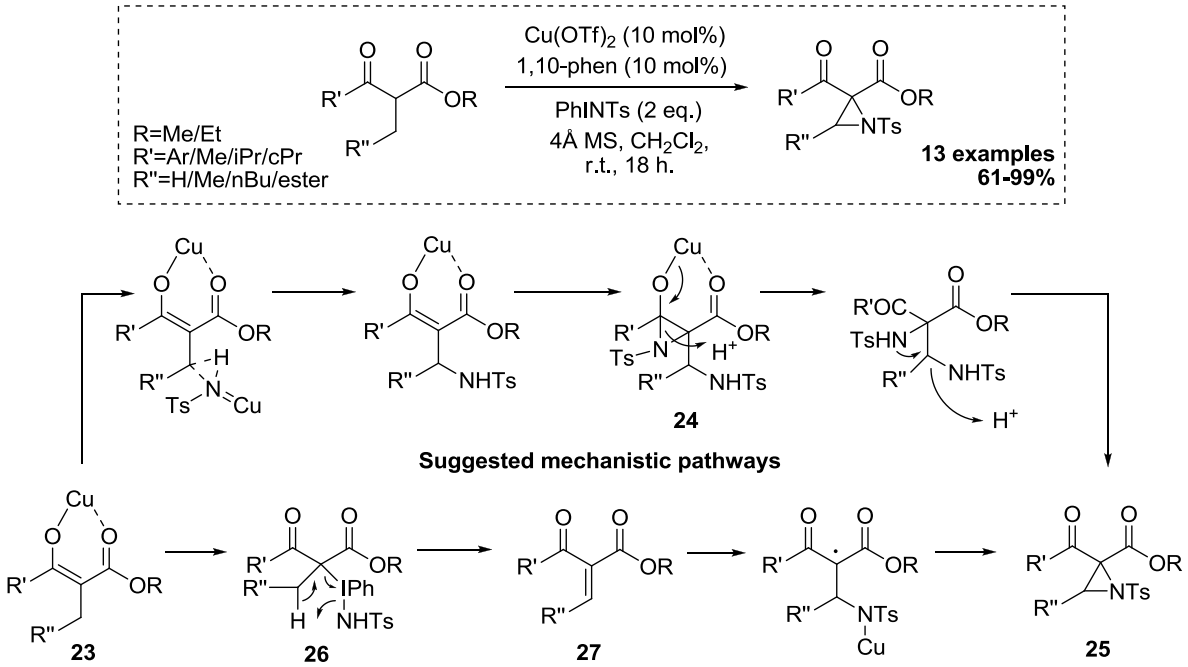
developed into a synthetically useful method with considerable substrate scope by Evans *et al.*, using copper catalysis.[44]

Evans identified both Cu(I) and Cu(II) complexes as efficient promoters of alkene aziridination using PhI=NTs. Asymmetric aziridination was realised through the use of C2-symmetric chrial bis-oxazoline ligands. Cinnamate esters were a particularly useful class of substrates, leading to *N*-tosyl aziridine-2-carboxylates. Optimisation of conditions specifically for these substrates, using bis-oxazoline **21** led to excellent ee's (94-97%) with only the *trans* diastereomers observed (**Scheme 18**). A transfer hydrogenation protocol was developed, demonstrating the synthetic utility of the aziridine-2-carboxylates as precursors to *N*-tosylated phenylalanine derivatives. In one case, the phenylalanine derivative **22** was used to assign the absolute stereochemistry of its aziridine precursor.[45] Scott and co-workers subsequently reported similar methodology using a copper biaryl Schiff base complex for enantioinduction (**Scheme 18**).[46]



Scheme 18: Asymmetric aziridination and transfer hydrogenation

Recent developments in copper-nitrenoid chemistry have led to the disclosure of a CH-activation protocol using a similar combination of reagents. Chan *et al.* were able to effect the aziridination of thirteen 2-alkyl-β-ketoesters in >61% yields, using $Cu(OTf)_2$ and PhINTs in the presence of 1,10-phenanthroline and 4Å molecular sieves (**Scheme 19**). Two mechanisms were suggested for the aziridination. Both involve the initial formation of a chelated copper enolate **23**. In the first pathway, dual-nitrene insertion into the allylic CH bond and at the α-position of the β-ketoester *via* a radical pathway, forms aziridine intermediate **24**. Collapse of the copper enolate followed by a second ring-closure generates the aziridine product **25**. The second pathway involves addition of copper enolate **23** to the electrophilic iodine species, to give hypervalent iodine species **26**. A cyclic mechanism generates olefin **27**. Addition of TsN=Cu to the alkene as detailed in the literature provides aziridine **25**.[47]

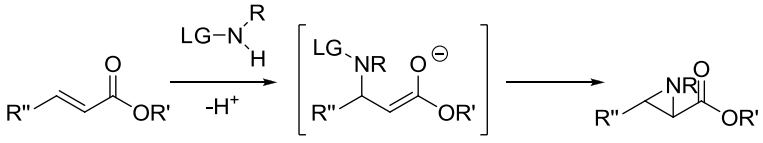


Scheme 19: 'CH-activation' to aziridine-2-carboxylates

N-Tosyl aziridines are common products in nitrenoid aziridination methodologies, owing to the stabilisation of the nitrenoid through electronic and steric effects. The high affinity of copper for nitrogen means that *N*-protection is required, and consequently, nitrenoid methodologies cannot be used to synthesise *NH*-aziridine-2-carboxylates directly.

Nucleophilic nitrogen

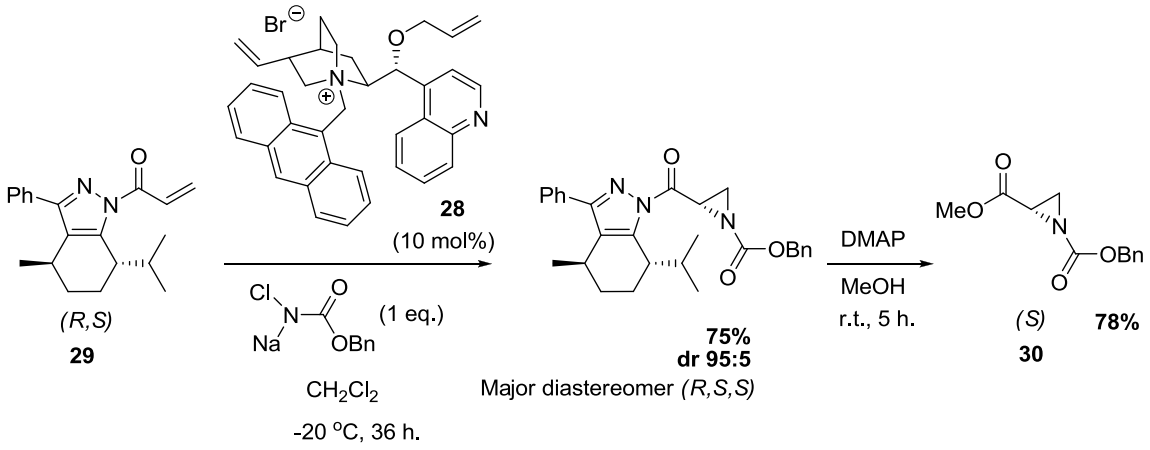
A milder method for generating aziridine-2-carboxylates from alkenes arises from the stepwise addition-elimination of a nitrogen nucleophile bearing a leaving group (**Scheme 20**). The increased nucleophilicity of nitrogen with respect to carbon means that initial deprotonation of the nucleophile is not necessary, thus avoiding the strongly basic conditions associated with analogous carbon-based reagents (*cf.* aza-Darzens chemistry). *trans*-Aziridines are the common products of this methodology, owing to bond rotation in the intermediate enolate allowing ring-closure to occur through the lowest-energy transition state.



Scheme 20: Nucleophilic nitrogen bearing a leaving group for aziridination

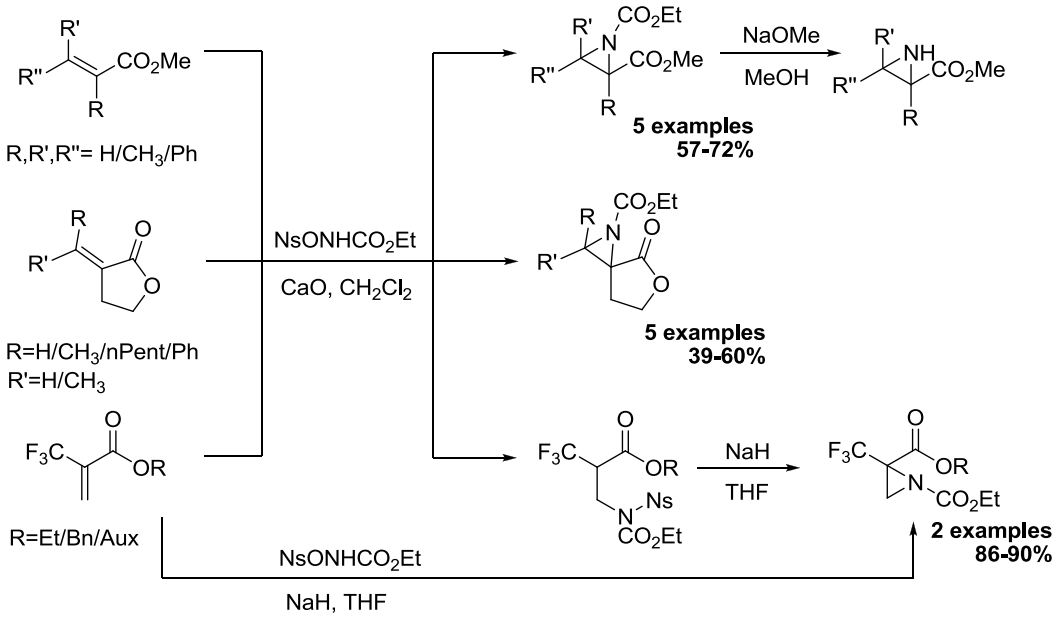
N-Chloro-*N*-sodiocarbamates[48] have been used in the phase-transfer catalysed aziridination of a chiral-auxiliary bearing enamide by Minikata. The chiral quaternary ammonium salt **28** was used as a matched ion pair for the chiral enolate of **29** following conjugate addition of the amine. The

menthol-derived auxiliary was found to be the most effective for high dr, with subsequent cleavage using DMAP in MeOH providing the *N*-Cbz-aziridine-carboxylic ester **30** in 78% yield (**Scheme 21**). Conjugate addition of the carbamate to the enamide is followed by stereoselective ring-closure, arising from a preferred conformation of the catalyst and the chiral enamide. The report focussed on optimisation of reaction conditions, such as catalyst, auxiliary and solvent. Substrate scope was not reported.[49]



Scheme 21: Example of Minikata's diastereoselective aziridination

Calcium oxide-mediated addition of ethyl nosyl carbamate to α,β-unsaturated esters has been used to furnish *N*-ethyl carbonate protected aziridines in moderate to good yields (57-72%) (**Scheme 22**). Deprotection of the aziridines with NaOMe in MeOH provided the *NH*-aziridine-2-carboxylates, although no yields were reported.[50] α-Ylidene γ-lactones were also susceptible to aziridination, resulting in spiro-aziridines.[51] The addition of ethyl nosyl carbamate to 2-(trifluromethyl)acrylates required strong base (NaH) for cyclisation. Under the CaO-mediated conditions, the adduct could be isolated, providing evidence for the stepwise addition-cyclisation mechanism.[52]

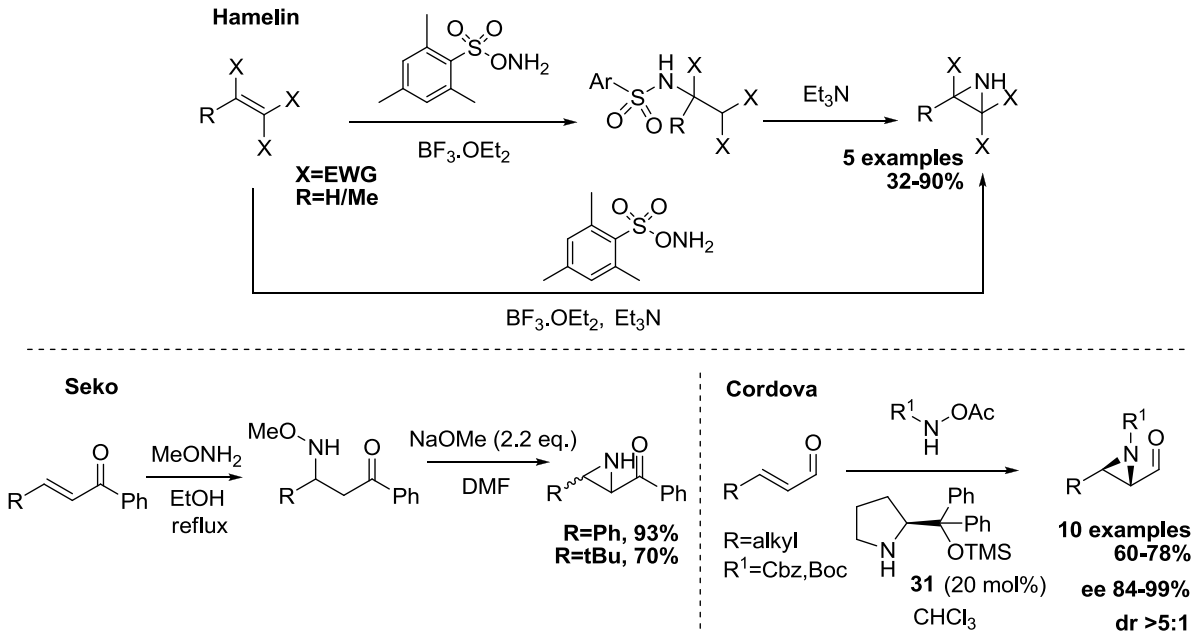


Scheme 22: *N*-ethyl carbonate aziridines from electron-poor alkenes

Addition-elimination to enoates provides an attractive potential route to *NH*-aziridine-2-carboxylates, through the use of a primary amine bearing a leaving group. However, such methodology has not been described in the literature, aside from two examples from Armstrong.[53] Protocols for the synthesis of *NH*-aziridines from enones *via* this chemistry are more readily available, and provide precedent for the applicability of this chemistry to enoates.

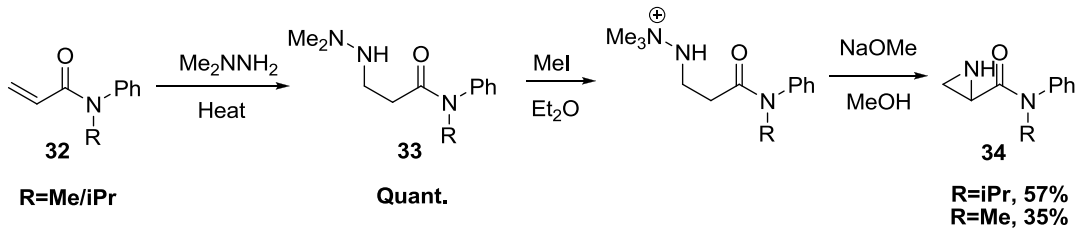
1.1.2 NH-aziridines via addition to electron-poor alkenes

Hydroxylamines are a class of reagents that have been used with success for this chemistry. *O*-Sulfonyl hydroxylamines were used by Hamelin to effect *NH*-aziridination of electron-deficient alkenes. Evidence for a stepwise mechanism arose from the isolation of an addition product in the absence of Et_3N to facilitate ring-closure (**Scheme 23**).[54] Interestingly, retention of olefin geometry was observed in a separate report, on reaction of electron-rich olefins with the analogous *p*-tosylhydroxylamine, implying a concerted nitrene-like mechanism.[55] Methoxyamine has also been used similarly by Seko, with the intermediate adduct isolated prior to aziridine ring-closure (**Scheme 23**). However, the scope of the procedure was limited, with only two enone substrates reported, and poor diastereoselectivity observed.[56] An enantioselective protocol utilising chiral iminium catalysis has also been developed by Córdova (**Scheme 23**). Nucleophilic addition of acetylated hydroxylamines to enals in the presence of the Jørgensen-Hayashi catalyst **31** provided chiral aziridines in good yields and ee's.[57] The methodology has recently been adapted to access terminal aziridines from the corresponding enals.[58]



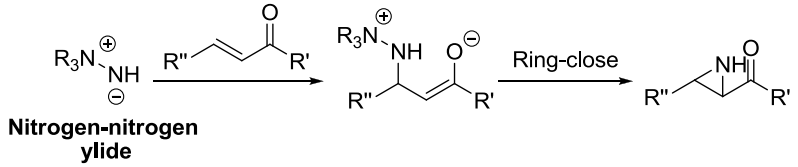
Scheme 23: Hydroxylamines in *NH*-aziridination

A hydrazine has been used in an analogous manner, detailed in a short communication from Harvey. The method was developed to access *NH*-aziridine-2-acrylanilide **34**, as established methodology had not been successful. Treatment of acrylanilide **32** with dimethyl hydrazine afforded the conjugate addition compound **33**. Selective methylation of the tertiary amine and base-mediated ring closure provided aziridine **34** (**Scheme 24**).[59]



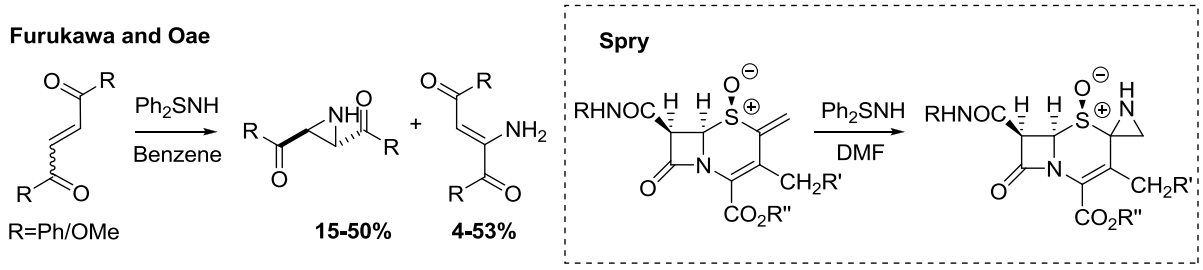
Scheme 24: Dimethylhydrazine as a reagent for nucleophilic aziridination

More recently, similar methodology employing nitrogen ylides has allowed the transformation of Harvey's methodology into a one-step protocol. Nitrogen-sulfur and nitrogen-nitrogen ylides have been used, with the key difference that the nitrogen or sulfur leaving group is pre-charged, negating the methylation step required in Harvey's chemistry (**Scheme 25**).



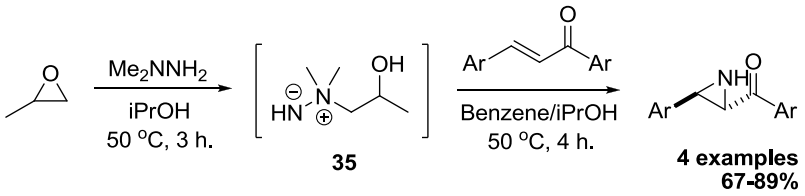
Scheme 25: A nitrogen-nitrogen ylide in aziridination

Furukawa and Oae were the first to use free diphenyl sulfinimine for ylide-mediated aziridination. Mixtures of *trans*-*NH*-aziridines and vinyl amines were produced following treatment of unsaturated 1,4-dicarbonyl compounds with the reagent, in modest to good yields (**Scheme 26**). Reaction of dimethylmaleate led to the *trans*-aziridine, and complete isomerisation of the recovered starting material. No isomerisation was observed in the absence of diphenyl sulfinimine, indicating reversibility of the initial conjugate addition.[60, 61] The methodology was used by Spry at Eli Lily, in the synthesis of C2-spiraziridino-cephalosporins (**Scheme 26**). Selectivity was observed for the γ,δ-olefin of an α,β,γ,δ-unsaturated ester, presumably due to steric encumbrance surrounding the α,β-system, and the added electron-withdrawing properties of the vinyl sulfoxide of the γ,δ-olefin.[62]



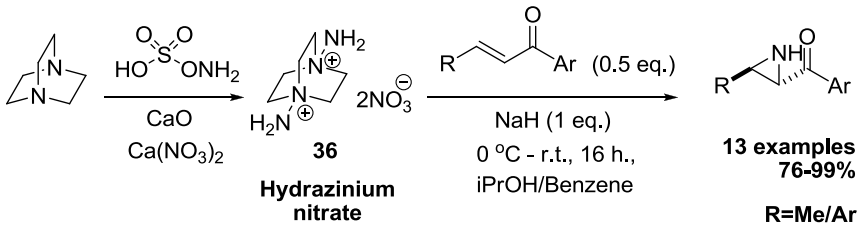
Scheme 26: Diphenylsulfinimine in the synthesis of *NH*-aziridines

Following Harvey's discovery, work from Ikeda led to the generation of a dimethyl hydrazine-derived ylide **35** *in situ* (**Scheme 27**). Whilst Harvey reported the primary amine as the nucleophilic site of the reagent, complimentary reactivity was observed by Ikeda. Reaction of dimethylhydrazine with methyloxirane proceeded through the initial attack of the tertiary amine at the unsubstituted epoxide-carbon. The quaternary amine was generated, followed by an intramolecular deprotonation to give ylide **35**. Once synthesised, the ylide was used *in situ*, forming the *NH*-aziridines from a range of chalcones in 67-89% yield. Complete diastereoselectivity for the *trans*-aziridines was observed.[63]



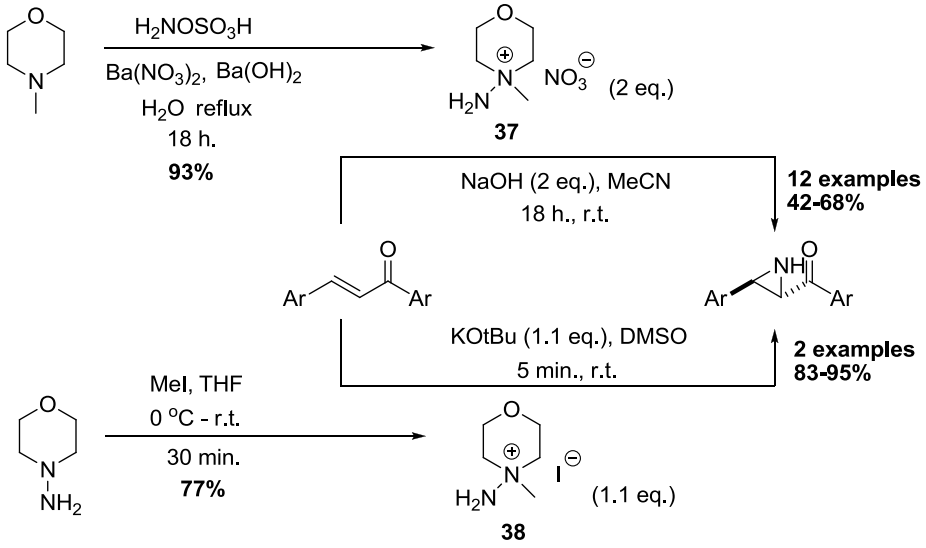
Scheme 27: Ikeda's ylide for aziridination

Xu *et al.* identified an isolable ylide precursor **36** on the amination of DABCO with hydroxylamine-*O*-sulfonic acid (HOSA). Treatment of thirteen α,β-unsaturated ketones with the reagent in the presence of base led to the derived aziridines in >76% yield (**Scheme 28**). Electron-poor (nitro-substituted) chalcones were a limitation of the methodology, with low isolated yields of 15 and 17%. Electron-rich styryl derivatives were unsuccessful substrates in the aziridination, suggestive of a nucleophilic stepwise mechanism, as opposed to nitrene reactivity.[64]



Scheme 28: Hydrazinium nitrate precursor for ylide-promoted aziridination

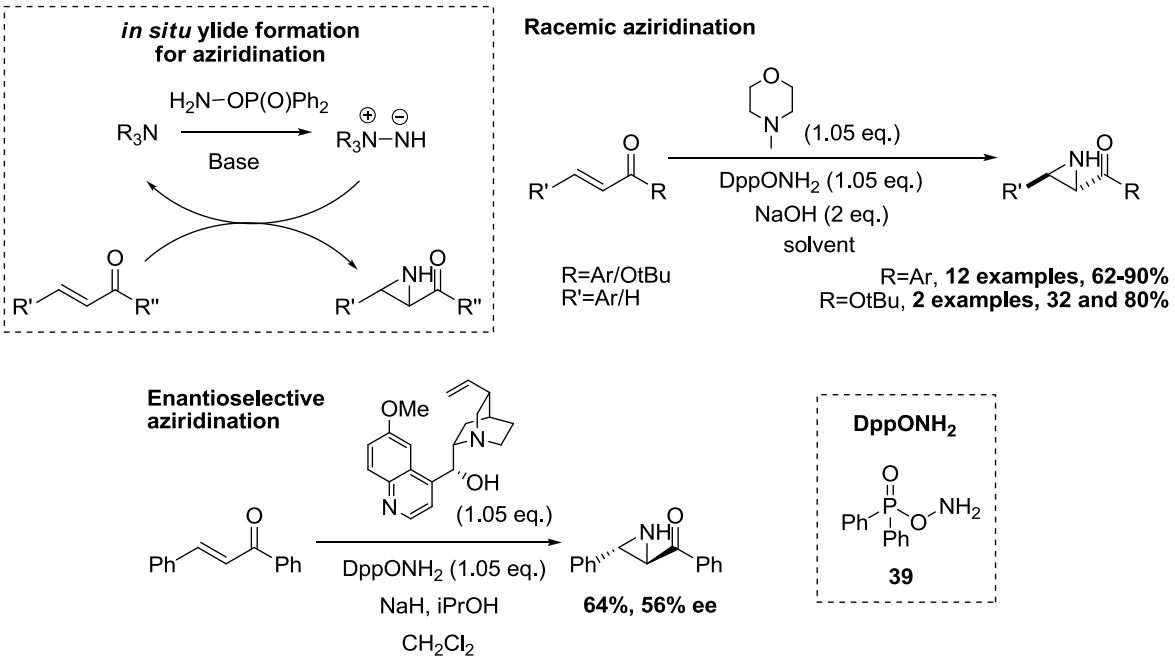
Following Xu's methodology, Armstrong and co-workers discovered that nitrogen ylides bearing the *N*-methylmorpholine scaffold were effective promoters of aziridination (**Scheme 29**). Optimisation of the aziridination of chalcone provided a 95% yield, identical to that observed by Xu, but under more amenable reaction conditions, using MeCN and NaOH. Two syntheses of the ylide precursor were developed, bearing nitrate and iodide counterions. Electron-poor substrates provided better yields with the nitrate salt **37**, whilst electron-rich performed optimally using the iodide salt **38**, under modified conditions. Aziridination proceeded with complete *trans*-diastereoselectivity.[65]



Scheme 29: *N*-methylmorpholinium salts in *NH*-aziridination

The method was further developed to involve *in situ* generation of the ylide (**Scheme 30**). *O*-(diphenylphosphinyl)hydroxylamine ($DppONH_2$) **39** was found to effect the *in situ* amination of NMM and subsequent formation of chalcone-derived aziridine in an excellent 88% yield. No aziridination occurred in the presence of $DppONH_2$ alone, and the secondary amine morpholine did not promote aziridination, providing support for the proposed aminimine pathway. Following optimisation, a range of α,β-unsaturated ketones were aziridinated in yields of >62%, superior to those observed using the hydrazinium salt chemistry. Reactions typically took place in 10-24 h.[66] Two *tert*-butyl enoate substrates were also tested, with the aziridine of *tert*-butyl acrylate isolated in 80% yield. *tert*-Butyl cinnamate proved to be the most challenging substrate tested; an isolated yield of just 32% was obtained after 40 h. The poor yield was attributed to the electron-rich substrate slowing the

nucleophilic aziridination. Investigation into enantioselective aziridination has highlighted quinine as the most effective promoter. The enantiomer shown was generated in 56% ee, using quinine under slightly modified conditions.[53, 67, 68] The *in situ* methodology has since been applied to α,β,γ,δ-unsaturated ketones, providing good yields of vinyl-aziridines in excellent *trans*-diastereoselectivity and excellent regioselectivity for the α,β-olefin.[69]



Scheme 30: Development of *in situ* aziridination

1.2 Project aims

Owing to the relative dearth of methodology to access *NH*-aziridine-2-carboxylates, the opportunity to develop the *in situ* aziridination for enoate substrates using Armstrong's methodology was realised. This would potentially allow expedient access to *NH*-aziridine-2-carboxylates from readily available starting materials, presenting an attractive alternative to current stepwise methodologies. Following this, the susceptibility of the non-activated *NH*-aziridines to nucleophilic ring-opening could be tested. If ring-opening was successful, it would be possible to access a range of biologically relevant structures from a common aziridine-2-carboxylate intermediate.

Thus, the aims of the project were:

- To optimise the *in situ* Armstrong methodology for enoate substrates, and examine the scope of the reaction;
- To subject the resulting *NH*-aziridine-2-carboxylates to nucleophilic ring-opening, to establish susceptibility to nucleophilic attack.

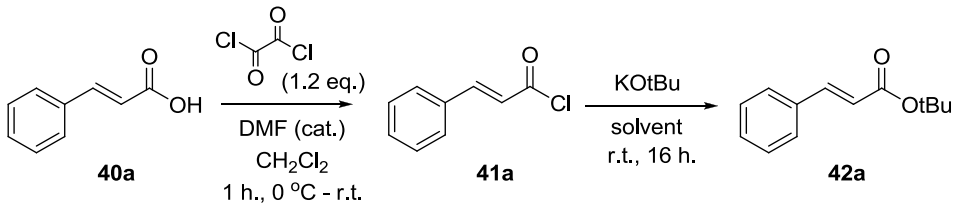
1.3 Results and Discussion

1.3.1 Optimising the enoate aziridination

1.3.1.1 Reagent synthesis

trans-tert-Butyl cinnamate **42a** was selected as the initial substrate for aziridination optimisation. The substrate was considered the more synthetically useful of the two *tert*-butyl enoate substrates reported in the original paper,[69] but the derived aziridine had only been isolated in 32% yield. Prior to commencing optimisation studies, a robust synthesis of the substrate was required, due to the high cost of the commercially available material. The ready availability of *trans*-cinnamic acid **40a** prompted a synthesis beginning with this reagent. Formation of cinnamoyl chloride **41a** was facile; on treatment of the starting acid with oxalyl chloride, complete conversion was observed by TLC analysis after 1 h. The volatiles were removed *in vacuo*, the acid chloride re-dissolved in THF and treated with commercial KO^{t}Bu (1 M in THF). After 16 h., work-up and chromatographic purification provided *trans-tert*-butyl cinnamate **42a** in 80% yield on a 7 mmol scale (**Table 1**, entry 1). Brief optimisation revealed that KO^{t}Bu (1 M in THF) was the most effective reagent for generation of the *tert*-butyl ester; re-dissolution of the acid chloride in *tert*-butanol and treatment with solid KO^{t}Bu caused complete hydrolysis to the starting acid (entry 2) and a considerably lower yield was observed on using commercial KO^{t}Bu (s) in THF (entry 3). Subsequent scale-up of the cinnamate synthesis provided the product in comparable yield (entries 4 and 5).

Table 1: *trans-tert*-Butyl cinnamate synthesis

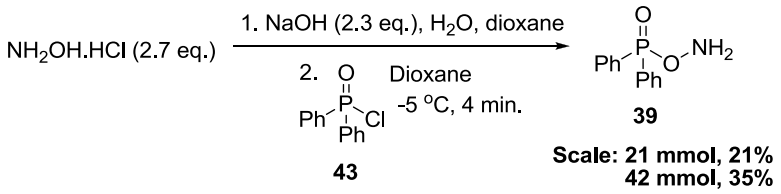


Entry	Scale (mmol)	Solvent	Form of KO^{t}Bu	Isolated yield (%)
1	7	THF	1M in THF	80
2	24	*t*-BuOH	(s)[a]	-[b]
3	7	THF	(s)	50
4	17	THF	1M in THF	73
5	24	THF	1M in THF	91

Reactions performed at a concentration of 0.7 M. [a] 1.05 eq. KO^{t}Bu [b] Complete hydrolysis to cinnamic acid observed by ^{1}H NMR analysis of the crude reaction mixture.

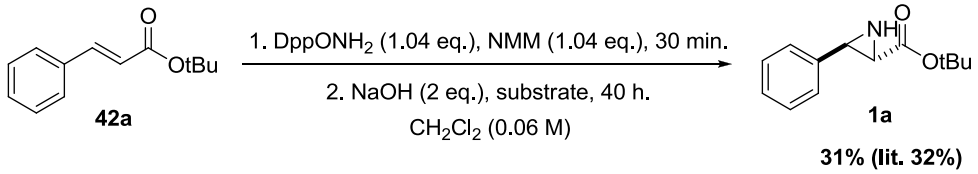
It was decided to initially validate the aziridination of *trans-tert*-butyl cinnamate by repeating the literature procedure. In order to do this, the aminating agent $DppONH_2$ (**39**)[70, 71] had to first be synthesised. Following the published protocol,[53] phosphinyl chloride **43** in dioxane was added at -5 °C to a stirred solution of hydroxylamine hydrochloride, pre-treated with aqueous sodium hydroxide (**Scheme 31**). The crude product was filtered and dried *in vacuo* before purification by slurrying in

aqueous sodium hydroxide and rigorous drying *in vacuo*. Although isolated in low yield, the aminating agent was judged of sufficient purity by NMR analyses (^{1}H and ^{31}P) to be used in the aziridination. More recently, an alternative synthesis of the aminating agent has been published.[72] The procedure differs in that Et_2O is used in place of dioxane, and mechanical stirring is required for complete mixing of the biphasic reaction. The Schotten-Baumann conditions allow considerably improved recovery of $DppONH_2$. Subsequent preparations of $DppONH_2$ were carried out following this procedure, which provides the reagent in high purity, and reproducible quantitative yield.



Scheme 31: $DppONH_2$ synthesis

With the aminating agent and cinnamate in hand, the first aziridination reaction could be carried out. Repeating the reported procedure, NMM was added dropwise to a suspension of the aminating agent in CH_2Cl_2 and stirred for 30 min., before the sequential addition of NaOH and *trans*-*tert*-butyl cinnamate. Work-up and analysis of the ^{1}H NMR spectrum of the crude material revealed a 35% conversion to aziridine **1a** with starting cinnamate the only other compound observable. Purification by column chromatography provided a 31% isolated yield of the aziridine as the single *trans*-diastereomer, comparable with the literature value of 32% (**Scheme 32**).



Scheme 32: Repeat of literature conditions for *tert*-butyl cinnamate aziridination

In order to speed up analysis during optimisation, it was decided to use the conversion observed by ^{1}H NMR of the crude material as a guide to the success of changes made to the reaction conditions. The conversion was calculated by measuring the integrals of three sets of selected peaks relating to both *tert*-butyl cinnamate and aziridine **1a** and inserting the values into (**Equation 1**). Three sets of peaks were compared for increased accuracy (**Table 2**), all with good chemical shift separation and no overlap with other signals.

$$\text{Conversion} = \frac{\text{Integral of selected aziridine peak}}{(\text{Integral of corresponding cinnamate peak})+(\text{Integral of selected aziridine peak})} \times 100$$

(Equation 1)

Table 2: Signals integrated to obtain conversion value

tert-Butyl cinnamate	Chemical shift (ppm)	Aziridine 1a	Chemical shift (ppm)
PhC**H**	7.60	PhC**H**NH	3.17
C(O)C**H**	6.42	C(O)C**H**NH	2.50
C(C**H**$_3$)$_3$	1.55	C(C**H**$_3$)$_3$	1.50

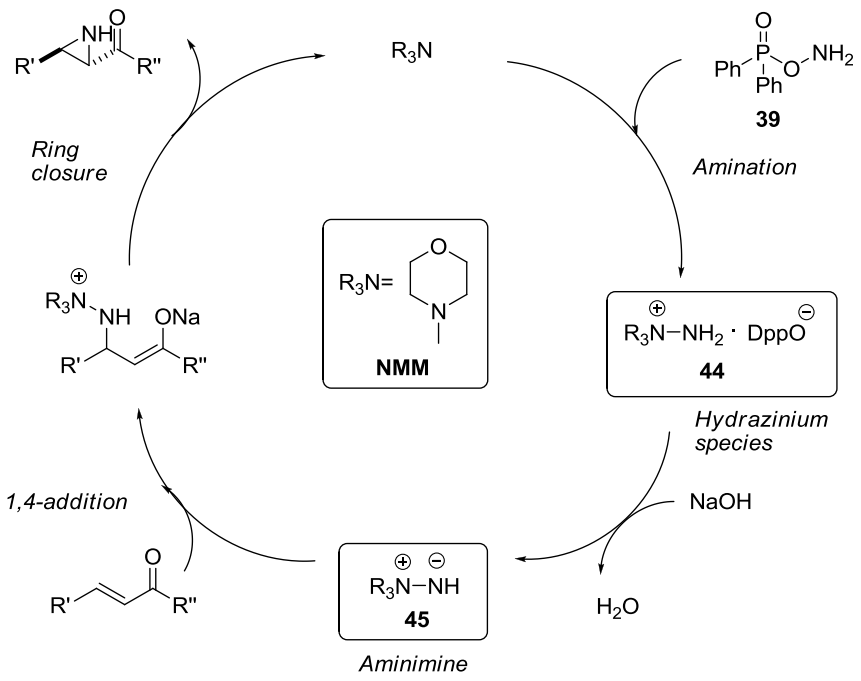
1.3.1.2 The catalytic cycle

To begin optimisation of the aziridination of *tert*-butyl cinnamate, the catalytic cycle of the aziridination was first considered (**Scheme 33**). The cycle begins with amination of NMM by $DppONH_2$, which generates the hydrazinium species **44**. Under basic conditions, the presumed active intermediate, aminimine **45** is formed, which adds in a conjugate fashion to the substrate. Ring-closure yields the aziridine and regenerates NMM.[53] Previous studies have shown that a tertiary amine is required for aziridination; the reaction does not proceed if a secondary amine is used, and $DppONH_2$ alone does not generate the aziridine.[67, 73] It is thought likely that the cycle proceeds under general base catalysis and that existence of the aminimine is transient. Hydrazinium salts have been isolated and characterised in previous work and the hydrazinium species has been observed by ^{1}H NMR (in d_6-DMSO), on treatment of NMM with $DppONH_2$.[67, 74] However, there is limited evidence for the existence of the aminimine. An attempt has been made to measure the pKa of the aminated hydrazinium salt of NMM using potentiometric titrations, to establish whether hydroxide and alkoxide bases used in the aziridination would be strong enough to effect deprotonation to form the aminimine.[67] A pKa value of greater than 12.5 was indicated, although a precise value could not be established, owing to the upper limit of the equipment (pH = 12.5).

The heterogenous nature of the aziridination has prevented any detailed kinetic studies, but circumstantial evidence suggests that the cyclisation step is rate-limiting. Original optimisation studies tested several tertiary amine promoters, and found that cyclic tertiary amines with lower pK_a values provided higher yields of aziridine. This could be related to the leaving-group ability of the tertiary amine in the final cyclisation step. Additionally, a clear trend in relative reactivity for electron rich and electron poor enones has not been observed, which suggests that the addition step is not rate-limiting.

Considerable effort in previous optimisation identified that DABCO, quinuclidine, NMP and NMM were the most favourable tertiary amine promoters for aziridination. Optimum solvents included MeCN, CH_2Cl_2, THF and DMF, and hydroxide or alkoxide bases were found to be most suitable.[73] These results were considered along with the catalytic cycle, in the optimisation of enoate-specific aziridination conditions. However, it was also realised that all previous studies had been carried out using enone substrates. The differing electronic properties of the two substrate classes could have

considerable implication on the catalytic cycle, and consequently, the optimum reagents for aziridination.



Scheme 33: Catalytic cycle for Armstrong aziridination

1.3.1.3 Towards a homogeneous aziridination

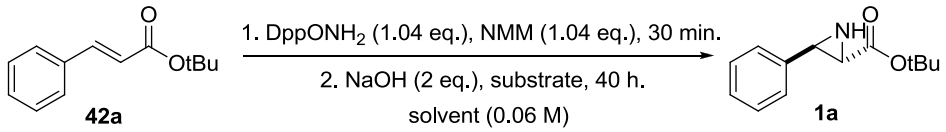
The heterogeneous nature of the reaction was highlighted as a possible cause for the low conversions to aziridine **1a** observed. Consequently, increasing the dissolution of the inorganic components, namely $DppONH_2$ and NaOH, was a first priority in optimisation.

Solvent choice

A range of anhydrous solvents were selected and tested under the published aziridination conditions. The polar solvent MeCN was chosen, which had been used with success for other substrates in the reported methodology, along with the alternative chlorinated solvents, dichloroethane and $CDCl_3$ (selected in the absence of anhydrous $CHCl_3$). The reaction remained heterogeneous in all three solvents, and no conversion to aziridine was observed (**Table 3**, entries 2-4). Quantitative recovery of starting cinnamate was observed by ^1H NMR analyses of the spectra of the crude material. It was observed that increasing the volume of solvent used led to increased dissolution of the inorganics and improved magnetic stirring. Consequently, further reactions were carried out at a decreased concentration of 0.03 M (with respect to the cinnamate), with the polar solvents MeOH, THF and diethyl ether, and also DMSO tested. DMSO and MeOH were the only two solvents in which the reaction components dissolved completely, but no conversion to aziridine was observed in either, nor was any conversion observed in the ether solvents (entries 5-8). Interestingly, the only solvent apart

from CH_2Cl_2 to provide any conversion to aziridine **1a** was toluene, in an identical 35% (entry 9). Due to the lower cost and higher volatility of CH_2Cl_2, further optimisation was carried out in this solvent. The phase transfer catalyst TBAB was included in two experiments in CH_2Cl_2, at 10 mol% and 100 mol% loadings (entries 10 and 11), but lower conversion to aziridine **1a** was observed in both experiments, and so the additive was omitted in further optimisation.

Table 3: Screen of solvents



42a 1a

Entry	Solvent	^{1}H NMR conversion (%)
1[a]	**CH_2Cl_2**	**35**
2[a]	MeCN	0
3	Dichloroethane	0
4	$CDCl_3$	0
5[b]	DMSO	0
6[b]	MeOH	0
7[b]	THF	0[c]
8[b]	Et_2O	0[c]
9[b]	Toluene	35
10[b,d]	CH_2Cl_2	17
11[b,e]	CH_2Cl_2	32

Reactions performed on 0.12 mmol scale of *tert*-butyl cinnamate. [a] 0.49 mmol scale. [b] Carried out at a concentration of 0.03 [M]. [c] Degradation observed by ^{1}H NMR analysis of crude material. [d] TBAB (100 mol%) added. [e] TBAB (10 mol%) added.

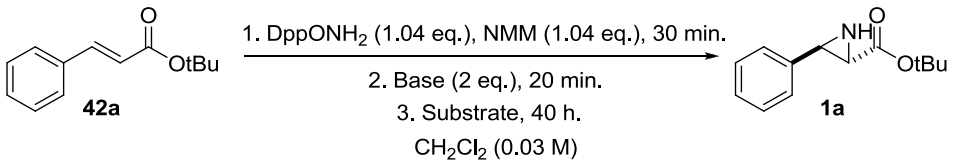
Base choice

It was suggested that the low conversions to aziridine observed might be due to instability of the reagents to the NaOH. To establish whether the aminating mixture (NMM and $DppONH_2$ pre-stirred in CH_2Cl_2 for 30 min.) was undergoing degradation under the reaction conditions, a reaction was set up using the standard conditions, and a second portion of aminating mixture was added to the aziridination after 20 h. An identical 35% conversion was obtained, which was inconclusive. Subsequent experimentation involved pre-stirring the aminating mixture with NaOH for set time intervals, prior to the addition of the cinnamate, reasoning that lower yields could indicate poor stability of the aminating agent to hydroxide. Interestingly, a time delay of 20 min. between NaOH and substrate addition was found to improve the conversion from 35 - 47% (**Table 4**, entry 1 *vs.* 2). It was suggested that this time delay could allow some initial deprotonation of the hydrazinium to occur thus increasing the rate of nucleophilic attack. However, stirring the aminating mixture with NaOH for a considerably longer time period (160 min.) prior to cinnamate addition did lead to decreased conversion (23%) (entry 3), suggesting that the aminating mixture is unstable when exposed to hydroxide for this longer time period. Optimisation therefore continued including 20 min. between base and substrate addition.

If the increased conversion observed with the 20 min. delay prior to NaOH addition was due to some initial hydrazinium deprotonation, then it was reasoned that a stronger base could allow a further increase in conversion to aziridine. KO^{t}Bu has enjoyed previous success in the aziridination methodology, when used as a commercial 1 M solution in THF.[67] Additionally, any transesterification with the reagent would regenerate the *tert*-butyl ester. Substituting KO^{t}Bu (1 M in THF) for NaOH under the optimised conditions led to a low conversion of 3% (entry 4), but with a good mass recovery of *tert*-butyl cinnamate obtained. The result suggested that the aminating mixture was unstable to the more strongly basic KO^{t}Bu. Some evidence for this hypothesis was obtained on repeating the reaction with sequential addition of KO^{t}Bu and *tert*-butyl cinnamate, and with increased equivalents of NMM and DppONH$_2$ with respect to KO^{t}Bu. In this case, conversion to the aziridine was a respectable 45% (entry 5). Treatment with LiO^{t}Bu under these modified conditions led to a lower conversion of 35% (entry 6). NaO^{i}Pr, synthesised *in situ* from NaH and ^{i}PrOH, had been used with success by a co-worker in the aziridination of sensitive α-enolisable substrates.[67] These conditions, albeit slightly modified, were tested in the aziridination of *tert*-butyl cinnamate. Conversions were below the optimum 47%, whether the base and ester were added sequentially, or the 20 min. delay between addition of reagents was included (entries 8 and 9).

Given this, attention was re-focussed on the optimum conditions that had provided the 47% conversion to aziridine, ensuring that the base was the sole variable in further testing. On testing solid KO^{t}Bu, a 15% conversion to aziridine was observed (entry 7). Consequently, further investigation into *tert*-butoxide bases was halted, given the poorer conversions observed with the reagents. An alternative hydroxide base, KOH, was selected but gave a low conversion to aziridine of 18% (entry 10). Two weaker bases, K_2CO_3 and Hünig's Base, provided no conversion to aziridine when substituted for NaOH (entries 11 and 12); seemingly both were too weakly basic to effect deprotonation and drive the aziridination forward. Finally, the aziridination was attempted using NaOH with mild heating, to try to increase the conversion further. However, reactions performed at 25 °C and 30 °C led to decreased conversions, possibly due to poor stability of the aminating agent at increased temperatures (entries 13 and 14). Reactions at temperatures of 40 °C and above led to a decrease in diastereoselectivity, along with impurity formation. Of the bases tested, NaOH had provided the optimum conversion to aziridine, and so was selected for continuing testing of other variables.

Table 4: Screen of bases



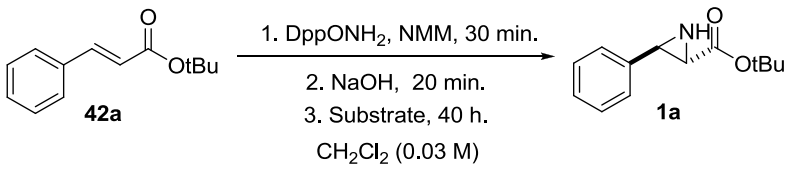
Entry	Base	^{1}H NMR conversion (%)
1[a,h]	NaOH	35
2	**NaOH**	**47**
3[b]	NaOH	23
4	KO^{t}Bu (1M in THF)	3
5[a,g]	KO^{t}Bu (1M in THF)	45
6[a,g]	LiO^{t}Bu (1M in THF)	35
7[c]	KO^{t}Bu (s)	15
8[d]	NaO^{i}Pr	20
9[a,d]	NaO^{i}Pr	30
10	KOH	18
11	K_2CO_3	0
12	Hünig's Base	0
13[e]	NaOH	35
14[f]	NaOH	38

Reactions performed on 0.12 mmol scale of *tert*-butyl cinnamate. [a] *tert*-butyl cinnamate and base added sequentially. [b] 160 min. between addition of *tert*-butyl cinnamate and NaOH. [c] KO^{t}Bu (s) purchased. [d] NaO^{i}Pr (4 eq.) synthesised *in situ* from NaH and ^{i}PrOH; performed at [0.06M]. [e] Hotplate set at 25 °C throughout reaction. [f] Hotplate set at 30 °C throughout reaction. [g] NMM (2 eq.), $DppONH_2$ (2 eq.), NaOH (3 eq.). [h] Performed at [0.06 M].

1.3.1.4 Investigating reagent stoichiometry

Next, reagent stoichiometry was considered, reasoning that this could have a considerable effect on the catalytic cycle, particularly due to the heterogeneous nature of the reaction. An increase in the stoichiometry of NaOH from 2 to 4 eq. provided a slightly better conversion of 50% (**Table 5**, entry 1 *vs.* 2). Interestingly, no conversion to aziridine was observed on using commercial NaOEt under analogous conditions (entry 3), providing further evidence that the aminating mixture is unstable to alkoxide base. A large excess of NaOH (20 eq.) only led to a slightly detrimental effect on the conversion (47%, entry 4). Since the optimum conversion observed to this point was 50%, it was suggested that a sub-stoichiometric loading of reagents could allow for increased conversion (as long as the CH_2Cl_2 was still saturated) due to lower quantities of insoluble inorganics in the reaction mixture. An excess of insoluble reagents could hinder aziridination, causing inefficient stirring and fewer productive molecular collisions. However, decreased conversions were observed for two reactions employing sub-stoichiometric loadings of NMM and $DppONH_2$ (entries 5 and 6). Increasing the equivalents of aminating agent and NMM also led to poorer conversions (37 and 33%, entries 7 and 8), whilst an excess of tertiary amine alone was found to provide a similar conversion of 36% (entry 9). The optimum conversion of 50% had been observed in this study on using 4 eq. of NaOH, and so this stoichiometry was used for further experimentation.

Table 5: Optimum reagent stoichiometry



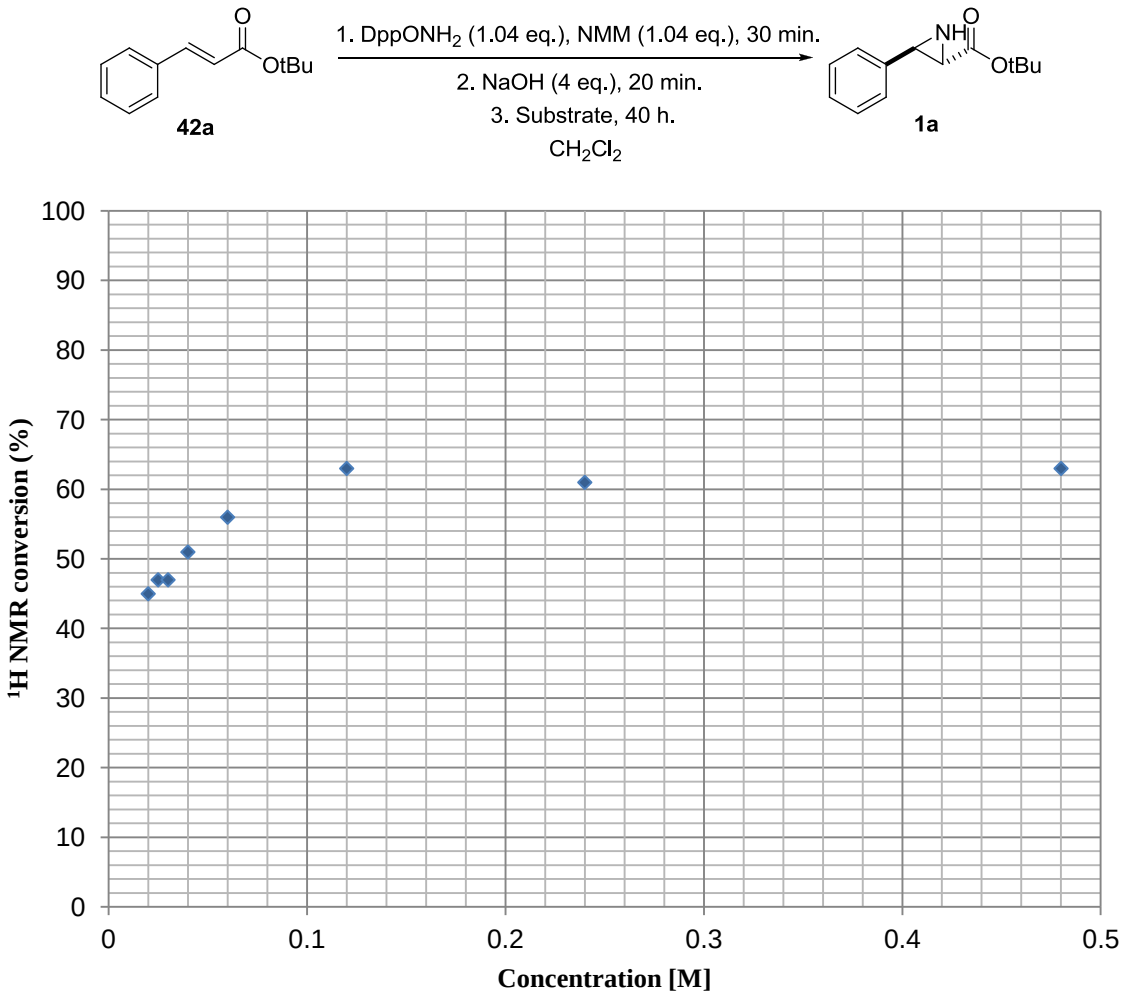
Entry	Equivalents of reagent			^{1}H NMR conversion (%)
	NMM	$DppONH_2$	NaOH	
1	1.04	1.04	2	47
2	**1.04**	**1.04**	**4**	**50**
3[a]	1.04	1.04	4	0
4	1.04	1.04	20	47
5	0.8	0.8	2	25
6	0.6	0.6	2	30
7	1.04	2	3	37
8	2	2	3	33
9	10	1.04	2	36

Reactions performed on a 0.12 mmol scale. [a] Reaction performed using NaOEt instead of NaOH.

1.3.1.5 The effect of concentration

With the newly optimised conditions, it was decided to investigate concentration more fully. Initial experiments had shown that a lower concentration of 0.03 M in comparison to the literature 0.06 M provided an increase in conversion to aziridine **1a** (**Table 4**, entry 1 *vs.* 2). An average of conversions in three experiments at this concentration was taken to ensure reproducibility, with a value of 47% obtained. Performing the aziridination at concentrations below 0.03 M gave similar conversion values, and so it was decided to test the chemistry at increased concentrations. Interestingly, a clear trend of conversion increasing with concentration could be observed (**Graph 1**). At a concentration of 0.06 M, an average conversion of 56% was obtained. This was the concentration used in the published aziridination protocol, with the key differences at this point being the increased NaOH stoichiometry (2 to 4 eq.) and the inclusion of the 20 min. time period between the addition of the base and the substrate to the aminating mixture. At concentrations of 0.12 M and greater, the conversion was observed to level off (**Graph 1**); indeed, at 0.48 M the heterogeneous reaction became too concentrated for efficient magnetic stirring. As better stirring was observed at 0.24 M, this was the selected concentration for further optimisation. An average conversion of 61% was observed on performing the reaction at this concentration. The increased conversions observed at higher concentrations suggest that good solubility of the reagents is not critical for good conversions in the aziridination.

Graph 1: *tert*-Butyl cinnamate aziridination: Concentration *vs.* ^{1}H NMR Conversion

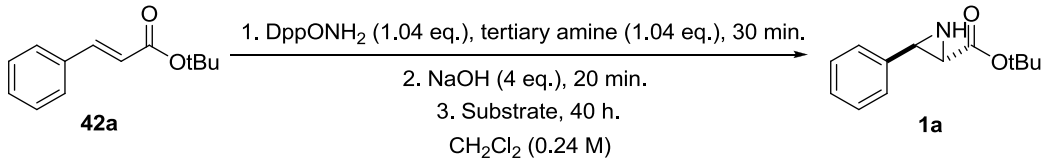


1.3.1.6 Alternative tertiary amines

Having established that increased concentration led to improved conversions to aziridine, alternative tertiary amine promoters were tested at 0.24 M. DABCO was trialled initially, owing to the success of isolated aminated salts of the reagent in the preceding aziridination methodology.[65] No conversion to aziridine was observed (**Table 6**, entry 2), suggesting either that amination of DABCO with $DppONH_2$ had not occurred, or that *tert*-butyl cinnamate was unreactive to the DABCO-derived hydrazinium. The DABCO-derived hydrazinium salt has been used with success on a range of chalcones, although no *tert*-butyl cinnamates.[65] Interestingly, Et_3N provided a conversion of 32% to aziridine, albeit significantly lower than the 61% obtained using NMM (entry 1 *vs.* 3). This result showed that a rigid cyclic structure is not a necessary feature of the tertiary amine promoter in order for aziridination to occur. *N*-Methyl piperidine was tested, as a structural analogue of NMM. The amine provided a 41% conversion to aziridine (entry 4) - 20% lower than the reaction promoted by NMM. This suggested that the increased electronegativity of the oxygen atom in the morpholine ring, in comparison to the carbon atom in the analogous piperidine, is beneficial for high conversions in the

aziridination. Quinuclidine had been tested in the aziridination under the dilute conditions (0.03 M in substrate), in the hope that this more nucleophilic tertiary amine might speed up the rate of amination, and hopefully, overall conversion to the aziridine. However, only a 10% conversion to aziridine was observed, considerably lower than the 47% optimum observed using NMM under these conditions (entry 5 *vs.* 6). The cinchona alkaloid quinine has been used as a chiral tertiary amine in the aziridination of chalcone, yielding the aziridine in 56% ee.[53] If quinine could be used as tertiary amine promoter for the aziridination of *tert*-butyl cinnamate, then the possibility for enantioinduction would arise. Quinine was substituted for NMM under the optimum conditions, but on work-up, no conversion to aziridine was observed by analysis of the ^{1}H NMR spectrum of the crude material (entry 7). A second experiment, employing the conditions developed for enantioselective aziridination was carried out.[53] The reaction was left for the extended time of 40 h. (*c.f.* 16 h. for chalcone using the published conditions) due to the lower reactivity of the substrate. However, using quinine as amine promoter, in the presence of NaH/^{i}PrOH, with sequential addition of the substrate and base led to no conversion to aziridine, and considerable degradation by ^{1}H NMR analysis of the crude material (entry 8). It is likely that the strongly basic conditions are incompatible with the *tert*-butyl cinnamate. Given that NMM displayed considerably superior conversions in the aziridination in comparison to other amines tested, it was decided to halt further investigation into alternative tertiary amines.

Table 6: Alternative tertiary amine promoters



42a 1a

Entry	Tertiary amine promoter	^{1}H NMR conversion (%)
1	**NMM**	**61**
2	DABCO	0
3	Et_3N	32
4	*N*-Methyl piperidine	41
5[a]	NMM	47
6[a]	Quinuclidine	10
7	Quinine	0
8[b]	Quinine	0

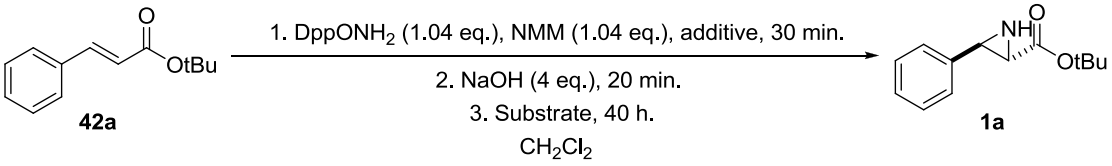
Reactions performed on a 0.12 mmol scale. [a] Performed at [0.03 M]. [b] Quinine (1.04 eq.), $DppONH_2$ (1.04 eq.), NaH (2 eq.), ^{i}PrOH (2 eq.) used.[53]

1.3.1.7 The effect of water

It was suggested that the equivalent of water produced in each catalytic cycle could be deactivating the aminimine *via* proton transfer, causing the ylide to become too transient to effect aziridination. To test this hypothesis, a drop of water (*ca.* 50 μL, 2.8 mmol) was added to a reaction. Although the 13% conversion was significantly lower than the optimum 47% under the same conditions without water added (**Table 7**, entry 1 *vs.* 2), it was interesting to see that the large excess of water (>20 eq.) did not

prevent aziridination altogether. Given the decreased conversion to aziridine in the presence of water, drying agents were added to three reactions (performed at lower concentrations to aid magnetic stirring). The addition of $MgSO_4$ (20 mg) provided a lower conversion of 45% than the 63% in the analogous reaction lacking the additive (entry 3 *vs.* 4). Similarly, lower conversions of 47% and 43% were observed on the addition of molecular sieves, *cf.* 56% in their absence (entries 6 and 7 *vs.* 5). The lower conversions were attributed to poorer magnetic stirring resulting from the addition of insoluble drying agents to the heterogeneous reaction mixture.

Table 7: The effect of water on the aziridination



Entry	Concentration [M]	Additive	Quantity (mg)	^{1}H NMR conversion (%)
1[a]	0.03	none	-	47
2[a]	0.03	H_2O	ca.50 (1 drop)	13
3	0.12	none	-	63
4	0.12	$MgSO_4$	20	45
5	0.06	none	-	56
6	0.06	4Å Mol sieves (powdered)	200	47
7	0.06	4Å Mol sieves (pellets)	200	43

Reactions performed on a 0.12 mmol scale. [a] Reaction performed using NaOH (2 eq.).

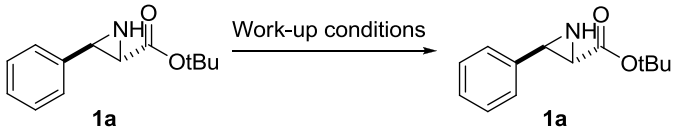
1.3.1.8 Scaling-up the aziridination

At this point, it was decided to perform a larger-scale aziridination of *tert*-butyl cinnamate using the optimised conditions, in order to bring through material for ring-opening experiments. 14 mMol of *tert*-butyl cinnamate was subjected to the optimum conditions at the increased concentration of 0.48 M, with the large volume of solvent used on this scale meaning that magnetic stirring was efficient at this higher concentration. Work-up of the reaction and ^{1}H NMR analysis of the crude material revealed a 68% conversion to aziridine **1a**, with no other products evident by ^{1}H NMR. Disappointingly, chromatographic purification on silica provided a 50% isolated yield of aziridine, considerably lower than the conversion value (**Table 9**, entry 1). The discrepancy between conversion and isolated yield required investigation. The starting cinnamate was also recovered in 26%, and the 'conversion' to aziridine calculated based on recovered starting material was 66%, comparable with the ^{1}H NMR conversion. A second large scale (10 mmol) aziridination scale provided a similar conversion (67%) and yield (50%), proving reproducibility (**Table 9**, entry 2). The similarity between the conversion values based on recovered starting material and ^{1}H NMR analysis provided some evidence that the starting cinnamate and aziridine were stable on silica gel; another possibility was

that both were undergoing degradation to the same extent, which seemed less likely. Thus it was decided to focus attention on the work-up procedure, to try to account for the loss in mass observed.

The work-up procedure for the aziridination involves quenching the reaction with NH_4Cl (sat. aq.), followed by extraction of the aqueous phase three times with CH_2Cl_2. The combined organics are then dried over $MgSO_4$ and concentrated *in vacuo*, and the remaining volatiles are removed under high vacuum for a brief period (*ca.* 10 min.). A portion of purified aziridine was subjected to the standard work-up conditions, and re-isolated. A poor mass recovery of 56% was obtained, which was verified on repeating the experiment using a different batch of aziridine (**Table 8**, entries 1 and 2). Reasoning that the mildly acidic wash could be causing decomposition of the aziridine, distilled water was used in place of NH_4Cl (sat. aq.), yet a similar mass recovery was obtained (entry 3). Subjecting the aziridine to high vacuum for 30 min. provided a quantitative return of starting material, showing that the aziridine was not volatile at room temperature under high vacuum (*ca.* 0.1 mm Hg, entry 4). $MgSO_4$ was next identified as a potential cause of the reduced mass recovered, due to its Lewis acidic nature. Substituting $MgSO_4$ with the non-Lewis acidic Na_2SO_4 in the work-up procedure resulted in a quantitative return of aziridine, suggesting that the drying agent could be the cause of the low recovered mass (entry 5).

