DEVELOPING NOVEL MULTI-COMPONENT COUPLING REACTIONS OF ARYNES

A Thesis Submitted by

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in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

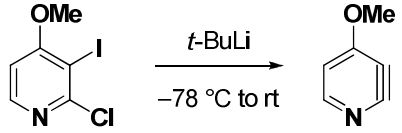
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Abstract

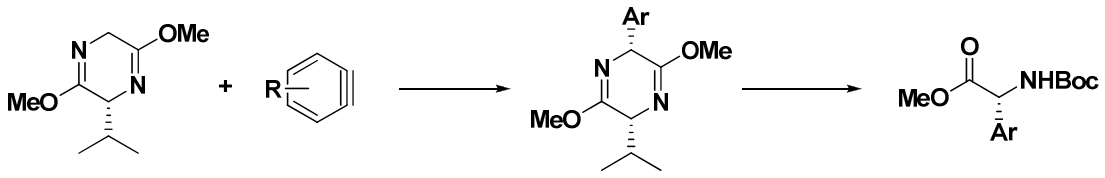
The development of novel three-component coupling reactions of arynes is under investigation. The emphasis is on efficient, concise and elegant routes to small, highly functionalised aromatic molecules.

In order to extend the three-component coupling methodology to the previously underexploited 2,3-pyridyne intermediate **2**, several strategies will be described, including the development and reactivity of novel halogen-metal exchange aryne precursor **1**.



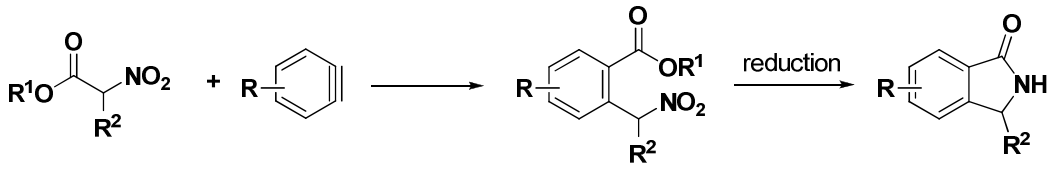
1 **2**

Approaches towards the use of arynes **4** as electrophilic α-arylating reagents for amino acids are also described. In order to circumvent undesired side-reactions it was found necessary to use lithiated Schöllkopf's bis-lactim ether **3** as the nucleophilic glycine equivalent. This route will be introduced and its development described, concluding in the presentation of a range of chiral, arylglycine derivatives, **6**, using this methodology. The extension of this technique to the synthesis of quaternary Schöllkopf adducts and the resulting hydrolysis reactions are also illustrated.



3 **4** **5** **6**

In addition, the discovery of an interesting side reaction, involving the use of nitroacetates **7** and arynes **4** for the synthesis of *iso*-indolinones **9** will be discussed.



7 **4** **8** **9**

Acknowledgements

Firstly, I would like to thank Tony Barrett for providing me with a challenging project and the opportunity to work within his excellent group. Additionally I would like to acknowledge my industrial supervisor, Peter Jones, for providing ongoing advice and for organising my placement in Sandwich which was genuinely rewarding. None of this would have been possible without the excellent support and administrative assistance of the various Barrett group PAs over the years: Mickie, Sam, Grae and Katie, who were always ready with a cup of tea in the morning and a glass of wine in the evening.

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“If I have a thousand ideas and only one turns out to be good, I am satisfied”
Alfred Nobel

Abbreviations

Å	Ångstrom
Ac	acetate
acac	acetylacetonate
Ad	adamantyl
Ar	aryl
BHT	2,6-di-*tert*-butyl-4-methylphenol
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	*tert*-butyloxycarbonyl
Bn	benzyl
br.	broad
Bt	benzotriazole
Bu	butyl
BuLi	butyllithium
Bz	benzoyl
^{o}C	degrees centigrade
cat.	catalytic
CI	chemical ionisation
cm	centimetre
coe	cyclooctene
CPME	cyclopentyl methylether
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
dd	doublet of doublets
decomp.	decomposition
DEPT	distortionless enhancement by polarisation transfer
dm	decimetre
DMAP	dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone
DMSO	dimethyl sulfoxide
dppbenz	1,2-bis(diphenylphosphinyl)benzene

dr	diastereomeric ratio
dt	doublet of triplets
E	electrophile
EDG	electron-donating group
ee	enantiomeric excess
EI	electron ionisation
Equiv./eq.	equivalent(s)
endo	*endocyclic*
er	enantiomeric ratio
ESI	electron spray ionisation
Et	ethyl
EWG	electron-withdrawing group
exo	*exocyclic*
g	gram(s)
GC-MS	gas chromatography-mass spectrometry
h	hour
HMBC	Heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
i	*iso*
i.e.	id est
IR	infrared spectroscopy
J	coupling constant
kcal	kilocalorie
l	liquid
L	ligand
LC-MS	liquid chromatography-mass spectrometry
LDA	lithium di-*iso*-propylamide
lit	literature
LUMO	lowest unoccupied molecular orbital
M	molar concentration (mol dm^{-3})
m	multiplet
m	*meta*
Me	methyl
Met	metal

mg	milligram(s)
min	minute(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
MOM	methoxymethyl
M.p.	melting point
Ms	mesyl
MS	mass spectrometry
m/z	mass/charge
n	normal
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
nm	nanometre
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nuc	nucleophile
o	*ortho*
ODG	*ortho*-directing group
P	protecting group
p	*para*
Ph	phenyl
PMP	*para*-methoxyphenyl
ppm	parts per million
Pr	propyl
PTSA	*para*-toluenesulfonic acid
q	quartet
R	general substituent
R_f	retention factor
rt	room temperature
s	singlet
s or *sec*	secondary
sat.	saturated
SM	starting material(s)
T	temperature
t	triplet
t or *tert*	tertiary

TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDPS	*tert*-butyl diphenylsilyl
TBS	*tert*-butyl dimethylsilyl
TEMP	2,2,6,6-tetramethylpiperidinyloxy
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6,tetramethylpiperidine
TMS	trimethylsilyl
Tol	toluene
trig	trigonal
Ts	tosyl
$TS^{\neq}$	transition state
UV	ultraviolet
v or V	volume
X	halogen
μm	micrometre(s)

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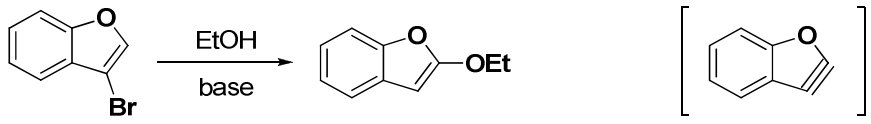
Chapter 1: Introduction to Arynes

1.1 Reactive Intermediates

Species that are created *in situ*, too unstable to be isolated, and that subsequently undergo interesting reactions of their own describe an important and widely used group of compounds known as reactive intermediates. Initially, these structures were tentatively suggested to account for certain, unexpected reaction outcomes and later further evidence established their existence and mechanism of formation. Although many reactive intermediates are charged species, there is also a series of neutral intermediates which have been increasingly employed over the past 100 years. This group comprises radicals, carbenes, nitrenes and arynes.[1] These reactive intermediates are able to undergo unique transformations and are used as tools to easily afford compounds which would be difficult or impossible to synthesise by conventional means.

1.2 Arynes: Structure and History

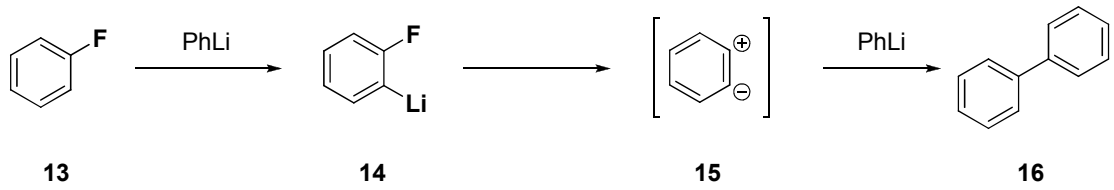
In 1902, Stoermer and Kahlert observed an unexpected outcome in a reaction between 3-bromofuran **10**, ethanol and base (Scheme 1).[2] The product of the reaction, 2-ethoxybenzofuran **(11)** could not be rationalised by known mechanistic chemistry at the time.



10 **11** **12**

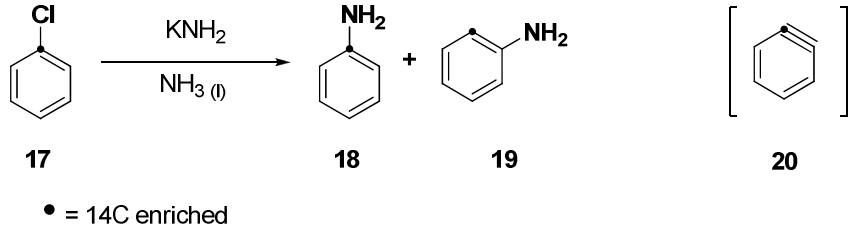
Scheme 1: Stoermer and Kahlert's first postulated aryne intermediate **12**

They explained this observation by the formation of a previously unknown, neutral, reactive intermediate, didehydrobenzofuran **(12)**, the first postulated aryne, formed by *ortho*-elimination of hydrogen bromide from **10**. Over the next 50 years, these aryne intermediates were suggested as explanations for unexpected product mixtures observed in reactions involving halobenzenes.[3,4,5] A particularly interesting example was Wittig's interpretation of the formation of biphenyl **(16)** when fluorobenzene **(13)** was allowed to react with phenyllithium (Scheme 2).[6] His rationalisation involved the proposal of a zwitterionic form of benzyne **15** formed upon loss of lithium fluoride from intermediate **14**.



Scheme 2: Wittig's proposal for the formation of diphenyl **16** from fluorobenzene **(13)** and phenyllithium

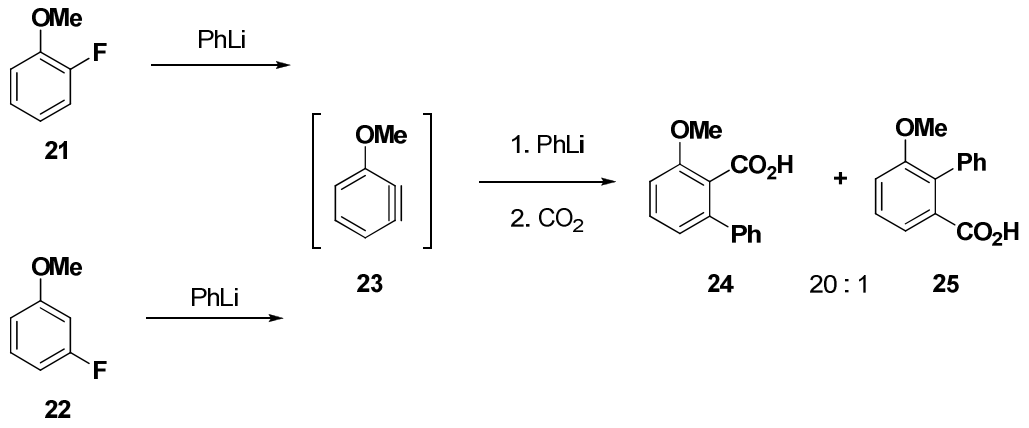
However, it was not until 1953 that the first conclusive evidence of an aryne intermediate was published. Roberts and co-workers monitored the outcome of the reaction between ^{14}C-enriched chlorobenzene **(17)** and potassium amide in liquid ammonia (Scheme 3).[7] An almost 1 : 1 ratio of aniline isomers **18** and **19** were formed with the ^{14}C in the *ipso* and *ortho* positions.



Scheme 3: Roberts' classic ^{14}C labelling experiment; evidence of benzyne **(20)**

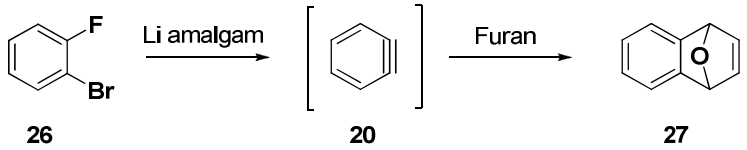
Roberts' explanation was a symmetrical, neutral, electrophilic intermediate which he postulated as benzyne **(20)**. The fact that *ortho*-substituted halobenzenes did not undergo similar reactions provided further evidence for benzyne formation.

At a similar time Huisgen[8] demonstrated that *ortho*- and *meta*- fluoroanisoles **(21)** and **(22)** both afforded identical mixtures of carboxylic acids **24** and **25** when treated with phenyllithium followed by carboxylation. This provided evidence to suggest 3-methoxybenzyne **(23)** as the common intermediate (Scheme 4).



Scheme 4: Huisgen's mechanistic evidence for 3-methoxybenzyne **23**

Wittig,[9] Huisgen[10] and Gilman[11] also provided further support of the theory by trapping benzyne **(20)** *in situ* with various dienes in cycloaddition reactions (Scheme 5).



Scheme 5: Wittig's Diels-Alder reaction

Although both *meta*- and *para*-arynes are known, this thesis will only involve the use of *ortho*-arynes and these intermediates will be referred to simply as arynes throughout.

Today, arynes are defined as uncharged reactive intermediates created by the formal removal of two vicinal hydrogen atoms from an aromatic molecule.[12-14] There are several different representations of benzyne which are commonly used: the most traditional alkyne-like structure **20**, the cumulene **28** or the bi-radical **29** (Figure 1).

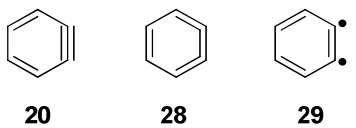


Figure 1: Different representations of *ortho*-benzyne

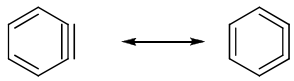
The first physical evidence of benzyne was attributed to the almost concurrent work of Fisher[15] and Berry[16,17] between 1962 and 1964. The former detected benzyne by mass

spectrometry upon pyrolysis of three isomeric diiodobenzenes and measurement of their ionisation potentials; the latter was able to characterise benzyne using both UV spectroscopy and mass spectrometry on investigating the photoinduced decomposition of benzenediazonium carboxylates in the gas phase.

The IR spectrum of benzyne was first obtained by Chapman[18,19] in 1973 by entrapment in a nitrogen matrix at low temperature. He determined the C≡C bond stretching vibration to be 2085 cm^{-1}. However his assignment was challenged in 1986 by Radziszewski when analysis of the photodetachment spectra[20] followed by further experimentation led to the assignment of the C≡C stretching frequency to be 1846 cm^{-1} in a neon matrix.[21] This supports the notion that the aryne bond is not a true triple-bond as this frequency is lower than that of the usual C≡C bond in traditional alkynes (*ca*. 2150 cm^{-1}) due to poor orbital overlap. The average bond order for species **20** and **28** can be considered as being 2.5, rather than 3.

Although a bi-radical structure has also been proposed, this theory is less supported than the strained alkyne one due to the large singlet-triplet splitting of 37.5 $kcal.mol^{-1}$ and the alkyne-like behaviour of arynes, in particular their ability to undergo Diels-Alder reactions.[22] Current calculations[23] indicate that the triple-bond length in benzyne is 1.259 Å (compared to 1.20 Å in acetylenes) and the enthalpy of formation of *ortho*-benzyne **(20)** was determined by Wenthold[24] to be 106.6 ± 3.0 $kcal.mol^{-1}$. A fascinating piece of work by Warmuth[25-27] facilitated the encapsulation of benzyne in a hemicarcerand (a type of molecular container), allowing the measurement of its NMR spectra in solution. Although this data indicated that benzyne consisted of a more cumulene type structure **28**, more recent *ab initio* calculations[28] have indicated a certain degree of localisation associated with the in plane π-bond, implying more acetylinic character.

Although, there is by no means a perfect description of the structure of benzyne, the acetylinic model **20** with a small contribution from resonance cumulene structure **28** (Figure 2) is currently the most accurate.



20 **28**

Figure 2: Most accurate description of benzyne, existing as a hybrid between resonance structures **20** and **28**

The structure (Figure 3, a) can be understood in terms of a new, strained π-bond, formed by the overlap of two sp^2 orbitals orthogonal to the aromatic π-system (Figure 3, c), which itself

remains unchanged (Figure 3, b). The weakness of the bond due to poor orbital overlap produces a highly unstable, electrophilic intermediate which has to be created *in situ*.

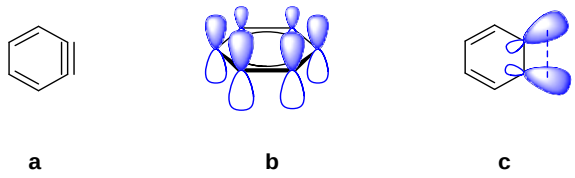
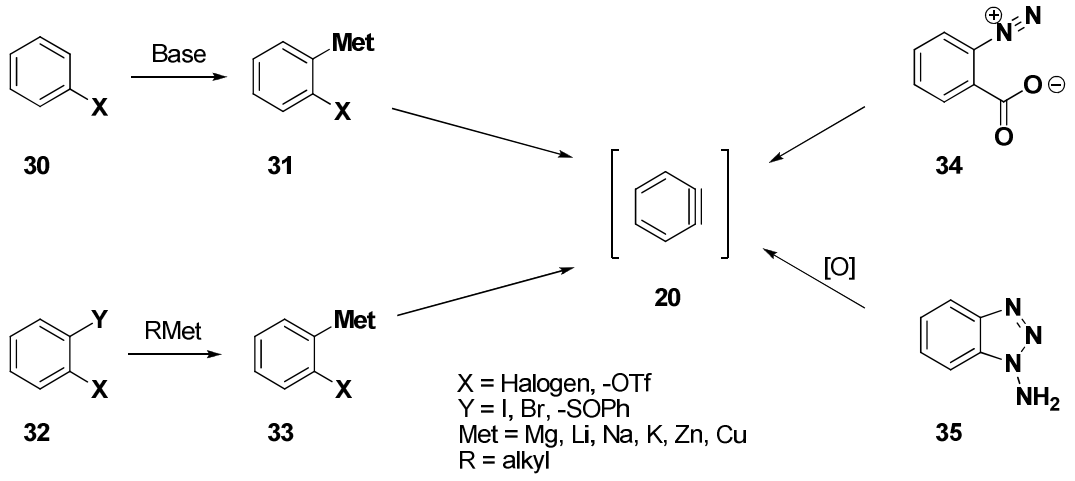


Figure 3: (a) *ortho*-Benzyne; (b) Overlap of p-orbitals to form aromatic π-system; (c) Overlap of sp^2 orbitals to form strained π-bond

1.3 Generation of Arynes

There are several different methods of aryne formation that have been developed since their initial discovery. The choice of technique depends on ease of synthesis of the precursor molecule, the type of reaction to be carried out with the resulting aryne and the properties of the other functional groups/reagents present.

Some of the classical methods are highlighted in Scheme 6. There are many examples in the literature of other procedures for benzyne formation, such as the recent work by Greaney[29] in palladium-catalysed *ortho* C-H activation of benzoic acids; however, in view of relevance to the projects within this thesis only the main types of procedure are discussed here.



Scheme 6: Established methods of aryne formation

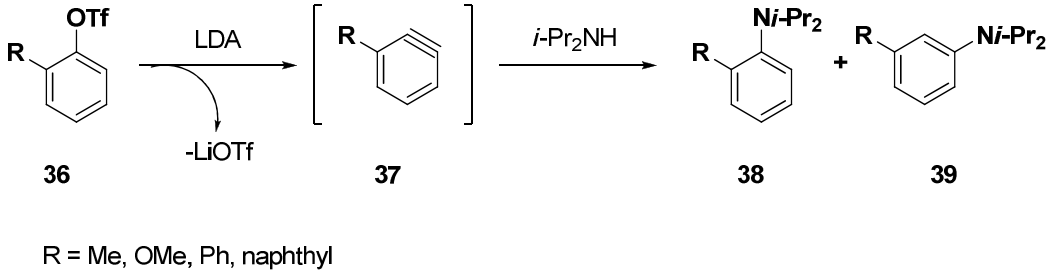
Several methods involve the elimination of good leaving groups, either after deprotonation of the *ortho* proton in species such as **30** to give **31** or after metal-halogen exchange in the *ortho*

position as in **32** to give **33**. Other established modes of formation include the thermal decomposition of benzenediazonium-2-carboxylate[30] **(34)** and the oxidative fragmentation of 1-aminobenzotriazole **(35)**.[31] The use of **34** as a benzyne precursor previously required careful handling techniques due to the potential explosive risk of the dry salt. Modern methods of carrying out aprotic diazotisation of anthranilic acid *in situ* have circumvented these issues.[32]

The most common methods used in this thesis will be described in more detail in the following sections.

1.3.1 *ortho*-Metalation

Electronegative atoms such as halogens (X = F, Cl, Br) or pseudohalogens (i.e. triflates) increase the acidity of the *ortho* proton such that strong bases will regioselectively deprotonate in this position at low temperatures.[3,4,12-14,33] At this point elimination of the metal halide/triflate salt occurs, either spontaneously at the same temperature or upon warming, to form the corresponding aryne. An example of this type of aryne generation was observed by Wittig when fluorobenzene **(13)** was treated with phenyllithium (Scheme 2).[6] Another example published by Wickham and Scott[34] involved the treatment of substituted aryl triflates **36** with lithium di-*iso*-propylamide. The benzynes formed following elimination of lithium triflate were trapped by di-*iso*-propylamine, generating di-*iso*-propylanilines **38** and **39**; the *cine*-substitution product **39** is again consistent with a benzyne intermediate **37** (Scheme 7).



Scheme 7: Wickham's formation of di-*iso*-propylaniline isomers **38** and **39**

This method is limited by lack of selectivity in deprotonation *ortho* to the leaving group resulting in regioisomeric benzynes as deprotonation can happen on either side of the leaving group. To control the regioselectivity of lithiation, it is common practice to use an *ortho*-directing group *meta* to the leaving group, which itself can not eliminate. As well as controlling *ortho*-lithiation by chelation, these functional groups further increase the acidity

of the *ortho*-proton. Examples of such precursors **40**,[35] **41**,[36] **43**[37] and **45**[38] are shown in Figure 4.

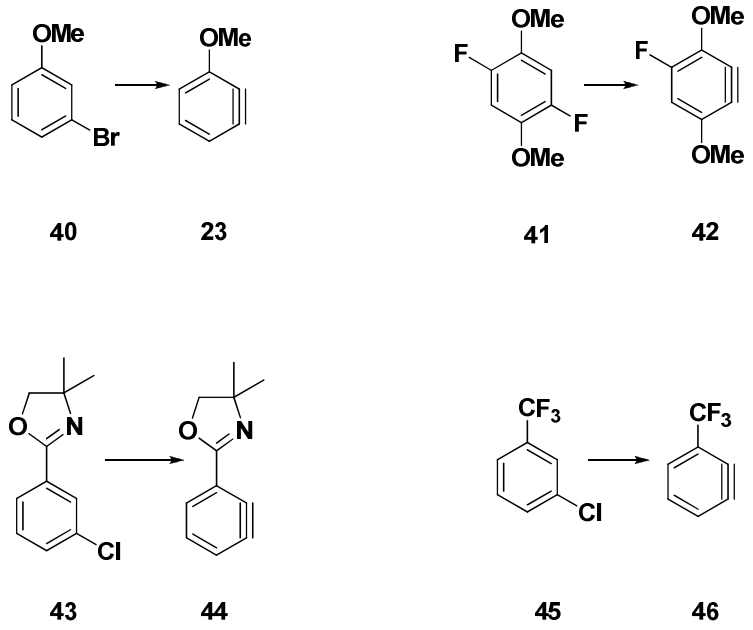
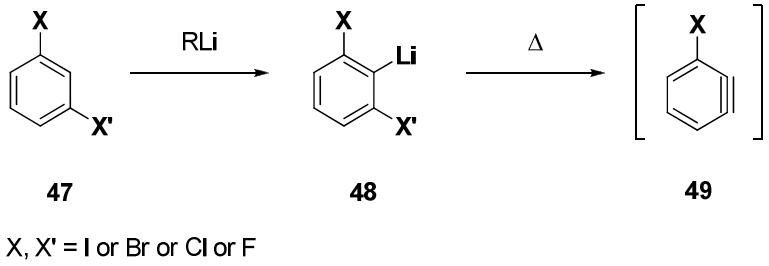


Figure 4: Various directed *ortho*-lithiation benzyne precursors

Aryne precursors containing *meta* halogens, **47**, prove particularly interesting. Metalation occurs exclusively between the two halogens affording **48**, followed by elimination of one of the halogens to aryne **49** (Scheme 8).[39,40]

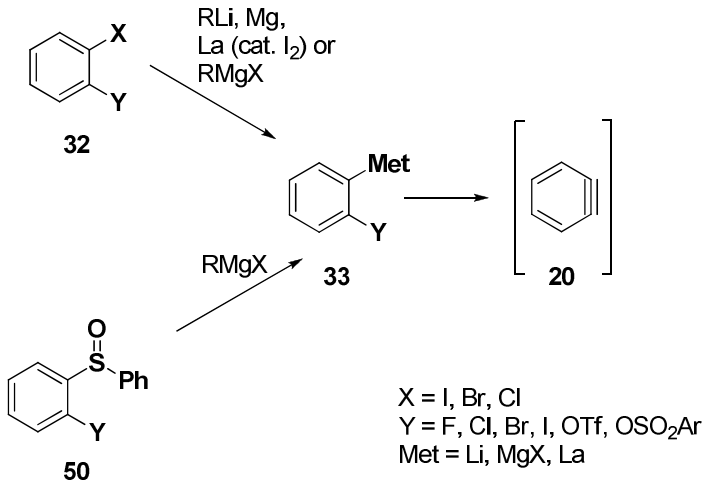


Scheme 8: Benzyne formation from *meta*-dihalogenated arenes

Originally it was postulated that in all cases the better leaving group eliminates, i.e. I > Br > Cl > F and this was indeed observed experimentally.[41] However, more recent research by Collum has demonstrated that in some cases the ability of halides to act as leaving groups depends on reaction conditions and solvation.[42,43]

1.3.2 Metal-Halogen Exchange

An alternative method for controlling the regioselectivity of metalation is to position a halogen or a sulfoxide *ortho* to the leaving group which is able to undergo exchange or insertion with a metal (Scheme 9) to create a formal carbanion which is able to eliminate to afford benzyne **(20)**. As before, commonly used leaving groups are halides or triflates. Treatment of dihaloarenes (X and Y = halogens) or halo-sulfonates (Y = OTf or OSO_2Ar), **32** with *n*-butyllithium,[39,44-46] magnesium metal[47,48] or Grignard reagents[49] are common techniques to bring about lithium-halogen exchange or magnesium insertion. Lanthanum metal in the presence of catalytic iodine can bring about a similar transformation.[50,51] Additionally Grignard reagents can also be employed to generate aryl Grignards **33** (Met = MgX) from aryl sulfoxides **50**.[52]

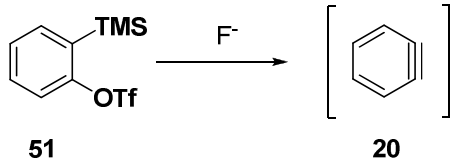


Scheme 9: Different methods of metal-halogen exchange

Pioneering work by Knochel[53-55] has shown that *ortho*-magnesiated diaryl sulfonates, prepared by metal-halogen exchange with *iso*-propyl magnesium chloride of the corresponding aryl-iodides are able to undergo elimination to arynes (i.e. when X = I and Y = OSO_2Ar). Tuning the electronic properties of the sulfonyl aryl group has been shown to affect the rate of elimination and hence the temperature at which efficient benzyne formation occurs. This method is particularly attractive due to its relatively mild, non-nucleophilic conditions and tolerance to a wide range of functional groups.

1.3.3 Fluoro-Desilylation Precursors

Although the above methods are often reliable, they can require the use of harsh and basic/nucleophilic conditions which are not compatible with other reagents or functionalities within the substrate and may also involve the use of toxic or explosive precursors. Many of these reactions also require careful monitoring of low temperature conditions. Kobayashi recently demonstrated the use of a silylaryl triflate benzyne precursor **51**, whereby the use of a fluoride source promotes benzyne formation (Scheme 10).[56] Due to the almost neutral reaction conditions associated with this type of substrate, the discovery of this benzyne precursor has much expanded the scope of aryne methodology over the past 30 years.[57]



51 **20**

Scheme 10: Fluoride-induced desilylation-elimination to form benzyne

As an extension to this approach, hypervalent iodine substituents have also been used as leaving groups *ortho* to trimethylsilyl groups.[58,59]

1.4 Reactions of Arynes

The high reactivity and electronic features of aryne molecules result in their use in several different types of organic reactions including: pericyclic and nucleophilic addition reactions as well as metal-catalysed aryne reactions. [12-14,57] This next section will focus on these reactions.

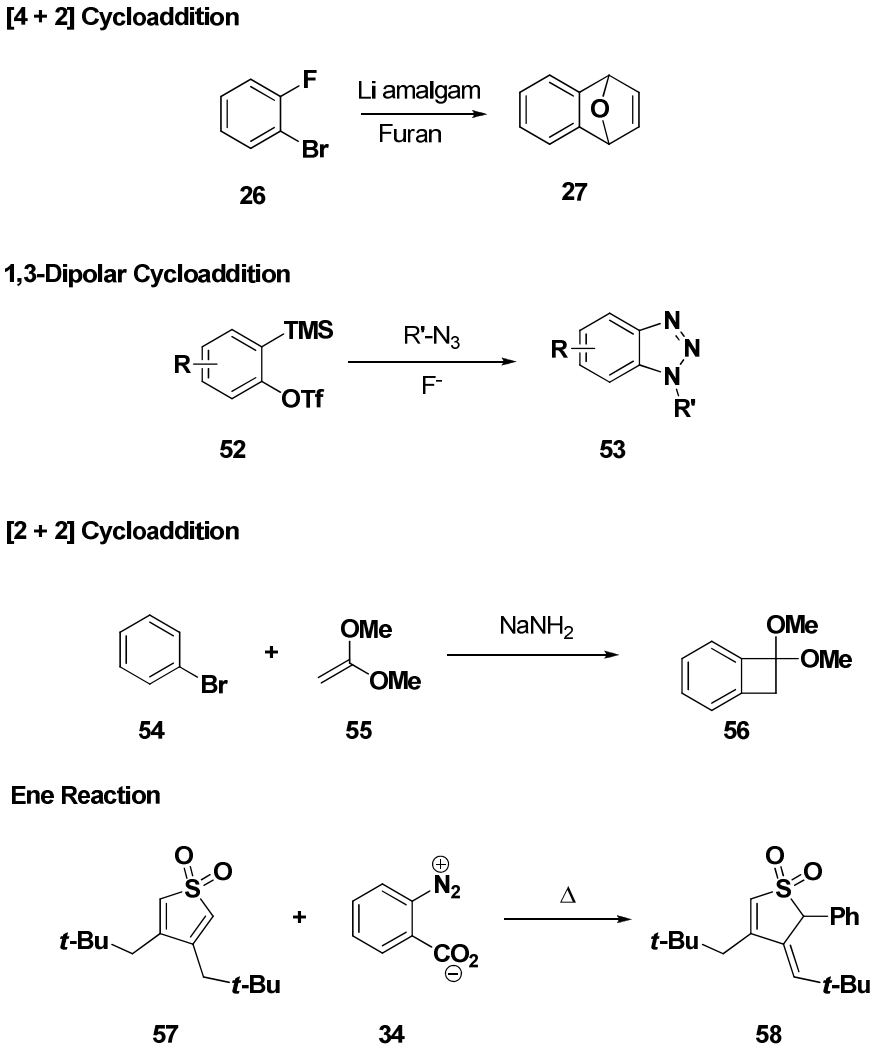
1.4.1 Pericyclic Reactions

Poor overlap of orbitals in the aryne moiety results in a low energy LUMO, making it an excellent dieneophile for cycloaddition reactions.

It has been found that arynes undergo both intra- and inter-molecular [4+2],[9,10,60-62] [2+2][63-65] and 1,3-dipolar cycloadditions[66-68] as well as ene reactions[69,70] (Scheme 11).

Diels-Alder cycloadditions with arynes are known for acyclic and cyclic dienes, the most useful being those employing five-membered heterocycles. This includes the famous

reaction between furan and benzyne **(20)**[9] to afford cycloadduct **27** (Scheme 11). Due to the short lifetime of benzyne, these reactions are superior if the diene predominately exists in the *s-cis* conformation as is found in furan.



Scheme 11: Examples of pericyclic reactions of arynes

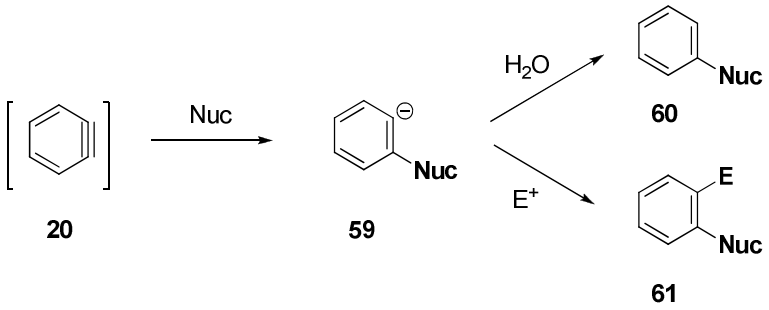
Larock demonstrated a 1,3-dipolar cycloaddition in the synthesis of functionalised benzotriazoles **53** from arynes and azides; an illustration of benzyne click chemistry under mild conditions (Scheme 11).[66]

An example of a [2 + 2] cycloaddition shows the reaction of dimethoxyethylene **(55)** and bromobenzyne **(54)** to provide benzocylobutene **56** (Scheme 11).[63]

An unanticipated ene reaction was observed when a Diels-Alder reaction between benzyne and 3,4-dineopentylthiphene **(57)** was attempted, furnishing **58** as the major product (Scheme 11).[69]

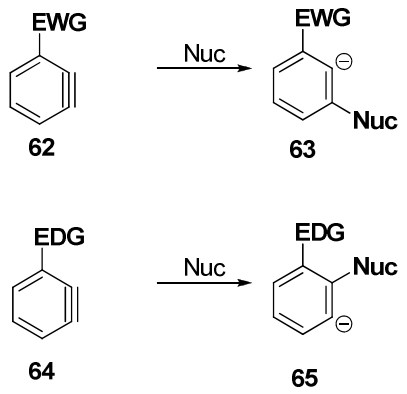
1.4.2 Nucleophilic Addition Reactions

The highly strained, electron-deficient aryne bond has a low lying LUMO. Consequently, the bond is highly electrophilic and is readily attacked by nucleophiles. The resulting anion formed, **59**, can either be protonated with water to produce a mono-substituted aromatic system **60** or allowed to react with an electrophile to afford an *ortho* di-substituted ring pattern as in **61** (Scheme 12).