Table 8: Stability of aziridine to work-up conditions



1a **1a**

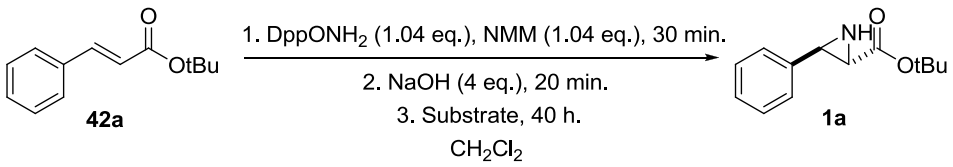
Entry	Work-up conditions		Mass recovery (%)
	Aqueous wash	Drying agent	
1[a]	NH_4Cl	$MgSO_4$	56
2[a]	NH_4Cl	$MgSO_4$	61
3[b]	H_2O	$MgSO_4$	54
4[c]	-	-	Quantitative
5[a]	NH_4Cl	Na_2SO_4	Quantitative

All experiments perfomed on 0.12 mmol of aziridine. CH_2Cl_2 used for aqueous extraction. [a] NH_4Cl (sat. aq.) used. [b] Distilled water used. [c] Aziridine subjected to high vacuum for 30 min.

An aziridination was performed on 0.5 mmol scale, substituting Na_2SO_4 for $MgSO_4$ in the work-up procedure. Despite a good ^1H NMR conversion of 61%, only a 28% yield of aziridine was isolated (**Table 9**, entry 3 *vs.* 1). Additionally, there was a considerable discrepancy between the ^1H NMR conversion and the conversion calculated based on the isolated yields, (61% *vs.* 48%). The lower value obtained following work-up indicated that the aziridine was unstable to the conditions used. In order to confirm that the discrepancy was not due to purification on silica gel, the reaction was repeated, purifying on basic alumina. Only 39% of aziridine was isolated, and the discrepancy between conversion values was again observed (55% *vs.* 63%, entry 4). Due to poorer isolated yields,

it was decided to cease investigation into alternative work-up conditions. Attention was instead turned to the stability of the cinnamate and aziridine to the reaction conditions, to see if the loss in mass could be accounted for.

Table 9: Alternative work-up and purification conditions in the aziridination



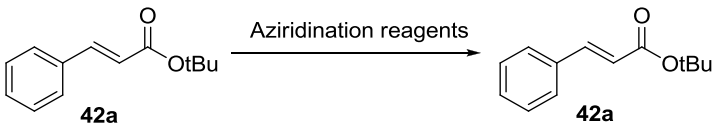
Entry	Drying agent	^{1}H NMR conversion (%)	Isolated yield (%)		Total isolated yield[a] (%)	Conversion[b] (%)
			Aziridine	Cinnamate		
1[c,e]	$MgSO_4$	68	50	26	76	66
2[c,f]	$MgSO_4$	67	50	30	80	63
3[c,d]	Na_2SO_4	61	28	30	58	48
4[d,g]	Na_2SO_4	63	39	32	71	55

[a] Combined yield (%) of starting material and product. [b] Calculated using isolated yields of aziridine and cinnamate. [c] Purification by column chromatography on silica. [d] Performed on 0.5 mmol scale. [e] Performed on 10.0 mmol scale. [f] Performed on 14.0 mmol scale. [g] Purification by column chromatography on basic alumina.

1.3.1.9 Investigating reagent and product stability

tert-Butyl cinnamate was first subjected to treatment with the aziridination reagents in various combinations. Standard aziridination conditions were used, except for the selected omitted reagents detailed (**Table 10**). Treatment with NaOH led to a quantitative mass recovery of *tert*-butyl cinnamate after work-up, demonstrating stability of the reagent to NaOH under the conditions (entry 1). The combination of NMM and NaOH yielded a lower recovered mass, of 80% (entry 2). Interestingly, NMM alone gave an identical mass recovery (entry 3), indicating that the cinnamate is unstable to the tertiary amine. Stirring the cinnamate with the aminating agent led to a quantitative recovery of starting material (entry 4), whilst a loss in recovered mass was observed on stirring with the aminating agent in the presence of NaOH (entry 5). This last result is particularly important in its own right; the aminating agent does not effect aziridination in the absence of the tertiary amine, suggestive that the aminimine pathway is in operation.

Table 10: Stability of tert-butyl cinnamate to aziridination reagents



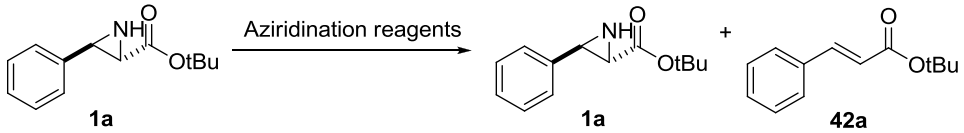
42a 42a

Entry	Reagent			Mass recovery (%)
	NMM	NaOH	$DppONH_2$	
1	×	✓	×	Quantitative
2	✓	✓	×	80
3	✓	×	×	80
4	×	×	✓	Quantitative
5	×	✓	✓	60

tert-Butyl cinnamate stirred with selected aziridination reagents under otherwise standard conditions. ✓ = Reagent included in experiment. × = Reagent omitted from experiment.

Similar experiments were performed to test the stability of the aziridine to the reaction conditions (**Table 11**). An initial result was pleasing; stirring in the presence of NaOH returned a quantitative yield of aziridine (entry 1). However, treatment with other reagents led to worrying mass recoveries. It appeared that NMM was a factor in the poor mass recoveries observed, which were all below 30% on treatment with the reagent (entries 2-4). In all control experiments, only starting material was observed by ^{1}H NMR analysis of the crude reaction mixture.

Table 11: Stability of aziridine to aziridination reagents

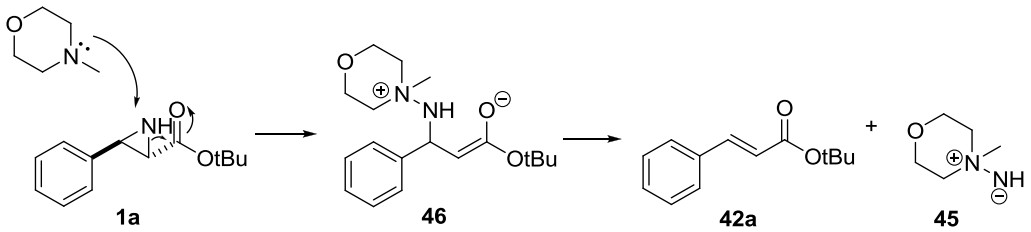


1a 1a 42a

Entry	Reagent			Mass recovery (%)	^{1}H NMR conversion to *tert*-butyl cinnamate (%)
	NMM	NaOH	$DppONH_2$		
1	×	✓	×	Quantitative	N/A[a]
2	✓	×	×	17	N/A[a]
3	✓	✓	×	30	2
4	✓	✓	✓	8	3

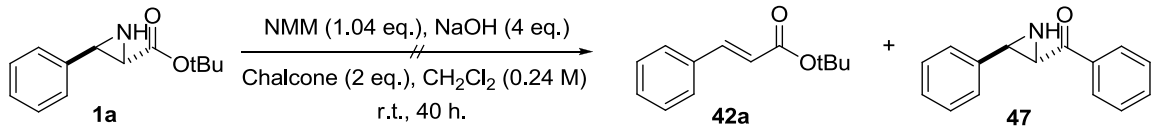
Aziridine stirred with selected aziridination reagents under otherwise standard conditions. ✓ = Reagent included in experiment. × = Reagent omitted from experiment. [a] Not applicable.

Interestingly, a very small level of conversion to *tert*-butyl cinnamate was observed in the presence of NMM and NaOH (entries 3 and 4). It was suggested that the aziridination could be reversible, with attack of the NMM at the aziridine nitrogen, and ring-opening to form enolate **46**. Collapse of the enolate could then generate *tert*-butyl cinnamate, with loss of the aminimine ylide **45** (**Scheme 34**). *tert*-Butyl cinnamate was only generated in the presence of NaOH; NMM alone did not effect the transformation, suggesting that basic conditions were necessary for aminimine stability. However the unusual nature of this mechanism was realised, with no examples of nitrogen nucleophiles attacking aziridine on nitrogen identified following a literature search.



Scheme 34: Suggested mechanism for formation of *tert*-butyl cinnamate from aziridine

As a test of this mechanistic proposal, which leads to the production of the NMM aminimine, the reaction was performed in the presence of chalcone, a known successful aziridination substrate, as an ylide trap. Chalcone was added to aziridine **1a** in CH_2Cl_2 in the presence of NMM and NaOH (**Scheme 35**). However, after 40 h., work-up and analysis of the ^1H NMR spectrum showed no conversion to the chalcone-derived aziridine **47**.



Scheme 35: Aziridine 1a as the aminating agent

An alternative mechanism in the presence of $DppONH_2$ was suggested; electrophilic amination of the aziridine nitrogen, followed by ring-opening and loss of diimide could generate *tert*-butyl cinnamate, although this did not provide an explanation for observation of the reagent in the absence of $DppONH_2$.

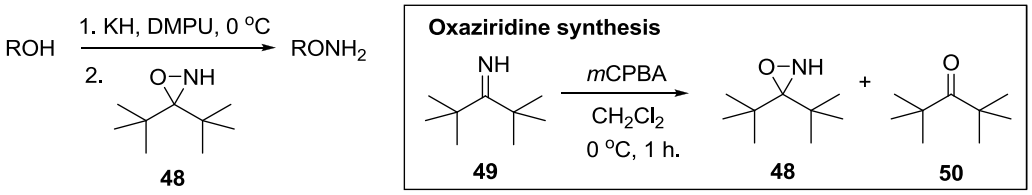
Owing to the poor mass recoveries observed on earlier treatment of the aziridine with NMM, it was suggested that avoidance of the reagent could lead to increased yields of aziridine. A previous screen of tertiary amines (*vide supra*) had revealed that NMM was considerably superior for the methodology. Additionally, it seemed likely that $DppONH_2$ was incompatible with the aziridine; a considerable drop in recovered mass was observed upon inclusion of the reagent in a control reaction (**Table 11**, entry 3 *vs.* 4). These considerations prompted investigation into the use of alternative aminating agents and tertiary amines which might be more appropriate for the aziridination of *tert*-butyl cinnamate.

1.3.1.10 An alternative aminating agent

Oxaziridines

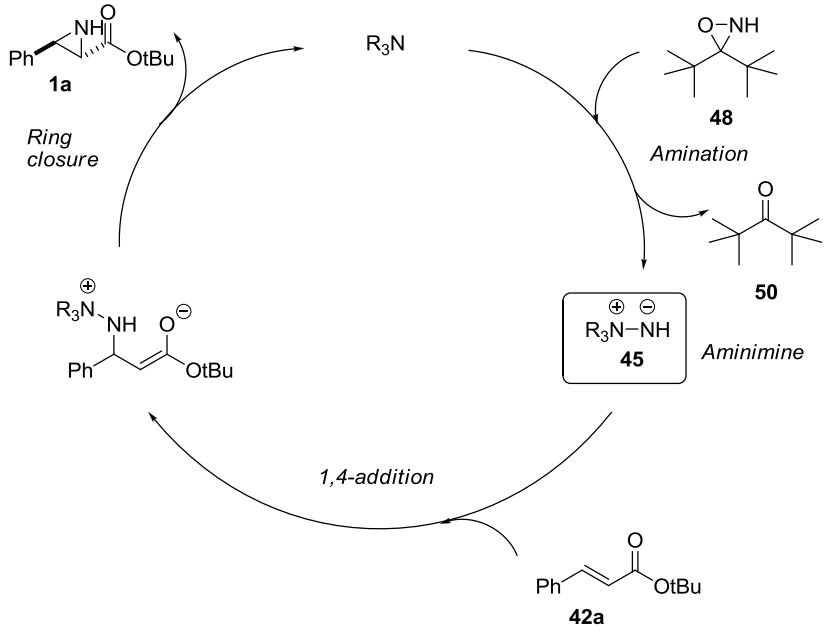
Oxaziridines are successful nitrogen transfer agents, and several literature examples exist of their use as a source of electrophilic nitrogen.[75] Oxaziridine **48** has been used by Ellman *et al*. as an electrophilic aminating agent, in the synthesis of *O*-alkyl oximes.[76] Treatment of potassium alkoxides

with **48** led to the formation of *O*-alkyl hydroxylamines, with di-*tert*-butyl ketone **50** generated as the by product (**Scheme 36**).



Scheme 36: Ellman's synthesis of *O*-alkyl hydroxylamines using di-*tert*-butyl oxaziridine

It was suggested that a nucleophilic tertiary amine could react with **48** in an analogous fashion, to provide aminimine **45** required for the aziridination protocol. If successful, alternative tertiary amines could be used, circumventing the stability problems observed with NMM. Furthermore, the proposed mechanism for amination would not require a base to drive the aziridination forward (**Scheme 37**).



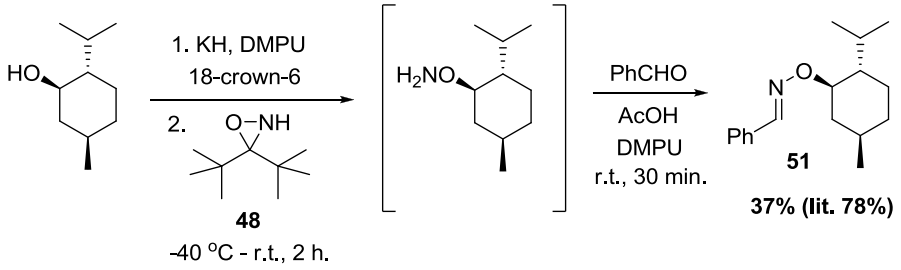
Scheme 37: Proposed catalytic cycle using di-*tert*-butyl oxaziridine as aminating agent

Synthesis and reactivity

Ellman's procedure was adapted for the synthesis of oxaziridine **48**. *m*CPBA was added over 1 h. to the commercial di-*tert*-butyl imine in CH_2Cl_2 at 0 °C. Removal of CH_2Cl_2 *in vacuo* provided the crude product. Washing with $NaHCO_3$ (sat. aq.) removed the *m*CBA by-product, and the oxaziridine was isolated in 88% purity by ^{1}H NMR, with a contaminant tentatively assigned as di-*tert*-butyl ketone **50**. Kugelrohr distillation improved the purity from 88 to 93%, although the similar volatilities of the ketone and oxaziridine at low pressure meant that pure oxaziridine could not be isolated. Additionally, chromatographic purification was not possible due to the instability of the oxaziridine on silica. The

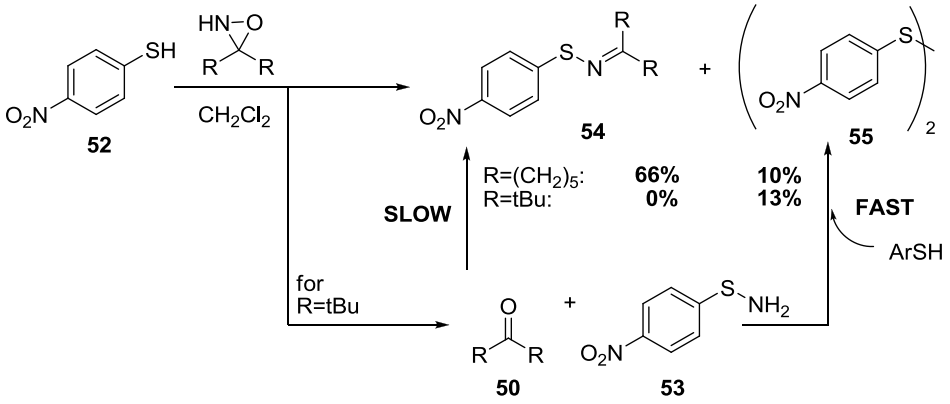
^{1}H NMR spectra of the starting imine **49** and the oxaziridine were similar, and so ^{13}C NMR was used as a better indication of product formation; re-hybridisation of the imine sp^2 carbon to the sp^3 carbon of the oxaziridine was marked by a shift from 194 ppm to 85 ppm.

To validate the aminating ability of oxaziridine **48**, *O*-menthol oxime **51** was synthesised according to Ellman's procedure (**Scheme 38**). Menthol was treated with washed KH in anhydrous DMPU, before the addition of oxaziridine **48** at -40 °C. After 2 h., benzaldehyde was added, and following work-up and chromatographic purification, menthol-oxime **51** was isolated in 37% yield. Although considerably lower than the literature value of 78%, formation of the oxime validated the use of oxaziridine **48** as an electrophilic nitrogen transfer agent.



Scheme 38: Synthesis of *O*-menthol oxime using oxaziridine 48

Having established the electrophilic nature of the oxaziridine in the presence of an alkoxide, the aminating ability of the oxaziridine with a weaker nucleophile was tested. This would establish precedent for use of the oxaziridine in the aziridination chemistry, with an amine or nucleophilic reagent with a similar pKa. The analogous *penta*-methylene oxaziridine has been observed to react with *p*-nitro benzene thiol (**52**) to give thiooximes in good yield, along with a small amount of disulfide (**Scheme 39**).[75] The literature conditions were repeated, substituting the *penta*-methylene oxaziridine for di-*tert*-butyl oxaziridine **48**. Disappointingly, formation of thiooxime **54** was not observed, but a 13% yield of the disulfide **55** was obtained (**Scheme 39**). TLC analysis of the starting thiol had not indicated the presence of the disulfide. It was suggested that initial amination of the thiol to give sulfinimine **53** was occurring, but that subsequent imine formation was significantly retarded owing to the hindered ketone. Instead, unstable sulfinimine **53** reacts with a second thiol molecule to generate disulfide **55** (**Scheme 39**). The tentatively assigned ketone **50** was observed by ^{1}H NMR analysis of the crude reaction mixture, although this could not be regarded as proof of the suggested pathway, owing to the initial presence of the ketone as an impurity in the oxaziridine.



Scheme 39: Reaction of *p*-nitrobenzene thiol with oxaziridines

Oxaziridine-promoted aziridination

As the proposed mechanism for disulfide formation involved the desired nucleophilic attack at the oxaziridine nitrogen, it was decided to test the oxaziridine as the aminating agent in the aziridination. Chalcone was selected as an initial substrate, as one of the most successful in the aziridination methodology. As a base is not required for the proposed aziridination pathway, NaOH was omitted. NMM was selected as an initial tertiary amine, owing to success in the enone aziridination. If aziridination of chalcone was observed, the incompatibility of the reagent with the *tert*-butyl cinnamate derived aziridine would be borne in mind for further experimentation. An excess of NMM was used, to maximise the rate of ylide formation, and the reaction was carried out in CH_2Cl_2 (0.12 M). Disappointingly, chalcone and oxaziridine were the only products observed by ^{1}H NMR analysis of the crude reaction mixture upon work-up after 20 h. at r.t. Ellman's use of the polar aprotic DMPU in the oxaziridine methodology, led to substitution of CH_2Cl_2 with this solvent. No aziridine formation was observed, with recovered starting material again observed in the ^{1}H NMR spectrum of the crude material. At this point, it was decided to perform an NMR experiment to establish whether any interaction of the NMM with the oxaziridine could be observed. Interestingly, the oxaziridine di-*tert*-butyl singlet was split into a broad doublet on addition of NMM in $CDCl_3$. The splitting did not appear to increase with time; the same ^{1}H NMR profile was observed both 5 min. and 2 h. after addition of NMM. The oxaziridine-*NH* peak also sharpened considerably on treatment with NMM. Increased equivalents of NMM caused the splitting to become increasingly complex, although no other change to the spectrum was observed. Importantly, neither di-*tert*-butyl ketone peaks nor any changes to the NMM signals were observed, indicating that the aminimine ylide was not forming.

To explain the observed changes to the ^{1}H NMR spectrum, a non-covalent interaction between the NMM and oxaziridine-*NH* was suggested. Hydrogen-bonding between the tertiary amine and the oxaziridine-*NH* could slow inversion at the oxaziridine nitrogen, causing the diastereotopic relationship of the two *tert*-butyl groups to become observable by ^{1}H NMR (**Fig. 5**). Further evidence

for this hypothesis lay in the sharpening of the oxaziridine-*NH* peak on treatment with the tertiary amines; the slower barrier to inversion at nitrogen would cause the nitrogen-proton to have a more defined environment, and a sharper signal. A pronounced singlet splitting was also observed in the presence of DMAP (**Fig. 5**). ^{1}H NMR analysis of the oxaziridine in d_4-MeOH showed a similar splitting of the *tert*-butyl singlet, presumably due to hydrogen-bonding with the solvent. Removal of the solvent *in vacuo* and re-analysis of the specimen by ^{1}H NMR in $CDCl_3$ saw the split signal revert to a singlet.

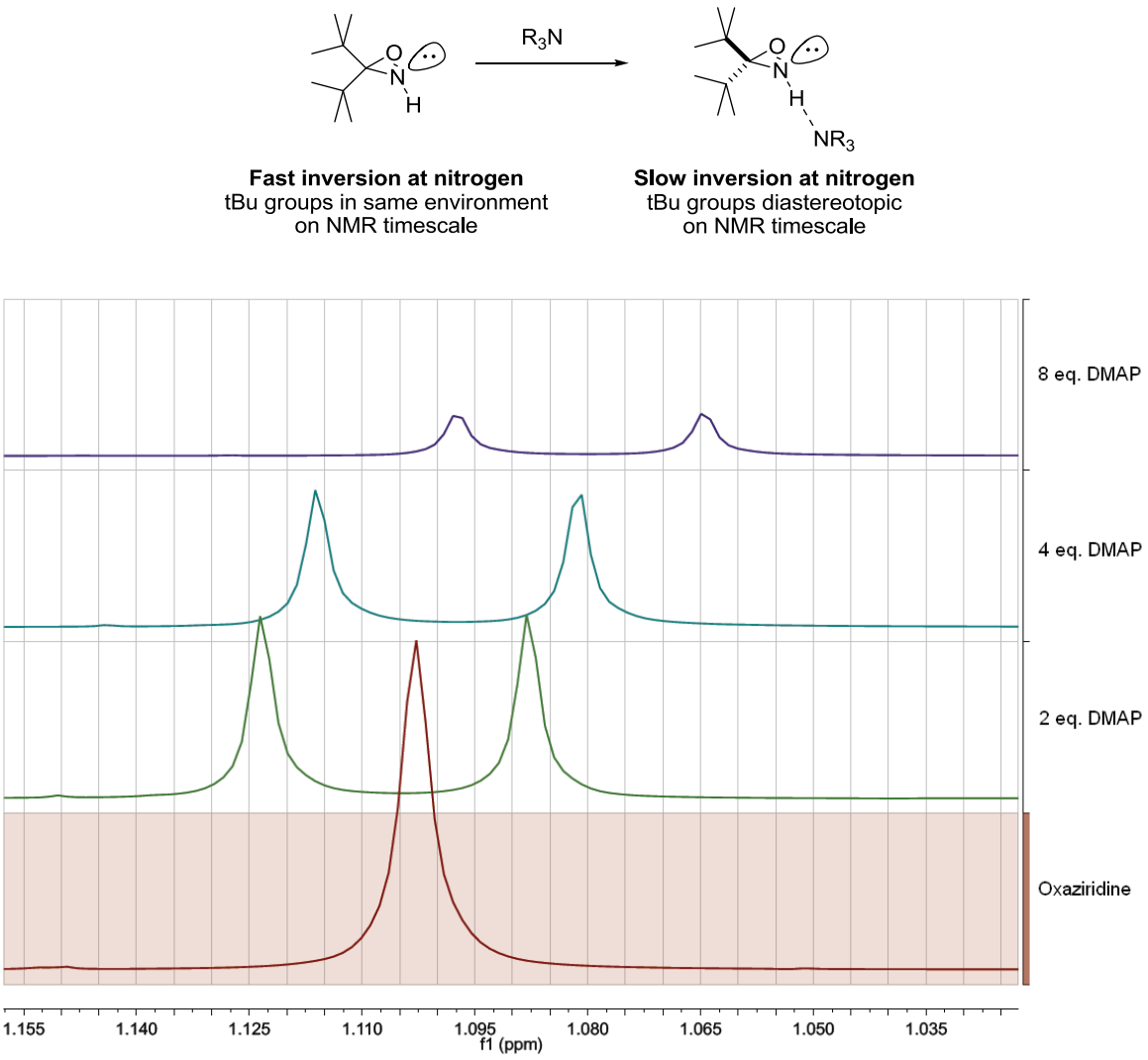
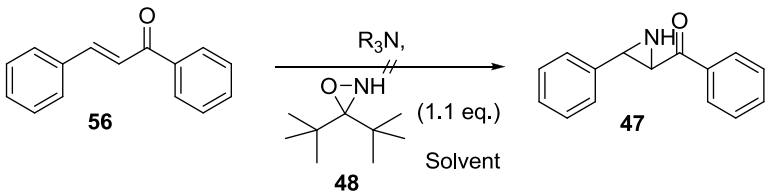


Fig. 5: Oxaziridine *tert*-butyl ^{1}H NMR signal splitting on treatment with DMAP

Although the hypothesised hydrogen-bonding interaction was not desirable for ylide formation, it was suggested that the interaction could be reversible, so ylide formation could still be realised. Further, if ylide formation was itself reversible and a small amount of the ylide existed in equilibrium, the presence of the chalcone substrate (**56**) might promote the collapse of the oxaziridine. DMAP was trialled initially as the tertiary amine promoter. However, two reactions at r.t. and 40 °C led to returned starting material, with some degradation to unidentified products observed at 40 °C (**Table**

12, entries 3 and 4). Treatment of the oxaziridine with either NMM or DMAP at higher temperatures, in an attempt to force the collapse of the strained ring, led to degradation to unidentified products as observed by ^{1}H NMR analysis.

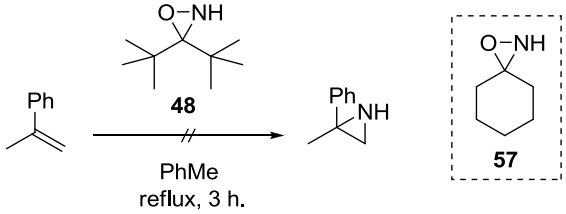
Table 12: Conditions attempted for oxaziridine-promoted aziridination



Entry	Tertiary amine	Solvent	Temperature
1	NMM	CH_2Cl_2	r.t.
2	NMM	DMPU	r.t.
3[a]	DMAP	$CHCl_3$	r.t.
4[a,b]	DMAP	$CHCl_3$	40

All reactions performed on 0.12 mmol scale, for 20 h, using 3.3 eq. R_3N. [a] 2.2 eq. DMAP used. [b] Reaction performed for 30 h.

Pentamethylene oxaziridine **57** has reportedly been used as a direct nitrogen source for the aziridination of electron-rich olefins.[77] To see whether oxaziridine **48** would display analogous reactivity, α-methyl styrene was treated with the reagent under the literature conditions. Both conventional and microwave heating were tested, but no aziridination was observed (**Scheme 40**). Given the lack of reactivity observed towards the selected olefins, it was decided to test an alternative aminating agent, with reported success for the aziridination of chalcone substrates.

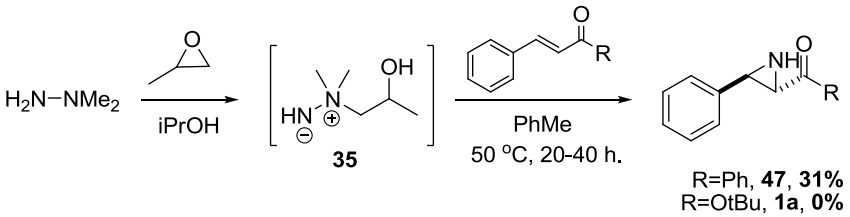


Scheme 40: Attempted aziridination of an electron-rich olefin

An alternative ylide

Nitrogen-nitrogen ylide **35**, generated *in situ* from dimethyl hydrazine and propylene oxide, has been used by Ikeda to effect the aziridination of chalcone substrates (*vide supra*).[63] Previous work in the group had led to a modified synthesis of the ylide, avoiding benzene as a toxic solvent, and negating the need for a pressurised reaction vessel.[78] According to this, propylene oxide was treated with dimethyl hydrazine in *iso*-propanol at r.t. After 24 h., chalcone was added in toluene, and heated to 50 °C for 20 h. Recrystalisation from methanol provided the *trans*-aziridine **47** in 31% yield (lit. 48%[78]) (**Scheme 41**).

Following the successful aziridination of chalcone, *tert*-butyl cinnamate was subjected to the reaction conditions. Disappointingly, aziridine **1a** was not observed, with some degradation to unidentified products observed by ^{1}H NMR analysis of the crude reaction mixture. The scope presented in the literature is limited to chalcones,[63] and perhaps the failure to aziridinate *tert*-butyl cinnamate is evidence of the substrate dependence of the procedure.



Scheme 41: Ikeda's ylide for aziridination

Due to the lack of success of these alternative aminating agents in the aziridination of *tert*-butyl cinnamate, it was decided to return to the optimised aziridination protocol using $DppONH_2$ and NMM. Although substrate instability to NMM had been observed, an improved isolated yield of 50% (*cf.* lit. 32%) had been obtained on a 14 mmol scale, and good recovery of the unreacted cinnamate meant that re-submission of the reagent to the reaction conditions would be possible.

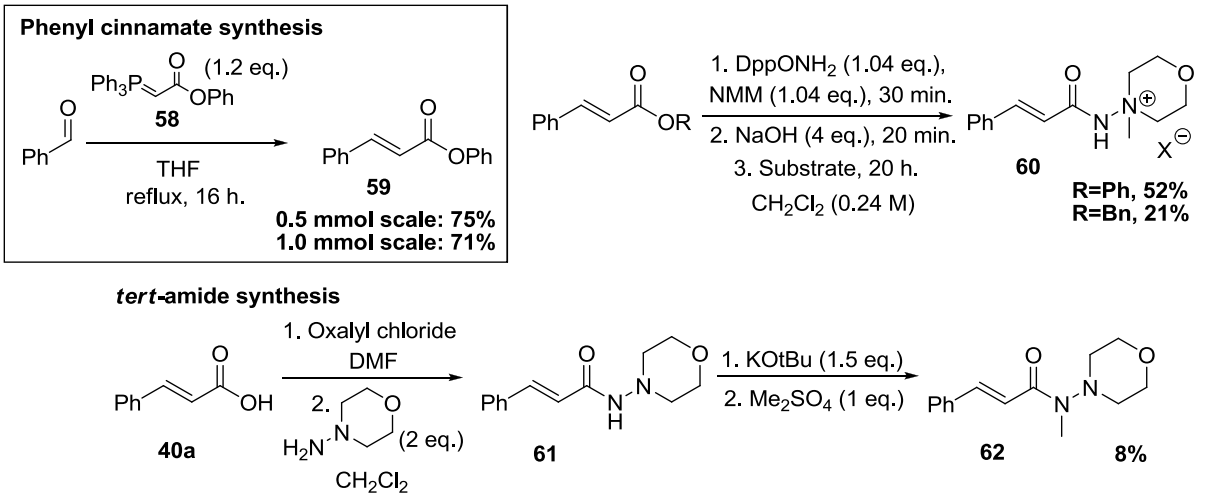
1.3.2 Probing the substrate scope

1.3.2.1 Alternative esters

It was decided to examine the substrate scope of the enoate aziridination, initially with respect to the ester moiety. It was suggested that using an ester moiety that was more electron-poor and ketone-like than the *tert*-butyl ester could increase substrate reactivity, drawing on the considerable success of enones in the methodology. However, it was realised that such substrates would be more reactive and would not benefit from the steric hindrance of the *tert*-butyl ester, therefore increasing the likelihood of 1,2-attack and ester hydrolysis. Alternative esters were selected using pK_a values (in DMSO) as an approximate guide to the electron density at the carbonyl centre.

Phenyl cinnamate **59** was selected as the initial alternative to *tert*-butyl cinnamate. It was realised that phenoxide (pK_{aH} *ca.* 10) is a considerably better leaving group than *tert*-butoxide (pK_{aH} *ca.* 19), and that the susceptibility of phenyl cinnamate to hydrolysis would be much increased in comparison to *tert*-butyl cinnamate. However, the delocalisation of the ester lone-pair into the aromatic system renders the substrate more 'ketone-like' than *tert*-butyl cinnamate, which was hoped to be advantageous for aziridination. Phenyl cinnamate was first synthesised from benzaldehyde and the commercially available phosphorane **58**. Heating at reflux in THF for 16 h. provided **59** in comparable yield on 0.5 and 1.0 mmol scales (**Scheme 42**). Treatment under the optimised

aziridination conditions led to complete consumption of phenyl cinnamate in 20 h. as judged by TLC analysis. On chromatographic purification, no aziridine was observed. Instead, a compound containing the morpholine scaffold was isolated. Analytical data were not conclusive as to the identity of the product, with both morpholinium salt **60** and *tert*-amide **62** (from base-mediated Stevens' rearrangement of the former) considered as possibilities (**Scheme 42**). In order to conclusively prove the identity of the product, the *tert*-amide **62** was synthesised *via* an alternative route. *N*-Aminomorpholine was added to cinnamoyl chloride to give the secondary amide **61** in 46%. Deprotonation of **61** with KO^{t}Bu followed by reaction with dimethyl sulfate led to the isolation of *tert*-amide **62** in 8% yield, following purification (**Scheme 42**). Comparison of ^{1}H NMR data showed that the product of the attempted aziridination of phenyl cinnamate was the cationic morpholinium **60**; the ^{1}H NMR shifts of the cation were considerably downfield by comparison with the *tert*-amide. Hydroxide was tentatively suggested as the counterion, as DppO$^-$ was not observed by ^{1}H NMR analysis. Benzyl cinnamate (pK_{aH} of benzyloxide *ca.* 15) was also subjected to the aziridination conditions, and interestingly, morpholinium **60** was again isolated in 21% yield.

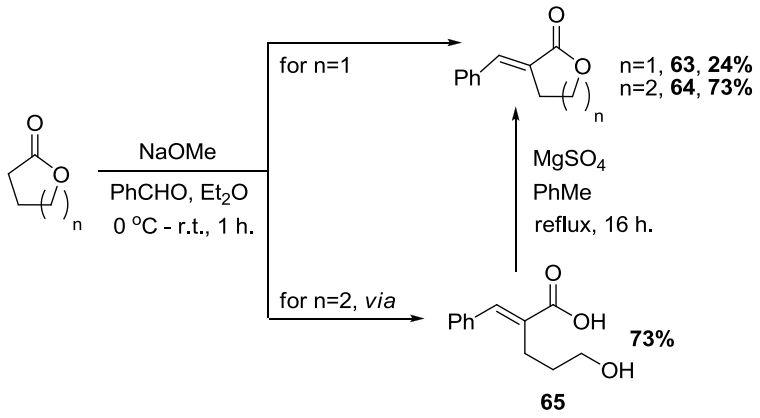


Scheme 42: Identification of morpholinium addition product

The constrained conformation of lactones prevents the stabilising anomeric effect present in esters, so it was rationalised that the increased reactivity of the former could improve yields in the aziridination. To probe lactone reactivity in the aziridination, the five- and six- membered α-benzilydene lactones **63** and **64** were selected for testing. pK_{aH} values of *ca.* 15 were suggested for both lactones, and it was hoped that each would be less susceptible to hydrolysis than phenyl cinnamate.

The enolate of γ-butyrolactone was prepared using NaOMe generated *in situ*, and condensed with benzaldehyde.[79] Work-up after 1 h. at 0 °C followed by chromatographic purification provided the lactone **63** in 24% yield as a single diastereomer (**Scheme 43**). An attempt to prepare the six-membered analogue using the chemistry described resulted in the isolation of hydroxy acid **65**, also as

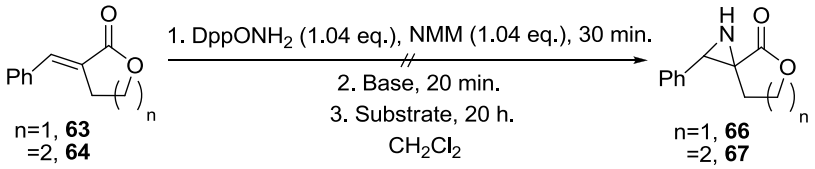
a single stereoisomer, in 73% yield (**Scheme 43**). Pleasingly, refluxing in toluene in the presence of $MgSO_4$ according to the literature procedure gave a quantitative yield of lactone **64** (**Scheme 43**).[80] *E*-Diastereoselectivity was assigned for both compounds, through correlation with ^{1}H NMR shifts from literature syntheses of the compounds. Additionally, the *E*-diastereomer is likely the thermodynamic product in each case, to avoid eclipsing interactions between the aromatic and carbonyl functionalities.



Scheme 43: Synthesis of α-benzilydene lactones

Formation of spiro-aziridine **66** from lactone **63** was attempted using the optimum conditions (**Table 13**, entry 1). Consumption of starting material was observed by TLC analysis after 3 h., but ^{1}H NMR analysis of the crude reaction mixture indicated complete degradation to unidentified products, and hydrolysis of lactone **63** was assumed. However, none of the corresponding hydroxy acid was observed by ^{1}H NMR, despite acidification and extraction of the aqueous phase during work-up, owing to the likely aqueous solubility of the compound. A control experiment lacking NMM (entry 2) showed consumption of the starting lactone by TLC analysis after 40 h., supporting the hypothesis, although instability of the lactone to the ylide was suggested, given the increased rate of substrate consumption in the presence of NMM. Decreasing the equivalents of NaOH to one in the aziridination led to a good mass recovery of starting material, although no aziridination was observed (entry 3). It was reasoned that the lactone might exhibit better stability to a less nucleophilic base, and so KO^{t}Bu was substituted for NaOH in the aziridination. However, the lactone proved to be unstable to this reagent; poor mass recovery and complete degradation to unidentified products by ^{1}H NMR was observed when either four or one equivalents were used in the aziridination (entries 4 and 5). Lactone **64** also proved to be susceptible to basic hydrolysis, although no degradation was observed in the attempted aziridination of this substrate. Instead, 78% conversion to the hydroxy acid **65** was observed by ^{1}H NMR analysis of the crude reaction mixture, after 3 h. under the aziridination conditions, with no spiro-aziridine **67** observed (entry 6).

Table 13: Attempted formation of spiro-aziridines

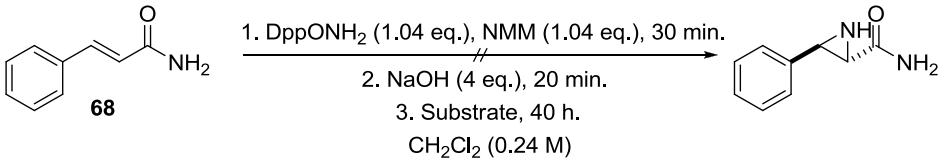


Entry	Compound number	Base (eq.)
1	**63**	NaOH (4)
2[a,b]	**63**	NaOH (4)
3	**63**	NaOH (1)
4	**63**	KO^{t}Bu (4)
5	**63**	KO^{t}Bu (1)
6[c]	**64**	NaOH (4)

All reactions performed on 0.24 mmol scale at [0.06 M]. [a] No NMM added. [b] 40 h. was required for complete consumption of the starting lactone. [c] 78% conversion by ^{1}H NMR analysis to hydroxy acid; performed at [0.24 M].

Commercial ethyl cinnamate was next tested, reasoning that ethoxide (pK_{aH} *ca.* 16) was only a slightly better leaving group than *tert*-butoxide. Potentially, the former could be slightly more prone to hydrolysis, but exhibit increased reactivity in the aziridination. Disappointingly, after 20 h., loss of starting material was observed by TLC, with no new non-baseline product spots observed. A poor mass recovery was obtained following work-up, with ^{1}H NMR analysis showing ethyl cinnamate along with considerable degradation. It seemed that ester hydrolysis was occurring faster than addition of the aminimine, resulting in the lack of aziridination and low mass recovery observed. Due to the lack of successful aziridination of lower esters and lactones, it was decided to cease investigation into alternative ester groups at this point.

It was reasoned that an amide (pK_{aH} *ca.* 35) would be less susceptible to basic hydrolysis, and so commercial cinnamamide (**68**) was subjected to the aziridination conditions (**Scheme 44**). The increased electron density at the carbonyl centre would likely render the amide substrate less reactive, but possibly lead to an improved total mass recovery of starting material and product by limiting direct addition to the carboxyl group. The susceptibility of the amide protons to deprotonation was also realised, which would deactivate the substrate further still to aziridination. Unfortunately, quantitative recovery of starting material was observed, proving that cinnamamide was not susceptible to aziridination under these conditions.

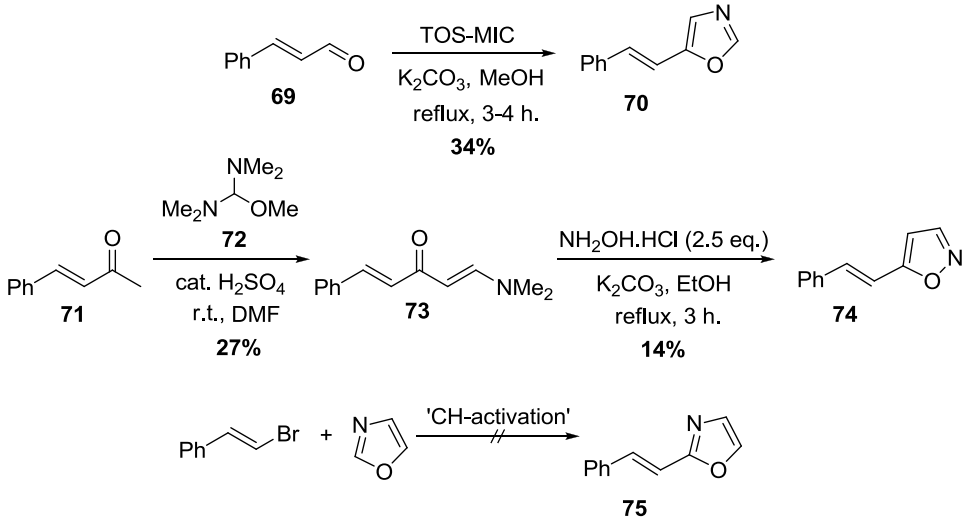


Scheme 44: Attempted aziridination of cinnamamide

1.3.2.2 Conjugated oxazoles

Alternative unsaturated electron-poor systems that have previously been tested by co-workers include α,β-unsaturated nitrates, aldehydes, sulfones and nitriles.[68, 73] To this point, the only substrates that have been used with success in the aziridination are enones and *tert*-butyl enoates. Aiming to expand the substrate scope further, it was decided to test the aziridination potential of substrates bearing electron-poor heteroaromatics instead of the carbonyl functionality. Oxazoles and isoxazoles were selected for investigation, due to the availability of literature syntheses of both heteroaromatics bearing styryl functionality at different positions on the ring. Styryl functionality was selected in order that the olefin substitution at the aromatic terminus was unchanged.

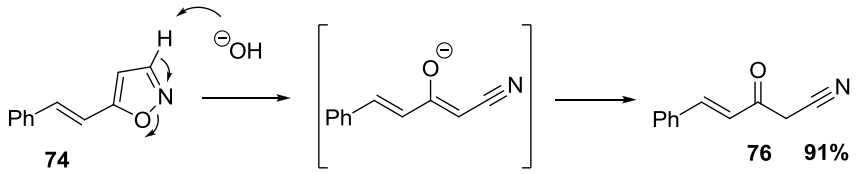
Literature procedures were followed for the synthesis of substrates **70** and **74** (**Scheme 45**). Van Leusen oxazole synthesis was used to access compound **70**.[81] TOS-MIC and cinnamaldehyde (**69**) were heated to reflux in MeOH in the presence of K_2CO_3. Work-up and chromatographic purification provided **70** in moderate yield (34%). Isoaxzole **74** was synthesised, albeit in poor yield (14%), by condensing enaminone **73** with hydroxylamine hydrochloride in refluxing ethanol.[82] The starting enaminone **73** was the product of benzylidene acetone (**71**) condensation with bis(dimethylamino)methoxymethane **72** in the presence of catalytic H_2SO_4, adapting the published procedure.[83] CH-activation of oxazole to form **75** is described in several recent literature accounts.[84, 85] Unfortunately, attempts to repeat these resulted in the isolation of starting material in all cases, with no evidence of product formation by TLC and ^{1}H NMR analysis.



Scheme 45: Synthesis of oxazole isomers

Owing to their wider substrate scope, the published aziridination conditions were initially applied to substrates **70** and **74**, as opposed to the newly-developed enoate-specific conditions.[53] Attempted aziridination of oxazole **70** in dichloromethane led to quantitative recovery of starting material.

Acetonitrile was also tested as a reaction solvent, although clean recovered starting material was again isolated. Isoxazole **74** showed complete conversion to a single product by TLC analysis, after 16 h. under aziridination conditions. Work-up and chromatographic purification yielded nitrile **76** in 91% (**Scheme 46**). The product had presumably arisen from deprotonation of isoxazole **74** by NaOH, followed by ring-opening by elimination and protonation of the resulting enolate.

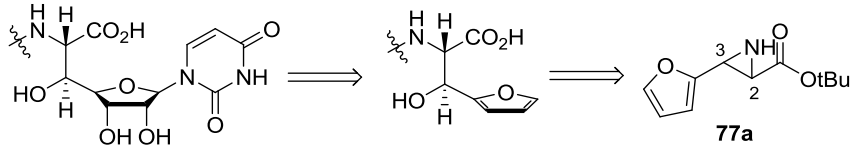


Scheme 46: Base-mediated rearrangement to nitrile 76

It seemed from experimentation to this point that the optimised enoate aziridination conditions were only applicable to *tert*-butyl esters. Although a limitation of the chemistry, *tert*-butyl esters are a synthetically useful functionality, with the advantage over other esters that they undergo facile deprotection under acidic conditions. With this in mind, it was decided to investigate the effect of altering the substituent at the aromatic terminus of *tert*-butyl cinnamate.

1.3.2.3 Furfuracrylates

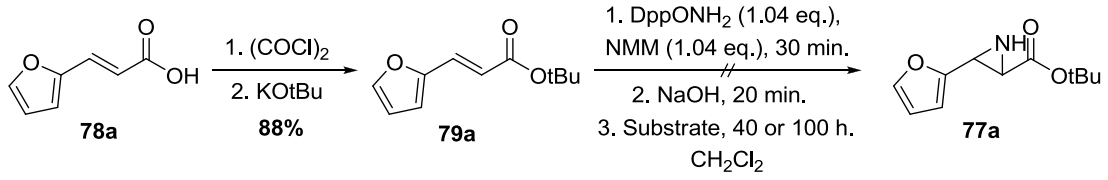
tert-Buyl enoates bearing a furan ring at the 3-position were considered interesting targets, following examination of a sub-unit of the natural product Muramycin. Muramycin is a structurally challenging target that has been shown to exhibit considerable antibiotic activity.[86, 87] Analogues are likely to have similar properties, and a simple synthetic strategy to access these would be desirable. It was envisaged that the ribose unit and a range of derivatives could be established using oxidative transformations on the furan ring. The furan amino-acid could potentially arise from the hydrolysis of aziridine **77a** (**Scheme 47**).



Scheme 47: Retrosynthesis of muramycin sub-unit

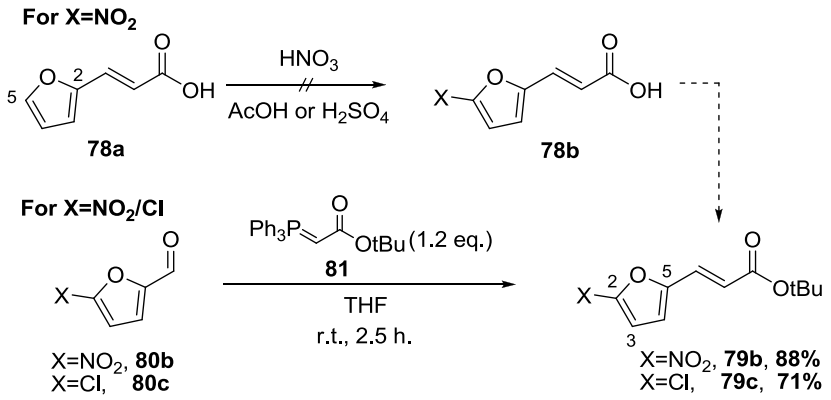
Whilst it was recognised from the outset that the electron-rich nature of the furan ring would likely make the unsaturated alkene less electrophilic than in *tert*-butyl cinnamate, the potential synthetic utility of the aziridine product prompted the preparation and testing of *tert*-butyl furfuracrylate **79a**. The substrate was synthesised in good yield (88%), using the previously-developed esterification chemistry (**Scheme 48**). Disappointingly, the substrate proved to be unreactive to aziridination, with

recovered starting material and a small amount of degradation to unidentified products observed by ^{1}H NMR analysis of the crude reaction mixture.



Scheme 48: Synthesis and attempted aziridination of *tert*-butyl furfuracrylate

It was reasoned that introduction of electron-withdrawing substituents on the furan ring might increase the susceptibility of the substrate to aziridination. The 5-nitro substituted analogue **78b** was suggested, as reduction of the nitro-group in a subsequent step could provide a functional amine handle for the introduction of the cyclic urea moiety present in Muramycin. Gilman and Wright describe the selective nitration of furfuracrylic acid **78a** at the 5-position to give nitro-derivative **78b**,[88] but unfortunately attempts to repeat the syntheses resulted in either return of starting material, or degradation to unidentified products by TLC and ^{1}H NMR analysis of crude reaction mixtures. As the nitro-furfuraldehyde **80b** is commercially available, a Wittig route was devised. Combination of the aldehyde with the commercial phosphorane **81** in THF for 2.5 h., followed by solvent removal and chromatographic purification, led to isolation of the crystalline *trans*-diastereomer **79b** in 88% (**Scheme 49**).

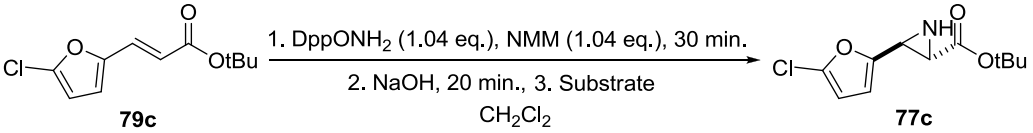


Scheme 49: Synthetic routes to *tert*-butyl furfuracrylate derivatives

With the nitro-analogue **79b** in hand, an aziridination reaction was attempted using the optimised enoate conditions. TLC and ^{1}H NMR analysis of the crude reaction mixture upon work-up showed considerable degradation to unidentified products, and a low recovered mass was noted. The difference in reactivities observed for *tert*-butyl furfuracrylate **79a** and the nitrated analogue **79b** under the aziridination conditions suggested that it might be possible to tune the reactivity of the substrate through selection of the appropriate furyl substituent. The chloro-derivative **79c** was mooted as an analogue with intermediate electronic properties. Additionally, a halogen at this position would

present the opportunity for cross-coupling chemistries for the introduction of the pendant cyclic urea later in the synthesis. Synthesis of the chloro-derivative **79c** was facile; utilising the Wittig route developed for the synthesis of the nitrated furfuracrylate provided the product in 71% isolated yield (**Scheme 49**). Subjection of the chloro-furfuracrylate **79c** to the optimised enoate aziridination conditions pleasingly led to isolation of the derived aziridine **77c**, albeit in a low yield of 11% (**Table 14**, entry 1). Aziridine **77c** was considerably more sensitive than the *tert*-butyl cinnamate derived analogue **1a**; no degradation has been observed of the latter after storage for 12 months at room temperature under air, but the former was observed to undergo complete degradation to unidentified products by ^{1}H NMR analysis after 5 days under the same conditions. It was also noted that the mass recovery of the crude product was low (48% calculated as a percentage of starting *tert*-butyl furfuracrylate mass, entry 1). Hypothesising that the poor mass recovery and low isolated yield could be attributed to substrate and/or product sensitivity to NaOH, a second aziridination was attempted, using 1 equiv. of the reagent for a shorter reaction time of 26 h. A lower conversion of 12% was observed, in comparison with the 39% conversion under the standard conditions (entry 1 *vs.* 2). However, the improved mass recovery (80%) prompted the shorter reaction time to be maintained and 4 eq. of NaOH to be re-introduced in a third experiment. Pleasingly, a 32% conversion, comparable with the initial result (39%) was observed, with a quantitative mass recovery (entry 3). A final aziridination, quenched after 16 h., led to a slightly diminished conversion (80%), but purification of the crude product from this reaction led to the isolation of aziridine **77c** in an improved 35% yield (entry 4). Aziridine **77c** displayed some interesting spectroscopic properties. The quaternary chloro-substituted C2-furyl carbon proved elusive in the ^{13}C NMR spectrum. Instead, an HMBC experiment showed a ^{2}J correlation between the C3-furyl proton and the C2-carbon, allowing the shift of the C2-carbon to be identified (see **Scheme 49** for numbering system).

Table 14: Aziridination of 5-chloro-*tert*-butyl furfuracrylate 79c



79c **77c**

Entry	NaOH (eq.)	Time (h.)	Crude mass recovery (%)[a]	^{1}H NMR conversion (%)[b]	Isolated yield (%)
1	4	40	48	39	11
2	1	26	80	12	n.d
3	4	20	Quant.	32	n.d
4[c]	4	16	80	27	35

All reactions performed on 0.11 mmol scale. [a] Calculated as a percentage of the mass of starting *tert*-butyl furfuracrylate. [b] Calculated using the relative intergrals of *tert*-butyl ester peaks in starting ester and product aziridine. [c] Performed on 0.22 mmol scale.

Although initial optimisation of the 5-chloro furfuracrylate aziridination had been promising, it was decided to postpone further investigation along with potential access to the muramycin subunit due to

the low yields and instability of the aziridine product. The observed dependence of the *tert*-butyl furfuracrylate aziridination on the electronic properties of the aromatic system led to refocus of investigative efforts on a similar study using *tert*-butyl cinnamate derivatives.

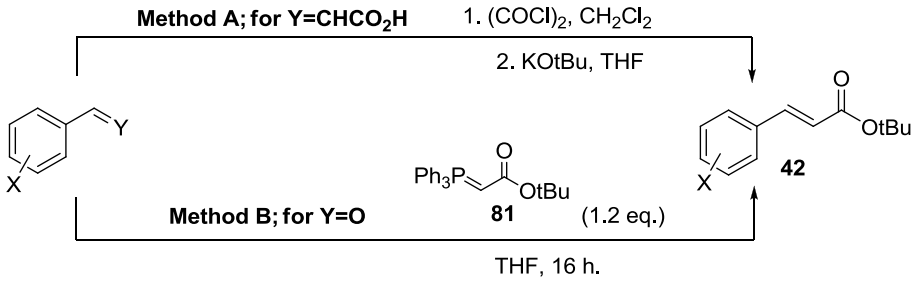
1.3.2.4 tert-Butyl cinnamates

Eight *trans*-*tert*-butyl cinnamate substrates bearing either electron-withdrawing or electron-donating groups at varying positions on the phenyl ring were selected for study. Five *para*-substituted examples were chosen, so that the electronic effect of substituents on the yield of the aziridination could be directly compared, without the added variables of ring-position and sterics. *para*-Substituents ranged from electron-withdrawing nitro- to electron-donating methyl- and methoxy-. *para*-Halo substitution was also selected, as the derived aziridine would bear functionality for further elaboration *via* cross-coupling. *meta*-Methoxy substitution was chosen, to observe the effect of moving the donating group out of conjugation with C3, the site of nucleophilic attack. *ortho*-Nitro and *ortho*-chloro *tert*-butyl cinnamates would provide an indication of the effect of steric bulk near the reacting C3-carbon, comparable with the *para*-substituted derivatives.

Substrate synthesis

Six of the substrates were synthesised using the esterification chemistry described for *tert*-butyl cinnamate (**Table 15**, entry 1-6). Synthesis was straightforward with the exception of the *ortho*-nitro substrate; a further portion of oxalyl chloride was required for full conversion to the acid chloride, and the *tert*-butyl ester **42g** was isolated in a poor 13% yield (entry 6). The *para*-iodo derivative **42h** was isolated in good yield (79%) *via* the Wittig chemistry used to access furfuracrylates **77b** and **77c** (entry 7).

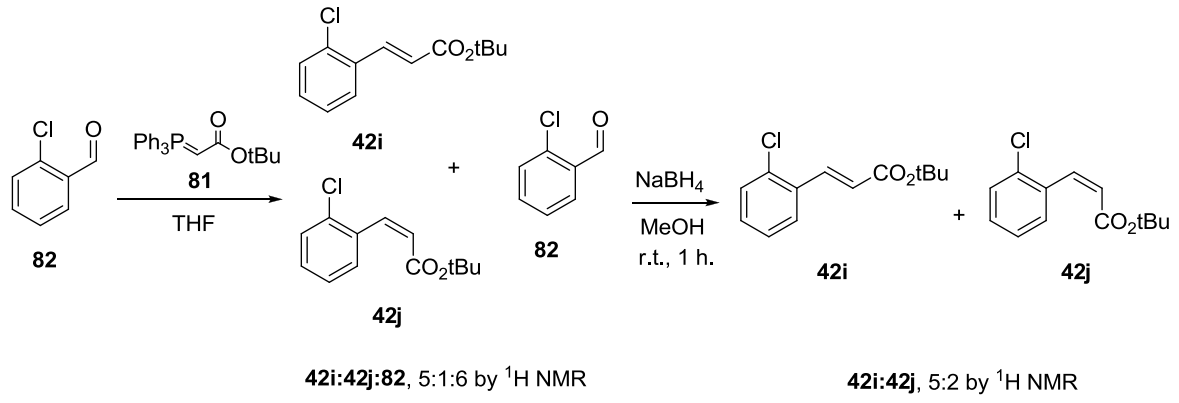
Table 15: Synthesis of *tert*-butyl cinnamates



Entry	X	Method	Compound number	Isolated yield (%)
1	*p*-OCH_3	A	**42b**	65
2	*p*-NO_2	A	**42c**	63
3	*p*-CH_3	A	**42d**	79
4	*p*-Cl	A	**42e**	84
5[a]	*m*-OMe	A	**42f**	Quant.
6[a,b]	*o*-NO_2	A	**42g**	13
7[c]	*p*-I	B	**42h**	79

All reactions performed on 2 mmol scale. [a] Performed on 4 mmol scale. [b] 2 x 1.05 eq. portions of oxalyl chloride required for full conversion to acid chloride. [c] Performed on 0.11 mmol scale.

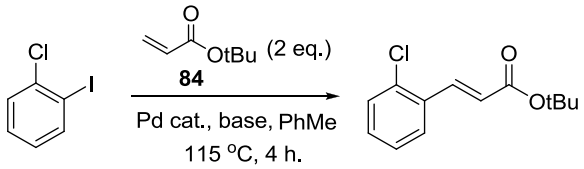
ortho-Chloro *tert*-butyl cinnamate **42i** proved to be the most challenging substrate to synthesise. The esterification chemistry was not a viable route, due to the limited availability of the starting acid. Wittig reaction from *ortho*-chloro benzaldehyde (**82**) led to a 5:1 mixture of *trans*:*cis* isomers, which were inseparable from both each other, and from unreacted starting aldehyde (*ca.* 50% of the crude product by relative integration of ^{1}H NMR signals) (**Scheme 50**). Treatment of the mixture with $NaBH_4$ in MeOH led to complete reduction of the aldehyde after 1 h. at r.t., allowing separation of the resulting alcohol from the isomers *via* column chromatography. However, the second purification led to erosion of the cinnamate *trans:cis* selectivity to 5:2 (**Scheme 50**). An alternative synthesis was sought, to provide the *trans*-cinnamate **42i** selectively, due to the observed difficulty in separation of the isomers.



Scheme 50: Mixtures of products following Wittig chemistry of *o*-Cl benzaldehyde

The Heck coupling is known to provide olefins in excellent *trans* selectivity. 1-Chloro-2-iodo benzene (**83**) and *tert*-butyl acrylate (**84**) were the required coupling partners, with the added advantage that the olefin is considered 'activated' with respect to Heck chemistry. As the synthesis of this cinnamate had not previously been reported in the literature, two palladium catalysts and two bases were selected that have enjoyed success in Heck chemistry, and combinations of the reagents tested. Three reactions were carried out in sealed tubes, heating to 115 °C. Pleasingly, the required product was isolated from all reactions (**Table 16**, entries 1-3), with no *cis* isomer observed by ^{1}H NMR analysis of the crude reaction mixture. The optimum set of conditions, employing $PdCl_2(PPh_3)_2$ in Et_3N as solvent, provided the product **42i** in 80% isolated yield (entry 2). A decrease in the reaction temperature to 95 °C saw a considerable drop in yield to 35% (entry 4). Re-introduction of the higher temperature (115 °C) and moderate scale-up led to an identical yield of 80% (entry 5).

Table 16: Optimisation of Heck route to *trans*-*o*-chloro *tert*-butyl cinnamate



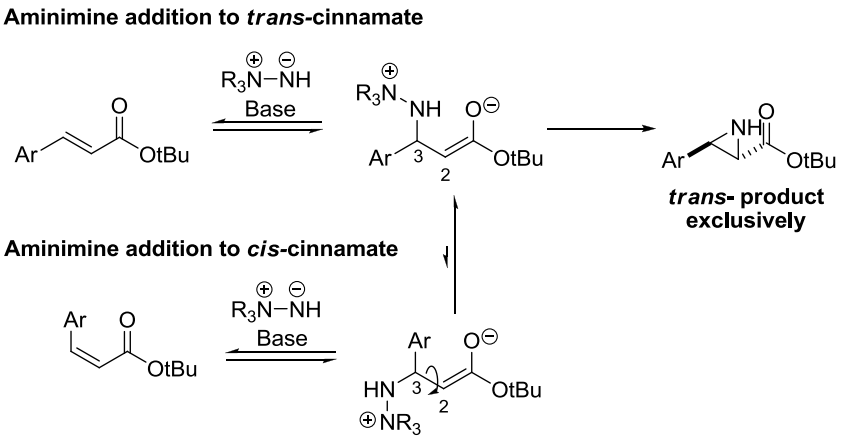
83 **42i**

Entry	Pd catalyst	Base	Isolated yield (%)
1	$PdCl_2(PPh_3)_2$	Cs_2CO_3	20
2	**$PdCl_2(PPh_3)_2$**	**Et_3N**[a]	**80**
3	$Pd_2(dba)_3$	Cs_2CO_3	42
4[b,c]	$PdCl_2(PPh_3)_2$	Et_3N	35
5[b]	$PdCl_2(PPh_3)_2$	Et_3N[a]	80

All reactions performed on 0.2 mmol scale with 0.2 eq. catalyst. [a] Base used as reaction solvent in place of PhMe. [b] Performed on 0.8 mmol scale [c] Performed at 95 °C.

Susceptibility to aziridination

With the purified *trans*-*tert*-butyl cinnamates in hand, testing of the substrates in the aziridination could begin. However, it was first decided to subject the crude mixture of *cis*- and *trans*-*ortho*-chloro cinnamates, **42i** and **42j** to the aziridination. Acyclic *cis*-enones and enoates have not been tested in the aziridination, as accessing such substrates in high diastereoselectivity is synthetically challenging. According to the proposed mechanism, the geometry of the starting alkene should not be reflected in the aziridine product; the intermediate prior to aziridine formation can undergo free rotation about the C2-C3 bond, leading to the most stable *trans*- configuration as observed (**Scheme 51**). Subjecting a *cis*-enoate to the aziridination would test this hypothesis, and provide further mechanistic understanding.



Scheme 51: *trans*-Selectivity in the aziridination

Accordingly, the optimised enoate aziridination conditions were applied to the isomeric mixture. Analysis of the ^{1}H NMR spectrum of the crude product showed complete consumption of the *trans*-cinnamate **42i**, which appeared to have undergone complete conversion to the *trans*-aziridine. Interestingly, it appeared that none of the *cis*- isomer **42j** had reacted; the relative integrals of the *cis*- and *trans*-isomers in the starting mixture were identical to those of the *trans*-aziridine and *cis*-cinnamate in the crude product.

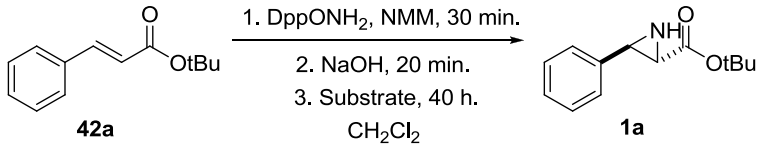
The apparent lack of conversion of the *cis*-cinnamate **42j** to aziridine indicated that the substrate was unreactive to the initial nucleophilic addition of the aminimine. If this step was occurring without subsequent ring-closure, then isomerisation to the *trans*-cinnamate would be expected, due to the reversible nature of the addition.

The other interesting feature of the reaction was the apparent complete conversion of the *trans*-cinnamate to aziridine, which has not previously been observed in enoate aziridination using this methodology. Following chromatographic purification, the aziridine was isolated in 35% yield, calculated using the mass of the isomeric mixture. Assuming non-reactivity of the *cis*-product **42j** in the mixture, an extrapolated yield of 51% was calculated, based on the percentage of *trans*-cinnamate in the starting mixture. Wondering whether the increased quantities of reagents used with respect to the *trans*-cinnamate were responsible for the yield (higher than the 50% observed with *tert*-butyl cinnamate), brief experimentation was carried out using increased reagent quantities with *tert*-butyl cinnamate.