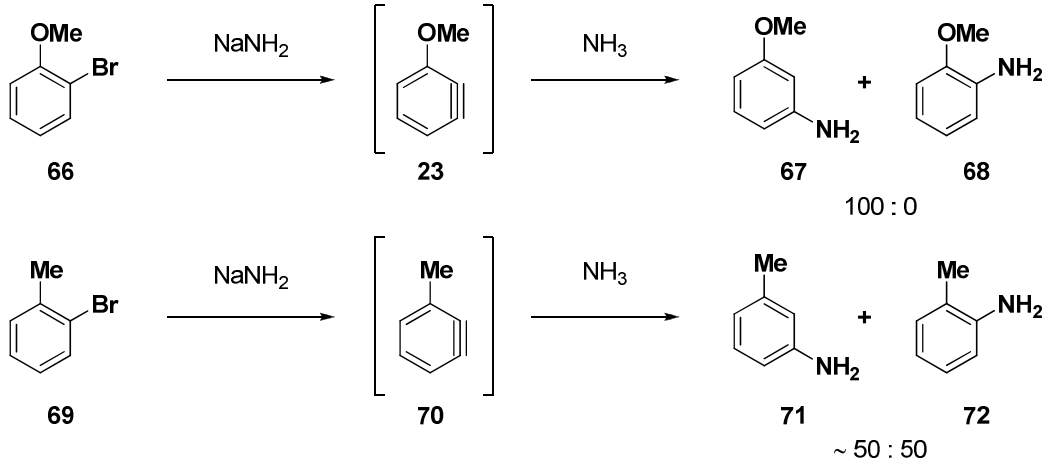
Scheme 12: Nucleophilic addition reactions involving arynes

With substituted aryne systems the position of attack depends on the position of substitution. As the orbitals involved are orthogonal to the π-system of the aromatic system, it is simply the σ-inductive effect of substituents on the ring which is relevant. *ortho* Electron-withdrawing groups (e.g. OMe), as illustrated in **62**, polarise the bond in favour of *meta* attack resulting in **63**, and stabilises the resultant carbanion. In contrast an electron-donating group (e.g. alkyl) as illustrated in **64** would polarise the bond in the opposite sense and hence *ortho* attack is preferred to give **65** (Scheme 13).[71,72] When the size of the substituent on the aromatic ring or the nucleophile becomes large, steric factors can also change the product ratio.[73]



Scheme 13: Regioselectivity in nucleophilic addition to benzynes

This is demonstrated in Roberts'[33] early observations when unsymmetrical arynes were trapped with nucleophilic ammonia. Addition of ammonia to 3-methoxybenzyne **(23)** displayed 100% regioselectivity for attack in the *meta* position, affording aniline **67**, whereas addition to 3-methylbenzyne **(70)** showed no preference and a 1 : 1 mixture of anilines **71** and **72** was afforded (Scheme 14). Biehl[71,72] proposed that this suggests a more pronounced polarisation of the aryne bond in 3-methoxybenzyne **(23)** due to the greater inductive effect of an alkoxy group over an alkyl group.



Scheme 14: Roberts' observations of nucleophilic attack on 3-substituted benzynes

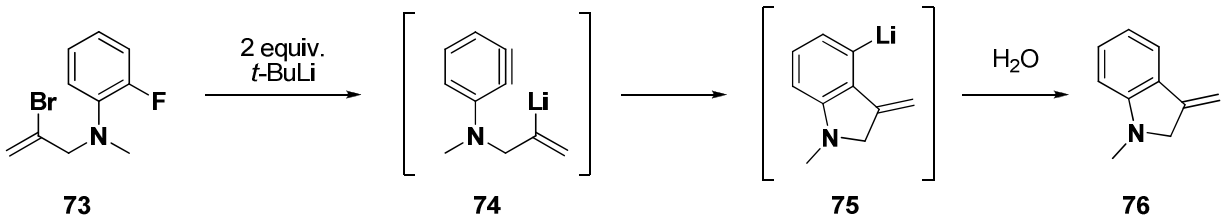
Arynes, with low energy LUMOs result in preferential attack of soft nucleophiles in such systems.[12-14] Reactions have been performed with both carbon and heteroatom nucleophiles and a range of charged and neutral species.

1.4.2.1 Addition of Carbon-Nucleophiles to Arynes

Research within the Barrett group has focussed on the addition of carbon nucleophiles to arynes, to generate new C-C bonds. Although there are many cross-coupling techniques available to construct sp^2-sp^2 C-C bonds, the addition of aliphatic carbon-nucleophiles to arynes provides an excellent method for the formation of sp^2-sp^3 bonds.

Traditional anionic carbon nucleophiles are all known to participate in aryne addition reactions, including alkyllithiums,[74] aryllithiums,[6,75] Grignard reagents[76] and cuprates.[77] A variety of stabilised carbanions can also be utilised, and will be discussed in Section *1.4.2.3*.

In many cases the organometallic reagent has a dual role. It can be used for metalation to form benzyne and subsequently as a nucleophile for the reaction by either adding in directly itself or indirectly by forming an incipient nucleophile by halogen-metal exchange. An example of this was seen in Barluenga's[78] synthesis of substituted indoles where *tert*-butyllithium is the reagent of choice to bring about this benzyne tethered intramolecular anionic cyclisation (Scheme 15). Tautomerisation of the resultant dihydroindole **76** gave the required indole.

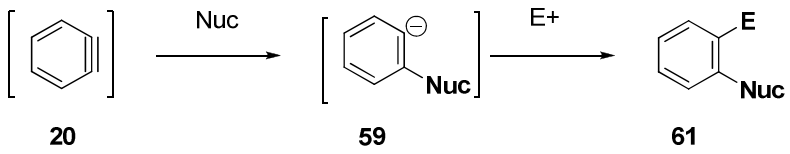


73 **74** **75** **76**

Scheme 15: Barluenga's benzyne tethered intramolecular cyclisation to dihydroindole **76** in the synthesis of substituted indoles

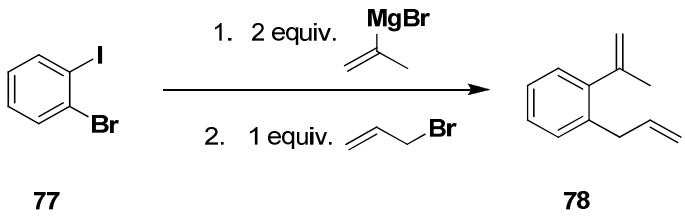
1.4.2.2 Multi-Component Coupling Reactions of Arynes

Advances in aryne chemistry have lead to the development of three-component coupling reactions in which two different aryne carbon-carbon or carbon-heteroatom bonds are formed consecutively in a one-pot reaction. These reactions exploit the electrophilic benzyne species **20** and the resultant aryl carbanion **59** after nucleophilic attack reacting with a further electrophile (Scheme 16).



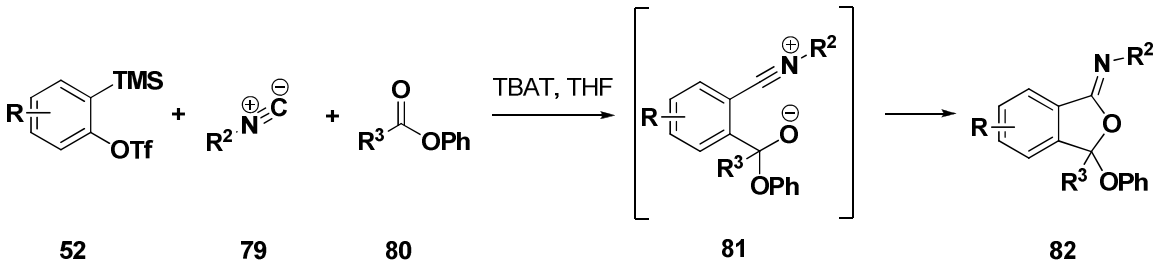
Scheme 16: Three-component coupling reactions of arynes

The multi-component reactions shown in Scheme 16 have many advantages such as the rapid construction of highly complex and diverse 1,2-disubstituted arene scaffolds. Hart demonstrated one of the earliest examples of such a synchronous introduction of two different functional groups.[76] Employing an iodine-magnesium exchange mechanism of benzyne formation he successfully coupled the aryne derived from **77** with a Grignard reagent and an allyl bromide to afford an arene with *ortho* vinyl and allyl substituents, **78** (Scheme 17). The title of the publication: *"A one-pot procedure for attaching two differentiated carbon side chains to adjacent carbons of an arene ring"*, summarises this style of reaction very succinctly.



Scheme 17: Hart's three-component benzyne reaction

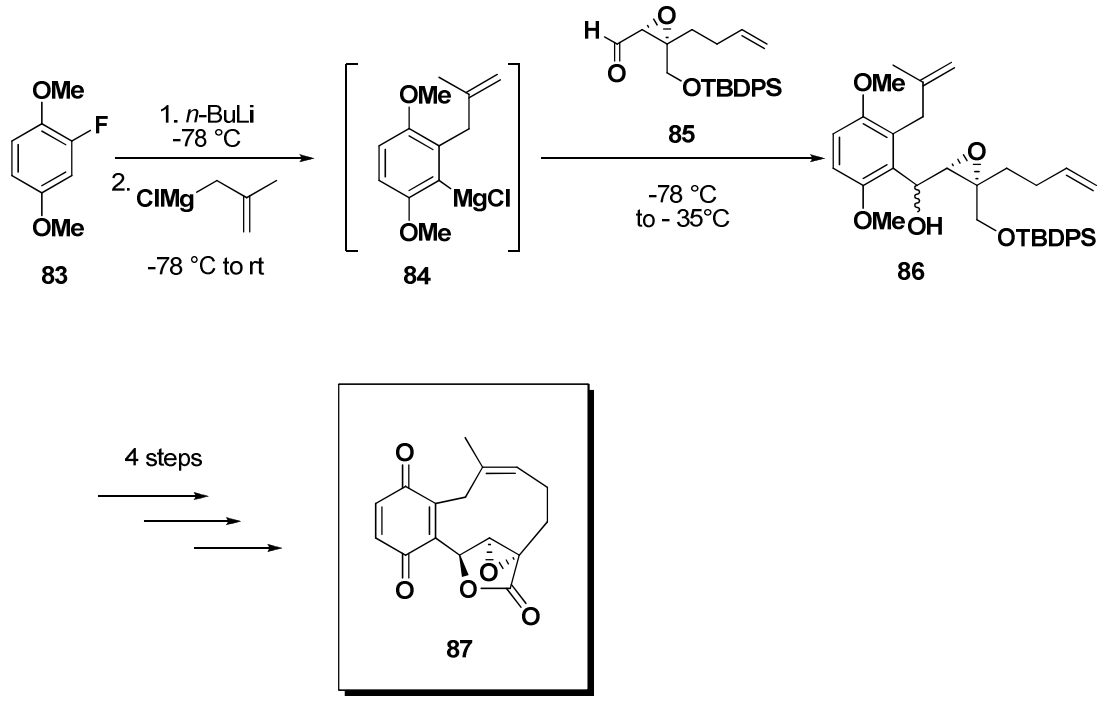
A more recent example illustrates the use of arynes derived from silylaryl triflates in a multi-component reaction. Stoltz[79] utilizes isocyanide nucleophiles **79** along with phenyl esters **80** as the electrophilic species in an aryne-intercepted Passerini style reaction as a facile procedure for the formation of phenoxy imino-*iso*-benzofuran motifs **82** (Scheme 18).



Scheme 18: Stoltz's formation of phenoxy imino-*iso*-benzofurans

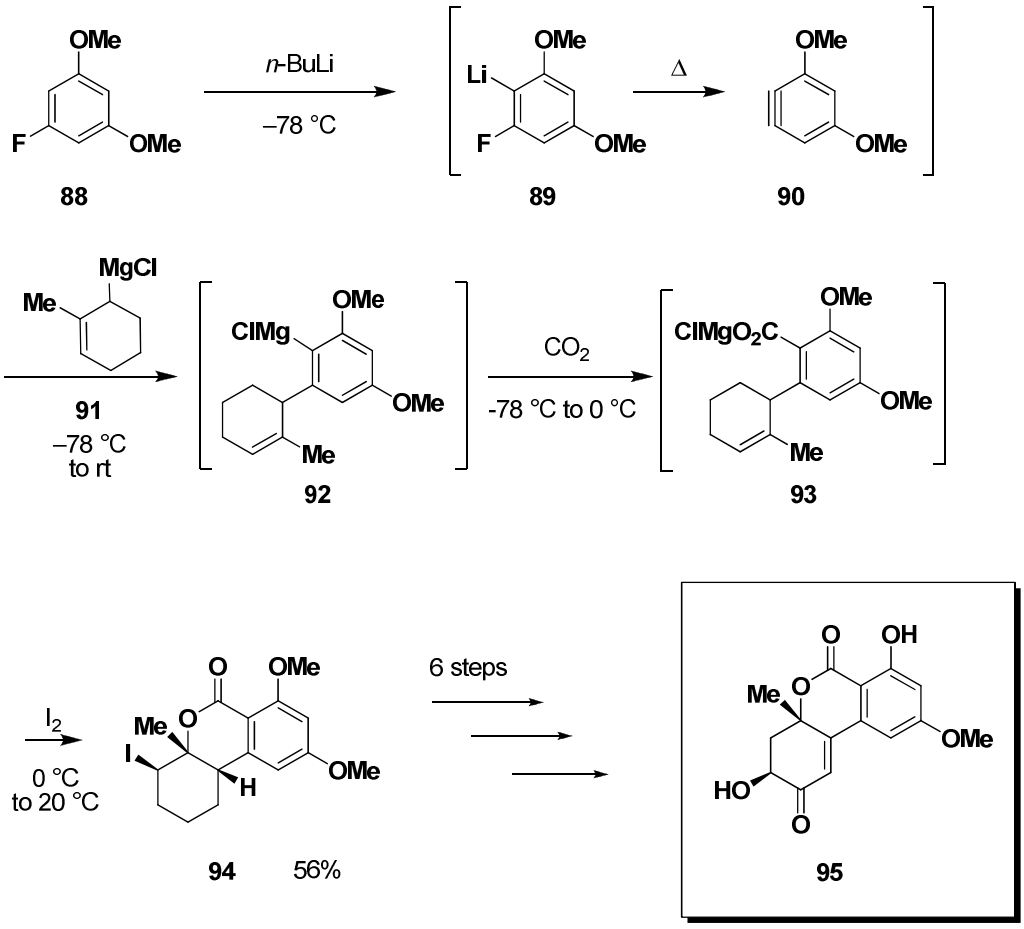
Recently, the Barrett group has employed multi-component benzyne reactions as the key step for the syntheses of two natural products.

Clavilactone B, **(87)**, a novel antibiotic natural product,[80] was afforded using aryl fluoride **83** as the benzyne precursor for the key step in which an allyl Grignard was used as the nucleophile to give **84** which was trapped with chiral aldehyde **85** to give **86** (Scheme 19).[81] Only four further synthetic steps were required to afford the natural product **87** in an overall yield of 17%.



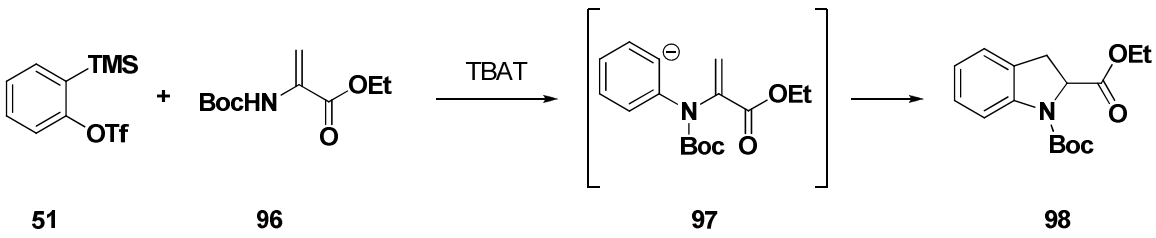
Scheme 19: Barrett's synthesis of clavilactone B **(87)**

An elegant synthesis of dehydroaltenuene B **(95)**, a marine natural product with antibiotic acitivity,[82] employed a four-component benzyne reaction as its key synthetic transformation. Dimethoxybenzyne **(90)** was generated from aryl fluoride **88** and subsequently treated with Grignard reagent **91** to afford the aryl Grignard **92** which was trapped with carbon dioxide. The magnesium carboxylate **93** then underwent an iodo-lactonisation to afford the tricyclic system **94**. This key intermediate **94** contained all three rings and much of the complexity of dehydroaltenuene B **(95)** (Scheme 20). The natural product was completed in seven steps and an overall yield of 14%.[83]



Scheme 20: Barrett's synthesis of Dehydroaltenuene B

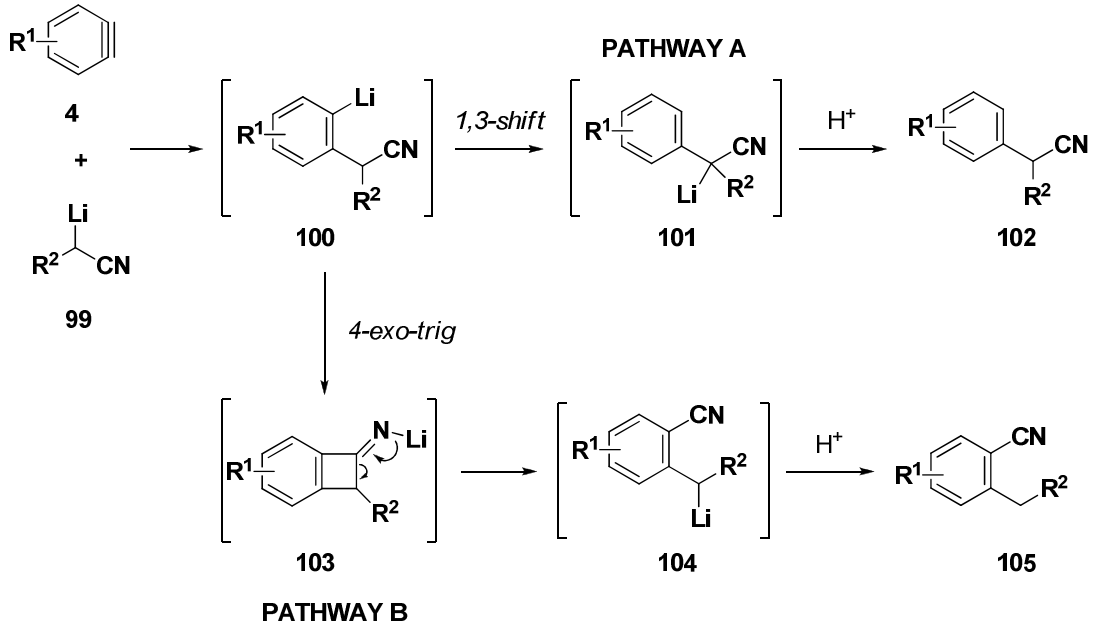
Various aryne multi-component reactions have also been conducted using amphoteric compounds, *i.e*. the nucleophilic and electrophilic components required for the aryne reaction are present within the same molecule. An illustration of this is Stoltz's synthesis of indoline **98** (Scheme 21).[84] *In situ* generation of benzyne in the presence of *N*-*tert*-butoxy carbonyl dehydroalinine ester **96** promoted an intermolecular nucleophilic coupling with the amine moiety, followed by intramolecular electrophilic cyclisation of **97** onto the α, β-unsaturated ester; a formal [3 + 2] cycloaddition.



Scheme 21: Stoltz's synthesis of indoline **98**

1.4.2.3 Addition of Stabilised Carbanions to Arynes

In 1963 Skorcz[85] reported the first intramolecular addition of lithioacetonitrile derivatives to benzyne. Following this, Biehl published in depth studies of the addition of various α-lithiated acetonitriles to arynes.[86,87] Two competing mechanistic pathways were observed, depending on the nature of the aryne and the lithioacetonitrile derivative (Scheme 22). Arynes, **4**, with at least one electron-releasing group (R^1 = EDG) which were allowed to react with aryl lithionitriles **99** (R^2 = Ar) followed Pathway B. The formal insertion products **105** were yielded by the addition of benzyne into the C-C bond, proceeding by a tandem addition-rearrangement pathway. In other cases (i.e. R^1 = EWG or R^2 = alkyl), then the usual aryne addition mechanism is observed and nitrile **102** is the major product (Pathway A).

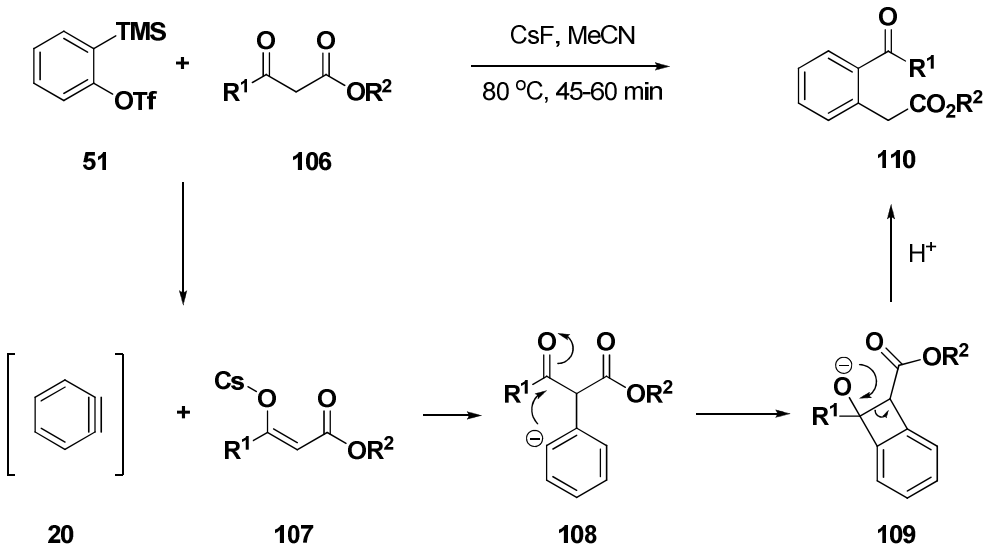


Scheme 22: Reactions of 2-lithionitriles **99** with arynes

Since these observations, many other cascade reactions triggered by nucleophilic attack of lithionitriles have been reported.[88-94]

Insertion of arynes into C-C bonds by means of addition-rearrangement mechanisms as seen in the above example (Scheme 22), is emerging as a powerful synthetic tool in organic chemistry.[95] These reactions can be viewed as a special case of a three-component coupling reaction in which the nucleophilic and electrophilic components are present in the same molecule.

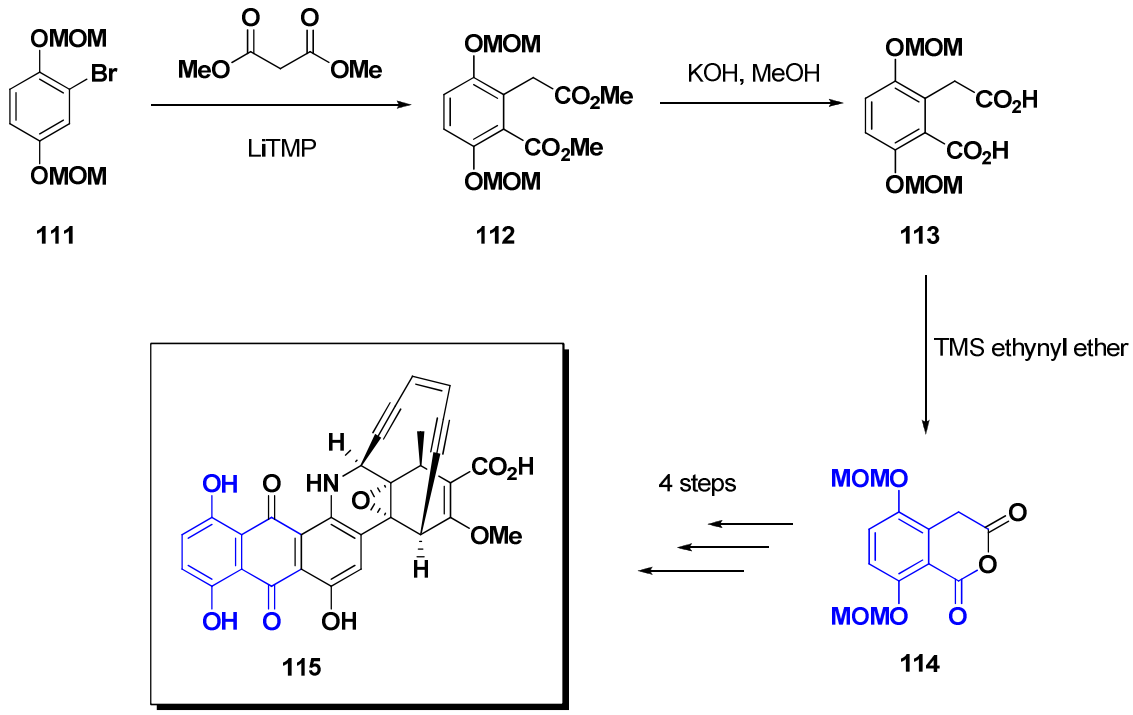
Of particular note is the insertion of an aryne into a C-C bond of a β-ketoester **106**. This was demonstrated by Stoltz[96] under mild conditions using benzyne precursor **51** to form **110** *via* a formal [2+2] cycloaddition followed by a fragmentation (Scheme 23), in a very similar mechanism to that seen in Scheme 22. Cesium fluoride effects both benzyne formation *via* desilylation and generates the necessary cesium enolate **107**. Nucleophilic attack of the aryl anion **108** onto the more electrophilic carbonyl moiety and subsequent ring-opening generates aryl ketone **110**.



Scheme 23: Stoltz's direct acyl-alkylation of arynes

Analogous C-C bond insertions have been reported for malonates,[97] β-diketones,[97] α-cyanocarbonyls,[98] α-sulfonyl ketones,[99, 100] and β-ketophosphonates.[101]

The use of such a malonate C-C insertion reaction was exploited by Danishefsky in the total synthesis of antibiotic dynemicin A **(115)** as a means to furnish key intermediate **114** after saponification and cyclodehydration (Scheme 24).[102]

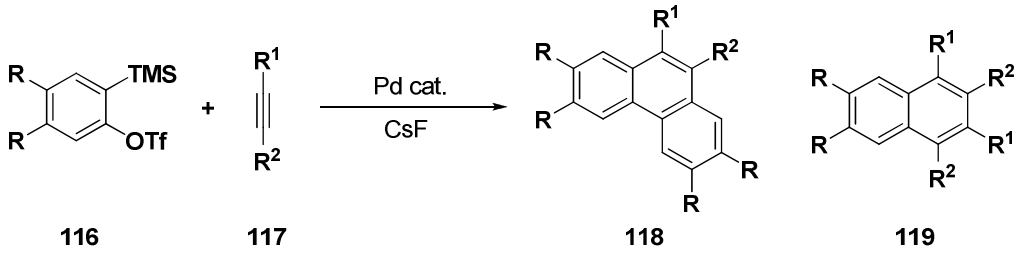


Scheme 24: Danishefsky's synthesis of anhydride **114**. A key step in the synthesis of dynemicin A **(115)**

The nucleophilic addition of enolates to arynes will be covered in detail in Chapter 3.

1.4.3 Transition-Metal Catalysed Reactions of Arynes

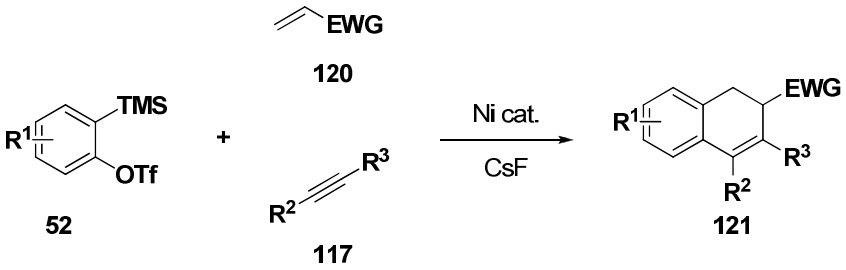
Pioneering work by Yamamoto[103] and Castedo[104] into the area of palladium-catalysed reactions of arynes has led to the development of co-cyclisation reactions of arynes **116** with alkynes **117** forming naphthalene **118** or phenanthrene **119** derivatives (Scheme 25).



Scheme 25: Co-cyclisation reactions of arynes with alkynes

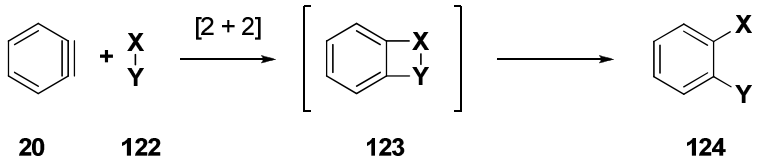
Other transition metal catalysts have also been employed for the rapid construction of complex molecules from readily available starting materials, as illustrated in Xie's nickel-

catalysed 3-component [2 + 2 + 2] cycloaddition reaction of arynes, alkenes **120** and alkynes **117** to generate dihydronapththalenes **121** (Scheme 26).[105]



Scheme 26: Xie's nickel catalysed multi-component aryne reaction

In Section *1.4.2.3*, insertion of arynes into C-C bonds was discussed. In addition to these reactions it is known that aromatic rings can undergo double *ortho* functionalisation *via* insertions of arynes into other nucleophilic-electrophilic σ-bonds (Scheme 27) sometimes requiring the presence of a metal catalyst, including when X-Y = Sn-C, N-C, Si-Si, Sn-Sn, S-Sn, N-Si, N-C, N-S, B-B and C-P.[95]



Scheme 27: Insertion of arynes into X-Y σ-bonds

1.5 Heteroarynes

The following heteroarynes are reported,[106,107] including pyridynes **(125)** and **(126)**, didehydropyridazines **(127)** and **(128)**, didehydropyrimidine **(129)**, didehydropyrazine **(130)**, didehydrofurans **(131)** and **(132)** and didehydropyrroles **(133)** and **(134)** (Figure 5).

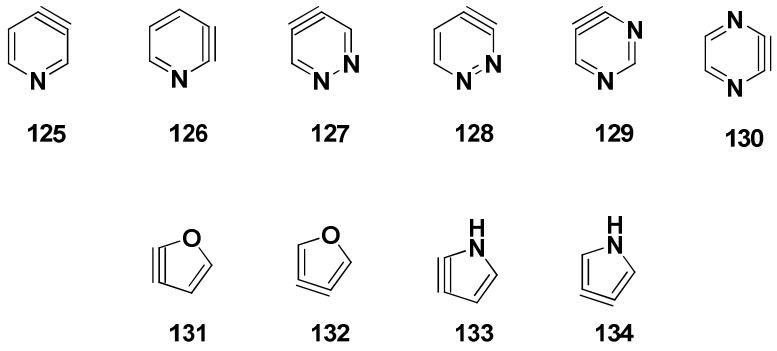
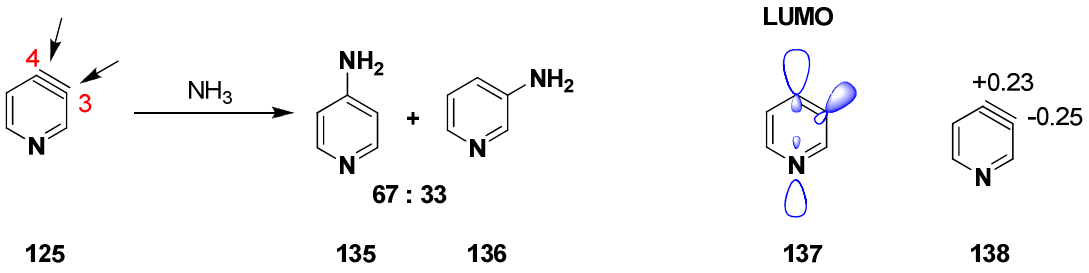


Figure 5: Five- and Six-membered heteroarynes

Heteroarynes, although less studied than benzynes are important and synthetically useful due to the large number of heteroatom containing aromatic systems both in natural product and medicinal chemistry. Methods of generation are similar to those of benzynes with α-elimination from metalated precursor molecules and fluoro-desilylation techniques being the most exploited.[12-14,106,107]

Heteroaryne intermediates have been shown to have similar reactivity to benzynes, namely nucleophilic addition and cycloaddition reactions. Additional regioselectivities are observed due to the heteroatoms' influence on the electronic properties of the ring.

For example, nucleophilic attack can occur at the 3- or the 4-position of 3,4-pyridyne **(125)** to give the two isomeric products **135** and **136** (Scheme 28).[107] Attack at C-4 is slightly favoured, due to the coefficient of the LUMO, **137**, being slightly larger on C-4 and the total charge distribution, **138**, also polarising the bond in favour of attack at C-4.[108,109]



Scheme 28: Different sites of nucleophilic attack on 3,4-pyridyne and LUMO and total charge distribution diagrams

If further substituents are added to the 3,4-pyridyne, then σ-induction rules also have to be taken into consideration as for benzynes, and will often suppress the effect of the remote

nitrogen atom. When various ethoxy-substituted 3,4-pyridynes underwent amination with potassium amide in liquid ammonia, the addition ratios were as shown in Figure 6.[110]

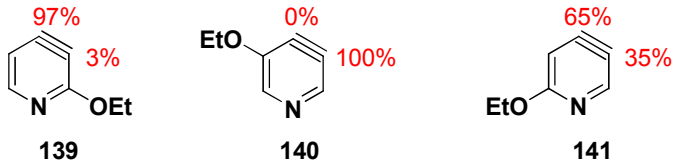
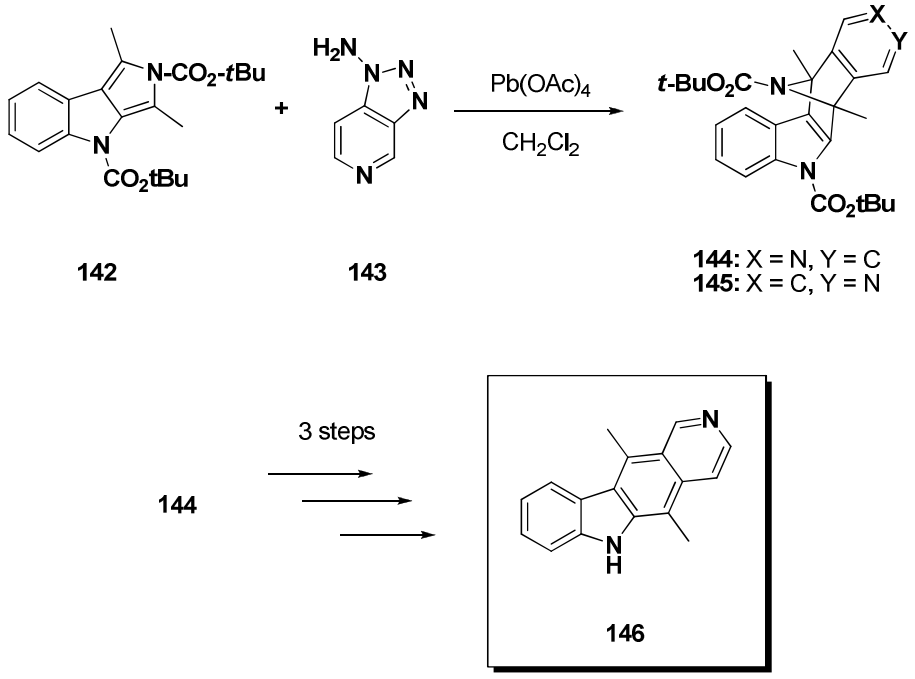


Figure 6: Addition ratios observed in the amination of various ethoxy-substituted 3,4-pyridynes

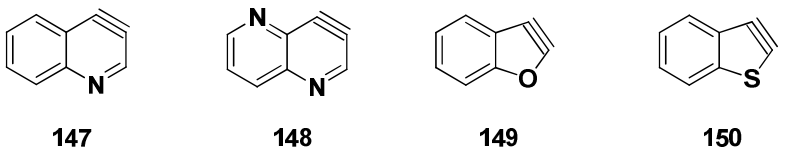
These ratios demonstrate that the *meta* directing effect of an *ortho* ethoxy group is far stronger than the effect of the ring nitrogen, as no addition to C-4 is observed for **140**. However when the ethoxy group is remote from the aryne bond as in **141**, the addition ratio is much the same as for unsubstituted 3,4-pyridyne.