The quantities of reagents used with respect to the *trans*-cinnamate were calculated to be 3 eq. each of NMM and $DppONH_2$, and 11 eq. of NaOH. *tert*-Butyl cinnamate was subjected to the aziridination, using the increased quantities, at the lower concentration of 0.12 M, to aid magnetic stirring of the heterogeneous reaction mixture. An optimum conversion of 78% was observed by ^{1}H NMR analysis

of the crude reaction mixture after 40 h., translating into an isolated yield of 60% after chromatographic purification (**Table 17**, entry 1). The large excess of NaOH (11 eq.) was found to be necessary; an analogous reaction using 6 eq. led to a considerably lower conversion of 60% (entry 2). Further increase of reagent stoichiometries to 5 eq. of tertiary amine and aminating agent each, and 20 eq. of NaOH provided complete conversion of starting cinnamate to aziridine, although a slight drop in isolated yield (56%) was observed (entry 3).

Table 17: Optimisation of super-stoichiometric aziridination conditions



42a **1a**

Entry	NMM (eq.)	$DppONH_2$ (eq.)	NaOH (eq.)	Concentration [M]	^{1}H NMR conversion (%)	Isolated yield (%)
1	**3**	**3**	**11**	**0.12**	**78**	**60**
2	3	3	6	0.12	60	n.d.[a]
3	5	5	20	0.09	Quant.	56

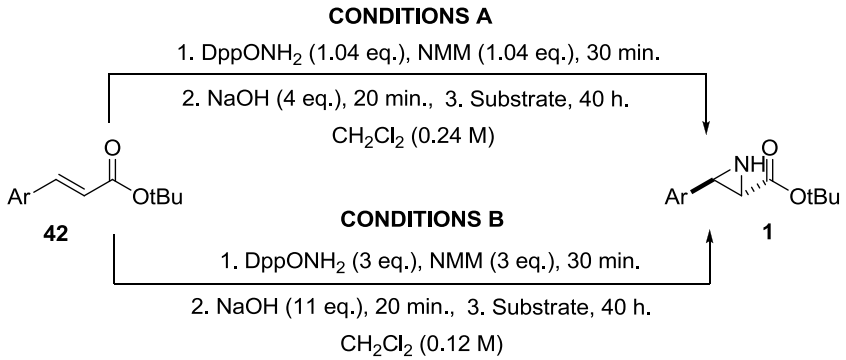
All reactions performed on 0.12 mmol scale of substrate. [a] Not determined.

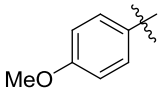
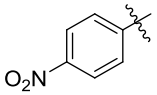
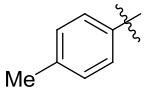
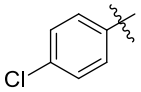
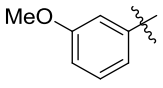
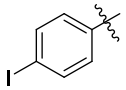
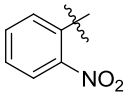
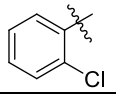
In the interests of time, further optimisation of these super-stoichiometric conditions was ceased. It was decided to test both these conditions and the previously optimised conditions on each of the *tert*-butyl substrates synthesised. The previously observed sensitivity of the furfuracrylates arising from electronic properties, led to the rationale that electron-poor substrates might be sensitive to the super-stoichiometric conditions.

The aziridination of the *tert*-butyl cinnamate substrates showed that isolated yields were largely dependent on the electronic properties of the aromatic in the substrate. Cinnamates with electron-rich aromatics gave low yields that were only marginally improved on application of the super-stoichiometric conditions B (**Table 18**, entries 2, 4, 6). The milder set of conditions (A) were found to be more appropriate for cinnamates with electron-poor aromatic systems (entries 3, 5, 8); this effect was particularly marked for the *p*-NO_2 system, where a good isolated yield of aziridine **1c** (76%) under conditions A was reduced to a meagre 9% using super-stoichiometric conditions B (entry 3). Reduced yields were observed for *ortho*-substituted cinnamates in comparison to their *para*-substituted analogues (for example, entry 3 *vs.* 8). Despite this, a moderate yield (47%) was still obtained for the *ortho*-chloro cinnamate **1i** under the super-stoichiometric conditions (entry 9). Moving the donating *para*-methoxy group out of conjugation into the *meta*-position, provided only a small difference in isolated yield of the derived aziridine **1f** (entry 2 *vs.* 6). The result indicates that the yield of aziridine is affected by the overall electron density of the aromatic system rather than conjugation effects. As described previously, the aziridination of *tert*-butyl cinnamate itself was

higher yielding (60%) under the super-stoichiometric conditions B, and this yield was further increased on moderate scale-up, to provide aziridine **1a** in 65% (entry 1). Interestingly, electron-poor cinnamates were observed to provide better yields in the aziridination than electron-rich. This is suggestive that the initial addition step of the catalytic cycle is rate limiting in the enoate aziridination. This opposes circumstantial evidence obtained from the study of enone reactivity in the aziridination, which indicated that the cyclisation step was rate-limiting for these substrates.

Table 18: Aziridination of *tert*-butyl cinnamates



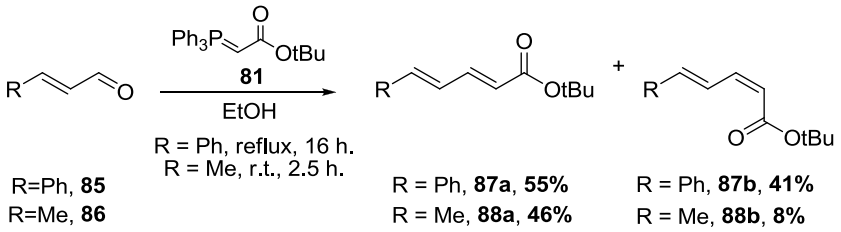
Entry	Ar	Aziridine number	Isolated yield of aziridine (%)	
			Conditions A	Conditions B
1		**1a**	50[a]	**60 (65)**[b]
2		**1b**	33[c]	**39**
3		**1c**	**76**[e]	9
4		**1d**	34[e]	**36**
5		**1e**	**53**[f]	19
6		**1f**	23	**32**
7		**1h**	**33**[g]	29[h]
8		**1g**	**40**	4
9		**1i**	24	**47**

Reactions performed between 0.12 and 0.24 mmol scale. [a] 10.0 mmol scale, [b] 3.0 mmol scale, [c] 0.71 mmol scale. Reactions performed at [d] [0.17 M]; [e] [0.12 M]; [f] [0.03 M]; [g] [0.15 M]; [h] [0.08 M].

The strong dependence of the enoate aziridination on the electronic properties of the aromatic system had been established. With that, it was decided to test enoate substrates bearing non-aromatic functionality at the β-position, to see whether any considerable difference in reactivity could be observed.

1.3.2.5 Dienoates

The successful aziridination of α,β,γ,δ-unsaturated ketones (dienones) has previously been reported using the methodology, under slightly modified conditions.[69] The derived aziridines are formed in excellent *trans* diastereoselectivity, with the aziridination completely regioselective for the α,β-olefin. Two α,β,γ,δ-unsaturated esters (dienoates) were tested as part of the substrate scope, with no conversion to the resulting aziridines observed. However, the dienoates had not been subjected to the conditions used for enoate aziridination in the original paper,[53] or the newly optimised enoate conditions. Accordingly, two *tert*-butyl dienoate substrates were selected as comparable with *tert*-butyl cinnamate; compound **88**, with an allyl moiety at the β-position, and compound **87**, with a styryl group at this position. The compounds were synthesised using Wittig chemistry, from the commercial phosphorane **81** and crotonaldehyde (**86**) or cinnamaldehyde (**85**) respectively. The crude dienoates were mixtures of diastereomers, with the major isomer the *trans,trans*-product, **87a** or **88a** in each case. Chromatographic purification allowed separation and isolation of all diastereomers (**Scheme 52**).



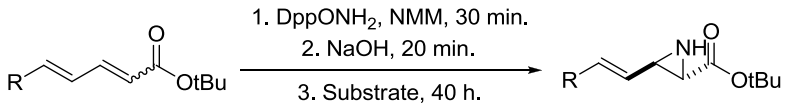
Scheme 52: Synthesis of dienoates 87 and 88

Initially, dienoate **88a** was subjected to aziridination. Application of both the moderate conditions (A) and the super-stoichiometric conditions (B) led to either no or very low conversions to aziridine, from comparison of ^{1}H NMR integrals in the spectrum of the crude product (**Table 19**, entries 1 and 2). Additionally, the mass recovery from both reactions was poor; *ca.* 25% of the mass of the starting dienoate. Concluding that the mass loss was likely due to instability of dienoate **88a** to the reaction conditions, attention was turned to the aziridination of dienoate **87a**. Improved reactivity was observed, with a 16% conversion to aziridine **89** on application of the super-stoichiometric conditions (B) (entry 4). Aziridine **89** was isolated in low yield (4%), following chromatographic purification, nonetheless providing sufficient material for the regiochemistry of aziridination to be confirmed at the α,β-olefin. A ^{4}J correlation between the γ-CH and the carbonyl carbon was observed using HMBC

spectrometry, with the same γ-CH correlating to the aromatic signals. *trans*-Diastereoselectivity was confirmed through the coupling constants of the aziridine-CH protons. The isolated aziridine **89** was observed to undergo degradation after 12 h. at room temperature, with ^{1}H NMR analysis showing considerable formation of unidentified products. Interestingly, the published aziridination conditions provided no conversion to aziridine, highlighting the necessity of the enoate-specific conditions for improved substrate scope (entry 5).

Following the previous observation that *cis*-cinnamates appeared unreactive to the aziridination, the *cis,trans*-isomer **87b** was subjected to the super-stoichiometric conditions (B) found to be optimum for aziridination of the *trans,trans*-isomer **87a**. Analysis of the ^{1}H NMR spectrum of the crude material showed no conversion to aziridine, and 3% isomerisation to the *trans,trans*-compound **87a**, with the *cis,trans*-starting material **87b** the main compound observed (entry 6). Additionally, mass recovery of the crude material was quantitative. To establish whether this isomerisation was being caused specifically by reversible addition of the aminimine, a control experiment was performed. The *cis,trans*-dienoate **87b** was treated with NaOH in the absence of tertiary amine and aminating agent, with 4% isomerisation to the *trans,trans* dienoate **87a** observed by ^{1}H NMR after 40 h (entry 7). This indicated that the isomerisation observed under the aziridination conditions was likely due to reversible nucleophilic addition of hydroxide, and that addition of the aminimine to dienoate **87b** had not occurred.

Table 19: Aziridination of dienoates



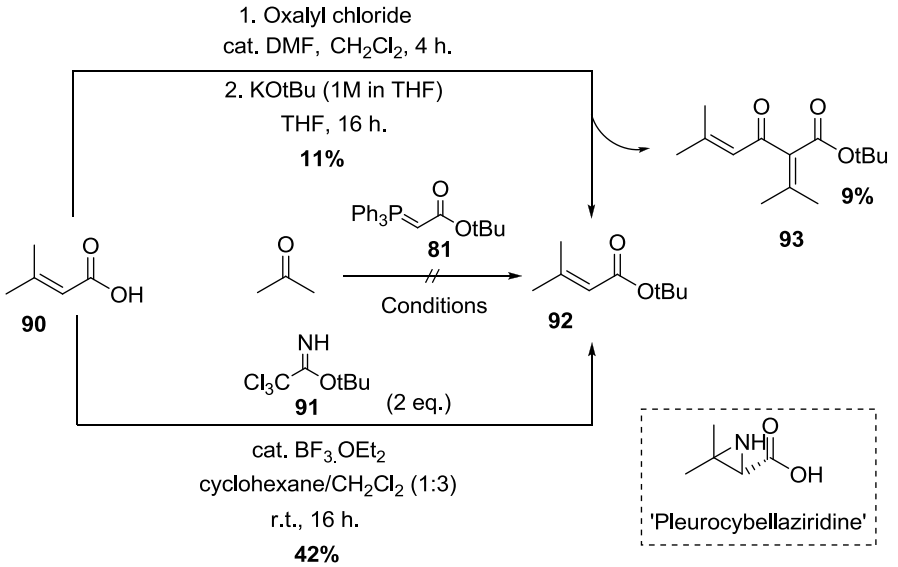
Entry	Dienoate	Conditions[a]	Product ratio (%)[b]	
			Starting dienoate	Aziridine
1	**88a**	A	100	0
2	**88a**	B	99	1
3	**87a**	A	96	4
4	**87a**	**B**	**84 (52)**	**16 (4)**
5	**87a**	-[c]	100	0
6	**87b**	B	97[d]	0
7	**87b**	-[e]	96[d]	0

All reactions performed on 0.11 mmol scale. Isolated yields in parentheses. [a] Conditions A: $DppONH_2$ (1.04 eq.), NMM (1.04 eq.), NaOH (4 eq.), CH_2Cl_2 (0.24 M); Conditions B: $DppONH_2$ (3 eq.), NMM (3 eq.), NaOH (11 eq.), CH_2Cl_2 (0.12 M). [b] Calculated using relative ^{1}H NMR integral of the starting material and product in the spectrum of the crude material. [c] Published aziridination condition used.[53] [d] Isomerisation to compound **87a** observed. [e] Dienoate stirred with NaOH (11 eq.).

Although aziridination of compound **87a** had been successful, the low isolated yield and observed instability of resulting aziridine **89** prompted further investigation to be halted. Attention was instead turned to the target synthesis of a small, naturally occurring, *NH*-aziridine-2-carboxylate.

1.3.2.6 Towards 'pleurocybellaziridine'

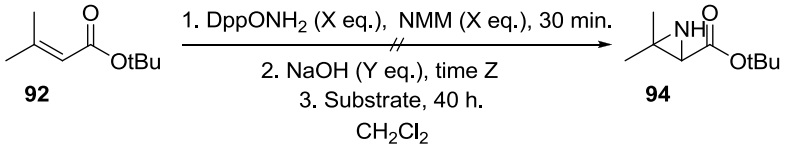
A timely publication from the group of Kan described the isolation of cytotoxic amino acids from the mushroom *Pleurocybella porrigens*.[89] The mushroom is eaten widely in Japan, and was believed to have caused 17 deaths from acute encephalopathy in 2004. The structural similarity of the amino acids led the group to propose a common *NH*-aziridine-2-carboxylate precursor, appropriately named 'pleurocybellaziridine' (**Scheme 53**). The group completed the enantioselective synthesis of the aziridine in six steps from D-Serine, using a triphenyl-phosphine-mediated ring-closure of the amino alcohol for the key aziridine-forming step. The aziridine presented an interesting structural target to test our chemistry, and accordingly, *gem*-dimethyl *tert*-butyl acrylate **92** was prepared. Synthesis was initially attempted using the esterification conditions optimised for *tert*-butyl cinnamate. *gem*-Dimethyl acrylic acid (**90**) was treated with oxalyl chloride, and complete conversion of the starting material was observed by TLC analysis after 4 h. Quenching the acid chloride with KO^{t}Bu (1 M in THF), and isolation of the crude material led to two products, as observed by TLC and ^{1}H NMR analysis. Chromatography on neutral alumina (due to instability of crude mixture on silica) provided the required product **92** in poor yield (11%) along with the *bis*-alkene **93** also in a low yield of 9% (**Scheme 53**). Although the required product had been isolated, a higher yielding synthesis was sought. Wittig chemistry was attempted, stirring the commercial phosphorane **81** with acetone used both stoichiometrically and as the reaction solvent. However, the required product was not observed in reactions performed both at room temperature and at reflux. Pleasingly, treatment of *gem*-dimethyl acrylic acid **90** with trichloroacetamide **91** in the presence of $BF_3.OEt_2$, following Jackson's procedure,[90] allowed isolation of product **92** in 42% yield, following filtration of the crude product through a silica pad (**Scheme 53**).



Scheme 53: Synthetic routes to *gem*-dimethyl *tert*-butyl acrylate

gem-Dimethyl *tert*-butyl acrylate **92** was subjected to the two sets of enoate aziridination conditions (**Table 20**, entries 1 and 2), and also the published conditions (entry 3).[53] Aziridine **94** was not observed upon work-up and analysis of the ^{1}H NMR spectra. Instead, a good mass recovery of clean starting material was observed, indicating that the substrate is unreactive to the conditions. It was hypothesised that the *gem*-dimethyl moiety rendered the olefin too electron-rich for the nucleophilic aziridination, and that the increased steric bulk at the β-position would also disfavour aminimine addition.

Table 20: Aziridination of *gem*-di-methyl *tert*-butyl acrylate 92



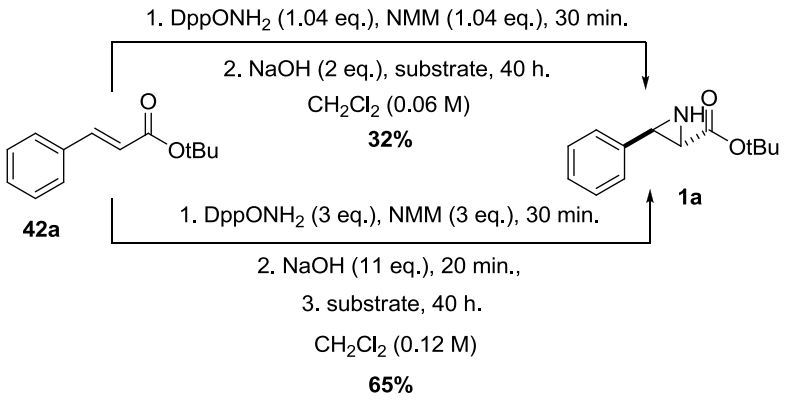
Entry	Scale (mmol)	Concentration [M]	X (eq.)	Y (eq.)	Z (min.)
1	0.32	0.32	1.04	4	20
2	0.16	0.16	3	11	20
3[53]	0.13	0.06	1.04	2	0

Owing to the poor reactivity of the β-alkyl *tert*-butyl enoates tested in the aziridination, it was decided not to pursue further investigation into this class of substrate. It should be noted that there is possibility for further investigation here, with the aim to expand the scope of the *tert*-butyl enoate aziridination. It is likely that the electronic properties of the β-alkyl substituent will have a large effect on the success of the aziridination, as observed for *tert*-butyl cinnamates. Further investigation should include alkyl substituents with varied electronic properties to probe this hypothesis.

1.3.3 Summary of the enoate aziridination

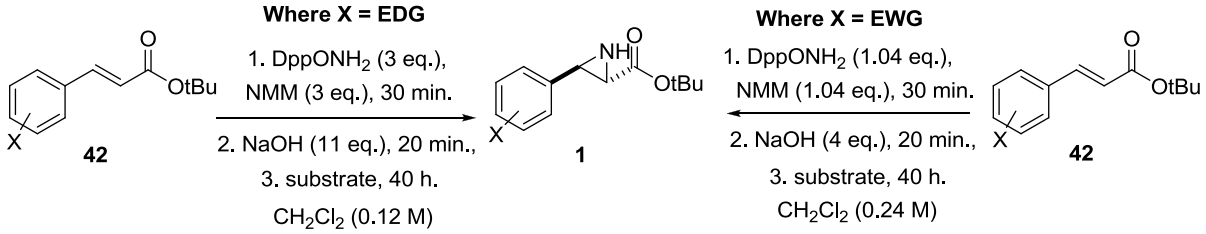
It was considered prudent at this point, to bring investigation into the *tert*-butyl enoate aziridination to a close, and move forward with the exploration of ring-opening methodology. Pleasingly, optimisation of the aziridination protocol had allowed an improvement in yield on small scale (0.12 mmol) from 32%, using the published aziridination conditions, to 60%. A larger scale (10.0 mmol) reaction provided an optimum 65% isolated yield of aziridine **1a** (**Scheme 54**). *En route* to the improved enoate-specific conditions, a range of tertiary amines, bases, solvents and aminating agents were tested, revealing that the combination of reagents used in the published conditions were indeed optimum. The main differences between the published and newly optimised conditions included:

a) An increase in concentration with respect to *tert*-butyl cinnamate
b) An increase in the equivalents of reagents
c) The inclusion of a 20 min. time delay between the addition of base and substrate



Scheme 54: Optimised conditions for the aziridination of *tert*-butyl cinnamate

The enoate aziridination conditions were found to be substrate specific; lower esters and lactones tested were susceptible to hydrolysis under the basic conditions. Furthermore, the aziridination was found to be highly dependent on the electronic properties of the *tert*-butyl cinnamate in question. A study of *tert*-butyl cinnamates bearing aromatics with varying electronic properties showed that electron-poor substrates were more reactive and gave better yields in the aziridination, whilst electron-rich systems were considerably less prone to degradation under the reaction conditions, but gave lower yields of aziridine. Indeed, two sets of aziridination conditions were developed to account for this; a moderate set and a super-stoichiometric, more forcing set (**Scheme 55**).



Scheme 55: Two sets of conditions for the aziridination of *tert*-butyl cinnamates

tert-Butyl enoates bearing non-aromatic β-functionality that were tested included two α,β,γ,δ-unsaturated substrates **87** and **88** and a *gem*-dimethyl enoate **92**, with the latter attempted to access a natural product. Dienoate substrate **87a** reacted to give regioselective aziridination at the α,β-position, although the resulting aziridine was isolated in poor yield. *gem*-Dimethyl *tert*-butyl acrylate **92** was found to be stable and unreactive to the aziridination, likely due to its electron-rich and sterically hindered nature. Further investigation into the susceptibility of of β-alkyl *tert*-butyl enoates to the aziridination has the potential to expand the scope of the methodology further.

A final large-scale aziridination was performed to access sufficient material for ring-opening. On standing overnight, the purified aziridine **1a** (a clear oil) was observed to crystallise, forming white plates. The crystals were of high quality, allowing X-Ray data to be obtained, clearly showing the

trans-relationship across the aziridine ring (**Fig. 6**). ^{1}H NMR confirmed the high purity of the material, which was taken forward for ring-opening experimentation.

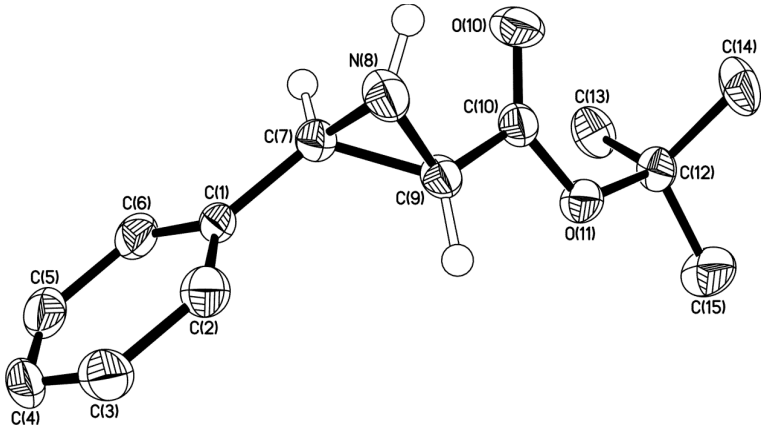
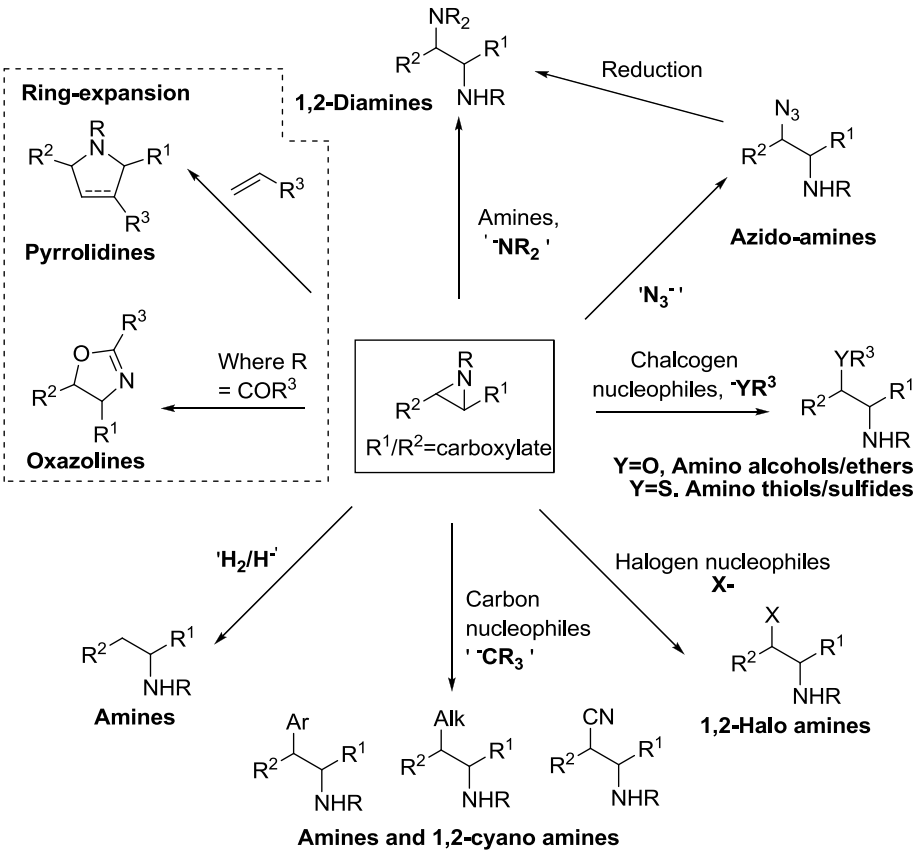


Fig. 6: Crystal structure of aziridine 1a

1.3.4 The ring-opening of aziridine-2-carboxylates

The ring-opening chemistry of *N*-functionalised aziridine-2-carboxylates is well documented, and a wide range of nucleophiles have been used with success (**Scheme 56**). The breadth of the area does not permit a full review herein; instead the interested reader is directed towards seminal review articles.[3, 11]



Scheme 56: Ring-opening of *N*-functionalised aziridine-2-carboxylates

As with all aziridine ring-opening chemistry,[2, 91] mixtures of product isomers may result, dependent on the mechanism and site of nucleophilic attack. Considering direct nucleophilic attack at the aziridine ring, four isomers are possible from the ring-opening of one aziridine substrate (**Fig. 7**). Regioisomers can result dependent on whether attack occurs at C2 or C3, and a *syn*- or *anti*-relationship between the nucleophile and the leaving group can arise from alternative mechanisms of nucleophilic attack, leading to diastereomers. An *anti*- relationship is most commonly observed *via* S_N2-like ring-opening, although *syn*-products can arise from reaction with an internal nucleophile, for example, nucleophilic functionality on the aziridine nitrogen, or *via* a mechanism of double inversion.

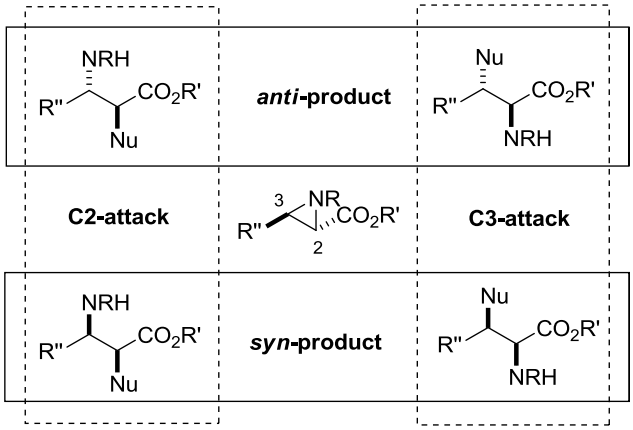
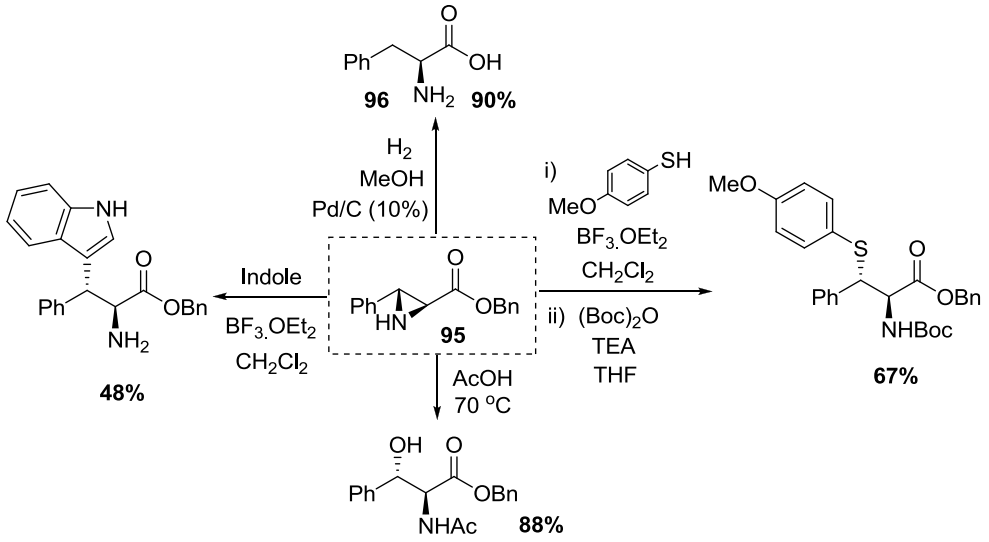


Fig. 7: Isomers arising from the direct ring-opening of an aziridine carboxylate

Although ring-opening chemistry is well established for *N*-functionalised substrates, only two methodological studies of ring-opening *NH*-aziridine-2-carboxylates exist. Letgers has demonstrated the propensity of methyl-ester substituted aziridines to ring-opening upon treatment with conc. hydrochloric acid, benzene thiol, indole and acetic acid. However, inseparable mixtures of regio- and diastereomers were obtained.[17] This poor selectivity was improved upon in methodology from Hruby, who showed that benzyl-cinnamate derived *NH*-aziridine **95** undergoes selective attack at C3 to yield *anti*-products exclusively. Nucleophiles used were indole, acetic acid and *p*-methoxy benzene thiol (**Scheme 57**). A hydrogenation protocol was also developed by Hruby, resulting in regioselective cleavage of the benzylic CN bond and concomitant benzyl ester hydrogenolysis to give phenylalanine (**96**) (**Scheme 57**).[18]



Scheme 57: Hruby's ring-opening of benzyl-cinnamate derived *NH*-aziridine 95[18]

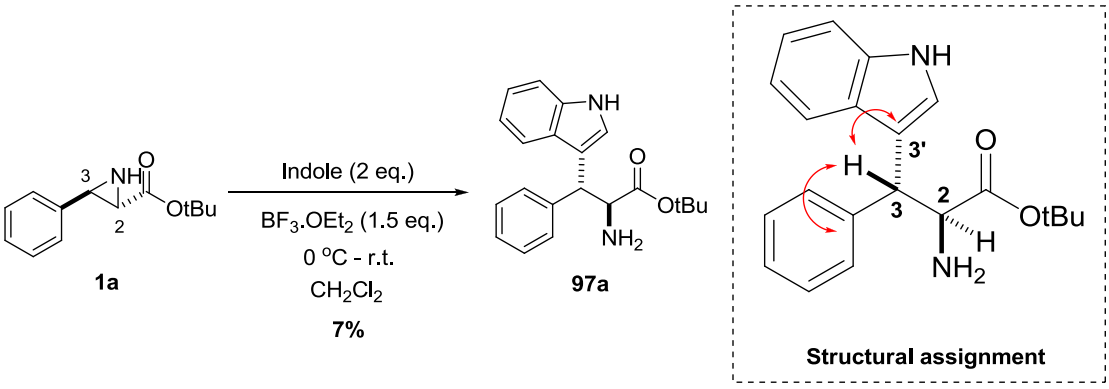
Drawing on this precedent, it was hoped that *tert*-butyl ester substituted *NH*-aziridine **1a** would be susceptible to ring-opening chemistry. If successful, the potential to expand the range of nucleophiles

from those used previously could be explored. Additionally, both literature reports described involve multi-step syntheses of the starting aziridines. Ring-opening of aziridine **1a** would provide access to ring-opening products in just two steps from readily available *tert*-butyl cinnamate.

1.3.4.1 Ring-opening with indole

Indole was selected as the initial nucleophile for the ring-opening of aziridine **1a**, taking a lead from Hruby's report.[18] To start, Hruby's conditions were applied; the aziridine and indole were dissolved in CH_2Cl_2 and cooled to 0 °C. $BF_3.OEt_2$ was added dropwise, and the reaction allowed to warm to r.t. After 2 h., the intense pink reaction mixture was quenched using $NaHCO_3$ (sat. aq.), and ^{1}H NMR analysis of the crude reaction mixture allowed identification of a ring-opened product, along with considerable conversion to other unidentified side-products. Chromatographic purification led to the isolation of the identified ring-opened product **97a** in a meagre 7% yield (**Scheme 58**).

Notwithstanding the low yield, careful analysis of NMR spectra allowed the selectivity of the reaction to be determined. Despite impurity formation, only a single ring-opened product had been observed in the ^{1}H NMR spectrum of the crude product, leading to the conclusion that inversion had occurred at C3 following S_N2-like reactivity. Although in theory, a single diastereomer could be observed with retention at C3, for example, following a double-inversion mechanism, no structural features of aziridine **1a** were identified that might cause this. The regiochemistry of substitution at the indole C3' rather than nitrogen could be confirmed, as a broad singlet at 8.19 ppm corresponding to the indole NH- proton was evident in the ^{1}H NMR spectrum of the pure compound. The regiochemistry of nucleophilic attack at the aziridine was confirmed using HMBC spectrocospy. The aromatic signals in the ^{1}H NMR spectrum of **97a** were assigned, and a ^2J correlation between the C3-proton and the *ipso*-carbons of both the indole and the phenyl groups could be observed (**Scheme 58**). No correlation was observed from the C2-proton to any aromatic carbon signals. Further confirmation of the regio- and stereochemical assignment was obtained through comparison with a literature preparation of tryptophan **97a**.[92] The synthetic strategy employed meant that the regiochemistry of the derivative was unambiguous. However, both *syn*- and *anti*-diastereomers of tryptophan **97a** were observed, with data provided for each. Comparison of ^{1}H NMR shift values revealed a close match for tryptophan **97a** with the literature values for the *anti*-diastereomer.



Scheme 58: Ring-opening of aziridine 1a with indole

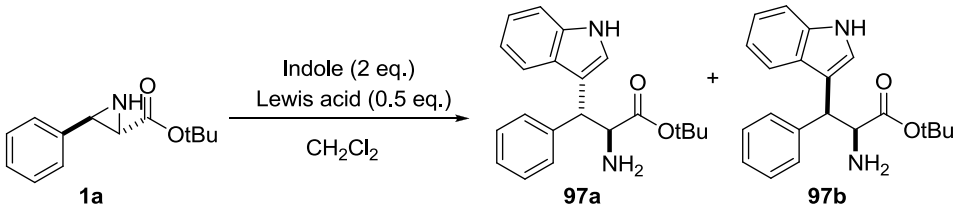
Limiting impurity formation

It was desirable to limit impurity formation in the indole ring-opening to obtain an increased yield of tryptophan **97a**. $BF_3.OEt_2$ is strongly activating, and has been used to catalyse many Lewis acid-mediated processes, so was highlighted as a possible cause of the degradation observed. Initial experimentation showed that impurity formation increased significantly at reaction times above 2 h., lending support to this hypothesis. In particular, $BF_3.OEt_2$ can used to hydrolyse *tert*-butyl esters, and this was recognised as a possible decomposition pathway. Consequently, initial optimisation focussed on limiting the quantity of this reagent used.

A control experiment lacking $BF_3.OEt_2$ provided a quantitative recovery of starting aziridine, despite an extended reaction time of 96 h., indicating that aziridine activation was necessary for ring-opening to occur (**Table 21**, entry 1). The $BF_3.OEt_2$ was re-introduced, but used in a catalytic quantity (0.5 eq.), and pleasingly provided considerably less by-product formation by TLC analysis upon quenching the reaction after 2 h. Indeed, analysis of the ^{1}H NMR spectrum of the crude material showed that impurity formation had been significantly prevented so as to allow calculation of an ^{1}H NMR conversion (51%), using relative integration of signals corresponding to the starting aziridine and the ring-opened product. Chromatographic purification allowed the isolation of the tryptophan derivative **97a** in an improved yield of 44% (entry 2). Halving the equivalents of indole used caused similarly low levels of impurity formation, but a decreased conversion of 36% to ring-opened product **97a** (entry 3). In each of these reactions, by-product formation had been limited to such an extent that a second ring-opened product had been observed in the ^{1}H NMR spectra of the crude material. The similarity of the ^{1}H NMR shifts of the C2- and C3-protons with those in the major product led to the product being tentatively assigned as the minor *syn*-diastereomer **97b**. The product had not formed in sufficient quantity to allow isolation in acceptable purity, so it was decided to maintain the focus of the investigation on increasing the yield of the major isomer, and to return at a later point to identification of the minor product.

Alternative Lewis acids ($InCl_3$ and $MgBr_2$) described in the literature[93] for the ring-opening of *N*-substituted aziridine-2-carboxylates were also tested, but these provided decreased conversions to **97a** of 21% and 0% respectively (entries 4 and 5). Returning to boron Lewis acids, the less activating BF_3.THF was next tested, rationalising that degradation of the reagents and/or product would be further reduced. A conversion of 86% to tryptophan **97a** was observed, although this translated to a considerably lower isolated yield (51%) (entry 6). Promisingly, the diastereomeric ratio calculated using the ^{1}H NMR spectrum of the crude material was improved (11:1), although this was also downgraded upon purification to 4:1. However, the longer reaction time of 24 h. had not led to increased impurity formation, in contrast to the analogous reaction with $BF_3.OEt_2$. In an attempt to further moderate the reactivity of the system, $BF_3.SMe_2$ was substituted as the Lewis acid. No conversion to product was observed after 20 h., with a good mass recovery of aziridine **1a** obtained following work-up (entry 7). Finally, it was found that an increased quantity of BF_3.THF (1.5 eq.) led to the optimum isolated yield, 63% (entry 8). A diastereomeric ratio of 10:1 was observed by ^{1}H NMR analysis of the crude product, although none of the minor diastereomer was isolated on purification.

Table 21: The effect of Lewis acid



1a **97a** **major** **97b** **minor** *tentatively assigned*

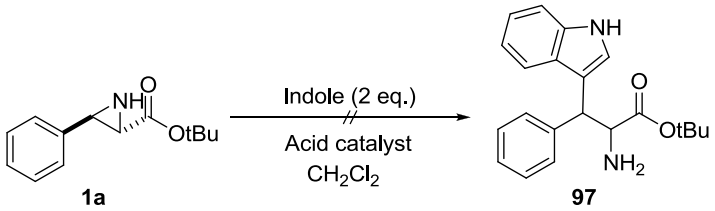
Entry	Lewis acid	Temperature (°C)	Time (h.)	^{1}H NMR conversion (%)[a]	dr[b]
1	-[c]	23	96	0	-[d]
2	$BF_3.OEt_2$	0 - 23	2	51 (44)	9:1
3[e]	$BF_3.OEt_2$	0 - 23	2	36	9:1
4	$InCl_3$	0 - 23	20	21	-[d]
5	$MgBr_2$	0 - 23	20	0	-[d]
6	BF_3.THF	0 - 23	24	86 (51)	11:1
7	$BF_3.SMe_2$	0 - 23	20	0	-[d]
8[f]	**BF_3.THF**	**0 - 23**	**24**	**87 (63)**	**10:1**[d]

All reactions performed on 0.11 mmol scale at [0.13 M]. [a] Conversion to **97a**, where applicable. Isolated yields in parentheses. [b] Diastereomeric ratio calculated using relative integrals in the ^{1}H NMR spectrum. [c] Lewis acid omitted. [d] No minor isomer observed. [e] Indole (1 eq.) used. [f] BF_3.THF (1.5 eq.) used.

It was noted that the BF_3.THF was mildly acidic (pH 3) on testing with pH paper, with the acidity presumably arising from the generation of HF on exposure of the reagent to atmospheric moisture. To establish whether the ring-opening was in fact acid catalysed, aziridine **1a** was treated with indole in the presence of BF_3.THF (0.5 equiv.) and Proton Sponge® (0.5 equiv.). Clean starting material was recovered in quantitative mass, upon work-up after 20 h. (**Table 22**, entry 1). It seemed likely that the

lack of degradation and conversion to product as observed by ^{1}H NMR and TLC analysis of the crude product was due to coordination of the boron reagent to the additive. To the same end, a range of acid catalysts were tested in place of the BF_3.THF. An excess (5 eq.) of the mild acid NH_4Cl did not provide any conversion to product by TLC analysis, at either r.t. or reflux, despite increased reaction times (entries 2 and 3). Additionally, stirring indole with aziridine **1a** in CH_2Cl_2 in the presence of silica gel (20 eq. w/w) provided a quantitative recovery of clean starting material upon filtration after 5 h. (entry 4). Camphor-sulfonic acid (CSA) was also chosen, owing to the poor nucleophilicity of the counter anion. No ring-opening was observed, although some degradation was seen by ^{1}H NMR analysis of the crude product (entry 5). Stronger acid catalysts bearing more nucleophilic counter-ions (AcOH, HCl) did provide conversion to the required product, although as mixtures with acetate and chloride ring-opened products (*vide infra*).

Table 22: Alternative catalysts for ring-opening with indole



1a **97**

Entry	Catalyst	Equivalents of catalyst	Time (h.)
1[a]	BF_3.THF	0.5	20
2[b]	NH_4Cl	5.0	40
3[c]	NH_4Cl	5.0	8
4	Silica gel	20.0[d]	5
5	CSA	0.2	40

All reactions performed on 0.11 mmol scale at [0.13 M] using indole (2 eq.). [a] Proton Sponge (0.5 eq.) added. [b] Performed at 23 °C. [c] Performed at reflux. [d] 20 eq. w/w.

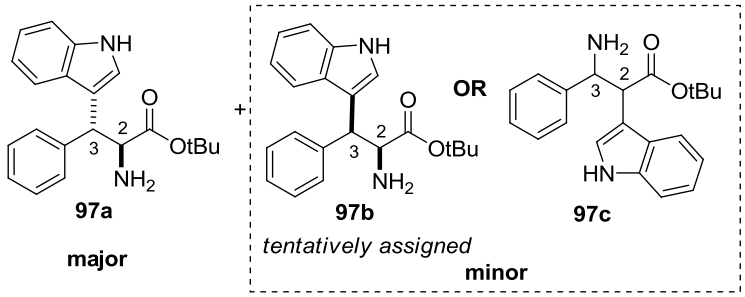
As none of the range of acids tested had provided either ring-opened product, further investigation into acid catalysis was halted. Having improved the yield of the major product of the ring-opening with indole from 7% to 63%, attention was turned to the identification of the minor product in the reaction.

Promoting formation of a minor product

The minor product had been tentatively assigned as the *syn*-diastereomer **97b**, resulting from borderline S_N2/S_N1 reactivity at C3 of the aziridine. Insufficient material had been obtained to collect characterisation data other than a ^{1}H NMR spectrum. The shifts of the C2- and C3-protons in the minor product were similar to those observed in the major product **97a** (**Table 23**), although it was very possible that product **97c**, arising from regioisomeric attack of the indole at C2, would present similar ^{1}H NMR shifts. Literature ^{1}H NMR data for compounds with comparable structures to the

regioisomer are not available. Thus, the aim was to promote the formation of the minor product, so that sufficient material could be isolated for full characterisation.

Table 23: ^{1}H NMR shifts in major and minor ring-opened products

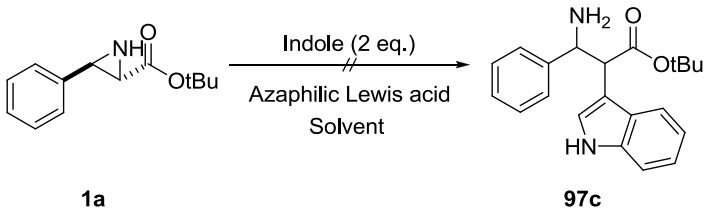


Proton	^{1}H NMR shift (ppm)[a]	
	Major	Minor
C2	4.17	4.07
C3	4.63	4.82

[a] Shift in $CDCl_3$

Initially several azaphilic Lewis acids were selected,[94] to test whether the regioselectivity of the ring-opening would be altered on their use in place of BF_3.THF. On stirring the aziridine with indole and the azaphilic Lewis acids, either complete degradation to unidentified products or clean recovered starting material was observed (**Table 24**). The lack of ring-opening observed in the presence of these catalysts prompted an alternative strategy to promote S_N1-like reactivity in the aziridination, and hopefully increase the formation of the minor product.

Table 24: 'Azaphilic' Lewis acids[94]

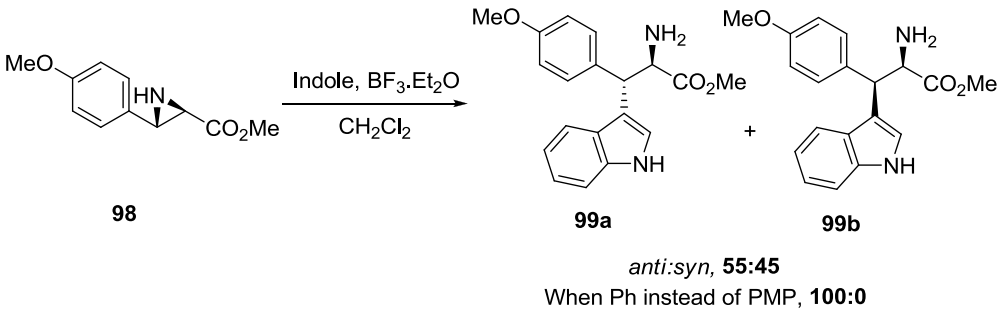


Entry	Lewis acid	Equivalents	Observations[a]
1	$Cu(OTf)_2$	0.5	-[b]
2	$CuCl_2$	0.5	R.S.M
3	$CuCl_2$	1.0	-[b]
4	CuCl	1.0	R.S.M
5	$CoCl_2$	0.5	-[b]

Reactions performed on 0.11 mmol scale in PhMe [0.13 M]. [a] Observations from analysis of crude reaction mixture by TLC and ^{1}H NMR. [b] Degradation to unidentified products.

As no ring-opening had been observed in this brief investigation, a second strategy was considered. An elegant experiment was reported by Letgers *et al.*, as part of investigation into the ring-opening chemistry of *NH*-aziridine-3-aryl-2-methyl esters with indole. Enantiopure PMP-derivative **98** was

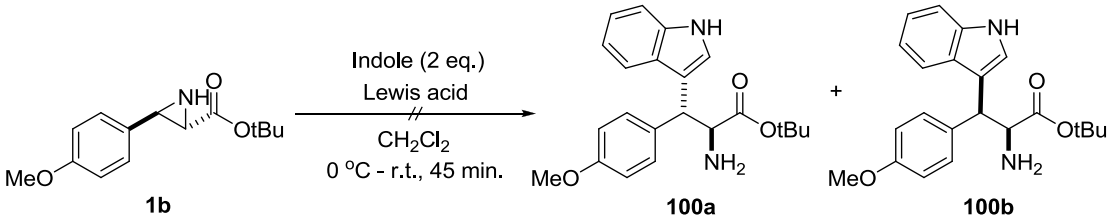
subjected to the reaction conditions, resulting in a mixture of C3 epimers **99a** and **99b**, whilst complete C3 inversion was observed with the corresponding phenyl-aziridine (**Scheme 59**). Electron donation from the *para*-methoxy group allowed stabilisation of positive charge build up at C3 during ring-opening, causing a change in mechanistic preference from S_N2-like to S_N1-like.[17]



Scheme 59: Diastereomeric ratios in Letgers' ring-opening with indole[17]

Taking a lead from Letgers, a batch of the required PMP-aziridine **1b** was prepared using the previously described chemistry (*vide supra*). Application of the literature conditions led to degradation of the starting aziridine to multiple unidentified products, as evidenced by ^{1}H NMR and TLC analysis of the crude reaction mixture.[95] As the *tert*-butyl ester analogues had proved sensitive to $BF_3.OEt_2$, the recently optimised conditions employing BF_3.THF were tested, using catalytic quantities of the boron reagent to minimise decomposition. Unfortunately, degradation of the aziridine to unidentified products was again observed, after a reaction time of 45 min. It was hypothesised that the increased electron-density of the PMP-aziridine caused increased reactivity of this substrate, and its observed incompatibility to the reaction conditions (**Table 25**).

Table 25: Attempting to promote an S_N1-like pathway



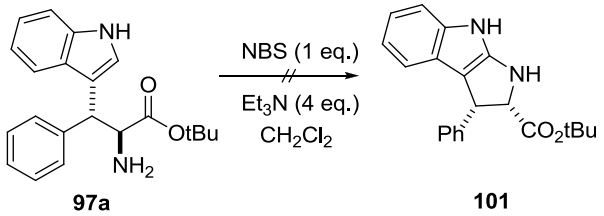
Entry	Lewis acid	Equivalents
1	$BF_3.OEt_2$	1.5
2[a]	BF_3.THF	0.5

All reactions performed on 0.11 mmol scale at [0.13 M]. [a] PhMe used as solvent

The chemistry of tryptophan 97a

As attempts to promote the formation of the minor product had been unsuccessful, it was decided not to pursue this avenue of research further, meaning that the minor product would remain uncharacterised and tentatively assigned. Instead, further reactivity of tryptophan **97a** was envisaged,

whereby electrophilic activation of the indole moiety followed by trapping with the free amine could lead to fused tricycle **101**. Cyclisation of a similar substrate in this manner is known in the literature, using *tert*-butyl hypochlorite as the electrophile.[7] In a preliminary experiment, NBS was used in a test reaction (**Scheme 60**). No conversion to product was observed by TLC analysis, after stirring tryptophan **97a** in the presence of NBS and Et_3N for 24 h. Subsequent heating to reflux for 4 h. did not cause any conversion of starting material. The lack of cyclisation could be attributed to interaction of the nucleophilic amine and NBS; the nitrogen nucleophile in the literature substrate was protected as an amide, a likely necessity in the presence of the strong electrophile.



97a **101**

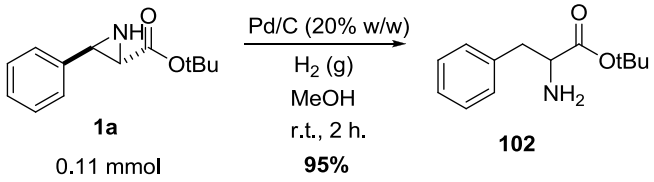
Scheme 60: Attempted tricycle formation

Following the unsuccessful formation of **101** from tryptophan derivative **97a**, it was decided to bring further experimentation surrounding the ring-opening with indole to a close. The ring-opening reaction had been significantly optimised, to provide a 63% yield of the tryptophan derivative **97a**, from an initial 7% using literature conditions. Full characterisation of a minor product arising from the reaction had not been possible. Alternative nucleophiles were next considered, to further probe the ring-opening susceptibility of aziridine **1a**.

1.3.4.2 Ring-opening with hydrogen

Hydrogenation of *N*-functionalised aziridines to the resulting amines is well documented in the literature.[96, 97] The regioselectivity of bond cleavage is dependent upon functionality at the aziridine carbon atoms; significantly weaker or less sterically encumbered CN- bonds can be hydrogenated selectively. A single example of hydrogenation of an *NH*-aziridine-2-carboxylate exists.[18] The substrate in question was a benzyl ester, thus hydrogenation yielded the free amino acid upon concomitant ring-opening and de-benzylation. If analogous ring-opening was observed with aziridine **1a** then the product would be isolated as the *tert*-butyl ester, with the advantage that this product would be easier to handle than the free amino acid isolated in the literature procedure.

Aziridine **1a** was treated with palladium on carbon under an atmosphere of hydrogen for 2 h., before filtration and work-up. Concentration of the organic phase provided pure phenylalanine *tert*-butyl ester **102** in 95% yield (**Scheme 61**). Hydrogenation of the benzylic CN- bond had occurred regioselectively, as evidenced by comparison with literature data for the product.

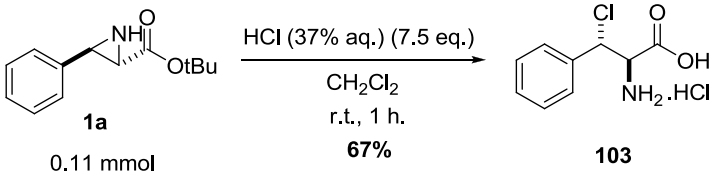


Scheme 61: Hydrogenation of aziridine 1a

The excellent selectivity and yield of the hydrogenation protocol meant that optimisation of the reaction was not required. Chloride was the next nucleophile of choice for the ring-opening of aziridine **1a**.

1.3.4.3 Ring-opening with chloride

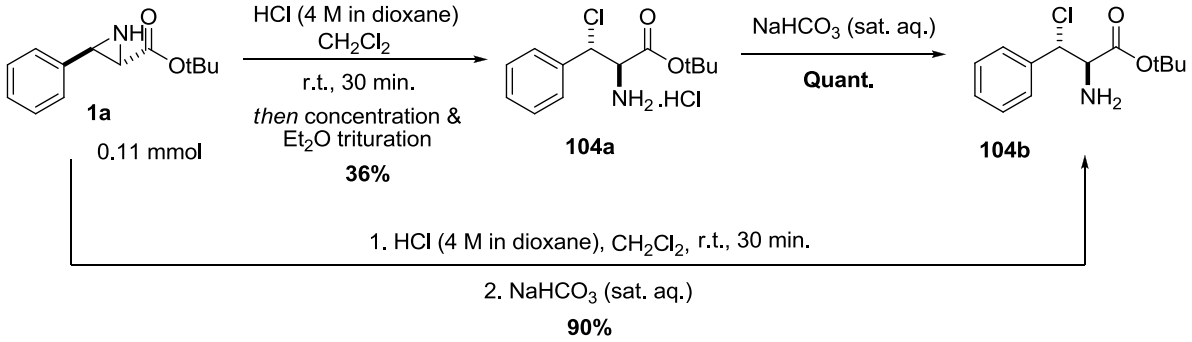
Chloride is a common nucleophile for the ring-opening of *N*-functionalised aziridines, but is less established for *NH*-aziridine-2-carboxylates. Only one example exists, and was neither accomplished regio- nor diastereoselectively.[17] Initially, aziridine **1a** was dissolved in CH_2Cl_2 and treated with an excess of HCl (37% aq.). After 20 min. at r.t. a white precipitate was seen forming, which was removed by filtration after 1 h. ^{1}H NMR analysis of the solid showed pure β-chloro phenylalanine **103**, isolated in 67% yield (**Scheme 62**). TLC analysis of the mother liquor showed no other products, confirmed by concentration of the phase *in vacuo*. It was presumed that the product had been isolated as the hydrochloride salt due to the complete insolubility of the product in CH_2Cl_2 and $CDCl_3$. No attempt was made to break the salt using a basic wash, owing to the likely difficult extraction of the free amino acid from an aqueous layer. Interestingly, analogous chemistry using HBr (48% aq.) resulted in the formation of a pale yellow precipitate, which showed significant degradation to unidentified products on ^{1}H NMR analysis.



Scheme 62: Ring-opening using HCl (37% aq.)

Following the observed cleavage of the *tert*-butyl ester using HCl (37% aq.), a milder source of HCl was proposed, reasoning that the *tert*-butyl ester might exhibit greater stability. Addition of commercial HCl in dioxane (4 M) to aziridine **1a** in CH_2Cl_2 resulted in complete consumption of starting material by TLC analysis after 30 min. Removal of volatiles *in vacuo* and ^{1}H NMR analysis of the crude reaction mixture revealed complete conversion to a single ring-opened product, with the *tert*-butyl ester intact. However, multiplets arising from unidentified by-products were observed in the ^{1}H NMR spectrum, between 3.60 and 3.85 ppm. Further investigation revealed that concentration of a portion of the commercial HCl in dioxane provided a residual oil that exhibited the same signals upon

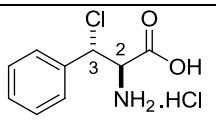
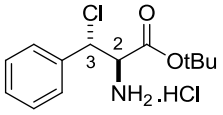
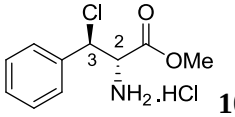
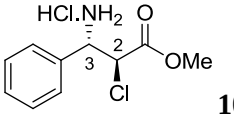
^{1}H NMR analysis. Thus, some polymerisation of dioxane in the presence of HCl was assumed, also observed in analyses of different batches of the reagent. Purification of an analytical sample of the ring-opened product was achieved *via* trituration from Et_2O in 36% yield, allowing its identification as β-chlorophenylalanine *tert*-butyl ester hydrochloride **104a** (**Scheme 63**). Evidence that the product had been isolated as the hydrochloride salt included an R*f* of 0.0 in EtOAc/MeOH (5%), and poor solubility of the product in common organic solvents (including $CDCl_3$ and Et_2O). This was confirmed on washing a CH_2Cl_2 solution of **104a** with $NaHCO_3$ (sat. aq.). Separation and concentration of the organic phase resulted in pure β-chlorophenylalanine *tert*-butyl ester **104b** (**Scheme 63**), bearing considerably different shifts on ^{1}H NMR analysis to the hydrochloride salt, and an R*f* of 0.8 in EtOAc/MeOH (5%). Gratifyingly, it was found that the aqueous bicarbonate wash was sufficient to remove the polymeric dioxane impurity, without necessity for trituration of the crude hydrochloride salt **104a** from Et_2O. As a result, inclusion of a bicarbonate wash in the work-up procedure following treatment of the aziridine with HCl in dioxane, provided β-chlorophenylalanine *tert*-butyl ester **104b** in 90% yield from aziridine **1a** (**Scheme 63**).



Scheme 63: Access to β-chlorophenylalanine derivatives

A single product was observed in the crude material of each reaction, following the ring-opening of aziridine **1a** with both HCl (37%) and HCl (4 M in dioxane). This suggested that an S_N2-like mechanism was in operation, and led to the assignment of **103**, **104a** and **104b** as the *anti*-diastereomers. Regiochemistry was assigned by comparison to known literature compounds (**Table 26**). The methyl ester analogue of **104a**, compound **105a** (entry 3) has been prepared as a 10:1 mixture with its regioisomer **105b**, allowing comparison with the ^{1}H NMR shifts of **104a** (entry 2). The C2-proton in *tert*-butyl ester **104a** exhibits a very similar shift (4.55 ppm) to the analogous proton in the methyl-ester **105a** (4.62 ppm). The C2-proton in regioisomer **105b** is deshielded by comparison, as demonstrated by the considerable downfield shift at 4.95 ppm. Similarly, a downfield shift is observed for the C3-protons in **104a** and **105a** (5.90 and 5.75 ppm respectively) in comparison to the analogous proton in **105b** (5.50 ppm). The regiochemistry of amino acid **103** was assigned similarly; values of 4.54 and 5.81 ppm were observed for the C2- and C3-protons respectively, comparable with analogues **104a** and **105a**.

Table 26: Regiochemical assignment of compounds 103 and 104a

Entry	Compound	^{1}H NMR shift (ppm)[a]	
		C3-proton	C2-proton
1	 **103**	5.81	4.54
2	 **104a**	5.90	4.55
3[17]	 **105a**	5.75	4.62
4[17]	 **105b**	5.50	4.95

[a] Values in d_6-DMSO. **105a** and **105b** synthesised as single enantiomers.

With good yields obtained for the synthesis of the β-chloro compounds **103**, **104a** and **104b**, ring-opening with oxygen-based nucleophiles became the new investigative target. Acetic acid is the only oxygen-based nucleophile known to ring-open *NH*-aziridine-2-carboxylates, with two reports provided by separate groups.[17, 18] As such, acetic acid was selected initially to establish precedent for the ring-opening of aziridine **1a** with oxygen-based nucleophiles.

1.3.4.4 Ring-opening with oxygen-based nucleophiles

Acetic acid

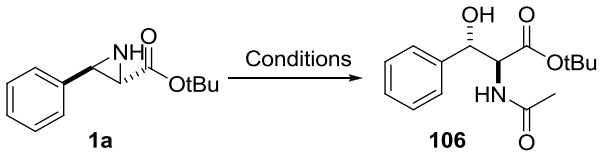
Analogous conditions are used in the two prior literature reports,[17, 18] and so these were applied to aziridine **1a**. The substrate was heated to 70 °C in AcOH, before concentration of the reaction mixture *in vacuo*. Addition of $NaHCO_3$ (sat. aq.) and extraction with CH_2Cl_2 provided the *N*-acylated derivative **106** as a single product by ^{1}H NMR analysis, in 88% yield (**Table 27**, entry 1). Acyl-group transfer from *O*- to *N*- (which had also been observed in both literature reports) was evidenced by:

(a) The amide stretch in the IR spectrum (1655 cm^{-1})
(b) Two broad signals in the ^{1}H NMR spectrum at 6.42 and 3.90 ppm, corresponding to the NH and OH protons respectively.

Despite the good yield, a brief optimisation study was carried out (**Table 27**), to try to circumvent the use of acetic acid as solvent. Aziridine **1a** was dissolved in MeCN and treated with a stoichiometric quantity (10 eq.) of AcOH at 70 °C. Only a 10% conversion to **106** was observed by ^{1}H NMR analysis upon work-up after 20 h. (entry 3). Reasoning that the more nucleophilic NaOAc might provide a better conversion, an analogous reaction was performed, using this reagent with 15-crown-5 (entry 4). However, no conversion to product was seen by ^{1}H NMR analysis after 2 h. at 70 °C; the same was

true of reactions performed with NaOAc in EtOH and H_2O (entries 5 and 6). It seemed that use of the acetic acid as solvent was necessary for good conversions to **106**, and so efforts were channelled into decreasing the temperature of the reaction. Although conversion to **106** was observed, the rate of reaction appeared to decrease considerably with decreasing temperature (entries 7 and 8). Given the good initial yield of 88%, further investigation was ceased.

Table 27: Attempted optimisation of acetate ring-opening



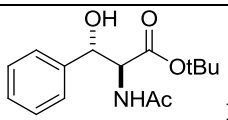
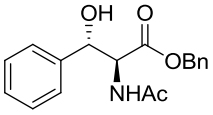
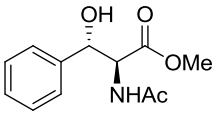
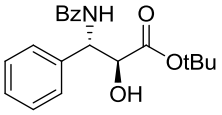
1a **106**

Entry	Solvent	Temperature (°C)	Time (h)	^{1}H NMR conversion (%)[a]
1	**AcOH**	**70**	**1.0**[b]	**100 (88)**
2	AcOH	70	1.5	100 (79)
3[c]	MeCN	70	20	10
4[d]	MeCN	70	2.0	0
5[d]	EtOH	70	5.0	0
6[d]	H_2O	70	5.0	0
7	AcOH	16	20.0	50
8	AcOH	50	5.0	40

All reactions performed on 0.11 mmol scale at [0.06 M]. Isolated yields in parentheses. [a] By relative integration of *tert*-butyl singlet in starting material and product. [b] Followed by an additional 16 h. at r.t. [c] AcOH (10 eq.) used. [d] NaOAc (10 eq.) and 15-crown-5 (10 eq.) used.

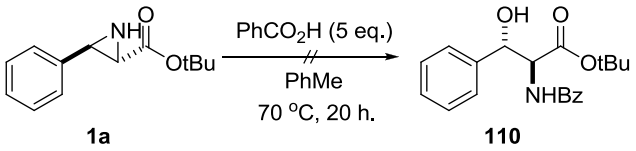
Once again, as a single product had been observed in by ^{1}H NMR analysis of the crude reaction mixture, S_N2-like reactivity was concluded, and a corresponding *anti*- relationship between the incoming nucleophile and amine leaving group. The regiochemistry was assigned by correlation with the benzyl and methyl ester analogues **107** and **108** (**Table 28**, entries 2 and 3). Additionally, comparison with regioisomeric analogue **109** showed a considerable difference in shift for the C2- and C3-protons.

Table 28: Regiochemical assignment of product 106

Entry	Compound	^{1}H NMR shift (ppm)[a]	
		C3-proton	C2-proton
1	 **106**	5.26	4.90
2[18]	 **107**	5.21	5.03
3[17]	 **108**	5.25	5.01
4[98]	 **109**	5.57	4.58

[a]Values in $CDCl_3$. Products **107**, **108** and **109** synthesised as single enantiomers.

Considering that benzoic acid has a similar pKa to acetic acid, it was suggested that this might be a suitable oxygen-based nucleophile for ring-opening. However, a test reaction employing 5 eq. of the reagent, and heating to 70 °C in toluene, provided recovered starting material after 20 h. (**Scheme 64**).