An example of heteroaryne chemistry in synthesis is the use of 3,4-pyridyne **(125)** derived from aminotriazole **143** in a [4 + 2] cycloaddition reaction with pyrrole **142** to give **144** and its regioisomeric isomer **145** in a 62% yield and a 55 : 45 ratio respectively. After separation, **144** proved to be an important intermediate in the synthesis of the antitumor alkaloid ellipticine **(146)** (Scheme 29).[111]



Scheme 29: Key synthetic transformation in the synthesis of ellipticine **(146)** using 3,4-pyridyne **(125)** as a reactive intermediate

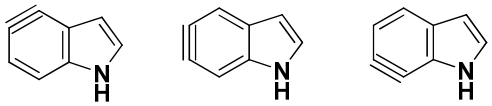
The intermediacy of bicyclic heteroarynes has also been well published,[107] including such species as quinolynes **(147)**, naphthyridynes **(148)**, dehyrdocoumarones **(149)** and thianaphthynes **(150)** (Figure 7). Again, their methods of preparation mirror those of benzyne and the regioselectivity of their reactions is influenced by the position of the heteroatoms in the bicyclic ring systems.



147 **148** **149** **150**

Figure 7: Some examples of bicyclic heteroarynes

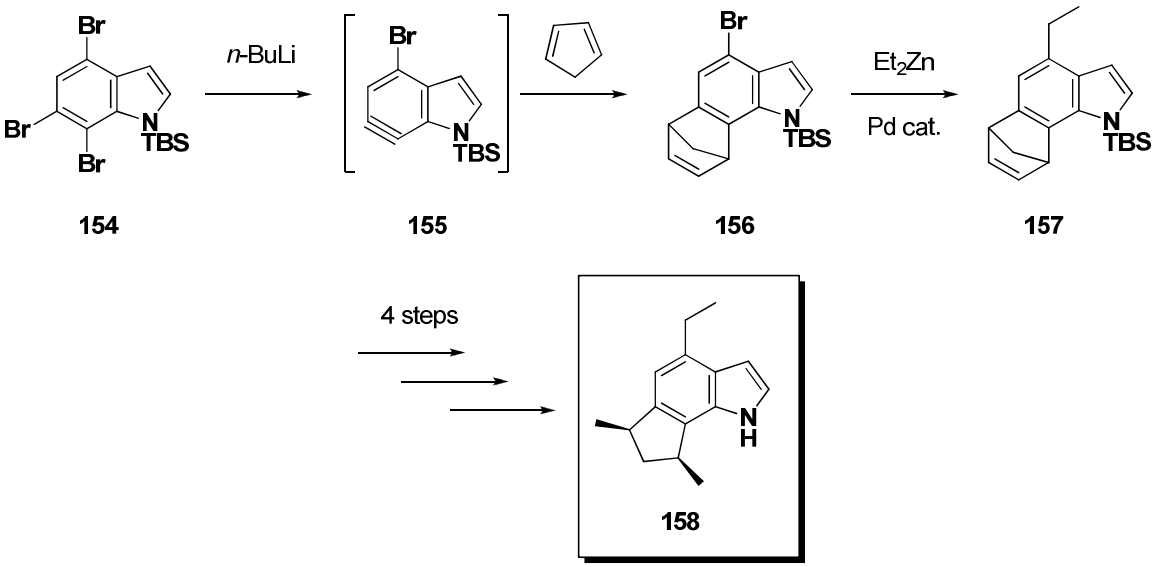
In the last 5 years there has been a particular interest in the use of indolynes **(151)**, **(152)** and **(153)** (Figure 8) by Buszek[112-114] and Garg[115] due the large number of natural products that feature substituted indole cores and their discovery of efficient metal-halogen exchange routes to these intermediates.



151 **152** **153**

Figure 8: 4,5-indolyne **(150)**, 5,6-indolyne **(151)** and 6,7-indolyne **(152)**

Buszek[114] used a tandem indolyne cycloaddition/Negishi coupling reaction as a crucial step in the synthesis of (±)-*cis*-trikentrin A **(158)**. Starting from 4,6,7-tribromoindole **154**, selective 6,7-indolyne **155** formation was triggered by a metal-halogen exchange at C-7 and trapped in a cycloaddition with cyclopentadiene. The remaining 4-bromo position in **156** was then available for further elaboration using a Negishi coupling protocol (Scheme 30).



154 155 156 157 158

Scheme 30: Tandem indolyne cycloaddition/Negishi reaction as the key step in the synthesis of (±)-*cis*-trikentrin A **(158)**

1.6 Scope for Extension of Methodology

The potential of the multi-component coupling reaction of arynes is vast and the diversity created by simply changing the nature of the aryne, nucleophile or electrophile could allow the extension of this methodology to provide flexible new routes to a wide range of aromatic and heterocyclic compounds including ones of pharmaceutical relevance.

In a natural progression from previous research, the three-component coupling reaction could be extended to heteroarynes, an under-explored area of aryne chemistry. There is also the potential to develop novel cyclisation reactions in which the nucleophilic and electrophilic entities are present within the same molecule. Further studies could also be conducted on stereo-controlled carbon-carbon bond construction within these reactions.

Over the next five chapters, details of several projects aimed at creating novel aryne multi-component methodology involving the addition of carbon nucleophiles will be described in full. In all projects, the focus is on efficient, concise and elegant routes to small, highly functionalised aromatic molecules.

Chapter 2: Results and Discussion: Developing Novel Reactions of 2,3-Pyridynes

2.1 Introduction

Pyridynes fall into two types: 3,4-pyridyne **(125)** and 2,3-pyridyne **(126)**. Due to the polarising effects of the pyridine ring nitrogen they are far less stable than their benzyne analogues (Figure 9).

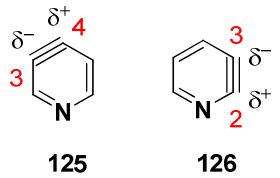


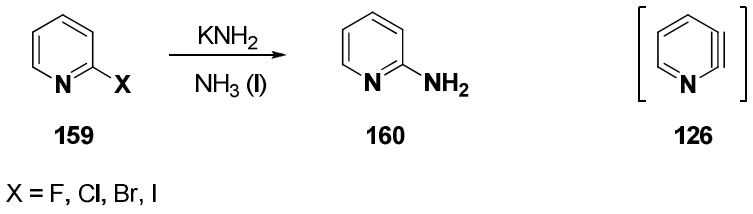
Figure 9: Polarisation of aryne bond in 3,4-Pyridyne **124** and 2,3-pyridyne **125**

Methods of generation and types of reactions possible generally parallel those of benzyne, with extra regioselectivity issues arising due to the desymmetrising nature of the nitrogen atom.[106,107] 3,4-Pyridynes have received a considerable amount of interest within the synthetic community,[111,116,117] whereas 2,3-pyridynes are much less explored and have generally been considered of low synthetic potential due to the low reported yields associated with these species. For this reason, work was focussed on these underexploited intermediates.

2.1.1 2,3-Pyridynes

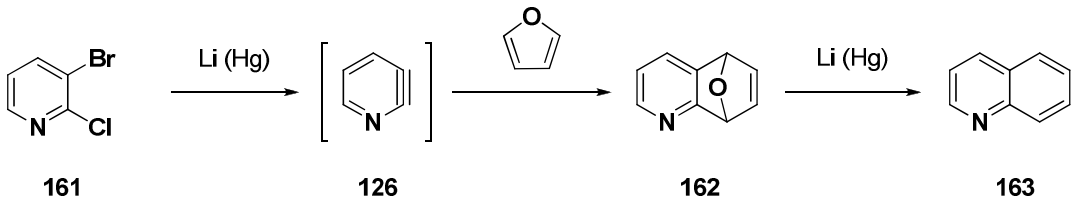
2.1.1.1 History, Regiochemistry and Modern Advancements

In 1961, an extensive examination of the aminations of halopyridines by Pietrese[118], postulated the intermediacy of 2,3-pyridyne **(126)**. Treatment of 2-halopyridines **159** with potassium amide and liquid ammonia afforded 2-aminopyridine **(160)** as the sole product (Scheme 31).



Scheme 31: Amination of 2-halopyridines

However, due to the lack of *cine*-addition products, an aryne intermediate could not be proved, as a more simple explanation would be for an addition-elimination mechanism to be occurring. It was not until 2,3-pyridyne **(126)** was trapped in a Diels-Alder cycloaddition with furan that the first evidence of its existence was confirmed. A small amount of quinoline **163** was isolated as a result of further reaction of lithium amalgam with adduct **162** (Scheme 32).[119,120]



Scheme 32: First evidence of 2,3-pyridyne; Diels-Alder reaction with furan

Molecular orbital calculations on 2,3-pyridyne **(126)** have since provided indication that nucleophilic attack would almost certainly occur entirely in the 2-position due to a larger LUMO coefficient at C-2, as seen in **164**.[108,109,121] The total charge distribution, **165**, also demonstrates that C-2 bears a partial positive charge (Figure 10).

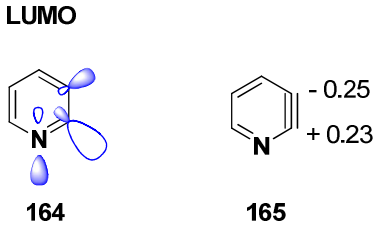


Figure 10: LUMO and total charge distribution for 2,3-pyridyne

2,3-pyridynes are far less stable than their 3,4 counterparts, due to considerable destabilisation of the strained aryne bond attributed to the proximity of the electronegative nitrogen atom. In the last decade Hegarty has established that 4-alkoxy groups significantly stabilise 2,3-pyridynes, affording better [4 + 2] cycloaddition yields with furan (up to 58%

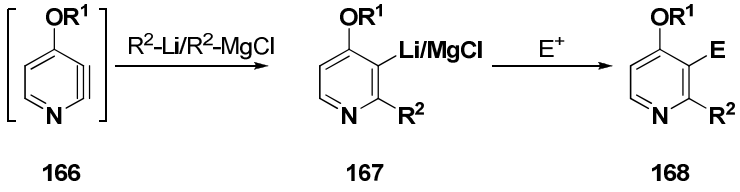
yield compared to 28% for un-substituted analogues).[122] The explanation is that the electron-donating substituent helps to counteract the polarisation effect of the pyridine nitrogen and hence increases stability and reactivity in cycloaddition reactions. Conversely, an aryl electron-withdrawing group would render the aromatic ring even more electron deficient, and hence the aryne more reactive and less stable.

2.1.1.2 Methods of Generation

The most common techniques used for the generation of 2,3-pyridynes **(126)** are lithium/halogen exchange,[123] directed *ortho*-lithiation,[122] oxidation of aminotriazolopyridine with lead tetracetate[124] or fluoride-induced desilylation-elimination (See Scheme 6, Section 1.3).[125]

2.1.2 Synthetic Plan

Of all the *N*-heterocycles, pyridine is the most abundantly used in pharmaceutical research.[126] To be able to functionalise the 2 and 3 positions of pyridine simultaneously in a multi-component aryne coupling reaction would be of high synthetic value. It was proposed that the addition of carbon nucleophiles (such as alkyllithiums and Grignard reagents) to alkoxy stabilised 2,3-pyridynes **166** would occur exclusively at the 2-position and that the resultant metalated intermediate **167** could be reacted with various electrophiles to afford compounds such as **168** (Scheme 33). At the onset of the project there were no examples of addition of carbon nucleophiles to 2,3-pyridynes **126**.



166 **167** **168**

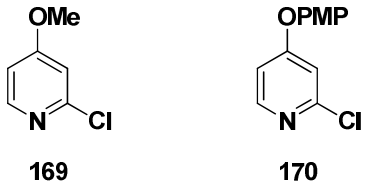
Scheme 33: Potential three-component coupling reactions of 2,3-pyridyne **166**

The initial proposal was to synthesise various alkoxy-stabilised 2,3-pyridyne precursors and investigate their potential for providing reactive intermediates for such multi-component coupling reactions.

2.2 *ortho*-Lithiation Pyridyne Precursors

2.2.1 Synthesis of Precursors

The first pyridyne precursor to be investigated was 2-chloro-4-methoxy pyridine **(169)**, due to its success in affording cycloadducts with furan in reasonable yields.[122] Although Hegarty found the *p*-methoxyphenoxy group in precursor **170** to provide the greatest stabilisation for Diels-Alder reactions, it was opted to use **169** due to the need to maintain a balance between stabilisation of the aryne, and electrophilicity of the 2 position (Figure 11).



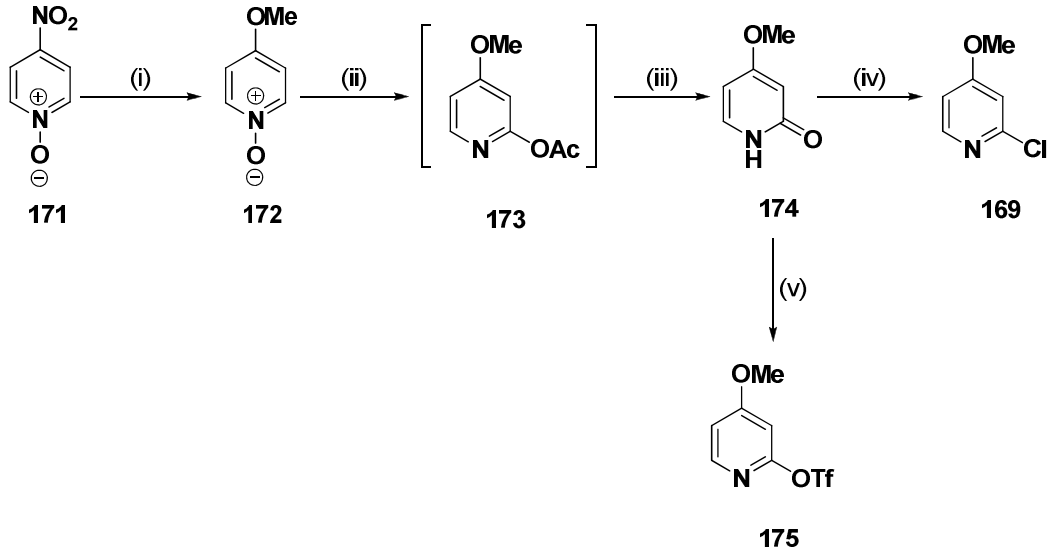
169 **170**

Figure 11: Hegarty's 2,3-pyridyne precursors **169** and **170**

Due to the commercial expense of pyridine **169** a synthetic route was desired. After attempting several reported routes and either finding them unsuccessful or inefficient, [122,127,128] a three step synthesis of **169** was completed from commercially available 4-nitropyridine-*N*-oxide **(171)** using the method of Morris.[128]

Ipso-Substitution of the nitro group was effected with sodium methoxide to give 4-methoxypyridine-*N*-oxide **(172)** in a 69% yield. Polonovsky rearrangement of *N*-oxide **172** with acetic anhydride afforded the intermediate 2-acetoxy-4-methoxypyridine **(173)** which was hydrolysed *in situ* to pyridone **174**. The reaction was capricious with yields varying from 20 to 59% dependent on the scale. Finally, chlorination of 4-methoxypyridin-2-one **(174)** with phosphorous oxychloride gave the corresponding chloropyridine **169** (Scheme 34).

A novel pyridyne precursor, triflate **175**, was also synthesised in excellent yield from intermediate pyridone **174** by treating with trifluoromethanesulfonyl anhydride in the presence of base. This precursor was thought to be interesting due to the greater leaving group ability of a triflate anion compared to that of a chloride anion.

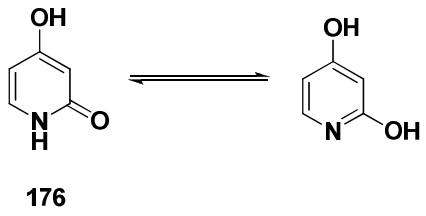


Reagents and Conditions: (i) NaOMe, MeOH, reflux, 8 h, 69%; (ii) Ac_2O, reflux, 6 h; (iii) MeOH/H_2O, rt, 1 h, 20-59% over two steps; (iv) $POCl_3$, 95 ^oC, 16 h, 45%; (v) Tf_2O, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, rt, 1 h, 93%.

Scheme 34: Synthesis of 2,3-pyridyne precursors **169** and **175**

Although the syntheses of these compounds were completed, large scale reactions were problematic due to the deleterious yields in scaling up the pyridone forming step. The reaction was capricious and not scalable. Therefore it was sought to develop a new route to this compound.

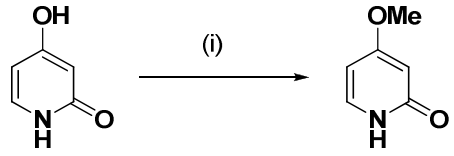
A new strategy was devised whereby 4-hydroxypyridin-2(1*H*)-one **(176)** was selectively methylated at the 4-position. Deprotonation of the hydroxyl group in the 4-position should be facile in comparison to the 2-position due to the large difference in pKa resulting from the presence of the pyridone tautomer (Scheme 35).



Scheme 35: Tautomers of 4-hydroxypyridin-2(1*H*)-one **(176)**

4-Hydroxypyridin-2(1*H*)-one **(176)** was subjected to many different bases, solvents and methylating agents, including diazomethane, dimethyl sulphate and iodomethane in an attempt to carry out this transformation based on precedent from similar 2,4-quinolinediol

structures.[129,130] Poor selectivity was attributed to the increased solubility of the products over the starting material in most common organic solvents. The best selectivity was observed using potassium carbonate and iodomethane in *N*,*N*-dimethylformamide (Scheme 36). A full conversion was observed by TLC, but poor yields were obtained due to problems with isolation.



176 **174**

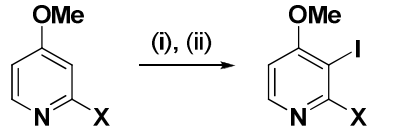
Reagents and Conditions: 1 equiv. K_2CO_3, 1 equiv. MeI, DMF, rt, 36 h, 60%.

Scheme 36: Selective methylation of 4-hydroxypyridin-2(1*H*)-one **(176)**

Other approaches to pyridone **174** were also investigated including the thermolysis of antimony compounds[131] and the selective mono-hydrolysis of 2,4-methoxypyridine.[132] None of these conditions proved successful.

2.2.2 Reactions of *ortho*-Lithiation Precursors

The lithiated species derived from 2-chloro-4-methoxy pyridine **(169)** does not collapse to form pyridyne at −78 ºC and warming is required to induce the elimination.[122] The stability of the triflate precursor **175** at low temperature however was unknown. Treatment of both precursors with LDA at −78 ºC followed by iodine afforded only iodinated compound **1** in 75% yield (Scheme 37). The lithiated species derived from triflate compound **175** appears to eliminate to afford 2,3-pyridyne at low temperature as no iodide **177** or starting material was detected.



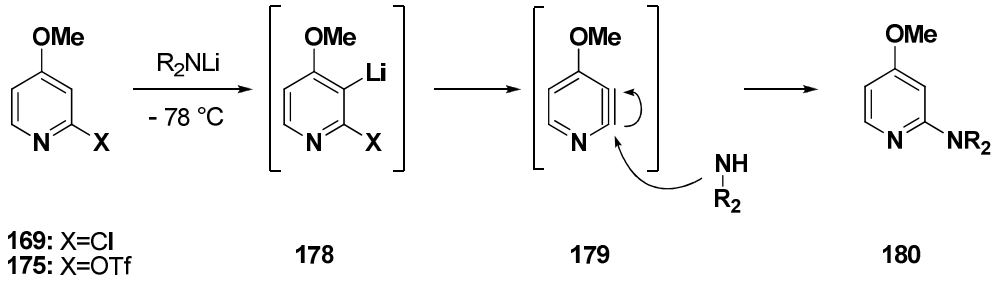
169: X = Cl
175: X = OTf

1: X = Cl
177: X = OTf

Reagents and Conditions: (i) LDA, THF, −78 ºC, 1 h; (ii) I_2, THF, −78 ºC, 1 h. 75% for **1**. 0% for **177**.

Scheme 37: *ortho*-Lithiation of 2,3-pyridyne precursors

Based on these results, reactions were conducted using both precursors under pyridyne forming conditions in the presence of furan in an attempt to trap any intermediate arynes in [4 + 2] cycloadditions. Nucleophilic addition of the secondary amines to the 2-position of the pyridyne afforded the major side-product **180** (Scheme 38).[117,122,127]

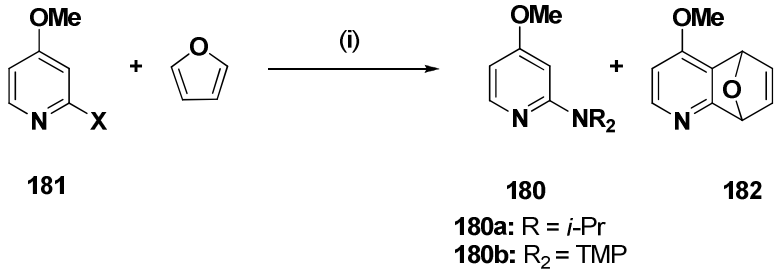


Scheme 38: Proposed mechanism for formation of side products in pyridyne cycloaddition reactions

Different lithium amide bases of varying bulkiness were employed with the aim of reducing the amount of these unwanted by-products (Scheme 39). In all cases the desired cycloadduct **182** was produced along with base addition products **180** and unreacted starting material was also detected (Scheme 39, Table 1).

These results demonstrate that the choice of base does not affect the result of the reaction employing chloroarene precursor **169**. The use of *n*-, *sec*- or *tert*-butyllithium to effect the *ortho*-lithiation was not feasible as they are known to undergo lithium-chlorine exchange with this molecule.[122]

The use of the triflate precursor **175** in conjunction with LiHMDS appeared promising (Entry 6) as no base-addition side products were initially observed. Unfortunately, all attempts to optimise this reaction to induce it to go to completion without the formation of by-products failed. Extended reaction times at low temperatures did not increase consumption of starting material and gentle warming resulted in the formation of the unwanted base-addition side products.



Reagents and Conditions: (i) See Table 1.

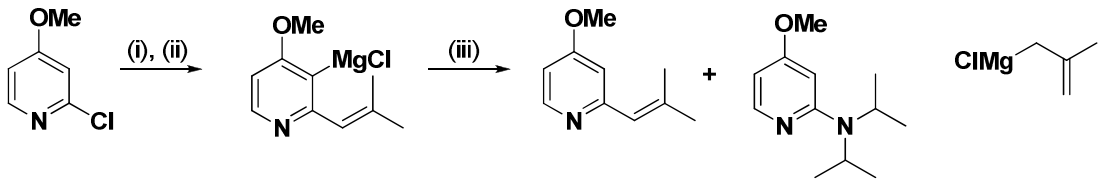
Scheme 39: Diels-Alder reactions between 2,3-pyridynes and furan

Table 1: Diels-Alder reactions between 2,3-pyridyne and furan

Entry[a]	X	Base	Ratio[d] of 181 : 180[e] : 182
1[b]	Cl	LDA	2.7 : 1.5 : 1
2[b]	Cl	LiTMP	2.5 : 1.5 : 1
3[b]	Cl	LiHMDS	SM recovered
4[c]	OTf	LDA	2.8 : 1 : 1.5
5[c]	OTf	LiTMP	1 : 1 : 1
6[c]	OTf	LiHMDS	1 : <0.1 : 1.5

[a]Typical reactions were carried out using 1.1 equiv. of base in anhydrous THF. [b]Deprotonation took place over 30 minutes at −78 °C then the reaction allowed to warm to rt overnight. [c]The reaction was maintained at −78 °C for 3 h. [d]Ratios determined by ^{1}H NMR analysis of the crude product. [e]NR_2 refers to the addition product from the base in question.

In order to test the potential of these precursors in reactions involving Grignard nucleophiles, 2-methylallylmagnesium chloride **(185)** was added to the lithiated species derived from 2-chloro-4-methoxypyridine **(169)** and warmed to room temperature, during which time pyridyne formation should have occurred (Scheme 40). A small amount of allylated pyridine **184** in which the double bond had isomerised in conjunction with the ring was isolated after column chromatography. The main product was the previously observed base-addition side product **180a** along with some unreacted starting material **169**.



Reagents and Conditions: (i) LDA, THF, −78 ºC, 1 h; (ii) 2-methylallylmagnesium chloride **(185)**, −78 ºC to rt, 16 h; (iii) H_2O, 3% **184**, 35% **180a**.

Scheme 40: Addition of allyl Grignard to 2,3-pyridyne

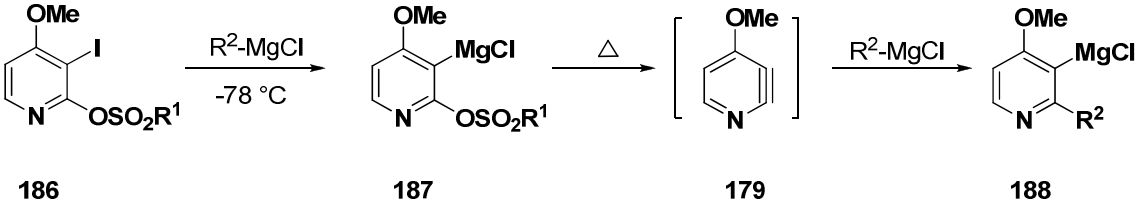
2.3 Metal-Halogen Exchange Pyridyne Precursors

2.3.1 Background

Although lithiation adjacent to the chlorine in precursor **169** is a controlled method of pyridyne formation, the disadvantage of this approach is the production of unwanted base-addition side products. The problem with precursor **175** is that collapse to pyridyne is spontaneous upon addition of base, so any nucleophile/diene that is to react with the pyridyne must be present in the reaction before the base is added and even then competitive addition of the base affords unwanted side products.

An alternative formation of arynes was reported by Knochel *via* the elimination of 2-magnesiated diaryl sulfonates following an iodine-magnesium exchange. This reaction was applied to both benzyne[53] and 3,4-pyridyne[116] formation (See Introduction, Scheme 9).

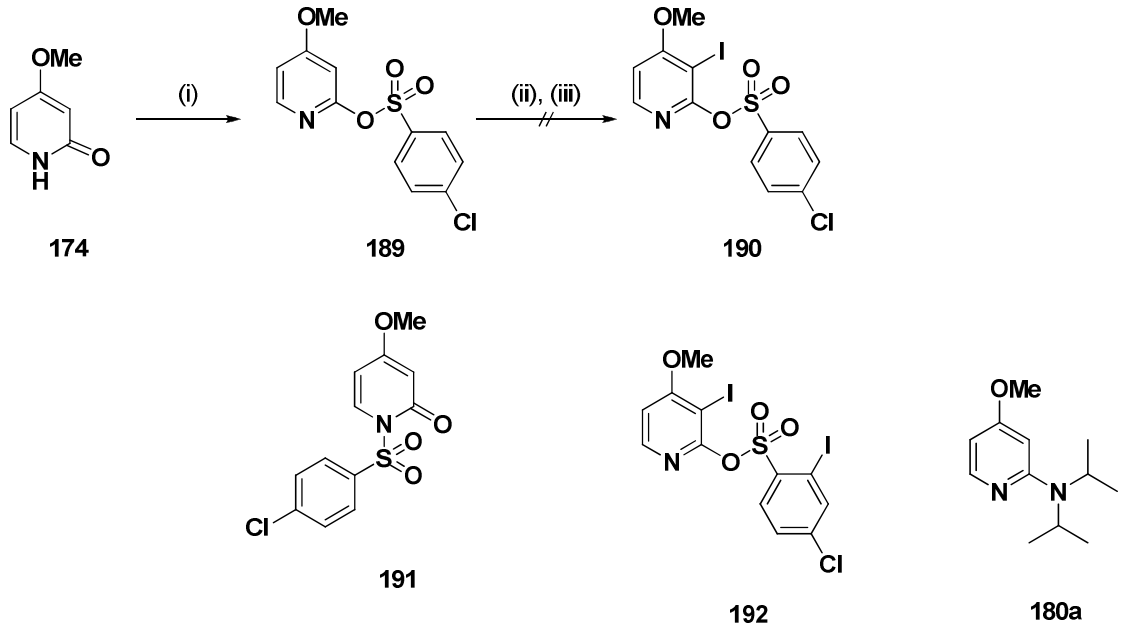
This methodology appears very attractive for extension to 2,3-pyridyne formation as neither of the two problems previously encountered are an issue in this case. Indeed it may be possible to further use this strategy advantageously by employing the same Grignard reagent to accomplish the iodine-magnesium exchange and to act as a nucleophile to attack the aryne (Scheme 41).



Scheme 41: Envisaged use of an I-Mg exchange precursor in 2,3-pyridyne reactions

2.3.2 Synthesis of Precursors

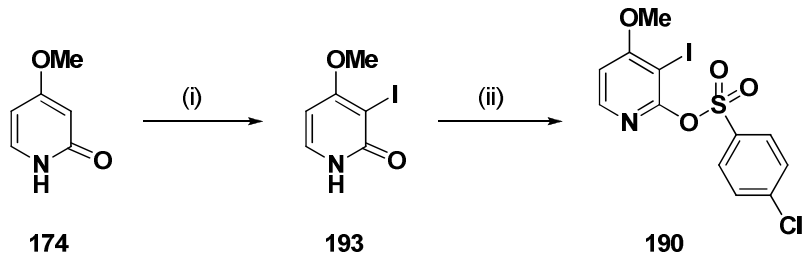
Knochel reported the best results were obtained using 4-chlorobenzenesulfonates. With this in mind, the aim was to synthesise an analogous 2,3-pyridyne precursor **190**, starting from 4-methoxy-2(1*H*) pyridone **(174)** (Scheme 42). The sulfonation was performed using 4-chlorobenzenesulfonyl chloride and both the desired sulfonate **189** and the corresponding *N*-sulfonated product **191** were isolated in 59 and 9% yield respectively. *ortho*-Lithiation in the 3-position with one equivalent of LDA, followed by quenching with one equivalent of iodine did not produce any of the desired iodinated compound **190**. The major product was identified as the doubly iodinated sulfone **192** in 43% yield, while the minor product amine **180a** (21% yield) is consistent with lithiation, elimination to the pyridyne and trapping with di-*iso*-propylamine (Scheme 42).



Reagents and Conditions: (i) 4-$ClC_6H_4SO_2Cl$, NEt_3, DMAP, CH_2Cl_2, rt, 16 h, 59%; (ii) LDA, −78 ºC, THF, 1 h; (iii) I_2, THF, −78 ºC, 1 h, 21% **180a**, 43% **192**.

Scheme 42: Double iodination of sulfonate **189**

Based on the previous results, reversing the order of the iodination and sulfonation would likely improve the synthesis of **190** (Scheme 43). Several iodination conditions were tested (Scheme 43, Table 2) for the regioselective iodination of pyridone **169** to **193**. The most promising result was iodine chloride generated *in situ* from sodium iodide and *N*-chlorosuccinimide.



Reagents and Conditions: (i) See Table 2; (ii) 4-$ClC_6H_4SO_2Cl$, NEt_3, DMAP, CH_2Cl_2, rt, 16 h, 19%.

Scheme 43: Synthesis of desired I-Mg exchange precursor

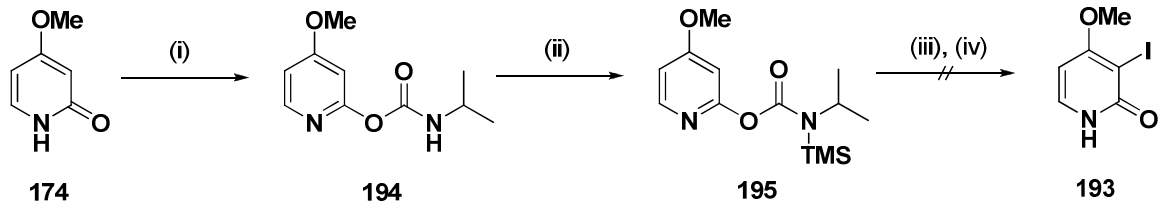
Table 2: Attempted Iodination of pyridone **174**

Entry	Conditions[a]	Yield[b] of 193/%
1	NIS, MeCN, rt, 16 h	0
2	NIS, CF_3SO_3H, rt, 16 h	20
3	NaI, NCS, AcOH-TFA (3:1 v/v), rt, 16 h	40
4	(i) *n*-BuLi, THF, rt, 30 min; (ii) I_2, THF, 4 h	25

[a]Typical reactions were conducted on a 25 mg scale. [b]Isolated yield after column chromatography.

Sulfonation was completed using the same conditions as before to afford the crude compound **190** in a modest yield. Isolation and purification were difficult as the product was unstable to silica gel chromatography and provided deleterious yields (Scheme 43). In this instance sulfonation also occurred predominantly on the nitrogen, likely due to the bulky nature of the *ortho*-substituent.

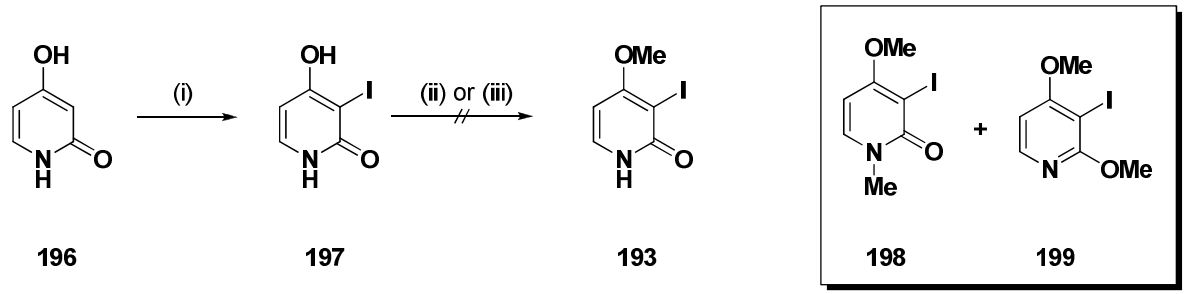
The next strategy employed Hoppe's iodination methodology,[133] involving *in situ* generation of an *N*-silylated *N*-*iso*-propyl carbamate **195** to direct lithiation. Unfortunately none of the desired iodination product **193** was observed (Scheme 44).



Reagents and Conditions: (i) *i*-PrNCO, 0.3 equiv. DMAP, THF, reflux, 72 h, 96%; (ii) TMSOTf, TMEDA, Et_2O, 0 °C to rt, 30 min; (iii) TMEDA, *n*-BuLi, −78 °C, 1 h; (iv) I_2, THF, −78 °C, 2 h then NaOH, EtOH.

Scheme 44: Attempted use of Hoppe's iodination methodology

An alternative strategy to iodo-pyridone **193** was also investigated to ascertain if the successful mono-methylation conditions found for pyridone **176** could be applied to this compound. Synthesis of iodide **197** was effected smoothly; however, the use of iodomethane and potassium carbonate at room temperature afforded a 1:1 mixture of overmethylated products **198** and **199** as well as unreacted starting material. The use of an alternative base, sodium hydride, and lowering the reaction temperatures followed by slow addition of methylating agent did not increase the selectivity (Scheme 45).

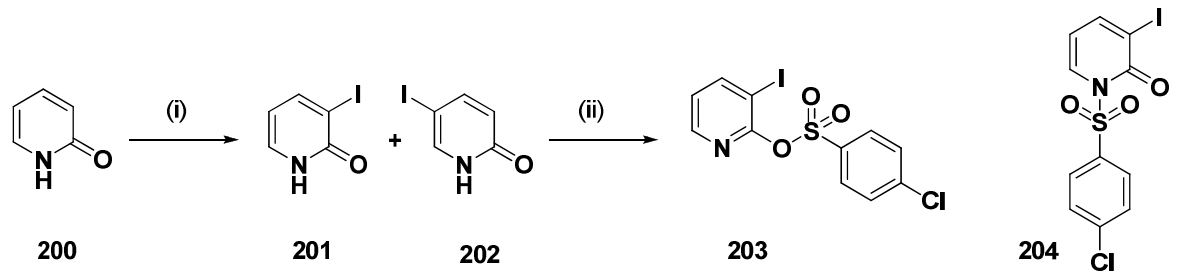


Reagents and Conditions: (i) I_2, Na_2CO_3, H_2O, dioxane, reflux, 20 h, 42%; (ii) MeI, K_2CO_3, DMF, rt, 18 h; (iii) MeI, NaH, DMF, 0 °C, 18 h.

Scheme 45: Attempted selective methylation of iodide **197**

Due to the problems associated with the synthesis of precursor **190**, it was thought that the use an alternative, simpler, precursor **203**, where no methoxy group is present, would be more appropriate.

Iodination of 2-hydroxypyridine **(200)** using *N*-iodosuccinimide in refluxing acetonitrile gave a mixture of *ortho*-**201**, *para*-**202** and di-iodinated products. Mono-iodinated compounds **201** and **202** could not be separated by chromatography or recrystallisation and hence were carried through to the next step as a mixture. Sulfonation gave a mixture of all four possible products (each was sulfonated on nitrogen and oxygen) which were separable, to afford desired precursor **203** and its *N*-sulfonated product **204** (Scheme 46).

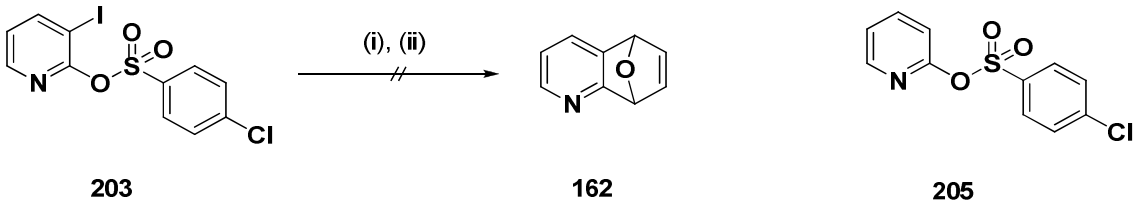


Reagents and Conditions: (i) NIS, MeCN, reflux, 18 h, 25%; (ii) NEt_3, DMAP, 4-$ClC_6H_4SO_2Cl$, CH_2Cl_2, rt, 16 h, 12% **203**.

Scheme 46: Synthesis of simple iodine-magnesium exchange precursor

2.3.3 Attempted Pyridyne Diels-Alder Reaction on 203

With **203** in hand, iodine-magnesium exchange was carried out using *iso*-propylmagnesium chloride at −78 ºC. However, addition of furan and warming resulted in only dehalogenation to form **205** and no desired **162** was observed. This result is consistent with the aryl Grignard reagent formed after halogen-metal exchange not collapsing to pyridyne at room temperature and protonation occurring when the reaction is quenched (Scheme 47).



Reagents and Conditions: (i) *i*-PrMgCl, THF, −78 ºC, 30 min or 2 equiv. *t*-BuLi, 12-crown-4, THF, −78 ºC, 30 min (ii) furan, −78 ºC to rt, 18 h.

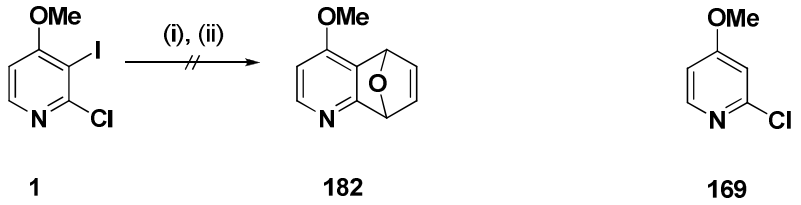
Scheme 47: Attempted Diels-Alder reaction employing iodide **203**

Although the magnesiated intermediate was stable at room temperature, it was hoped that the corresponding lithiated species might be less stable and collapse to the pyridyne at room temperature. However, lithium-iodine exchange with *tert*-butyllithium and warming in the presence of furan, afforded only dehalogenated compound **205**. Addition of 12-crown-4, to help prevent chelation of the lithiated species with the sulfone and hence aid elimination, was not successful either.

2.4 An Alternative Metal-Halogen Exchange Precursor

Due to the failure of the magnesiated and lithiated species of precursor **203** to eliminate, it was sought to test the potential use of a more accessible iodine-magnesium exchange precursor, 2-chloro-3-iodo-4-methoxypyridine **(1)** (Section 2.2.2). It was hoped that this species would undergo iodine-magnesium exchange at low temperatures and upon warming would eliminate lithium chloride to form 2,3-pyridyne.

Although iodine-magnesium exchange occurred readily at −78 °C, addition of furan and warming did not result in formation of cycloadduct **182**; only de-iodination was observed, to give **169** (Scheme 48).

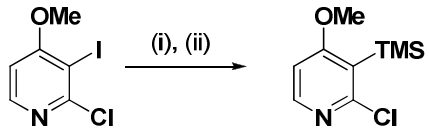


1 **182** **169**

Reagents and Conditions: (i) *i*-PrMgCl, −78 ºC, THF, 45 min; (ii) furan, −78 ºC to rt, 2 h.

Scheme 48: Attempted Diels-Alder reaction using an iodine-magnesium exchange strategy

As in the case of sulfonyl precursor **203**, it was then discovered that the lack of pyridyne formation was because the aryl Grignard formed after iodine-magnesium exchange is stable at room temperature. Indeed, it was trapped by chlorotrimethylsilane at this temperature to form **206** (Scheme 49).



1 **206**

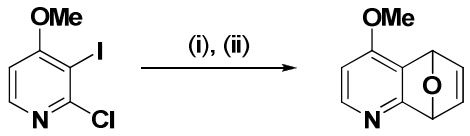
Reagents and Conditions: (i) *i*-PrMgCl, rt, THF, 30 min; (ii) TMSCl, rt, 16 h, 88%.

Scheme 49: Reaction to demonstrate stability of aryl Grignard formed after magnesium-iodine exchange at room temperature

The use of *iso*-propylmagnesium bromide as the exchange reagent or trying to heat the reaction in the presence of furan did not afford any of the desired product.

The next strategy was to employ an iodine-lithium exchange with *tert*-butyllithium with the expectation that the corresponding lithium species would collapse. This approach was considered promising due to the fact that (2-chloro-4-methoxypyridin-3-yl)lithium **(178)** does eliminate lithium chloride to generate pyridyne, as seen in the previous section.

Treatment of **1** with two equivalents of *tert*-butyllithium at low temperature, addition of furan and warming to room temperature afforded, gratifyingly, the only characterisable product of the reaction by ^{1}H NMR as the desired [4 + 2] cycloadduct **182** in 35% yield. No base-addition side products, starting materials, or de-iodinated products were observed. The remainder of the mass balance was assumed to be insoluble polymeric material (black residue in the reaction flask) (Scheme 50). This was an excellent result as this is comparable in yield to the 37% obtained by Hegarty's *ortho*-lithiation approach with a methoxy stabilised precursor[122] and only slightly less than Walters' optimised cycloaddition yield of 43% with a similar alkoxy-stabilised metal-bromine exchange precursor.[123]

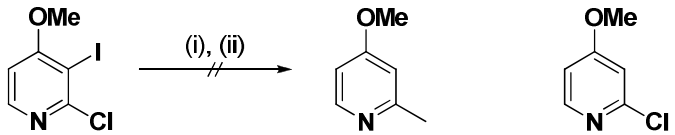


1 **182**

Reagents and Conditions: (i) 2 equiv. *t*-BuLi, THF, −78 ºC, 30 min; (ii) furan, −78 ºC to rt, 18 h, 35%.

Scheme 50: Diels-Alder cycloaddition of 2,3-pyridyne with furan

After this promising result, nucleophilic additions were then attempted with various carbon nucleophiles. Reaction with an excess of methyl magnesium chloride after the iodine-lithium exchange and warming did not give any of the desired product **207**, only de-iodinated **169** (Scheme 51).

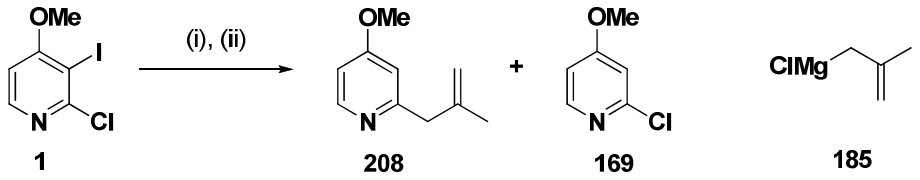


1 **207** **169**

Reagents and Conditions: (i) 2 equiv. *t*-BuLi, THF, −78 ºC, 30 min; (ii) 5 equiv. MeMgCl, −78 ºC to rt, 18 h.

Scheme 51: Attempted addition of methyl magnesium chloride to 2,3-pyridyne

Changing to a different Grignard reagent, (2-methylallyl)magnesium chloride **(185)** was more encouraging. The desired addition product **208** was achieved in a 15% yield, again along with **169** and insoluble polymeric material (Scheme 52).

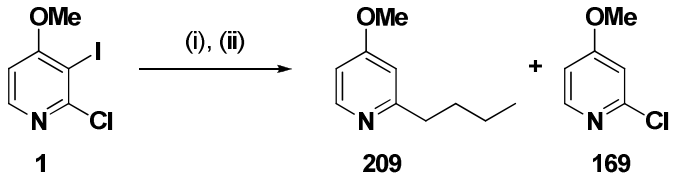


1 208 169 185

Reagents and Conditions: (i) 2 equiv. *t*-BuLi, THF, −78 ºC, 30 min; (ii) 1.5 equiv. **185**, −78 ºC to rt, 18 h, 15%.

Scheme 52: Addition of 2-methyl allylmagnesium chloride reagent to 2,3-pyridyne

An alkyllithium nucleophile was also investigated, namely *n*-butyllithium. Again, nucleophilic addition was achieved to give **209** in 13% yield with de-iodinated **169** (Scheme 53).

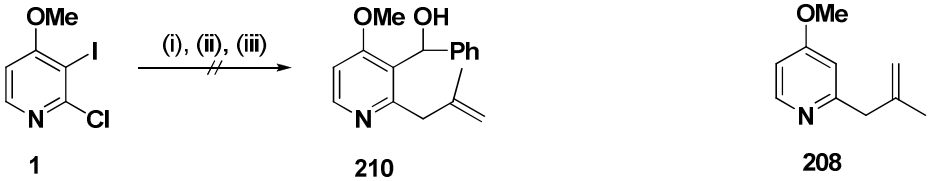


1 209 169

Reagents and Conditions: (i) 2 equiv. *t*-BuLi, THF, −78 ºC, 30 min; (ii) 1.5 equiv. *n*-BuLi, −78 ºC to rt, 18 h, 13%.

Scheme 53: Addition of alkyllithium to 2,3-pyridyne

Unfortunately, an attempt at a three-component coupling using benzaldehyde as the electrophile did not afford desired alcohol **210**; only addition product **208** was isolated, in a 10% yield (Scheme 54).

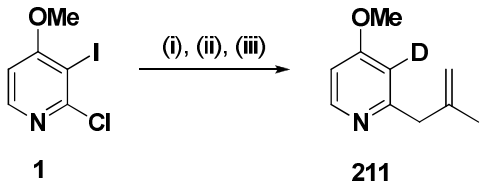


1 210 208

Reagents and Conditions: (i) 2 equiv. *t*-BuLi, THF, −78 ºC, 30 min; (ii) 1.5 equiv. **185**, −78 ºC to rt, 2 h; (iii) PhCHO, −78 ºC.

Scheme 54: Attempted three-component coupling reaction of 2, 3-pyridyne

Attempting to quench the *ortho*-anion with D_2O rather than H_2O to give **211** (Scheme 55), did indicate some product formation by GC-MS. Unfortunately isolation of this species was not possible, most likely due to the low yields of this compound compared to the undesired side-products and polymeric material.



1 **211**

Reagents and Conditions: (i) 2 equiv. *t*-BuLi, THF, −78 ºC, 30 min; (ii) 1.5 equiv. **185**, −78 ºC to rt, 2 h; (iii) D_2O, rt.

Scheme 55: D_2O Quench, following nucleophilic attack of Grignard reagent

2.5 Conclusions and Future Work

A novel metal-halogen 2,3-pyridyne precursor, namely, 2-chloro-3-iodo-4-methoxypyridine **(1)** has been synthesised. Although magnesium-iodine exchange failed to generate 2,3-pyridyne with this precursor, lithium-halogen exchange with *tert*-butyllithium was able to promote pyridyne formation as evidenced by trapping in a Diels-Alder reaction with furan, in a comparable yield to other methods in the literature.

The nucleophilic addition of simple Grignard reagents and alkyllithiums to this intermediate was demonstrated in low yields and with minimal isolable side-products, albeit the formation of polymeric nitrogen-containing insoluble material was an unresolved problem in all reactions. Although GC-MS analysis indicated that the anion generated following nucleophilic attack could be quenched with deuterium oxide, neither this species nor other 3-component coupling products could be isolated, most likely due to the very low yields associated with such compounds.

Future work would be to carry out a more detailed temperature profile. If the exact temperature of elimination to pyridyne could be established, the reaction could be held at this intermediate temperature, reducing the concentration of aryne present, thereby possibly reducing the amount of polymerisation.

Chapter 3: Introduction to Aryl Amino Acids, α-Arylation Reactions and Enolate Additions to Arynes

3.1 Aryl Amino Acids

The ability to synthesise both tertiary (R = H) and quaternary (R = alkyl, aryl) unnatural aryl amino acids **212** (Figure 12), has facilitated their application in multiple areas of organic chemistry.

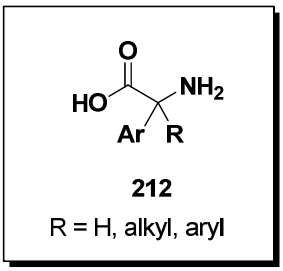


Figure 12: Aryl amino acids

Such units are found in a multitude of biologically interesting natural products and have been incorporated into several drug molecules (Figure 13).

The glycopeptide antibiotics, including vancomycin[134] **(213)** and teicoplanin[135] amongst others,[136-138] contain peptides with contain 3- and 5-arylglycine residues respectively. A family of naturally-occurring β-lactam antibiotics, with the most active member being nocardicin A[139] **(216)**, all contain a *para*-phenolic glycine moiety. Several synthetic antibiotics such as cephalexin[140] **(215)** and cefrozil[141] **(218)** also include phenylglycine side chains, which are known to help increase oral absorption of these drugs. Clopidogrel[142] **(217)**, an anti-coagulant used in the treatment of cardiovascular disease, incorporates a chloro-substituted aryl amino acid unit. An example of an antibiotic natural product containing a quaternary aryl glycine type unit is fumimycin[143] **(214)**.

Beyond well established medicinal compounds, the incorporation of aryl amino acids into peptidomimetics is also an important field of research. Replacing a natural amino acid residue with a more hydrophobic aryl analogue not only affects lipophilicity, but also secondary structure and hence conformational rigidity.[144-148] Quaternary aryl amino acids in particular[149] can restrict conformational flexibility, and impart increased resistance to both enzymatic and chemical degradation in foldamers containing these units.

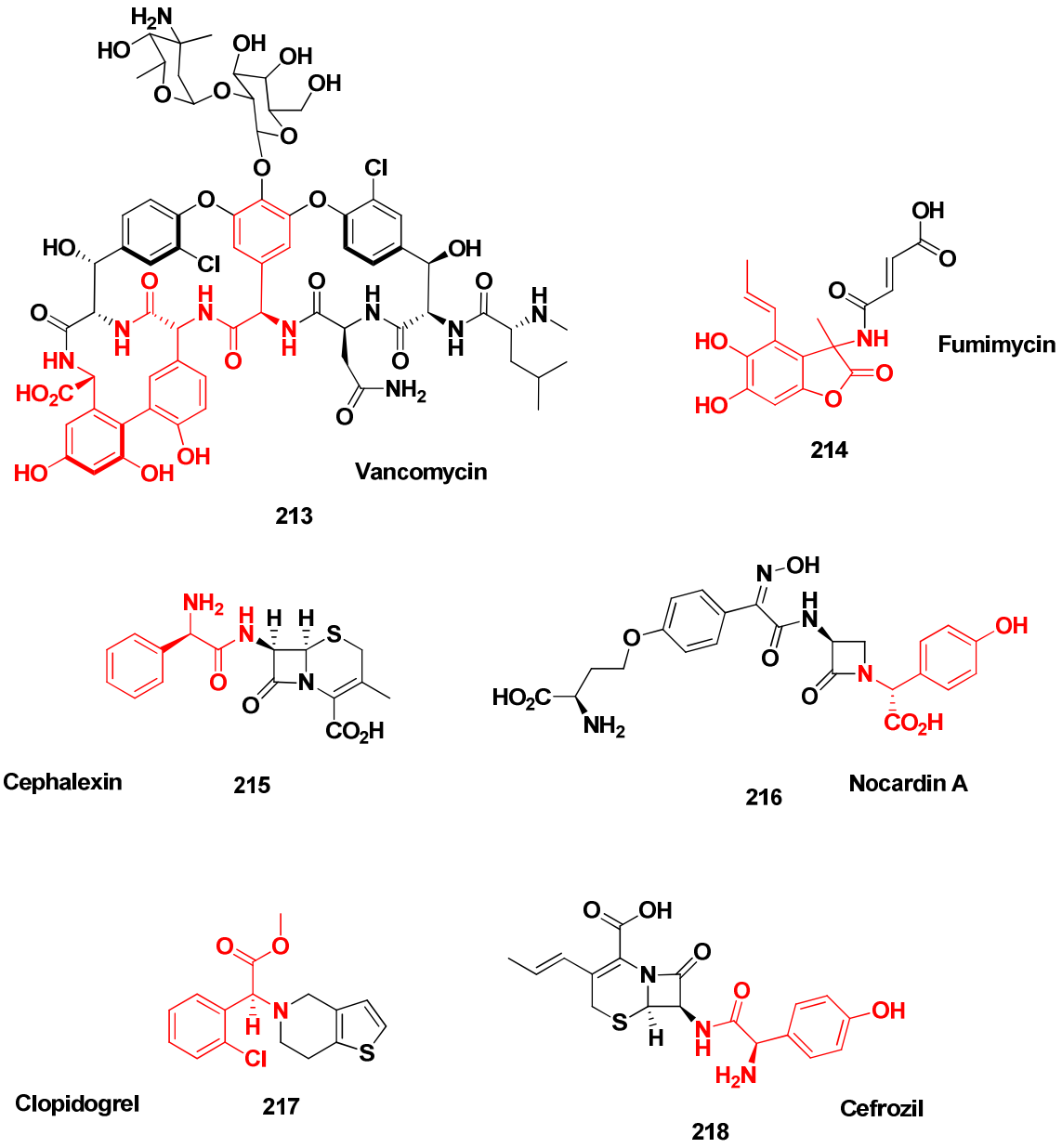


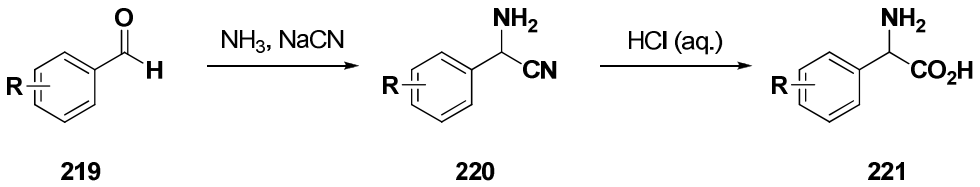
Figure 13: Biologically active molecules containing arylglycine residues

Novel routes to arylglycines are currently key goals within the scientific community.[150] Of particular interest is the development of catalytic, asymmetric routes to α-aryl amino acids, as not only does this encourage the development of novel disconnections but also could increase the scope of substitution patterns that ccould be incorporated within the aryl ring, which could enable the construction of improved biologically active molecules.

In this Chapter, a brief review of synthetic strategies to afford aryl glycines will be described, followed by the proposed incorporation of aryne chemistry into this rapidly growing field of research.

3.2 α-Arylation Reactions of Amino Acid Derivatives

Traditional methods towards chiral arylglycines require starting materials already containing the crucial carbon-aryl bond. The Strecker reaction is an efficient way to generate a diverse array of arylglycines. Reaction of an aryl aldehyde **219**, ammonia and a cyanide source produces α-aminoarylacetonitrile derivatives **220** which, upon acidic hydrolysis, afford the desired arylglycines **221** (Scheme 56).[151]



Scheme 56: Classical Strecker synthesis of arylglycines

Due to the high acidity of the α-aryl proton, late-stage resolution approaches are often applied after racemic syntheses, such as the separation of diastereomeric salts[152] or dynamic kinetic resolution.[153]

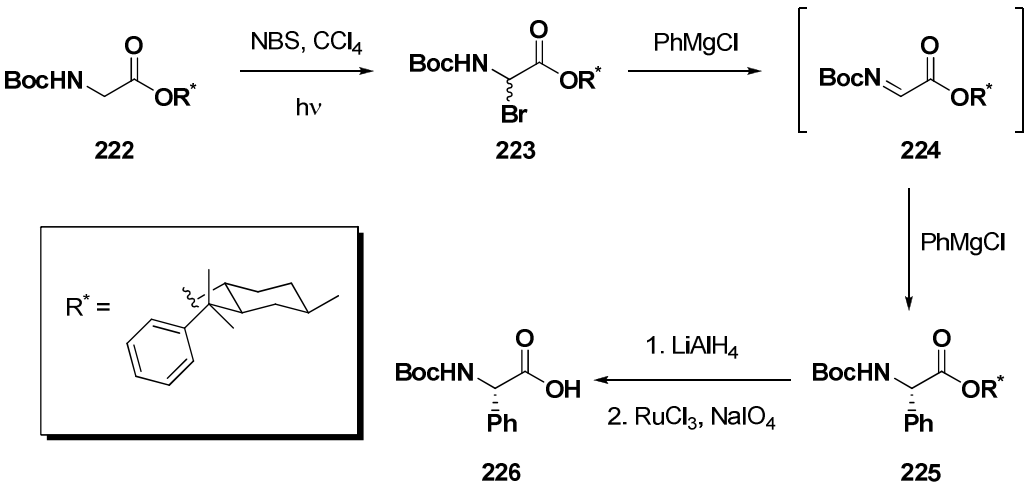
The pioneering work of many research groups over the last 50 years has produced a large tool box of asymmetric aryl glycine syntheses, beginning with the emergence of asymmetric variants of the Strecker synthesis.[154] A large number of stereoselective methods for generating such species with the vital carbon-aryl bond in place have been developed including the nucleophilic and electrophilic amination of α-substituted acids and the aminohydroxylation of styrenes. There are several excellent reviews on this topic.[150,152,155,156]

This section will contain a brief review of various asymmetric methods for synthesising α-aryl amino acids that require generating the aryl stereocentre, namely α-arylation type reactions, as this is directly relevant to the proposed use of arynes in these reactions. This review is by no means exhaustive but gives an overview of main reaction trends.

3.2.1 α-Arylations Employing Electrophilic Glycine Equivalents

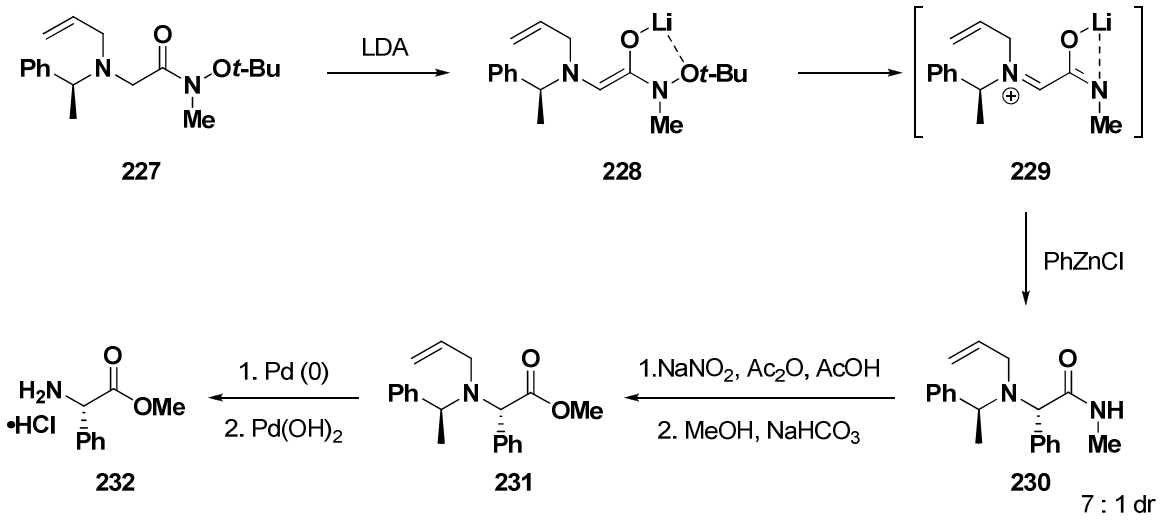
Due to a long history and understanding of nucleophilic aryl species such as Grignard reagents, it is logical that a number of α-arylation reactions use these compounds in conjunction with electrophilic glycine partners. Common amino acid derivatives with umpolung, electrophilic reactivity at the α-position are α-imino or α-iminium acetates, with chiral auxiliaries to control the stereochemistry of the reaction.

In 1988, Obrecht used an imine generated *in situ* for such a transformation.[157] *N-tert*-Butoxy carbonyl protected (-)-8-phenylmenthol **(222)** was brominated with *N*-bromosuccinimide to afford **223** which when treated with an excess of phenylmagnesium chloride promoted elimination of HBr to generate imine **224**. The metalated aryl species then adds to the imine from the less hindered face to give **225**. A reduction-oxidation sequence of the ester then afforded *N-tert*-butoxy carbonyl phenylglycine **(226)** in 82% ee and 78% yield (Scheme 57).



Scheme 57: Obrecht's synthesis of *N-tert*-butoxy carbonyl phenylglycine

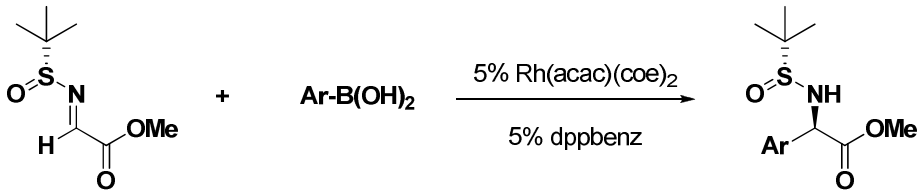
An example of an *in situ* generated iminium electrophile was demonstrated by Somfai.[158] Deprotonation of chiral Weinreb amide **227** with LDA generated enolate **228**, which subsequently underwent elimination of *tert*-butoxide by the lone pair on the conjugated nitrogen centre to reveal the desired iminium ion **229** which was trapped with PhZnCl to give amide **230** in a 7 : 1 dr. Separation of the diastereoisomers, conversion into methyl ester **231** and subsequent deallylation and hydrogenolysis gave enantiomerically pure **232** (Scheme 58).



227 228 229 230 231 232

Scheme 58: Synthesis of phenylglycine **232** *via* attack of PhZnCl on *in situ*-generated iminium

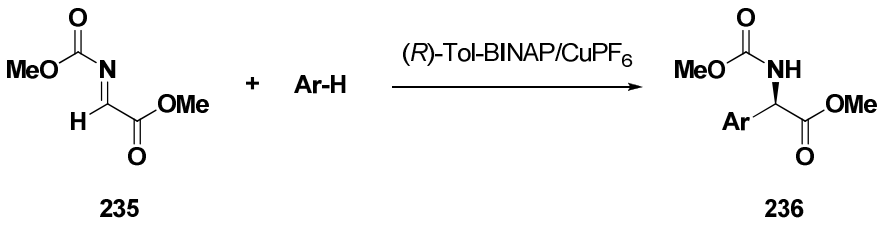
As an extension of the well precedented chiral amine synthesis, Ellman and co-workers employed the *tert*-butylsulfinamine auxiliary for the synthesis of aryl amino acids. A pre-formed chiral sulfinylimino ester **233** was the substrate for a rhodium-catalysed addition of arylboronic esters to produce protected aryl amino acids **234** in excellent yields and enantiopurity (Scheme 59).[159]



233 234

Scheme 59: Ellman's synthesis of protected arylglycines

An alternative strategy employs electrophilic glycines in a classical Friedel-Crafts reaction. Jørgensen's catalytic enantioselective *aza*-Friedel-Crafts reaction between electron-rich aromatic compounds and iminoesters **235** is an excellent example of this approach. The use of a copper-based, chiral Lewis acid complex imparts the stereocontrol in this reaction, affording aromatic α-amino acids **236** (Scheme 60).[160]

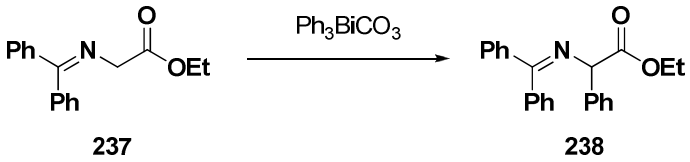


Scheme 60: Aza Friedel-Crafts reaction to give optically active protected aryl amino acids

3.2.2 α-Arylations Employing Nucleophilic Glycine Equivalents

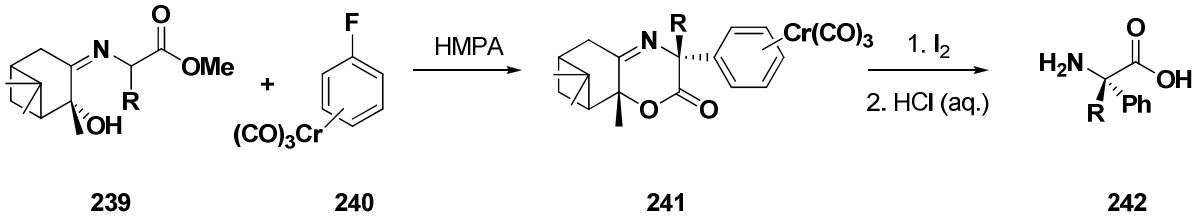
A variety of α-arylation methodologies have been established which exploit the natural reactivity of the α-carbon in glycine *via* enolate formation.

In 1989 O'Donnell[161] reported the monophenylation of imine **237** employing triphenylbismuth carbonate[162] as the *C*-phenylating reagent under neutral conditions (Scheme 61).



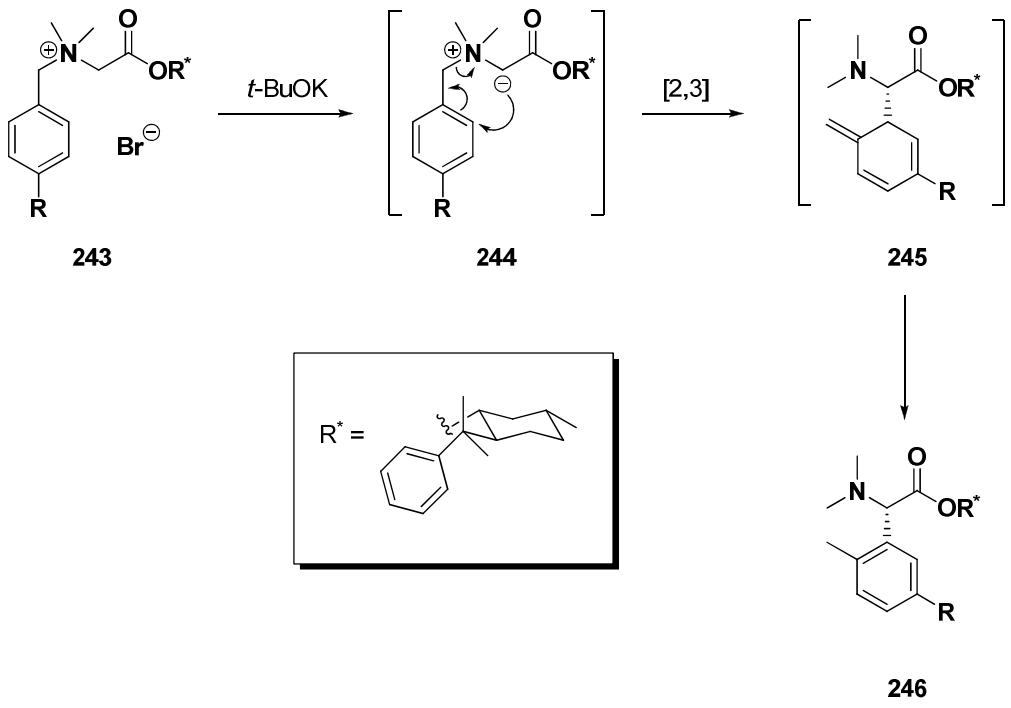
Scheme 61: O'Donnell's phenylation reaction

Lavergne subsequently developed an asymmetric α-arylation by the addition of the enolate of chiral imine **239** to an electrophilic aryl source, fluorobenzene tricarbonylchromium complex **(240)**. Decomplexation and hydrolysis furnished the final quaternary aryl amino acids **242** (Scheme 62).[163] However, reaction conditions were harsh and as a result the diastereoselectivity was modest (approx. 3 : 1 dr).