1a **110**

Scheme 64: Attempted ring-opening with benzoic acid

Alcohols

The ring-opening of *NH*-aziridine-2-carboxylates with alcohols is unexplored. If successful, such chemistry would provide access to *O*-functionalised 1,2-amino alcohols, synthetically useful intermediates whose *O*-functionality can either be removed or elaborated dependent upon synthetic requirements. Methanol was selected as an initial nucleophile owing to ready availability.

Methanol

Encouraged by the success of Brønsted acid catalysis in previous ring-openings, aziridine **1a** was treated with a solution of methanolic HCl (2 M), synthesised *in situ* from AcCl, in order to omit nucleophilic water. After 1 h., complete consumption of aziridine **1a** was noted by TLC analysis of the reaction mixture. On removal of volatiles *in vacuo* and analysis of the resulting oil using ^{1}H NMR, complete conversion to the chloride ring-opened product **103a** was observed. Decreasing the

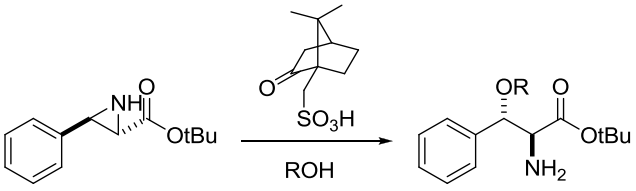
concentration of the methanolic HCl (0.5 M) led to mixtures of chloride- and methoxy-ring-opened products according to ^{1}H NMR analysis of the crude product, along with unreacted aziridine **1a**.

It was clear that suppressing the nucleophilicity of chloride sufficiently so as to provide the methoxy-ring-opened product selectively would be difficult. Consequently, camphor-sulfonic acid (CSA), which bears a poorly nucleophilic counter anion, was selected as an alternative catalyst. Initially, a 2 M solution of CSA in methanol was prepared and used to treat aziridine **1a**. Basic work-up after 1.5 h., followed by chromatographic purification allowed isolation of the methoxy-ring-opened product **111** in 49% yield (**Table 29**, entry 1). No other products had been observed by analysis of ^{1}H NMR or the crude reaction mixture, although starting aziridine remained, in a 1:2 ratio with compound **111**. Reasoning that a longer reaction time might allow complete conversion of aziridine **1a**, a second experiment using a stoichiometric quantity (5 eq.) of CSA was set up, and monitored by TLC analysis, until disappearance of starting material was observed (6 h.). Work-up and concentration of the organic phase *in vacuo* provided pure compound **111** in quantitative yield (entry 2). Further experimentation revealed that 1 equiv. of CSA was sufficient to provide the product quantitatively after an identical reaction time (entry 3). An endeavour to use methanol stoichiometrically (5 eq.) resulted in a low (30%) conversion to compound **111** after 20 h. (entry 4), with the remaining material identified as unreacted aziridine by ^{1}H NMR analysis of the crude reaction material.

Benzyl and allyl alcohols

With methanol used successfully as a nucleophile in the ring-opening chemistry, similar methodology was applied using allyl- and benzyl- alcohols. It was found that an increased stoichiometry of CSA (2.5 eq.) and a longer reaction time (20 h.) with each alcohol as solvent provided complete conversion to the ring-opened products. Chromatographic purification was called for in each case to remove minimal quantities of unidentified degradation products, although no regio- or diastereomers were present by ^{1}H NMR analysis of the crude products. It should be noted that the lower isolated yields observed for ring-opening with allyl and benzyl alcohols (57 and 46% respectively, (**Table 29** entries 5 and 6) are un-optimised. Loss of material possibly occurred in the work-up procedures in each case, which involved multiple aqueous washes for complete removal of the polar alcoholic solvents. Optimisation would likely allow greatly improved yields in these reactions. Furthermore, these two products bear useful functionalities. The allyl group in **112** could potentially serve as a functional handle in a synthetic strategy. *O*-Benzylated **113** would allow access to the free amino alcohol on deprotection, and further, bears orthogonal protection to the *N*-acylated derivative **106** discussed previously.

Table 29: Ring-opening with alcoholic nucleophiles



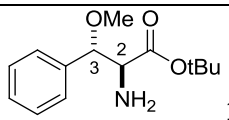
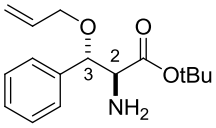
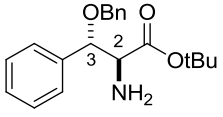
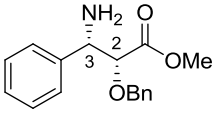
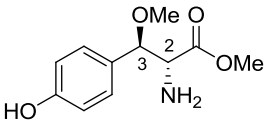
1a 111-113

Entry	R=	CSA (eq.)	Time (h.)	Product	Isolated yield (%)
1[a]	Me	2 M solution	1.5	**111**	49
2	Me	5.0	6.0	**111**	Quant.[b]
3	Me	1.0	6.0	**111**	Quant.[b]
4[c]	Me	1.0	20.0	**111**	(30)
5	$H_2C=CHH_2$	2.5	20.0	**112**	57
6	Bn	2.5	20.0	**113**	46

All reactions performed on 0.11 mmol scale in ROH at [0.11 M]. ^{1}H NMR conversion in parentheses. [a] Performed at [0.06]. [b] Purification not required. [c] Reaction performed in CH_2Cl_2 using MeOH (5 eq.).

The complete stereoselectivity of the alcoholic ring-openings allowed assignment of compounds **111**, **112** and **113** as the *anti*-products, arising from an S_N2-like mechanism. Comparison of benzylated **113** with regioisomeric analogue **114** showed a considerable difference in shifts (*ca.* 0.30 ppm) for both the C2- and C3-protons (**Table 30**, entries 3 and 4). Similarly, inspection of these signals in regio-analogous methoxy-compounds **111** and **115** revealed only a small difference in shift values between the two compounds. Indeed, careful analysis of the ^{1}H NMR spectra of compounds **111**, **112** and **113** provided further confirmation that the assignments of signals corresponding to the C2- and C3-protons had been made correctly, and the products had arisen from attack at C3. The shifts of the C2-protons differ only slightly (by 0.06 ppm) across the series, owing to their similar chemical environments (entries 1-3). The C3-protons exhibit greater variance in shift values (0.22 ppm), with the shift to downfield ppm exaggerated with increasing inductive effect of the *O*-alkyl group.

Table 30: Regioisomeric assignments of compounds 111, 112 and 113

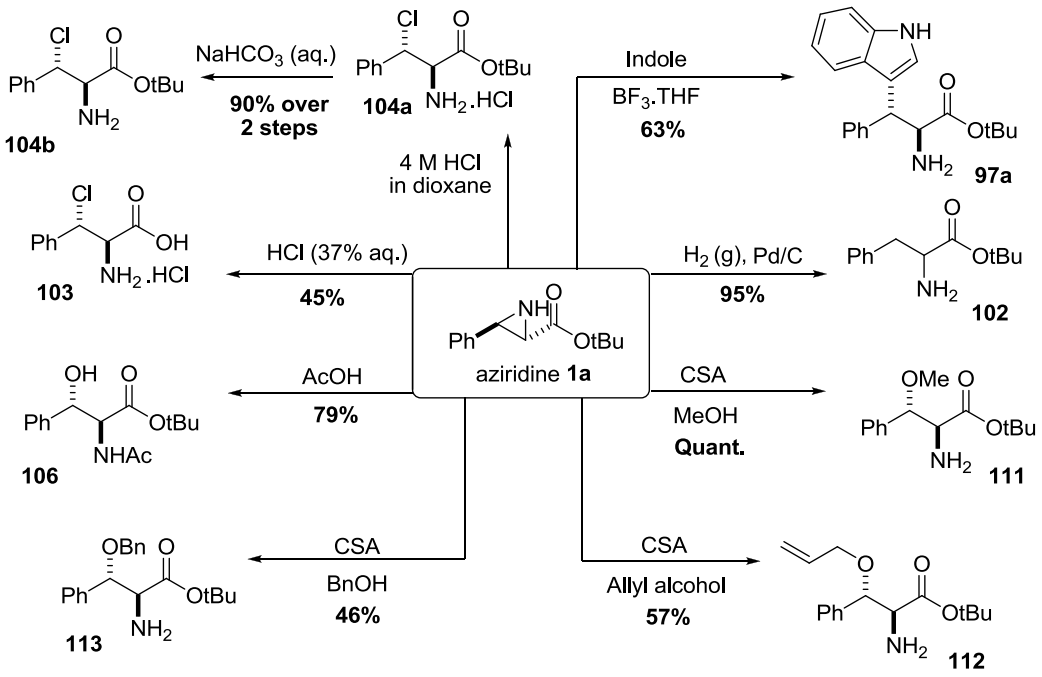
Entry	Compound	^{1}H NMR shift (ppm)[a]	
		C3-proton	C2-proton
1	 **111**	4.39	3.67
2	 **112**	4.52	3.66
3	 **113**	4.61	3.72
4[99]	 **114**	4.32	4.06
5[100]	 **115**	4.31	3.64

[a]Values in $CDCl_3$. Products **114** and **115** synthesised as single enantiomers.

1.4 Conclusions

Stereoselective ring-opening of aziridine **1a** had been observed with all the nucleophiles tested (**Scheme 65**). Despite the lack of an *N*-activating group, complete consumption of aziridine **1a** had been observed in all cases, following relatively short reaction times (<20 h.). Moreover, the majority of reactions had occurred at r.t., further exemplifying the susceptibility of aziridine **1a** to nucleophiles. Ring-opening with indole showcased an interesting carbon-carbon bond forming methodology. The novel openings with alcoholic nucleophiles yielded *O*-alkyl amino alcohols, presenting the possibility of selecting appropriate alkyl functionality for a given synthesis. Compound **113** in particular bears orthogonal protection to product **106**; such simple access to orthogonally protected compounds is an attractive feature of the methodology. Appropriate choice of chloride source was shown to provide β-chloro phenylalanine derivatives, with or without the *tert*-butyl ester intact.

The range of examples proves the susceptibility of aziridine **1a** to nucleophilic ring-opening (**Scheme 65**). Although further scope was not examined in this study, it seems likely that similar products could be accessed using alternative nucleophiles under Lewis or Brønsted acid activation of the aziridine.

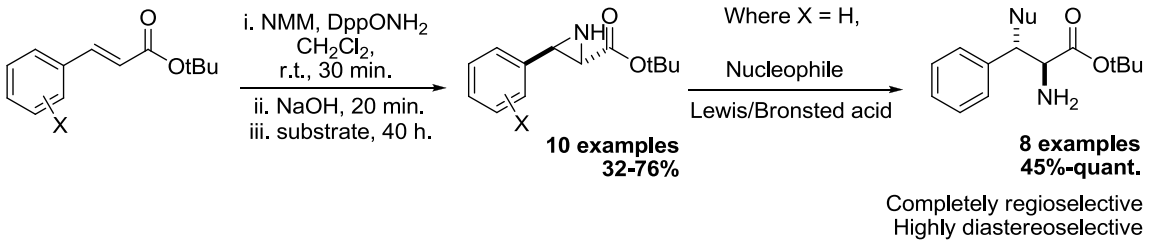


Scheme 65: Ring-opening compounds of aziridine 1a

To conclude part one of this thesis, it has been possible to access amino acid derivatives in two steps from readily available starting materials, from the ring-opening of *NH*-aziridine-2-carboxylates derived from enoates (**Scheme 66**).[101] Although the aziridination of some *tert*-butyl cinnamates proceeds in moderate yield, the chemistry is competitive with current multi-step protocols, owing to:

a) the direct aziridination methodology employed
b) the lack of necessity for deprotection of the amino-acid derivative.

The aziridination is currently limited in scope although more work can be carried out here, for example, investigating the potential for β-alkyl *tert*-butyl enoates as substrates. The high susceptibility to ring-opening of an *NH*-aziridine-2-carboxylate has been demonstrated; other nucleophiles and aziridine substrates could be tested here to further increase the scope of the chemistry.



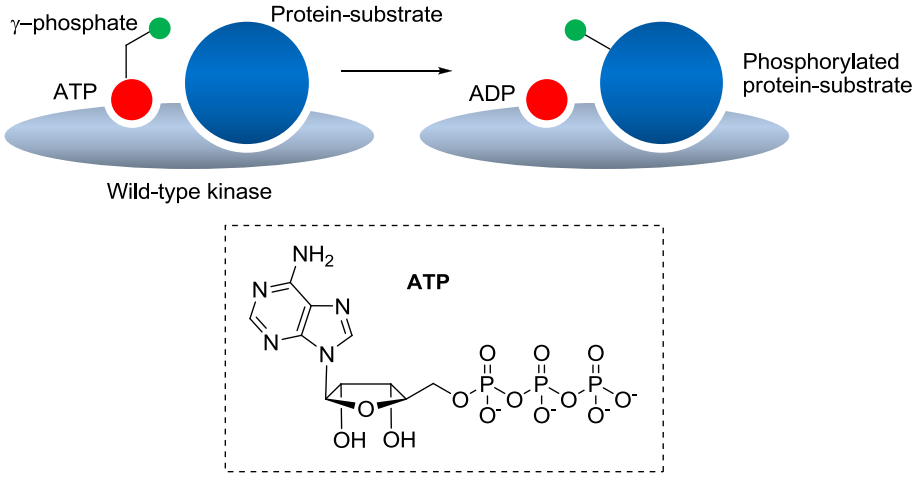
Scheme 66: Amino acid derivatives in two steps from readily available starting materials

2. Novel Pyrazolo[3,4-*d*]pyrimidines for Kinase-substrate Identification

2.1 Introduction

2.1.1 A novel method for kinase protein-substrate identification

Kinases are enzymes that regulate protein-phosphorylation, a post-translational protein modification that is fundamental in cell signalling pathways. Kinases bind ATP and a protein-substrate in two spatially adjacent surface binding pockets, in order that the ATP can transfer its γ-phosphate to a residue of the protein-substrate (**Scheme 67**). In eukaryotic cells, serine/threonine residues are most commonly phosphorylated, accounting for 97-98% of all phosphorylation.[102]

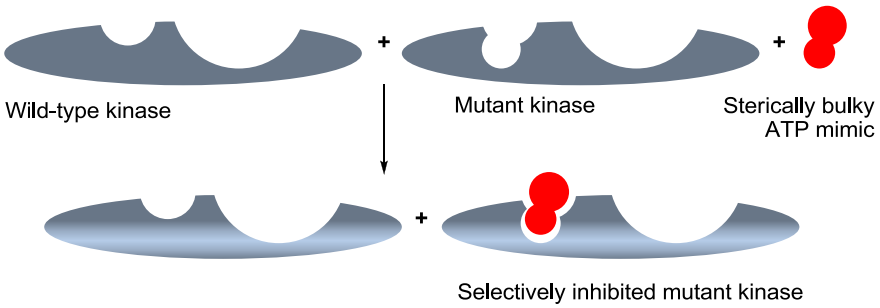


Scheme 67: Kinase-templated protein phosphorylation

There are 518 identified human kinases, collectively known as the kinome, each with a specific set of protein-substrates. Approaches to identify kinase protein-substrate sets *in vitro* include library-based methods[103, 104] and methods to exploit the physical association between the kinase and its protein-substrate, for example using affinity chromatography.[105] Substrate determination *in vivo* is more challenging, with the majority of methods involving the exclusion of kinase activity from the cell system. Genetic modification can be used for 'knock-out' experiments,[106] where the function of wild-type and modified cells are compared to identify pathways the kinase is involved in. However, this approach is inapplicable to kinases that are essential for survival. Small molecule inhibition is attractive, although most kinase inhibitors are ATP competitive. The highly conserved shape of the ATP binding site across the kinome means that these strategies suffer from poor selectivity. Consequently, a selective method to identify kinase protein-substrate sets that is applicable *in vivo* is desired. This would allow further understanding of cell cycle processes, leading, for example, to the development of new treatments for cellular disease.

It is possible to address the selectivity issue arising from small-molecule inhibition *via* a steric complementation approach known as 'bump-hole inhibition'. This involves mutating a kinase of

interest to have an enlarged ATP binding site, by reducing the size of the 'gate-keeper' residue. Incubation with a sterically bulky ATP mimic results in the selective targeting of this mutant kinase in the presence of wild-type kinases (**Scheme 68**).



Scheme 68: Selectivity *via* steric complementation: Bump-hole inhibition

Shokat has used the bump-hole approach to target protein tyrosine kinase v-Src.[107] An alkyl group was installed at *N4* of ATP, to act as the 'bump' (**Fig. 8**). *N4*-(Cyclopentyl) and *N4*-(benzyl) were found to exhibit particularly high affinity for mutant v-Src (V323A, I338A) in the presence of its wild-type. However, the method was not applicable *in vivo* owing to the triphosphate rendering the ATP derivatives cell-impermeable. Further development of the methodology by Shokat led to the identification of the C3-substituted pyrazolo[3,4-*d*]pyrimidine scaffold, as an alternative to the first-generation ATP-derivatives (**Fig. 8**).[108, 109] Compounds based on the pyrazolo[3,4-*d*]pyrimidine scaffold have been used with success as ATP mimics in other methodologies.[110, 111] The C3-substituent is the 'bump' in Shokat's inhibitors, with several C3-aryl pyrazolo[3,4-*d*]pyrimidines **116** identified as particularly potent inhibitors of mutant tyrosine-kinases. An advantage of the bump-hole strategy is that it has the potential to be applied to a wide range of kinases, as long as the mutant form is accessible.

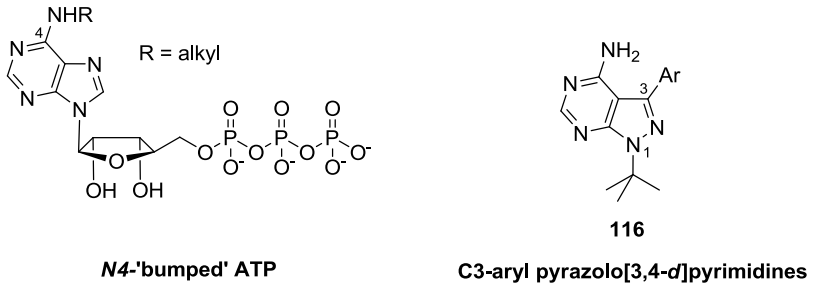


Fig. 8: Shokat's compounds for kinase 'bump-hole' inhibition

Following Shokat's seminal work, work in our laboratories resulted in the design of compounds **2** (**Fig. 9**), based on the pyrazolo[3,4-*d*]pyrimidine scaffold, that would utilise the bump-hole inhibition methodology to label the protein-substrate of a kinase of interest. The work specifically targeted PKC*α*, a tyrosine-kinase involved in the regulation of gene expression, cell migration and cell growth

and regulation. The protein-substrates of PKCα are known, making it a suitable substrate for initial investigation and proof of concept. Mutant PKCα (M417A) was generated, and was shown to retain its phosphorylation activity. *N1-tert*-Butyl analogues **116** (**Fig. 8**) were then synthesised, to identify the optimum C3-aryl group for inhibition of PKCα (M417A). Six C3-aryl pyrazolo[3,4-*d*]pyrimidines were identified with IC_{50} values in the nanomolar range. These six scaffolds would be further elaborated with a cross-linker, necessary for covalent cross-linking to the kinase protein-substrate (**Fig. 9**).[112]

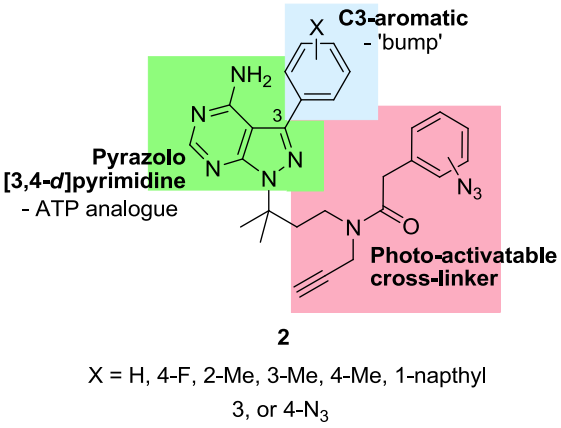
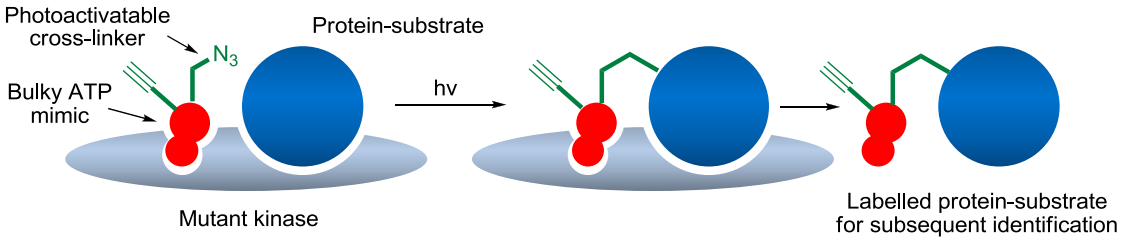


Fig. 9: Target compounds 2 for kinase protein-substrate identification

It is hoped that following selective binding of the C3-aryl pyrazolo[3,4-*d*]pyrimidine unit of **2** to the ATP-site of the mutant kinase of interest, the cross-linker will be held in the correct orientation to bind with the docked protein-substrate. The azide is key to this methodology; application of UV light transforms the functionality into a reactive nitrene precursor necessary for cross-linking. Once labelled, the alkyne would provide a functional handle for the attachment of a biotin molecule and/or a fluorophore, allowing separation and identification of the labelled protein-substrate (**Scheme 69**).

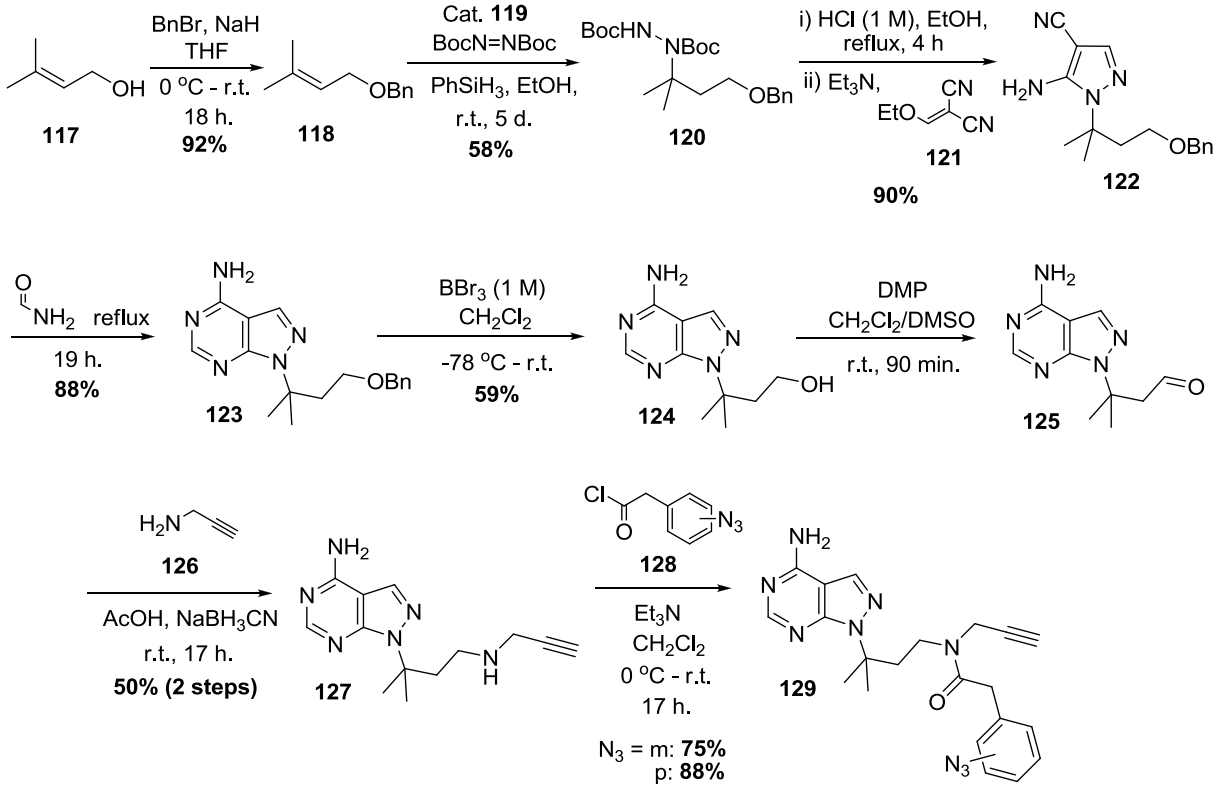


Scheme 69: A novel kinase protein-substrate identification strategy

This technique is novel, in that it combines two previously recognised methodologies, bump-hole inhibition and photoactivatable cross-linking for kinase protein-substrate identification. Considerable research went towards the design of compounds **2** for these purposes; for a full account, the reader is directed towards the relevant thesis.[112]

2.1.2 Synthesis of C3-unfunctionalised pyrazolo[3,4-d]pyrimidines

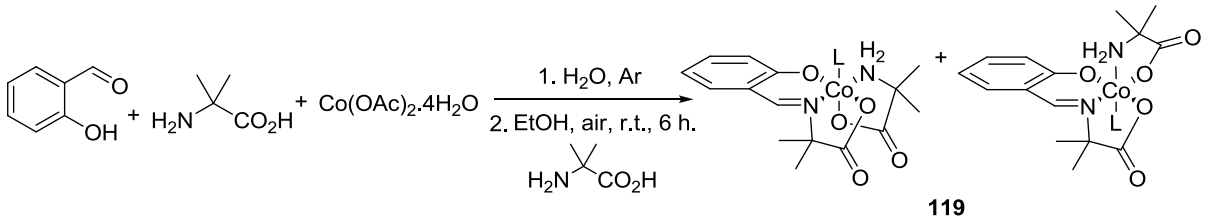
One of the key synthetic challenges was the development of methodology to incorporate the α-*tert*-alkyl amine cross-linker side-chain. A synthetic route to access the C3-hydro analogues **129** lacking the C3-aryl functionality had previously been developed (**Scheme 70**), in order to test whether cross-linking to substrates of wild-type PKCα could be successfully achieved. Synthesis began with benzylation of prenyl alcohol (**117**) in 92% yield, followed by the installation of the α-*tert*-amine functionality, using a hydrohydrazination procedure to give **120**.[113] Acidic hydrolysis followed by condensation with enol ether **121** provided pyrazole **122** in 90%. Treatment of **122** with formamide established the pyrazolo[3,4-*d*]pyrimidine core, and the resulting product **123** was de-benzylated and oxidised to give aldehyde **125**. Crude **125** underwent reductive amination, to install the terminal alkyne in 50% yield over two steps. A final amidation step was used to install the aryl azide functionality; the synthesis diverged at this step, with the coupling of two regioisomeric aryl azides, as the optimum position of the azide motif for cross linking (*meta* or *para*) was not known. Inhibition of PKCα was observed with both regioisomers of **129** (100 μM, 30-50%). However, upon incubation and photolysis of the compounds with PKCα, no labelling was observed. It was suggested that the lack of labelling may be due to the low affinity of the C3-hydro derivatives for the wild-type kinase. Indeed, it was shown in the *N1*-*tert*-butyl series that C3-aryl 'bumped' inhibitors and mutant kinase pairs bind with higher affinity than C3-unsubstituted inhibitors do with the wild-type kinase.[112] As a result, the synthesis of the C3-aryl substituted compounds was required for continued investigation.



Scheme 70: Access to C3-hydro pyrazolo[3,4-*d*]pyrimidines 129 with cross linker[112]

2.2 Project aims

In the *N-tert*-butyl series **116** (**Fig. 8**), an efficient synthesis allowing late-stage introduction of the C3-aryl had been developed, using halogenation and subsequent arylation. However, halogentation at C3 of **123** (**Scheme 70**) had not proved possible, so the strategy could not be used to access the C3-aryl target compounds.[112] Further to this, the synthetic route also required optimisation at the key α-*tert* hydrazine forming step. The hydrohydrazination procedure used was lengthy and capricious, and required initial synthesis of cobalt catalyst **119** whose purity is difficult to determine (**Scheme 71**). A more robust synthesis was sought in order to carry sufficient material through the remaining steps of the linear synthesis.



Scheme 71: Synthesis of cobalt catalyst 119[113]

Presented with these two synthetic problems, the aims of the project were clear:

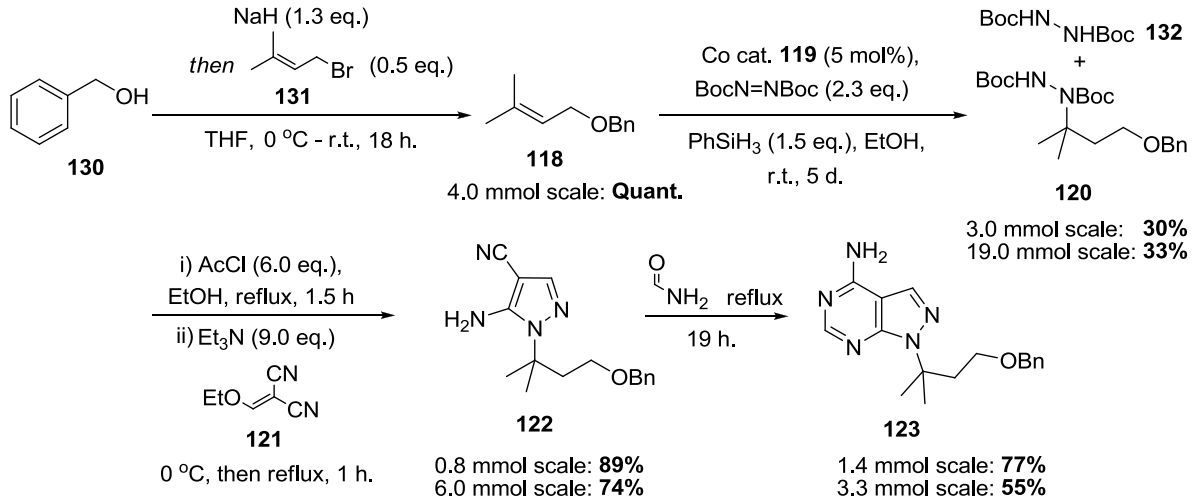
1. To develop a synthetic strategy to C3-aryl pyrazolo[3,4,*d*]pyrimidines **2**
2. To avoid the hydrohydrazination step *en route* to the pyrazolo[3,4,*d*]pyrimidine core of **129**.

2.3 Results and discussion

2.3.1 Synthesis of pyrazolo[3,4,d]pyrimidine 123

As a start point, it was decided to investigate CH activation methodologies for the C3-aryl functionalisation of pyrazolo[3,4-*d*]pyrimidine **123**. Recent literature documenting the direct-CH-activation of heteroaromatics suggested that direct arylation at C3 of **123** could be possible. Although the C3 is regarded to be the least 'activated' of the pyrazole carbon atoms with respect to CH-activation,[114] examples are known (*vide infra*). Additionally, pyrazole **123** bears functionality at all positions aside from C3, thus arylation is only possible at the desired position.

Accordingly, the developed route (**Scheme 70**) was followed to bring through material. Initial benzylation of prenyl alcohol led to variable yields of compound **118**, and the isolated product was contaminated with inseparable impurities, arising from the degradation of benzyl bromide on silica. As the first intermediate in the route, the purity of **118** was considered important, and following brief optimisation, reaction of prenyl bromide and benzyl alcohol in the presence of NaH provided pure **118** in quantitative yield (**Scheme 72**).[115] The hydrohydrazination step led to disappointing yields of **120** on both 3 and 19 mmol scales. In addition, a large quantity (52%) of di-*tert*-butyl hydrazodiformate **132** was isolated on 19 mmol scale (and observed by TLC on 3 mmol scale), proving that reduction of the diazo-compound was occurring at a faster rate than amination. Gratifyingly, pyrazole formation was facile, proceeding to **122** in reproducible yield on small and moderate scales. Finally, reflux of **122** in formamide led to **123** in good yield, providing high purity formamide was used (**Scheme 72**).



Scheme 72: Synthesis of pyrazolo[3,4-*d*]pyrimidine 123 using reported chemistry

Due to the low-yielding hydrohydrazination step, an insufficient quantity of pyrazolo[3,4-*d*]pyrimidine **123** had been accessed for rigorous testing of CH-activation conditions.

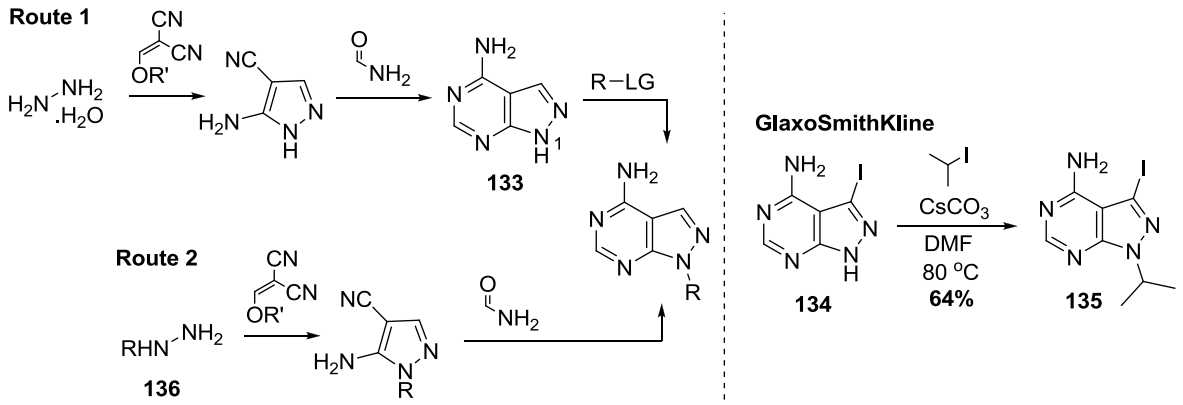
Given this, it was considered prudent to first re-examine the synthetic strategy, to provide the derivative in higher yield.

2.3.1.1 Strategies to N-tert-alkyl pyrazolo[3,4-d]pyrimidines

Despite the widespread use of the pyrazolo[3,4-*d*]pyrimidine motif as an ATP mimic, *N*-substituted α-*tert*-alkyl pyrazolo[3,4-*d*]pyrimidines are unknown in the literature, aside from *N*-*tert*-butyl derivatives. The dearth of other *N*-*tert*-alkyl derivatives can be attributed to the difficulty in synthesising the structures.

The two most commonly used synthetic methods used to access *N*-alkyl-pyrazolo[3,4-*d*]pyrimidines are not applicable for varied *tert*-alkyl derivatives. The first method involves the initial synthesis of an *N1*-unfunctionalised pyrazolo[3,4-*d*]pyrimidine **133** (**Scheme 73**). *N*-Alkyl functionality is then established using S_N2 chemistry, so access to a wide variety of *N*-primary and *N*-secondary substituents is possible, but *N*-tertiary alkylation cannot be accomplished (**Scheme 73**). Researchers in Washington State recently used this method to access a range of *N*-alkyl pyrazolo[3,4,*d*]pyrimidines as kinase inhibitors for the parasite *Toxoplasma gondii.* Twenty one mesyl-alcohols were synthesised and reacted with *N*-unfunctionalised pyrazolo[3,4-*d*]pyrimidines.[116] Such chemistry was also exemplified by GlaxoSmithKline in their synthesis of inhibitors of the PERK enzyme, which has been identified as a potential drug target in the treatment of cellular disease. *N*-Unfunctionalised pyrazolo[3,4-*d*]pyrimidine **134** was treated with 2-iodopropane and $CsCO_3$ in DMF at 80 °C, to yield the C3-iodo *N*-isopropyl compound **135**, which was subjected to derivatisation at C3 (**Scheme 73**).[117]

The second widely used method to access *N*-alkyl pyrazolo[3,4-*d*]pyrimidines involves an *N*-alkyl hydrazine **136** in the initial pyrazole-forming step (**Scheme 73**). Simple, commercially available *N*-alkyl hydrazines are often reaction partners, owing to the desire to avoid expensive reagents at the initial step. However, the methodology presents an opportunity to install elaborate *N*-*tert*-alkyl functionality if required. This is limited in practise, due to the difficult synthesis of *N*-*tert*-alkyl hydrazines. The functional group has previously been accessed using S_N1 chemistry from the parent *tert*-halo or *tert*-alcohol compounds,[118, 119] although yields are often low, and the strongly acidic conditions allow for limited alkyl functionality.



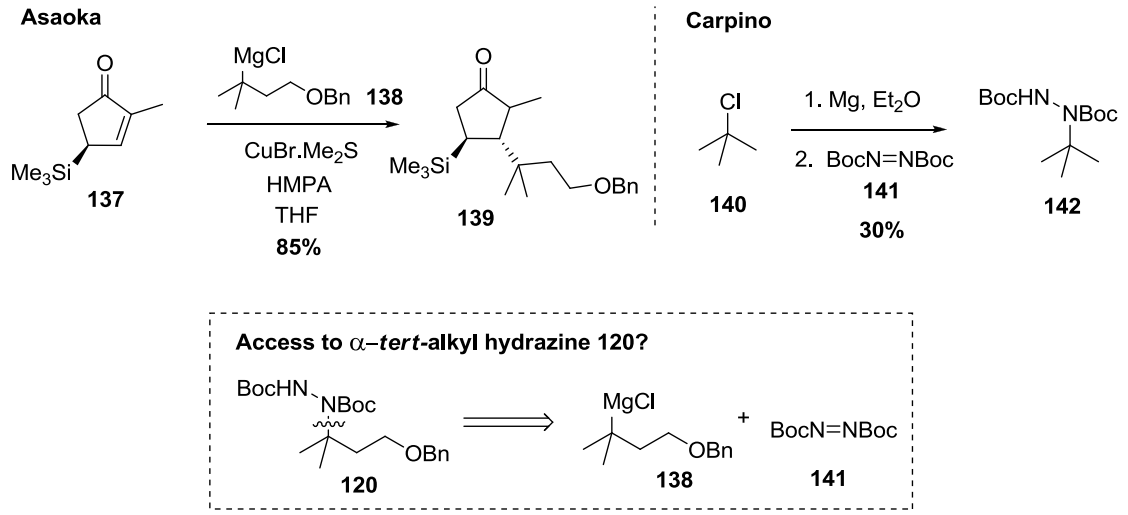
Scheme 73: Synthetic routes to *N*-alkyl pyrazolo[3,4-*d*]pyrimidines

Development of a more compatible synthetic strategy is clearly required, so that elaborate *tert*-alkyl hydrazines can be more readily accessed. Notwithstanding use of the methodology in the project discussed herein, this would allow for the synthesis of highly derivatised *N*-*tert*-alkyl pyrazolo[3,4-*d*]pyrimidines that could be tested as ATP mimics. Crystal structure data have shown the *N*-alkyl functionality sitting outside the kinase ATP binding site on inhibition of a kinase with an *N*-alkyl pyrazolo[3,4-*d*]pyrimidine, analogous to the phosphate tail of ATP.[116] Despite its external location, the *N*-alkyl functionality has been shown to play an important role in binding, with specific secondary binding interactions identified for some alkyl motifs.[116] Additionally, a study comparing *N*-*tert*-butyl and *N*-isopropyl C3-aryl pyrazolo[3,4-*d*]pyrimidine analogues showed the former to be a considerably more potent inhibitior of calcium-dependent protein kinases.[120] Simple access to varied *N*-*tert*-alkyl pyrazolo[3,4-*d*]pyrimidines would allow testing, to establish whether a correlation between *tert*-alkyl functionality and increased potency exists.

2.3.1.2 An alternative synthesis of an α-tert-alkyl hydrazine

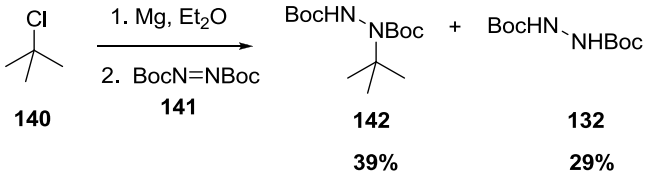
Grignard reagent addition to an *azo*-dicarboxylate

It was hoped that through investigation of an alternative methodology to access α-*tert*-alkyl hydrazine **120,** a more general approach to α-*tert* hydrazines might be developed. Literature precedent exists for the addition of *tert*-butyl magnesium chloride into the diazo-linker of di-*tert*-butyl azodicarboxylate **141** (**Scheme 74**).[121] A moderate yield (30%) is reported, although after a more amenable reaction time (10 h.) than the hydrohydrazination protocol (5 d.). Additionally, a protocol exists documenting the conjugate addition of tertiary Grignard reagent **138** to enone **137** in good yield (85%) (**Scheme 74**).[122] It was hoped amalgamation of the two procedures would provide access to hydrazine **120** in superior yield following a diminished reaction time in comparison with the current protocol.



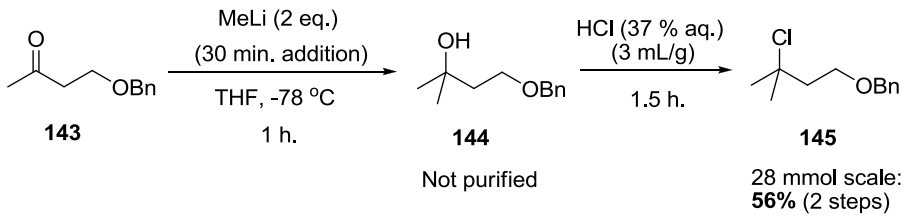
Scheme 74: Synthesis and reactivity of tertiary Grignard reagents

To evaluate the feasibility of the proposed route, addition of *tert*-butyl magnesium chloride into di-*tert*-butyl azodicarboxylate was first carried out. Following the literature procedure, the Grignard reagent was synthesised from *tert*-butyl chloride **140** and magnesium turnings (washed in hexane) in THF, with a crystal of iodine required for activation. The solution was transferred *via* cannula to azodicarboxylate **141**; work-up after 2 h. and chromatographic purification provided the addition product **142** in 39% yield. Dicarbamate **132** was also isolated in 29%, presumably from reduction of the diazo- compound by the hindered Grignard reagent (**Scheme 75**). A control reaction, in which the azodicarboxylate was stirred at r.t. in THF under argon, saw no reduction product by TLC analysis after 24 h., lending support to the hypothesis.



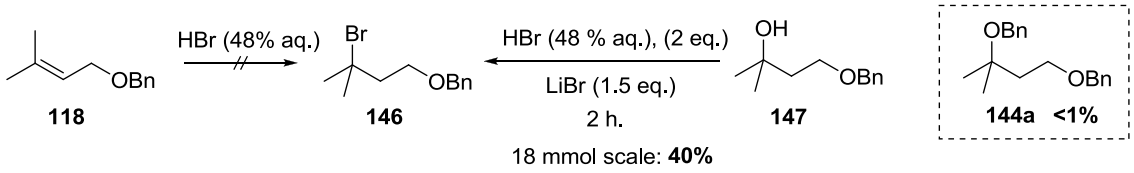
Scheme 75: Grignard reagent addition to an azo-dicarboxylate

Encouraged by this result, chloro-alkane **145** was synthesised according to the literature procedure.[122] Methyl lithium was added to commercial ketone **143** over 30 min. at -78 °C, before a quench after a further 30 min. at this temperature. Purification provided the *tert*-alcohol **144** in 84% yield, which was then treated with HCl (37% aq.) to yield the *tert*-chloro compound **145** in 60% yield following purification. Brief optimisation indicated that 2 equiv. of methyl lithium were necessary for complete consumption of ketone **143**, and quenching the reaction at -78 °C was required to limit impurity formation. Employing these conditions, the crude *tert*-alcohol **144** could be isolated in sufficient purity for immediate use in the chlorination step, providing an improved 56% yield of the *tert*-chloro compound **145** over two steps (**Scheme 76**).



Scheme 76: Synthesis of *tert*-chloro alkane 145

Accordingly, formation of Grignard reagent **138** was attempted with a plethora of activation methods on various scales of the chloro-alkane, in different ether solvents. No obvious initiation was observed, and subsequent addition of the mixture to the diazo-compound resulted in return of chloro-alkane **145** on work-up, indicating that formation of the Grignard reagent had not occurred. Further to this, the remaining magnesium turnings from one reaction were washed and weighed; quantitative mass recovery provided further evidence that magnesium insertion into the carbon-chlorine bond had not occurred. As such, it was hypothesised that the strength of the carbon-chlorine bond might be preventing formation of the Grignard reagent. This led to the proposal of the *tert*-bromo derivative **146** (**Scheme 77**) as an alternative substrate. Interestingly, synthesis of **146** was less facile than the chlorinated compound. Analogous treatment of *tert*-alcohol **147** with HBr (48% aq.) led to complete conversion to the *tert*-bromo alkane, although impurity formation was observed by ^{1}H NMR analysis of the crude reaction mixture, which worsened upon silica chromatography. Silica catalysed degradation of **146** was suspected; indeed a small quantity of the di-benzylated derivative **144a** was isolated following chromatography, which had not been observed in the ^{1}H NMR spectrum of the crude material. Accordingly, the crude product was subjected to distillation at reduced pressure. However, co-distillation of impurities led to an alternative synthesis being sought. Markovnikov addition of HBr to olefin **118** was attempted (**Scheme 77**), although degradation was observed by ^{1}H NMR analysis upon work-up. The use of LiBr to control impurity formation in the synthesis of *tert*-bromo alkanes from *tert*-alcohols has been reported.[123] Pleasingly, addition of the salt to neat alcohol **147** followed by treatment with 2 equiv. HBr (48% aq.) led to the isolation of bromo-alkane **146** in sufficient purity to attempt formation of the Grignard reagent.



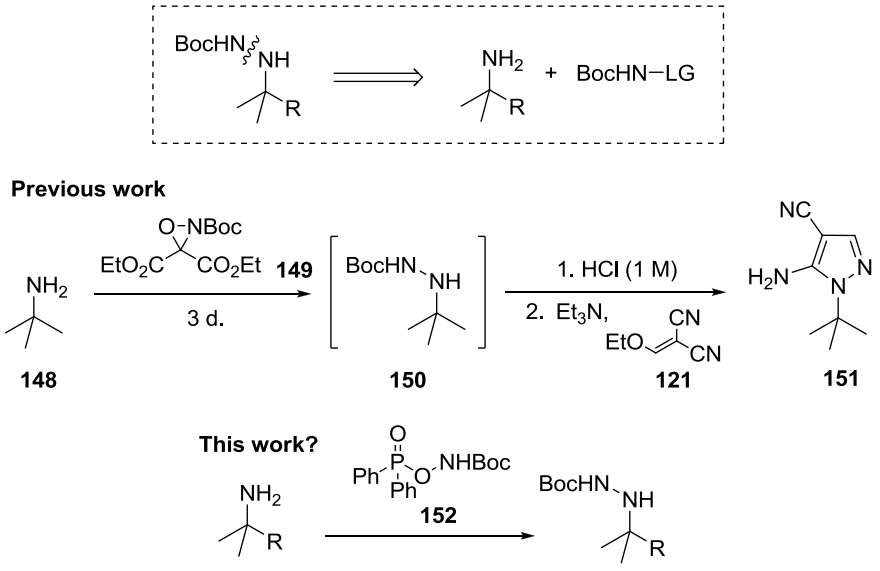
Scheme 77: Synthetic routes to *tert*-bromo alkane 146

Reflux of **146** in THF in the presence of magnesium turnings led to no obvious initiation of Grignard reagent formation, although on addition of the mixture to the diazo-compound **140**, reduction to dicarbamate **132** was observed. It is known that hindered Grignard reagents can act selectively as

hydride transfer agents.[124] To establish whether such a process could be responsible for the reduction observed, a control experiment was set up heating the diazo-compound under analogous conditions, in the absence of the Grignard reagent. However, dicarbamate **132** was observed, showing that formation occurs under the reaction conditions, in the absence of the 'Grignard reagent' solution. The control experiment provided further evidence that Grignard reagent formation was not occurring. Given the difficulty observed in forming the Grignard reagents from either *tert*-halo compound **145** or **146**, it was considered prudent to adopt an alternative strategy to α-*tert*-amine **120**.

Amine amination

Disconnection of the nitrogen-nitrogen bond of a hydrazine was mooted, so that the synthesis would begin with the α-*tert*-amine functionality in place. This amination approach had previously been explored by a co-worker, who had established that *tert*-butyl amine **148** could be aminated using electrophilic oxaziridine **149**,[125] and subsequently converted to pyrazole **151** in a one-pot transformation (**Scheme 78**).[112] Despite the success of the procedure, synthesis of oxaziridine **149** is multi-step. However, it is possible to synthesise the *N*-Boc protected analogue of $DppONH_2$, the electrophilic aminating agent discussed in Chapter 1 of this thesis. The *N*-Boc protected analogue **152** (DppONHBoc) can be synthesised in a single step from commercial *N*-Boc-hydroxylamine. Previous work within the group has shown that the reagent can effect enone aziridination,[67] and so it was decided to test the potential of this reagent for the electrophilic amination of hindered amines (**Scheme 78**). The reagent (prepared by a co-worker) was first tested using *tert*-butyl amine as a model substrate.

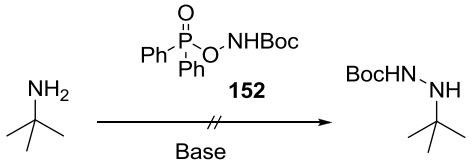


Scheme 78: Disconnection of the nitrogen-nitrogen bond in a hydrazine

Initially, the conditions discovered for the aziridination of enones with DppONHBoc **152** were applied in the amination of *tert*-butyl amine **148** (**Table 31**, entry 1). Work-up and analysis of the

crude reaction mixture by ^{1}H NMR showed un-reacted aminating agent, along with minimal amine. It was suggested that the volatility of the amine could account for the lack of reactivity, and so an excess of this reagent was used in a second reaction. Again, no conversion to product was observed (entry 2), and so a solvent and base switch to MeCN and NaOH, a combination used with considerable success in the aziridination, was trialled. When again, no amination was observed (entry 3), it was suggested that product volatility might be a problem. A final reaction was performed in an NMR tube in d_3-MeCN, under analogous conditions. Although formation of the phosphinic acid was observed, no amine amination occurred over a time-period of 4 d. (entry 4).

Table 31: Attempted amination of *tert*-butyl amine using DppONHBoc



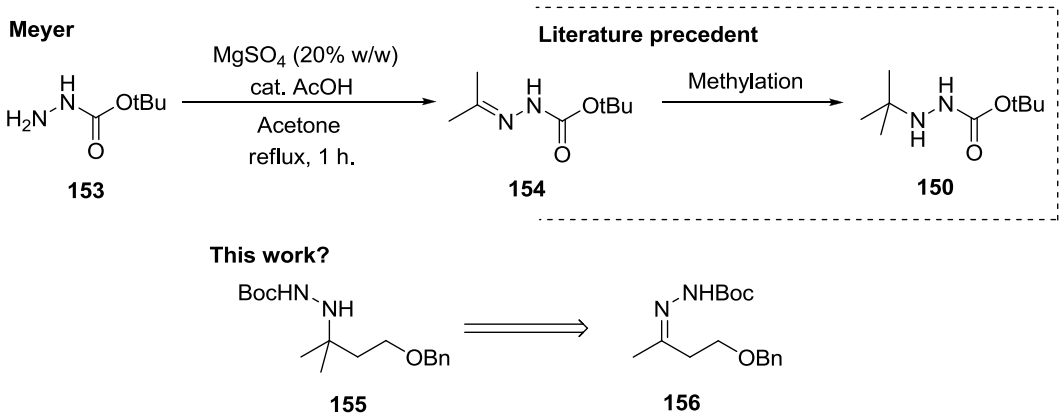
148 150

Entry	*tert*-Butyl amine (eq.)	DppONHBoc (eq.)	Base (eq.)	Solvent	Time (h.)
1	1	2	Cs_2CO_3 (3)	CH_2Cl_2	2
2	4	1	Cs_2CO_3 (2)	CH_2Cl_2	20
3	4	1	NaOH (2)	MeCN	40
4[a]	4	1	NaOH (2)	d_3-MeCN	96

All reactions performed on 0.75 mmol scale of limiting reagent. [a] Performed on 0.02 mmol scale of DppONHBoc.

Hydrazone alkylation

The lack of amination observed meant that further investigation was halted, and an alternative route to the α-*tert*-amine was sought. A third retrosynthesis was considered, with the key α-*tert*-amine-forming step arising from alkylation of a hydrazone. The synthesis of hydrazone **154** is described in the literature,[126] and it was suggested that access to derivative **156** might also be possible, using similar chemistry (**Scheme 79**). Methylation of **156** would establish the required α-*tert*-amine functionality, providing compound **155**, analogous to **120**. As hydrazone **154** is readily available, this was selected as a test substrate for methylation. A brief literature search revealed that alkylation of activated hydrazones (where the α-nitrogen bears a conjugating electron-withdrawing group) is common, although methyl nucleophiles are relatively rare. Notwithstanding, hydrazone **154** was synthesised following reflux of *tert*-butyl carbazate **153** in acetone. Work-up was facile, with filtration and evaporation of the reaction mixture providing the pure compound in quantitative yield, reproducible on large scale (76 mmol).

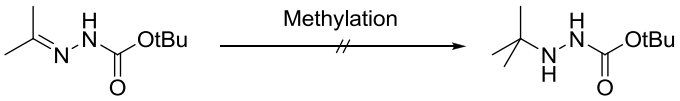


Scheme 79: Hydrazone alkylation as a synthetic strategy

Having prepared the substrate, common methylating agents were selected for testing. In each case, two equiv. of methylating agent were used, to account for initial deprotonation of the carbamate nitrogen. There was also concern for the stability of the carbamate functionality under the reducing conditions.

However, treatment with methyl lithium at -78 °C followed by warming to r.t. for 1 h. led to quantitative recovery of starting material **154** (**Table 32**, entry 1). Methyl magnesium chloride and bromide were selected as 'softer' methylating agents, but treatment of hydrazone **154** with each, again led to quantitative recovered starting material, despite reflux of the reaction using the former reagent (entries 2 and 3). It seemed likely that the initial deprotonation was significantly reducing the electron-withdrawing capability of the carbamate functionality, rendering the hydrazone less reactive towards nucleophilic attack. Reasoning that a softer nucleophile might be more compatible with the hydrazone, dimethylcuprate was prepared *in situ* and added to the hydrazone in THF at 0 °C. Interestingly, the reagent caused complete degradation of the hydrazone to unidentified products by ^{1}H NMR analysis of the crude material upon work-up, and a poor mass recovery was observed (entry 4). An attempt to control the reactivity was made, by performing the reaction at -40 °C, although similar degradation and mass loss was observed (entry 5).

Table 32: Attempted methylation of hydrazone 153

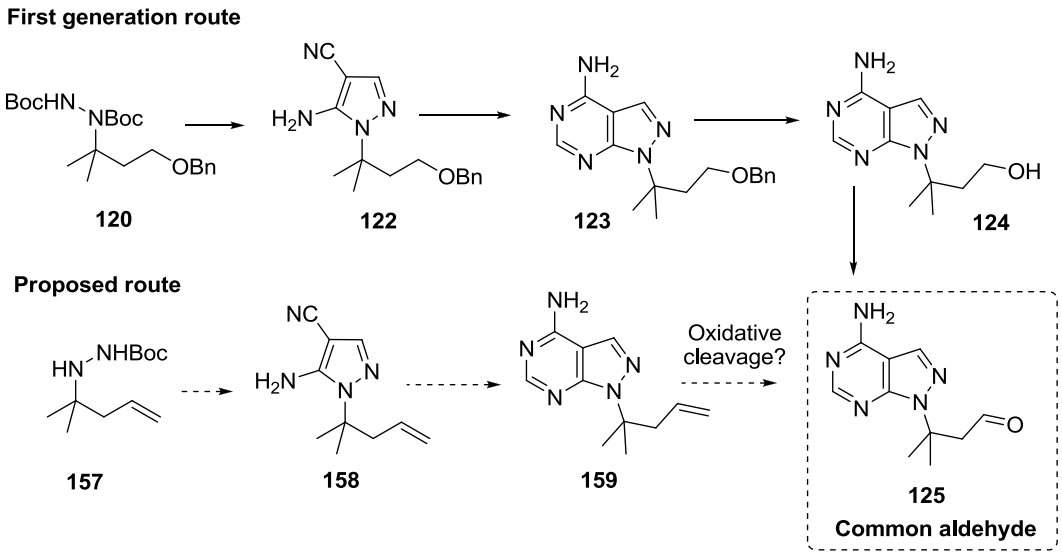


154 150

Entry	Methylating agent	Temp (°C)	Solvent	Observations[a]
1	MeLi	-78 to 23	THF	R.S.M.[b]
2	MeMgCl	-78 to 50	THF	R.S.M.[b]
3[c]	MeMgBr	-78 to 23	THF	R.S.M.[b]
4	Me_2CuLi	0 to 10	Et_2O	Degradation
5[d]	Me_2CuLi	-40	Et_2O	Degradation

All reactions performed on 1.7 mmol scale. [a] By ^{1}H NMR analysis of the crude material. [b] Recovered starting material. [c] 0.6 mmol scale. [d] 0.9 mmol scale.

Returning to the literature, a procedure was found in which hydrazone **154** was treated with allyl magnesium bromide, to access α-*tert*-amine **157** in 51% yield.[127] Analysis of compound **157** led to the proposal of a modified route (**Scheme 80**). The olefin provided an alternative to the benzyl ether functionality, which had presented problems in the original synthetic strategy. Benzyl group removal had been troublesome, providing alcohol **124** in moderate yield (59%) upon treatment with BBr_3 (**Scheme 70**). It was suggested that oxidative cleavage of the olefin following pyrazolo[3,4-*d*]pyrimidine formation from α-*tert*-amine **157** could provide access to the late-stage aldehyde **125** required for reductive amination (**Scheme 80**).

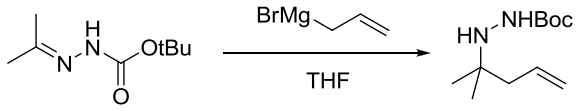


Scheme 80: A common aldehyde intermediate of the first generation and proposed routes

Hydrazone **154** was treated with allyl magnesium bromide according to the literature procedure. The substrate was dissolved in THF and cooled to 0 °C, prior to dropwise addition of the Grignard reagent. A further 1 h. at 0 °C, followed by the same time at r.t. led to complete consumption of hydrazone by TLC analysis, although unreacted starting material was observed in a 1:3 ratio with

product by ^{1}H NMR analysis of the crude mixture. Gratifyingly, work-up and purification allowed isolation of the required hydrazine **157**, albeit in low yield (26%) (**Table 33**, entry 1). Given the successful alkylation observed using allyl magnesium bromide, it was suggested that initial deprotonation of the carbamate nitrogen was not occurring, causing increased electrophilicity of the substrate. To evaluate this, an analogous reaction was performed using 1 equiv. of the Grignard reagent, although no conversion to product was seen by ^{1}H NMR analysis on work-up, suggesting that anion formation was in fact occurring prior to nucleophilic addition (entry 2). Additionally, a pale green colour had been seen intensifying in the initial experiment, throughout addition of the first equivalent of the Grignard reagent, which turned immediately to yellow once the quantity of the reagent exceeded 1 equiv. Hydrazone **154** was next treated with three equiv. of Grignard reagent, to promote complete consumption of starting material. Although the quantity of unreacted starting material appeared to have decreased, considerable conversion to unidentified side-products was also observed in the ^{1}H NMR sprectrum of the crude reaction mixture (entry 3). A reaction in diethyl ether provided a poorer conversion of starting material and increased side-product formation than the analogous reaction in THF (entry 4). Finally, the effect of temperature was tested, in a reaction that was kept at 0 °C for 2 h. Predictably, a lower conversion of starting hydrazone **154** was observed, yet conversely, side-product formation was increased, by comparison with the reaction warmed to r.t. for 1 h (entry 5). Remarkably, the scale of the reaction appeared to have a considerable effect on the consumption of starting material and purity of the crude product. In a large-scale reaction (33 mmol), starting material and product were the only compounds observed by ^{1}H NMR of the crude reaction mixture, in a 1:5 ratio. Chromatographic purification provided the α-*tert*-amine **157** in considerably improved yield (68%) than observed on 0.6 mmol scale (entry 6). This good yield was found to be reproducible, with two identical yields of 70% observed on 50 mmol scale (entry 7).

Table 33: Allylation of hydrazone 154



154 **157**

Entry	Scale (mmol)	Grignard reagent (eq.)	Temperature (°C)	Isolated yield (%)
1	0.6	2	0 (1 h.) – 23 (1 h.)	26
2	0.3	1	0 (1 h.) – 23 (1 h.)	N.D.[a(i)]
3	0.3	3	0 (1 h.) – 23 (1 h.)	N.D.[a(ii)]
4[b]	0.3	2	0 (1 h.) – 23 (1 h.)	N.D. [a(ii)]
5	0.3	2	0 (2 h.)	N.D. [a(ii)]
6	33.0	2	0 (1 h.) – 23 (1 h.)	68
7[c]	50.0	2	0 (1 h.) – 23 (1 h.)	70

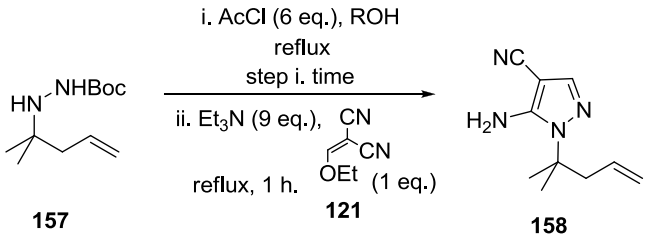
All reactions performed in THF at [0.1 M]. [a] Isolated yield not determined: ^{1}H NMR observations of crude reaction mixture: [(i)] Starting hydrazone only; [(ii)] Starting hydrazone, required product, and unidentified side-products. [b] Reaction performed in Et_2O. [c] Performed twice with identical yield observed.

Furthermore, the applicability of the chemistry to alternative hydrazone substrates (synthesised in turn from readily available ketones) could be envisaged. Potentially, access to a range of α-*tert*-hydrazines would be possible, bearing an olefinic functional handle for later elaboration. However, it was felt prudent to first assess the validity of the alkene-bearing substrate in the forward synthesis.

2.3.1.3 Towards a common aldehyde

Pyrazole formation was attempted, as in the first generation route. Reflux in ethanolic HCl was found to effect hydrolysis of the Boc- moiety, with complete consumption of starting material observed by TLC analysis after just 20 min. The time compared favourably with the 1.5 h. required for α-*tert*-amine **120** in the first generation route. The decreased reaction time was attributed to the single Boc- moiety in compound **157**, whereas hydrolysis of two Boc- groups was required in the original α-*tert*-amine substrate. The reaction mixture was basified, before the addition of enol ether **121** (synthesised from malononitrile and triethylorthoformate in 68% yield).[128] TLC analysis showed complete consumption of enol ether **121** after a further 1 h. at reflux; an analogous reaction time to that observed in the first generation pyrazole synthesis. Work-up and chromatographic purification provided pyrazole **158** in 55% yield on 0.5 mmol scale (**Table 34**, entry 1). A comparable yield of 59% was observed for a larger scale reaction on 5.0 mmol of substrate (entry 2). Despite the good yields obtained, a disadvantage at this step was the large quantity of ethanol solvent required, which was subject to distillation and rigorous drying prior to use. Pleasingly, a solvent swap to more readily available anhydrous methanol, led to the isolation of pyrazole **158** in an improved yield of 71% on 0.5 mmol scale (entry 3), with a slight drop in yield to 63% observed on scale-up to 21.0 mmol (entry 4). A slight increase in reaction time for the first step to 1 h. was required, likely due to the lower reflux temperature of methanol.

Table 34: Formation of pyrazole 158



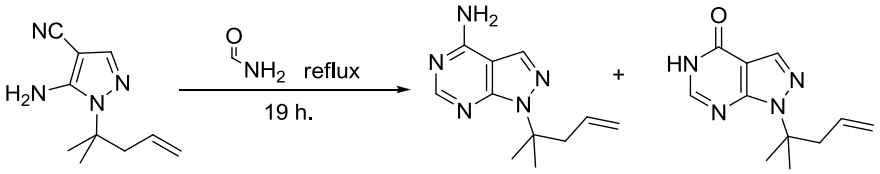
157 121 158

Entry	Scale (mmol)	Solvent	Step i. time (min.)	Isolated yield (%)
1	0.5	EtOH	20	55
2	5.0	EtOH	20	59
3	0.5	MeOH	60	71
4	21.0	MeOH	60	63

Following synthesis of pyrazole **158**, the intermediate was heated to reflux in formamide for pyrimidine formation, in accordance with the first generation route. It had been noted when repeating

the first generation synthesis, that fresh formamide was required for a good yield of the pyrimidine, and to avoid troublesome emulsions during work-up. Purification of the crude material following 19 h. at reflux in formamide led to the isolation of pyrimidine **159** in 76%, along with pyrimidone **161** in 21% (**Table 35**, entry 1). Careful chromatographic separation was required due to the similar R*f* values of the compounds. The by-product was assumed to have arisen from hydrolysis of the nitrile by trace water under the forcing reaction conditions, or indeed from hydrolysis of the product itself; the analogous benzyl-ether derivative had been observed in the first generation route. In order to circumvent pyrimidone formation, and improve the yield with respect to pyrimidine **159**, analogous reactions were performed using; a) formamide stored over molecular sieves and b) molecular sieves as an additive in the reaction. However, neither method appeared to decrease formation of pyrimidone **161** by TLC or ^{1}H NMR analysis and, and so further attempts to remove water from the reaction were not pursued. Scale-up of the reaction led to slightly diminished, yet reproducible yields (entries 2 and 3).

Table 35: Pyrimidine formation



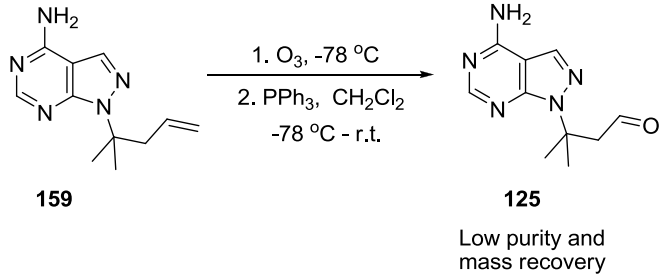
158 **159** **161**

Entry	Scale (mmol)	Isolated yield (%)	
		Pyrimidine 159	Pyrimidone 161
1	0.5	76	21
2	10.5	63	N.D[a]
3	13.0	66	N.D[a]

All reactions performed at [0.5 M]. [a] Isolated yield not determined.

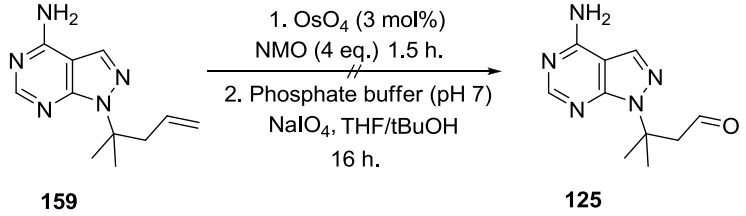
Having accessed pyrazolo[3,4-*d*]pyrimidine **159** bearing the terminal olefin, oxidative cleavage to provide the aldehyde and reconnect with the first generation route would be the test for the strategy. Consultation of the literature highlighted an ozonolysis protocol used on a molecule with a similar southern fragment to compound **159**.[129] To follow the procedure, pyrazolo[3,4-*d*]pyrimidine **159** was dissolved in dichloromethane and cooled to -78 °C. Ozone gas was bubbled through the solution until a blue colour persisted, prior to the addition of dimethyl sulfide and warming to -10 °C. The reaction mixture was concentrated and the crude material analysed by ^{1}H NMR; considerable degradation to unidentified products was observed, along with minimal starting material and no signal in the aldehyde region. Additionally, mass recovery was poor. Subsequently, an analogous reaction was performed, calculating the output of the ozoniser. This was done using a calibration chart provided with the ozoniser, and monitoring gas output using a flow meter, to limit the quantity of ozone bubbled through the reaction mixture to 1 equiv. ^{1}H NMR analysis of the resulting crude material

revealed starting material, along with some degradation. Again, no aldehyde proton was observed. A solvent swap to MeOH, commonly used for ozonolysis, along with similar control of ozone quantity, led to a similar ^{1}H NMR spectrum of the crude material. A final experiment was set up, with careful TLC monitoring of reaction progress at regular intervals, until consumption of starting material was observed, followed by reductive work-up with PPh_3. Chromatographic purification of the crude product provided the required aldehyde **125**, but in poor purity and low mass (**Scheme 81**). Given this, it was decided not to pursue ozonolytic cleavage methods further. It seemed likely that the electron-rich aromatic nature of pyrazolo[3,4-*d*]pyrimidine **159** was the cause of degradation under the reaction conditions, and consequently the poor mass recoveries observed.



Scheme 81: Ozonolysis to aldehyde 125

Johnson-Lemieux oxidation was next investigated to provide access to aldehyde **125**. A one-pot protocol was tested, according to a literature procedure.[130] Catalytic OsO_4 and excess NMO were added to pyrazolo[3,4-*d*]pyrimidine in a THF/^{t}BuOH solvent mixture. TLC analysis showed complete consumption of starting material after 1.5 h., at which point a phosphate buffer (pH 7) was added, followed by $NaIO_4$. Work-up after 16 h. necessitated the use of an extremely polar organic solvent combination of $CHCl_3$/EtOH (2:1) for complete extraction of the aqueous phase. However, ensuing analysis of the crude reaction mixture revealed degradation, and no evidence of the required diol or aldehyde (**Scheme 82**).



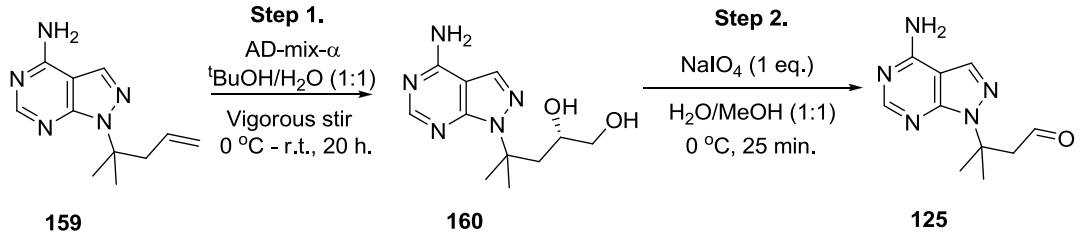
Scheme 82: A one-pot dihydroxylation and cleavage approach

As the dihydroxylation step appeared to have proceeded smoothly by TLC analysis, a two step procedure was next investigated. Pyrazolo[3,4-*d*]pyrimidine **159** was treated with AD-mix-α in ^{t}BuOH/H_2O, according to Sharpless' procedure.[131] Work-up that included extraction of the aqueous phase with $CHCl_3$/EtOH (2:1) led to isolation of the required diol **160** in moderate yield (39%) (**Table 36**, entry 1). The exceedingly polar diol had precipitated out of the organic phase in high purity,

negating the need for chromatographic purification. However, analysis of the mother liquor following filtration revealed that starting material was still present, along with some product diol. As no other compounds were observed, it was clear that complete consumption of starting material would allow improved recovery of product, following simple removal of work-up solvent. Vigorous stirring of the heterogeneous reaction mixture was found to be key; an analogous reaction at high r.p.m, using two magnetic stirrer bars led to complete consumption of starting olefin **159** after 20 h., and an improved isolated yield (72%) of pure diol **160** on a 0.5 mmol scale (entry 2).

Diol cleavage was attempted using $NaIO_4$ in water. Five equiv. of the periodate reagent were used in an initial reaction, following a literature method.[132] However, removal of the reagent during work-up was troublesome, with partial solubility observed in both the aqueous and organic phases. Additionally, the periodate caused signal broadening in the ^1H NMR of the crude reaction mixture, making visualisation of other peaks exceedingly difficult. An alternative set of conditions, employing one equiv. of $NaIO_4$ in $MeOH/H_2O$, meant that work up was more facile. Chromatographic purification led to isolation of the required aldehyde **125** in excellent yield (83%) (**Table 36**, entry 3). Purification of the aldehyde had been problematic in the first generation route, resulting in the crude aldehyde being used directly in the reductive amination step. Isolation of aldehyde **125** *via* the new strategy presented a considerable improvement to the synthesis. Both dihydroxylation and cleavage steps were found to be amenable to scale-up (3.0 mmol), with a quantitative yield of diol **160** isolated, which underwent cleavage to the pure aldehyde **125** in 82% yield (entry 4).

Table 36: Dihydroxylation and cleavage with $NaIO_4$



159 **160** **125**

Entry	Scale (mmol)	Isolated yield (%)	
		Step 1	Step 2
1	0.5	39[a]	n/a[b]
2	0.5	72	n/a[b]
3	0.2	n/a[b]	83
4	3.0	Quant.	82

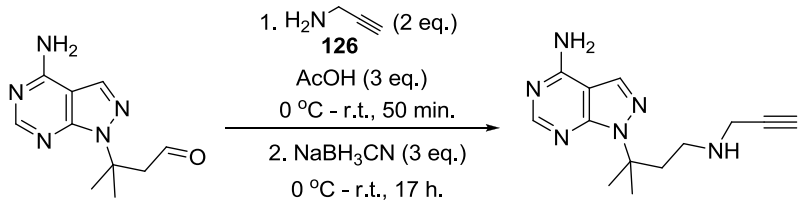
[a] Moderate stirring, leading to incomplete conversion to aldehyde. [b] Not applicable.

2.3.1.4 Rejoining the first generation strategy

A more robust synthesis to the key intermediate aldehyde **125** had been developed. To access the linker-bearing pyrazolo[3,4-*d*]pyrimidines, the two final steps of the first generation strategy were all that remained. The penultimate step, a reductive amination with propargyl amine (**126**), was required

to establish the terminal alkyne necessary for "click chemistry" separation and labelling. Accordingly, aldehyde **125** was treated with propargyl amine and acetic acid in methanol. $NaCNBH_3$ reduction resulted in isolation of the crude amine after a reaction time of 17 h., and extraction from a neutral aqueous phase on work-up. Chromatographic purification led to the isolation of compound **127** in a moderate yield of 42% (**Table 37**, entry 1), although a small amount of an unidentified impurity was present by ^{1}H NMR analysis. Indeed the same impurity was observed in the isolated product in two subsequent reactions. However, further attempts to remove the impurity were not made due to the highly polar nature of the amine. It was felt that purification would be substantially easier following amide formation. Amine **127** was synthesised in three batches on similar scales, in reproducible yield (**Table 37**).

Table 37: Reductive amination

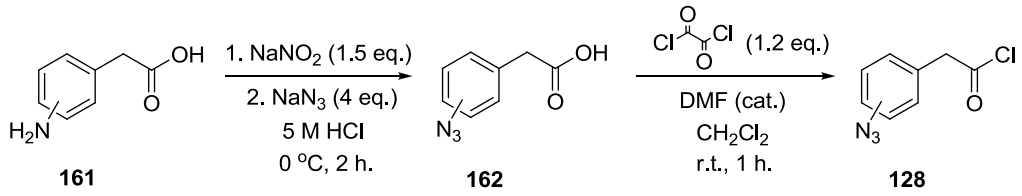


125 127

Entry	Scale (mmol)	Isolated yield[a] (%)
1	0.5	42
2	0.5	44
3	0.9	48

[a] Containing a small amount of unidentified impurity.

The final amide coupling would install the aryl azide necessary for cross-linking of the molecule to a kinase protein-substrate. Prior to amide formation, synthesis of the aryl azide coupling partners **162** was required. The chemistry described in the first generation route was followed (**Scheme 83**), starting from the commercial anilines (**161**).[112] Diazotisation followed by *ipso*-substitution with azide provided **162** in 80-89% yield.



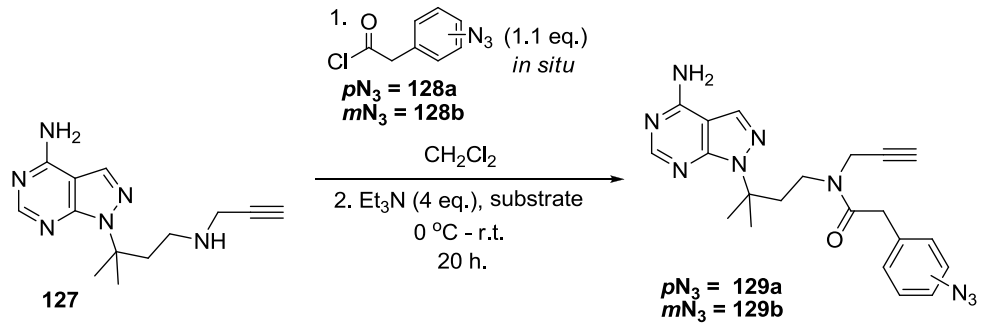
161 162 128

Scheme 83: First generation route; formation of acid chlorides

In the first generation route, the resulting carboxylic acids are transformed into acid chlorides through reaction with oxalyl chloride, and fully characterised (**Scheme 83**). Following previous success generating acid chlorides *in situ* (*vide* Chapter 1) it was considered prudent to attempt acid chloride formation *in situ*, thus avoiding any hydrolysis over long-term storage. Amide formation using the

para-azide coupling partner **128a** was attempted first. Treatment of the carboxylic acid with oxalyl chloride showed complete consumption of **128a** by TLC analysis after 1 h. The acid chloride solution was transferred to a reaction vessel containing amine **127** in dichloromethane and triethylamine. Work-up after 20 h. revealed degradation to unidentified products, with no starting material or amide observed. It was suggested that the triethylamine could be at fault, due to lack of purification prior to use. The reagent was distilled and stored over molecular sieves, before repetition of the reaction. It was also decided to remove reaction volatiles *in vacuo* following acid chloride formation. The acidic nature of remaining oxalyl chloride and its associated decomposition products could also have been responsible for the lack of amidation observed. Applying these changes in an analogous reaction led to isolation of the final *para*-azido product **129a** in reproducible 50% yield on 0.2 mmol scale, following chromatographic purification (**Table 38**, entries 1 and 2). The amide bearing azide functionality in the *meta*-position, **129b**, was accessed in 40% yield on the same scale (entry 3). Both compounds exist as rotamers as observed by ^{1}H NMR, in a ratio of *ca*. 2:1. Analytical data for the final compounds was in complete agreement with that obtained from the first generation synthesis.

Table 38: Final step amide formation



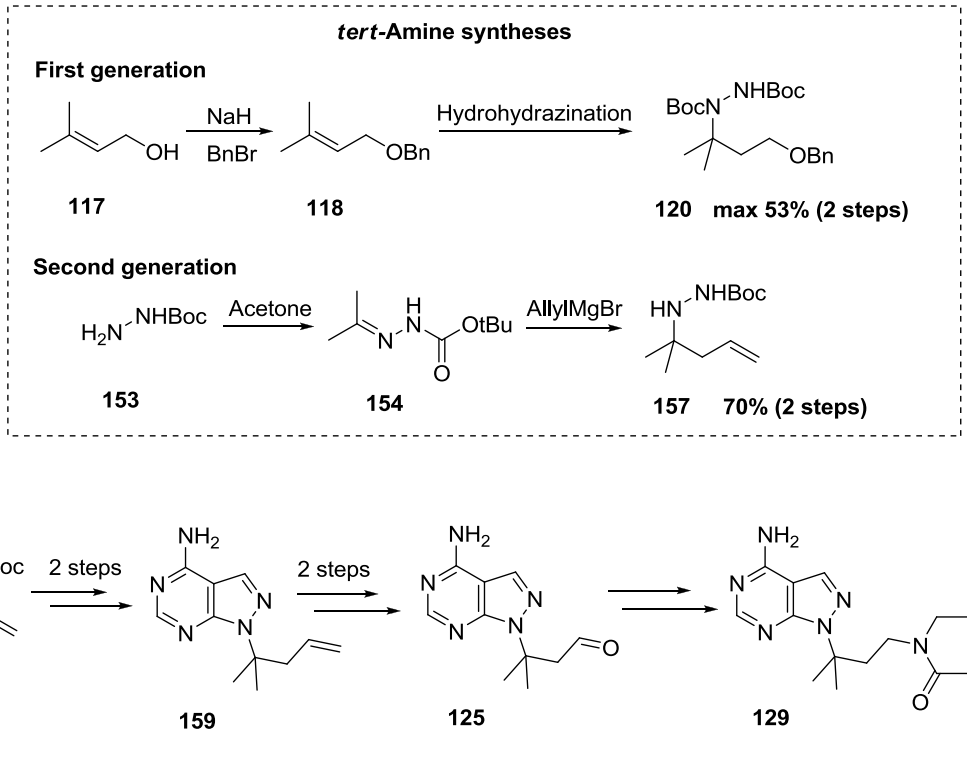
Entry	Azide position	Isolated yield (%)
1	*para*, **129a**	50
2	*para*, **129a**	53
3	*meta*, **129b**	40

All reactions performed on 0.2 mmol scale.

2.3.2 Summary of the second generation synthesis

An alternative, more robust synthesis of the C3-hydro target compounds had been developed. The troublesome hydrohydrazination step of the first generation route had been bypassed, with a hydrazone reduction exploited as the key α-*tert*-hydrazine forming step. The two steps to provide this intermediate had proved reproducible on scales of >30 mmol. The α-*tert*-hydrazine **157** was accessed in 70% yield over two steps, by comparison with a maximum 53% yield to analogue **120** in the first generation route (**Scheme 84**). Subsequent formation of the pyrazolo[3,4-*d*]pyrimidine moiety had proceeded smoothly with the second-generation hydrazine. It was possible to oxidatively cleave the

terminal olefin to access the late stage aldehyde **125** and thus reconnect with the first generation synthetic route to access the target compounds.



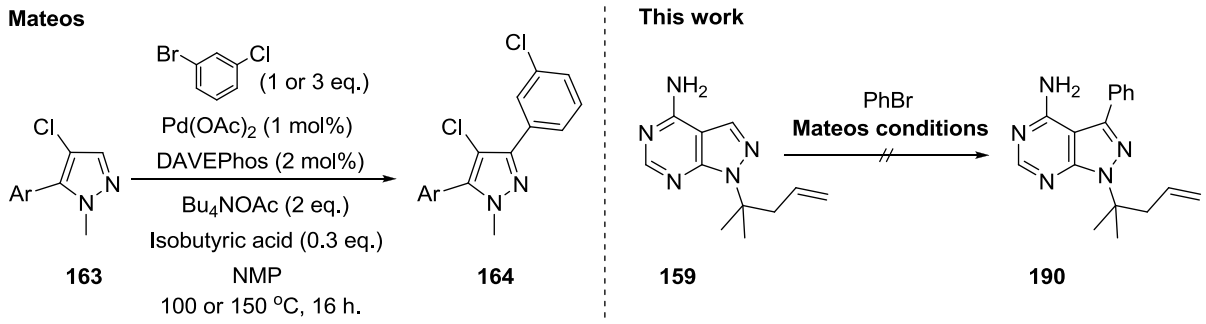
Scheme 84: Comparison of first and second generation routes

2.3.3 C3-functionalisation of pyrazole 159

2.3.3.1 CH-activation

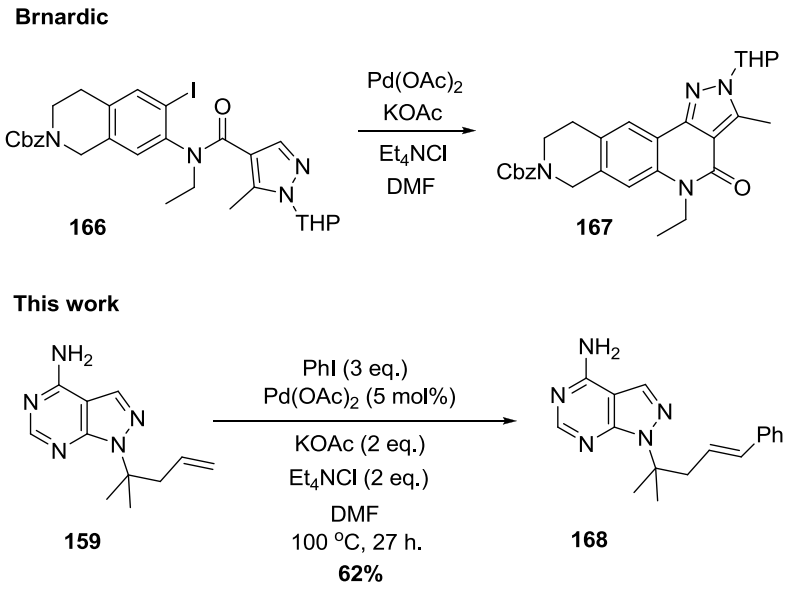
With a high-yielding and reproducible route to the α-*tert*-hydrazine developed, it was possible to access a sufficient quantity of the intermediate pyrazolo[3,4-*d*]pyrimidine **159** to begin rigorous investigation into C3-arylation.

Initial review of the literature revealed that Mateos *et al.* used a Design of Experiments strategy to identify optimum conditions for pyrazole arylation. Preference for C5-substitution was observed, but in cases where this position was blocked such as **163**, C3-arylation took place (**Scheme 85**).[133] Two sets of conditions were found to be applicable; a standard set, and a more forcing set for troublesome substrates. Both sets were applied to pyrazole **159** using phenyl bromide as the coupling partner, but unfortunately no C3-arylation was observed. Return of starting material was observed in both cases, with some degradation seen under the more forcing conditions.



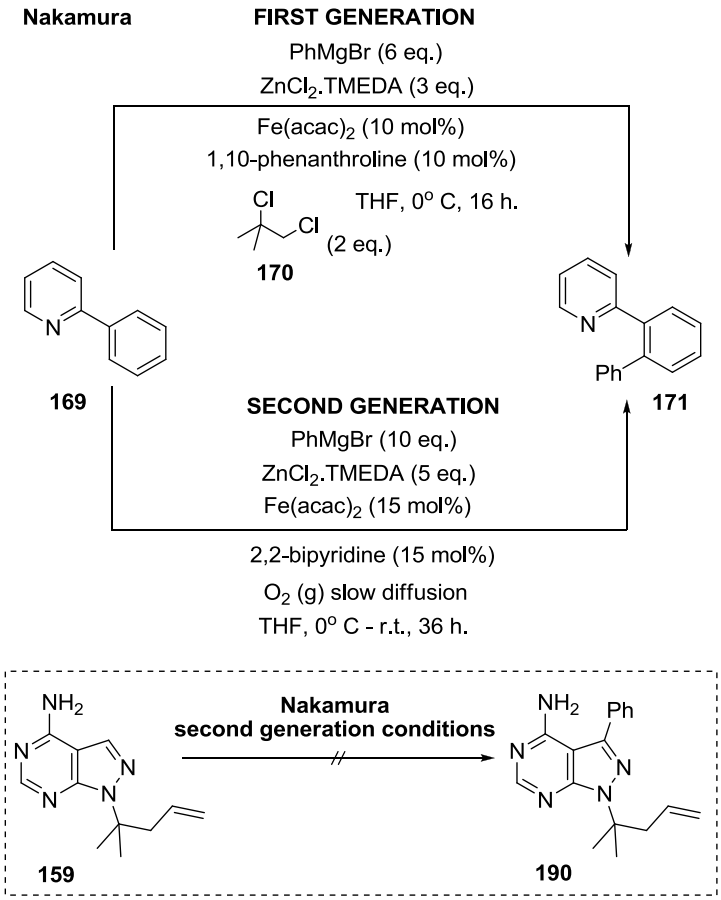
Scheme 85: Mateos' conditions for pyrazole arylation

The lack of success was attributed to the increased complexity of pyrazole **159** in comparison to the literature substrates. In particular, the primary amine of **159** was identified as a potential contributor to the lack of conversion; amines are known to poison palladium catalysts and thus limit reactivity.[134] Mindful of this, an intramolecular palladium-catalysed C3-arylation protocol was identified for further experimentation.[135] The reaction is used in a literature report as a key cyclisation step in the synthesis of a Chk1 kinase inhibitor. Additionally, substrate **166** bears considerable functionality which is not reported to affect the procedure (**Scheme 86**). Considering that the methodology might be appropriate for highly functionalised pyrazole **159**, a test reaction was carried out. The report provides no experimental detail or quantities of reagents, and so these were estimated using mechanistic understanding. Analysis of the crude product by ^{1}H NMR after 18 h., revealed starting material and the tentatively assigned Heck product **168**. On chromatographic purification, both compounds eluted with the same R*f* values and could not be separated. A second reaction was left for a longer time period, allowing complete conversion to the Heck product, whose identity was confirmed upon isolation in 62% yield (**Scheme 86**). Interestingly, the isolation of **168** in good yield shows that the palladium catalyst is not poisoned by the primary amine to any significant extent.



Scheme 86: Intramolecular coupling conditions

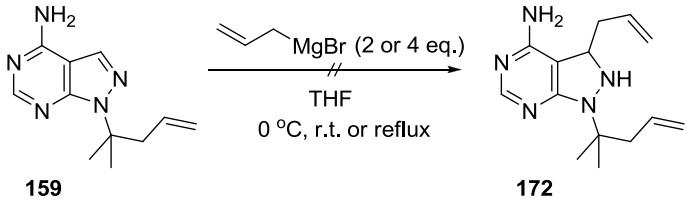
Nakamura *et al.* disclosed a nitrogen-directed CH-bond activation protocol for aryl-aryl coupling. The chemistry is iron-catalysed, taking place in the presence of a zinc-TMEDA complex with dichloro-alkane **170** as a re-oxidant (**Scheme 87**).[136] It was suggested that the exocyclic pyrimidine nitrogen in compound **159** might be suitably located to direct pyrazole arylation at C3 (**Scheme 87**). A facile reaction, treating a THF solution saturated with $ZnCl_2$ provided the required zinc-TMEDA complex, but unfortunately, dichloro-alkane **170** did not prove accessible. The reagent is expensive to purchase, and so Markovnikov addition of HCl (37% aq.) to *iso*-crotyl chloride was attempted. However, the reaction led to a mixture of products that could not be separated upon purification. Pleasingly, a second generation protocol from the same group uses oxygen gas as the re-oxidant, negating the necessity for the costly chloro-alkane (**Scheme 87**).[137] Pyrazolo[3,4-*d*]pyrimidine **159** was treated under the literature conditions, but unfortunately quantitative recovery of starting material was observed. Indeed, the directing-groups in the published scope are limited to tertiary amines, and it was plausible that the primary pyrimidine nitrogen was incompatible with the chemistry.



Scheme 87: Nitrogen-directed CH-arylation

2.3.3.2 Nucleophilic addition

As CH-pyrazole activation of compound **159** had thus far proved unattainable, it was decided to investigate some alternative strategies to C3-functionalisation. As discussed previously, the addition of allyl magnesium bromide to a hydrazone had been successfully exploited to provide access to the key α-*tert*-amine intermediate **157** in the second generation synthesis of the C3-hydro target compounds. It was mooted that similar chemistry might be possible at the hydrazone-like C3-position of **159**, with subsequent oxidation necessary to regenerate the aromatic structure. Unfortunately, two experiments set up with super-stoichiometric quantities of the Grignard reagent, led to recovered starting material on work-up, despite elevated reaction temperatures (**Scheme 88**).

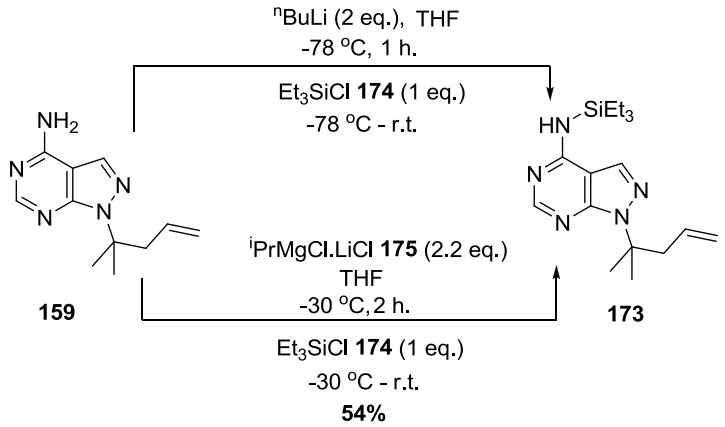


Scheme 88: Attempted C3-allylation

2.3.3.3 Metallation

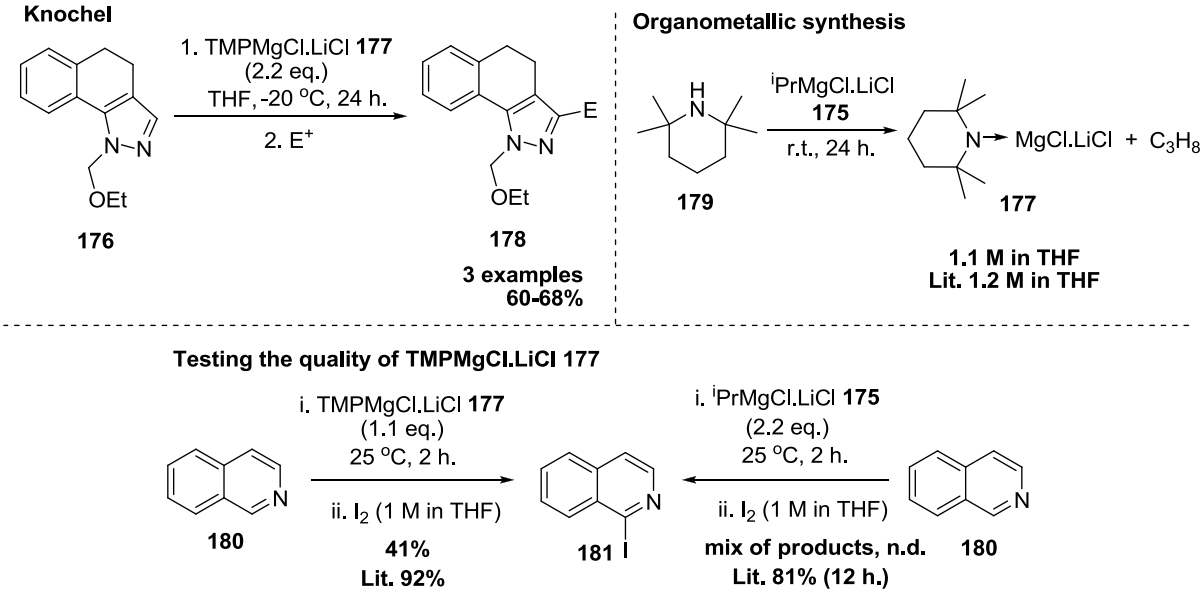
Heteroaromatic deprotonation followed by electrophilic trapping is a common functionalisation method. Literature examples of pyrazole metallation occur preferentially at the C5-position,[133, 138] but as this position is substituted in compound **159**, it was considered prudent to attempt deprotonation at C3. It was clear that initial deprotonation would occur at the pyrimidine amine, but it was hoped that treatment with an excess of strong base would effect a second deprotonation at C3. Subsequent electrophilic trapping would then occur initially at the more basic anion. ^{n}Butyl lithium has been reported to lithiate at the C5-position of pyrazoles, with a range of electrophiles used to trap the resulting anion.[138] Of these, Et_3SiCl was selected, owing to its compatibility with other functional groups in the substrate. Treatment of pyrazole **159** with 2 equiv. of ^{n}BuLi at -78 °C, followed by a quench with the chloro-silane at this temperature after 1 h., provided complete conversion by ^{1}H NMR analysis of the crude product to *N*-silylated **173** (**Scheme 89**). Reasoning that the steric bulk of the silane might be preventing trapping of the C3-anion, the reaction was repeated, quenching with D_2O. However, no C3-deuteration was observed on analysis of the crude product by ^{1}H NMR.

Knochel *et al.* have prepared a range of specialised mixed-metal organometallics that have been reported to directly metallate pyrazoles in high regioselectivity, as evidenced by subsequent electrophilic quench. Once such reagent, iPrMgCl.LiCl **175**, is commercially available, and so was applied to pyrazole **159** according to the literature method (using an extra equiv. to account for initial deprotonation of the free amine).[139] The chloro-silane electrophile **174** was also used by Knochel, and so the reagent was again used to quench, at -30 °C after 2 h. Complete conversion to *N*-silylated amine **173** was observed by ^{1}H NMR analysis of the crude material, and the product was subsequently isolated (54%) (**Scheme 89**). The moderate yield was attributed to the difficulty in purifying **173**; despite a considerable difference in R*f* values, the product co-eluted with the starting chloro-silane **174** during chromatographic purification.



Scheme 89: Formation of *N*-silylated amine

This class of specialised organometallic reagents also includes TMPMgCl.LiCl **177**, synthesised from the commercial ^{i}PrMgCl.LiCl **175** and 2,2,4,4-tetramethylpiperidine **179** (TMPH) (**Scheme 90**). Knochel *et al.* have demonstrated the successful use of **177** for C3-pyrazole metallation, following with electrophilic trapping (**Scheme 90**).[139, 140] Organometallic **177** was prepared on the same scale as the literature procedure; TMPH **179** was added dropwise to freshly titrated commercial ^{i}PrMgCl.LiCl **175** and stirred until gas evolution ceased (24 h.). A concentration of 1.11 M in THF (lit. 1.20 M in THF) was calculated following titration with salicalhydrazone.[141] To test for the formation of the organometallic, Knochel reports the *ortho*-iodination of isoquinoline (**180**) in 92% yield, following treatment with **177** and quench with iodine after 2 h. By analogy, ^{i}PrMgCl.LiCl **175** which required 12 h. for comparable metallation, provided 81% of the iodinated product **181**, following an iodine quench (**Scheme 90**).[139] Accordingly, **180** was treated with the synthesised TMPMgCl.LiCl **177**, and iodine quench after 2 h. led to a 41% isolated yield of the *ortho*-iodo product **181** (**Scheme 90**). A simultaneous reaction using commercial ^{i}PrMgCl.LiCl **175** for metallation, followed by iodine quench after 2 h., led to no required product formation by TLC analysis. The reaction was carried out under an argon balloon, likely accounting for the considerably lower isolated yield of **181** (41%) following TMPMgCl.LiCl and iodine treatment than the literature value (92%), obtained using Schlenk technique. Despite this, the reagent quality was deemed satisfactory, given the considerable difference in reactivity observed on comparing TMPMgCl.LiCl **177** and commercial ^{i}PrMgCl.LiCl **175**.

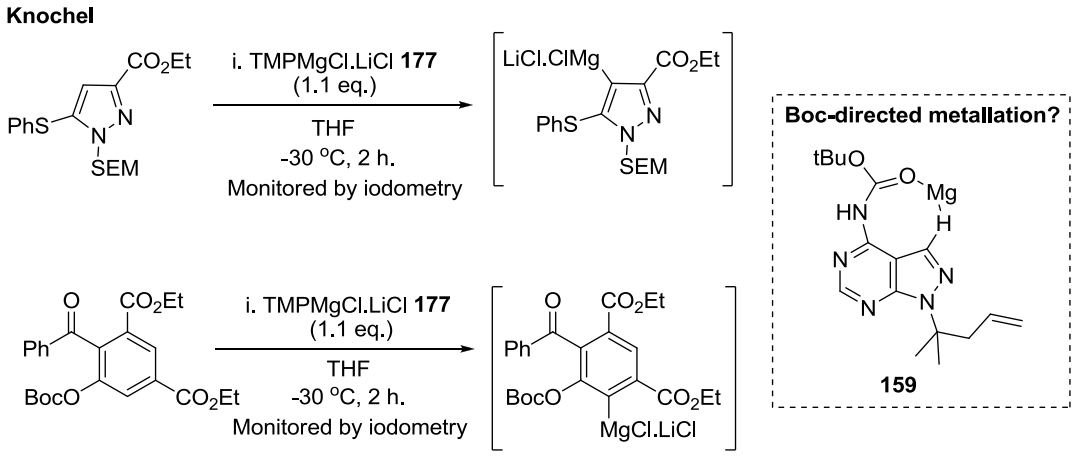


Scheme 90: Chemistry of Knochel's organometallics

The TMP-organometallic **177** was applied to pyrazole **159**, using a range of conditions, adapted from the literature. D_2O was selected for electrophilic quench, as deuterium incorporation would be easily observed by ^{1}H NMR analysis of the crude product. However, no C3-deuteration was observed,

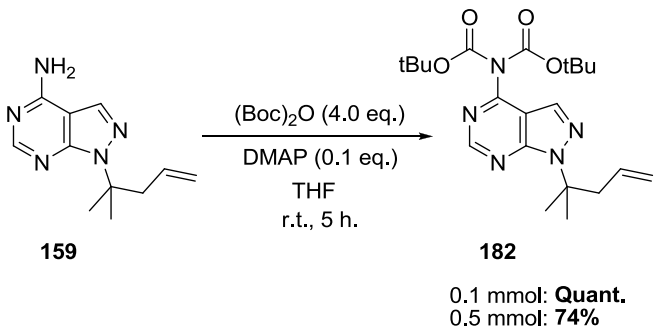
although a decrease in the integral of the pyrimidine amine protons was noted, indicating deprotonation.

From these results, and preceding experiments, it was suggested that competing amine deprotonation could be preventing C3-functioanlisation. It seemed possible that formation of the di-anion was too unfavourable under the conditions. As such, a protective-group strategy was envisaged. Ester-directed metallation has been observed by Knochel (**Scheme 91**).[142, 143] It was suggested that *N*-Boc-protection could serve not only to limit initial deprotonation at the exocyclic pyrimidine nitrogen, but also might direct metallation at C3 of pyrazole **159** (**Scheme 91**).



Scheme 91: Ester-directed metallation of aromatics

Initial attempts to Boc-protect the exocyclic pyrimidine nitrogen revealed the reduced reactivity of the group in comparison to the aniline motif. Boc-protection did not occur under standard conditions,[144] and so it was suggested that full deprotonation of the pyrimidine could first be accomplished using strong base (as observed previously) followed by quenching with Boc-anhydride. However, treatment under these conditions returned an inseparable mixture of the mono- and bis-Boc protected pyrimidines. In due course, a set of conditions employing DMAP as a nucleophilic catalyst was found to be the most suitable.[145] Rapid formation of the mono-Boc pyrimidine **186** was observed by TLC analysis, with concurrent gradual formation of the bis-Boc pyrimidine **182**. Due to difficult separation, it was decided to effect full formation of **182**, which occurred in 5 h. (**Scheme 92**). An added advantage of this strategy was the lack of acidic protons in the final bis-Boc compound, meaning that subsequent treatment with organometallics could not lead to unwanted deprotonation.



Scheme 92: bis-Boc protection of pyrimidine 159

Consequently, bis-Boc pyrimidine **182** was treated with TMPMgCl.LiCl **177** at r.t. for 2 h., before electrophilic quench with D_2O. Upon work-up and chromatographic purification, the mono-Boc pyrimidine **186** was isolated in 47% yield, along with a second product identified as nitrile **183**, in 21% (**Table 39**, entry 1). No starting material was observed. Nitrile **183** had presumably formed from deprotonation at C3 followed by collapse of the pyrazole. Evidence of note for the structural assignment included a) the nitrile stretch at 2222 cm^{-1} in the infra-red spectrum; b) the considerable upfield shift of the protons in the α-*tert*-amine unit, by analogy with those in the mono-Boc compound **186**. In addition, a clear trend was observed on comparing the shift of C* (78 ppm) with the analogous carbon in similar heteroaromatics (**Fig. 10**).

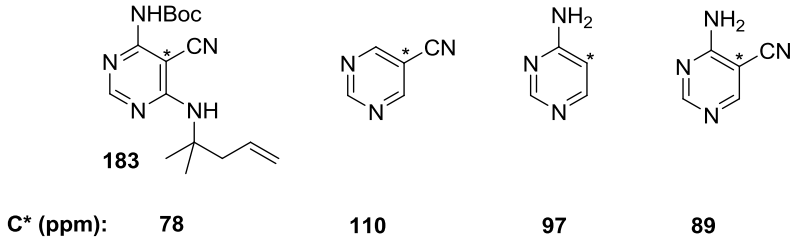
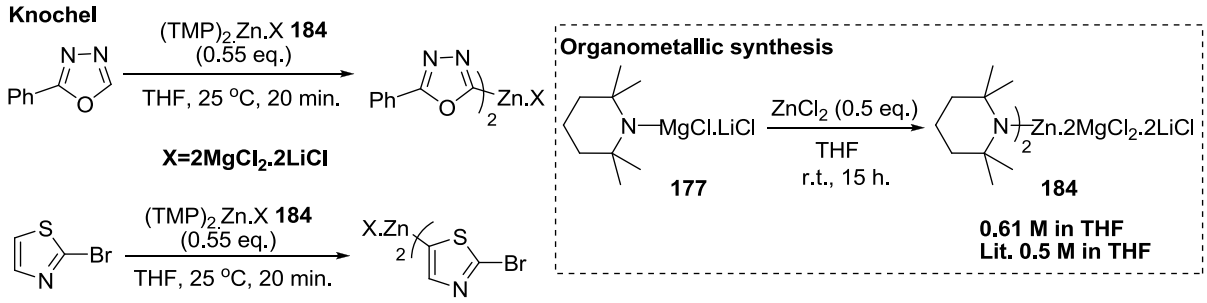


Fig. 10: ^{13}C shifts for cyano-pyrimidines and related structures

Formation of nitrile **183** suggested that metallation at the pyrazole C3- had occurred. It was hoped that the proposed magnesiate intermediate would exhibit greater stability at lower temperature, and so an analogous reaction was performed at 0 °C. However, after work-up, analysis of the crude product by ^{1}H NMR showed mainly starting material (72%), along with mono-Boc pyrimidine **186** (18%) and nitrile **183** (9%) (**Table 39**, entry 2), indicating that the lower temperature had served to decrease the reaction rate rather than stabilise the intermediate magnesiate. A reaction at -20 °C further confirmed this, with no nitrile observed upon work-up. A short reaction time was suggested, to trap the seemingly transient metallo-pyrazole. However, 20 min. at 0 °C again provided mixtures of the Boc-protected pyrimidines **182** and **186** and nitrile **183** (entry 3). Intriguingly, treatment of the mono-Boc compound **186** with the organometallic led to recovered starting material after 2 h., indicating that nitrile **183** was derived from bis-Boc pyrimidine **182**, with Boc-group removal occurring subsequently.

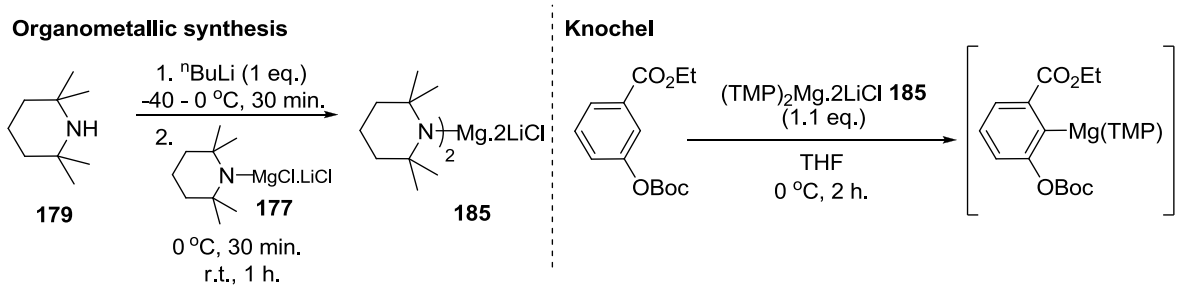
In an effort to promote the longevity of the metallated pyrazole intermediate, a mixed zinc-magnesiate reagent **184** was prepared. **184** is reported to be particularly suitable for sensitive aromatics, such as oxadiazoles and thiazoles, which are prone to degradation, often *via* ring-opening, on treatment with strong base.[146] TMPMgCl.LiCl **177** was added to anhydrous zinc chloride (dried at 140 °C, under high vacuum, 8 h.) at r.t. and stirred for 15 h., to generate $(TMP)_2Zn.2MgCl_2.2LiCl$ **184** (**Scheme 93**). A concentration of 0.61 M in THF was calculated, following titration with salicalhydrazone, comparable to the literature value of 0.50 M. Unfortunately, neither a quantitative nor qualitative test of reagent quality is reported in the literature.



Scheme 93: Chemistry of Knochel's zinc-magnesiate 184

The zinc-magnesiate was used immediately once prepared, and added to the bis-Boc pyrimidine **182** at r.t., following a literature procedure. Quench with D_2O after 2 h., revealed a 50% conversion by ^1H NMR to the mono-Boc pyrimidine **186**, although neither nitrile **183** nor C3-deuteration were observed (**Table 39**, entry 4). Formation of the latter two compounds was not promoted by a decrease in reaction time to 20 min. (entry 5).

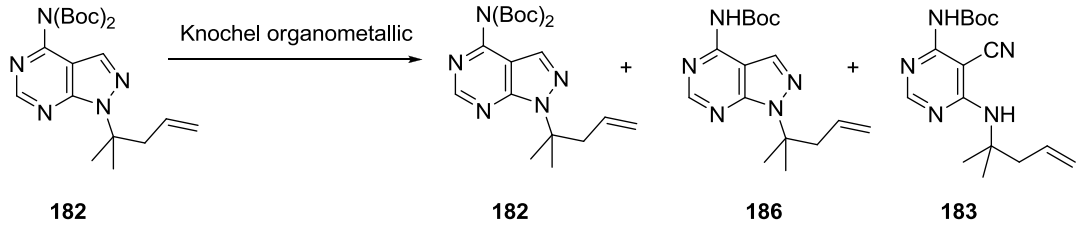
The zinc-magnesiate **184** did not appear to be strong enough to effect C3-metallation. Accordingly, a third of Knochel's organometallics, reported to be particularly effective for ester-directed metallation,[147] was prepared, using Schlenk technique. Lithium-TMP was first synthesised from treatment of TMPH with ^{n}BuLi at -40 °C, before the addition of TMPMgCl.LiCl. The volatiles were removed *in vacuo*, and the resulting solid re-dissolved in THF, to provide $TMP_2Mg.2LiCl$ **185** as a 0.56 M solution in THF (lit. 0.70 M) (**Scheme 94**).



Scheme 94: Chemistry of $(TMP)_2Mg.2LiCl$, 185

On treatment of the bis-Boc pyrimidine **182** with organometallic **185** at r.t., starting material, the mono-Boc pyrimidine **186** and nitrile **183** were again isolated (**Table 39**, entry 6). Reactions performed at lower temperatures with fewer equivalents of the organometallic resulted in no conversion of the bis-Boc pyrimidine **182** (entry 7).

Table 39: Selected pyrazole metallations with Knochel organometallics



182 **182** **186** **183**

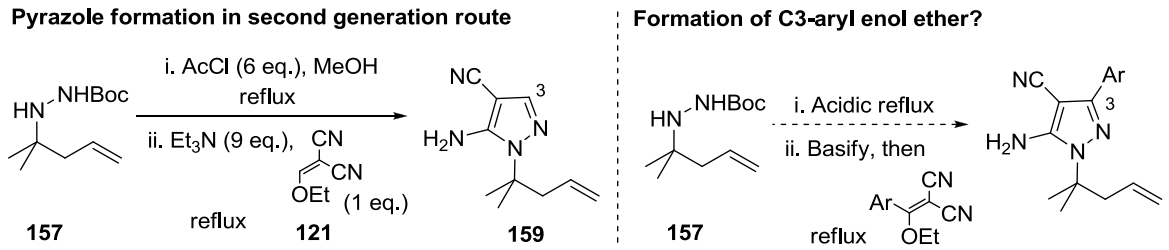
Entry	Organometallic (eq.)	Temperature (°C)	Time (h.)	Product ratio[a]		
				182	**186**	**183**
1	**177** (2.5)	23	2.0	0	(47)	(21)
2	**177** (2.5)	0	2.0	72	18	9
3	**177** (2.5)	0	0.3	80	10	10
4	**184** (0.6)	23	2.0	50	50	0
5	**184** (0.6)	23	0.3	66	33	0
6	**185** (2.5)	23	2.0	(16)	(16)	(21)
7[b]	**185** (1.1)	0	2.0	100	0	0

All reactions performed on 0.12 mmol scale, at [0.12 M], quenching with D_2O at the reaction temperature. Isolated yields in parentheses. [a] Calculated from relative intensities of signals in ^1H NMR of the crude product. [b] Quench with Et_3SiCl.

It seemed that the intermediate derived from C3-metallation using the Knochel reagents was too transient for electrophilic trapping prior to pyrazole collapse. Given the lack of success at C3-functionalisation of **159** despite the variety of methods attempted, it was considered prudent to adopt an alternative strategy to install the C3-aromatic.

2.3.3.4 An alternative enol ether

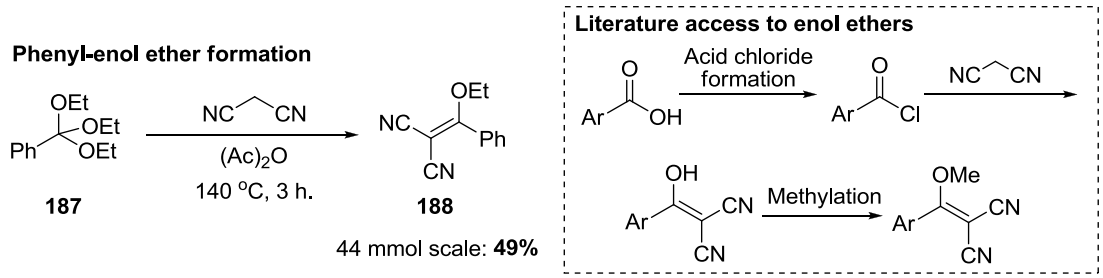
Review of the intermediate immediately prior to the pyrazolo[3,4-*d*]pyrimidine in the synthetic strategy offered a potential alternative for C3-functionalisation. The intermediate in question, pyrazole **159** is synthesised from condensation of the α-*tert*-amine **157** (pre-treated with acid for Boc-group hydrolysis) with enol ether **121** (**Scheme 95**). The enol ether bears a proton at the position that is to become the C3 of pyrazole **159**; would it be possible to condense an aryl-bearing enol ether with the α-*tert*-amine to establish C3-functionality at this step? Although this route would require installation of the C3-aromatic derivative relatively early in the synthesis, an advantage would be the lack of requirement for an extra synthetic step for C3-functionalisation.



Scheme 95: An aryl-enol ether for C3-aromatic installation

A literature search revealed that enol ethers bearing varied aromatic functionality are easily accessed from the corresponding benzoic acids.[148, 149] Formation of the acid chloride followed by condensation with malononitrile establishes the parent enol, and methylation provides the enol ether in reportedly good yields (**Scheme 96**). Additionally, phenyl-enol ether **188** can be prepared in a single step from the commercial phenyl-ortho ester **187** (**Scheme 96**).[150]

As it was unclear as to whether an aryl-enol ether would be reactive enough for condensation in the pyrazole-forming step, the readily accessible phenyl-enol ether was synthesised for testing. As in the synthesis of unsubstituted enol ether **121**, ortho ester **187** was treated with malononitrile in acetic anhydride, although an increased reaction temperature of 140 °C was required for phenyl-enol ether formation (cf. 80 °C for the hydro-enol ether **121**). Chromatographic purification provided the required compound **188** in 49% yield (**Scheme 96**).

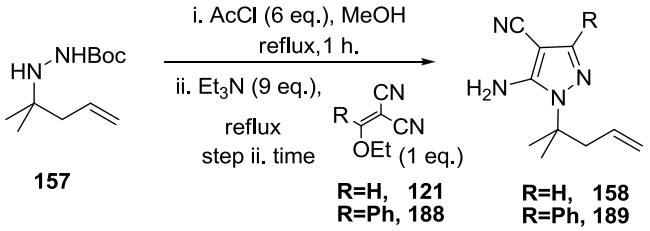


Scheme 96: Enol ether syntheses

Phenyl-enol ether **188** was applied in the pyrazole-forming step. Reflux of α-*tert*-amine **157** in acidic methanol led to the consumption of starting material by TLC analysis after 1 h., as observed previously. The reaction mixture was basified with triethylamine prior to the addition of phenyl-enol ether **188**. Further reflux of the reaction mixture led to complete consumption of enol ether **188** by TLC analysis after the slightly extended time of 2 h. 30 min. (*cf.* 1 h. for hydro-enol ether **121**). Work-up and chromatographic purification gratifyingly provided the C3-phenyl pyrazole **189** in 65% yield on 0.5 mmol scale (**Table 40**, entry 1). Moderate scale-up of the chemistry to 9.3 mmol led to a slight reduction in isolated yield (52%) (entry 2). Formation of the C3-phenyl compound **189** was somewhat lower yielding on moderate scale than the analogous C3-hydro pyrazole **158** (entry 2 *vs.* 3). It was

rationalised that the extended conjugation in phenyl-enol ether **188** decreased the relative reactivity of the substrate in comparison to the hydro-analogue **121**. Although complete consumption of the phenyl-enol ether was observed by TLC analysis prior to work-up, it is possible that the substrate is unstable to prolonged reflux under the basic conditions, leading to the decreased yield observed.

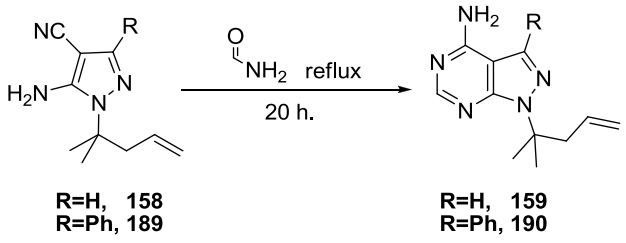
Table 40: Pyrazole formation



Entry	C3-functionality	Scale (mmol)	Step ii. time (h.)	Isolated yield (%)
1	Ph	0.5	2.5	65
2	Ph	9.3	2.5	52
3	H	21.0	1.0	63

Pyrimidine formation was subsequently tested on a 0.4 mmol scale. Complete conversion to a single product was observed by TLC analysis after reflux in formamide (20 h.). Purification by chromatography provided pyrimidine **190** in a moderate yield of 39% (*cf.* 66% isolated yield for C3-hydro pyrimidine **159**) (**Table 41**, entry 1 *vs.* 3). Interestingly, no by-product pyrimidone was detected by TLC or ^{1}H NMR analysis of the crude reaction mixture, despite the analogous by-product having been isolated from the pyrimidine-forming step for the C3-hydro compounds. Although the reaction was low-yielding, it was felt that continuing with the synthetic strategy to test the applicability of the C3-phenyl bearing intermediate to the developed route was of greater importance than optimisation of pyrimidine formation at this stage. As such, the reaction was scaled to 4.4 mmol, providing compound **190** in an identical yield (39%), proving reproducibility (entry 2).

Table 41: Pyrimidine formation

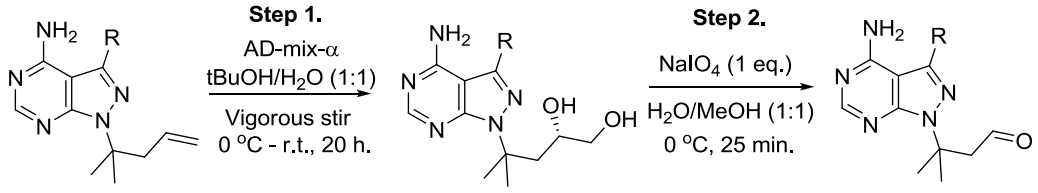


Entry	C3-functionality	Scale (mmol)	Isolated yield (%)
1	Ph	0.4	39
2	Ph	4.4	39
3	H	13.0	66

Ensuing treatment of compound **190** with AD-mix-α in ^{t}BuOH/H_2O successfully provided diol **191** in 93% on 0.34 mmol scale (**Table 42**, entry 1). The C3-phenyl diol **191** was found to be considerably

less polar than the C3-hydro derivative **160**, with EtOAc sufficient for extraction during work-up. A reaction on 3.1 mmol scale provided diol **191** in a slightly lower yield (79%, entry 2). Diol cleavage with periodate was high yielding, with reproducible isolated yields of aldehyde **192** on both small and moderate scales (entries 4 and 5). Yields at this step were comparable with those obtained for the C3-hydro aldehyde **125** (entry 3).

Table 42: Oxidative cleavage of alkene



R=H, 159
R=Ph, 190

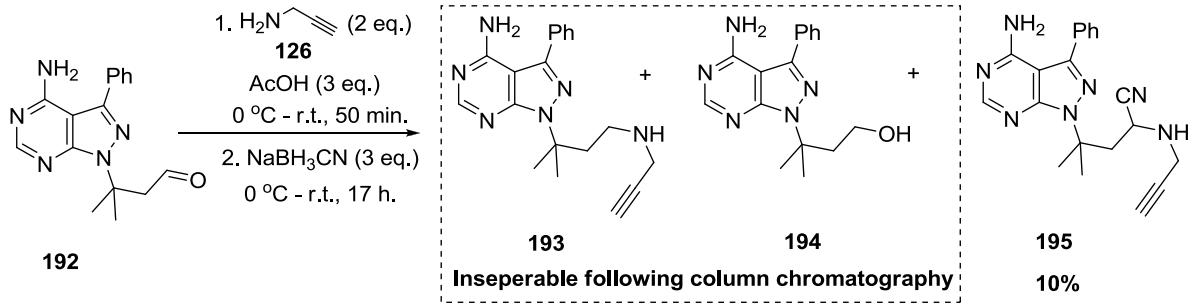
R=H, 160
R=Ph, 191

R=H, 125
R=Ph, 192

Entry	C3-functionality	Scale (mmol)	Isolated yield (%)	
			Step 1	Step 2
1	Ph	0.34	93	n/a[a]
2	Ph	3.10	79	n/a[a]
3	H	3.10	Quant.	82
4	Ph	0.15	n/a[a]	84
5	Ph	1.26	n/a[a]	78

[a] Not applicable

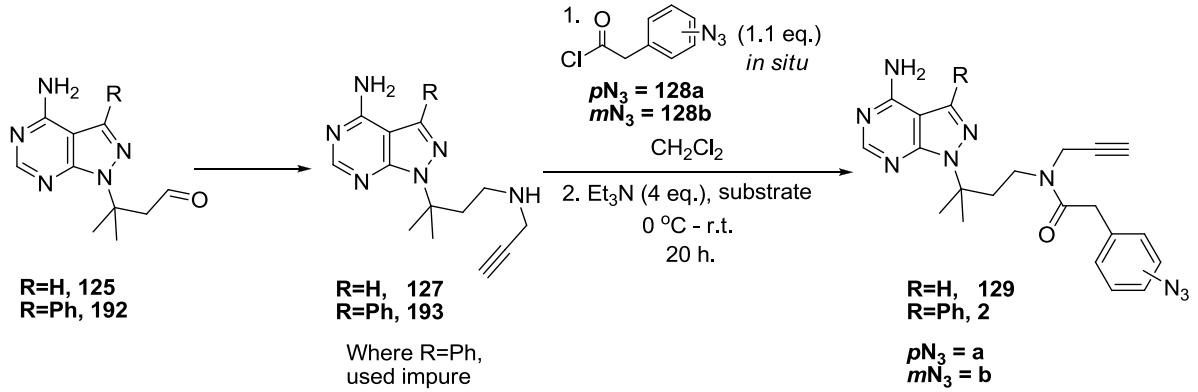
The penultimate synthetic step, reductive amination, proved to be challenging for C3-phenyl aldehyde **192**. Treatment with propargyl amine (**126**) in the presence of $NaCNBH_3$ under the previously described conditions, provided a mixture of products by TLC analysis after 17 h. Chromatographic purification of the crude reaction mixture yielded the required amine **193** as a 2:1 mixture with an impurity, tentatively assigned as primary alcohol **194** resulting from reduction of aldehyde **192** (**Scheme 97**). Despite considerable effort, a solvent system could not be found to separate the two compounds. Consequently, it was decided to proceed with the final amidation step using the crude material, in the hope that purification of the final compounds would be more facile. Scale-up of the reaction to 0.69 mmol afforded the crude amine in a poorer 1:1 mixture with the impurity. The increased scale of this reaction allowed the isolation of a second impurity, identified as nitrile **195**, in 10% yield (**Scheme 97**). Clearly the compound had arisen from addition of cyanide from the reducing agent into the imine, and could potentially be avoided through the use of an alternative reductant.



Scheme 97: Reductive amination of C3-phenyl aldehyde 192

The optimised amidation conditions for the final step were applied to the crude amine **193**. Thankfully, coupling with each of the acid chlorides **128a** and **b**, bearing the *para*- and *meta*-azido aryl functionalities, was successful. Chromatographic purification led to the isolation of the pure target compounds **2a** and **b** in similar yields which were calculated over two steps from aldehyde **192** (**Table 43**, entries 1 and 2). The yields were also comparable to the C3-hydro target compounds **129a** and **b**, when calculated over the final two steps (entries 3 and 4).

Table 43: Final-step amidation



Entry	C3-functionality	Scale (mmol)	Azide position	Isolated yield (%)[a]
1	Ph	0.25	*para*	34, **2a**
2	Ph	0.49	*meta*	30, **2b**
3	H	0.20	*para*	43, **129a**
4	H	0.20	*meta*	33, **129b**

[a] Yield calculated over 2 steps.

2.4 Conclusions

The synthesis of the C3-hydro target compounds had been improved, avoiding the capricious hydrohydrazination step. The α-*tert*-hydrazine motif had proved difficult to establish; Grignard reagent addition to an azodicarboxylate had not proved possible, due to difficulty in preparing the required tertiary organometallic. Similarly, amination of *tert*-butylamine with DppONHBoc had returned unreacted starting material. Synthesis of hydrazone **154** derived from *tert*-butyl carbazate

(**153**) and acetone, followed by reduction with allyl magnesium bromide had finally provided robust access to an analogous α-*tert*-hydrazine **157** to that used in the first generation route (**Scheme 99**). Allyl magnesium bromide was the only reagent of several attempted, observed to alkylate the hydrazone. It was possible to rejoin the first generation route at a late stage aldehyde **125**; the second generation route provided access to the intermediate in high purity, which had not proved possible with the first generation strategy. The penultimate step of the first generation route provided alkyne **127** in comparable yield. Treatment of **127** with acid chlorides **128a** and **b** synthesised *in situ* to install the aryl-azide functionality, provided the C3-hydro target compounds **129** in moderate yield (**Scheme 99**).

C3-functionalisation of the intermediate C3-hydro pyrazolo[3,4-*d*]pyrimidine **159** (**Fig. 11**) was attempted, using literature CH activation protocols and specialised organometallic reagents. Return of starting material in the majority of cases led to the free amine of the pyrimidine being protected as its di-Boc derivative **182** (**Fig. 11**). Evidence of C3-metallation of this analogue was provided on the isolation of nitrile **183** (**Fig. 11**) following treatment with an organometallic, assumed to have arisen from pyrazole collapse following C3-anion formation. Stabilisation of the anion for electrophillic trapping prior to pyrazole collapse did not prove possible, despite using lower reaction temperatures and alternative organometallic reagents.