Scheme 62: Lavergne's asymmetric synthesis of α-aryl amino acids

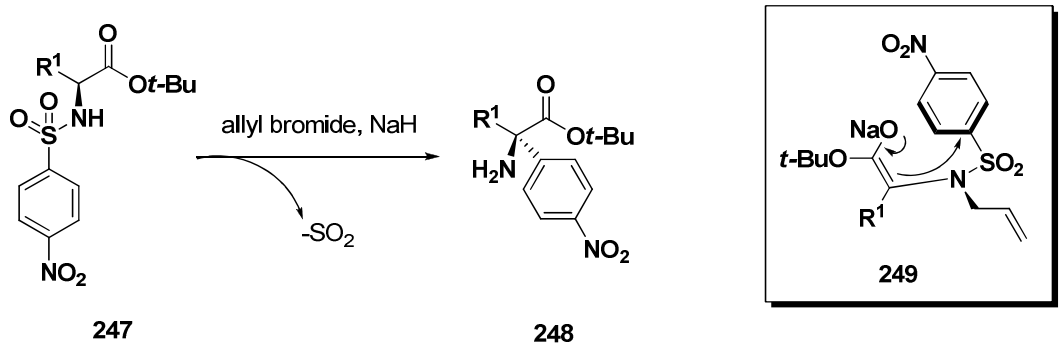
Another efficient route to optically active aryl-amino acids uses the Sommelet-Hauser rearrangement. Tayama demonstrated that *N*-benzylic ammonium ylides **244** derived from *N*-benzylic ammonium glycine (−)-8-phenylmenthol ester **243** underwent a [2,3] sigmatropic shift to give acid derivatives **246** with high levels of stereoselectivity (Scheme 63).[164]



243 **244** **245** **246**

Scheme 63: Asymmetric Sommelet-Hauser rearrangement of *N*-benzylic ammonium salts

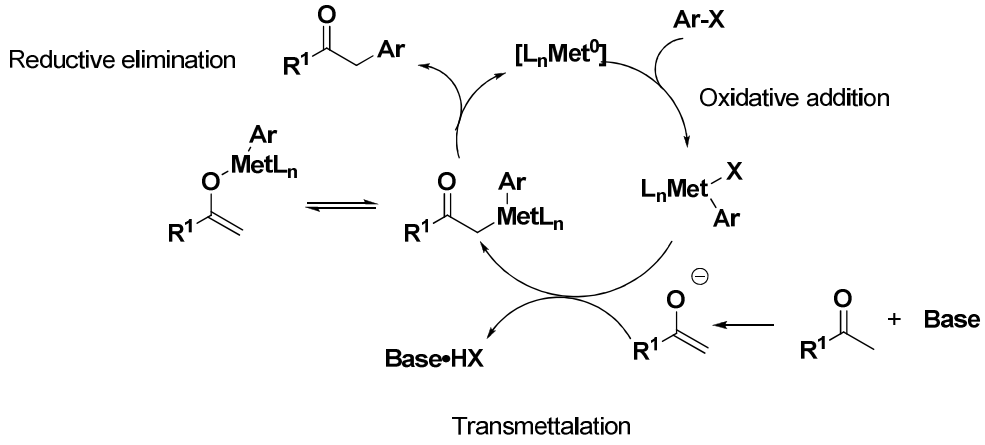
An interesting rearrangement published by Lupi showed an intramolecular *N*→*C* migration of a *para*-nitrophenyl group and the loss of sulphur dioxide, triggered by *N*-allylation of nosyl protected amido-ester **247**. The stereochemistry is transferred from the *N*-alkylated sulfonamide to the final product **248** *via* memory of chirality from the stabilised non-racemic enolate **249** (Scheme 64).[165]



Scheme 64: Lupi's intramolecular α-arylation

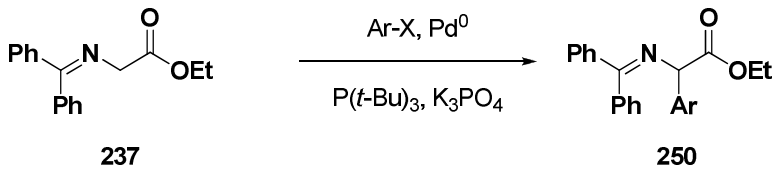
3.2.3 Palladium-Catalysed α-Arylations

The introduction of the metal-catalysed α-arylation of carbonyl compounds has led to a rapid growth of research into this area over the past decade.[166,167] The mechanism proceeds *via* a metal enolate which undergoes transmetallation with the oxidation product of the transition metal and the aryl halide. Finally reductive elimination generates a new C-C bond (Scheme 65).



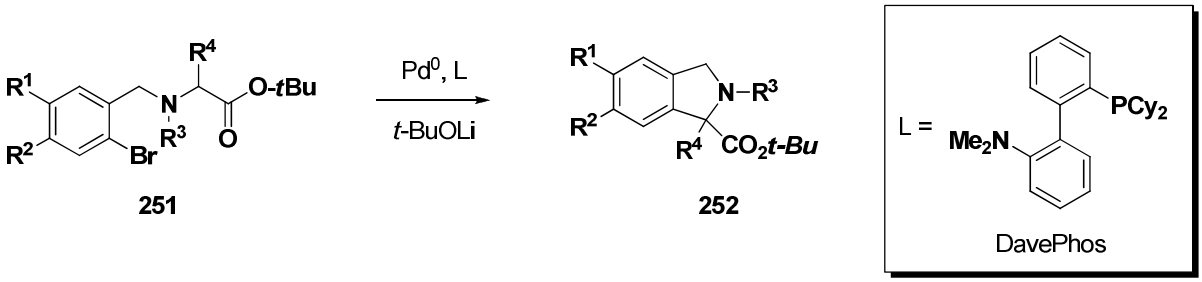
Scheme 65: Catalytic cycle for metal catalysed α-arylation of carbonyl compounds

In 2001 Hartwig and co-workers[168] were the first to demonstrate a palladium-catalysed α-arylation of a protected amino acid. It was shown that imine **237** would undergo α-arylation with a wide range of arylhalides using P(*t*-Bu)$_3$ as a ligand and K_3PO_4 as base (Scheme 66).



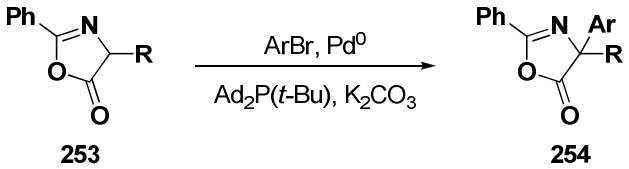
Scheme 66: Hartwig's palladium-catalysed α-arylation of protected amino acids

One year later, using a similar C-H activation strategy, Buchwald[169] reported the palladium-catalysed intramolecular α-arylation of amino acid esters **251**, generating tertiary (R^4 = H) and quaternary (R^4 = alkyl) dihydro-*iso*-indole esters **252** (Scheme 67).



Scheme 67: Buchwald's intramolecular α-arylation

Hartwig[170] subsequently reported an α-arylation of aza-lactones **253** to afford quaternary aryl amino acid derivatives **254** (Scheme 68).

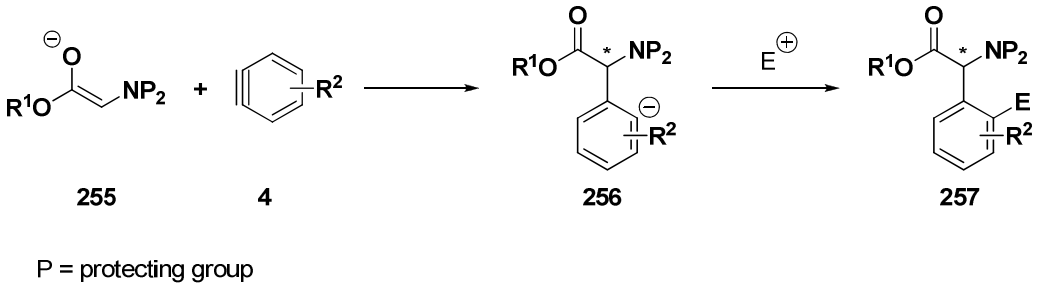


Scheme 68: Hartwig's α-arylation of aza-lactones

Although these techniques are vastly superior methods of generating aryl amino acids, there has yet to be an asymmetric variant reported.

3.3 Synthetic Plan

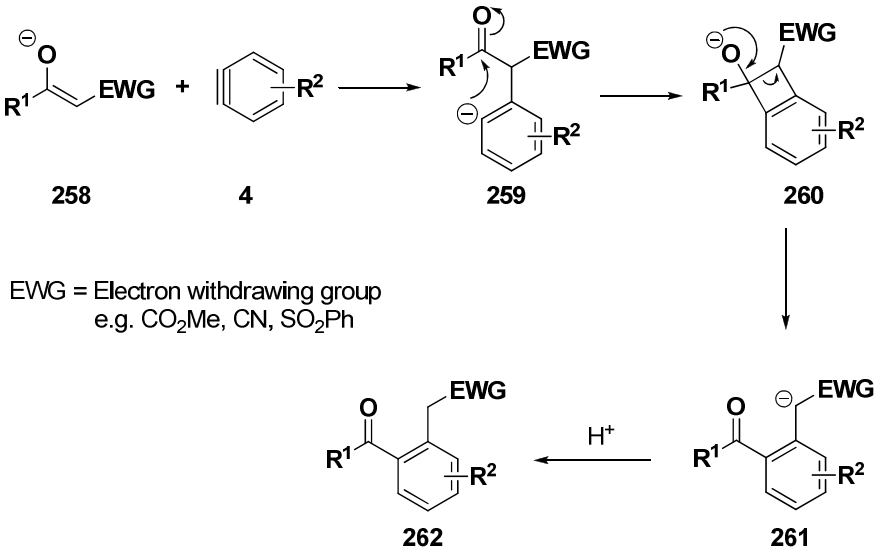
Arynes are extremely attractive candidates for the α-arylation of glycines and other enolisable starting materials. Their intrinsic electrophilicity should allow for nucleophilic addition by a suitably protected glycine enolate **255** and then subsequent reaction of the resulting anion **256** with electrophiles should provide diverse derivatives of phenylglycine **257** (Scheme 69). Use of a chiral auxiliary ($R^1 = R^*$) should control the stereochemistry of the reaction.



Scheme 69: Proposed aryne three-component coupling reaction involving protected glycine enolates

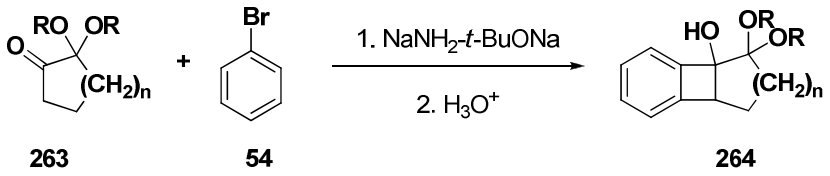
3.4 Addition of Enolates to Arynes

Before embarking on endeavours towards the α-arylation of glycine using arynes, it is important to give a brief historical overview of previous additions of enolates to arynes. As discussed in Chapter 1 (Section *1.4.2.3*), the addition of stabilised enolates to arynes, results in a formal C-C insertion reaction (Scheme 70).



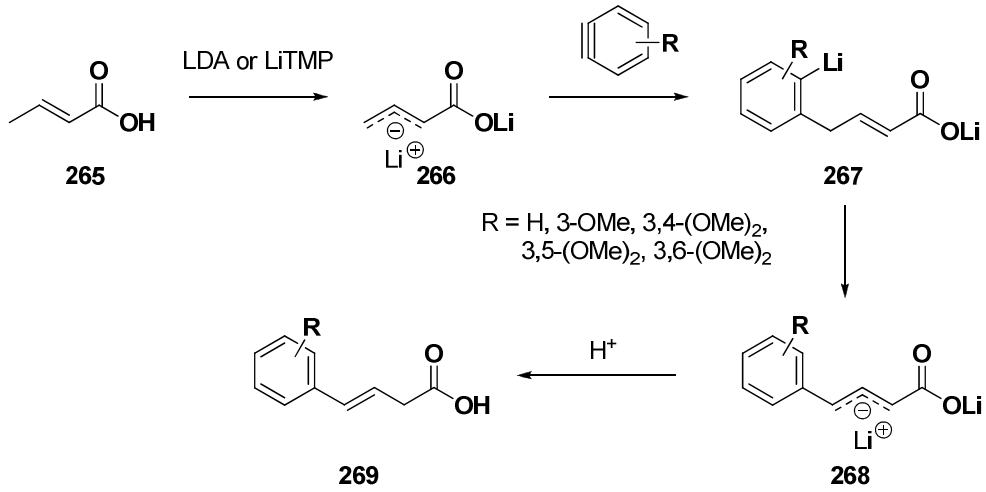
Scheme 70: Addition of stabilised enolates to arynes; formal C-C bond insertion reactions

Between 1978 and 1991, Caubere published a series of papers in which he documented the addition of cyclic ketone enolates to arynes.[171-174] When cyclic ketones **263** were treated with complex base $NaNH_2$-*t*-BuONa in the presence of bromobenzene **(54)**, benzocyclobutenols **264** were afforded after work-up, again due to cyclisation of the aryl anion onto the ketone (Scheme 71).



Scheme 71: Formation of benzocyclobutenols by the addition of cyclic ketone enolates to arynes

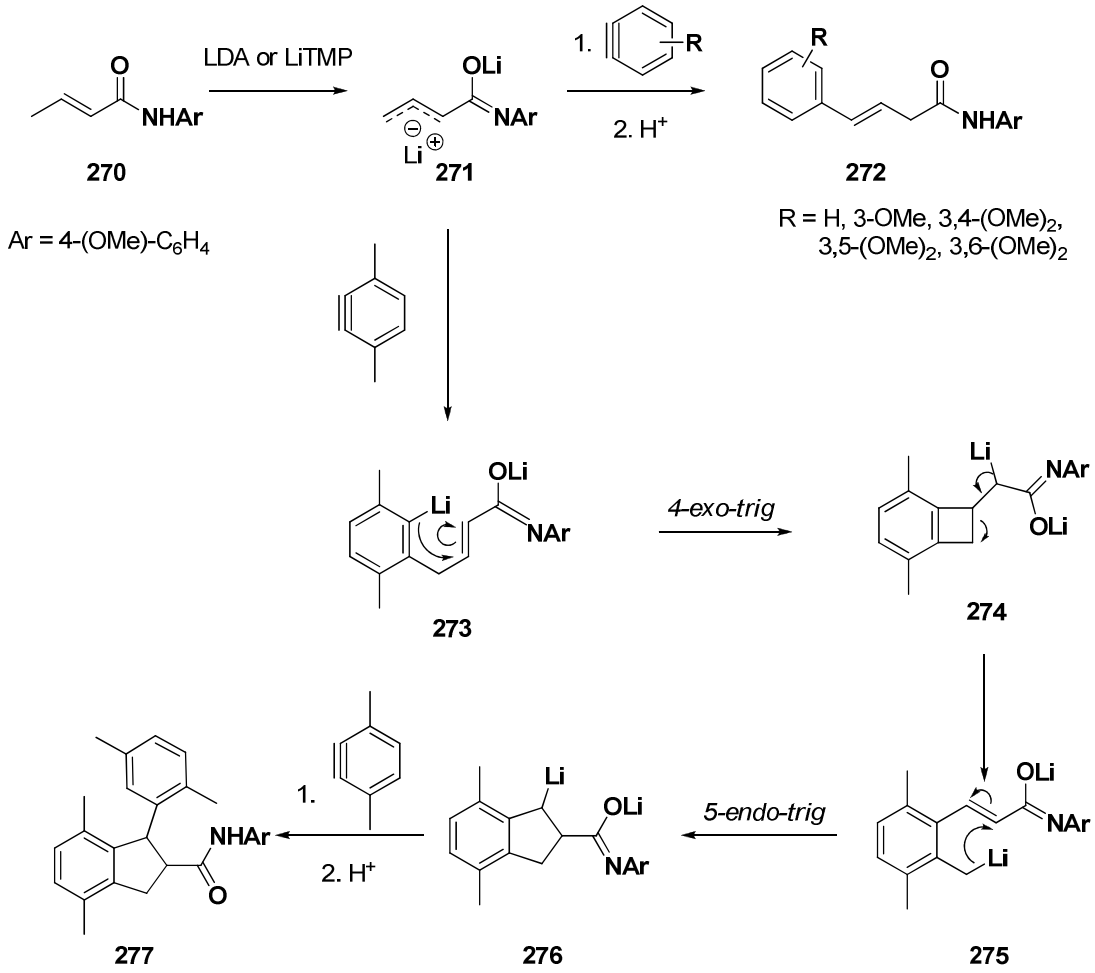
Biehl[175] reported the outcome when 2-butenoic acid dianion **(266)** was reacted with methoxy-substituted arynes. Arylation occurs exclusively in the 4-position of this extended enolate to form **267**, which after proton transfer and proton quench gave 4-arylated acid **269** (Scheme 72).



Scheme 72: Reaction of 2-butenoic acid dianion **266** with methoxybenzynes

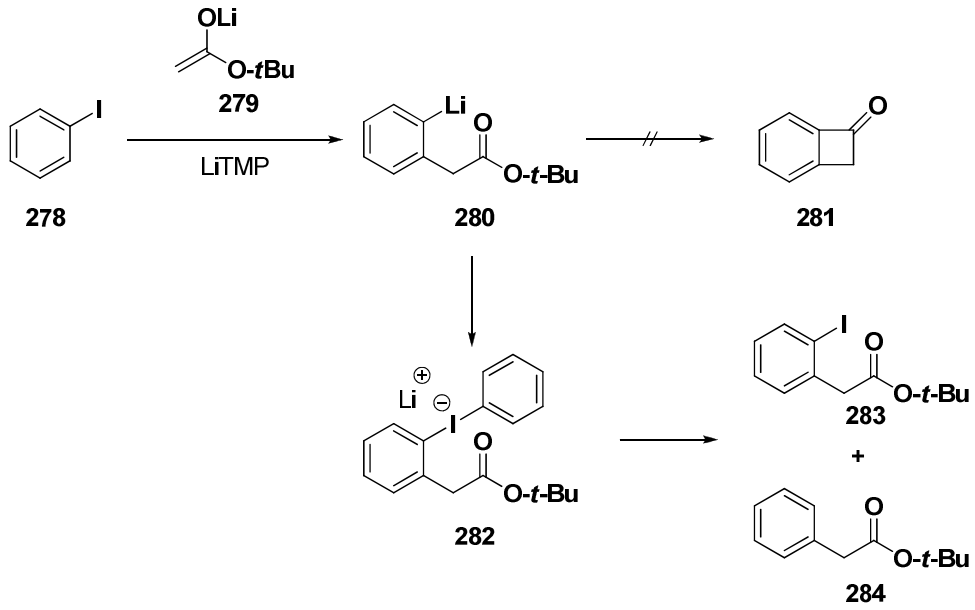
A similar result[175] was observed for the corresponding *N*-(4-methoxyphenyl)amide dianion **(271)** when reacted with similar methoxy substituted arynes, to generate amides **272** (Scheme 73). However when dimethylbenzyne was used in its place, a rearrangement reaction took place to afford indane **277** as the major product.[176] In this instance, after nucleophilic attack of the extended enolate, the aryl anion **273** undergoes a *4-exo-trig* cyclisation onto the α,β-unsaturated system to give cyclobutane **274** which upon ring opening affords benzyl anion

275. The dianion can then undergo a *5-endo-trig* cyclisation to form lithiated intermediate **276** which after addition to another equivalent of dimethylbenzyne and work-up gave indane **277** in 51% yield (Scheme 73).



Scheme 73: Biehl's observation of different products in the reaction of *N*-(4-methoxyphenyl)-2-butenamide **270** with various substituted arynes

The only example in the literature when the anion following nucleophilic attack of a non-extended enolate to benzyne does not cyclise onto the carbonyl group, was described by Durst.[177] Addition of *tert*-butyl ester enolate **279** to the benzyne derived from iodobenzene **(278)** and LiTMP does not undergo cyclisation to cyclobutanone **281** as formation of hypervalent iodine (ate) complex **282** is faster. Transfer of iodine from **282** afforded the major product **283** and fragmentation gave the minor product **284** (Scheme 74).



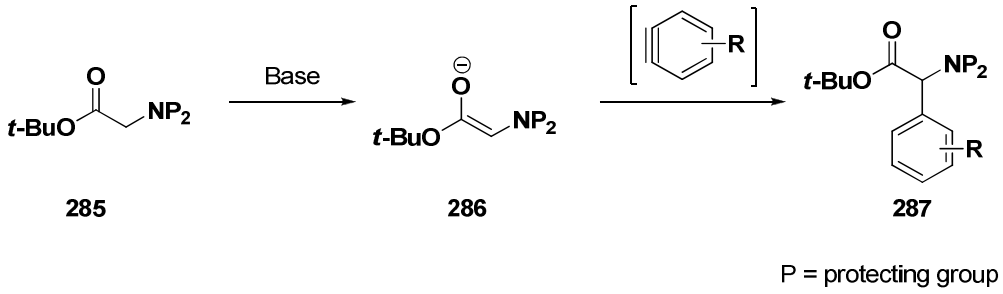
Scheme 74: Addition of enolate to benzyne followed by hypervalent iodine (ate) complex formation

Chapter 4: Results and Discussion: Investigations into the Addition of Protected Glycine Enolates to Arynes

4.1 Introduction

Before any multi-component coupling reactions or stereoselective syntheses could be conducted, the first task was to investigate the reactivity of glycine enolates in α-arylation reactions with benzyne. Little precedent exists for this reaction and previous reports of enolate addition to benzynes demonstrate that the resultant aryl anion cyclises onto the carbonyl group (see Section 3.4), therefore it was anticipated that this would be a challenging transformation.

The choice of the glycine enolate **286** was consequently crucial to the success of the reaction. It was decided to protect the carboxylic acid moiety as the corresponding *tert*-butyl ester. As most examples report cyclisation of the carbanion onto ketones or in a few cases methyl esters, it was envisaged that the sterically hindered *tert*-butyl ester would suppress this undesired pathway. The amine functionality must also be suitably protected so as to be inert to the reaction conditions (Scheme 75).

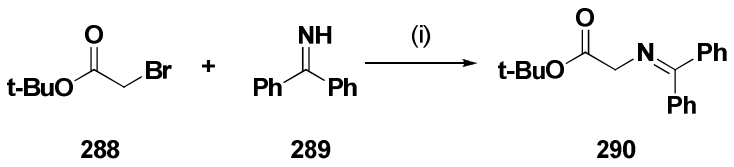


Scheme 75: Proposed addition of protected glycine **286** to benzyne

4.2 The Use of Benzophenone Imine Protected Glycine Derivatives

The first protected glycine to be examined was benzophenone imine **290**. This is easily prepared, and the methylene protons readily deprotonated with relatively mild bases. The free amine can be liberated following the reaction by weak acid hydrolysis of the imine. These compounds have previously been employed in the preparation of α-amino acids, particularly in combination with phase-transfer catalysis.[178,179]

tert-Butyl 2-bromoacetate **(288)** and benzophenonimine **(289)** were treated with di-*iso*-propylethylamine to give the desired imine **290** in 99% yield (Scheme 76).[180]



288 **289** **290**

Reagents and Conditions: (i) *i*-Pr_2NEt, MeCN, reflux, 12 h, 99%.

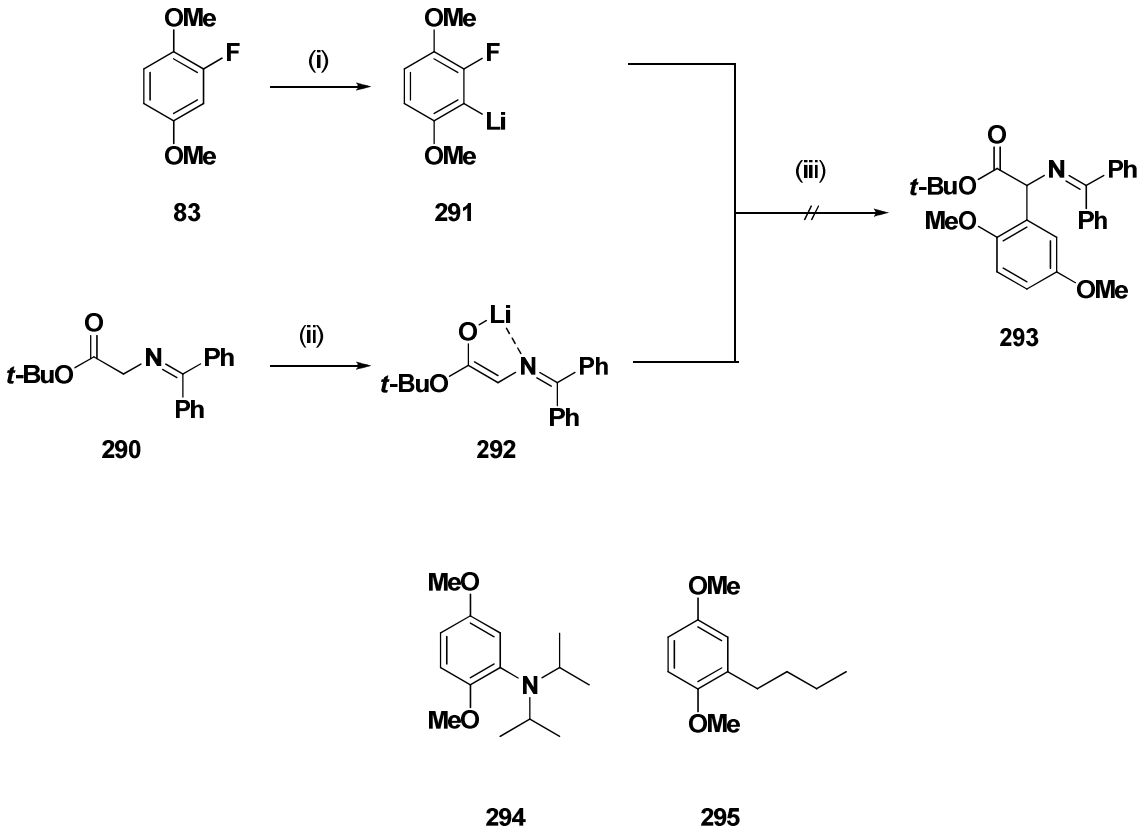
Scheme 76: Synthesis of imine **290**

With imine **290** in hand, alpha-arylation reactions with arynes could be attempted.

4.2.1 Employing an *ortho*-Lithiation Benzyne Precursor

It is well precedented that treatment of protected glycine **290** with lithium amide bases such as LDA, affords the (Z)-enolate **292** stereoselectively due to internal chelation between nitrogen and lithium.[181] The benzyne precursor tested in conjunction with this nucleophile was 1,4-dimethoxy-2-fluorobenzne **(83)** which undergoes *ortho*-lithiation at −78 ºC to give **291** and then eliminates lithium fluoride to form dimethoxybenzyne upon warming to room temperature.[81]

Unfortunately all attempts to react enolate **292** with this benzyne proved unsuccessful (Scheme 77). The order of addition of lithiated species **292** and **291** to each other was altered and the use of different lithiating reagents such as LiTMP or *n*-butyllithium investigated. The silyl ketene acetal of this ester was also tested,[182] but none of the desired product **293** was detected. Starting material was recovered in each case as well as the detection of base addition side products **294** and **295**.



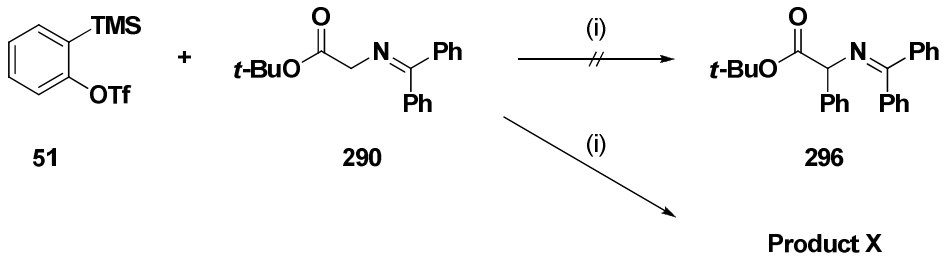
294 295

Reagents and Conditions: (i) *n*-BuLi, THF, −78 ºC; (ii) LDA or LiTMP or *n*-BuLi, THF, −78 ºC; (iii) −78 ºC to rt.

Scheme 77: Attempted addition of enolate **292** to dimethoxybenzyne

4.2.2 Use of a *ortho*-Silylaryl Triflate Precursor

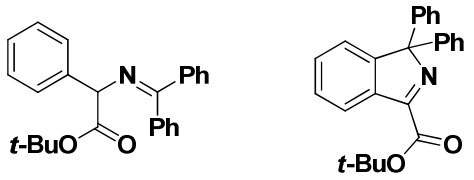
Due to the difficulties encountered with the previous strategy, a different benzyne precursor, 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **(51)**, which forms benzyne *via* a desilylation-elimination mechanism upon treatment with a fluoride source under mild conditions, was utilised.[56] Cesium fluoride was chosen as the fluoride source to induce benzyne formation and it was investigated whether it would act as the base to deprotonate α to the carbonyl. The imine **290** and benzyne precursor **51** were heated in the presence of cesium fluoride until all starting material had been consumed as monitored by TLC (Scheme 78).



Reagents and Conditions: (i) 3 equiv. CsF, MeCN, 80 ºC, 45 min.

Scheme 78: Reaction between Schiff base **290** and *ortho*-silylaryl triflate benzyne precursor **51**

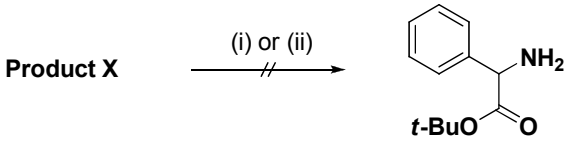
After column chromatography the major product of the reaction was isolated in 63% yield and initially assigned as the desired ester **296** (Figure 14). Mass spectroscopy confirmed the required mass, but doubts arose due to the low chemical shift of the CH proton α to the ester. On becoming benzylic as in **296**, it would be expected that this proton would shift downfield from the original imine, but in fact it had shifted upfield by 0.3 ppm. Another proposed product was cyclised structure **297** (Figure 14), that could have arisen though a [3 + 2] cycloaddition reaction,[183] but this was soon discounted due to its incompatibility with the NMR data.



296 **297**

Figure 14: Proposed products of reaction between Schiff base **290** and benzyne

In an attempt to confirm the structure as **296**, hydrolysis of the imine was attempted under standard conditions to give the corresponding phenylglycine *tert*-butyl ester **(298)**. However treatment with either citric acid at room temperature or hydrochloric acid at reflux resulted only in decomposition and no product was observed (Scheme 79).

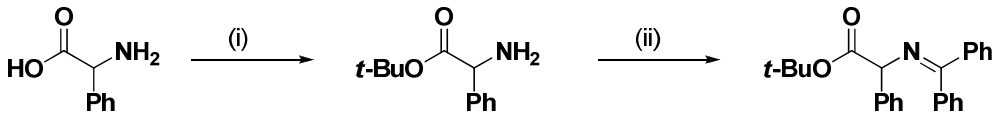


298

Reagents and Conditions: (i) 15 % citric acid, THF, rt, 16 h; (ii) 1M HCl, THF, reflux, 12 h.

Scheme 79: Attempted imine hydrolysis reactions

An authentic sample of the initially proposed product **296** was then synthesised. Phenyl glycine **(299)** was esterified by treatment with *tert*-butylacetate and perchloric acid,[184] followed by condensation with benzophenonimine **289** (Scheme 80).



299 **300** **296**

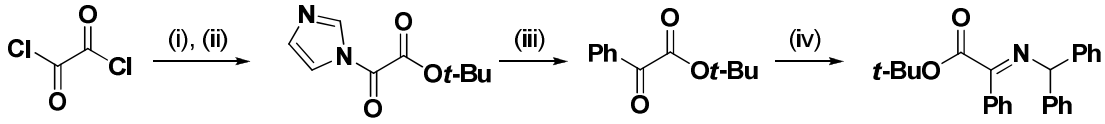
Reagents and Conditions: (i) *t*-BuOAc, $HClO_4$, rt, 12 h, 64%; (ii) $Ph_2C{=}NH$ **289**, CH_2Cl_2, rt, 36 h, 10%.

Scheme 80: Synthesis of imine **296**

The NMR data from this product was clearly different to that of the product formed during the benzyne reaction and as expected the CH proton had shifted downfield.

It was then hypothesised that this unknown compound may be the α-imino ester **304**, resulting from the isomerisation of the imine double bond under the basic reaction conditions.[185]

To test this theory, the imino ester **304** was synthesised using an alternative procedure. Employing a robust two-step method,[186] *tert*-butyl α-oxo-*1H*-imidazole-1-acetate **(302)** was prepared in 89% yield by the addition of imidazole to *tert*-butyl oxalyl chloride (generated *in situ*) followed by the addition of phenylmagnesium bromide to this compound to afford α-keto ester **303**. α-Imino ketone **304** was formed *via* a condensation reaction with neat dibenzylamine in the presence of *para*-toluenesulfonic acid and 4 Å molecular sieves (Scheme 81).



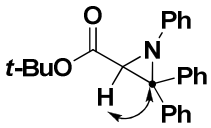
301 **302** **303** **304**

Reagents and Conditions: (i) *t*-BuOH, THF, 0 ºC, 1 h; (ii) imidazole, THF, 0 ºC, 45 min, 89%; (iii) PhMgBr, THF, 0 ºC to rt, 4 h, 81%; (iv) $NH_2CH(Ph)_2$, PTSA, 4 Å MS, 27%.

Scheme 81: Synthesis of α-imino ester **304**

Spectral analysis of this compound also indicated that the structure is inconsistent with that of the previously obtained compound.

Finally, exhaustive 2D NMR analysis revealed the identity of the mystery compound as aziridine **305**. The HMBC shows a clear coupling between the proton on the α-carbon to the ester and the aliphatic quaternary carbon in the molecule (Figure 15).

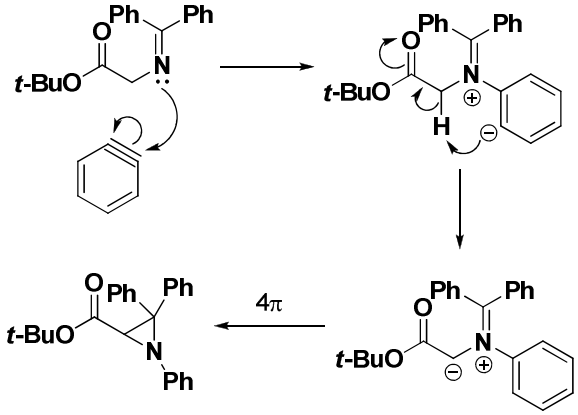


305

Figure 15: Key HMBC coupling between the α-proton and the quaternary aziridine carbon

The aziridine structure proposed is consistent with all of the spectral data and also explains the low chemical shift of the α-proton to the ester, due to ring strain. This data was similar to those of analogous compounds reported in the literature,[187,188] thus providing support for this characterisation.

A mechanism was proposed in which the nitrogen lone pair of the imine acted as the nucleophile towards benzyne. The resulting aza-methine ylide **306** subsequently undergoes a 4π-electrocyclisation to afford aziridine **305** (Scheme 82).[189]



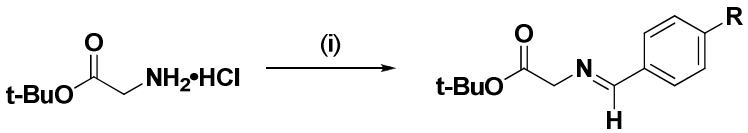
305 **306**

Scheme 82: Proposed mechanism for aziridine **305** formation

Although the desired α-arylation product was not found, this reaction was thought interesting, and deserved further investigation.

4.2.2.1 Aziridination Reactions

It was interesting to test this reaction further and apply it to other systems and to observe whether there is any diastereoselectivity for unsymmetrical imines. To investigate this, two imines **308a** and **308b** were synthesised by the condensation of the *tert*-butyl aminoacetate hydrochloride **(307)** with the appropriate aldehyde (Scheme 83).

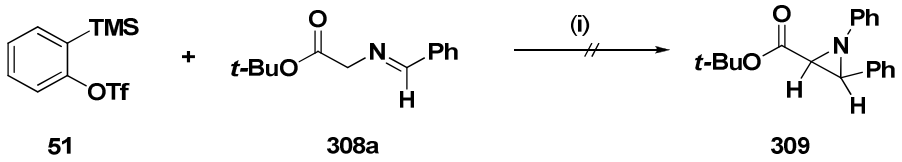


307 **308a:** R=H **308b:** R=Cl

Reagents and Conditions: (i) NEt_3, $MgSO_4$, CH_2Cl_2, rt, 1 h then 4-R-PhCHO, rt, 12 h, 93% for **308a**, 90% for **308b**.

Scheme 83: Formation of imines

However, when the same aziridination conditions were applied to **308a**, none of the desired aziridine diastereoisomers **309** were observed, only starting materials were recovered or an intractable mixture formed (Scheme 84, Table 3). Several conditions were employed to try to promote the reaction, including prolonged reaction times (Table 3, Entry 2), increased pressure (Table 3, Entry 3) and a different fluoride source and solvent (Table 3, Entries 4 and 5).



51 308a 309

Reagents and Conditions: (i) See Table 3.