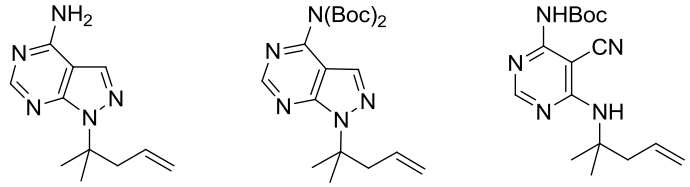
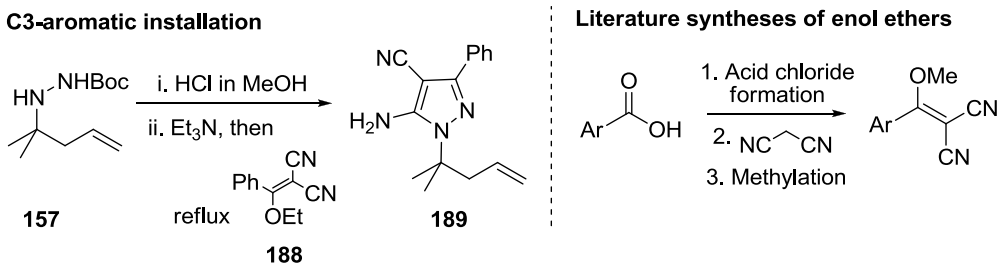


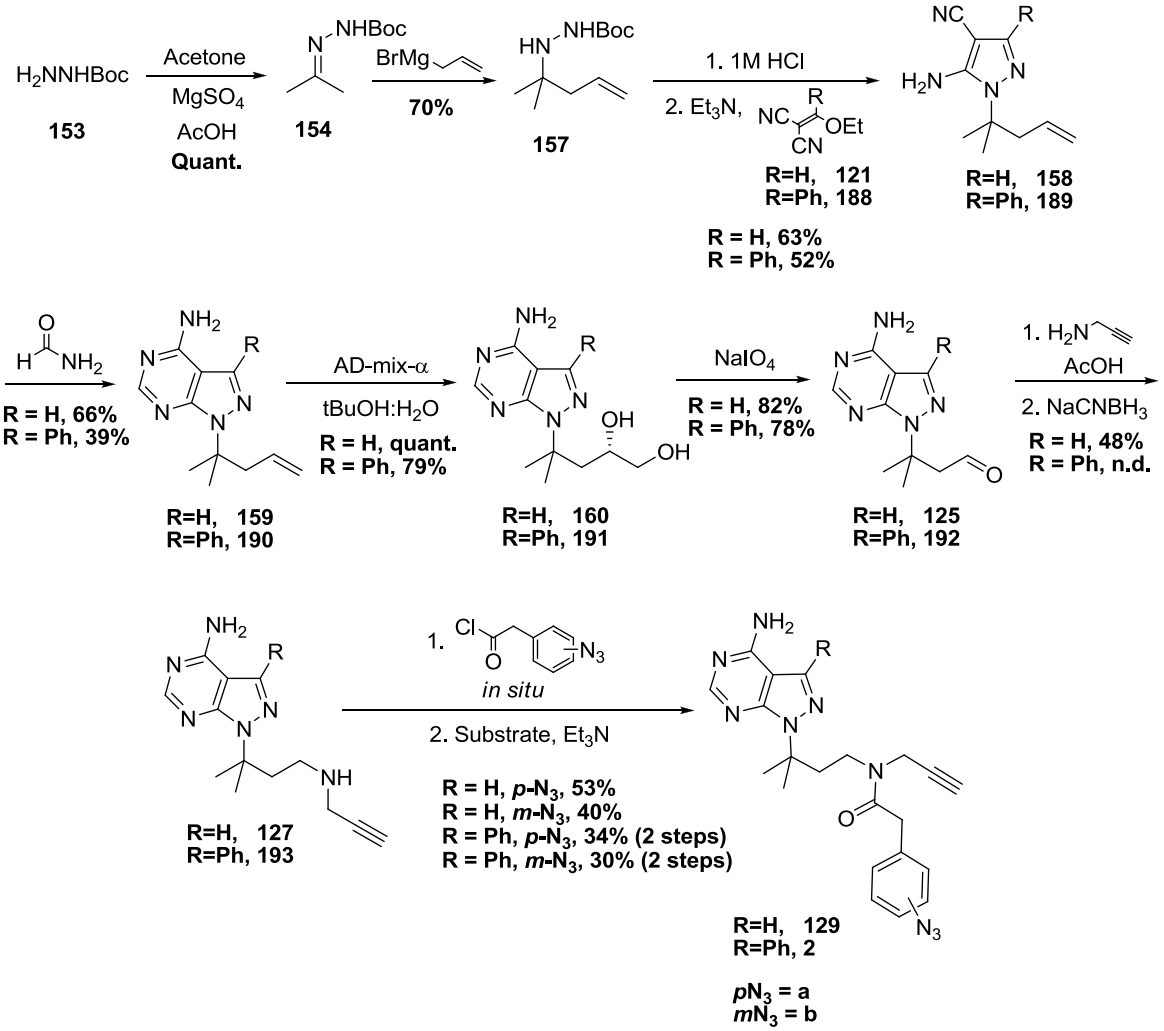
Fig. 11: Pyrimidine derivatives

An alternative strategy was opted for, whereby the required C3-aromaic functionality was incorporated in the enol ether used at the pyrazole-forming step (**Scheme 98**). Although this route required early installation of the C3-aromatic, which was less desirable due to the derivatisation required at this position, no extra step(s) for C3-functionalisation were required. Additionally literature syntheses exist to access a variety of aryl-enol ethers using simple chemistry from benzoic acid derivatives (**Scheme 98**).



Scheme 98: Aryl enol ether synthesis and reactivity

Use of the the phenyl enol ether in the second generation route led to the isolation of two target pyrazolo[3,4-*d*]pyrimidines **2a** and **b** (**Scheme 99**).



Scheme 99: Second generation route to C3-hydro and C3-phenyl target compounds

Further work on this project includes the incubation of the target compounds with PKCα (M417A) to establish proof of concept cross-linking. If successful, then the remaining C3-arylated target compounds **2** should be synthesised and subject to testing.

In terms of methodological development, the susceptibility of alternative hydrazones (synthesised from readily available ketones) to treatment with allyl magnesium bromide could be investigated. If the chemistry has considerable scope, then this methodology provides a useable synthetic method to access α-*tert*-hydrazines and thus, α-*tert*-pyrazolo[3,4-*d*]pyrimidines. As a result, varied α-*tert*-pyrazolo[3,4-*d*]pyrimidines could be tested as ATP mimics, which has not previously been possible due to the lack of available synthetic methods to access the structural motif.

3. Experimental

3.1 General procedures

All reactions were carried out under an Argon atmosphere in oven (160 °C) or flame-dried glassware unless otherwise stated.

Solvents: EtOH was distilled from MgOEt and stored over 4Å molecular sieves; Et_2O, THF, CH_2Cl_2, and PhMe were purified by Innovative Technology Inc. PureSolv™ Solvent Purification System. H_2O was distilled for use in reactions. Acetone was used as commercially supplied. Where solvent mixtures were used, the ratios refer to component volumes.

Reagents: Formamide was purchased and used within 2 months. For the final step amidation to access the C3-aryl pyrazolo[3,4-*d*]pyrimidines, Et_3N was distilled and stored over 3Å molecular sieves. CH_2Cl_2 solutions of *m*CPBA were washed with a phosphate buffer (pH = 7.4) and dried ($MgSO_4$). KH was washed with hexane (x 3) and dried under high vacuum for 5 min. γ-Butyrolactone was distilled. NaOH was ground to a fine powder immediately prior to use in all aziridination protocols. Anhydrous NMM was purchased for aziridinations and used as supplied. Anhydrous ^{i}PrOH was purchased and used as supplied. Indole was recrystalised from hexane. Commercial organometallic solutions were titrated against salicalhydrazine[141] prior to use. All other reagents were used as commercially supplied.

Chromatography: Flash chromatography was carried out using silica gel (Merck Kieselgel 60 F_{254} 230-400 mesh) or neutral aluminium oxide (Merck, 63-200 μm). TLC was performed using glass-backed plates pre-coated with silica gel 60 F_{254} or Merck aluminium backed silica gel 60 F_{254} plates, and visualised by UV radiation (254 nm) or $KMnO_4$ in water as stated.

IR spectroscopy: Spectra were recorded on a Perkin Elmer Spectrum FT-IR Spectrometer; absorbancies (ν_{max}) are recorded in wavenumbers (cm^{-1}).

NMR spectroscopy: All chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane (0.00 ppm). All coupling constants are reported in Hertz (Hz).
^{1}H NMR spectroscopy: Spectra were recorded at 400 and 500 MHz on Bruker AV400, AV500 or DRX-400 spectrometers, in $CDCl_3$, d_6-DMSO, CD_3OD, with reported values referenced to the residual protic solvent peak; $CDCl_3$ (δH = 7.26), d_6-DMSO (δH = 2.50), CD_3OD (δH = 3.30). Data are reported as follows: chemical shift (δ) (to the nearest 0.01 ppm), (number of protons, multiplicity, coupling constant *J* (Hz, reported to the nearest 0.1 Hz), assignment. The term 'multiplet' is only used for symmetrically centred peaks.

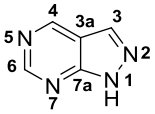
^{13}C NMR spectroscopy: Spectra were recorded at 101 and 126 MHz on Bruker AV400, AV500 or DRX-400 spectrometers, in $CDCl_3$, d_6-DMSO, CD_3OD, with reported values referenced to the appropriate solvent peak; $CDCl_3$ (δC = 77.0), d_6-DMSO (δC = 39.5), CD_3OD (δC = 49.1). Chemical shifts are reported to the nearest 0.1 ppm.

^{31}P NMR spectroscopy: Spectra were recorded at 162 MHz on a Bruker AV400 spectrometer, in $CDCl_3$, or d_6-DMSO. Chemical shifts are reported to the nearest 0.1 ppm.

Mass spectrometry: Low resolution mass spectra (*m/z*) were recorded on VG Platform II or VG AutoSpec spectrometers, with only molecular ions (*e.g.* MH^+), and major fragmentation peaks reported. High resolution mass spectra were recorded on a VG AutoSpec spectrometer.

Melting points: Melting points were determined on a Reichert microscope melting point apparatus.

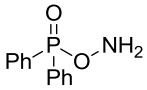
Nomenclature: Compounds are names according to IUPAC nomenclature. Skeleton carbon/nitrogen atoms in compounds containing the pyrazolo[3,4-*d*]pyrimidine ring system are numbered according to IUPAC conventions:



3.2 Experimental details

3.2.1 Aziridination and ring-opening

O-Diphenylphosphinyl hydroxylamine, 39[53]



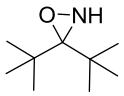
Adapted from the procedure of Armstrong *et al.*[53] Aqueous NaOH (3.89 g, 97.5 mmol in 14.0 mL H_2O) was added to a stirred solution of hydroxylamine hydrochloride (7.93 g, 114.5 mmol) in H_2O (17 mL) in air. Dioxane (60 mL) was added and the solution cooled to -3 °C using an ice-salt bath. Diphenylphosphinic chloride (10.00 g) in dioxane (50 mL) was added in one portion with vigorous stirring. Rapid precipitation ensued and the flask contents were swirled manually when magnetic stirring failed. After 5 min., H_2O was added (60 mL). The slurry was filtered and washed with H_2O (60 mL). The white, tacky solid produced was dried in a dessicator for 3 h. The solid was then slurried with NaOH (1 g in 100 mL H_2O). After 30 min., the slurry was filtered and the white tacky product dried in a dessicatior for 18 h. The pure product was isolated as white crumbly solid (4.40 g, 45%). Mp > 130 ° C [lit. >130 ° C[53]]; δH ($CDCl_3$, 400 MHz) 7.82-7.87 (4H, Ar**H**), 7.57-7.54 (2H, Ar**H**),

7.50-7.47 (4H, Ar**H**), 5.90 (2H, br s, N**H**$_2$); δP ($CDCl_3$, 162 MHz) δ 37.6. All data are in agreement with reported values.[53]

Alternative synthesis

According to the procedure of Lahulé *et al*.[72] Hydroxylamine hydrochloride (6.46 g, 93 mmol) was dissolved in H_2O (20 mL) and cooled to -10 °C (acetone/dry ice, bath temperature) with overhead stirring. A solution of NaOH (3.58 g, 89 mmol) in H_2O was prepared and cooled to 0 °C. The NaOH solution was added to the hydroxylamine solution at -10 °C. Et_2O (180 mL) was added, and the solution cooled to -15 °C (bath temperature). Diphenylphosphinic chloride (10.00 g, 42.3 mmol) was added at this temperature, in one portion *via* syringe. Copius precipitation of white solid was observed, and the reaction mixture was stirred vigorously at -15 °C for 10 min. The acetone/dry ice bath was removed and the reaction vessel quickly submerged in an ice bath at 0 °C. The reaction was stirred at 0 °C (bath temperature) for a further 15 min. The reaction mixture was filtered, washing with cold (4 °C) distilled water (60 mL) then Et_2O (70 mL). The resulting white solid was dried in air for 4 h., before drying under high vacuum for 14 h. A solution of NaOH (1.20 g, 30 mmol) in distilled water (120 mL) was prepared and cooled to 0 °C. The crude product was slurried in the NaOH solution and stirred at 0 °C for 30 min. The solution was filtered, and washed with cold (8 °C) distilled water (40 mL). The resulting white solid was dried in air for 1.5 h., before freeze drying for 20 h. The pure product was provided as a white powdery solid (10.30 g, quant.).

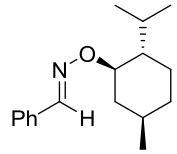
3,3'-Di-*tert*-butyl oxaziridine, 48[76]



Adapted from the procedures of Kostyanovskii *et al.*[151] and Ellman *et al.*[76] 2,2,4,4,tetramethyl pentanone imine (2.0 g, 14.0 mmol) was added to CH_2Cl_2 (10 mL), and cooled to 0 °C. *m*CPBA (2.7 g, 16.0 mmol) in CH_2Cl_2 (50 mL) was added *via* dropping funnel over 1.5 h. behind a blast shield, maintaining the temperature between -2 °C and +3 °C. After the addition, the reaction was stirred at 0 °C for 1 h. $NaHCO_3$ (sat. aq., 60 mL) was added, and the aqueous phase extracted with CH_2Cl_2 (3 x 40 mL). The organic phases were combined and dried over $MgSO_4$ and concentrated *in vacuo*, with the rotary evaporator behind a blast shield. Kugelrohr distillation (2 mm Hg, 21 °C) provided the oxaziridine (1.3 g, 60%) as a pale yellow runny oil (93% purity by ^{1}H NMR, with 7% di-*tert*-butyl ketone). R*f* 0.50 ($KMnO_4$ dip, EtOAc/petroleum ether, 1:10); ν_{max}/cm^{-1} 2962 (br), 1684, 1484, 1368, 1192; δH ($CDCl_3$, 400 MHz) 1.15 (18H, s, C(C**H**$_3$)); δC ($CDCl_3$, 101 MHz) 85.2, 37.5, 28.0; *m/z* HRMS (NH_3 CI$^+$), found: MH$^+$, 158.1551. $C_9H_{19}NOH$ requires 158.1546, Δ 3.8 ppm. All data are in agreement with reported values.[76] NB: Although no problems were observed during the preparation

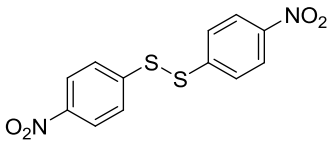
and handling of oxaziridine **48**, the potentially explosive nature of the reagents and product should be realised. Manipulations should be performed behind a blast shield where possible.

Benzaldehyde *O*-(1*R*, 2*S*, 5*R*)-(-)-menthol oxime, 51[76]



Adapted from the procedure of Ellman *et al.*[76] A solution of menthol (120 mg, 0.77 mmol) and 18-crown-6 (20 mg, 0.07 mmol) in anhydrous DMPU (1 mL) was transferred *via* cannula over 15 min to a suspension of washed KH (40 mg, 0.92 mmol) in DMPU (1 mL) at r.t. After 1 h., the alkoxide solution was added dropwise over 10 min. to a solution of 3,3'-di-*tert*-butyl oxaziridine **48** (377 mg, 1.54 mmol, ca. 90% pure) in DMPU (1 mL) at -40 °C. The solution was warmed to r.t. over 2 h. Benzaldehyde (0.1 mL, 0.92 mmol) was added followed by AcOH (1 drop). On the addition of the benzaldehyde, the solution turned from yellow to brown. After 0.5 h, the reaction was diluted with Et_2O (30 mL) and washed with NaCl (sat. aq., 8 x 30 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to provide the crude product as yellow oil (305 mg). Purification by column chromatography eluting with EtOAc/petroleum ether (1:100) provided the pure product as clear oil (74 mg, 37%). R*f* 0.40 (UV 254 nm, EtOAc/petroleum ether, 100:1); ν_{max}/cm^{-1} 2960 (CH), 2930 (CH), 2878 (CH), 1454 (CH); δH ($CDCl_3$, 400 MHz) 8.08 (1H, s, NC**H**), 7.61 (2H, m, Ar**H**), 7.40 (3H, m, Ar**H**), 4.08 (1H, dt, *J* 10.0 and 4.4, **H**CON), 2.29 (1H, m), 2.22 (1H, dquin, *J* 6.8 and 2.8), 1.75 (2H, m), 1.57-1.43 (2H), 1.17-1.09 (2H), 0.97 (6H, m, *J* 7.2), 0.88 (4H, d, *J* 6.8); δC ($CDCl_3$, 101 MHz) 147.5, 132.9, 129.4, 128.6, 126.8, 83.0, 47.0, 41.5, 34.6, 31.6, 26.1, 23.8, 22.3, 20.8, 16.6; *m/z* HRMS (NH_3 CI^+), found: MH^+, 260.2010. $C_{17}H_{25}NOH$ requires 260.2014, Δ 1.5 ppm. All data are in agreement with reported values.[76]

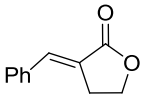
***Bis*(4-nitrophenyl)disulfide, 55**[152]



Adapted from the procedure of Schmitz *et al.*[75] 3,3'-Di-*tert*-butyl oxaziridine **48** (33 mg, 21 mmol) was dissolved in CH_2Cl_2 (1 mL), and nitrobenzene thiol (30 mg, 19 mmol) added. The mixture was stirred for 45 min. at r.t., at which time a yellow precipitate was seen forming. The sample was concentrated *in vacuo*, providing the crude product as a yellow powder (11 mg). Purification by column chromatography eluting with EtOAc/petroleum ether (1:5) provided the pure disulfide as a yellow powder (8 mg, 13%). Mp 185-188 °C [lit. 177-178 °C[153]]; R*f* 0.40 (UV 254 nm, EtOAc/petroleum ether, 1:5); ν_{max}/cm^{-1} 3100 (CH), 2925 (CH), 1597, 1545, 1476; δH ($CDCl_3$, 400

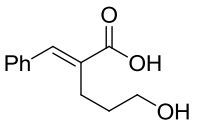
MHz) 8.24 (4H, dt, *J* 8.8 and 2.4 Ar**H**), 7.66 (4H, dt, *J* 8.8 and 2, Ar**H**); δC ($CDCl_3$, 101 MHz) 147.0, 144.1, 126.4, 124.5; *m/z* HRMS (NH_3 CI^+), found: MNH_4^+, 326.0271. $C_{12}H_{12}N_3O_4S_2$ requires 326.0269, Δ 0.5 ppm. All data are in agreement with reported values.[152]

(3*E*)-3-Benzylidenedihydrofuran-2(3*H*)-one, 63[154]



Adapted from the procedures of Lewis *et al.*[154] Anhydrous hexane (5 mL) was added to freshly cut Na (0.5 g, 22 mmol) and cooled to 0 °C. MeOH (7 mL, 176 mmol) was added dropwise over 20 min. After addition was complete, the ice-bath was removed and the reaction was stirred until no Na (s) remained. The solvent was removed under reduced pressure, and the resulting NaOMe (white solid) was suspended in Et_2O (12 mL). γ-Butyrolactone (1.48 mL, 18 mmol) in Et_2O (4 mL) was added in one portion, followed by freshly distilled benzaldehyde (2.12 mL, 20 mmol) in Et_2O (4 mL), also in one portion. On addition of the benzaldehyde, precipitation was noted, and the reaction turned from clear to bright cloudy yellow. An exotherm was also noted. After 1 h, H_2O (10 mL) was added, followed by HCl (aq., 1M, 15 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL), the organics washed with Na_2SO_3 (sat. aq., 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*, to provide the crude product as pale yellow solid (1.26 g). Column chromatography eluting with EtOAc/petroleum ether (3:1) provided the pure product as white flaky crystals (0.87 g, 24%). Mp 117-20 °C [lit. 117 °C[154]]; R*f* 0.4 ($KMnO_4$ dip, petroleum ether/EtOAc, 3:1); ν_{max}/cm^{-1} 1738 (s) (C=O); δH ($CDCl_3$, 400 MHz) 7.59 (1H, t, *J* 3.0, PhC**H**), 7.55-7.41 (5H, Ph**H**), 4.48 (2H, t, *J* 7.6, $CO_2C\mathbf{H}_2$), 3.26 (2H, dt, *J* 7.6 and 3.0, CHCC$\mathbf{H}_2$); δC ($CDCl_3$, 101 MHz) 172.5, 136.7, 134.7, 130.0, 129.9, 128.9, 123.5, 65.4, 27.5.[154] *m/z* HRMS (NH_3 CI^+), found: MH^+, 175.0755. $C_{11}H_{11}O_2$ requires 175.0759, Δ 2.3 ppm. All data are in agreement with reported values.[154]

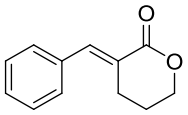
(2*E*)-2-Benzylidene-5-hydroxypentanoic acid, 65[80]



Adapted from the procedure of Lewis *et al.*[154] Anhydrous hexane (5 mL) was added to freshly cut Na (0.67 g, 29 mmol) and cooled to 0 °C. MeOH (7 mL, 176 mmol) was added dropwise over 15 min. After the addition was complete, the ice-bath was removed and the reaction was stirred until no Na (s) remained. The solvent was removed *in vacuo*, and the resulting NaOMe (white solid) was suspended in Et_2O (12 mL). δ-Valerolactone (1.74 mL, 18 mmol) in Et_2O (4 mL) was added in one portion. The mixture was then cooled to 0°C, and benzaldehyde (2.12 mL, 20 mmol) in Et_2O (4 mL), added in one portion. On the addition of benzaldehyde, a yellow precipitate was observed forming. After 1 h., H_2O

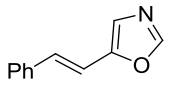
(10 mL) was added, followed by HCl (aq., 1M, 15 mL). The aqueous phase was extracted with Et_2O (3 x 20 mL), the organics washed with Na_2SO_3 (sat. aq., 10 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*, to provide the crude product as pale yellow solid (1.26 g) in a 1:2.3 ratio with the cyclised lactone, visible by ^{1}H NMR. Recrystalisation (Et_2O) provided the hydroxy acid as white flaky crystals (166 mg, 6%). Mp 97-102 °C [lit. 99-100 °C[80]]; R_f 0.0 (UV 254 nm, petroleum ether/EtOAc, 3:1); ν_{max}/cm^{-1} 3288 (br) (OH), 2529 (br) (OH), 1674 (s) (C=O); δH (CD_3OD, 400 MHz) 7.73 (1H, s, PhC**H**), 7.49-7.35 (5H, Ph**H**), 3.64 (2H, t, *J* 6.8, C**H**$_2$OH), 2.66 (2H, m, PhCHCC**H**$_2$), 1.86 (2H, m, HOCH$_2$C**H**$_2$); *m/z* HRMS (NH_3 CI^+), found: MH^+, 207.1028, $C_{12}H_{15}O_3$ requires 207.1021, Δ 3.3 ppm. All data are in agreement with reported values.[80]

(3*E*)-3-Benzylidenetetrahydro-2*H*-pyran-2-one, 64[80]



Adapted from the procedure of Six *et al*.[80] 2-benzilydene-propanoic acid-5-ol **65** (236 mg, 1.14 mmol) was dissolved in and toluene (20 mL), $MgSO_4$ (200 mg, 1.67 mmol) added, and the reaction heated to 120 °C. After 20 h., the heat source was removed and the reaction allowed to cool. The $MgSO_4$ was filtered off, and the solvent removed *in vacuo* to provide the pure product as a clear oil in quantitative yield. R*f* 0.50 (UV 254 nm, EtOAc/petroleum ether, 1:3); ν_{max}/cm^{-1} 2937 (CH), 2860 (CH), 1707 (s) (C=O), 1616; δH ($CDCl_3$, 400 MHz) 7.93 (1H, t, *J* 2.4, PhC**H**), 7.46-7.33 (5H, Ph**H**), 4.41 (2H, m, OC**H**$_2$), 2.90 (2H, m, CHCC**H**$_2$), 2.00 (2H, m, OCH$_2$C**H**$_2$); δC ($CDCl_3$, 101 MHz) 167.0, 141.6, 135.0, 130.2, 129.1, 128.6, 125.8, 68.7, 25.9, 23.0; *m/z* HRMS (ESI^+), found: MH^+, 189.0920. $C_{12}H_{13}O_2$ requires 189.0916, Δ 2.1 ppm. All data are in agreement with reported values.[80]

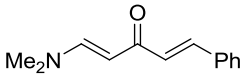
5-[(*E*)-2-Phenylethenyl]-1,3-oxazole, 70[81]



According to the procedure of Šagud.[81] MeOH (4.5 mL) was added to TosMIC (148 mg, 0.76 mmol) and K_2CO_3 (105 mg, 0.76 mmol), followed by cinnamaldehyde (95 μL, 0.76 mmol). The mixture was heated to reflux, and after 15 min. heating, all solid had dissolved to give a clear yellow solution. After 4 h., the heat was removed and the reaction allowed to cool to r.t. The volatiles were removed *in vacuo* and H_2O (10 mL) added. The aqueous phase was extracted with Et_2O (3 x 10 mL), and dried over $MgSO_4$. The organic phase was concentrated *in vacuo* to give a yellow oil (968 mg). Purification by column chromatography eluting with EtOAc/petroleum ether (1:5) provided the pure product as a beige powder (44 mg, 34%). R*f* 0.20 (UV, 254 nm, EtOAc/petroleum ether 1:5); δH ($CDCl_3$, 400 MHz) 7.84 (1H, s, oxazole N=C**H**), 7.50-7.45 (2H, m, Ph**H**), 7.39-7.34 (2H, t, *J* 7.3, Ph**H**), 7.32-7.26 (1H, tt, *J* 7.3 and 2.3, Ph**H**), 7.12 (1H, d, *J* 16.3, alkene C**H**), 7.07 (1H, s, oxazole OC=C**H**), 6.93

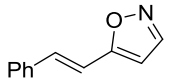
(1H, d, *J* 16.3, alkene C**H**); δC ($CDCl_3$, 101 MHz) 150.5, 150.4, 136.2, 130.3, 128.8, 128.4, 126.6, 124.1, 112.9. All data are in agreement with reported values.[81]

(1*E*,4*E*)-1-(Dimethylamino)-5-phenylpenta-1,4-dien-3-one, 73[82]



Adapted from the procedure of Tobinaga *et al.*[83] Benzylideneacetone (500 mg, 3.4 mmol) was dissolved in anhydrous DMF (3 mL) and bis(dimethylamino)methoxymethane (523 μL, 3.4 mmol) added in one portion. Concentrated H_2SO_4 (one drop) was added, and the reaction turned from clear to cloudy. After stirring at r.t. for 1 h. 30 min., EtOAc (10 mL) was added, and the organic phase washed with brine (6 x 10 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to provide the crude product as a yellow oil. Purification by column chromatography eluting with EtOAc provided the pure product as a yellow solid (187 mg, 27%). Mp 75-77 °C [lit. 87-89[83]]; R*f* 0.20 (UV, 254 nm, EtOAc); ν_{max}/cm^{-1} 3026 (CH), 2928 (CH), 1657 (C=O), 1610; δH ($CDCl_3$, 400 MHz) 7.83 (1H, d, *J* 12.7, NMe_2C**H**), 7.60 (1H, d, *J* 16.1, PhC**H**), 7.56-7.53 (2H, Ph**H**), 7.38-7.30 (3H, Ph**H**), 6.81 (1H, d, *J* 16.1, PhCHC**H**), 5.30 (1H, d, *J* 12.7, NMe_2CHC**H**), 3.14 (3H, br s, NC**H**$_3$), 2.91 (3H, br s, NC**H**$_3$); δC ($CDCl_3$, 101 MHz) 186.3, 153.4, 138.5, 135.8, 129.2, 128.7, 128.3, 127.9, 96.4, 45.0, 37.2; *m/z* HRMS (EI^-), Found: M-H, 200.1073. $C_{13}H_{14}NO$ requires 200.1069, Δ 1.7 ppm.

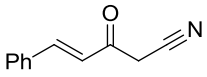
5-[(*E*)-2-Phenylethenyl]-1,2-oxazole, 74[82]



Adapted from the procedure of Takeuchi *et al.*[82] Hydroxylamnine hydrochloride (166 mg, 2.6 mmol) and K_2CO_3 (165 mg, 1.3 mmol) were added to a flame dried flask followed by 1-dimethylamino-5-phenyl-1,4-pentadien-3-one **73** (187 mg, 0.9 mmol) as a solution in anhydrous EtOH (3 mL). The mixture was heated to reflux for 3 h., when TLC analysis showed complete consumption of starting enaminone. The heat was removed and the reaction allowed to cool before the volatiles were removed *in vacuo*. The residue was dissolved in $CHCl_3$ (10 mL) and washed with H_2O (10 mL). The aqueous phase was extracted with further portions of $CHCl_3$ (2 x 10 mL). The organics were combined and washed with HCl (aq., 1M, 15 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to provide the crude product as a yellow oil (147 mg). Purification by column chromatography eluting with EtOAc/petroleum ether (1:10) provided the pure product as a white oil (22 mg, 14%). R*f* 0.30 (UV, 254 nm, EtOAc/petroleum ether 1:10); ν_{max}/cm^{-1} 3060 (CH), 1653, 1585; δH ($CDCl_3$, 400 MHz) 8.23 (1H, d, *J* 1.6, isoxazole-C(**H**)N), 7.54-7.51 (2H, Ph**H**), 7.41-7.32 (3H, Ph**H**), 7.41 (1H, d, J 16.4, alkene-C**H**), 7.02 (1H, d, *J* 16.4, alkene-C**H**), 6.27 (1H, d, *J* 1.6, isoxazole-

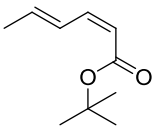
C(**H**)C(H)N); δC ($CDCl_3$, 101 MHz) 167.9, 150.6, 135.5, 135.0, 129.2, 128.9, 127.1, 112.9, 100.7; *m/z* HRMS (NH_3 CI^+), found: MH^+, 172.0754. $C_{11}H_{10}NO$ requires 172.0762, Δ 4.6 ppm.

(4*E*)-3-Oxo-5-phenylpent-4-enenitrile, 76



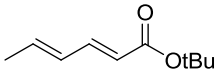
Adapted from the procedure of Armstrong *et al.*[53] $DppONH_2$ (31 mg, 0.13 mmol) was suspended in anhydrous MeCN (2 mL). NMM (15 μL, 0.13 mmol) was added dropwise over 1 min., and the resulting suspension stirred for 30 min. NaOH (10 mg, 0.26 mmol) was added, followed by *trans*-5-styrylisoxazole (22 mg, 0.13 mmol) in MeCN (0.5 mL). The reaction was stirred at r.t. for 16 h. NH_4Cl (sat. aq., 7 mL) was added, and the aqueous phase extracted with CH_2Cl_2 (3 x 7 mL). The organic phase was dried over $MgSO_4$ and and concentrated *in vacuo* to provide the crude product as a yellow solid (27 mg). Purification by column chromatography eluting with EtOAc/petroleum ether (1:3) provided the pure product as a white solid (20 mg, 91%). Mp 99-101 °C [lit. 97-8 °C[155]]; R*f* 0.20 (UV, 254 nm, EtOAc/petroleum ether 1:3); ν_{max}/cm^{-1} 3064 (CH), 2958 (CH), 2261 (C≡N), 1678 (C=O); δH ($CDCl_3$, 400 MHz) 7.70 (1H, d, *J* 15.9, PhC**H**), 7.60-7.57 (2H, Ph**H**), 7.49-7.41 (3H, Ph**H**), 6.89 (1H, d, *J* 15.9, PhCHC**H**), 3.72 (2H, s, C(O)C$\mathbf{H_2}$); δC ($CDCl_3$, 101 MHz) 186.4, 146.6, 133.4, 131.7, 129.2, 128.9, 122.4, 114.0, 30.9; *m/z* HRMS (NH_3 CI^+), found: MNH_4^+, 189.1026. $C_{11}H_{13}N_2O$ requires 189.1028, Δ 1.1 ppm.

***tert*-Butyl (2*Z*,4*E*)-hexa-2,4-dienoate, 88b**



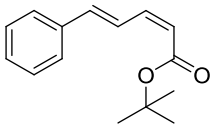
(*tert*-Butoxycarbonylmethylene)triphenylphosphorane **81** (1.41 g, 3.75 mmol) was dissolved in anhydrous EtOH (25 mL). *trans*-Crotonaldehyde (0.31 mL, 3.75 mmol) was added in one portion and the reaction mixture stirred at r.t. After 2 h. 30 min., the volatiles were removed *in vacuo*. Purification by column chromatography eluting with EtOAc/petroleum ether (1:50) provided the pure product as a clear oil (0.05 g, 8%). R*f* 0.70 (UV, 254 nm, EtOAc/petroleum ether 1:10); ν_{max}/cm^{-1} 2979 (CH), 1712 (C=O), 1644; δH ($CDCl_3$, 400 MHz) 7.39 (1H, m, alkene-**H**), 6.48 (1H, m, *J* 12.3, alkene-**H**), 6.07 (1H, m, alkene-**H**), 5.47 (1H, d, *J* 12.3, C(O)C**H**), 1.86 (3H, d, *J* 6.4, C$\mathbf{H_3}$), 1.48 (9H, s, C(C$\mathbf{H_3}$)$_3$); δC ($CDCl_3$, 101 MHz) 166.1, 144.1, 139.5, 128.3, 117.3, 80.0, 28.2, 18.6. *m/z* HRMS (NH_3 CI+), found: MH^+, 169.1233. $C_{10}H_{17}O_2$ requires 169.1229, Δ 2.8 ppm.

***tert*-Butyl (2*E*,4*E*)-hexa-2,4-dienoate, 88a**[156]



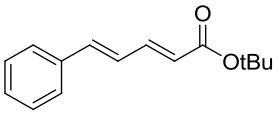
The title compound was synthesised according to the procedure for **88b**. (0.29 g, 46%). R*f* 0.50 (UV, 254 nm, EtOAc/petroleum ether 1:10); δH ($CDCl_3$, 400 MHz) 7.17 (1H, m, alkene-**H**), 6.19-6.03 (2H, alkene-**H**), 5.70 (1H, d, *J* 15.1, C(O)C**H**), 1.83 (3H, d, *J* 6.3, C$\mathbf{H_3}$), 1.47 (9H, s, C(C$\mathbf{H_3}$)$_3$); δC ($CDCl_3$, 101 MHz) 166.7, 143.9, 138.5, 129.8, 121.0, 80.0, 28.2, 18.6. All data are in agreement with reported values.[156]

***tert*-Butyl (2*Z*,4*E*)-5-phenylpenta-2,4-dienoate, 87b**



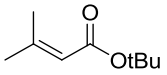
(*tert*-Butoxycarbonylmethylene)triphenylphosphorane **81** (1.41 g, 3.75 mmol) was dissolved in anhydrous EtOH (25 mL). *trans*-Cinnamaldehyde (0.47 mL, 3.75 mmol) was added in one portion and the reaction mixture heated to reflux. After 16 h., the reaction was allowed to cool, and the volatiles removed *in vacuo*. Purification by column chromatography eluting with EtOAc/petroleum ether (1:50) provided the pure product as a clear oil (0.36 g, 41%). R*f* 0.45 (UV, 254 nm, EtOAc/petroleum ether 1:20); ν_{max}/cm^{-1} 2984 (CH), 1704 (C=O), 1624; δH ($CDCl_3$, 400 MHz) 8.16 (1H, ddd, *J* 15.7, 11.2 and 1.0, alkene-**H**), 7.53-7.51 (2H, Ar**H**), 7.36-7.27 (3H, Ar**H**), 6.80 (1H, d, *J* 15.7, alkene-**H**), 6.70 (1H, m, alkene-**H**), 5.66 (1H, d, *J* 11.2, C(O)C**H**), 1.54 (9H, s, C(C$\mathbf{H_3}$)$_3$); δC ($CDCl_3$, 101 MHz) 166.1, 143.6, 140.6, 136.5, 128.8, 128.7, 127.4, 125.0, 119.6, 80.3, 28.3; *m/z* HRMS (NH_3 CI+), found: MNH_4^+, 248.1646. $C_{15}H_{22}NO_2$ requires 248.1651, Δ 2.0 ppm.

***tert*-Butyl (2*E*,4*E*)-5-phenylpenta-2,4-dienoate, 87a**[157]



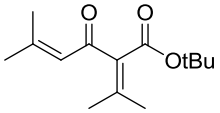
The title compound was synthesised according to the procedure for **87b**. Clear oil (0.48 g, 55%). R*f* 0.35 (UV, 254 nm, EtOAc/petroleum ether 1:20); δH ($CDCl_3$, 400 MHz) 7.47-7.45 (2H, Ar**H**), 7.38-7.28 (4H, Ar**H** and alkene-**H**), 6.87-6.85 (2H, Ar**H**), 5.94 (1H, d, *J* 15.0, C(O)C**H**), 1.52 (9H, s, C(C$\mathbf{H_3}$)$_3$); δC ($CDCl_3$, 101 MHz) 166.4, 143.5, 139.7, 136.2, 128.9, 128.8, 127.1, 126.4, 123.4, 80.3, 28.2. All data are in agreement with reported values.[157]

***tert*-Butyl 3-methylbut-2-enoate, 92**[158]



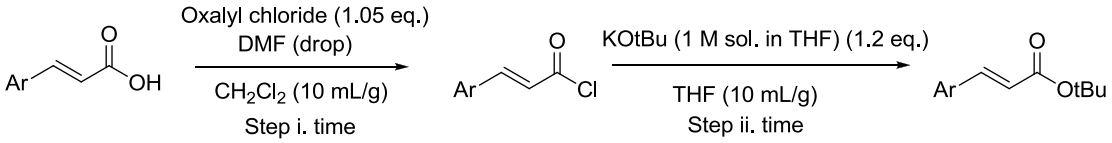
Adapted from the procedure of Jackson *et al.*[90] *di*-Methyl acrylic acid (0.50 g, 0.5 mmol) was dissolved in CH_2Cl_2 (0.50 mL) with sonication. *tert*-Butyl 2,2,2-trichloroacetimidate (1.33 mL, 1.0 mmol) was dissolved in cyclohexane (2.0 mL) and added in one portion to the CH_2Cl_2 solution, followed by $BF_3.OEt_2$ (10 μl, 0.1 mmol). On addition of the $BF_3.OEt_2$ white solid formed immediately, and an exotherm was noted. After 16 h., solid $NaHCO_3$ was added, followed by cold hexane (4 mL). The reaction mixture was filtered through a short plug of silica, washing with cold hexane, and the solvent was removed *in vacuo*. The pure product was isolated as a clear oil (0.33 g, 42%). R*f* 0.50 (UV 254 nm, EtOAc/petroleum ether, 1:100); ν_{max}/cm^{-1} 2981 (CH), 2929 (CH), 1713 (C=O), 1662, 1135; δH ($CDCl_3$, 400 MHz) 5.58 (1H, quin, *J* 1.0, C(O)C**H**), 2.10 (3H, d, *J* 1.5, CHC(C**H**$_3$)$_2$), 1.83 (3H, d, *J* 1.2, CHC(C**H**$_3$)$_2$), 1.44 (9H, s, $CO_2C(C\mathbf{H}_3)_3$); δC ($CDCl_3$, 101 MHz) 166.3, 154.6, 117.8, 79.4, 28.2, 27.2, 19.9; *m/z* (NH_3 CI+) 157 (MH^+ 100). All data were in agreement with reported values.[158]

***tert*-Butyl 5-methyl-3-oxo-2-(propan-2-ylidene)hex-4-enoate, 93**



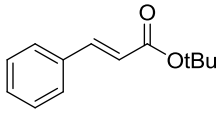
di-Methyl acrylic acid (0.50 g, 5.00 mmol) was added to anhydrous CH_2Cl_2 (5 mL), and cooled to 0 °C. Oxalyl chloride (0.44 mL, 5.24 mmol) was added over 3 min., followed by a drop of DMF. On addition, the reaction colour changed from clear to translucent yellow. After 5 min. stirring at 0 °C, the reaction was allowed to warm to room temperature. After 4 h., the CH_2Cl_2 was removed *in vacuo* and the resulting yellow oily solid dissolved in anhydrous THF (5 mL). The solution was cooled to 0 °C, and KOtBu (6.00 mL, 1 M in THF) was added over 5 min. The reaction mixture turned from yellow to dark orange. After 16 h., H_2O (25 mL) was added, and the aqueous phase was extracted with Et_2O (3 x 25 mL). The organic phase was washed with HCl (aq., 1 M, 25 mL), and dried over $MgSO_4$. The solvent was removed *in vacuo*, to provide the crude product as a brown oil (0.30 g). Purification by column chromatography (alumina) eluting with EtOAc/petroleum ether (1:40) provided the pure product as a clear oil (0.05 g, 9%). R*f* 0.45 (UV 254 nm, EtOAc/petroleum ether, 1:40); ν_{max}/cm^{-1} 2986 (CH), 2927 (CH), 1719 (C=O), 1617, 1156; δH ($CDCl_3$, 500 MHz) 6.08 (1H, sept, *J* 1.3, C(O)C**H**), 2.13 (3H, d, *J* 1.3, C**H**$_3$C=CH), 2.05 (3H, s, C**H**$_3$C=C), 1.89 (3H, d, *J* 1.3, C**H**$_3$C=CH), 1.87 (3H, s, C**H**$_3$C=C), 1.44 (9H, s, $C(C\mathbf{H}_3)_3$); δC ($CDCl_3$, 101 MHz) 193.2, 165.4, 155.0, 150.6, 134.6, 125.1, 81.2, 28.0, 27.7, 23.1, 22.6, 20.7; *m/z* HRMS (NH_3 CI+), found: MH^+, 239.1649. $C_{14}H_{23}O_3$ requires 239.1647, Δ 0.8 ppm.

General procedure A:



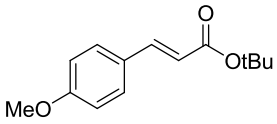
Oxalyl chloride (1.05 eq.) was added dropwise to the required cinnamic acid (1 eq.) in CH_2Cl_2 (10 mL/g), followed by a drop of DMF. Once all the starting acid had been consumed (TLC analysis of an aliquot after a MeOH quench), the solvent was removed *in vacuo*. THF (10 mL/g) was added and the mixture cooled to 0 °C. KO^{t}Bu (1M solution in THF, 1.2 eq.) was added. After 10 min. at 0 °C, the ice bath was removed and the reaction stirred at r.t. Once TLC analysis showed consumption of starting acid chloride, the reaction was diluted with diethyl ether (30 mL/g) and washed with water (30 mL/g). The aqueous phase was extracted with diethyl ether (3 x 30 mL/g), and the combined organic phases dried over $MgSO_4$, and concentrated *in vacuo*.

***tert*-Butyl (2*E*)-3-phenylprop-2-enoate, 42a**[159]



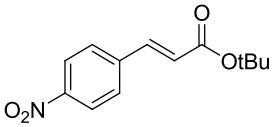
Following general procedure A; time for step i.: 2 h.; time for step ii.: 16 h. Cinnamic acid (3.62 g, 24 mmol) provided the title compound as a yellow oil (4.49 g, 90%), with no need for purification. R*f* 0.35 (UV 254 nm, EtOAc/petroleum ether, 1:20); δH ($CDCl_3$, 400 MHz) 7.60 (1H, d, *J* 16.0, PhC**H**), 7.56-7.52 (2H, Ar**H**), 7.43-7.38 (3H, Ar**H**), 6.42 (1H, d, *J* 16.0, ^{t}BuOC(O)C**H**), 1.55 (9H, s, C(C**H**$_3$)$_3$). All data are in agreement with literature values.[159]

***tert*-Butyl (2*E*)-3-(4-methoxyphenyl)prop-2-enoate, 42b**[46]



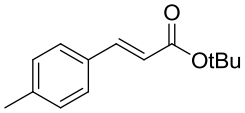
Following general procedure A; time for step i.: 30 min.; time for step ii.: 16 h. 4-Methoxycinnamic acid (0.50 g, 2.8 mmol) provided the title compound as a white powdery solid (0.43 g, 65%), after chromatographic purification (EtOAc/petroleum ether, 1:20). Mp 43-44 °C [lit. 41-44 °C[46]]; R*f* 0.30 (UV 254 nm, EtOAc/petroleum ether, 1:20); δH ($CDCl_3$, 400 MHz) 7.55 (1H, d, *J* 16.0, ArC**H**), 7.47 (2H, dt, *J* 8.8 and 2.0, OCH_3CCHC**H**), 6.91 (2H, dt, *J* 8.8 and 2.0, OCH_3CC**H**), 6.25 (1H, d, *J* 16.0, ^{t}BuOC(O)C**H**), 3.86 (3H, s, OC**H**$_3$), 1.55 (9H, s, C(C**H**$_3$)$_3$). All data are in agreement with literature values.[46]

***tert*-Butyl (2*E*)-3-(4-nitrophenyl)prop-2-enoate, 42c**[46]



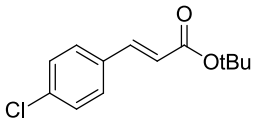
Following general procedure A; time for step i.: 50 min.; time for step ii.: 4 h. 4-Nitrocinnamic acid (0.50 g, 2.3 mmol) provided the title compound as a brown solid (0.41 g, 63%), with no need for purification. Mp 152-55 °C [lit. 155-57 °C[46]]; R*f* 0.25 (UV 254 nm, EtOAc/petroleum ether, 1:10); δH ($CDCl_3$, 400 MHz) 8.26 (2H, d, *J* 8.4, NO_2CC**H**), 7.67 (2H, d, *J* 8.4, NO_2CCHC**H**), 7.62 (1H, d, *J* 16.0, ArC**H**), 6.50 (1H, d, *J* 16.0, ^{t}BuOC(O)C**H**), 1.56 (9H, s, $C(C\mathbf{H_3})_3$). All data are in agreement with literature values.[46]

***tert*-Butyl (2*E*)-3-(4-methylphenyl)prop-2-enoate, 42d**[46]



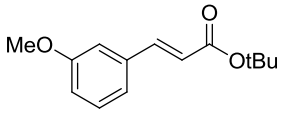
Following general procedure A; time for step i.: 50 min.; time for step ii.: 4 h. 4-Methylcinnamic acid (0.50 g, 3.1 mmol) provided the title compound as a brown oil (0.53 g, 79%), with no need for purification. R*f* 0.35 (UV 254 nm, EtOAc/petroleum ether, 1:10); δH ($CDCl_3$, 400 MHz) 7.57 (1H, d, *J* 16.0, ArC**H**), 7.42 (2H, d, *J* 8.0, CH_3CCHC**H**), 7.19 (2H, d, *J* 8.0, CH_3CC**H**), 6.33 (1H, d, *J* 16.0, ^{t}BuOC(O)C**H**), 2.39 (3H, s, $ArC\mathbf{H_3}$), 1.56 (9H, s, $C(C\mathbf{H_3})_3$). All data are in agreement with literature values.[46]

***tert*-Butyl (2*E*)-3-(4-chlorophenyl)prop-2-enoate, 42e**[46]



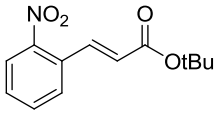
Following general procedure A; time for step i.: 1 h.; time for step ii.: 16 h. 4-Chlorocinnamic acid (0.50 g, 2.7 mmol) provided the title compound as a white solid (0.55 g, 84%), after chromatographic purification (EtOAc/petroleum ether, 1:20). Mp 70-72 °C [lit. 69-71 °C[46]]; R*f* 0.35 (UV 254 nm, EtOAc/petroleum ether, 1:20); δH ($CDCl_3$, 400 MHz) 7.54 (1H, d, *J* 15.6, ArC**H**), 7.46 (2H, dt, *J* 8.8 and 2.0, ClCC**H**), 7.36 (2H, dt, *J* 8.8 and 2.0, ClCCHC**H**), 6.35 (1H, d, *J* 15.6, ^{t}BuOC(O)C**H**), 1.56 (9H, s, $C(C\mathbf{H_3})_3$). All data are in agreement with literature values.[46]

***tert*-Butyl (2*E*)-3-(3-methoxyphenyl)prop-2-enoate, 42f**[160]



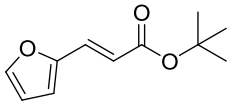
Following general procedure A; time for step i.: 1 h 30 min.; time for step ii.: 4 h. 3-Methoxycinnamic acid (1.00 g, 5.7 mmol) provided the title compound as a yellow oil (1.32 g, quant.), with no need for purification. R*f* 0.40 (UV 254 nm, EtOAc/petroleum ether, 1:20); δH ($CDCl_3$, 400 MHz) 7.57 (1H, d, *J* 16.1, ArC**H**), 7.30 (1H, t, *J* 8.1, Ar**H**), 7.11 (1H, d, *J* 7.4, Ar**H**), 7.03 (1H, br t, *J* 2.4, Ar**H**), 6.93 (1H, dd, *J* 8.1 and 2.4, Ar**H**), 6.37 (1H, d, *J* 16.1, C(O)C**H**), 3.82 (3H, s, OC$\mathbf{H_3}$), 1.54 (9H, s, C(C$\mathbf{H_3}$)$_\mathbf{3}$). All data are in agreement with literature values.[160]

***tert*-Butyl (2*E*)-3-(2-nitrophenyl)prop-2-enoate, 42g**[161]



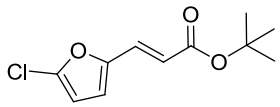
Following general procedure A; time for step i.: 2 h., then further portion of oxalyl chloride (1.05 eq.) added, then 50 min.; time for step ii.: 16 h. 2-Nitrocinnamic acid (1.00 g, 5.2 mmol) provided the title compound as a yellow oil (0.17 g, 13%), after chromatographic purification (EtOAc/petroleum ether, 1:5). R*f* 0.40 (UV 254 nm, EtOAc/petroleum ether, 1:5); ν_{max}/cm^{-1} 2990 (CH), 1736 (C=O), 1524, 1332 (NO_2), 1145; δH ($CDCl_3$, 400 MHz) 8.01 (1H, d *J* 15.6, ArC**H**), 8.01 (1H, d *J* 7.6, Ar**H**), 7.64 (2H, Ar**H**), 7.55 (1H, m, Ar**H**), 6.32 (1H, d, *J* 15.6, ArCHC**H**), 1.53 (9H, s, C(C$\mathbf{H_3}$)$_\mathbf{3}$); δC ($CDCl_3$, 101 MHz) 165.0, 148.3, 138.7, 133.4, 130.7, 130.1, 129.1, 125.2, 124.8, 81.1, 28.1. All data are in agreement with literature values.[161]

***tert*-Butyl (2*E*)-3-(furan-2-yl)prop-2-enoate, 79a**[162]



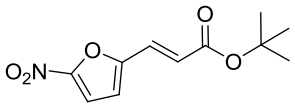
Following general procedure A; time for step i.: 30 min.; time for step ii.: 16 h. Furylacrylic acid (1.00 g, 7.2 mmol) provided the title compound as a brown oil (1.24 g, 88%), with no need for purification. R*f* 0.80 (UV 254 nm EtOAc/petroleum ether, 1:5); ν_{max}/cm^{-1} 2982 (CH), 1707 (C=O), 1639; δH (CDCl3, 400 MHz) 7.45 (1H, m, furyl-OC**H**), 7.35 (1H, d, *J* 16.0, ArC**H**), 6.57 (1H, d, *J* 3.6, furyl-OCC**H**), 6.49 (1H, m, furyl-OCHC**H**), 6.30 (1H, d, *J* 16.0, COC**H**), 1.57 (9H, s, C(C$\mathbf{H_3}$)$_\mathbf{3}$); δC (CDCl3, 101 MHz) 166.4, 151.2, 144.4, 130.1, 118.0, 114.0, 112.1, 80.4, 28.2. *m/z* HRMS (NH_3 CI+), found: MNH_3^+, 212.1288. $C_{11}H_{18}NO_3$ requires 212.1287, Δ 0.6 ppm. All data are in agreement with literature values.[162]

***tert*-Butyl (2*E*)-3-(furan-2-yl)prop-2-enoate, 79c**



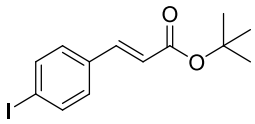
tert-Butoxycarbonyl-methylene)triphenyl-phosphorane **81** (0.50 g, 1.3 mmol) was dissolved in THF (10 mL). 2-chlorofuraldehyde (0.15 g, 1.1 mmol) in THF (5 mL) was added over 5 min. After 2 h., the solvent was removed *in vacuo*. Column chromatography, eluting with EtOAc/petroleum ether (1:20) provided the pure product as a white crystalline solid (0.17 g, 71%). Mp 44-47 °C; R*f* 0.25 (UV 254 nm, EtOAc/petroleum ether, 1:20); ν_{max}/cm^{-1} 3154 (CH), 2975 (CH), 1704 (C=O), 1645, 1156; δH ($CDCl_3$, 400 MHz) 7.20 (1H, d, *J* 15.7, CC**H**), 6.50 (1H, d, *J* 3.4, Ar**H**), 6.21 (1H, d, *J* 15.7, C(O)C**H**), 6.20 (1H, d, *J* 3.4, Ar**H**), 1.48 (9H, s, C(C**H**$_3$)$_3$; δC ($CDCl_3$, 101 MHz) 166.0, 150.7, 138.9, 128.9, 118.3, 115.8, 109.0, 80.5, 28.1; *m/z* HRMS (NH_3 CI+), found: MNH_4^+, 246.0905. $C_{11}H_{17}NO_3Cl$ requires 246.0897, Δ 3.3 ppm.

***tert*-Butyl (2*E*)-3-(5-nitrofuran-2-yl)prop-2-enoate, 79b**



tert-Butoxycarbonyl-methylene)triphenyl-phosphorane **81** (0.50 g, 1.3 mmol) was dissolved in THF (10 mL) 2-nitrofuraldehyde (0.14 mL) in THF (5 mL) was added over 5 min. After 2.5 h., the solvent was removed *in vacuo*. Column chromatography, eluting with EtOAc/petroleum ether (1:5) provided the pure product as flaky bright yellow crystals (0.23 g, 88%). Mp 96-99 °C; R*f* 0.20 (UV 254 nm, EtOAc/petroleum ether, 1:5); ν_{max}/cm^{-1} 2992 (CH), 1704 (C=O), 1530 (NO_2), 1355 (NO_2); δH (CDCl3, 400 MHz) 7.33 (1H, d, *J* 3.8, Ar**H**), 7.33 (1H, d, *J* 16.1, ArC**H**), 6.73 (1H, d, *J* 3.8, Ar**H**), 6.60 (1H, d, *J* 16.1, C(O)C**H**), 1.52 (9H, s, C(C**H**$_3$)$_3$; δC (CDCl3, 125 MHz) 164.8, 152.8, 152.2, 127.7, 125.0, 114.7, 113.0, 81.6, 28.1; *m/z* HRMS (ESI+), found: MH^+, 239.0796. $C_{11}H_{13}NO_5$ requires 239.0794, Δ 0.8 ppm.

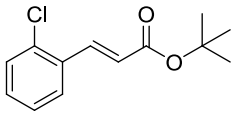
***tert*-Butyl (2*E*)-3-(4-iodophenyl)prop-2-enoate, 42h**[163]



tert-Butoxycarbonyl-methylene)triphenyl-phosphorane) **81** (49 mg, 0.13 mmol) was dissolved in THF (2 mL). 4-iodobenzaldehyde (25 mg, 0.11 mmol) in THF (1 mL) was added over 5 min. After 16 h., the solvent was removed *in vacuo* to provide the crude product as yellow oil. Column chromatography, eluting with EtOAc/petroleum ether (1:10) provided the pure product as a pale yellow solid (28 mg, 79%). M.p 65-67 °C [lit. 65-66°C[163]]; R*f* 0.80 (UV 254 nm, EtOAc/petroleum

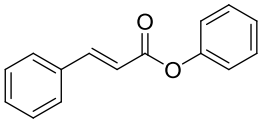
ether, 1:10); δH ($CDCl_3$, 400 MHz) 7.71 (2H, d, *J* 9.0, ArC**H**), 7.51 (1H, d, *J* 16.2, ArC**H**), 7.24 (2H, d, *J* 9.0, Ar**H**), 6.38 (1H, d, *J* 16.2, C(O)C**H**), 1.52 (9H, s, C(C**H**$_3$)$_3$); *m/z* HRMS (NH_3 CI+), found: MNH_3^+, 348.0466. $C_{13}H_{19}NO_2I$ requires 348.0461, Δ 1.4 ppm. All data are in agreement with literature values.[163]

tert-Butyl (2*E*)-3-(2-chlorophenyl)prop-2-enoate, 42i[164]



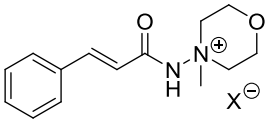
$PdCl_2(PPh_3)_2$ (0.118 g, 0.17 mmol) was added to a Wheaton vial. The vial was flushed with Ar (g), before the addition of Et_3N (12 mL), 1-chloro,2-iodobenzene (0.200 g, 0.84 mmol) and *tert*-butyl acrylate (0.212 mL, 1.68 mmol) sequentially. The vial was sealed and heated to 115 °C. After 18 h., the heat source was removed, and NH_4Cl (sat. aq., 15 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL) and the organic phase was dried over Na_2SO_4. The solvent was removed *in vacuo* to provide the crude product as a pale yellow solid (0.447 g). Column chromatography, eluting with EtOAc/Petroleum ether (1:30) provided the pure product as yellow oil (0.186 g, 93%). R*f* 0.25 (UV 254 nm, petroleum ether/EtOAc, 30:1); ν_{max}/cm^{-1} 2979 (CH), 1714 (C=O), 1155; δH ($CDCl_3$, 400 MHz) 8.02 (1H, d, *J* 16.2, ArC**H**), 7.61-7.59 (1H, m, Ar**H**), 7.41-7.38 (1H, Ar**H**), 7.30-7.23 (2H, Ar**H**), 6.38 (1H, d, *J* 15.9), 1.54 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 165.8, 139.4, 134.8, 132.9, 130.7, 130.1, 127.6, 127.0, 122.8, 80.8, 28.2; *m/z* HRMS (NH_3 CI+), found: MNH_4^+, 256.1100. $C_{13}H_{19}NO_2Cl$ requires 256.1104, Δ 1.6 ppm. All data are in agreement with literature values.[164]

Phenyl (2*E*)-3-phenylprop-2-enoate, 59[165]



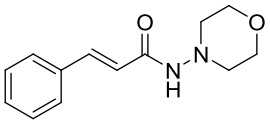
Phenoxycarbonyl-methylene)triphenyl-phosphorane **81** (0.50 g, 1.26 mmol) and benzaldehyde (0.11 mL, 1.05 mmol) were added to anhydrous THF (15 mL) in a flame dried flask. The reaction mixture was heated to 70 °C for 6.5 h. After this time, the solvent was removed *in vacuo*. Column chromatography, eluting with EtOAc/petroleum ether (1:10) provided the product as a white crystalline solid (0.17 g, 71%). Mp 64-67 °C [lit. 73 °C[166]]; R*f* 0.50 (UV 254 nm, EtOAc/petroleum ether, 1:10); ν_{max}/cm^{-1} 3063 (CH), 1725 (C=O); δH (CDCl3, 400 MHz) 7.90 (1H, d, 15.6, PhC**H**), 7.61-7.59 (2H, m, Ar**H**), 7.45-7.35 (5H, Ar**H**), 7.28 (1H, m, Ar**H**), 7.20 (2H, m, Ar**H**), 6.67 (1H, d, 15.6, COC**H**); δC (CDCl3, 101 MHz) 165.4, 150.8, 146.6, 134.2, 130.7, 129.5, 129.0, 128.3, 125.8, 121.7, 117.3. *m/z* HRMS (NH_3 CI+), found: MH^+, 225.0920. $C_{15}H_{13}O_2$ requires 225.0916, Δ 2.0 ppm. All data are in agreement with literature values.[165]

4-Methyl-4-{[(2*E*)-3-phenylprop-2-enoyl]amino}morpholin-4-ium, 60



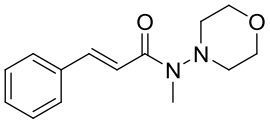
Adapted from the procedure of Armstrong *et al.*[53] *N*-methyl morpholine (12.7 μL, 0.12 mmol) was added to a stirred solution of *O*-diphenylphosphinyl hydroxylamine (27 mg, 0.12 mmol) in CH_2Cl_2 (0.5 mL). The reaction was stirred at r.t. for 30 min. NaOH (17.8 mg, 0.45 mmol) was added in one portion, and the reaction stirred for a further 20 min. Phenyl cinnamate (25 mg, 0.11 mmol) was then added in one portion. The reaction was stirred at r.t. for 20 h. NH_4Cl (3 mL, sat. aq.) was added, and the aqueous phase extracted with CH_2Cl_2 (3 x 3 mL). The organic phase was dried over $MgSO_4$, and concentrated *in vacuo* to provide the crude product as a white solid (37 mg). Column chromatography eluting with MeOH/EtOAc (1:4) provided the pure compound as a white solid (14 mg, 51%). Mp 182-85 °C; R*f* 0.20 (UV 254 nm, MeOH/EtOAc, 1:4); ν_{max}/cm^{-1} 2873 (NH), 1647 (C=O), 1573, 1118; δH ($CDCl_3$, 500 MHz) 7.51 (2H, Ar**H**), 7.45 (1H, d, *J* 16.0, ArC**H**), 7.33 (2H, Ar**H**), 7.27 (1H, Ar**H**), 6.60 (1H, d, *J* 16.0, COC**H**), 4.39 (2H, br d, *J* 11.0, 2 x morpholine-eq.-OC**H**), 4.29 (2H, dt, *J* 13.0 and 1.9, 2 x morpholine-ax.-OC**H**), 3.80 (2H, br d, *J* 12.5, 2 x morpholine-eq.-NC**H**), 3.55 (3H, s, C**H**$_3$), 3.20 (2H, dt, *J* 11.7 and 3.6, 2 x morpholine-ax.-NC**H**); δC ($CDCl_3$, 101 MHz) 170.5, 136.4, 135.9, 128.6, 128.3, 127.4, 126.2, 62.5, 61.7, 53.5; *m/z* HRMS (NH_3 CI+), found: MH^+, 247.1455. $C_{14}H_{19}N_2O_2$ requires 247.1447, Δ 0.8 ppm.

(2*E*)-*N*-(morpholin-4-yl)-3-phenylprop-2-enamide, 61



Following general procedure A; time for step i.: 1 h. 20 min.; time for step ii.: 4 h. Work-up: The reaction was quenched with NaOH (aq., 1 M, 25 mL) and extracted with EtOAc (3 x 25 mL). The organic phase was dried over $MgSO_4$, and concentrated *in vacuo* to provide the crude product as a white solid. 0.50 g of cinnamic acid provided the title compound as a white needles (0.36 g, 46%), following recrystalisation from EtOAc. R*f* 0.20 (UV 254 nm, EtOAc); ν_{max}/cm^{-1} 3188 (NH), 3056 (CH), 2869 (CH), 1658 (C=O), 1632; δH (d_6-DMSO, 400 MHz, mixture of rotamers) 9.22 (0.69 x 1H, s, N**H**), 8.76 (0.31 x 1H, s, N**H**), 7.66-7.33 (6H Ar**H** and 0.31 x 1H, alkene-**H**), 6.55 (0.69 X 1H, d, *J* 16.2, COC**H**), 3.65 (4H, m, 2 x morpholine OC**H**$_2$), 2.81 (2H, m, morpholine 2 x ax.-NC**H**), 2.75 (2H, br s, morpholine 2 x eq.-NC**H**); δC (d_6-DMSO, 101 MHz, mixture of rotamers) 167.2, 162.8, 141.6, 139.4, 135.5, 135.4, 130.1, 130.0, 129.4, 129.3, 128.4, 128.0, 121.4, 118.3, 66.4, 66.3, 56.6, 55.2; *m/z* HRMS (ES+), found: MH^+, 233.1294. $C_{13}H_{17}N_2O_2$ requires 233.1290, Δ 1.7 ppm.

(2*E*)-*N*-Methyl-*N*-(morpholin-4-yl)-3-phenylprop-2-enamide, 62



Amide **61** (50 mg, 0.22 mmol) was suspended in anhydrous THF (2 mL) and cooled to 0 °C. KOtBu (1M in THF, 0.33 mL) was added dropwise. The reaction mixture turned from colourless to bright yellow on addition of the reagent. After 30 min. at 0 °C, dimethyl sulfate (21 μL, 0.22 mmol) was added. The ice-bath was removed, and a gradual colour change from bright yellow to grey was noted. After 10 min. warming to r.t., the reaction was quenched with NaOH (aq., 1 M, 4 mL). After a 2 min. stir, the aqueous phase was extracted with EtOAc (3 x 5 mL). The organic phase was dried over $MgSO_4$, and concentrated *in vacuo* to provide the crude product. Column chromatography eluting with EtOAc/petroleum ether (1:1) provided the pure compound as a clear oil (4 mg, 8%). R*f* 0.20 (UV 254 nm, EtOAc/petroleum ether, 1:1); ν_{max}/cm^{-1} 2971 (CH), 2852 (CH), 1653 (C=O), 1623; δH ($CDCl_3$, 400 MHz) 7.71 (1H, d, *J* 15.8, ArC**H**), 7.57-7.54 (2H, Ar**H**) 7.56 (1H, *J* 15.8, C(O)C**H**), 7.41-7.33 (3H, Ar**H**), 3.97-3.93 (2H, m, 2 x morpholine-eq.-OC**H**), 3.80 (2H, dt, *J* 11.0 and 2.4, 2 x morpholine-ax.-OC**H**), 3.06 (3H, s, C**H**$_3$), 3.07-3.00 (2H, dt, *J* 11.0 and 3.3, 2 x morphline-ax.-NC**H**), 2.70 (2H, br d, *J* 11.0, 2 x morphline-eq.-NC**H**); δC ($CDCl_3$, 101 MHz) 168.3, 142.2, 135.7, 129.5, 128.8, 127.9, 117.4, 66.8, 51.7, 24.1; *m/z* HRMS (NH_3 CI+), found: MH^+, 247.1455. $C_{14}H_{19}N_2O_2$ requires 247.1447, Δ 0.8 ppm.

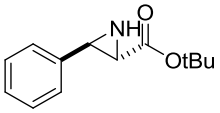
General procedure B

$DppONH_2$ (3 eq.) was suspended in anhydrous CH_2Cl_2 (0.12 M), and NMM (3 eq.) added dropwise over 1 min. The reaction was stirred for 30 min. NaOH (11 eq.) (ground to a fine powder immediately prior to use) was added, and the reaction stirred for a further 20 min. The required cinnamate ester (1 eq.) was then added. After 40 h. stirring at r.t., NH_4Cl (sat. aq. 60 mL/g) was added, and the aqueous phase extracted with CH_2Cl_2 (3 x 60 mL/g). The organic phase was dried over Na_2SO_4, and the solvent removed *in vacuo*.

General procedure C

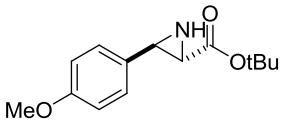
$DppONH_2$ (1.04 eq.) was added to anhydrous CH_2Cl_2 (0.24 M) and NMM (1.04 eq.) added dropwise over 1 min. The reaction was stirred for 30 min. NaOH (4 eq.) (ground to a fine powder immediately prior to use) was added, and the reaction stirred for a further 20 min. The required cinnamate ester (1 eq.) was then added. After 40 h. stirring at r.t., NH_4Cl (sat. aq. 60 mL/g) was added, and the aqueous phase extracted with CH_2Cl_2 (3 x 60 mL/g). The organic phase was dried over Na_2SO_4, and the solvent removed *in vacuo*.

(±)*tert*-Butyl *trans*-aziridine-3-prop-2-enoate, 1a[53]



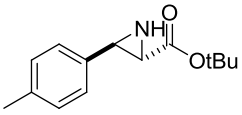
Following general procedure B, *tert*-butyl cinnamate (0.58 g, 2.9 mmol) provided the title compound as a white crystalline solid (0.40 g, 65%), after chromatographic purification (EtOAc/petroleum ether 1:10). Mp 63-66 °C; R*f* 0.20 (EtOAc/petroleum ether, 1:10); δH ($CDCl_3$, 400 MHz) 7.34-7.27 (5H, Ph**H**), 3.17 (1H, br s, C**H**NH), 2.50 (1H, br s, C**H**NH), 1.82 (1H, br s, N**H**), 1.50 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 170.8, 138.2, 128.4, 127.7, 126.2, 82.4, 40.4, 39.9, 28.1. All data are in agreement with literature values.[53] A crystal structure was obtained for aziridine **1a**; see Appendix 1.

(±)*tert*-Butyl *trans*-aziridine-3-(4-methoxyphenyl)prop-2-enoate, 1b



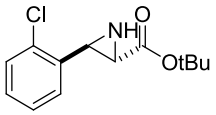
Following general procedure B, 4-methoxy-*tert*-butyl cinnamate (50 mg, 0.21 mmol) provided the title compound as a pale yellow powder (21 mg, 39%) after chromatographic purification (EtOAc/petroleum ether, 1:10). Mp 79-81 °C; R*f* 0.40 ($KMnO_4$ dip, EtOAc/petroleum ether, 1:10); ν_{max}/cm^{-1} 3291 (NH), 2986 (CH), 2947 (CH), 1715 (C=O); δH ($CDCl_3$, 400 MHz) 7.21 (2H, dt, *J* 8.7 and 2.6, Ar**H**), 6.87 (2H, dt, *J* 8.7 and 2.6, Ar**H**), 3.82 (3H, s, OC**H**$_3$), 3.14 (1H, dd, *J* 7.6 and 2.4,C**H**NH), 2.47 (1H, dd, *J* 7.6 and 2.4, C**H**NH), 1.78 (1H, br t, *J* 7.6, CHN**H**),1.53 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 170.9, 159.3, 130.2, 127.3, 113.9, 82.2, 55.3, 40.3, 39.6, 28.1; *m/z* HRMS (ES+), found: MNa^+, 272.1269. $C_{14}H_{19}NO_3Na$ requires 272.1263, Δ 2.2 ppm.

(±)*tert*-Butyl *trans*-aziridine-3-(4-methylphenyl)prop-2-enoate, 1d



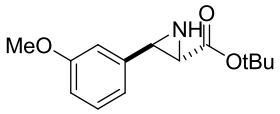
Following general procedure B, 4-methyl-*tert*-butyl cinnamate (50 mg, 0.23 mmol) provided the title compound as a white powder (19 mg, 36%) after chromatographic purification (EtOAc/petroleum ether (1:50 to 1:10). Mp 62-65 °C; R*f* 0.25 ($KMnO_4$ dip, EtOAc/petroleum ether 1:10); ν_{max}/cm^{-1} 3275 (NH), 2981 (CH), 2933 (CH), 1714 (C=O); δH ($CDCl_3$, 400 MHz) 7.21-7.14 (4H, m, Ar**H**), 3.14 (1H, dd, 8.8 and 2.7, C**H**NH), 2.48 (1H, dd, *J* 8.8 and 2.7, C**H**NH), 2.36 (3H, s, C**H**$_3$), 1.80 (1H, br t, *J* 8.8, CHN**H**), 1.52 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 170.9, 137.4, 135.2, 129.1, 126.0, 82.3, 40.4, 39.8, 28.1, 21.1; *m/z* HRMS (NH_3 CI+), Found: MH^+, 234.1505. $C_{14}H_{20}NO_2$ requires 234.1494, Δ 4.7 ppm.

(±)*tert*-Butyl *trans*-aziridine-3-(2-chlorophenyl)prop-2-enoate, 1i



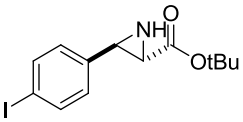
Following general procedure B, 2-chloro-*tert*-butyl cinnamate (50 mg, 0.21 mmol) provided the title compound as a clear oil (25 mg, 47%) after chromatographic purification (EtOAc/petroleum ether, 1:30 to 1:20). R*f* 0.20 (UV 254 nm, EtOAc/petroleum ether, 1:20); ν_{max}/cm^{-1} 3293 (NH), 2982 (CH), 1729 (C=O), 1229, 1161; δH ($CDCl_3$, 400 MHz) 7.35-7.33 (2H, m, Ar**H**), 7.24-7.17 (2H, m, Ar**H**), 3.45 (1H, br s, ArC**H**), 2.39 (1H, br s, C(O)C**H**), 1.74 (1H, br s, N**H**), 1.51 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 170.7, 135.8, 134.2, 129.0, 128.6, 127.2, 126.9, 82.4, 39.4, 37.8, 28.1; *m/z* HRMS (NH_3 CI+), found: MH^+, 254.0947. $C_{13}H_{17}NO_2Cl$ requires 254.0948, Δ 0.4 ppm.

(±)*tert*-Butyl *trans*-aziridine-3-(3-methoxyphenyl)prop-2-enoate, 1f



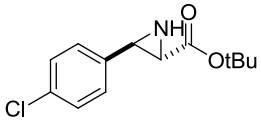
Following general procedure B, 3-methoxy-*tert*-butyl cinnamate (50 mg, 0.21 mmol) provided the title compound as a clear oil (17 mg, 32%) after chromatographic purification (EtOAc/petroleum ether, 1:20 to 1:10). R*f* 0.20 (UV 254 nm, EtOAc/petroleum ether, 1:10); ν_{max}/cm^{-1} 2987 (CH), 1719 (C=O), 1234, 1156; δH ($CDCl_3$, 400 MHz) 7.25-7.20 (1H, m, ArC**H**), 6.89 (1H, d, *J* 7.3, Ar**H**), 6.83-6.80 (2H, Ar**H**), 3.80 (3H, s, OC**H**$_3$), 3.15 (1H, d, *J* 2.3 ArC**H**), 2.50 (1H, d, *J* 2.3, C(O)C**H**), 1.74 (1H, br s, N**H**), 1.50 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 170.7, 159.8, 139.9, 129.4, 118.7, 113.6, 111.1, 82.3, 55.3, 40.4, 39.9, 28.1; *m/z* HRMS (NH_3 CI+), found: MH^+, 250.1441. $C_{14}H_{20}NO_3$ requires 250.1441, Δ 0.0 ppm.

(±)*tert*-butyl *trans*-aziridine-3-(4-iodophenyl)prop-2-enoate, 1h



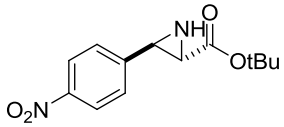
Following general procedure C, 4-iodo-*tert*-butyl cinnamate (50 mg, 15 mmol) provided the title compound as a white solid (17 mg, 33%) after chromatographic purification (EtOAc/petroleum ether, 1:30 to 1:20). M.p 83-85 °C; R*f* 0.40 (UV 254 nm, EtOAc/petroleum ether, 1:20); ν_{max}/cm^{-1} 3273 (NH), 2979 (CH), 1717 (C=O), 1360, 1151; δH ($CDCl_3$, 400 MHz) 7.64 (2H, d, *J* 8.5, Ar**H**), 7.03 (2H, d, *J* 8.5, Ar**H**), 3.11 (1H, d, *J* 2.0, ArC**H**), 2.44 (1H, d, *J* 2.0, C(O)C**H**), 1.76 (1H, br s, N**H**), 1.49 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 170.5, 138.0, 137.4, 128.1, 93.0, 82.6, 40.5, 39.4, 28.1; *m/z* HRMS (NH_3 CI+), found: MH^+, 346.0295. $C_{13}H_{17}NO_2I$ requires 346.0304, Δ 2.6 ppm.

(±)*tert*-Butyl *trans*-aziridine-3-(4-chlorophenyl)prop-2-enoate, 1e



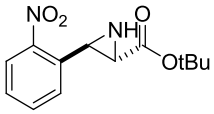
Following general procedure C, 4-chloro-*tert*-butyl cinnamate (57 mg, 24 mmol) provided the title compound as a white oil (32 mg, 53%) after chromatographic purification (EtOAc/petroleum ether, 1:15). R*f* 0.35 ($KMnO_4$ dip, EtOAc/petroleum ether, 1:15); ν_{max}/cm^{-1} 3289 (NH), 2984 (CH), 2933 (CH), 1723 (C=O); δH ($CDCl_3$, 400 MHz) 7.33-7.29 (2H, m, Ar**H**), 7.26-7.23 (2H, m, Ar**H**), 3.16 (1H, br d, *J* 4.8, C**H**NH), 2.48 (1H, br s, C**H**NH), 1.86 (1H, br s, CHN**H**), 1.53 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 170.5, 136.8, 133.4, 128.5, 127.5, 82.5, 40.5, 39.2, 28.1; *m/z* HRMS (NH_3 CI+), found: MH^+, 254.0952. $C_{13}H_{17}NO_2Cl$ requires 254.0948, Δ 1.6 ppm.

(±)*tert*-Butyl *trans*-aziridine-3-(4-nitrophenyl)prop-2-enoate, 1c



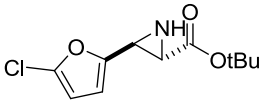
Following general procedure C, 4-nitro-*tert*-butyl cinnamate (63 mg, 0.25 mmol) provided the title compound as a yellow powder (51 mg, 76%) after chromatographic purification (EtOAc/petroleum ether (1:5). Mp 90-92 °C; R*f* 0.25 ($KMnO_4$ dip, EtOAc/petroleum ether, 1:5); ν_{max}/cm^{-1} 3281 (NH), 2984 (CH), 2972 (CH), 1709 (C=O); δH ($CDCl_3$, 400 MHz) 8.22-8.19 (2H, m, Ar**H**), 7.50-7.46 (2H, m, Ar**H**), 3.27 (1H, br s, C**H**NH), 2.52 (1H, br s, C**H**NH), 1.97 (1H, br s, CHN**H**), 1.54 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 169.9, 147.5, 145.8, 127.1, 123.7, 83.0, 41.0, 39.0, 28.0; *m/z* HRMS (NH_3 CI+), found: MH^+, 265.1196. $C_{13}H_{17}N_2O_4$ requires 265.1188, Δ 3.0 ppm.

(±)*tert*-Butyl *trans*-aziridine-3-(2-nitrophenyl)prop-2-enoate, 1g



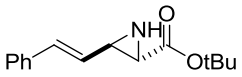
Following general procedure C, 2-nitro-*tert*-butyl cinnamate (50 mg, 0.20 mmol) provided the title compound as a white oil (21 mg, 40%) after chromatographic purification (EtOAc/petroleum ether, 1:10). R*f* 0.40 (UV 254 nm, EtOAc/petroleum ether, 1:10); ν_{max}/cm^{-1} 3298 (NH), 2991 (CH), 1722 (C=O), 1525 (NO_2), 1346 (NO_2); δH ($CDCl_3$, 400 MHz) 8.09 (1H, dd, *J* 8.4 and 1.0, Ar**H**), 7.74 (1H, d, *J* 7.5, Ar**H**), 7.62 (1H, t, *J* 7.5, Ar**H**), 7.45 (1H, t, *J* 8.4, Ar**H**), 3.69 (1H, d, *J* 5.8, ArC**H**), 2.41 (1H, d, *J* 5.8, C(O)C**H**), 1.86 (1H, m, N**H**), 1.53 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 170.4, 148.7, 134.0, 133.8, 128.9, 128.3, 124.7, 82.7, 39.5, 38.1, 28.0; *m/z* HRMS (NH_3 CI+), found: MH^+, 265.1190. $C_{13}H_{17}N_2O_4$ requires 265.1188, Δ 0.8 ppm.

(±)*tert*-Butyl *trans*-aziridine-3-(5-chlorofuryl)prop-2-enoate, 77c



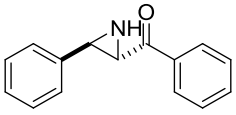
Following general procedure C, quenching the reaction after 20 h., 5-chloro-*tert*-butyl furfural (50 mg, 22 mmol) provided the title compound as a yellow oil (19 mg, 35%) after chromatographic purification (EtOAc/petroleum ether, 1:10). R*f* 0.25 (UV 254 nm, EtOAc/petroleum ether, 1:10); ν_{max}/cm^{-1} 2987 (CH), 1722 (C=O), 1531, 1233, 1158; δH ($CDCl_3$, 400 MHz) 6.27 (1H, d, *J* 3.1, Ar**H**), 6.09 (1H, d, *J* 3.1, Ar**H**), 3.15 (1H, dd, *J* 9.1 and 2.3, C**H**N), 2.76 (1H, dd, *J* 9.1 and 2.3, C**H**N), 1.75 (1H, br t, *J* 9.1, N**H**), 1.50 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 170.1, 150.9, 135.7, 109.6, 107.1, 82.8, 37.6, 33.7, 28.0; *m/z* HRMS (ESI+), found: MH_3O^+, 262.0832. $C_{11}H_{17}NO_4Cl$ requires 262.0846, Δ 5.3 ppm.

(±)*tert*-Butyl 3-[*trans*-2-phenylethenyl]aziridine-2-carboxylate, 89



Following general procedure B, dienoate **87a** (25 mg, 0.11 mmol) provided the title compound as a gritty oil (2 mg, 8%), after chromatographic purification (EtOAc/petroleum ether, 1:10) R*f* 0.20 (UV, 254 nm, EtOAc/petroleum ether, 1:10); ν_{max}/cm^{-1} 3290 (NH), 2984 (CH), 1726 (C=O); δH ($CDCl_3$, 400 MHz) 7.37-7.21 (5H, Ar**H**), 6.74 (1H, d, *J* 16.2, ArC**H**), 5.89 (1H, dd, *J* 16.2 and 7.9, ArCHC**H**), 2.84 (1H, dd, *J* 7.9 and 2.2, ArCHCHC**H**), 2.48 (1H, d, *J* 2.5, C(O)C**H**), 1.64 (1H, br s, N**H**), 1.50 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 170.9, 136.3, 132.9, 128.6, 127.8, 127.7, 126.2, 82.3, 39.8, 38.2, 28.1; *m/z* HRMS (ES+), found: MH^+, 246.1495. $C_{15}H_{20}NO_2$ requires 246.1494, Δ 0.4 ppm.

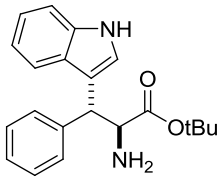
(±)Phenyl(*trans*-3-phenylaziridin-2-yl)methanone, 47[53]



Adapted from the procedure of Ikeda *et al.*[63] Anhydrous ^{i}PrOH (1.5 mL), dimethylhydrazine (0.19 mL, 2.5 mmol) and propylene oxide (0.17 mL, 2.5 mmol) were combined and stirred in a tightly sealed vessel for 24 h. at r.t. Chalcone (0.43 g, 2.1 mmol) was dissolved in PhMe (2 mL) and *i*PrOH (6 mL), and added to the reaction mixture. After heating to 50 °C for 1 h., the mixture had turned from orange to bright red. After 20 h., the reaction mixture was concentrated *in vacuo*, to give a red oily solid. Recrystalisation from MeOH provided the pure product as an orange solid (0.15 g, 31%). Mp 103-106 °C [lit. 98-100 °C[66]]; R*f* 0.30 (UV 254 nm, EtOAc/petroleum ether, 2:3); ν_{max}/cm^{-1} 3225 (NH), 1666 (C=O), 1455, 1265; δH ($CDCl_3$, 400 MHz) 8.05-8.01 (2H, Ar**H**), 7.67-7.62 (1H, m, Ar**H**), 7.55-7.50 (2H, m, Ar**H**), 7.44-7.32 (5H, Ar**H**), 3.56 (1H, d, *J* 2.4, C**H**NH), 3.24 (1H, d, *J* 2.4,

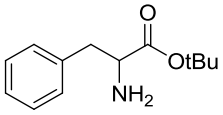
C**H**NH), 2.85 (1H, br s, N**H**). δC ($CDCl_3$, 101 MHz) 195.8, 138.4, 136.0, 133.9, 128.9, 128.6, 128.4, 127.9, 126.2, 44.1, 43.6; *m/z* HRMS (NH_3 CI+), found: MH^+, 224.1076. $C_{15}H_{14}NO$ requires 224.1075, Δ 0.3 ppm. All data are in agreement with literature values.[63]

(±)*tert*-Butyl-2-amino-3-phenyl-3-(indol-3-yl)propanoate, 97a[92]



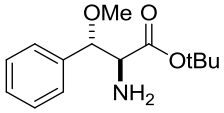
Aziridine **1a** (25 mg, 0.11 mmol) and indole (27 mg, 0.23 mmol) were dissolved in CH_2Cl_2 (1 mL), and cooled to 0 °C. BF_3.THF (19 μl, 0.17 mmol) was added over 30 s. The mixture was stirred at 0 °C for 5 mins., before warming to r.t., and after 24 h., the reaction was quenched with $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), dried over Na_2SO_4, and concentrated *in vacuo* to provide the crude product as yellow oil (59 mg). Column chromatography eluting with EtOAc/petroleum ether (2:3) provided the pure product as a white solid (24 mg, 63%). Mp 167-169 °C [lit. 175-176 °C]; R*f* 0.10 (UV 254 nm, EtOAc/petroleum ether 2:3); ν_{max}/cm^{-1} 3419 (NH), 2962 (CH), 2928 (CH), 1722 (C=O); δH ($CDCl_3$, 500 MHz) 8.22 (1H, br s, ArNH), 7.49 (1H, d, *J* 8.0, Ar**H**), 7.40 (2H, d, *J* 7.5, Ar**H**), 7.33-7.25 (4H, Ar**H**), 7.23 (1H, tt, *J* 7.5 and 1.5, Ar**H**), 7.17 (1H, m, Ar**H**), 7.06 (1H, m, Ar**H**), 4.65 (1H, d, *J* 6.5, ArC**H**), 4.20 (1H, br s, NH_2C**H**), 1.72 (2H, br s, NH_2), 1.26 (9H, s, C(C**H**)$_3$); δC ($CDCl_3$, 101 MHz) 173.7, 140.6, 136.1, 129.0, 128.4, 127.0, 126.8, 122.3, 122.0, 119.4, 119.4, 116.6, 111.0, 81.2, 59.5, 47.3, 27.8; *m/z* HRMS (NH_3 CI+), found: MH^+, 337.1916. $C_{21}H_{25}N_2O_2$ requires 337.1916, Δ 0.0 ppm. All data are in agreement with literature values.[92]

(±)Phenylalanine-*tert*-butyl ester, 102[167]



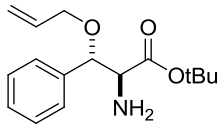
Aziridine **1a** (25 mg, 0.11 mmol) and Pd/C (5 mg, 20% w/w) were added to MeOH (1 mL). The flask was evacuated and re-filled with H_2 (g), and the reaction stirred under a H_2 atmosphere (balloon). After 3 h., the Pd/C was removed by filtration, and the filtrate washed with CH_2Cl_2 (10 mL). The solvent was removed *in vacuo* to provide the pure product as clear oil (24 mg, 95%). R*f* 0.45 (UV 254 nm, MeOH/EtOAc, 1:5); ν_{max}/cm^{-1} 3388 (NH), 2984 (CH), 1730 (C=O); δH ($CDCl_3$, 400 MHz) 7.31-7.20 (5H, Ar**H**), 3.63 (1H, br t, *J* 6.2, NH_2C**H**), 3.06 (1H, dd, *J* 13.8 and 6.2, ArC**H**H), 2.87 (1H, dd, *J* 13.8 and 8.0, ArCH**H**), 1.52 (2H, br s, NH_2), 1.42 (9H, s, C(C**H**$_3$)$_3$**;** δC ($CDCl_3$, 101 MHz) 174.3, 137.6, 129.4, 128.4, 126.7, 81.2, 56.3, 41.3, 28.0; *m/z* (ESI+) 222 (M+), 150 (- OtBu). All data are in agreement with literature values.[167]

(±)*tert*-Butyl-2-amino-3-phenyl-3-(methoxy)propanoate, 111



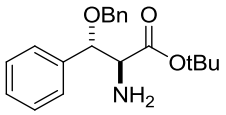
CSA (27 mg, 0.11 mmol) was added to anhydrous MeOH (1 mL) at 0 °C. After 2 min., the ice bath was removed and aziridine **1a** (25 mg, 0.11 mmol) added immediately. After 6 h., the reaction was quenched with $NaHCO_3$ (sat. aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic phases dried over Na_2SO_4. The solvent was removed *in vacuo* to provide the pure product as a clear oil (29 mg, quant.). R*f* 0.45 (UV 254 nm, MeOH/EtOAc, 1:50); ν_{max}/cm^{-1} 3399 (NH), 2982 (CH), 1735 (C=O), 1370, 1159; δH ($CDCl_3$, 400 MHz) 7.41-7.28 (5H, Ar**H**), 4.39 (1H, d, *J* 5.9, ArC**H**), 3.67 (1H, d, *J* 5.9, C(O)C**H**), 3.27 (3H, s, OC$\mathbf{H_3}$), 1.58 (2H, br s NH_2), 1.42 (9H, s, C(C$\mathbf{H_3}$)$_3$); δC ($CDCl_3$, 101 MHz) 172.1, 137.4, 128.3, 128.3, 127.6, 85.4, 81.4, 60.5, 57.2, 28.0; *m/z* HRMS (NH_3 CI+), Found: MH^+, 252.1602. $C_{14}H_{22}NO_3$ requires 252.1600, Δ 0.8 ppm.

(±)*tert*-Butyl-2-amino-3-phenyl-3-(hydroxyallyl)propanoate, 112



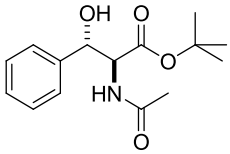
CSA (66 mg, 0.29 mmol) was added to allyl alcohol (1 mL) at 0 °C. After 2 min., the ice bath was removed and aziridine **1a** (25 mg, 0.11 mmol) added immediately. After 16 h, the reaction was quenched with $NaHCO_3$ (sat. aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic phases dried over Na_2SO_4. The solvent was removed *in vacuo* to provide the crude product as a yellow oil (30 mg). Column chromatography, eluting with EtOAc/petroleum ether (1:10) then (1:2) provided the pure product as a clear oil (18 mg, 57%). R*f* 0.25 ($KMnO_4$ dip, EtOAc/petroleum ether, 1:2); ν_{max}/cm^{-1} 2984 (CH), 2867 (CH), 1737 (C=O), 1368, 1156; δH ($CDCl_3$, 400 MHz) 7.37-7.29 (5H, m, Ar**H**), 5.91-5.81 (1H, m, H_2C=C**H**), 5.25 (1H, dq, J_{trans} 17.5 and 1.5, **H**HC=CH), 5.16 (1H, dquart, J_{cis} 10.4 and 1.5 H**H**C=CH), 4.52 (1H, d, *J* 7.2, ArC**H**), 3.98 (1H, ddt, *J* 12.8, 5.7 and 1.5, OCH**H**), 3.82 (1H, ddt, *J* 12.8, 5.7 and 1.4, OC**H**H), 3.66 (1H, d, *J* 6.5, NC**H**), 1.47 (2H, br s, NH_2), 1.43 (9H, s, C(C$\mathbf{H_3}$)$_3$); δC ($CDCl_3$, 101 MHz) 172.3, 137.8, 134.5, 128.3, 128.3, 127.7, 116.9, 83.1, 81.4, 69.9, 60.7, 28.0; *m/z* HRMS (NH_3 CI+), found: MH^+, 278.1766. $C_{16}H_{24}NO_3$ requires 278.1756, Δ 4.0 ppm.

(±)*tert*-Butyl-2-amino-3-phenyl-3-(hydroxybenzyl)propanoate, 113



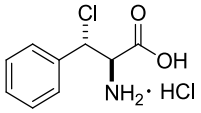
CSA (66 mg, 0.29 mmol) was added to benzyl alcohol (1 mL) at 0 °C. After 2 min. stirring, the ice bath was removed and aziridine **1a** (25 mg, 0.11 mmol) added immediately. After 16 h stirring under Ar (g), the reaction was quenched with $NaHCO_3$ (sat. aq., 5 mL). The aqueous phase was extracted with hexane (3 x 5 mL). The organic phases were combined and washed with H_2O (3 x 8 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo*. Column chromatography, eluting with EtOAc/petroleum ether (1:5) then (1:3) provided the pure product as a clear oil (17 mg, 46%). R*f* 0.20 (UV 254 nm, EtOAc/petroleum ether, 1:3); ν_{max}/cm^{-1} 2982 (CH), 1730 (C=O), 1372, 1153; δH ($CDCl_3$, 400 MHz) 7.39-7.27 (10H, Ar**H**), 4.61 (1H, d, *J* 6.5 BnOC**H**), 4.51 (1H, d, *J* 11.8, PhC**H**H), 4.35 (1H, d, *J* 11.8, PhCH**H**), 3.72 (1H, d, *J* 6.5, NC**H**), 1.67 (2H, br s, NH_2), 1.41 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 172.0, 137.9, 137.6, 128.4, 128.4, 128.3, 127.8, 127.7, 127.6, 83.2, 81.4, 70.8, 60.7, 28.0; *m/z* HRMS (NH_3 CI+), found: MH^+, 328.1903. $C_{20}H_{26}NO_3$ requires 328.1913, Δ 3.0 ppm.

(±)*tert*-Butyl-2-acetylamino-3-phenyl-3-(hydroxyl)propanoate, 106



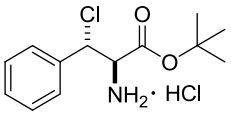
tert-Butyl aziridine **1a** (25 mg, 0.11 mmol) was suspended in acetic acid (2 mL) and heated to 70 °C. After 2 h., the heat source was removed and the reaction cooled. The acetic acid was removed *in vacuo*, and the resulting white crystals dissolved in CH_2Cl_2 (4 mL). The organic phase was washed with $NaHCO_3$ and the aqueous phase extracted with CH_2Cl_2 (3 x 4 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to provide the pure product (27 mg, 79%). Mp 173-174 °C; R*f* 0.20 ($KMnO_4$ dip, EtOAc/petroleum ether, 1:1); ν_{max}/cm^{-1} 3357 (br) (Het-H), 3266 (Het-H), 2931 (CH), 2861 (CH), 1734 (s) (C=O), 1652 (s) (C=O); δH ($CDCl_3$, 400 MHz) 7.34-7.24 (5H, m, Ar**H**), 6.42 (1H, d, *J* 6.7, NH), 5.26 (1H, d, *J* 3.0, ArC**H**), 4.90 (1H, dd, *J* 6.7 and 3.0, COC**H**), 4.30 (1H, br s, O**H**), 2.02 (3H, s, COC**H**$_3$), 1.41 (9H, s, OC(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 171.7, 168.4, 139.5, 128.1, 127.8, 126.0, 83.4, 75.3, 59.8, 27.9, 23.0; *m/z* (NH_3 CI+), found: MH^+, 280.1551. $C_{15}H_{22}NO_4$ requires 280.1549, Δ 0.7 ppm.

(±)3-Chloro-3-phenylalanine hydrochloride, 103



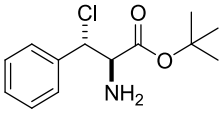
tert-Butyl aziridine **1a** (25 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (1 mL) and HCl (37% aq., 10 drops) added. After 20 mins, a white precipitate was observed. After 2 h., the precipitate was filtered off and washed with CH_2Cl_2 (4 mL). The precipitate was dried *in vacuo* for 15 min., providing the pure compound as a white flaky solid (12 mg, 45%). M.p 164-166 °C; R*f* 0.0 (UV 254 nm, petroleum ether/EtOAc, 3:1); ν_{max}/cm^{-1} 2978 (br) (Het-H), 2904 (CH), 1739 (C=O), 1208; δH (d_6-DMSO, 400 MHz) 8.98 (2.5H, br s, O**H**/NH_2), 7.60-7.55 (2H, Ar**H**), 7.49-7.40 (3H, Ar**H**), 5.86 (1H, d, *J* 4.1, ArC**H**), 4.59 (1H, d, 4.28), 3.86 (0.5H, br s, O**H**/NH_2); δC (CD_3OD, 101 MHz) 166.5, 134.4, 129.3, 128.6, 127.5, 59.3, 59.2; *m/z* HRMS (ESI+), found: MH^+, 200.0473. $C_9H_{11}NO_2{}^{35}Cl$ requires 200.0478, Δ 2.5 ppm.

(±)3-Chloro-3-phenylalanine hydrochloride-*tert*-butyl ester, 104a



tert-Butyl aziridine **1a** (25 mg, 0.11 mmol) dissolved in CH_2Cl_2 (1 mL) and HCl (2 mL, 4M in dioxane) was added. After 30 min., the reaction solvent was removed *in vacuo* to yield the crude product as an off white solid. Et_2O (10 mL) was added, and the insoluble white solid collected by filtration. Removal of solvent from the solid *in vacuo* yielded the pure product as a white solid (12 mg, 36%). Mp 155-158 °C; R*f* 0.0 (UV 254 nm, MeOH/EtOAc, 20:1); ν_{max}/cm^{-1} 2967 (CH), 1729 (C=O), 1264, 1154; δH (CD_3OD, 400 MHz) 7.59 (2H, Ar**H**), 7.52 (3H, Ar**H**), 5.68 (1H, d, *J* 4.4, ArC**H**), 4.65 (1H, d, *J* 4.4, NH_2C**H**), 1.43 (9H, s, C(C**H**$_3$)$_3$); δC (CD_3OD, 101 MHz) 164.4, 134.8, 129.1, 128.5, 127.4, 84.8, 59.7, 59.2, 26.6; *m/z* HRMS (ESI+), found: MH^+, 256.1096. $C_{13}H_{19}NO_2{}^{35}Cl$ requires 256.1104, Δ 3.1 ppm.

(±)3-Chloro-3-phenylalanine *tert*-butyl ester, 104b

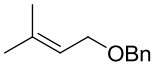


tert-Butyl aziridine **1a** (24 mg, 0.11 mmol) was dissolved in CH_2Cl_2 (1 mL), and HCl (2 mL, 4M in dioxane) was added. After 1h., the reaction solvent was removed *in vacuo* to yield the product as the hydrochloride salt. The salt was dissolved in CH_2Cl_2 (4 mL) and washed with $NaHCO_3$ (4 mL, sat. aq.). The organic phase was dried over Na_2SO_4 and the solvent removed *in vacuo*, to provide the title compound as a clear oil (25 mg, 90%). R*f* 0.8 (UV 254 nm, MeOH/EtOAc, 1:20); ν_{max}/cm^{-1} 3394

(NH), 2979 (CH), 1731 (C=O), 1371, 1153; δH ($CDCl_3$, 400 MHz) 7.43-7.32 (5H, Ar**H**), 5.06 (1H, d, *J* 7.2, ArC**H**), 3.87 (1H, d, *J* 7.2, C(O)C**H**), 1.52 (2H, br s, NH), 1.47 (9H, s, C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 170.9, 137.3, 128.9, 128.6, 128.2, 82.3, 64.0, 62.2, 28.0; *m/z* HRMS (NH_3 CI+), found: MH^+, 256.1105. $C_{13}H_{19}NO_2{}^{35}Cl$ requires 256.1104, Δ 0.4 ppm.

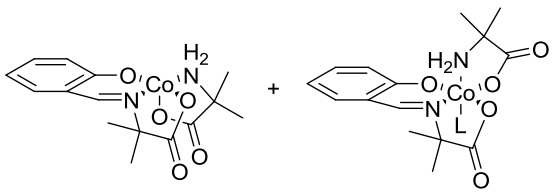
3.2.2 Pyrazolo[3,4-d]pyrimidine synthesis

(3-Methylbut-2enyloxymethyl)-benzene, 118[115]



Adapted from the procedure of Kawasaki,[115] NaH (0.17 g, 4.4 mmol, 60% in mineral oil) was suspended in anhydrous THF and cooled to 0 °C. BnOH (0.39 mL, 3.4 mmol) was added dropwise over 1 min. to the mixture, and stirred at 0° C for 3 min. The ice bath was removed, and the reaction allowed to warm to r.t. for 15 min. The reaction was then cooled to 0 °C, and prenyl bromide (0.39 mL, 3.4 mmol) added dropwise over 1 min. The reaction was stirred at 0 °C for 3 min., after which the ice-bath was removed and the reaction allowed to warm to r.t. After 20 h., H_2O (10 mL) was added, and the aqueous phase extracted with hexane (3 x 10 mL). The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo* to provide the crude product (0.63 g). Purification by column chromatography eluting with EtOAc/petroleum ether (1:40) provided the pure product as clear oil (0.33 g, 52%). R*f* 0.25 ($KMnO_4$, EtOAc/petroleum ether, 1:40); δH ($CDCl_3$, 400 MHz) 7.37-7.27 (5H, Ar**H**), 5.45-5.41 (2H, m, alkene-**H**), 4.52 (2H, s, PhC**H**$_2$), 4.03 (2H, br d, *J* 6.9, $(CH_3)_2CCHC\mathbf{H}_2$) 1.78 (3H, s, C**H**$_3$), 1.68 (3H, s, C**H**$_3$); δC ($CDCl_3$, 101 MHz) 138.6, 137.2, 128.4, 127.8, 127.5, 121.1, 72.1, 66.6, 25.8, 18.1; *m/z* HRMS (NH_3, CI+), found: MNH_3^+, 194.1537. $C_{12}H_{20}NO$ requires 194.1545, Δ 4.1 ppm. All data are in agreement with reported values.[115]

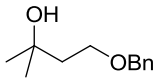
[*N*-Salicylidene-2-aminoisobutyrato]-[2-aminoisobutyrato]-cobalt (III), 119[113]



Adapted from the procedure of Carreira,[113] salicaldehyde (2.13 mL, 20.1 mmol) and 2-aminoisobutyric acid (2.07 g, 20.1 mmol) were suspended in H_2O under Ar for 5 min., before the addition of $Co(OAc)_2.4H_2O$ (5 g, 20.1 mmol). The reaction was heated to reflux for 2 h., after which the brown-red solid that had formed was filtered off and washed with H_2O (20 mL). The solid was dried *in vacuo* for 12 h, to yield a dry brown-red solid (2.87 g). A portion (1g) of the solid was suspended in EtOH:H_2O (30 mL:12 mL) in air and 2-aminoisobutyric acid (0.32 g) added. After 6 h. stirring at r.t., the solvent was removed *in vacuo*, and the resulting red-solid concentrated from CH_2Cl_2 (2 x 20 mL) and EtOH (20 mL), before drying *in vacuo* (80 °C, 6 h.). Purification by column

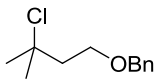
chromatography eluting with CH_2Cl_2/MeOH (10:1 then 1:1) provided the product as dark red crystals as a mixture of two isomers (1.15 g, quantitative yield, 83% pure by NMR, with reference to Bn_2O as an internal standard.) R*f* 0.3 and 0.2 (UV 254 nm, CH_2Cl_2/MeOH, 10:1); 8.62 ($0.32H_{minor,}$ s, N=C**H**), 8.31 ($0.68H_{major,}$ s, N=C**H**), 7.56 ($0.32H_{minor,}$ d, *J* 7.9, Ar**H**), 7.52 ($0.68H_{major,}$ dd *J* 7.9 and 1.6, Ar**H**), 7.29-7.21 (1H, m, Ar**H**), 7.11 (1H, d, *J* 8.8, Ar**H**), 6.71-6.63 (1H, m, Ar**H**), 1.84 ($1H_{minor,}$ s, C$\mathbf{H_3}$), 1.82 ($1H_{minor,}$ s, C$\mathbf{H_3}$), 1.79 ($2H_{major,}$ s, C$\mathbf{H_3}$), 1.71 ($1H_{minor,}$ s, C$\mathbf{H_3}$), 1.68 ($2H_{major,}$ s, C$\mathbf{H_3}$), 1.62 ($1H_{minor,}$ s, C$\mathbf{H_3}$), 1.33 ($2H_{major,}$ s, C$\mathbf{H_3}$), 1.27 ($2H_{major,}$ s, C$\mathbf{H_3}$); *m/z* HRMS (ESI+), found: MH^+, 367.0693. $C_{15}H_{20}CoN_2O_5$ requires 367.0705, Δ 3.3 ppm. All data are in agreement with reported values.[113]

4-(Benzyloxy)-2-methylbutan-2-ol, 144[122]



Adapted from the procedure of Asaoka.[122] 4-Benzyloxy-2-butanone (1g, 5.6 mmol) was added to anhydrous THF (22 mL) and cooled to -78 °C. MeLi (7 mL, 11.2 mmol, 1.6 M solution in Et_2O) was added dropwise over 22 min., maintaining the temperature below -75 °C. The reaction was stirred for a further 50 min. at -78 °C, and then quenched at this temperature with NH_4Cl (sat. aq., 20 mL). Et_2O (20 mL) was added, followed by H_2O (20 mL). The organic phase was separated, and the aqueous phase extracted with Et_2O (3 x 20 mL). The organic phases were combined and dried over $MgSO_4$, and the solvent removed *in vacuo*. The crude product was isolated as a clear oil (1.13 g). Purification by column chromatography eluting with Et_2O/petroleum ether (1:4 then 1:1) provided the pure product as clear oil (0.92 g, 84%). R*f* 0.20 (UV 254 nm, Et_2O/petroleum ether, 1:4); ν_{max}/cm^{-1} 3432 (OH), 2978 (CH), 2943 (CH), 2870, 1457; δH ($CDCl_3$, 400 MHz) 7.37-7.26 (5H, Ar**H**), 4.52 (2H, s, PhC$\mathbf{H_2}$), 3.73 (2H, t, *J* 6.0, OC$\mathbf{H_2}$), 3.26 (1H, s, O**H**), 1.82 (2H, t, *J* 6.0, $OCH_2C\mathbf{H_2}$), 1.23 (6H, s, 2 x C$\mathbf{H_3}$); δC ($CDCl_3$, 101 MHz) 137.8, 128.5, 127.8, 127.7, 73.4, 70.5, 67.7, 41.6, 29.4; *m/z* HRMS (NH_3, CI+) found: MH^+, 195.1388. $C_{12}H_{19}O_2$ requires 195.1385, Δ 1.5 ppm. All data are in agreement with reported values.[122]

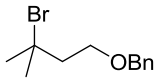
Benzyl 3-chloro-3-methylbutyl ether, 145[122]



Adapted from the method of Asaoka.[122] 4-Benzyloxy-2-butanone (5g, 28 mmol) was dissolved in anhydrous THF (100 mL) and cooled to -78 °C. MeLi (36 mL, 56 mmol, 1.55 M solution in Et_2O) was added dropwise over 25 min., maintaining the temperature below -76 °C. The reaction was stirred for a further 1 h. at -78 °C, before the cooling bath was removed, and the reaction quenched immediately with NH_4Cl (sat. aq., 100 mL). H_2O (100 mL) was added, and the aqueous phase extracted with Et_2O (3 x 100 mL). The organic phase was dried over $MgSO_4$, and the solvent removed

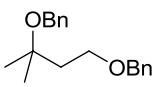
in vacuo. Crude alcohol **144** was isolated as a clear oil (6.72 g), and suspended in HCl (37% aq., 20 mL) under Ar with rapid stirring. After 1 h. 35 min., H_2O (50 mL) and Et_2O (50 mL) were added. $NaHCO_3$ (s) was added until the solution reached a pH of 7. Further portions of H_2O (50 mL) and Et_2O (50 mL) were added, and the organic phase separated. The aqueous phase was extracted with Et_2O (2 x 100 mL), dried over $MgSO_4$ and concentrated *in vacuuo* to provide the crude product as a yellow oil (7.93 g). Purification by column chromatography eluting with EtOAc/petroleum ether (1:100) provided the pure product as clear oil (3.43 g, 56%). R*f* 0.20 (UV 254 nm, EtOAc/petroleum ether, 1:100); ν_{max}/cm^{-1} 1458, 1370, 1104; δH ($CDCl_3$, 400 MHz) 7.38-7.27 (5H, Ar**H**), 4.52 (2H, s, PhC**H**$_2$), 3.74 (2H, t, *J* 6.7, CH_2C**H**$_2$OBn), 2.14 (2H, t, *J* 6.7, C**H**$_2CH_2$OBn), 1.62 (6H, s, 2 x C**H**$_3$); δC ($CDCl_3$, 101 MHz) 138.3, 128.4, 127.7, 127.6, 73.1, 69.6, 67.4, 45.2, 33.0; *m/z* HRMS (NH_3, CI+) found: MNH_4^+, 230.1301. $C_{12}H_{21}NO^{35}Cl$ requires 230.1312, Δ 4.8 ppm. All data are in agreement with reported values.[122]

Benzyl 3-bromo-3-methylbutyl ether, 146



Adapted from the procedure of Masada,[123] LiBr (2.37 g, 27 mmol) was added to alcohol **144** (3.54 g, 18 mmol) and cooled to 0 °C. On cooling, the alcohol froze, and the mixture became a gum which and stirring ceased. HBr (4.20 mL, 36 mmol) was added to the mixture, and the cooling bath removed after the addition. On warming to room temperature, the reaction became liquid and changed from beige to pink in colour. After 2 h., the organic phase was separated, and ethylene glycol (8 mL) added, forming an emulsion. The emulsion was extracted with Et_2O (3 x 25 mL), and the combined organics washed with H_2O (2 x 20 mL). The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo* to provide the crude product as a yellow oil (3.79 g, 85%) in sufficient purity. R*f* 0.25 (UV 254 nm, EtOAc/petroleum ether, 1:50); ν_{max}/cm^{-1} 2971 (CH), 2868 (CH), 1457, 1371; δH ($CDCl_3$, 400 MHz) 7.43-7.30 (5H, Ar**H**), 4.56 (2H, PhC**H**$_2$), 3.79 (2H, t, *J* 6.7, CH_2C**H**$_2$OBn), 2.23 (2H, t, *J* 6.7 C**H**$_2CH_2$OBn), 1.84 (6H, s, 2 x C**H**$_3$); δC ($CDCl_3$, 101 MHz) 138.3, 128.4, 127.6, 127.6, 73.1, 68.5, 66.0, 46.6, 34.9; *m/z* HRMS (NH_3 CI+) found: MNH_4^+, 274.0808. $C_{12}H_{21}NO^{79}Br$ requires 274.0807, Δ 0.4 ppm.

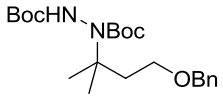
1,1'-[(3-Methylbutane-1,3-diyl)bis(oxymethanediyl)]dibenzene, 144a



HBr (49% aq., 15 mL) was added to alcohol **144** (5.53 g, 28 mmol, 88% pure containing 4-benzyloxy-2-butanone) and stirred in air. On addition of the HBr the mixture turned from clear to pink. After 3 h., $NaHCO_3$ (s) was added until the reaction reached pH 7. H_2O (15 mL) and Et_2O (15

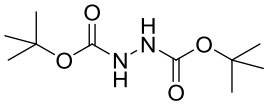
mL) were added to the mixture. The aqueous phase was extracted with Et_2O (3 x 15 mL), and the organics combined and dried over $MgSO_4$. The solvent was removed *in vacuo*. Purification by column chromatography eluting with EtOAc/petroleum ether (1:50) provided the pure product as clear oil (0.06 g, 1%). R*f* 0.20 (UV 254 nm, EtOAc/petroleum ether, 1:50); ν_{max}/cm^{-1} 2978 (CH), 2869 (CH), 1457, 1362; δH ($CDCl_3$, 400 MHz) 7.42-7.27 (10 H, Ar**H**), 4.56 (2H, s, PhC**H$_2$**), 4.47 (2H, s, PhC**H$_2$**), 3.72 (2H, t, *J* 7.2, $CH_2C\mathbf{H_2}OBn$), 2.04 (2H, t, *J* 7.2 $C\mathbf{H_2}CH_2OBn$), 1.34 (6H, s, 2 x C**H$_3$**); δC ($CDCl_3$, 101 MHz) 139.7, 138.6, 128.4, 128.3, 127.7, 127.6, 127.4, 127.2, 74.4, 73.1, 66.8, 63.7, 40.0, 26.2; *m/z* HRMS (NH_3 CI+) found: MH^+, 285.1857. $C_{19}H_{25}O_2$ requires 285.1855, Δ 0.7 ppm.

_N_-(3-Benzyloxy-1,1-dimethylpropyl)-_N_'-(*tert*-butoxycarbonyl)hydrazinecarboxylic acid *tert*-butyl ester, 120[112]



Adapted from the procedure of McCague,[112] catalyst **119** (0.35 g, 1 mmol) was added to anhydrous EtOH (90 mL) at room temperature. Alkene **118** (3.33 g, 19 mmol), $PhSiH_3$ (3.06 g, 28 mmol) and di-*tert*-butylazodicarboxylate (9.79 g, 43 mol) were added sequentially. After 5 min., an exotherm was noted, and the reaction was cooled to 0°C. After 10 min. at 0°C the ice bath was removed, and the reaction stirred at r.t. for 7 d. The reaction was quenched with brine (200 mL, sat. aq.), and H_2O (50 mL) was added. The aqueous phase was extracted with EtOAc (3 x 200 mL), and the organic phase dried over $MgSO_4$. The solvent was removed *in vacuo* to provide the crude product as a brown oily solid. Purification by column chromatography eluting with EtOAc/petroleum ether (1:50, 1:10, 1:5) provided the pure product as clear viscous oil (2.60 g, 33%). R*f* 0.25 (UV 254 nm, EtOAc/petroleum ether, 1:5); δH ($CDCl_3$, 400 MHz, mixture of rotamers) 7.37-7.27 (5H, Ar**H**), 6.25 (0.68 x 1H, br s, N**H**), 5.92 (0.32 x 1H, br s, N**H**), 4.47 (2H, s, PhC**H$_2$**), 3.64-3.47 (2H, m, $PhCH_2OC\mathbf{H_2}$), 2.43-2.34 (1H, m, $(CH_3)_2CCH\mathbf{H}$), 1.83-1.73 (1H, m, $(CH_3)_2CC\mathbf{H}H$), 1.53 (3H, s, C**H$_3$**), 1.45 (9H, s, $C(C\mathbf{H_3})_3$), 1.39 (9H, s, $C(C\mathbf{H_3})_3$), 1.28 (3H, s, C**H$_3$**); *m/z* HRMS (ESI+) found: MH^+, 409.2709. $C_{22}H_{37}N_2O_5$ requires 409.2716, Δ 1.7 ppm. All data are in agreement with reported values.[112]

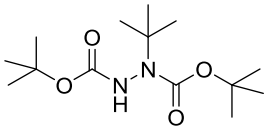
Di-*tert*-butyl hydrazine-1,2-dicarboxylate, 132[168]



Following the procedure used to prepare hydrazine **120**, di-*tert*-butylazodicarboxylate (9.79 g, 43 mmol) provided the title compound as white powdery crystals (5.11 g, 52%), after purification by column chromatography, eluting with EtOAc/petroleum ether (1:5, 1:3). Mp 124-126 °C [lit. 124-126 °C[168]]; R*f* 0.15 ($KMnO_4$, EtOAc/petroleum ether, 1:5); ν_{max}/cm^{-1} 3321 (NH), 2987 (CH), 1739 (C=O);

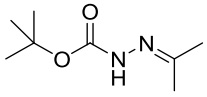
δH ($CDCl_3$, 400 MHz) 6.36 (2H, br s, C(O)N**H**), 1.45 (18H, s, 2 x C(C**H**$_3$)$_3$); δC ($CDCl_3$, 101 MHz) 155.8, 81.4, 28.2; *m/z* (NH_3, CI+) 250 ($M+NH_4^+$). All data are in agreement with reported values.[169]

Di-*tert*-butyl 1-*tert*-butylhydrazine-1,2-dicarboxylate, 142[121]



Adapted from the procedure of Crowley *et al*.,[121] Mg turnings (0.24 g, 10.0 mmol) were washed with hexane (3 x 3 mL) and dried under high vacuum (5min., r.t.). A portion of *tert*-butyl chloride (0.6 mL from 1.10 mL, 10.0 mmol) was added to the Mg turnings, with a crystal of I_2, and the reaction heated gently (ca. 40 °C) for 3 min. The remaining *tert*-butyl chloride (0.5 mL) was dissolved in dry THF (10 mL) in a separate flask, and a portion (3 mL) of this solution added to the reaction flask. Initiation was observed, and reflux was maintained through heating and slow addition of the *tert*-butyl chloride/THF solution. After the addition was complete, the reaction was heated at reflux for 25 min., after which the heat source was removed. The Grignard reagent was allowed to cool to *ca*. 50 °C, before transferring *via* cannula over 5 min. to a cooled (0 °C) solution of *tert*-butylazodiformate (1.00 g, 4.3 mmol) in THF (10 mL). The reaction was warmed to r.t. and stirred for 1 h. 45 min. The reaction was diluted with Et_2O (20 mL), and H_2O (45 mL) added (NaCl (s) required to separate the phases). The aqueous phase was extracted with Et_2O (3 x 20 mL) and the organics dried over $MgSO_4$. The solution was concentrated *in vacuo* to provide the crude product as brown oil (1.05 g). Purification by column chromatography eluting with EtOAc/petroleum ether (1:20, 1:10, 1:5) provided the pure product as white solid (0.49 g, 39%). Mp 139-140 °C [lit. 136-137 °C[121]]; R*f* 0.20 ($KMnO_4$, EtOAc/petroleum ether, 1:20); ν_{max}/cm^{-1} 3310 (NH), 2985 (CH), 1739 (C=O), 1687 (C=O), 1370; δH ($CDCl_3$, 400 MHz, mixture of rotamers) 6.18 (0.66 x 1H, br s, N**H**), 5.89 (0.33 x 1H, br s, N**H**), 1.51-1.48 (18H, C(C**H**$_3$)$_3$,), 1.43-1.39 (9H, N(C**H**$_3$)$_3$,); δC ($CDCl_3$, 101 MHz, broadened peaks, mixture of rotamers) 156.4, 156.1, 154.7, 154.1, 81.1, 80.6, 80.5, 59.3, 28.5, 28.3, 28.2; *m/z* HRMS (NH_3, CI+) found: MH^+, 289.2127. $C_{14}H_{29}N_2O_4$ requires 289.2127, Δ 0.0 ppm.

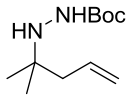
***tert*-Butyl 2-(propan-2-ylidene)hydrazinecarboxylate, 154**[126]



According to the procedure of Meyer,[126] *tert*-butylcarbazate (10 g, 76 mmol) and $MgSO_4$ (2 g, 20% w/w) were added to acetone (80 mL). AcOH (10 drops) was added, and the reaction heated to reflux for 1 h. The heat was removed and the reaction allowed to cool to room temperature. The reaction mixture was filtered, and the mother liquor concentrated *in vacuo* to provide the pure product as white crystals. Mp 83-86 °C [lit. 87-90 °C[127]]; R*f* 0.15 (UV 254 nm, Et_2O/petroleum ether, 1:1); ν_{max}/cm^{-1}

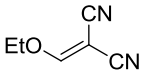
3251 (NH), 2981 (CH), 1708 (C=O), 1527; δH ($CDCl_3$, 400 MHz) 7.38 (1H, br s, N**H**), 2.02 (3H, s, N=CC**H$_3$**), 1.80 (3H, s, N=CC**H$_3$**), 1.49 (9H, s, C(C**H$_3$**)$_3$); δC ($CDCl_3$, 101 MHz) 152.8, 149.7, 80.7, 28.3, 25.4, 16.0; *m/z* HRMS (NH_3 CI+) found: MNH_4^+, 173.1292. $C_8H_{17}N_2O_2$ requires 173.1290, Δ 1.2 ppm. All data are in agreement with literature values.[126]

tert-Butyl 2-(2-methylpent-4-en-2-yl)hydrazinecarboxylate, 157[127]



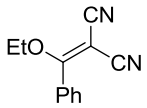
According to the procedure of Wolfe.[127] Hydrazone **154** (8.61 g, 50 mmol) was dissolved in anhydrous THF (500 mL). The mixture was cooled to 0 °C and allyl magnesium bromide (100 mL, 100 mmol, 1M solution in Et_2O) added over 12 min. A gradual colour change from clear to pale green was noted during the addition of the first eq. of Grignard reagent, with a sharp end point to yellow on exceeding 1 eq. The temperature was maintained between 1-0 °C for a further hour after the addition, after which time, the ice-bath was removed, and the reaction stirred at room temperature for a further 1 h. The reaction was cooled to 0 °C and quenched with NaOH (1M aq., 200 mL). The aqueous phase was extracted with Et_2O (3 x 200 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*, to provide the crude product as a clear oil. Purification by column chromatography eluting with EtOAc/petroleum ether (1:7) provided the pure product as clear oil (7.51 g, 70%). R*f* 0.15 ($KMnO_4$, EtOAc/petroleum ether, 1:7); ν_{max}/cm^{-1} 3306 (NH), 2983 (CH), 1712 (C=O); δH ($CDCl_3$, 400 MHz) 5.90 (1H, br s, amide-N**H**), 5.89-5.79 (1H, m, H_2C=C**H**), 5.08 (1H, m, **H**HC=CH), 5.06-5.03 (1H, m, H**H**C=CH), 3.82 (1H, br s, amine-N**H**), 2.13 (2H, dt, *J* 7.3 and 1.2, H_2C=CHC**H$_2$**), 1.44 (9H, s, C(C**H$_3$**)$_3$), 1.02 (6H, s, 2 x C**H$_3$**); δC ($CDCl_3$, 101 MHz) 157.2, 134.6, 117.8, 80.2, 56.8, 44.4, 28.3, 24.8; *m/z* HRMS (NH_3 CI+), found: MH^+, 215.1759. $C_{11}H_{23}N_2O_2$ requires 215.1760, Δ 0.5 ppm. All data are in agreement with literature values.[127]

(Ethoxymethylidene)propanedinitrile, 121[128]



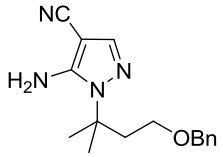
Adapted from the procedure of Quinn.[128] Malononitrile (8.0 g, 121 mmol), Ac_2O (40 mL) and triethyl orthoformate (30 mL, 182 mmol) were combined and heated to reflux for 5 h. The heat source was removed, and the reaction allowed to cool to r. t., before concentration of the reaction mixture *in vacuo*. The resulting solid was recrystalised from Et_2O, and dried *in vacuo* for 3 h., providing the pure product as pale brown crystals (10.1 g, 68%). Mp 66-68 °C [lit. 66-67 °C[128]]; R*f* 0.40 (UV 254 nm, EtOAc/petroleum ether, 1:2); δH ($CDCl_3$, 400 MHz) 7.59 (1H, s, alkene-**H**), 4.43 (2H, quart, *J* 7.5, OC**H$_2$**CH_3), 1.49 (3H, t, *J* 7.5, OCH_2C**H$_3$**). All data is in agreement with literature values.[128]

[Ethoxy(phenyl)methylidene]propanedinitrile, 188[150]



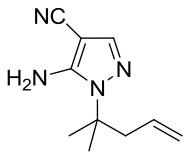
Adapted from the procedure of Bontems *et al.*[150] Triethyl orthobenzoate (10 mL, 44 mmol), malononitrile (2.99 g, 45 mmol) and acetic anhydride (85 mL) were combined and heated to reflux. A colour change was observed on heating, from yellow to dark brown. After 3 h. at reflux, the heat source was removed, and the reaction mixture concentrated *in vacuo*. Purification by column chromatography, eluting with EtOAc/petroleum ether (1:4) provided the pure product as yellow crystalline powder (4.26 g, 49%). Mp 88-92 °C [lit. 84-85 °C[150]]; R*f* 0.30 (UV 254 nm, EtOAc/petroleum ether, 1:4); δH ($CDCl_3$, 400 MHz) 7.65-7.49 (5H, Ph**H**), 4.22 (2H, q, *J* 6.9, OC**H**$_2$), 1.39 (3H, t, *J* 6.9, OCH_2C**H**$_3$); *m/z* (NH_3 CI+), 216 ($M+NH_4^+$). All data are in agreement with literature values.[150]

5-Amino-1-(3-benzyloxy-1,1-dimethylpropyl)-1*H*-pyrazole-4-carbonitrile, 122[112]



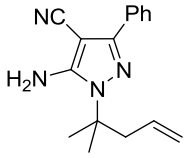
Adapted from the procedure of McCague.[112] AcCl (2.72 mL, 38.3 mmol) was added to anhydrous EtOH (35 mL) at 0 °C. The solution was warmed to r.t., and hydrazine **120** (2.60 g, 6.4 mmol) added. The reaction was heated at reflux for 1.5 h., before cooling to 0 °C. Et_3N (7.95 mL, 57.3 mmol) was added, followed by enol ether **121** (0.78 g, 6.4 mmol). The reaction was heated to reflux for 1.5 h., whereupon the heat source was removed, and the reaction allowed to cool to r.t. The solvent was removed *in vacuo*, before the addition of H_2O (100 mL), and brine (100 mL) to the brown solid residue. The aqueous phase was extracted with EtOAc (3 x 100 mL), and the organic phases combined and dried over $MgSO_4$. The solution was concentrated *in vacuo* to provide the crude product as brown oil (2.00 g). Purification by column chromatography eluting with EtOAc/petroleum ether (1:3) provided the pure product as yellow oil (1.35 g, 74%). R*f* 0.15 (UV 254 nm, EtOAc/petroleum ether, 1:3); δH ($CDCl_3$, 400 MHz) 7.39 (1H, s, pyrazole-**H**), 7.34-7.21 (5H, Ph**H**), 4.49 (2H, br s, N**H**$_2$), 4.37 (2H, s, PhC**H**$_2$), 3.43 (2H, t, *J* 6.4, CH_2C**H**$_2$O), 2.19 (2H, t, *J* 6.4, C**H**$_2CH_2$O), 1.62 (6H, s, 2 x C**H**$_3$); δC ($CDCl_3$, 101 MHz) 151.1, 138.5, 137.8, 128.5, 127.9, 127.7, 114.6, 78.1, 73.2, 66.4, 61.9, 40.6, 28.1. All data are in agreement with reported values.[112]

5-Amino-1-(1,1-dimethylbut-3-enyl)-1*H*-pyrazole-4-carbonitrile, 158



Adapted from the procedure of McCague.[112] AcCl (8.86 mL, 125 mmol) was added dropwise to anhydrous MeOH (125 mL) at 0 °C. The mixture was allowed to warm to r. t., and hydrazine **157** (4.45 g, 21 mmol) was added in one portion. The mixture was heated to reflux for 1 h. The reaction was cooled to 0 °C, and basified with Et_3N (26 mL, 187 mmol). Enol ether **121** (2.30 g, 21 mmol) was added in one portion. The reaction mixture was heated to reflux for 1 h. The heat source was removed, and the reaction allowed to cool to r. t. The solvent was removed *in vacuo*, before the addition of brine (5 mL) and H_2O (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the organics combined and dried over $MgSO_4$. The solvent was removed *in vacuo* to provide the crude product as a brown oil. Purification by column chromatography, eluting with EtOAc/petroleum ether (1:5) provided the pure product as an off-white powder (2.50 g, 63%). Mp 95-97 °C; R*f* 0.15 (UV 254 nm, EtOAc/petroleum ether, 1:5); ν_{max}/cm^{-1} 3421 (NH), 3331 (NH), 3244 (NH), 2219 (C≡N), 1648; δH ($CDCl_3$, 400 MHz) 7.41 (1H, s, pyrazole-**H**), 5.62-5.52 (1H, m, H_2C=C**H**), 5.08 (1H, m, **H**HC=CH), 5.06-5.04 (1H, m, **H**HC=CH), 4.44 (2H, br s, N**H$_2$**), 2.61 (2H, d, *J* 7.1, H_2C=CHC**H$_2$**), 1.61 (6H, s, 2 x C**H$_3$**); δC ($CDCl_3$, 101 MHz) 150.5, 138.5, 132.4, 119.5, 114.6, 78.0, 62.6, 45.3, 27.1; *m/z* HRMS (NH_3 CI+), found: MH^+, 191.1299. $C_{10}H_{15}N_4$ requires 191.1297, Δ 1.0 ppm.

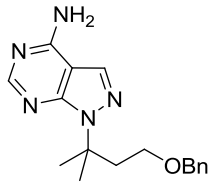
5-Amino-1-(1,1-dimethylbut-3-enyl)-3-phenyl-1*H*-pyrazole-4-carbonitrile, 189



Adapted from the procedure of McCague.[112] AcCl (4.0 mL, 60 mmol) was added dropwise to anhydrous MeOH at 0 °C. Hydrazine **157** (2.0 g, 9.3 mmol) was added in one portion, and the mixture heated to reflux. After 70 min., the reaction was cooled to 0 °C, and basified with Et_3N (11.7 mL, 83.7 mmol). Enol ether **188** (1.8 g, 9.3 mmol) was added in one portion, and the reaction heated to reflux. After 2 h. 10 min., the heat source was removed, and the reaction allowed to cool to r. t. The solvent was removed *in vacuo*, before the addition of brine (80 mL) and H_2O (80 mL). The aqueous phase was extracted with EtOAc (3 x 80 mL) and the organics combined and dried over $MgSO_4$. The solvent was removed *in vacuo* to provide the crude product as brown oil (2.60 g). Purification by column chromatography, eluting with EtOAc/petroleum ether (1:10 then 1:5) provided the pure product as a yellow solid (1.3 g, 52%). Mp 98-100 °C; R*f* 0.20 (UV 254 nm, EtOAc/petroleum ether, 1:5); ν_{max}/cm^{-1} 3474 (NH), 3355 (NH), 3017 (CH), 2988 (CH), 2212 (C≡N), 1623; δH ($CDCl_3$,

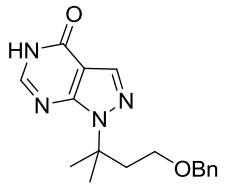
400 MHz) 7.94-7.92 (2H, Ar**H**), 7.44-7.34 (3H, Ar**H**), 5.72-5.62 (1H, m, H_2C=C**H**), 5.13-5.12 (1H, m, CH**H**CH), 5.09 (1H, m, C**H**HCH), 4.50 (2H, br s, N$\mathbf{H_2}$), 2.69 (2H, d, *J* 7.4, H_2C=CHC$\mathbf{H_2}$), 1.66 (6H, s, 2 x C$\mathbf{H_3}$); δC ($CDCl_3$, 101 MHz) 152.0, 148.3, 132.8, 131.7, 128.8, 128.7, 126.2, 119.4, 115.8, 75.5, 62.8, 45.5, 27.2; *m/z* (NH_3 CI+), found: MH^+, 267.1608. $C_{16}H_{19}N_4$ requires 267.1610, Δ 0.7 ppm.