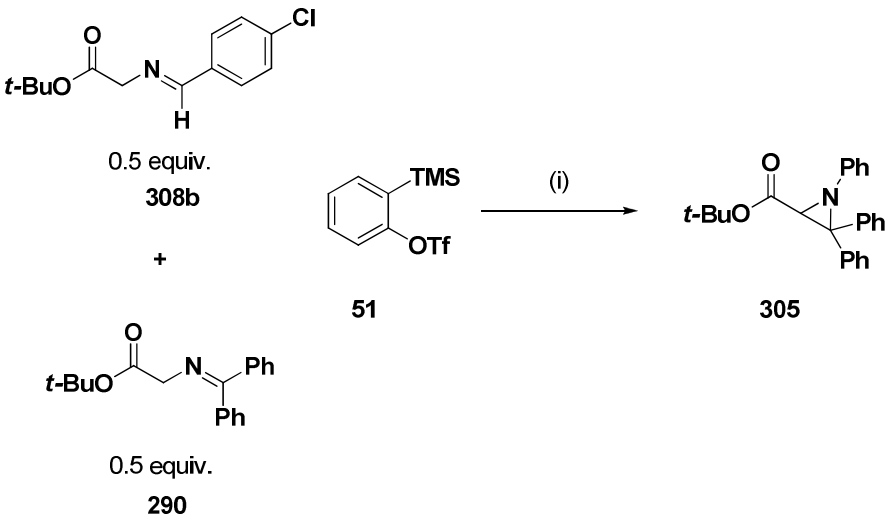
Scheme 84: Attempted aziridination reaction with unsymmetrical imines

Table 3: Conditions for attempted aziridinations of unsymmetrical imines

Entry[a]	Reagents and Conditions	Concentration /M	Result[b]
1	CsF, MeCN, 80 ºC, 45 min	0.07	SMs
2	CsF, MeCN, 80 ºC, 18 h	0.1	Complex mixture
3	CsF, MeCN, 80 ºC, sealed tube, 3 h	0.1	SMs
4	KF/18-crown-6, THF, 0 ºC, 5 h	0.25	Complex mixture
5	KF/18-crown-6, THF, 0 ºC to rt, 6 h	0.25	SMs

[a]Typical reactions were performed on a 0.5 mmol scale. [b]Determined by analysis of the ^{1}H NMR of the crude reaction material after work-up.

To determine whether the reactivity issues were specific to the imine derived from benzaldehyde, the reaction was conducted with **308b**, without success. What was curious about these reactions was that in each case unreacted benzyne precursor **51** was recovered and in the original aziridination reaction (Scheme 78) the precursor was consumed. A competition experiment was carried out between imine **290** (0.5 equivalents) and imine **308b** (0.5 equivalents) under the previous reaction conditions (Scheme 85).

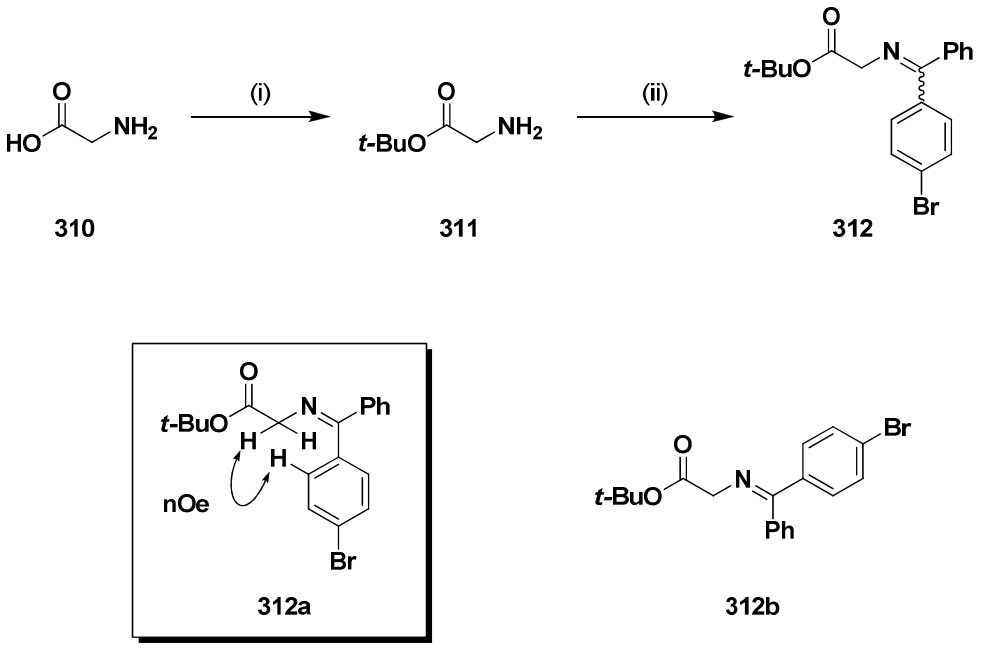


Reagents and Conditions: (i) CsF, MeCN, 80 ºC, 45 min.

Scheme 85: Competition aziridination reaction

The ^{1}H NMR spectrum of the crude reaction mixture showed the presence of aziridine **305**, unreacted **308b** and imine **290** in an approximately 1 : 2 : 1 ratio respectively. Unreacted precursor **51** was also observed, demonstrating that imine **308b** would appear to inhibit benzyne formation and hence decrease the degree of conversion of symmetrical imine **290** to its corresponding aziridine. No further investigation was made into this reaction.

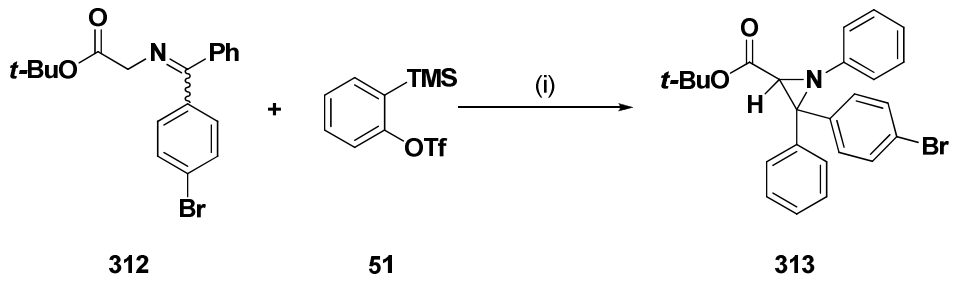
Instead, an unsymmetrical, bi-aryl imine **312** was synthesised to test the stereoselectivity of these reactions. Condensation of *tert*-butyl aminoacetate **(311)** with 4-bromophenone in the presence of 4 Å molecular sieves (Scheme 86) gave **312** as a 3 : 1 mixture of isomers. The major isomer was determined to be (*Z*)-ketimine **312a** by nOe analysis.



Reagents and Conditions: (i) *t*-BuOAc, $HClO_4$, rt, 18 h, 28%; (ii) 4-Br-PhCOPh, cat. CSA, benzene, 4 Å MS, 90 ºC, 3 days, 4%, dr 3 : 1 **312a** : **312b**.

Scheme 86: Synthesis of imine **312** and nOe analysis

When this mixture of isomers was subjected to the same aziridination reaction conditions as before, a 1 : 1 mixture of diastereoisomers of aziridine **313** were formed along with recovered starting material, now in a 1 : 1.5 ratio of **312a** to **312b** (Scheme 87, Table 4, Entry 1). This indicated that either the starting imine or the transient iminium intermediate was isomerising under the reaction conditions or the major isomer **312a** was reacting faster than **312b**. When the reaction was conducted at ambient temperature instead, one diastereoisomer of the aziridine was formed in a 11 : 1 ratio. As in the previous reaction more of the minor isomer **312b** remained than the major **312a** (Table 4, Entry 2). This indicates the major imine isomer **312a** forms its corresponding aziridine much faster than the minor isomer.



312 51 313

Reagents and Conditions: (i) See Table 4.

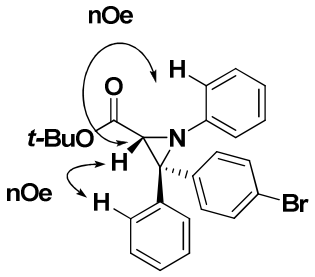
Scheme 87: Aziridination reaction of unsymmetrical imine

Table 4: Aziridination conditions

Entry	Reagents and Conditions	Ratio of unreacted SM isomers[a] (Major 312a : Minor 312b)	dr[a] 313	Yield[b] 313 /%
1	CsF, MeCN, 1 h, 80 °C	1 : 1.5	1:1	44
2	CsF, MeCN, 18 h, rt	1 : 1.5	11:1	40

[a]As determined by integration of the ^{1}H NMR of the crude reaction material. [b]Isolated after column chromatography.

nOe measurements on the major aziridine diastereoisomer confirmed it to be the one in which the α-proton and the unsubstituted phenyl group were of *syn* geometry (Figure 16).



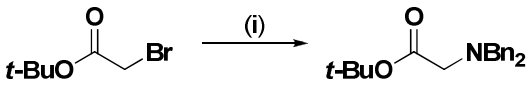
313

Figure 16: Major aziridine diastereoisomer showing key nOe correlations

This result is consistent with a stereospecific conrotatory 4π electrocyclisation of major diastereoisomer **312a**.

4.3 Dibenzyl Protected Glycine Derivatives

Although interesting, the results from the previous section indicated that the electrophilic nature of imine **290** would be problematic in any further reactions involving arynes. Similarly Durst and co-workers observed [3+2] cycloadditions of aza-methine ylides derived from similar compounds.[183] It was therefore decided to use a more electrophilically inert protecting group for the amine functionality in the glycine molecule. To this end, *tert*-butyl dibenzylamine acetate **(314)** was synthesised according to a literature procedure (Scheme 88).[190]



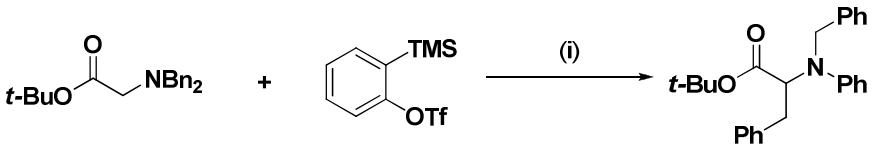
288 **314**

Reagents and Conditions: (i) $NH(Bn)_2$, EtOH, dioxane, reflux, 4 h, 90%.

Scheme 88: Synthesis of dibenzyl-protected glycine ester **314**

4.3.1 Employing Desilylation-Elimination Benzyne Precursor

Without the interference of the electrophilic imine, the same conditions that gave the aziridine **305** from imine **290** were applied to ester **314**. Surprisingly, the only product isolated was the α-benzyl compound **315** in 47% yield (Scheme 89).

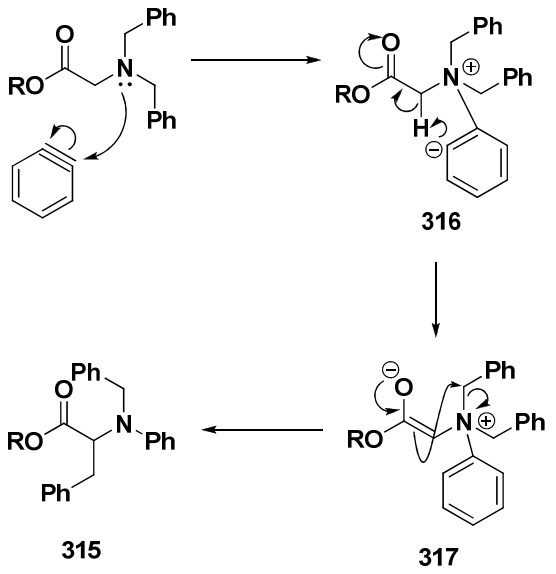


314 **51** **315**

Reagents and Conditions: (i) CsF, MeCN, 80 ºC, 45 min, 47%.

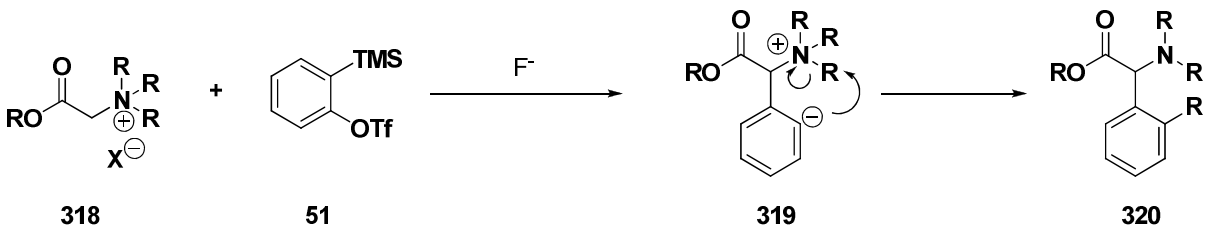
Scheme 89: Reaction between dibenzyl protected glycine ester **314** and benzyne

An aryne-induced Stevens rearrangement was proposed for the formation of this product **315**. Initial attack of the tertiary amine on the benzyne would afford zwitterionic species **316** and subsequent 1,4-proton transfer would form enolate **317** which could undergo a 1,2-alkyl shift with migration of the benzyl group to afford product **315** (Scheme 90).



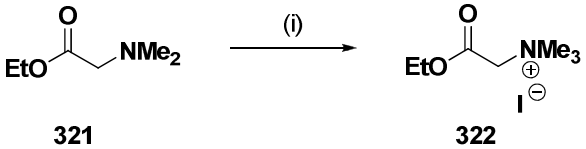
Scheme 90: Proposed mechanism for formation of **315** *via* an aryne-induced Stevens rearrangement

Based on this rearrangement, a new strategy was designed. It was anticipated that if a quaternary ammonium salt **318** was used in place of the tertiary amine **314**, the electron-withdrawing effect of the positively charged nitrogen would be enough to render the α-carbonyl protons acidic enough to be deprotonated by a fluoride base. It was then envisioned that the resulting anion following α-arylation, **319**, would promote an intramolecular migration of one of the alkyl groups from nitrogen to carbon, resulting in **320** (Scheme 91).



Scheme 91: Proposed reaction between quaternary ammonium salts **318** and benzyne

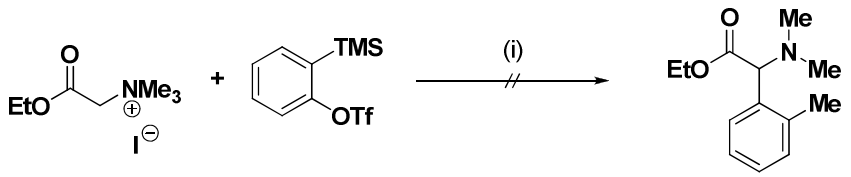
To validate this theory, the previously-described trimethyl ammonium iodide salt **322** was prepared from dimethyl amine **321** in 81% following a simple procedure (Scheme 92).[191]



Reagents and Conditions: (i) MeI, CH_2Cl_2, −15 ºC to rt, 48 h, 81%.

Scheme 92: Synthesis of 2-ethoxy-*N*,*N*,*N*-trimethyl-2-oxoethanaminium iodide **(322)**

However, difficulties arose when trying to use this salt in a benzyne reaction. Trimethyl ammonium salt **322** was completely insoluble in acetonitrile, and hence the cesium fluoride/acetonitrile combination could not be used. It was partially soluble in THF, but a reaction between benzyne precursor **51**, salt **322** and potassium fluoride in the presence of 18-crown-6 gave none of the desired amine **323** (Scheme 93). It was speculated that the proton was still not acidic enough for potassium fluoride to deprotonate, even with an ammonium ion adjacent to it.



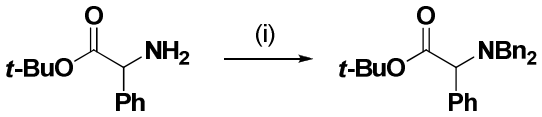
322 **51** **323**

Reagents and Conditions: (i) KF/18-crown-6, THF, rt.

Scheme 93: Unsuccessful reaction between quaternary ammonium salt **322** and benzyne

These results suggest the need for a stronger base than cesium fluoride to effect enolate formation in order to encourage the protected glycine to act as a carbon rather than a nitrogen nucleophile whilst still using **51** as the benzyne source.

To simplify monitoring and analysis of these reactions, the arylated product **324** was prepared separately by benzylation of previously synthesised phenylglycine ester **300** (Scheme 94).

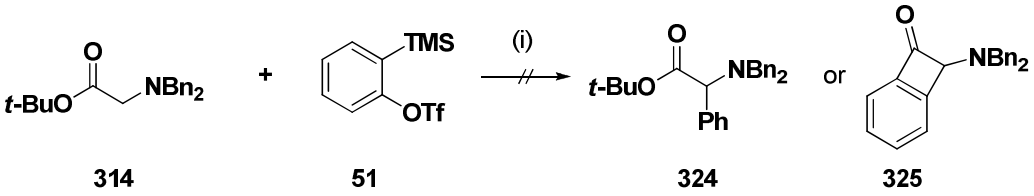


300 **324**

Reagents and Conditions: (i) BnBr, Cs_2CO_3, *n*-Bu_4NI, DMF, 100 °C, 18 h, 25%.

Scheme 94: Synthesis of desired reaction product

Reactions were then performed using a variety of strong bases for deprotonation of **314** coupled with different fluoride sources for benzyne formation. It was anticipated that a potential by-product **325** could also be formed (Scheme 95, Table 5, Entries 1-5).



314 51 324 325

Reagents and Conditions: (i) See Table 5.

Scheme 95: Attempted addition of glycine enolate to benzyne

Table 5: Investigations into benzyne additions of **314** enolates

Entry[a]	Base[b]	Fluoride Source[c]	Order of addition to 314	Result[d]
1	LDA	CsF	Base, then **51**, then F^-	Starting materials[e]
2	LDA	KF/18-crown-6	Base, then **51**, then F^-	Starting materials[e]
3	NaH	CsF	Base, then **51**, then F^-	Starting materials
4	NaH	KF/18-crown-6	Base, then **51**, then F^-	Starting materials + **315**
5	KH	KF/18-crown-6	Base & F^-, then **51**	Starting materials[e]

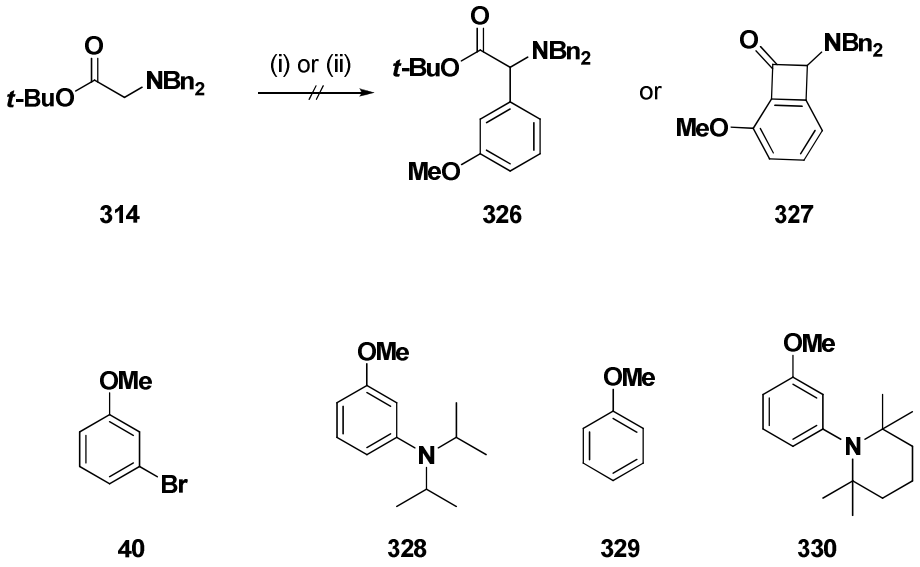
[a]Reactions were performed on a 100 mg scale in anhydrous THF using 1 equiv. of base and 3 equiv. of fluoride reagent and monitored over a 6 h period. [b]Deprotonations were carried out at −78 °C using LDA and at rt using NaH or KH. [c]CsF desilylations were carried out at rt and at 0 °C using KF. [d]Determined by ^{1}H NMR spectroscopy and GC-MS analysis of the reaction mixture. [e]There was also a large number of unidentifiable side products as seen by TLC and GC-MS analysis.

These results demonstrate the incompatibility of benzyne precursor **51** under these reaction conditions as unreacted **51** was detected in the presence of excess fluoride in all cases (Table 5, Entries 1-5).

4.3.2 3-Bromoanisole (40) as a Benzyne Precursor

Lithiation of 3-Bromoanisole **(40)** is known to be regioselective for the 2-position and elimination of LiBr to methoxybenzyne occurs at −78 °C.[192] Protected glycine **314** was treated with LDA to form the corresponding enolate, followed by addition of an equivalent of *n*-butyllithium to regenerate LDA *in situ* before 3-bromoanisole **(40)** was added at −78 °C. It was envisioned that LDA would generate methoxybenzyne in the presence of the lithium enolate and the desired enolate addition would occur. Monitoring the reaction by GC-MS and analysis of the crude reaction mixture by ^{1}H NMR showed only unreacted starting materials along with base addition side-product **328** and dehalogenated **329**. Replacement of

LDA with more hindered LiTMP in the presence of HMPA to increase the nucleophilicity of the enolate produced the same result, with **330** detected (Scheme 96).



314 **326** **327** **40** **328** **329** **330**

Reagents and Conditions: (i) a) LDA (1.1 equiv.), THF, −78 ºC, 30 mins, b) *n*-BuLi (1 equiv.), −78 ºC, 15 mins, c) 3-bromoanisole **(40)**, THF, −78 ºC to rt, 12 h; (ii) a) LiTMP (1.1 equiv.), THF, −78 ºC, 30 mins, b) *n*-BuLi (1 equiv.), −78 ºC, 15 mins, c) 3-bromoanisole **(40)**, THF, HMPA, −78 ºC to rt, 12 h.

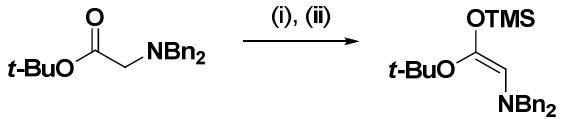
Scheme 96: Attempted α-arylation reaction using 3-bromoanisole **(40)** as the benzyne precursor

The above experiments demonstrate that using a lithium amide base for enolate formation is problematic due to the nucleophilic nature of the conjugate acid, e.g. di-*iso*-propylamine. A method was required in which enolate formation could be achieved without the use of such a base.

4.4 Silyl Ketene Acetals

An alternative strategy was to synthesise the corresponding silyl ketene acetal **331**, which could subsequently undergo a silyl-lithium exchange to form the corresponding lithium enolate without the presence of a nucleophilic amine.

The (*E*)-*tert*-butyl trimethylsilyl ketene acetal **(331)** was prepared stereoselectively using Tanabe's methodology (Scheme 97).[193]

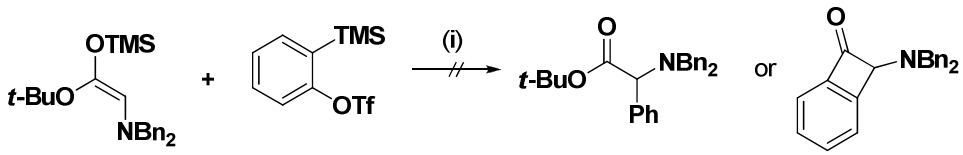


314 **331**

Reagents and Conditions: (i) LDA (1.1 equiv.), CPME, 0-5 ºC, 30 min; (ii) TMSCl, 0-5 ºC, 30 min then rt 1.5 h, 89%.

Scheme 97: Silyl ketene acetal formation

Before attempting the silyl-lithium exchange it was investigated whether a fluoride source could be used to generate the enolate from the silyl ketene acetal **331** and generate benzyne simultaneously. Silyl ketene acetal **331** and benzyne precursor **51** were treated with different fluorinating agents (Scheme 98, Table 6, Entries 1-3). Unfortunately none of these attempts were successful and only rearrangement product **315** was observed.



331 **51** **324** **325**

Reagents and Conditions: (i) See Table 6.

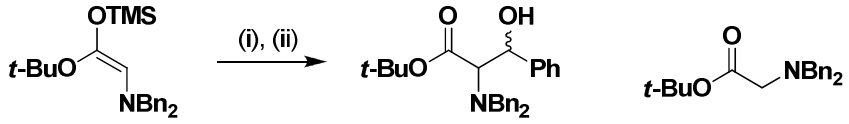
Scheme 98: Attempted reaction between silyl ketene acetal **331** and benzyne generated from precursor **51** using a fluoride source

Table 6: Different fluoride sources investigated in benzyne formation

Entry[a]	Fluoride Source	Solvent	Temperature /ºC	Result[b]
1	CsF	MeCN	20 to 80	**314** + **315**
2	KF/18-crown-6	THF	0 to 20	**314** + **315**
3	TBAF	THF	0 to 20	**314** + **315**[c]

[a]Reactions performed on a 150 mg scale and monitored over the course of 6 h. [b]As determined by ^{1}H NMR spectroscopy of the crude product. [c]The crude reaction mixture also contained a number of unidentifiable products.

The next task was to establish the optimal conditions for silyl-lithium exchange for the silyl ketene acetal. Silyl ketene acetal **331** was treated with one equivalent of methyllithium at various temperatures and then the resulting enolate treated with benzaldehyde to afford *syn*- and *anti*- diastereoisomers of alcohol **332** (Scheme 99).[194]



331 **332** **314**

Reagents and Conditions: (i) See Table 7; (ii) PhCHO, −78 °C, 30 min.

Scheme 99: Optimisation of silyl-lithium exchange by trapping enolate with benzaldehyde

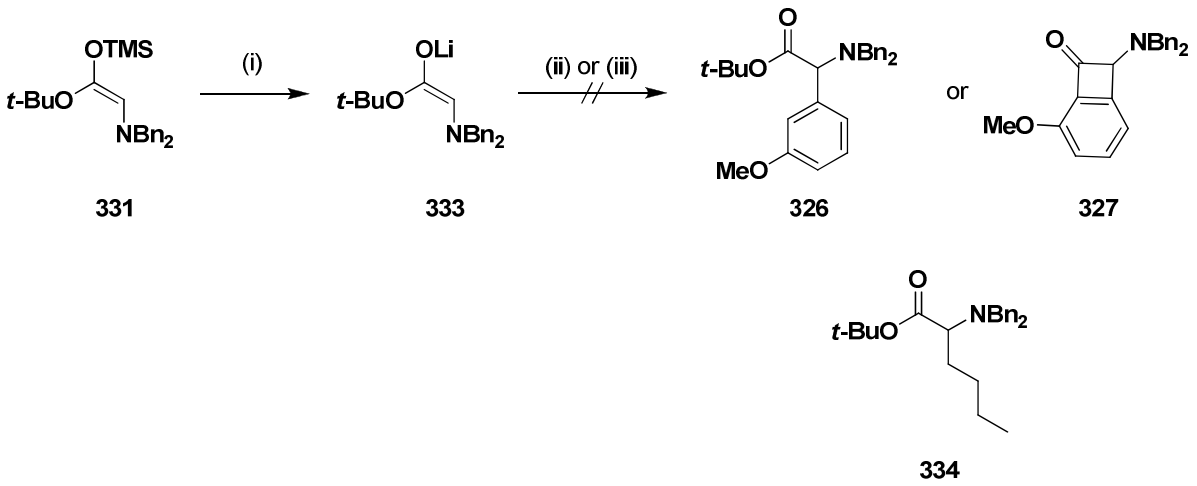
Table 7: Investigations into silyl-lithium exchange conditions

Entry[a]	Temperature of MeLi addition /°C[b]	Final Reaction Temperature /°C[c]	Product Ratio 314 : 332[d]
1	0	0	100 : 0
2	−78	−78	25 : 75
3	−78	−60	25 : 75
4	−78	−45	50 : 50
5	−78	−15	6 : 94

[a]Typical reactions performed on a 200 mg scale. [b]MeLi added dropwise at stated temperature. [c]Stirred at this temperature for 1 h before being cooled to −78 °C at which point benzaldehyde is added and stirred for a further 30 min at −78 °C. [d]As determined by analysis of the ^{1}H NMR spectra of the crude product.

4.4.1 3-Bromoanisole (40) as the Benzyne Precursor

Having determined the optimal conditions for silyl-lithium exchange (Table 7, Entry 5), 3-bromoanisole **(40)** was again investigated as the benzyne precursor. To enolate **333** was added one equivalent of *n*-butyllithium at −78 °C followed by 3-bromoanisole **(40)**. The order of addition was also reversed and the benzyne precursor **40** added before the base (Scheme 100). Unfortunately, neither of the expected products **326** or **327** were detected, only alkylated compound **334** was isolated in 25 % yield. This presumably is formed by a lithium-bromine exchange between butyllithium and bromoanisole, generating bromobutane which is alkylating the enolate. Due to the facile halogen-lithium exchange, 3-bromoanisole **(40)** is not a suitable benzyne precursor.



331 **333** **326** **327** **334**

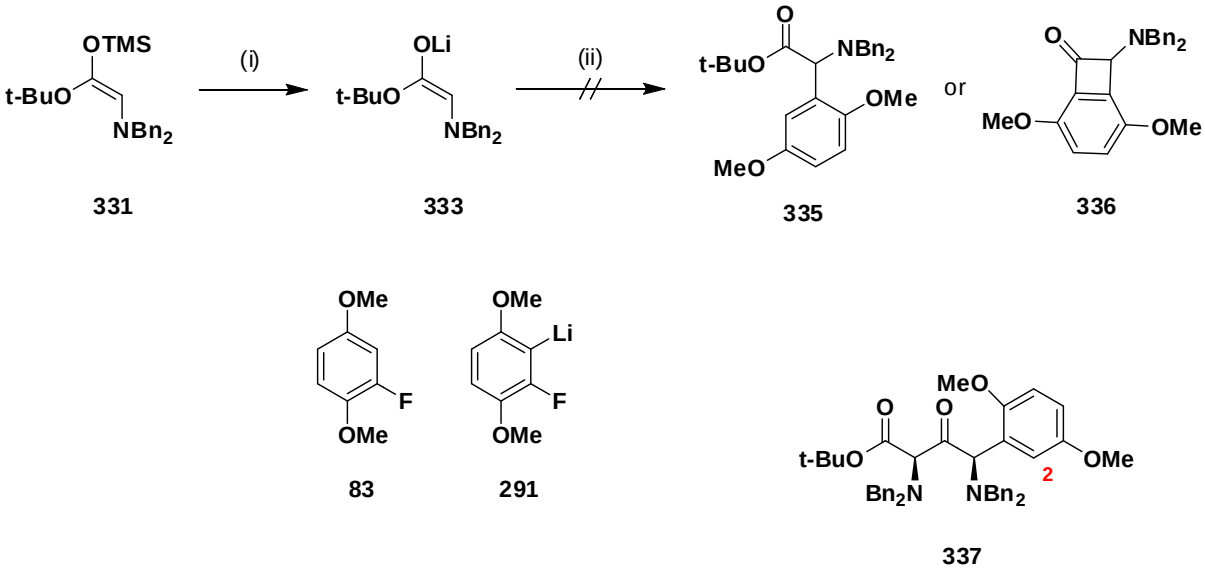
Reagents and Conditions: (i) MeLi (1 equiv.), THF, −78 °C then −15 °C 1 h; (ii) *n*-BuLi, −78 °C, 15 min then **40**; (iii) **40**, −78 °C then *n*-BuLi.

Scheme 100: Reaction between silyl ketene acetal **331** and 3-bromoanisole

4.4.2 1,4-Dimethoxy-2-fluorobenzene (83) as the Benzyne Precursor

Attention was once again focused on 1,4-dimethoxy-2-fluorobenzene **(83)** as a benzyne precursor, as this does not undergo halogen-lithium exchange.

The same process of silyl-lithium exchange was again performed. 1,4-Dimethoxy-2-fluorobenzene **(83)** and an equivalent of *n*-butyllithium were added and the reaction monitored upon warming to room temperature (Scheme 101). Addition of **291**, or **83** followed by *n*-butyllithium at −78 ºC and subsequent warming to room temperature (Table 8, Entries 1 and 3) resulted in a complex mixture of products. Performing the lithiation of the benzyne precursor at −20 ºC (Table 8, Entry 2) produced fewer by-products and a characterisable new product. Although purification was difficult, a pure sample of this product was obtained which was confirmed to be a single diastereoisomer of ester **337**. The IR and ^{13}C NMR spectra clearly show the presence of an ester and a ketone. DEPT analysis indicates that the dimethoxyarene has only been mono-substituted, and the proton in the 2-position is clearly visible by ^{1}H NMR. X-ray quality crystals of **337** were acquired, showing the stereochemistry of the two dibenzyl-protected amines to be *syn* (Figure 17).



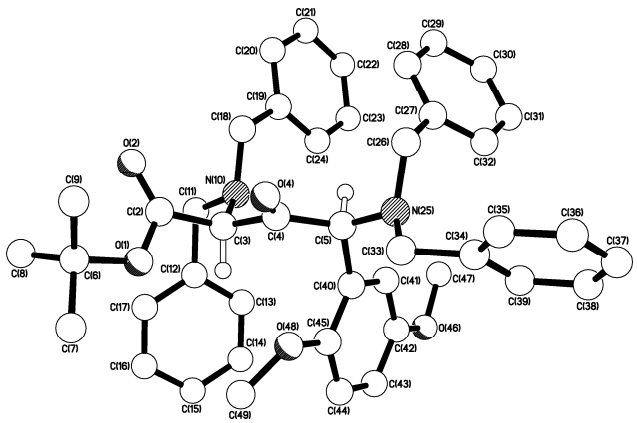
Reagents and Conditions: (i) MeLi, THF, −78 °C, then −15 °C 1 h; (ii) See Table 8.

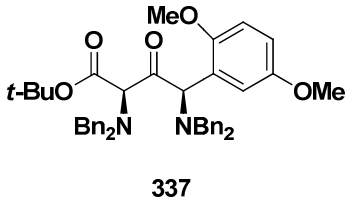
Scheme 101: Reactions between silyl ketene acetal **331** and dimethoxybenzyne

Table 8: Investigations using 1,4-dimethoxy-2-fluorobenzene **(83)** as a benzyne precursor

Entry[a]	Order of addition	Temperature /°C	Result[b]
1	**291** to **333**	−78 to rt	**314**[c]
2	**83** to **333** then *n*-BuLi	−20 to rt	**314**: **337** (5%)[d] 1: 1.9[e]
3	**83** to **333** then *n*-BuLi	−78 to rt	**314**[c]

[a]Typical reactions were performed on a 300 mg scale in anhydrous THF (0.2 M). [b]As determined by LC-MS and ^{1}H NMR analysis of the crude reaction mixture. [c]A large number of unidentifiable side products were also observed. [d]Isolated by column chromatography. [e]Determined by integration of the *t*-Bu peak in ^{1}H NMR of the crude reaction material.





337

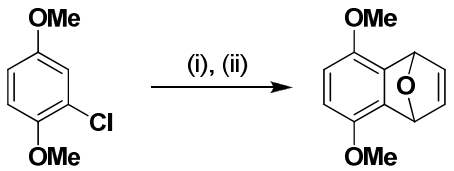
Figure 17: X-Ray crystal structure of diastereoisomer **337**

These results were promising although the reaction produces by-products after the initial enolate addition. It was hoped that careful adjustment of reaction conditions could induce the reaction to stop after the first attack.