1-(3-Benzyloxy-1,1-dimethylpropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine, 123[112]



Adapted from the procedure of McCague.[112] Pyrazole **122** (0.40 g, 1.4 mmol) and formamide (4 mL) were combined and heated to 180 °C. After 16 h., the heat source was removed, and the dark-brown reaction allowed to cool. The mixture was poured into brine (18 mL), and the aqueous phase extracted with EtOAc (3 x 18 mL). Emulsions were observed on extraction of the aqueous phase, which separated slowly. The organic phase was extracted with brine (2 x 18 mL) and dried over $MgSO_4$, to provide the crude product as yellow oil (0.35 g). Purification by column chromatography eluting with EtOAc/petroleum ether (1:3, 1:1 then 1:0) provided the pure product as clear oil (0.34 g, 77%). R*f* 0.15 (UV 254 nm, EtOAc/petroleum ether, 1:3); ν_{max}/cm^{-1} 3330 (NH), 3138, 1643, 1596; δH ($CDCl_3$, 400 MHz) 8.32 (1H, s, pyrimidine-**H**), 7.80 (1H, s, pyrazole-**H**), 7.28-7.17 (5H, Ar**H**), 6.15 (2H, br s, N$\mathbf{H_2}$), 4.33 (2H, s, PhC$\mathbf{H_2}$), 3.38 (2H, t, *J* 6.8, $CH_2C\mathbf{H_2}OBn$), 2.57 (2H, t, *J* 6.8, $C\mathbf{H_2}CH_2OBn$), 1.83 (6H, s, 2 x C$\mathbf{H_3}$); δC ($CDCl_3$, 101 MHz) 157.8, 154.4, 153.5, 138.3, 128.9, 128.3, 127.5, 127.4, 102.0, 72.8, 66.7, 62.1, 40.2, 27.8; *m/z* (NH_3, CI+) found: MH^+, 312.1827. $C_{17}H_{22}N_5O$ requires 312.1824, Δ 1.0 ppm. All data are in agreement with literature values.[112]

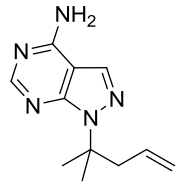
1-(3-Benzyloxy-1,1-dimethylpropyl)-1,5-dihydropyrazolo[3,4-*d*]pyrimidin-4-one, 123a[112]



The title compound was synthesised according to the procedure used to synthesise pyrimidine **123**. Purification by column chromatography eluting with EtOAc/petroleum ether (1:3, then 1:1) provided the pure product as a yellow oil (53 mg, 12%). R*f* 0.18 (UV 254 nm, EtOAc/petroleum ether, 1:3); ν_{max}/cm^{-1} 2883 (CH), 1684 (C=O), 1603; δH ($CDCl_3$, 400 MHz) 12.20 (1H, br s, pyrimidone-N**H**), 8.06 (1H, s, pyrimidone-**H**), 7.92 (1H, s, pyrazole-**H**), 7.30-7.19 (5H, Ph**H**), 4.34 (2H, s, PhC$\mathbf{H_2}$), 3.39 (2H, t, *J* 6.5, $CH_2C\mathbf{H_2}OBn$), 2.53 (2H, t, *J* 6.5, $C\mathbf{H_2}CH_2OBn$), 1.82 (6H, s, 2 x C$\mathbf{H_3}$); δC ($CDCl_3$, 101

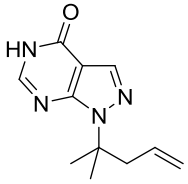
MHz) 160.3, 152.0, 144.1, 138.2, 133.0, 128.6, 128.3, 127.5, 107.4, 72.9, 66.5, 62.8, 40.5, 27.9; *m/z* HRMS (NH_3, CI+) found: MH^+, 313.1669. $C_{17}H_{21}N_4O_2$ requires 313.1665, Δ 1.3 ppm. All data are in agreement with literature values.[112]

1-(1,1-Dimethylbut-3-enyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine, 159



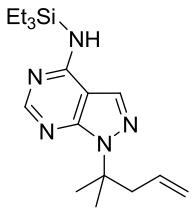
Adapted from the procedure of McCague.[112] Pyrazole **158** (2.5 g, 13 mmol) and formamide (20 mL) were combined and heated to reflux. After 16 h., the heat source was removed, and the dark-brown reaction allowed to cool to room temperature. Brine (50 mL) was added, followed by EtOAc (50 mL), forming a suspension that slowly separated. The aqueous phase extracted with further portions of EtOAc (2 x 60 mL). The organics were combined and dried over $MgSO_4$ and the solvent removed *in vacuuo*. Purification by column chromatography, eluting with EtOAc/petroleum ether (1:1) provided the pure product as a white solid (1.89 g, 66%). Mp 117-120; R*f* 0.20 (UV 254 nm, EtOAc/petroleum ether, 1:1); ν_{max}/cm^{-1} 3315 (NH), 3092 (CH), 2868 (CH), 1670, 1597; δH ($CDCl_3$, 400 MHz) 8.34 (1H, s, pyrimidine-**H**), 7.86 (1H, s, pyrazole-**H**), 6.35 (2H, br s, N**H**$_2$), 5.58-5.74 (1H, m, CH_2C**H**), 4.97-4.95 (1H, m, CH**H**CH), 4.92-4.90 (1H, m, C**HH**CH), 2.95 (2H, d, *J* 7.2, C**H**$_2$CH), 1.79 (6H, s, 2 x C**H**$_3$); δC ($CDCl_3$, 101 MHz) 157.9, 154.3, 153.4, 133.4, 128.8, 118.4, 102.0, 62.7, 45.1, 27.1; *m/z* HRMS (NH_3 CI+) found: MH^+, 218.1399. $C_{10}H_{20}NO_4$ requires 218.1406, Δ 3.2 ppm.

1-(1,1-Dimethylbut-3-enyl)-1,5-dihydropyrazolo[3,4-*d*]pyrimidin-4-one, 161



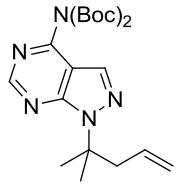
The title compound was synthesised from pyrazole **158** (100 mg, 0.53 mmol), according to the procedure used to synthesise pyrimidine **159**. Purification by column chromatography, eluting with EtOAc/petroleum ether (1:1) provided the pure product as white powder (36 mg, 31%). Mp 125-30 °C; R*f* 0.25 (UV 254 nm, EtOAc/petroleum ether, 1:1); ν_{max}/cm^{-1} 2284, 1696, 1605, 1319; δH ($CDCl_3$, 400 MHz) 12.06 (1H, br s, N**H**), 8.10 (1H, s, pyrimidone-**H**), 7.98 (1H, s, pyrazole-**H**), 5.63-5.52 (1H, m, CH_2C**H**), 5.02-5.01 (1H, m, CH**H**CH), 4.98 (1H, m, C**H**HCH), 2.93 (2H, d, *J* 7.8, C**H**$_2$CH), 1.81 (6H, s, 2 x C**H**$_3$); δC ($CDCl_3$, 101 MHz) 160.2, 151.9, 144.0, 133.1, 133.0, 118.7, 107.4, 63.5, 45.6, 27.2; *m/z* HRMS (NH_3 CI+) found: MH^+, 219.1243. $C_{11}H_{15}N_4O$ requires 219.1246, Δ 1.4 ppm.

[1-(1,1-Dimethylbut-3-enyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl]-triethylsilanylamine, 173



Pyrazolo[3,4-*d*]pyrimidine **159** (25 mg, 0.12 mmol) was dissolved in anhydrous THF (1 mL) and cooled to -30 °C. iPrMgCl.LiCl (1.24 M solution in THF, 0.25 mmol, 0.20 mL) was added dropwise over 1 min., and the solution turned from clear to yellow. The reaction was maintained between -35°C and -22°C for 2 h. Et_3SiCl (13 μL, 0.12 mmol) was added at -32 °C, and the reaction was allowed to warm slowly to 25 °C for 40 min. $NaHCO_3$ (sat., aq., 2 mL) was added, and the aqueous phase extracted with Et_2O (3 x 5 mL). The organic phase was washed with brine (10 mL) and dried over $MgSO_4$, to provide the crude product as a white solid (46 mg). Purification by column chromatography eluting with EtOAc/petroleum ether (1:1) provided the pure product as a white solid (25 mg, 53%). Mp 125-126 °C; R*f* 0.15 (UV, 254 nm, EtOAc/petroleum ether, 1:1); ν_{max}/cm^{-1} 3286 (NH), 2954 (CH), 1598, 1559; δH ($CDCl_3$, 400 MHz) 8.34 (1H, s, pyrimidine-**H**), 7.83 (1H, s, pyrazole-**H**), 5.59-5.48 (1H, m, H_2C=C**H**), 5.00-4.93 (2H, $\mathbf{H_2}C$=CH), 4.63 (1H, br s, N**H**), 2.96 (2H, d, *J* 7.3, H_2C=CHC$\mathbf{H_2}$), 1.78 (6H, s, 2 x C$\mathbf{H_3}$), 1.02-0.98 (9H, m, 3 x $SiCH_2C\mathbf{H_3}$), 0.93-0.87 (6H, m, $SiC\mathbf{H_2}CH_3$); δC ($CDCl_3$, 101 MHz) 160.1, 154.3, 153.5, 133.6, 128.5, 118.2, 103.8, 62.5, 45.1, 27.0, 7.0, 4.3; *m/z* HRMS (NH_3 CI+), found: MH^+, 332.2270. $C_{17}H_{30}N_5Si$ requires 332.2270, Δ 0.0 ppm.

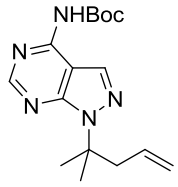
[1-(1,1-Dimethylbut-3-enyl)-1*H*-pyrazolo[3,4,*d*]pyrimidin-4-yl]-dicarbamic acid di-*tert*-butyl ester, 182



According to the procedure of Garner.[145] Pyrazolo[3,4-*d*]pyrimidine **159** (100 mg, 0.46 mmol) and DMAP (5 mg, 9 μmol) were dissolved in anhydrous THF (2.5 mL), and $(Boc)_2O$ (400 mg, 1.84 mmol) added at r.t.. On addition of the $(Boc)_2O$, the reaction mixture turned from clear to yellow. The reaction was stirred at r.t. for 5 h. NH_4Cl (sat. aq., 20 mL) was added, and the aqueous phase extracted with Et_2O (3 x 20 mL). The organics were combined and dried over $MgSO_4$ and the solvent removed *in vacuo* to provide the crude product as a clear oil. Purification by column chromatography eluting with EtOAc/petroleum ether (1:10) provided the pure product as white sticky crystals (142 mg, 74%). Mp 69-72 °C; R*f* 0.30 (UV, 254 nm, EtOAc/petroleum ether, 1:10); ν_{max}/cm^{-1} 2984 (CH), 2937 (CH), 1785, 1746 (C=O); δH ($CDCl_3$, 400 MHz) 8.74 (1H, s, pyrimidine-**H**), 8.00 (1H, s, pyrazole-**H**), 5.57-5.46 (1H, m, **H**C=CH_2), 4.92 (1H, m, HC=CH**H**), 4.88 (1H, m, HC=C**H**H), 2.96 (2H, d, *J* 7.3,

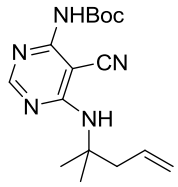
H_2C=CHC**H_2**), 1.82 (6H, s, 2 x C**H_3**), 1.50 (18H, s, 2 x C(C**H_3**)$_3$**);** δC ($CDCl_3$, 101 MHz) 154.4, 153.2, 152.9, 150.3, 133.2, 131.1, 118.5, 108.7, 84.4, 63.2, 45.1, 27.7, 27.1; *m/z* HRMS (ES+), found: MH^+, 418.2447. $C_{21}H_{32}N_5O_4$ requires 418.2454, Δ 1.7 ppm.

[1-(1,1-Dimethylbut-3-enyl)-1*H*-pyrazolo[3,4,*d*]pyrimidin-4-yl]-carbamic acid *tert*-butyl ester, 186



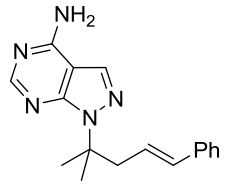
Pyrazolo[3,4-*d*]pyrimidine **159** (25 mg, 0.06 mmol) was dissolved in anhydrous THF (0.2 mL) and $(TMP)_2.2MgCl_2.2LiCl$[147] (0.25 mL, 0.56 M in THF, 0.14 mmol) was added dropwise. The reaction was stirred for 2 h. at r.t. D_2O was added, and the reaction stirred for a further 30 min. NH_4Cl (sat. aq., 5 mL) was added, and the aqueous phase extracted with Et_2O (3 x 5 mL). The organics were dried over $MgSO_4$ and the solvent removed *in vacuo* to provide the crude product as a brown oil. Purification by column chromatography eluting with EtOAc/petroleum ether (1:10, 1:5) provided the pure product as a white oil (3 mg, 16%). R*f* 0.25 (UV, 254 nm, EtOAc/petroleum ether, 1:5); ν_{max}/cm^{-1} 3171 (NH), 2988 (CH), 1755 (C=O), 1602 ; δH ($CDCl_3$, 400 MHz) 8.59 (1H, s, pyrimidine-**H**), 8.53 (1H, s, pyrazole-**H**), 8.47 (1H, br s, N**H**), 5.59-5.48 (1H, m, **H**C=CH_2), 4.96-4.92 (2H, HC=C**H_2**), 2.98 (2H, d, *J* 7.1, H_2C=CHC**H_2**), 1.81 (6H, s, 2 x C**H_3**), 1.57 (9H, s, C(C**H_3**)$_3$); δC ($CDCl_3$, 101 MHz) 154.3, 152.6, 152.4, 151.1, 134.4, 133.5, 118.4, 104.1, 82.5, 62.8, 44.9, 28.1, 27.0; *m/z* HRMS (ES+), found: MH^+, 318.1928. $C_{16}H_{24}N_5O_2$ requires 318.1930, Δ 0.6 ppm.

[5-Cyano-6-(1,1-dimethylbut-3-enylamino)-pyrimidin-4-yl]carbamic acid *tert*-butyl ester, 183



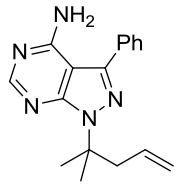
The title compound was synthesised according to the procedure used to synthesise pyrimidine **186**.
White oil (4 mg, 21%). R*f* 0.15 (UV, 254 nm, EtOAc/petroleum ether, 1:5); ν_{max}/cm^{-1} 3154 (NH), 2975 (CH), 2222 (C≡N), 1746 (C=O); δH ($CDCl_3$, 400 MHz) 8.44 (1H, s, pyrimidine-**H**), 7.38 (1H, br s, amide-N**H**), 5.84-5.74 (1H, m, **H**C=CH_2), 5.51 (1H, br s, **amine-NH**) 5.18-5.12 (2H, HC=C**H_2**), 2.59 (2H, d, *J* 6.8, H_2C=CHC**H_2**), 1.54 (9H, s, C(C**H_3**)$_3$) 1.49 (6H, s, 2 x C**H_3**); δC ($CDCl_3$, 101 MHz) 162.5, 159.3, 158.9, 149.8, 133.2, 119.7, 114.1, 83.0, 78.3, 55.5, 45.3, 27.9, 27.0; *m/z* HRMS (ES+), found: MH^+, 318.1940. $C_{16}H_{24}N_5O_2$ requires 318.1930, Δ 3.1 ppm.

1-[(*E*)-1,1-Dimethyl-4-phenylbut-3-enyl]-1*H*-pyrazolo[3,4,*d*]pyrimidin-4-ylamine, 168



A tapered microwave vial was charged with pyrazole **159** (26 mg, 0.12 mmol), KOAc (23 mg, 0.23 mmol), Et_4NCl (38 mg, 0.23 mmol) and $Pd(OAc)_2$ (2 mg, 8 mol%). PhI (38 μL, 0.35 mmol) and anhydrous DMF (0.25 mL) were added, and the tube sealed and the reaction heated to 100 °C for 27 h. After this time, the heat source was removed and the reaction allowed to cool. EtOAc (4 mL) was added, and the organic phase washed with brine (4 x 5 mL). A further portion of EtOAc (5 mL) was added to the organic phase, which was dried over $MgSO_4$. The crude product was isolated as a brown solid (29 mg). Purification by column chromatography eluting with EtOAc/petroleum ether (1:1) provided the product as a white solid (21 mg, 62%). Mp 152-155 °C; R*f* 0.20 (UV, 254 nm, EtOAc/petroleum ether, 1:1); ν_{max}/cm^{-1} 3333 (NH), 1644, 1602, 1564; δH ($CDCl_3$, 400 MHz) 8.35 (1H, s, pyrimidine-**H**), 7.85 (1H, s, pyrazole-**H**), 7.25-7.16 (5H, Ph**H**), 6.32 (1H, d, *J* 16.2, ArC**H**), 5.98 (1H, dt, *J* 16.2 and 7.7, PhCHC**H**), 5.89 (2H, br s, N**H₂**), 3.10 (2H, d, *J* 7.7, CHC**H₂**), 1.84 (6H, s, 2 x C**H₃**); δC ($CDCl_3$, 101 MHz) 157.6, 154.2, 153.5, 137.4, 133.4, 128.8, 128.4, 127.1, 126.1, 125.3, 101.9, 63.2, 44.4, 27.2; *m/z* HRMS (ES+), found: MH^+, 294.1717. $C_{17}H_{20}N_5$ requires 294.1719, Δ 0.7 ppm.

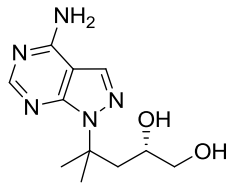
1-(1,1-Dimethylbut-3-enyl)-3-phenyl-1*H*-pyrazolo[3,4,*d*]pyrimidin-4-ylamine, 190



Adapted from the method of McCague.[112] Pyrazole **189** (1.16 g, 4.4 mmol) and formamide (12 mL) were combined and heated to reflux. After 20 h., the heat source was removed, and the brown reaction allowed to cool to room temperature. Brine (25 mL) was added, followed by EtOAc (25 mL), forming a suspension that slowly separated. The aqueous phase extracted with further portions of EtOAc (2 x 25 mL). The organics were dried over $MgSO_4$ and the solvent removed *in vacuuo*. Purification by column chromatography, eluting with EtOAc/petroleum ether (1:3) provided the pure product as white crystals (0.60 g, 47%). Mp 156-159 °C; R*f* 0.15 (UV 254 nm, Petroleum ether/EtOAc, 3:1); ν_{max}/cm^{-1} 3464 (NH), 3073 (CH), 1645, 1598, 1560; δH ($CDCl_3$, 400 MHz) 8.36 (1H, s, pyrimidine-**H**), 7.70-7.67 (2H, Ar**H**), 7.55-7.43 (3H, Ar**H**), 5.69-5.58 (1H, m, H_2C=C**H**), 5.36 (2H, br s, N**H₂**), 5.03-4.96 (2H, **H₂**C=CH), 3.01 (2H, d, *J* 7.3, H_2C=CHC**H₂**), 1.83 (6H, s, 2 x C**H₃**); δC ($CDCl_3$, 101

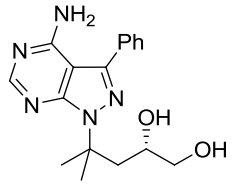
MHz) 158.1, 154.4, 154.2, 142.3, 133.8, 129.3, 128.8, 128.6, 126.3, 118.3, 99.6, 62.8, 45.2, 27.1; *m/z* HRMS (NH_3 CI+), found: MH^+, 294.1709. $C_{17}H_{20}N_5$ requires 294.1719, Δ 3.4 ppm.

4-(4-Aminopyrazolo[3,4,*d*]pyrimidin-1-yl)-4-methylpentane-1,2-diol, 160



Adapted from the method of Sharpless *et al.*[131] AD-mix-α (4.34 g, 1.4 g/mmol) was added to *tert*-BuOH:H_2O (1:1, 31 mL) and cooled to 0 °C. Alkene **159** (0.67 g, 3.1 mmol) was added and the reaction warmed to r.t. and strired vigorously for 24 h, when the reaction was judged to be complete by TLC analysis. Vigorous stirring was necessary to allow for complete consumption of the starting alkene. The reaction was cooled to 0 °C and Na_2SO_3 (4.7 g) was added. The reaction mixture was warmed to r.t. and stirred for 30 min. The aqueous phase was extracted with $CHCl_3$/EtOH (2:1) (3 x 15 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The pure product was isolated as a white solid (0.78 g, quant.). Mp 187-9 °C; R*f* 0.40 (UV 254 nm, $CHCl_3$/EtOH, 2:1); ν_{max}/cm^{-1} 3423 (Het-H), 3192 (CH), 2560, 1662, 1607; δH (d_6-DMSO, 400 MHz) 8.17 (1H, s, pyrimidine-**H**), 8.07 (1H, s, pyrazole-**H**), 7.61 (2H, br s, N**H**$_2$), 4.47 (1H, t, *J* 5.8, CH_2O**H**), 4.30 (1H, d, *J* 5.2 CHO**H**), 3.36-3.28 (1H, m, C**H**OH), 3.16-3.09 (1H, m, CH**H**OH), 3.07-2.99 (1H, m, C**H**HOH), 2.46 (1H, dd, *J* 14.6 and 2.2, C**H**HC$(CH_3)_2$N), 1.95 (1H, dd, *J* 14.6 and 8.3, CH**H**C$(CH_3)_2$N), 1.84 (3H, s, C**H**$_3$), 1.76 (3H, s, C**H**$_3$); δC (d_6-DMSO, 101 MHz) 158.6, 155.1, 153.4, 130.4, 101.9, 68.8, 66.9, 62.2, 44.3, 28.8, 27.5; *m/z* HRMS (NH_3 CI+), found: MH^+, 252.1457. $C_{11}H_{18}N_5O_2$ requires 252.1461, Δ 1.6 ppm.

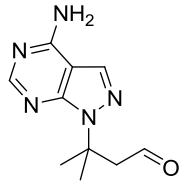
4-(4-Amino-3-phenylpyrazolo[3,4,*d*]pyrimidin-1-yl)-4-methylpentane-1,2-diol, 191



Adapted from the method of Sharpless *et al.*[131] AD-mix-α (4.34 g) was added to *tert*-BuOH:H_2O (1:1, 31 mL) and cooled to 0 °C. Alkene **190** (0.92 g, 3.1 mmol) was added and the reaction warmed to r.t. and strired for 40 h., when the reaction was judged to be complete by TLC analysis. Vigorous stirring was necessary to allow for complete consumption of the starting alkene. The reaction was cooled to 0 °C and Na_2SO_3 (4.8 g) was added. The reaction mixture was warmed to r.t. and stirred for 30 min. The aqueous phase was extracted with EtOAc (3 x 30 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The pure product was isolated as a white solid (0.48 g, 79%). Mp 55-58 °C. R*f* 0.25 (UV 254 nm, EtOAc); ν_{max}/cm^{-1} 3473 (Het-H), 3324 (Het-H), 3171 (CH), 1632; δH (d_6-DMSO, 400 MHz) 8.25

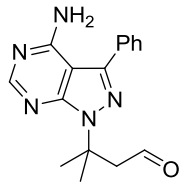
(1H, s, pyrimidine-**H**), 7.69-7.67 (2H, Ar**H**), 7.59-7.54 (2H, Ar**H**), 7.52-7.47 (1H, Ar**H**), 6.70 (2H, br s, N**H**$_2$), 4.45 (1H, t, *J* 5.5, CH_2O**H**), 4.31 (1H, d, *J* 5.5, CHO**H**), 3.39 (1H, m, C**H**OH), 3.20-3.13 (1H, m, CH**H**OH), 3.09-3.04 (1H, m, C**H**HOH), 2.50 (1H, dd, *J* 14.4 and 2.1, CH**H**C$(CH_3)_2$N), 2.01 (1H, m, C**H**HC$(CH_3)_2$N), 1.88 (3H, s, C**H**$_3$) 1.80 (3H, s, C**H**$_3$)**;** δC (d_6-DMSO, 101 MHz) 158.6, 154.9, 142.0, 133.8, 129.5, 128.9, 99.1, 79.6, 68.8, 67.0, 62.7, 44.3, 28.7, 27.5, 19.0; *m/z* HRMS (ES+), found: MH^+, 328.1761. $C_{17}H_{22}N_5O_2$ requires 328.1774, Δ 4.0 ppm.

3-(4-Aminopyrazolo[3,4-*d*]pyrimidin-1-yl)-3-methylbutyraldehyde, 125[112]



Diol **160** (0.78 g, 3.1 mmol) was dissolved in H_2O:MeOH (60 mL, 1:1) and cooled to 0 °C in air. $NaIO_4$ (0.66 g, 3.1 mmol) was added in one portion. The reaction was stirred at 0 °C for 25 min., when complete consumption of starting material was observed by TLC. EtOAc (60 mL) was added, followed by H_2O (30 mL) and brine (30 mL). The organic phase was removed, and the aqueous phase extracted with further portions of EtOAc (2 x 60 mL). NaCl (s) was added to aid the separation of the emulsion that formed in the second extraction. The organics were combined and dried over $MgSO_4$, and the solvent removed *in vacuuo*. Purification by column chromatography, eluting with EtOAc/petroleum ether (2:1 then 1:0) provided the pure product as white crystalline foam (0.56 g, 82%). Mp 60-63 °C; R*f* 0.25 (UV 254 nm, EtOAc); ν_{max}/cm^{-1} 3183, 1721 (C=O), 1602, 1564; δH ($CDCl_3$, 400 MHz) 9.69 (1H, t, *J* 2.3 C**H**O), 8.30 (1H, s, pyrimidine-**H**), 7.85 (1H, s, pyrazole-**H**), 6.08 (2H, br s, N**H**$_2$), 3.25 (2H, d, *J* 2.3), 1.88 (6H, s, 2 x C**H**$_3$); δC ($CDCl_3$, 101 MHz) 200.7, 157.7, 154.8, 153.4, 129.3, 102.1, 60.7, 53.2, 27.6; *m/z* (ES+), 220 ($M+H^+$). All data is in agreement with literature values.[112]

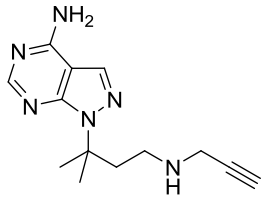
3-(4-Amino-3-phenylpyrazolo[3,4-*d*]pyrimidin-1-yl)-3-methylbutyraldehyde, 192



Diol **191** (411 mg, 1.26 mmol) was dissolved in H_2O:MeOH (34 mL, 1:1) and cooled to 0 °C in air. $NaIO_4$ (269 mg, 1.26 mmol) was added in one portion. The reaction was stirred at 0 °C for 1 h. 30 min., when complete consumption of starting material was observed by TLC. EtOAc (35 mL) was added, followed by H_2O (35 mL). The organic phase was removed, and the aqueous phase extracted with further portions of EtOAc (2 x 35 mL). NaCl (s) was added to aid the separation of the emulsion

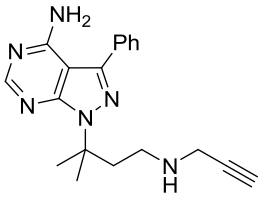
that formed in the second extraction. The organics were combined and dried over $MgSO_4$, and the solvent removed *in vacuuo*. Purification by column chromatography, eluting with EtOAc provided the pure product as white powdery solid (291 mg, 79%). Mp 164-166 °C; R*f* 0.40 (UV 254 nm, EtOAc); ν_{max}/cm^{-1} 3472 (NH), 3111, 1717 (C=O), 1644; δH ($CDCl_3$, 400 MHz) 9.77 (1H, t, *J* 2.3, C**H**O), 8.32 (1H, s, pyrimidine-**H**), 7.68-7.66 (2H, Ar**H**), 7.54-7.44 (3H, Ar**H**), 5.82 (2H, br s, N**H$_2$**), 3.28 (2H, d, *J* 2.3, C**H$_2$**CHO), 1.93 (6H, s, 2 x C**H$_3$**); δC ($CDCl_3$, 101 MHz) 200.7, 158.0, 154.8, 154.4, 142.8, 133.3, 129.3, 129.0, 128.5, 99.8, 60.9, 53.3, 27.7; *m/z* HRMS (ES+), found: MH^+, 296.1505. $C_{16}H_{18}N_5O$ requires 296.1511, Δ 2.0 ppm.

1-(1,1-Dimethyl-3-prop-2-ynylaminopropyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine, 127[112]



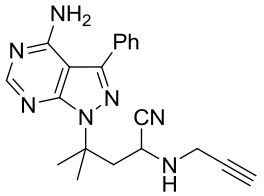
According to the procedure of McCague.[112] Aldehyde **125** (191 mg, 0.87 mmol) was dissolved in MeOH (14 mL) and cooled to 0 °C. Propargylamine (112 μL, 1.74 mmol) and AcOH (150 μL, 2.62 mmol) were added sequentially. The reaction was allowed to warm to r.t. and stirred for 50 min., before cooling to 0 °C. $NaCNBH_3$ (164 mg, 2.62 mmol) was added in one portion, and the rection allowed to warm to r.t. and stirred for 17 h. The reaction was cooled to 0 °C and HCl (0.5M, aq., 40 mL) added. The reaction was warmed to r.t. and neutralised with $NaHCO_3$ (s). The aqueous phase extracted with EtOAc (3 x 50 mL), the organics were dried over $MgSO_4$and the solvent removed *in vacuo* to provide the crude product as a white foam. Purification by column chromatography eluting with EtOAc/MeOH/Et_3N (1:0:0 then 90:5:5) provided the pure product as clear oil (107 mg, 48%). R*f* 0.30 (UV, 254 nm, EtOAc/MeOH/Et_3N, 90:5:5); ν_{max}/cm^{-1} 3482 (NH), 3304 (NH), 1635, 1584; δH ($CDCl_3$, 400 MHz) 8.27 (1H, s, pyrimidine-**H**), 7.84 (1H, s, pyrazole-**H**), 6.23 (2H, br s, N**H$_2$**), 3.28 (2H, d, *J* 2.4, HCCC**H$_2$**), 2.51-2.47 (2H, m, CH_2C**H$_2$**NH), 2.39-2.35 (2H, m, C**H$_2$**CH_2NH), 2.09 (1H, t, *J* 2.4, CC**H**), 1.77 (6H, s, 2 x C**H$_3$**); δC ($CDCl_3$, 101 MHz) 157.8, 154.5, 153.4, 129.1, 101.9, 81.9, 71.3, 62.1, 44.0, 40.5, 38.0, 27.6; *m/z* HRMS (ES+), found: MH^+, 259.1664. $C_{13}H_{19}N_6$ requires 259.1671, Δ 2.7 ppm. All data is in agreement with literature values.[112]

1-(1,1-Dimethyl-3-prop-2-ynylaminopropyl)-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine, 193



Adapted from the procedure of McCague.[112] Aldehyde **192** (203 mg, 0.69 mmol) was dissolved in MeOH (14 mL) and cooled to 0 °C. Propargylamine (88 μL, 1.37 mmol) and AcOH (118 μL, 2.08 mmol) were added sequentially. The reaction was allowed to warm to r.t. and stirred for 50 min., before cooling to 0 °C. $NaCNBH_3$ (131 mg, 2.08 mmol) was added in one portion, and the reaction allowed to warm to r.t. and stirred for 17 h. The reaction was cooled to 0 °C and HCl (0.5M, aq., 40 mL) added. The reaction was warmed to r.t. and neutralised with $NaHCO_3$ (s). The aqueous phase extracted with EtOAc (3 x 50 mL), the organics were dried over $MgSO_4$ and the solvent removed *in vacuo* to provide the crude product as a white solid. Purification by column chromatography eluting with EtOAc/MeOH/Et_3N (1:0:0 then 190:5:5) provided the product as clear oil (163 mg, in 1:1 ratio with tentatively assigned alcohol). R*f* 0.40 (UV, 254 nm, EtOAc/MeOH/Et_3N, 190:5:5); ν_{max}/cm^{-1} 3482 (NH), 3303 (NH), 1635, 1584; δH ($CDCl_3$, 400 MHz) 8.28 (1H, s, pyrimidine-**H**), 7.69-7.64 (2H, Ar**H**), 7.52-7.44 (3H, Ar**H**), 6.00 (2H, br s, N**H$_2$**), 3.32 (2H, d, *J* 2.5, HCCC**H$_2$**), 2.60-2.57 (2H, m, CH_2C**H$_2$**NH), 2.44-2.40 (2H, m, C**H$_2$**CH_2NH), 2.09 (1H, t, *J* 2.5, CC**H**), 1.83 (6H, s, 2 x C**H$_3$**); δC ($CDCl_3$, 101 MHz) 158.1, 154.5, 142.4, 133.7, 129.3, 129.2, 128.8, 128.6, 99.6, 82.1, 71.2, 62.3, 44.1, 40.6, 38.1, 27.7; *m/z* HRMS (ES+), found: MH^+, 335.1981. $C_{19}H_{23}N_6$ requires 335.1984, Δ 0.9 ppm.

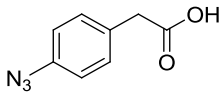
4-(4-Amino-3-phenylpyrazolo[3,4,*d*]pyrimidin-1-yl)-4-methyl-2-prop-2-ynylaminopentanenitrile, 195



The title compound was synthesised according to the procedure used to synthesise alkyne **193**. Purification by column chromatography eluting with EtOAc provided the product as gritty oil (24 mg, 10%). R*f* 0.50 (UV, 254 nm, EtOAc); ν_{max}/cm^{-1} 3486 (NH), 3311 (NH), 2984 (CH), 2365 (C≡N), 1624; δH ($CDCl_3$, 400 MHz) 8.32 (1H, s, pyrimidine-**H**), 7.70-7.68 (2H, Ar**H**), 7.55-7.45 (3H, Ar**H**), 5.69 (2H, br s, N**H$_2$**), 3.80 (1H, br s, NCC**H**), 3.53 (1H, br d, *J* 17.0, HC≡CC**H**H), 3.41 (1H, br d, *J* 17.0, HC≡CCH**H**), 2.89 (1H, dd, *J* 14.7 and 7.6, N≡CCHC**H**H), 2.70 (1H, dd, *J* 14.7 and 5.1, N≡CCHCH**H**), 2.10 (1H, t, *J* 2.6, alkyne-**H**), 1.95 (3H, s, C**H$_3$**), 1.90 (3H, s, C**H$_3$**), 1.50 (1H, br s, N**H**); δC ($CDCl_3$, 101 MHz) 158.0, 154.9, 154.8, 143.1, 133.4, 129.3, 129.0, 128.6, 119.4, 100.0,

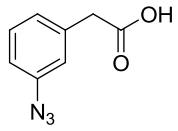
79.7, 72.6, 61.3, 45.4, 44.1, 36.3, 27.8, 27.6; *m/z* HRMS (NH_3 CI+), found: MH^+, 360.1938. $C_{20}H_{22}N_7$ requires 360.1937, Δ 0.3 ppm.

(4-Azidophenyl)-acetic acid, 162a[112]



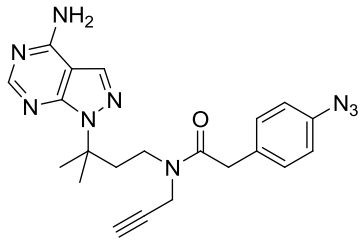
Adapted from the procedure of McCague.[112] 4-aminophenylacetic acid (0.50 g, 3.3 mmol) was added to HCl (5 M, aq., 6.6 mL) and cooled to 0 °C. $NaNO_2$ (0.34 g, 5.0 mmol) was added portionwise, with effervescence noted on each addition. NaN_3 (0.86 g, 13.2 mmol) was added portionwise, with effervescence noted. The brown reaction mixture was stirred in an ice-bath warming slowly to room temperature over 3 h. $NaHCO_3$ (s) was added until pH 3 was reached. The aqueous phase was extracted with EtOAc (3 x 15 mL), and the organic phase dried over $MgSO_4$. The solvent was removed *in vacuo* to provide the required product as a yellow solid (0.49 g, 84%). Mp 89-91 °C; ν_{max}/cm^{-1} 3022 (CH), 2121 (N_3), 1696 (C=O); δH ($CDCl_3$, 400 MHz) 7.28 (2H, d, *J* 8.3, Ar**H**), 7.01 (2H, d, *J* 8.3, Ar**H**), 3.63 (2H, s, ArC**H**$_2$); δC ($CDCl_3$, 101 MHz) 177.3, 139.3, 130.8, 129.9, 119.3, 40.3; *m/z* HRMS (NH_3 CI+), found: MNH_3^+, 195.0885. $C_8H_{11}N_4O_2$ requires 195.0882, Δ 1.5 ppm. All data are in agreement with reported values.[112]

(3-Azidophenyl)-acetic acid, 162b[112]



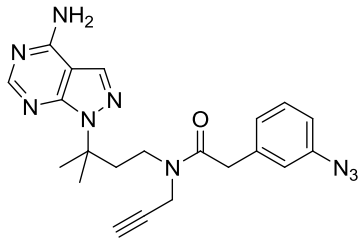
Adapted from the procedure of McCague.[112] 3-aminophenylacetic acid (1.00 g, 6.6 mmol) was added to HCl (5 M, aq., 12 mL) and cooled to 0 °C. $NaNO_2$ (0.68 g, 9.9 mmol) was added portionwise, with effervescence noted on each addition. NaN_3 (1.72 g, 26.4 mmol) was added portionwise, with effervescence noted. The brown reaction mixture was stirred in an ice-bath warming slowly to room temperature over 3 h. $NaHCO_3$ (s) was added until pH 3 was reached. The aqueous phase was extracted with EtOAc (3 x 30 mL), and the organic phase dried over $MgSO_4$. The solvent was removed *in vacuo* to provide the required product as a yellow solid (1.04 g, 89%). Mp 65-67 °C; ν_{max}/cm^{-1} 2894 (br s) (CH), 2117 (N_3), 1695 (C=O); δH ($CDCl_3$, 400 MHz) 11.24 (1H, br s, COO**H**), 7.38 (1H, t, *J* 7.9, Ar**H**), 7.11 (1H, d, *J* 7.9, Ar**H**), 7.01-6.99 (2H, Ar**H**), 3.68 (2H, C**H**$_2$COOH); δC ($CDCl_3$, 101 MHz) 177.7, 140.4, 135.1, 130.0, 126.0, 120.1, 118.1, 40.8; *m/z* HRMS (NH_3 CI+), found: MNH_4^+, 195.0876. $C_8H_{11}N_4O_2$ requires 195.0882, Δ 3.1 ppm. All data are in agreement with literature values.[112]

***N*-[3-(4-Aminopyrazolo[3,4-*d*]pyrimidin-1-yl)-3-methylbutyl]-2-(4-azidophenyl)-*N*-prop-2-ynylacetamide, 129a**[112]



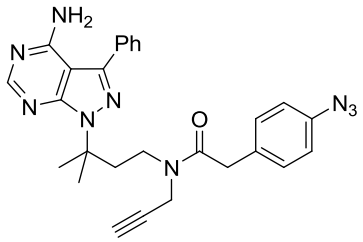
Adapted from the procedure of McCague.[112] Carboxylic acid **162a** (39 mg, 0.22 mmol) was suspended in anhydrous CH_2Cl_2 (2.5 mL). The mixture was cooled to 0 °C and oxalyl chloride (23 μl, 0.26 mmol) was added followed by DMF (1 drop). The reaction was warmed slowly to 23 °C. After 40 mins, complete consumption of starting acid was observed by TLC analysis (MeOH quench of an aliquot). The volatiles were removed *in vacuo* and the resulting acid chloride, a red oil, was re-dissolved in anhydrous CH_2Cl_2 (2.5 mL). In a separate vessel, amine **127** (52 mg, 0.20 mmol) was dissolved in anhydrous CH_2Cl_2 (2.5 mL), and the mixture was cooled to 0 °C. Et_3N (112 μl, 0.81 mmol) was added, followed by the acid chloride solution, dropwise. After the addition, the ice-bath was removed and the reaction stirred at 23 °C for 18 h. $NaHCO_3$ (sat. aq., 10 mL) was added, and the aqueous phase extracted with EtOAc (3 x 10 mL). The organics were combined and dried over $MgSO_4$ and the solvent removed *in vacuo* to provide the crude product as a yellow oil. Purification by column chromatography eluting with EtOAc/petroleum ether (1:1 then 1:0) provided the pure product as a clear foam (42 mg, 50%). Mp 59-62 °C [lit.50-52 °C[112]]; R*f* 0.40 (UV, 254 nm, EtOAc); ν_{max}/cm^{-1} 3315 (NH), 2117 (N_3), 1636 (C=O); δH ($CDCl_3$, 400 MHz, mixture of rotamers) 8.30 (0.61 x 1H, s, pyrimidine-**H**), 8.29 (0.39 x 1H, s, pyrimidine-**H**), 7.96 (0.61 x 1H, s, pyrazole-**H**), 7.94 (0.39 x 2H, s, pyrazole-**H**), 7.19-7.16 (0.39 x 2H, Ar**H**), 7.00-6.98 (0.61 x 2H, Ar**H**), 6.94-6.92 (0.39 x 2H, Ar**H**), 6.88-6.86 (0.61 x 2H, Ar**H**), 6.11 (0.61 x 2H, br s, N$\mathbf{H_2}$), 6.02 (0.39 x 2H, br s, N$\mathbf{H_2}$), 4.17 (0.61 x 2H, d *J* 2.4, HC≡CC$\mathbf{H_2}$), 3.93 (0.39 x 2H, d *J* 2.4, HC≡CC$\mathbf{H_2}$), 3.68 (0.39 x 2H, s, ArC$\mathbf{H_2}$), 3.49 (0.61 x 2H, s, ArC$\mathbf{H_2}$), 3.32-3.28 (0.39 x 2H, m, $CCH_2C\mathbf{H_2}$), 3.24-3.19 (0.61 x 2H, m, $CCH_2C\mathbf{H_2}$), 2.55-2.48 (2H, m, $CC\mathbf{H_2}CH_2$), 2.20 (0.39 x 1H, t, *J* 2.2, alkyne-**H**), 2.12 (0.61 x 1H, t, *J* 2.2, alkyne-**H**), 1.79 (0.61 x 6H, s, 2 x C$\mathbf{H_3}$), 1.77 (0.39 x 6H, s, 2 x C$\mathbf{H_3}$); δC ($CDCl_3$, 101 MHz, mixture of rotamers) 170.5, 170.5, 157.9, 157.8, 154.9, 154.6, 153.6, 153.5, 138.7, 138.6, 131.4, 131.4, 130.5, 130.1, 129.7, 129.5, 119.3, 119.2, 102.0, 101.9, 78.8, 78.4, 72.8, 72.0, 61.9, 61.4, 43.3, 42.7, 40.0, 39.4, 39.0, 37.7, 37.6, 34.6, 27.6, 27.5; *m/z* HRMS (ES+), found: MH^+, 418.2105. $C_{21}H_{24}N_9O$ requires 418.2104, Δ 0.2 ppm. Data is in agreement with literature values.[112]

***N*-[3-(4-Aminopyrazolo[3,4-*d*]pyrimidin-1-yl)-3-methylbutyl]-2-(3-azidophenyl)-*N*-prop-2-ynylacetamide, 129b**[112]



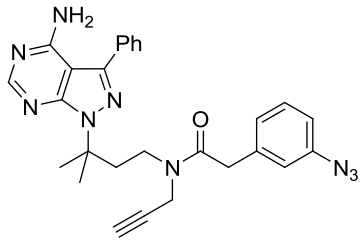
Adapted from the procedure of McCague.[112] Carboxylic acid **162b** (42 mg, 0.24 mmol) was suspended in anhydrous CH_2Cl_2 (2.5 mL) and cooled to 0 °C. Oxalyl chloride (24 μl, 0.28 mmol) was added followed by DMF (1 drop). The reaction was warmed slowly to 23 °C. After 1 h., complete consumption of starting acid was observed by TLC analysis (MeOH quench of an aliquot). The volatiles were removed *in vacuo* and the resulting acid chloride, an orange oily solid, was re-dissolved in anhydrous CH_2Cl_2 (2.5 mL). In a separate vessel, amine **127** (56 mg, 0.22 mmol) was dissolved in anhydrous CH_2Cl_2 (2.5 mL), and the mixture was cooled to 0 °C. Et_3N (120 μl, 0.87 mmol) was added, followed by the acid chloride solution, dropwise. After the addition, the ice-bath was removed and the reaction stirred at 23 °C for 18 h. $NaHCO_3$ (sat. aq., 10 mL) was added, and the aqueous phase extracted with EtOAc (3 x 10 mL). The organics were dried over $MgSO_4$ and the solvent removed *in vacuo* to provide the crude product as a yellow oil. Purification by column chromatography eluting with EtOAc/petroleum ether (1:1 then 1:0) provided the pure product as a cream foam (36 mg, 40%). Mp 27-30 °C [lit. 44-46 °C[112]]; R*f* 0.25 (UV, 254 nm, EtOAc); ν_{max}/cm^{-1} 3315 (NH), 3197 (CH), 2988 (CH), 2121 (N_3), 1636 (C=O); δH ($CDCl_3$, 400 MHz, mixture of rotamers) 8.31 (0.65 x 1H, s, pyrimidine-**H**), 8.30 (0.35 x 1H, s, pyrimidine-**H**), 7.88 (0.65 x 1H, s, pyrazole-**H**), 7.85 (0.35 x 1H, s, pyrazole-**H**), 7.28 (0.35 x 1H, t, *J* 7.2, Ar**H**), 7.22 (0.65 x 1H, t, *J* 7.8, Ar**H**), 6.98 (0.35 x 1H, d, *J* 8.2, Ar**H**), 6.89-6.80 (2H, Ar**H**), 6.70 (0.65 x 1H, s, Ar**H**), 6.00 (0.65 x 2H, br s, N$\mathbf{H_2}$), 5.94 (0.35 x 2H, br s, N$\mathbf{H_2}$), 4.18 (0.65 x 2H, d *J* 2.4, HC≡CC$\mathbf{H_2}$), 3.94 (0.35 x 2H, d *J* 2.4, HC≡CC$\mathbf{H_2}$), 3.69 (0.65 x 2H, s, ArC$\mathbf{H_2}$), 3.51 (0.35 x 2H, s, ArC$\mathbf{H_2}$), 3.33-3.29 (0.35 x 2H, m, $CCH_2C\mathbf{H_2}$), 3.26-3.21 (0.65 x 2H, m, $CCH_2C\mathbf{H_2}$), 2.56-2.50 (2H, m, $CC\mathbf{H_2}CH_2$), 2.21 (0.35 x 1H, t, *J* 2.4, alkyne-**H**), 2.13 (0.65 x 1H, t, *J* 2.4, alkyne-**H**), 1.79 (0.65 x 6H, s, 2 x C$\mathbf{H_3}$), 1.77 (0.35 x 6H, s, 2 x C$\mathbf{H_3}$); δC ($CDCl_3$, 101 MHz, mixture of rotamers) 170.2, 170.1, 157.8, 157.7, 154.9, 154.6, 153.6, 153.5, 140.3, 140.2, 136.7, 136.6, 130.0, 129.9, 129.7, 129.5, 125.7, 125.4, 119.7, 119.4, 117.7, 117.5, 102.0, 101.9, 78.7, 78.4, 72.8, 72.0, 61.9, 61.4, 43.4, 42.7, 40.4, 39.8, 39.1, 37.8, 37.6, 34.6, 27.5, 27.5; *m/z* HRMS (ES+), found: MH^+, 418.2086. $C_{21}H_{24}N_9O$ requires 418.2104, Δ 4.3 ppm. Data is in agreement with literature values.[112]

***N*-[3-(4-Amino-3-phenylpyrazolo[3,4-*d*]pyrimidin-1-yl)-3-methylbutyl]-2-(4-azidophenyl)-*N*-prop-2-ynylacetamide, 2a**



Adapted from the procedure of McCague.[112] Carboxylic acid **162a** (48 mg, 0.27 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL) and cooled to 0 °C. Oxalyl chloride (28 μl, 0.33 mmol) was added followed by DMF (1 drop). The reaction was warmed slowly to 23 °C. After 1 h., complete consumption of starting acid was observed by TLC analysis (MeOH quench of an aliquot). The volatiles were removed *in vacuo* and the resulting acid chloride, an orange oily solid, was re-dissolved in anhydrous CH_2Cl_2 (3 mL). In a separate vessel, amine **193** (83 mg, 0.25 mmol) was dissolved in anhydrous CH_2Cl_2 (3 mL), and the mixture cooled to 0 °C. Et_3N (138 μl, 0.99 mmol) was added, followed by the acid chloride solution, dropwise. After the addition, the ice-bath was removed and the reaction stirred at 23 °C for 18 h. $NaHCO_3$ (sat. aq., 10 mL) was added, and the aqueous phase extracted with EtOAc (3 x 10 mL). The organics were dried over $MgSO_4$ and the solvent removed *in vacuo* to provide the crude product as a yellow oil. Purification by column chromatography eluting with EtOAc/petroleum ether (3:2) provided the pure product as a yellow foam (48 mg, 34% over 2 steps from aldehyde **192**). Mp 29-33 °C; R*f* 0.15 (UV, 254 nm, EtOAc/petroleum ether, 3:2); ν_{max}/cm^{-1} 3477 (NH), 3249 (NH), 2929 (CH), 2116 (N_3), 1624 (C=O); δH ($CDCl_3$, 400 MHz, mixture of rotamers) 8.34 (0.68 x 1H, s, pyrimidine-**H**), 8.31 (0.32 x 1H, s, pyrimidine-**H**), 7.70-7.62 and 7.54-7.44 (5H, Ar**H**), 7.21-7.19 and 6.97-6.92 and 6.84-6.82 (4H, Ar**H**), 5.78 (2H, br s, N**H$_2$**), 4.21 (0.68 x 2H, d *J* 2.4, HC≡CC**H$_2$**), 3.98 (0.32 x 2H, d *J* 2.4, HC≡CC**H$_2$**), 3.70 (0.32 x 2H, s, ArC**H$_2$**), 3.50 (0.68 x 2H, s, ArC**H$_2$**), 3.45-3.41 (0.32 x 2H, m, CCH_2C**H$_2$**), 3.34-3.30 (0.68 x 2H, m, CCH_2C**H$_2$**), 2.58-2.52 (2H, m, CC**H$_2$**CH_2), 2.20 (0.32 x 1H, t, *J* 2.4, C≡C**H**), 2.13 (0.68 x 1H, t, *J* 2.4, C≡C**H**), 1.84 (0.68 x 6H, s, 2 x C**H$_3$**), 1.82 (0.32 x 6H, s, 2 x C**H$_3$**); δC ($CDCl_3$, 101 MHz, mixture of rotamers) 170.4, 170.3, 158.0, 158.0, 154.9, 154.9, 154.6, 154.5, 142.9, 142.7, 138.7, 138.4, 133.6, 133.3, 131.5, 131.5, 130.4, 130.0, 129.4, 129.3, 129.1, 128.9, 128.5, 128.5, 119.3, 119.1, 99.6, 99.6, 78.9, 78.6, 72.6, 71.9, 62.1, 61.6, 43.3, 42.7, 40.0, 39.5, 39.3, 37.7, 37.6, 34.5, 27.6, 27.5; *m/z* HRMS (ES+), found: MH^+, 494.2404. $C_{27}H_{28}N_9O$ requires 494.2417, Δ 2.6 ppm.

***N*-[3-(4-Amino-3-phenylpyrazolo[3,4-*d*]pyrimidin-1-yl)-3-methylbutyl]-2-(3-azidophenyl)-*N*-prop-2-ynylacetamide, 2b**



Adapted from the procedure of McCague.[112] Carboxylic acid **162b** (94 mg, 0.53 mmol) was dissolved in anhydrous CH_2Cl_2 (6 mL) and cooled to 0 °C. Oxalyl chloride (55 μl, 0.64 mmol) added followed by DMF (1 drop). The reaction was warmed slowly to 23 °C. After 1 h., complete consumption of starting acid was observed by TLC analysis (MeOH quench of an aliquot). The volatiles were removed *in vacuo* and the resulting acid chloride, an orange oily solid, was re-dissolved in anhydrous CH_2Cl_2 (6 mL). In a separate vessel, amine **193** (163 mg, 0.49 mmol) was dissolved in anhydrous CH_2Cl_2 (6 mL), and the mixture was cooled to 0 °C. Et_3N (271 μl, 1.96 mmol) was added, followed by the acid chloride solution, dropwise. After the addition, the ice-bath was removed and the reaction stirred at 23 °C for 18 h. $NaHCO_3$ (sat. aq., 20 mL) was added, and the aqueous phase extracted with EtOAc (3 x 20 mL). The organics were dried over $MgSO_4$ and the solvent removed *in vacuo* to provide the crude product as a yellow oil. Purification by column chromatography eluting with EtOAc/petroleum ether (3:2) provided the pure product as a yellow foam (90 mg, 30% over 2 steps from aldehyde **192**). Mp 38-42 °C; R*f* 0.15 (UV, 254 nm, EtOAc/petroleum ether, 3:2); ν_{max}/cm^{-1} 3477 (NH), 3294 (NH), 2971 (CH), 2108 (N_3), 1624 (C=O); δH ($CDCl_3$, 400 MHz) mixture of rotamers 8.33 (0.61 x 1H, s, pyrimidine-**H**), 8.31 (0.39 x 1H, s, pyrimidine-**H**), 7.70 (0.39 x 2H, d, *J* 7.4, Ar**H**), 7.64 (0.61 x 2H, d, *J* 7.5, Ar**H**), 7.53-7.43 (3H, m, Ar**H**), (7.29-7.25, (Ar**H**), 7.18 (t, *J* 7.9, Ar**H**), 7.00 (d, *J* 8.4, Ar**H**), 6.91-6.89 (Ar**H**), 6.84 (d, *J* 8.2, Ar**H**), 6.74 (d, *J* 7.5, Ar**H**), 6.66 (s, Ar**H**) all peaks totalling 4**H**), 5.89 (2H, br s, N**H₂**), 4.21 (0.61 x 2H, d, *J* 2.3, HC≡CC**H₂**), 3.98 (0.39 x 2H, d, *J* 2.3, HC≡CC**H₂**), 3.71 (0.39 x 2H, s, ArC**H₂**), 3.53 (0.61 x 2H, s, ArC**H₂**), 3.46-3.42 (0.39 x 2H, m, CCH_2C**H₂**), 3.37-3.32 (0.61 x 2H, m, CCH_2C**H₂**), 2.58-2.54 (2H, m, CC**H₂**CH_2), 2.21 (0.39 x 1H, t, *J* 2.5, C≡C**H**), 2.14 (0.61 x 1H, t, *J* 2.5, C≡C**H**), 1.84 (0.61 x 6H, s, 2 x C**H₃**), 1.82 (0.39 x 6H, s, 2 x C**H₃**); δC ($CDCl_3$, 101 MHz) 170.0, 170.0, 158.1, 158.1, 154.9, 154.6, 154.6, 154.5, 143.0, 142.7, 140.3, 140.1, 136.8, 136.7, 133.6, 133.3, 130.0, 130.0, 129.3, 129.3, 129.1, 128.9, 128.6, 128.5, 125.7, 125.3, 119.6, 119.3, 117.6, 117.4, 99.6, 99.6, 78.9, 78.6, 72.7, 71.9, 62.1, 61.6, 43.4, 42.7, 40.4, 39.9, 39.3, 37.7, 37.7, 34.6, 27.6, 27.5; *m/z* HRMS (ES+), found: MH^+, 494.2409. $C_{27}H_{28}N_9O$ requires 494.2417, Δ 1.6 ppm.

4. Appendix

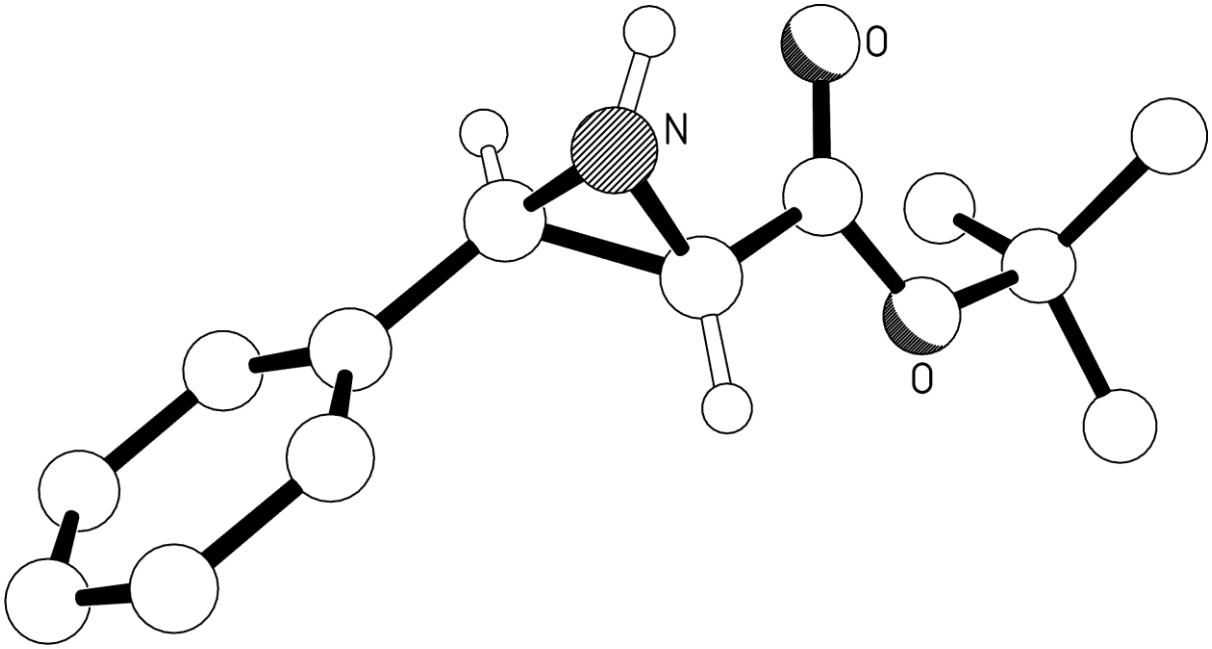


Fig. A1 The crystal structure of **1a**.

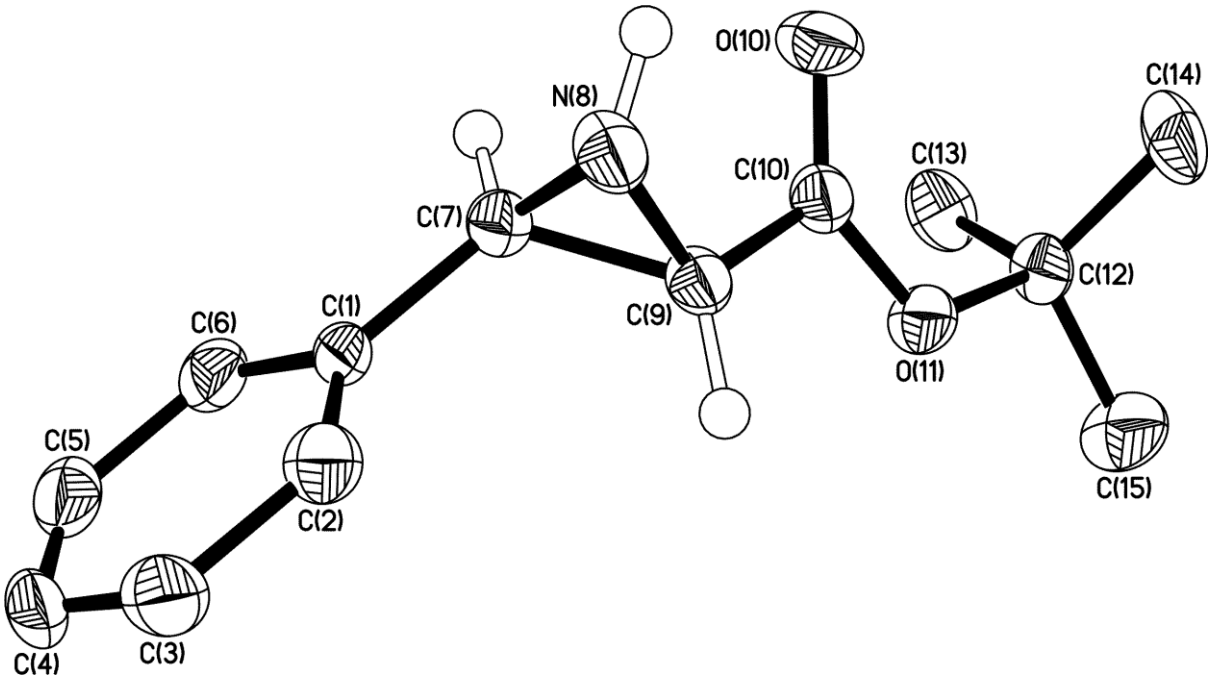


Fig. A2 The crystal structure of **1a** (50% probability ellipsoids).

Table 1. Crystal data and structure refinement for **1a**

Identification code	AA1001
Formula	C13 H17 N O2
Formula weight	219.28
Temperature	173 K

Diffractometer, wavelength	OD Xcalibur 3, 0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/n
Unit cell dimensions	a = 5.7745(3) Å α = 90°
	b = 20.4714(8) Å β = 98.175(4)°
	c = 10.5178(4) Å γ = 90°
Volume, Z	1230.70(9) $Å^3$, 4
Density (calculated)	1.183 Mg/m^3
Absorption coefficient	0.080 mm^{-1}
F(000)	472
Crystal colour / morphology	Colourless thin plates
Crystal size	0.30 x 0.11 x 0.01 mm^3
θ range for data collection	3.57 to 28.09°
Index ranges	-7<=h<=4, -18<=k<=26, -10<=l<=13
Reflns collected / unique	4462 / 2454 [R(int) = 0.0295]
Reflns observed [F>4σ(F)]	1619
Absorption correction	Analytical
Max. and min. transmission	0.999 and 0.989
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2454 / 56 / 167
Goodness-of-fit on F^2	0.993
Final R indices [F>4σ(F)]	R1 = 0.0487, wR2 = 0.0961
R indices (all data)	R1 = 0.0876, wR2 = 0.1092
Extinction coefficient	0.0074(18)
Largest diff. peak, hole	0.198, -0.165 $eÅ^{-3}$
Mean and maximum shift/error	0.000 and 0.000

Table 2. Bond lengths [Å] and angles [°] for AA1001.

C(1)-C(2)	1.386(2)
C(1)-C(6)	1.388(2)
C(1)-C(7)	1.486(2)
C(2)-C(3)	1.377(2)
C(3)-C(4)	1.381(3)
C(4)-C(5)	1.374(3)
C(5)-C(6)	1.389(3)
C(7)-N(8)	1.462(2)
C(7)-C(9)	1.503(2)
N(8)-C(9)	1.464(2)
C(9)-C(10)	1.487(2)
C(10)-O(10)	1.210(2)
C(10)-O(11)	1.334(2)
O(11)-C(12')	1.480(16)
O(11)-C(12)	1.491(3)
C(12)-C(15)	1.510(4)
C(12)-C(13)	1.514(4)
C(12)-C(14)	1.514(4)
C(12')-C(14')	1.507(14)
C(12')-C(13')	1.509(13)
C(12')-C(15')	1.510(14)

C(2)-C(1)-C(6)	118.45(16)
C(2)-C(1)-C(7)	121.38(14)
C(6)-C(1)-C(7)	120.17(17)
C(3)-C(2)-C(1)	120.91(17)
C(2)-C(3)-C(4)	120.3(2)
C(5)-C(4)-C(3)	119.68(18)
C(4)-C(5)-C(6)	120.07(18)
C(1)-C(6)-C(5)	120.61(19)
N(8)-C(7)-C(1)	116.94(15)
N(8)-C(7)-C(9)	59.14(9)
C(1)-C(7)-C(9)	121.23(15)
C(7)-N(8)-C(9)	61.80(10)
N(8)-C(9)-C(10)	117.26(15)
N(8)-C(9)-C(7)	59.06(10)
C(10)-C(9)-C(7)	115.47(15)

O(10)-C(10)-O(11)	125.31(17)
O(10)-C(10)-C(9)	123.40(16)
O(11)-C(10)-C(9)	111.27(16)
C(10)-O(11)-C(12')	122.4(8)
C(10)-O(11)-C(12)	120.7(2)
O(11)-C(12)-C(15)	101.9(3)
O(11)-C(12)-C(13)	109.2(4)
C(15)-C(12)-C(13)	110.6(3)
O(11)-C(12)-C(14)	111.6(3)
C(15)-C(12)-C(14)	110.9(3)
C(13)-C(12)-C(14)	112.1(3)
O(11)-C(12')-C(14')	101.6(18)
O(11)-C(12')-C(13')	113(2)
C(14')-C(12')-C(13')	112.0(12)
O(11)-C(12')-C(15')	105.3(16)
C(14')-C(12')-C(15')	112.0(12)
C(13')-C(12')-C(15')	112.4(12)

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