4.4.3 1-Chloro-2,5-dimethoxybenzene (338) as the Benzyne Precursor

It was thought that lowering the temperature of benzyne formation in the previous reactions might result in controlled enolate addition and limit the amount of side reactions occurring.

1-Chloro-2,5-dimethoxybenzene **(338)** can be regioselectively *ortho*-lithiated at a lower temperature than the fluorine analogue **83** using *sec*-butyllithium at −95 ºC.[195] Warming to room temperature would result in elimination of LiCl and benzyne formation.[195,196] In order to determine the temperature at which benzyne formation occurs, a series of reactions were run in parallel in which *ortho*-lithiation was performed with *sec*-butyllithium at −95 ºC followed by the addition of furan and warming. The reactions were quenched at different temperatures and analysed by GC-MS for the presence of Diels-Alder cycloadduct **339**, indicating benzyne formation. Cycloadduct **339** was first observed at −60 ºC, indicating benzyne formation was occurring (Scheme 102).



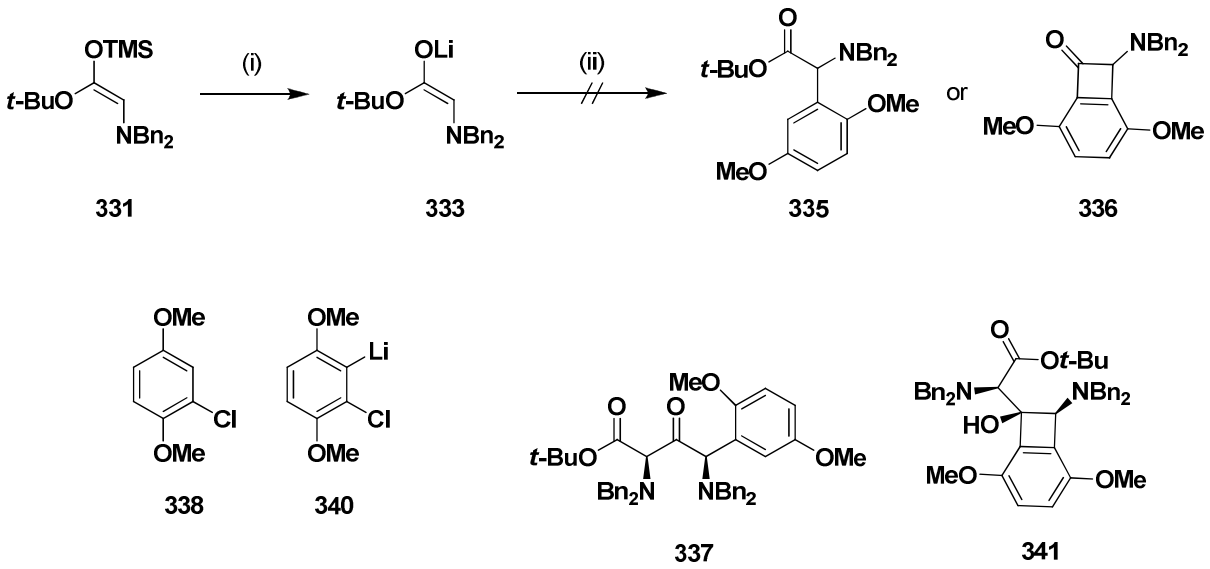
338 **339**

Reagents and Conditions: (i) *s*-BuLi, THF, − 95 ºC, 15 min; (ii) furan, − 95 ºC to − 60 ºC then H_2O.

Scheme 102: Diels-Alder reactions between dimethoxybenzyne and furan

Similar reactions were performed to the ones using the fluoride precursor **83** (Scheme 103). The reactions were not warmed to room temperature in order to try to suppress side reactions (Table 9, Entries 1-3). Greater dilutions were also employed to suppress intermolecular reactions after the initial enolate addition (Table 9, Entries 1, 3 and 4).

These reactions appeared more promising with characterisable products formed in each case.



Reagents and Conditions: (i) MeLi, THF, −78 ºC then −15 ºC 1 h; (ii) see Table 9.

Scheme 103: Reactions between silyl ketene acetal **331** and dimethoxybenzyne from precursor **338**

Table 9: Investigations into enolate addition using benzyne precursor **338**

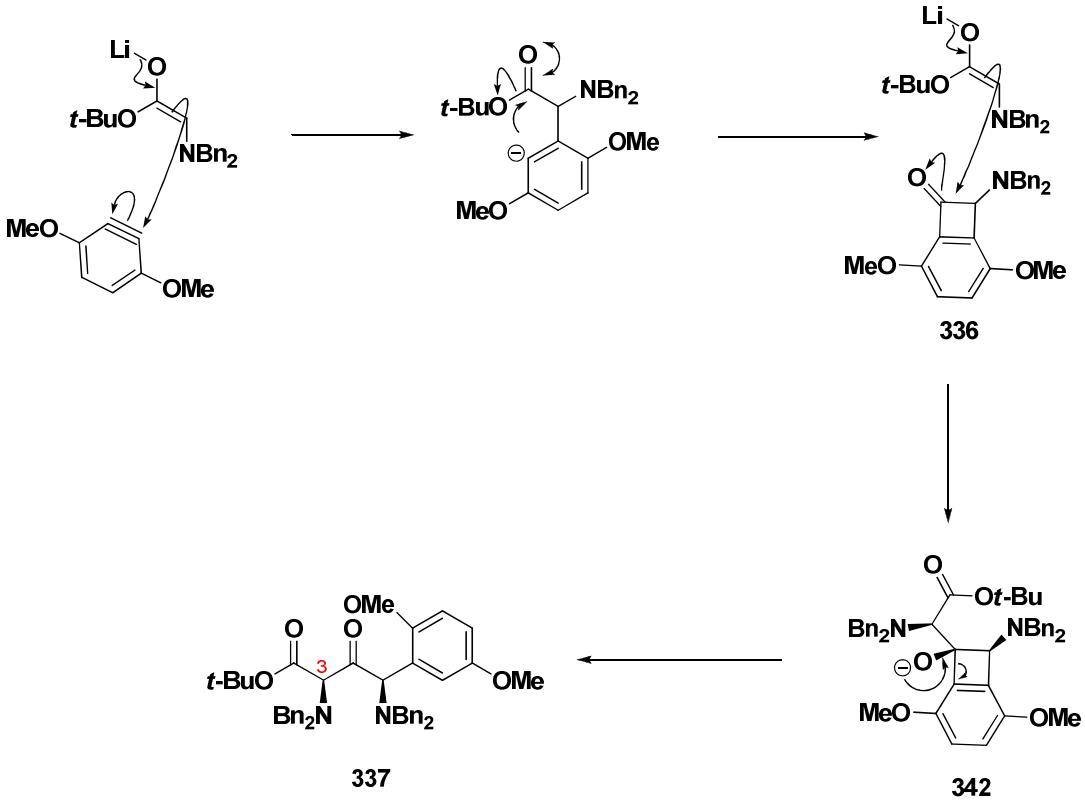
Entry[a]	Order of addition	Temperature /ºC	Concentration /M	Result[b]
1	**338** to **333** then *s*-BuLi	−95 to −40	0.1	**314** and **341** (24%)[c]
2	**338** to **333** then *s*-BuLi	−95 to −60	0.25	Only starting materials
3	**340** to **333**	−95 to −40	0.1	Only starting materials
4	**338** to 2 equiv. of **333** then *s*-BuLi	−95 to rt	0.1	**314** and **337** (17%)[c]

[a]Typical reactions carried out on a 300 mg scale in anhydrous THF. [b]As determined by LC-MS and ^{1}H NMR analysis of the crude reaction mixture. [c]Isolated yield after column chromatography

When the reaction was allowed to warm to −40 ºC at higher dilution (Table 9, Entry 1), a single product was isolated, cyclobutanol **341**. In this case, IR and ^{13}C NMR showed the presence of only one carbonyl group and DEPT analysis suggested that the dimethoxybenzene had been *ortho*-disubstituted. There was also a clear HMBC coupling pattern which indicated the presence of the 4-membered ring.

To push the reaction to completion it was repeated with two equivalents of enolate and allowed to warm to room temperature (Table 9, Entry 4). Under these conditions only product **337** was observed as in the reaction involving fluoride precursor **83**.

The proposed mechanism for the formation of both products is shown in Scheme 104. Addition of the enolate **333** to dimethoxybenzyne followed by cyclisation on the ester and subsequent addition of another equivalent of enolate to the highly reactive cyclobutanone ring **336** afforded **342**. Under the basic conditions of the reaction, a ring opening reaction could give **337**.



Scheme 104: Proposed mechanism for the formation of **337** and **341**

This proposed mechanism also explains the *syn* relationship between the alcohol and the dibenzyl protected amine in **341**. A model of the addition to the cyclobutanone **336** predicts this stereochemical outcome (Figure 18). This stereochemistry is retained in the ring-opened product **337** and only a single diastereoisomer is observed due to the non-epimerisable nature of the C-3 position.

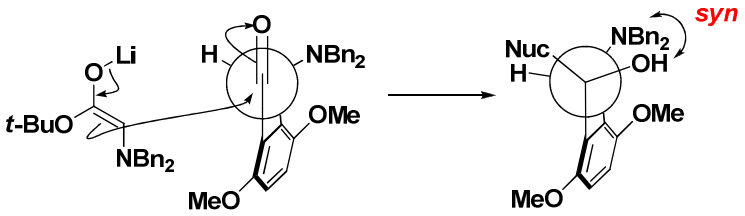
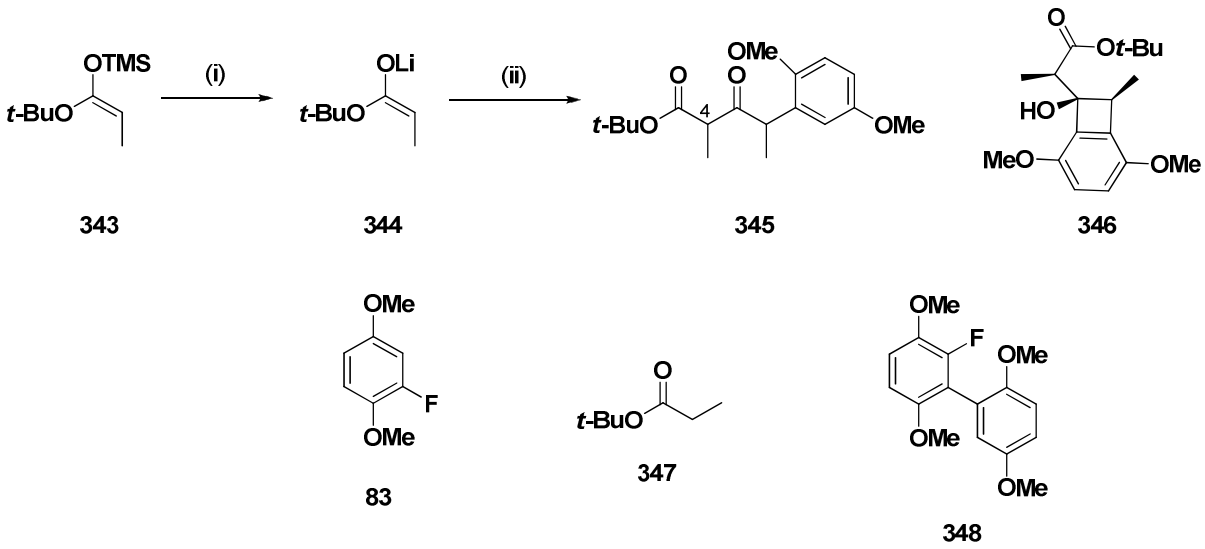


Figure 18: Model for attack of enolate on cyclobutanone **336**

An alternative mechanism involving an initial condensation reaction between two molecules of the enolate, and then further deprotonation and addition to benzyne under the basic reaction conditions would not explain the diastereoselectivity.

4.4.4 A Model Silyl Ketene Acetal

For further exploration, a simpler silyl ketene acetal **343**, without the protected amine group was employed. Under similar reaction conditions, both the cyclic **346** and open chain **345** compounds were isolated (Scheme 105, Table 10, entries 1-4). The open chain compound **345** was isolated as an inseparable mixture of diastereoisomers (dr 2 : 1) as the C-4 position is epimerisable.



Reagents and Conditions: (i) MeLi, THF, −78 ºC then −15 ºC 1 h; (ii) See Table 10.

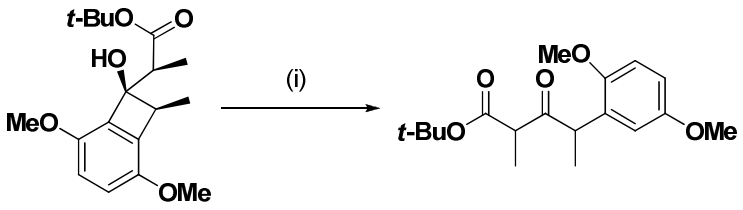
Scheme 105: Reactions of model silyl ketene acetal precursor

Table 10: Investigations into enolate addition of **344** to arynes

Entry[a]	Order of addition	Temperature /ºC	Concentration /M	Result[b]
1	**83** to **344** then *n*-BuLi	−78 to rt	0.1	**347** and **346** (25%)[c]
2	3 equiv. **83** to **344** then *n*-BuLi	−78 to 0	0.05	**347, 348**, **345** (7%)[c], **346** (5%)[c]
3	3 equiv. **83** to **344** then *n*-BuLi	−78 to −20	0.05	**347** : **348** (1:1)[b]
4	**83** to 2 equiv. **344** then *n*-BuLi	−78 to −20	0.1	**345** (22%)[c] : **346** (2:1)[b]

[a]Typical reactions carried out on a 200 mg scale in anhydrous THF. [b]As determined by GC-MS and ^{1}H NMR analysis of the crude reaction mixture. [c]Isolated yield after column chromatography.

To probe the proposed reaction mechanism, **346** was treated with *n*-butyllithium at room temperature, affording quantitative conversion to the open-chain form (Scheme 106). This reaction is consistent with the base-mediated ring-opening mechanism proposed in Scheme 94.

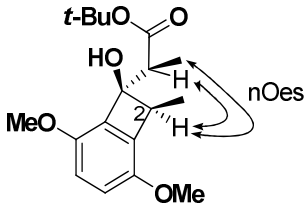


346 **345**

Reagents and Conditions: (i) *n*-BuLi, THF, 12 h, rt, 100% by NMR.

Scheme 106: Base-induced ring-opening reaction of **346**

nOe signals of cyclobutanol **346** were in agreement with the *syn*-relationship between the alcohol and the methyl group in the four membered ring. nOes signals were observed from the proton in the 2-position to the α-proton and the methyl group on the same face of the ring (Figure 19).



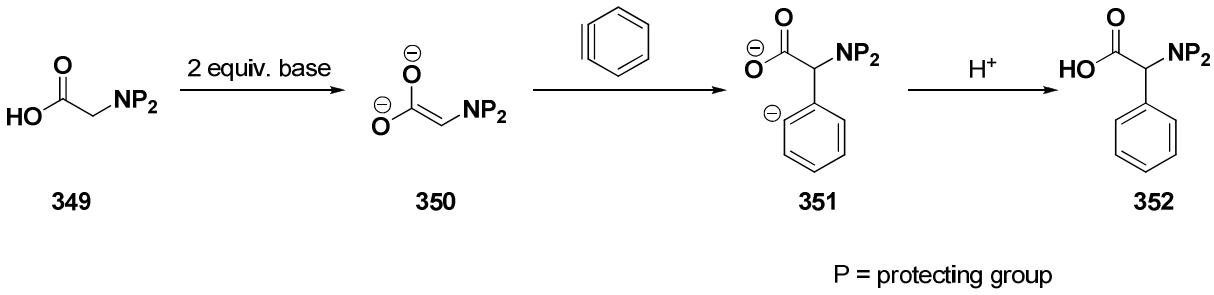
346

Figure 19: nOes observed from the C-2 proton

4.5 Use of Glycine Carboxylic Acids

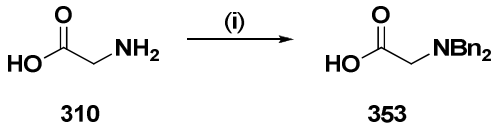
Despite considerable effort, the results in the previous sections demonstrate that even if the crucial carbon-carbon bond can be formed in an α-arylation reaction, cyclisation onto the *tert*-butyl ester still occurs.

An idea to prevent cyclisation onto the carbonyl was to use the carboxylic acid rather than the ester functional group. It was envisioned that formation of the acid dianion **350** followed by arylation with benzyne, in a similar fashion to the work carried out by Biehl (see Section 3.4), would afford carbanion **351** which would not be able to cyclise onto the acid anion, and hence could undergo a protic quench at this stage (Scheme 107).



Scheme 107: Proposed α-arylation of glycine carboxylic acid **349**

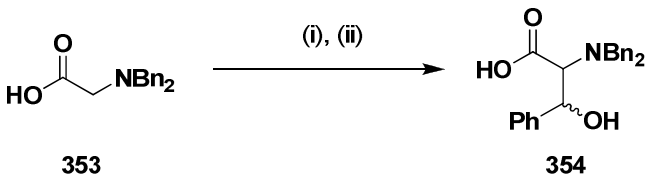
Treatment of glycine with benzyl bromide and KOH afforded the desired protected glycine acid **353** (Scheme 108).[197]



Reagents and Conditions: (i) H_2O, KOH, EtOH, BnBr, rt 16 h, then reflux 30 mins, 52%.

Scheme 108: Synthesis of dibenzyl protected glycine acid

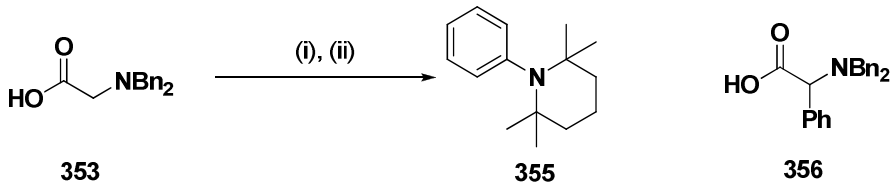
Treatment of **353** with 2 equivalents of LiTMP and warming to −40 °C before addition of benzaldehyde afforded only starting materials. The reaction was allowed to warm to 0 °C before being re-cooled for reaction with benzaldehyde, and this time the ^{1}H NMR showed the complete conversion to alcohol **354** (both *syn* and *anti* isomers) (Scheme 109).



Reagents and Conditions: (i) 2 equiv. LiTMP, THF, −78 °C to 0 °C, 1 h; (ii) PhCHO, −78 °C, 30 min, 100% by NMR.

Scheme 109: Dianion trapping with benzaldehyde

Now that the temperature of dianion formation had been established, a benzyne α-arylation reaction was attempted. This time 3 equivalents of LiTMP were used, and after warming to 0 °C, the reaction was cooled to −40 °C and bromobenzene was added (Scheme 110).[175] ^{1}H NMR and LC-MS data showed the major product to be amine addition species **365**, along with a minor amount of desired compound **356**.

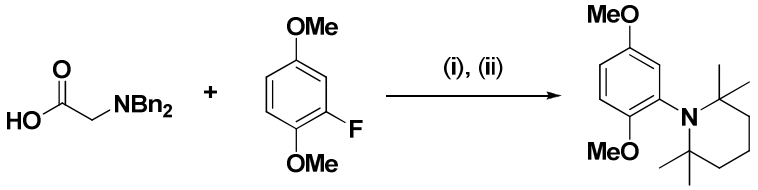


353 355 356

Reagents and Conditions: (i) 3 equiv. LiTMP, THF, −78 ºC to 0 ºC, 1 h; (ii) C_6H_5Br, −40 ºC to rt, 18 h.

Scheme 110: Attempted α-arylation of glycine acid with benzyne

Alternative addition of fluoride precursor **83** at −78 °C followed by slow warming to room temperature produced only base-addition product **357** and recovered starting materials (Scheme 111).



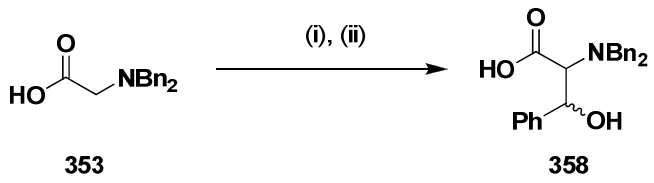
353 83 357

Reagents and Conditions: (i) 3 equiv. LiTMP, THF, −78 °C to 0 °C, 1 h; (ii) **83**, −78 °C to rt, 18 h.

Scheme 111: Attempted α-arylation of glycine acid with dimethoxy-benzyne

It was envisioned that the base-addition product could be suppressed by switching from LiTMP to *n*-butyllithium. Regular alkyllithium bases are not usually used to form enolates due to competing nucleophilic attack at the carbonyl moiety, but in this case as the carbonyl functionality is the unreactive, non-electrophilic carboxylic acid, this was thought not to be an issue.

After some optimisation, it was found that treatment of acid **353** with 2.5 equivalents of *n*-butyllithium in a mixture of THF and DMPU (to increase the solubility of the dianion), with warming from −78 °C to 0 °C and addition of benzaldehyde, gave complete conversion to alcohols **358** by NMR analysis of the crude reaction mixture (Scheme 112).

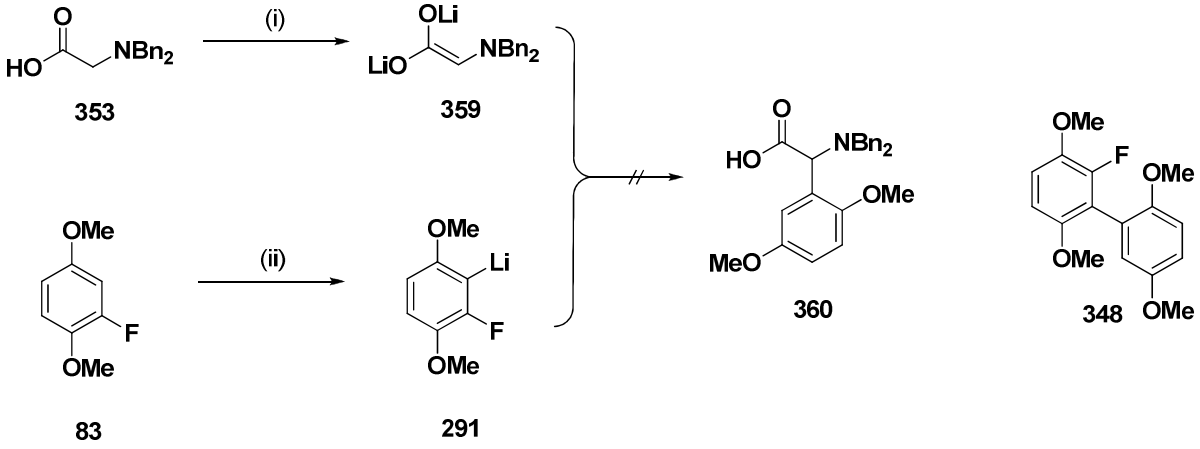


353 358

Reagents and Conditions: (i) 2.5 equiv. *n*-BuLi, THF/DMPU (4.5 : 1), −78 ºC to 0 ºC, 1 h; (ii) PhCHO, 0 ºC, 18 h, 100% by NMR.

Scheme 112: Formation and trapping of dianion

When dianion **359** was added to the pre-lithiated benzyne precursor **291** at low temperature, upon warming none of the desired product **360** was detected. GC-MS analysis showed acid **353** along with benzyne polymerisation products such as **348** as the major products of the reaction (Scheme 113). This is most likely due to the reduced nucleophilicity of the dianion compared to the lithiated benzyne precursor at low temperature.



353 359 83 291 360 348

Reagents and Conditions: (i) 2.5 equiv. *n*-BuLi, THF/DMPU (4.5 : 1), −78 ºC to 0 ºC, 1 h; (ii) 1.1 equiv. *n*-BuLi, THF, −78 ºC, 30 min.

Scheme 113: Attempted α-arylation of *n*-butyllithium formed dianion

4.6 Conclusions

Initial studies revealed the predominance of amine addition products to arynes if lithium amide bases were used to generate the necessary glycine enolates. The use of silylaryl triflate benzyne precursor **51** with protected glycines in the presence of a fluoride source resulted in the discovery of an unusual aziridination reaction *via* a 4-π electrocyclisation and also an unexpected Stevens rearrangement depending on the nature of the nitrogen protecting group, but none of the desired α-arylated product.

To form the crucial carbon-aryl bond, it was found essential to use the protected glycine silyl ketene acetal **331**, from which the lithium enolate can be released by treatment with methyllithium. However, although the α-arylation was occurring, cyclisation onto the *tert*-butylester was observed in all cases.

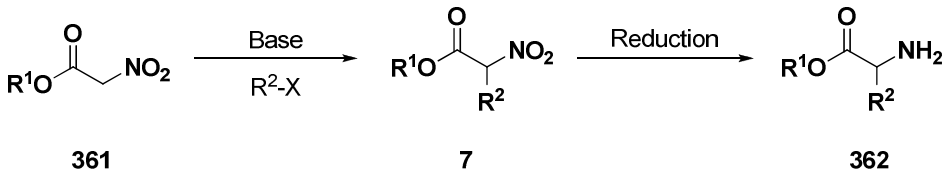
Use of the corresponding glycine acid dianion, to suppress cyclisation was unsuccessful, due to the low solubility and hence nucleophilicity of the dianion compared to lithiated benzyne precursors at low temperature.

Chapter 5: Results and Discussion: Investigations into the Reactions of Nitroesters with Arynes

5.1 Introduction

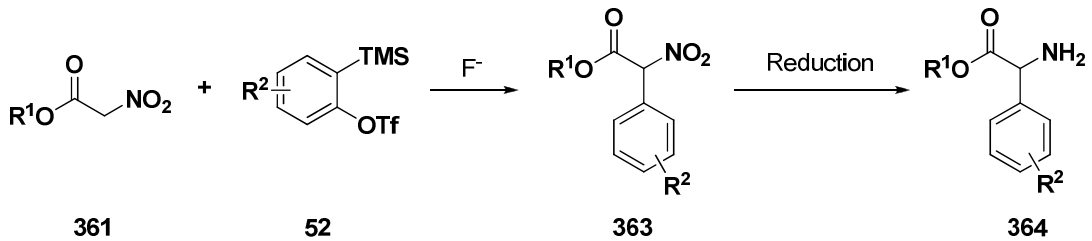
The previous Chapter described how protected glycine enolates were ineffective starting materials for α–arylation reactions with benzynes. In this Chapter a new method will be introduced that aimed at avoiding the undesired side reactions seen previously.

The strategy was to use nitroacetates **361** as masked amino acids. Due to their active methylene group, these compounds have been widely used in the formation of α–amino acids. Carbon-carbon bond formation with a wide range of electrophiles gives α–substituted β-nitroesters **7**, which upon reduction of the nitro functionality gives the desired amines **362** (Scheme 114).[198-203]



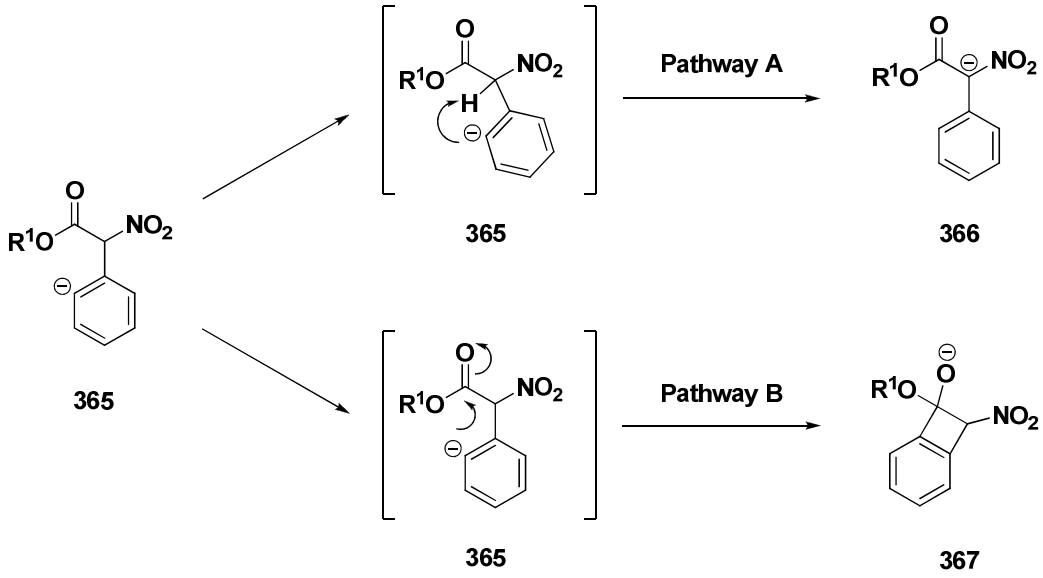
Scheme 114: Synthesis of α-amino acid esters **362** from nitroesters **361**

Nitroesters are particularly attractive intermediates for α-arylation reactions with benzyne. The basicity of the nitrogen in the nitro group is much lower than that of the tertiary amines used in Chapter 4, therefore the unusual rearrangement reactions, triggered by nucleophilic attack of nitrogen on benzyne (see sections 4.2.2 and 4.3.1) should be avoided. The acidity of the methylene protons ($pK_a \approx 5.7$[204,205]) due to the electron withdrawing effect of the nitro group, should enable a fluoride base (used for benzyne formation from silylaryl triflate precursors) to also allow enolate formation (Scheme 115).



Scheme 115: Proposed use of nitroacetates **361** in α-arylation reaction with benzynes derived from precursor **52**

It was appreciated that cyclisation of the aryl carbanion onto the ester might still be an unresolved problem and again consideration of the electrophilicity of the ester will be important. However, precedent for cyclisation onto esters is rare compared to ketones.[97] The α–proton is also much more acidic than that of a malonate ($pK_a \approx 5.7$ compared to $pK_a \approx 13$), which should promote intra- or inter-molecular proton transfer of **365** (Scheme 116, Pathway A) rather than cyclisation (Scheme 116, Pathway B).



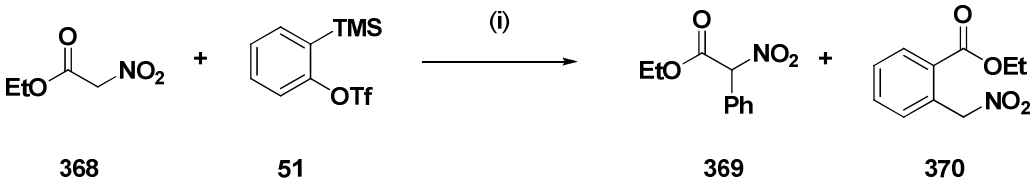
Scheme 116: Possible competing pathways in α-arylation of nitroacetates

5.2 Attempted α-Arylation Reactions of Nitroesters

5.2.1 Initial Observations

*5.2.1.1 Ethyl nitroacetate **(368)***

To examine the theory, commercially available ethyl nitroacetate **(368)** and benzyne precursor **51** were heated to 80 ºC in acetonitrile in the presence of cesium fluoride (Scheme 117). After quenching any remaining anionic centres with water, the α-arylation product **369** was isolated in addition to almost twice the amount of rearrangement product **370** (1 : 1.7, **369** : **370**) formed through pathway B. The two compounds were inseparable by column chromatography and therefore isolated together in a 47% yield.

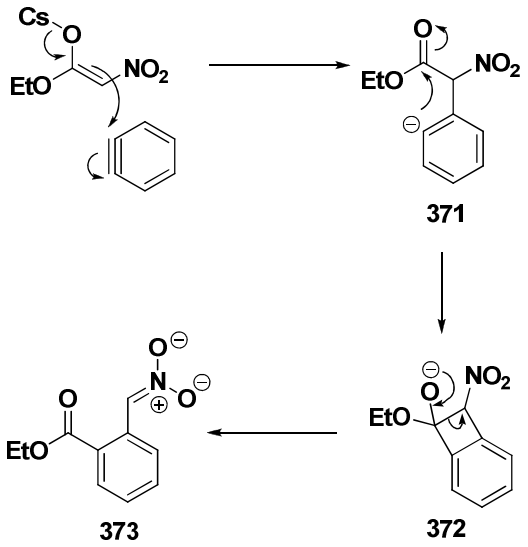


368 51 369 370

Reagents and Conditions: (i) CsF, MeCN, 80 ºC, 4 h, 47%.

Scheme 117: Reaction of ethyl nitroacetate **(368)** with benzyne

As described in Section 3.4, generation of rearrangement product **370** was not unexpected and a proposed mechanism for its formation is shown in Scheme 118. The aryl anion formed after addition of the enolate to benzyne, **371**, condenses with the ester to form **372**. Elimination of the α-nitro stabilised carbanion occurs due to its superior leaving group ability, and release of ring strain in **373** (Scheme 118).



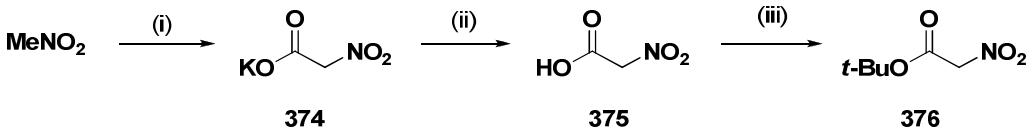
Scheme 118: Proposed mechanism of formation of **370**

*5.2.1.2 tert-Butyl nitroacetate **(376)***

It was envisioned that changing to a more bulky ester such as *tert*-butyl nitroacetate **(376)** would reduce the amount of cyclisation by the anionic intermediate and increase the ratio of α-arylated product.

The first route to ester **376** followed the procedure of Mioskowski.[206] Reaction between nitromethane, KOH and water precipitated potassium nitroacetate **(374)**, which upon acidification with L-tartaric acid at low temperature afforded nitroacetic acid **(375)**. This compound was found to be extremely labile and prone to decarboxylation, requiring the entire work-up procedure to be undertaken at 0 ºC. Esterification with DCC and *tert*-butanol

furnished *tert*-butyl nitroacetate **(376)**, in a low overall yield, likely due to the rapid decarboxylation of nitroacetic acid **(375)** (Scheme 119).



374 **375** **376**

Reagents and Conditions: (i) KOH, H_2O, 95 ºC, 5 h; (ii) L-tartaric acid, H_2O, 0 ºC, 1 h; (iii) DCC, *t*-BuOH, THF, 0 ºC to rt, 18 h, 12% over 2 steps.

Scheme 119: Synthesis of *tert*-butyl nitroacetate **(376)** using Mioskowski's method

Due to the problematic nature of this route, it was thought that a simple displacement of *tert*-butyl bromoacetate **(288)** with sodium nitrite would be a more efficient process (Scheme 120). Unfortunately, this approach afforded only the corresponding hydroxyl acetate **378**, a hydrolysis product of the intermediate nitrite ester **377**.[207]

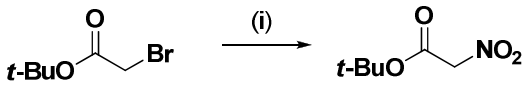


288 **376** **377** **378**

Reagents and Conditions: (i) $NaNO_2$, DMF, 100 ºC, 18 h.

Scheme 120: Attempted synthesis of *tert*-butyl nitroacetate **(376)** by displacement reaction

A solution to this problem was established by the chemistry of Righi and co-workers[208] who found that the use of a polymer-supported nitrite anion at low temperature prevented this unwanted side reaction and led to the desired nitroacetic esters in moderate yields. Treatment of **288** with polymer-supported nitrite anion (Amberlite IRA 900, NO_2^- form) in acetonitrile at −15 ºC gave the desired ester **376** in 53% yield (Scheme 121).



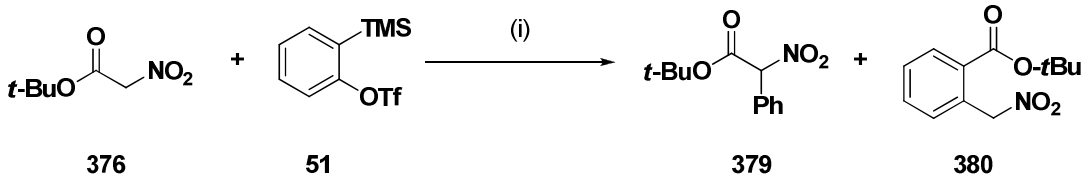
288 **376**

Reagents and Conditions: (i) polymer-supported nitrite, MeCN, −15 ºC, 8 h, 53%.

Scheme 121: Formation of nitroacetic acid ester using polymer-supported nitrite anion

With the bulkier nitroacetate **376** in hand, the analogous conditions were applied as for ethyl nitroacetate **(368**) (Scheme 122). This time there was a slight improvement in the ratio of

desired ester **379** to rearrangement product **380** (1 : 1 ratio), but isolation again proved complicated.



376 **51** **379** **380**

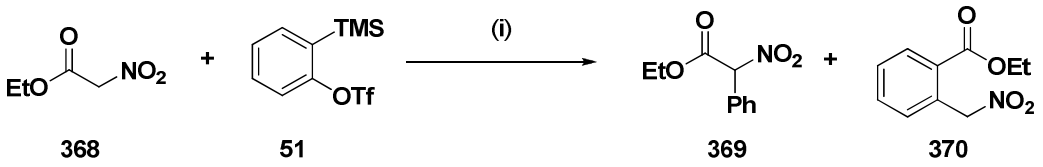
Reagents and Conditions: (i) CsF, MeCN, 80 ºC, 2.5 h, 1 : 1 ratio of **379 : 380**.

Scheme 122: Reaction of *tert*-butyl nitroacetate **(376)** with benzyne

5.2.2 Optimisation Studies

Although the ratio of α-arylated product was slightly superior for *tert*-butyl nitroacetate **(376)**, ethyl nitroacetate **(368)** was selected for optimisation studies due to its commercial availability and the ease of product isolation. A range of different conditions were tested in order to try to improve the ratio of compound **369** compared to side-product **370** and also to increase the reaction yield (Scheme 123, Table 11).

It was found that decreasing the temperature slightly increased the amount of **369**, but below 40 ºC the reaction did not work (Entries 2 and 3). It was more favourable to increase, rather than decrease the concentration of the reaction (Entries 4 and 5). The best ratio of **369** : **370** was observed employing cesium fluoride in acetonitrile (1 M) at 80 ºC (Entry 5), of 1.4 : 1, but with a poor yield of product. Changing solvent resulted in no reaction (Entries 6-8), and the use of TBAT as a fluoride source was also ineffective, due to the low yield associated with this reagent (Entry 9). A good yield was achieved using potassium fluoride in THF (Entry 10); however the ratio was biased towards the undesired product **370**.



368 51 369 370

Reagents and Conditions: (i) See Table 11.

Scheme 123: α-Arylation of ethyl nitroacetate **(368)** with benzyne

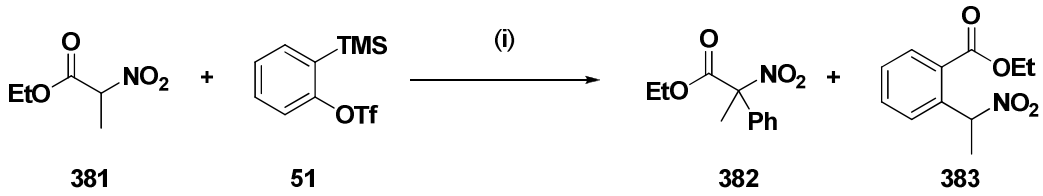
Table 11: Attempted optimisation of α-arylation of ethyl nitroacetate

Entry[a]	Fluoride Source	Solvent	Temperature /°C	Concentration /M	Time[b] /h	Ratio[c] of 369 : 370	Combined Yield[d] /%
1	CsF	MeCN	80	0.2	3.5	1 : 1.7	48
2	CsF	MeCN	40	0.2	120	1 : 1	18
3	CsF	MeCN	rt	0.2		no reaction	
4	CsF	MeCN	80	0.02	3.5	1 : 1.6	48
5	CsF	MeCN	80	1	18	1.4 : 1	24
6	CsF	PhMe	100	0.2		no reaction	
7	CsF	PhMe/ MeCN (1 : 1)	100	0.2		no reaction	
8	CsF	THF	60	0.2		no reaction	
9	TBAT	MeCN	80	0.2	1	1 : 1.2	10
10	KF/18-crown-6	THF	0 to rt	0.2	48	1 : 2.8	67
11	KF/18-crown-6	THF	60	0.2	18	1 : 2	26

[a]Reactions performed on a 1 mmol scale. [b]As monitored by TLC for consumption of **51**. [c]As determined by integration of the ^{1}H NMR spectrum of the crude product. [d]Isolated yield after column chromatography.

5.2.3 Arylation of α-Substituted Nitroacetates

To probe the effect of having an α-alkyl substituent already in place with the aim of examining the scope of the reaction, ethyl 2-nitropropanoate **(381)** was investigated as a starting material for α-arylation (Scheme 124, Table 12).



381 **51** **382** **383**

Reagents and Conditions: (i) See Table 12.

Scheme 124: α-Arylation of ethyl 2-nitropropanoate **(381)** with benzyne

Table 12: Attempted optimisation of α-arylation of ethyl 2-nitropropanoate **(381)**

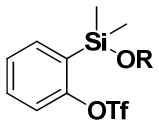
Entry[a]	Fluoride Source	Solvent	Temperature /°C	no. of equiv. of 51	Time[b] /h	Ratio[c] of 382 : 383	Combined Yield[d] /%
1	CsF	MeCN	80	1.25	2.5	1 : 0	27
2	KF/18-crown-6	THF	rt	1.25	1.5	1 : 3.5	66
3	CsF	MeCN	80	2.5	18	1 : 0	30

[a]Reactions performed on a 1 mmol scale. [b]As monitored by TLC for consumption of **51**. [c]As determined by integration of the ^{1}H NMR spectrum of the crude material. [d]Isolated yield after column chromatography.

The standard conditions were applied, using both cesium (Table 12, Entries 1 and 3) and potassium fluoride (Entry 2). Using the latter gave the usual mixture of desired α–arylated product **382** and rearrangement product **383**, in a good yield, but again as an inseparable mixture and favouring the undesired product **383** (Entry 2). Surprisingly, using cesium fluoride gave exclusively the desired product **382**, albeit in a low yield and with recovered starting material (Entry 1). As TLC analysis had shown total consumption of benzyne precursor **51** but not of starting material **381**, the reaction was performed using 2.5 equivalents of **51**, as opposed to 1.25 equivalents, but the yield did not increase, although all starting material had been consumed (Entry 3).

5.2.4 Synthesis of a New Benzyne Precursor

It was thought that if a benzyne precursor could be used which was similar to **51**, but would collapse faster to form benzyne, it might be possible to carry out the reaction at a lower temperature and hence reduce the amount of rearrangement product. The idea was to synthesise precursor **384**, in which one of the silyl methyl groups has been replaced by an alkoxy group (Figure 20). It was hoped that the electronegative nature of the oxygen would destabilise the pentavalent silyl species after fluoride anion attack, and encourage faster elimination to benzyne.[209]

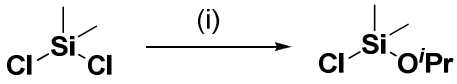


384

Figure 20: New benzyne precursor to be synthesised

It was expected that such a compound would be prone to hydrolysis, so the alkoxy group chosen was *iso*-propoxy (R = *i*-Pr), as this should be more stable than its methoxy analogue (R = Me).

Synthesis of chloro(*iso*-propoxy)dimethylsilane **(386)** followed a literature procedure.[210] Dichlorodimethylsilane **(385)** was treated with *iso*-propanol and urea and a fractional distillation afforded the product in 66% yield (Scheme 125).

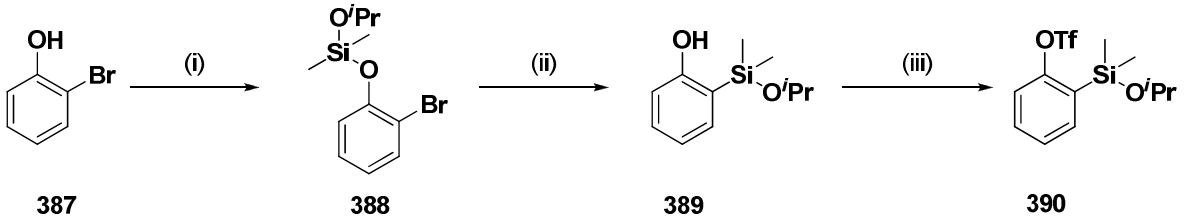


385 **386**

Reagents and Conditions: (i) *i*-PrOH, urea, rt, 4h, 66%.

Scheme 125: Synthesis of chloro(*iso*-propoxy)dimethylsilane **(386)**

A three-step procedure was then implemented to generate new benzyne precursor **390** (Scheme 126). Slow addition of bromophenol **(387)** to silylating reagent **386** at room temperature provided silane **388** after distillation in low yield, as displacement of *iso*-propoxide also occurred. Treatment of **388** with two equivalents of *tert*-butyllithium at −78 ºC followed by slow warming to room temperature, initiated a retro-Brook rearrangement to afford phenol **389**. Triflation was completed using triflic anhydride in good yield. The use of a non-aqueous work-up proved essential in this reaction.

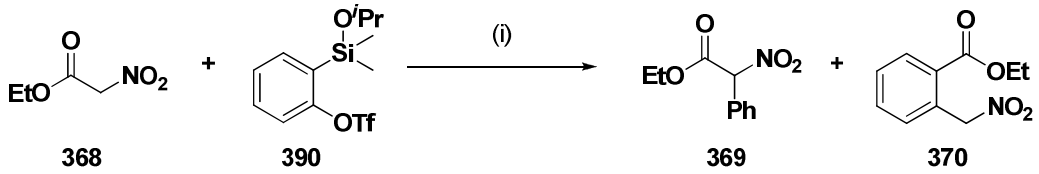


387 **388** **389** **390**

Reagents and Conditions: (i) **386**, rt, 4 h, 33%; (ii) 2 equiv. *t*-BuLi, THF, −78 ºC to rt, 18 h, 58%; (iii) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 ºC, 84%.

Scheme 126: Synthesis of precursor **390**

This precursor was then tested in the α-arylation conditions with cesium fluoride and acetonitrile, to see if the reaction could be performed at lower temperatures (Scheme 127, Table 13).



368 **390** **369** **370**

Reagents and Conditions: (i) CsF, MeCN, see Table 13.

Scheme 127: α-Arylation using new benzyne precursor **390**

Table 13: α-Arylation conditions for new precursor **390**

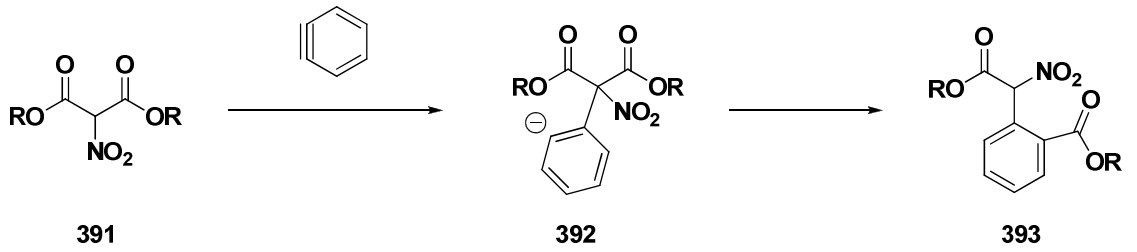
Entry[a]	Temperature /ºC	Time /h	Ratio[c] of 368 : 369 : 370
1	rt	48	50 : 1 : 1
2	40[b]	18	1.8 : 1 : 1
3	60	18	1 : 3.7 : 3.3

[a]Reactions performed on a 1 mmol scale using 2.5 equiv. CsF in MeCN (0.1M). [b]Reaction carried out in sealed tube. [c]As determined by integration of the ^{1}H NMR spectrum of the crude reaction material.

The reactions were difficult to monitor by TLC as precursor **390** was unstable on silica and products **369** and **370** had the same retention time as the starting material **368**. From Table 13 it is clear that reactions can be carried out at lower temperatures compared to the original precursor, but reactions were still very slow at these reduced temperatures. The ratio of desired product **369** to undesired **370** was also marginally improved, but not significantly so.

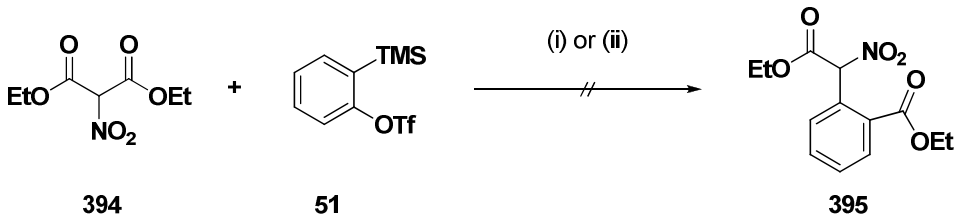
5.2.5 Use of Nitromalonates

To exploit the natural tendency of the aryl anion to cyclise onto the ester, the nitromalonate **391** was explored. It was hoped that initial arylation with benzyne would afford intermediate **392**. Condensation with one of the esters and elimination of the whole nitroacetate moiety could afford **393**, the product of α-arylation and ester migration to the *ortho* position of the phenyl ring (Scheme 128).



Scheme 128: Proposed reaction of nitromalonates with benzyne

The reaction was attempted using diethyl nitromalonate **(394)** and benzyne precursor **51**. Again both successful fluoride sources were investigated (Scheme 129). Unfortunately none of the desired compound **395** was formed, only an intractable mixture of products. Mass spectrometry did not indicate that any of the desired product had been produced.



Reagents and Conditions: (i) CsF, MeCN, 80 ºC; (ii) KF/18-crown-6, THF, rt.

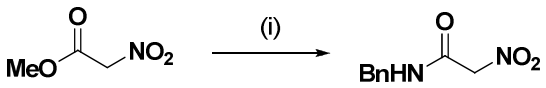
Scheme 129: Attempted α-arylation reaction using diethyl-nitromalonate **(394)**

5.3 Attempted α-Arylation Reactions of Nitroamides

Thus far, all attempted arylation reactions have employed esters as the protecting group of the carboxylic acid. It was hoped that changing this functionality to an amide would assist in preventing the disadvantageous cyclisation side reaction, due to the decreased electrophilicity of the amide moiety compared to the ester.

5.3.1 *N*-benzyl-2-nitroacetamide (397)

The synthesis of *N*-benzyl-2-nitroacetamide **(397)** is previously described[211] and is a straightforward coupling between commercial reagents. Hence methyl nitroacetate **(396)** was reacted with the required amine to give **397** in 45% yield (Scheme 130).

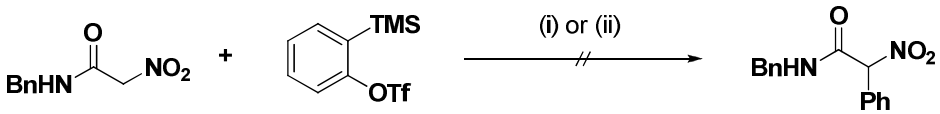


396 **397**

Reagents and Conditions: (i) 5 equiv. H_2NBn, MeOH, rt, 3 d, 45%.

Scheme 130: Synthesis of *N*-benzyl-2-nitroacetamide **(397)**

Unfortunately, attempted α-arylation employing both cesium fluoride and potassium fluoride gave complex mixtures of products, none of which contained the correct mass of the product **398** (Scheme 131).



397 **51** **398**

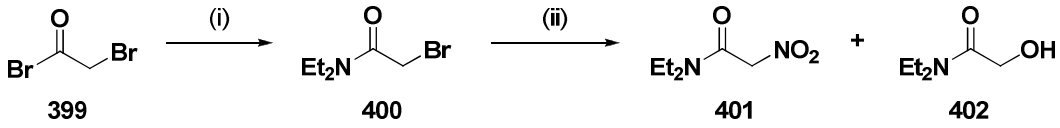
Reagents and Conditions: (i) CsF, MeCN, 80 ºC; (ii) KF/18-crown-6, THF, rt.

Scheme 131: Attempted α-arylation of nitroacetamide **398**

It was clear that a different nitroamide would be required if this idea was to be further explored.

5.3.2 *N*, *N*-diethyl-2-nitroacetamide (401)

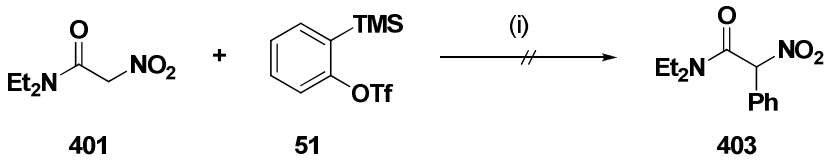
The lack of success in the previous reaction could be attributed to the acidic proton on the secondary amide, and hence a tertiary amide needed to be tested to see if in fact this was the problem. The acetamide synthesised for such a reaction was *N*,*N*-diethyl-2-nitroacetamide **(401)**. Formation of the bromoacetamide **400** was completed by treatment of bromoacetyl bromide **(399)** with diethylamine.[212] Subsequent reaction with solid-supported nitrite at −15 °C[208] afforded desired acetamide **401** and alcohol **402** as the expected side product (Scheme 132)



Reagents and Conditions: (i) Et_2NH, CH_2Cl_2, 0 °C to rt, 72 h, 85%; (ii) solid-supported nitrite, MeCN, −15 °C, 48 h, 10% **401**.

Scheme 132: Synthesis of acetamide **401**

Subjection of **401** to the standard benzyne formation conditions again led to a complex mixture of products, none of which could be identified as desired product **403** (Scheme 133).



Reagents and Conditions: (i) CsF, MeCN, 80 °C, 3 h.

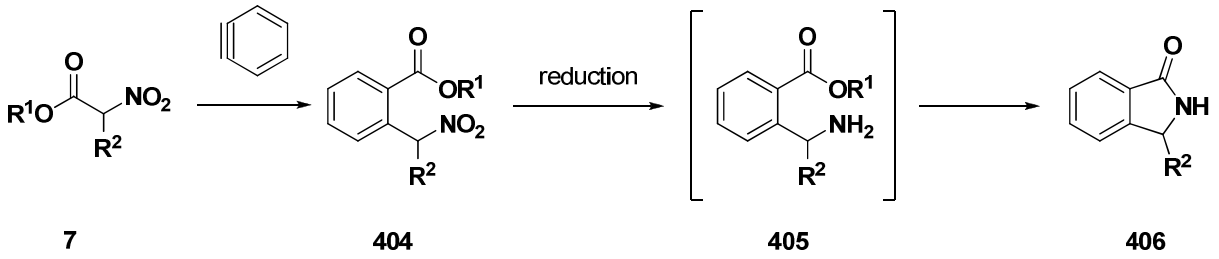
Scheme 133: Attempted α-arylation of acetamide **403**

The problem with both these reactions appears to be the vast number of side-reactions that can occur. Perhaps this is to be expected as both Greeney[213] and Larock[214] have recently demonstrated the possible insertion of arynes into the C-N bond of amides and also Miyabe[215] has reported on the insertion into the π-bond of amides.

5.4 Rearrangement Reactions of Nitroacetates and Benzyne

In section 5.2 it was shown that under certain conditions benzyne can be encouraged to undergo an insertion into the C-C bond of ethyl nitroacetate **(368)** as the major reaction pathway. Although this was not the original goal of these experiments, this reaction presents itself as an exciting opportunity for further exploration, and this Section will describe the additional investigations undertaken.

As described in the introduction (see section *1.4.2.3*) the insertion of arynes into certain C-C bonds has been well documented, but there is no example of such an insertion into the C-C bond of an α-nitro carbonyl species. This reaction also provides further areas for expansion, as reduction of the product **404** should provide amine **405** which could cyclise to form lactam **406**. Therefore this reaction could provide a novel, efficient route into substituted *iso*-indolinones **406** (Scheme 134).



Scheme 134: Proposed formation of *iso*-indolinones **406** *via* an aryne C-C insertion reaction

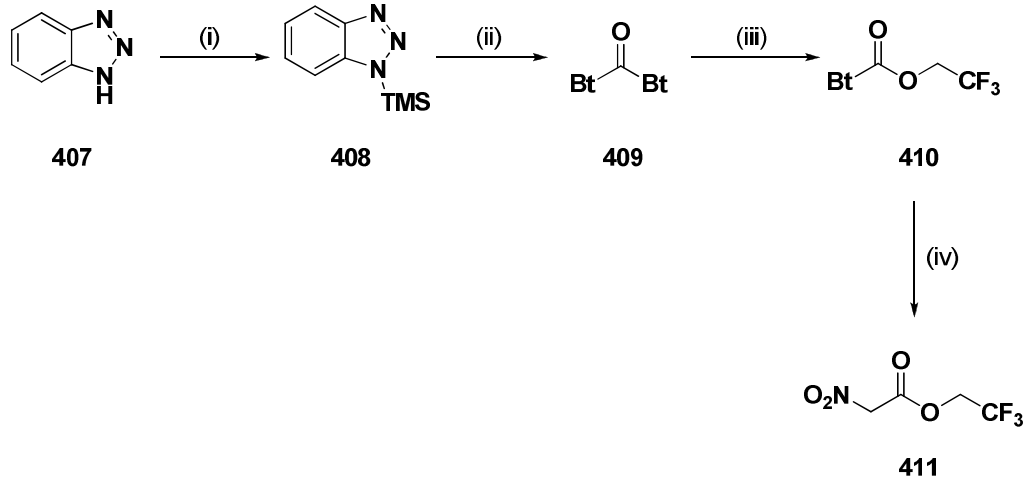
The best results so far have been found for ethyl nitro acetate **(368)** and benzyne precursor **51**, which in the presence of potassium fluoride gave a 67% yield of **369** and **370** with a ratio of 1 : 2.8 respectively (Scheme 123).

5.4.1 Use of More Electrophilic Esters

To promote the reaction that was originally necessary to be suppressed required an alteration of strategy. It was thought that increasing the electrophilicity of the ester functionality should increase the amount of rearrangement product afforded. Careful choice of ester was required as the potential alcohol leaving group could not be better than the α-nitro group. Therefore an ester with an alcohol component with a pK_a of 10 or higher was required.

The first target ester was 2,2,2-trifluoroethyl 2-nitroacetate **(411**). A simple route was devised, which was anticipated to eliminate some of the hydroxyl side products encountered in the other routes to such compounds (see Schemes 120 and 132). Following a literature

procedure[216] TMS protection of benzotriazole **(407)** with hexamethyldisilazane gave **408**, which was then treated with half an equivalent of phosgene to give carbonyldibenzotriazole **(409)** in 67% yield after recrystallisation from toluene and then subsequently stirring in excess 2,2,2-trifluoroethanol gave **410**. Katritzky[217] demonstrated that the potassium salt of nitromethane can be used to displace benzotriazole from similar compounds. Indeed, pre-forming potassium nitromethane in DMSO and treating with **410** gave crude **411** which after a careful low temperature work-up and distillation afforded pure product as a highly volatile oil (Scheme 135).

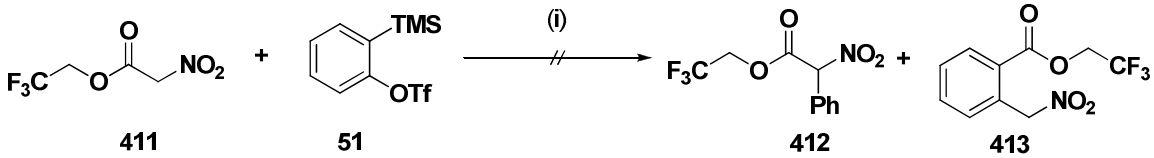


407 408 409 410 411

Reagents and Conditions: (i) HMDS, THF, reflux, 18 h; (ii) Cl_2CO (20% in PhMe), CH_2Cl_2, 0 ºC to rt, 1 h, 67% over 2 steps; (iii) $HOCH_2CF_3$, rt, 18 h, 66%; (iv) KCH_2NO_2, DMSO, 10 ºC to rt, 16 h, 31%.

Scheme 135: Formation of **411**

With desired acetate **411** in hand, it was possible to test its reactivity in the C-C insertion reaction (Scheme 136). Unfortunately, reaction with **51** under standard conditions did not give any of the expected products **412** or **413**. In fact degradation seemed to have occurred as there were no CH_2NO_2 or CH_2CF_3 peaks in the crude ^{1}H NMR of the reaction. The high volatility of **411** and its failure to undergo the required reaction, indicated that this substrate was not suitable to aid with the optimisation of this reaction.



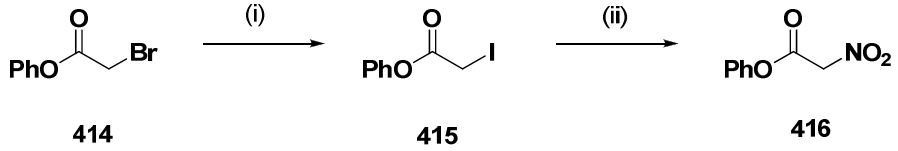
411 51 412 413

Reagents and Conditions: (i) KF/18-crown-6, THF, rt.

Scheme 136: Attempted reaction of acetate **411** with benzyne

The next ester to be synthesised was the phenyl ester **416**. Although the pKa of phenol is similar to that of the nitromethane leaving group, it was hoped that it would be sufficiently larger, and hence the rearrangement would still occur.

Ester **416** was accessible by two different routes. Firstly a Finkelstein reaction on α-bromo ester **414** to give iodide **415**, followed by a very slow displacement reaction with silver nitrite[218] gave desired ester **416**, but in a very low yield for the last step (Scheme 137).

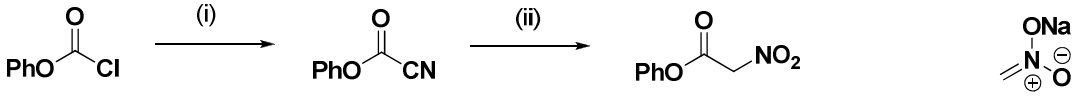


414 415 416

Reagents and Conditions: (i) NaI, acetone, rt, 16 h, then reflux 4 h, 74%; (ii) $AgNO_2$, Et_2O, rt, 5 d, 10%.

Scheme 137: First synthesis of **416**

An alternative synthesis was investigated, involving the formation of the cyanoformate **418** from the chloroformate **417**.[219] Displacement of the cyano group with the sodium salt of nitromethane, **419**,[220] gave the desired product **416**, but again in a very low yield for the final step (Scheme 138).

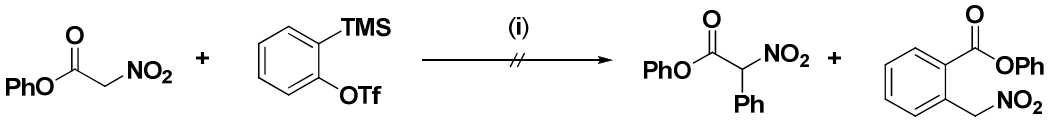


417 418 416 419

Reagents and Conditions: (i) TMSCN, DABCO, rt 18 h, 88%; (ii) **419**, THF, rt, 48 h, 5%.

Scheme 138: Alternative synthesis of ester **416**

Even though the synthetic route was clearly flawed, there was enough material to test in the C-C insertion reaction. However subjection to the standard reaction conditions resulted in only decomposition and none of **420** or **421** was identified (Scheme 139).



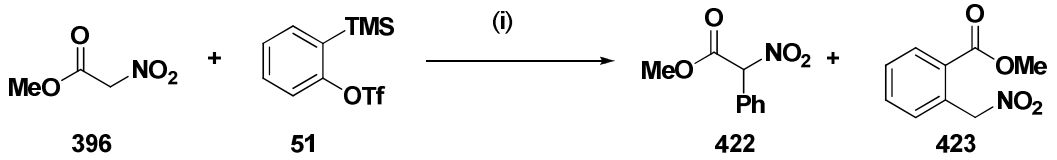
416 51 420 421

Reagents and Conditions: (i) KF/18-crown-6, THF, rt 12 h.

Scheme 139: Attempted benzyne C-C insertion into ester **416**

5.4.2 Use of Methyl Nitroacetate

As the use of more electrophilic esters had proven unsuccessful, it was hoped that swapping ethyl nitroacetate **(368)** for the less sterically encumbered commercially available methyl nitroacetate **(396)** would promote the desired reaction. Indeed, this reagent gave greater yields of desired **423** over α-arylated product **422** (Scheme 140, Table 14).



Reagents and Conditions: See Table 14.

Scheme 140: Reaction of methyl nitroacetate **(396)** with benzyne

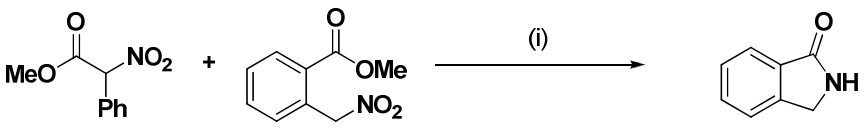
Table 14: Optimisation of C-C insertion reaction with methyl nitroacetate **(396)**

Entry[a]	Conditions	equiv. of 51	Ratio of 422 : 423[b]	Combined Yield /%[c]
1	KF/18-crown-6, THF, rt, 0.1M, 30 h	1.25	1 : 4.5	24
2	KF/18-crown-6, THF, rt, 0.25M, 48 h	1.75	1 : 5.3	65
3	KF/18-crown-6, $Sc(OTf)_3$, THF, rt, 0.25 M, 24h	2.0	1 : 4	22[d]

[a]Reactions were carried out on a 1 mmol scale and monitored by TLC. [b]As determined by integration of the ^{1}H NMR of the crude reaction mixture. [c]After column chromatography. [d]In this case pure **423** was isolated.

Changing the number of equivalents of benzyne precursor **51** from 1.25 to 1.75 and increasing the concentration (Table 14, Entries 1 and 2) gave a 65% yield of combined products in a 1 : 5.3 ratio. The use of an oxyphilic Lewis acid to aid cyclisation onto the ester (Entry 3) enabled isolation of pure **423**, in low yield.

The reduction and cyclisation to *iso*-indolinone **9a** was then undertaken; the combined product mixture from the best conditions found in Table 14 (Entry 2) was subjected to nickel boride reduction by treatment with sodium borohydride and nickel (II) chloride hexahydrate. The resultant *iso*-indolinone **9a** was isolated in a 77% yield (Scheme 141).



422 **423** **9a**

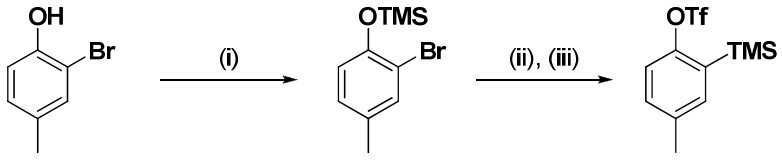
1 : 5.5

Reagents and Conditions: (i) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, 0 ºC to rt, 4 h, 77%.

Scheme 141: Reduction and cyclisation to *iso*-indolinone **9a**

5.4.3 Scope of Reaction

Using optimised conditions the reaction scope was investigated to determine if alkyl substituents would be tolerated on either the benzyne precursor or the nitroester. A model methyl substituted benzyne precursor **426** was synthesised. In a similar procedure to the synthesis of novel benzyne precursor **390** (Scheme 126), silyl protection of bromo phenol **424** afforded **425** which underwent the required retro-Brook rearrangement and triflation to furnish **426** (Scheme 142).

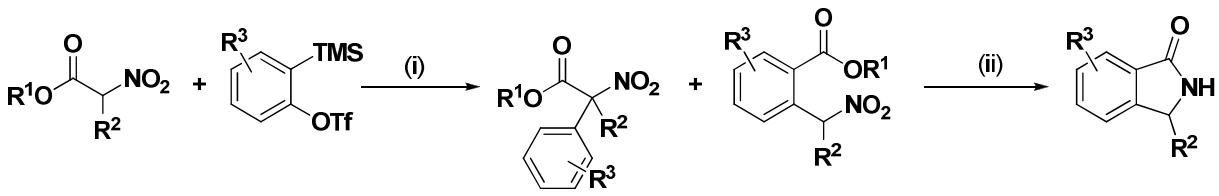


424 **425** **426**

Reagents and Conditions: (i) HMDS, THF, reflux, 18 h; (ii) *n*-BuLi, THF, −78 ºC to rt, 1 h; (iii) Tf_2O, −78 ºC, 20 min, 76% over 3 steps.

Scheme 142: Synthesis of methyl benzyne precursor **426**

Various nitroacetates were reacted with benzyne precursors **51** and **426** under the optimised reaction conditions and the products of C-C insertion reduced to the desired *iso*-indolinones **9a-d** (Scheme 143, Table 15).

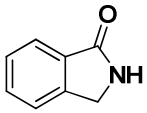
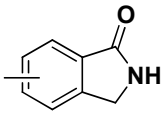
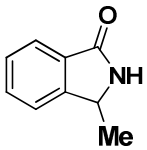
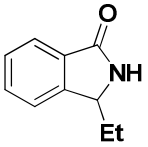


7 52 427 8 9a-d

Reagents and Conditions: (i) KF/18-crown-6, THF, rt; (ii) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 0 ºC to rt, 4 h.

Scheme 143: Scope of C-C insertion reaction followed by *iso*-indolinone synthesis

Table 15: Scope of reaction

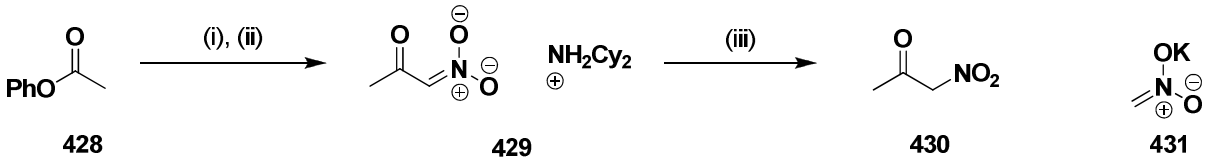
Entry[a]	R^1	R^2	R^3	Time / h	Combined Yield 427 and 9 /%	Ratio 428 : 9	Yield 9 /%	Product
1	Me	H	H	48	65	1 : 5.5	77	 **9a**
2	Me	H	4-Me	48	-[b]	-[c]	13[d]	 **9b**[e]
3	Et	Me	H	1.5	66	1 : 3.5	70	 **9c**
4	Et	Et	H	1	-[b]	-[c]	25[d]	 **9d**

[a]Reactions were carried out on a 1 mmol scale, employing 1.75 equiv. benzyne precursor in THF (0.25 M), KF (4 equiv.) and 18-crown-6 (4 equiv.). [b]Isolation without impurities was impossible at this stage. [c]The ratio was not determined due to the inability to identify the two main species in an impure product mixture. [d]Yield over 2 steps.[e] Isolated as a 1 : 1.2 mixture of regioisomers.

Use of benzyne precursor **426** (Table 15, Entry 2) provided the two regioisomeric *iso*-indolinones **9b** in 13% yield over two steps. Nitroacetates bearing α-alkyl substituents (Entries 3 and 4) were much faster to react in the C-C insertion reactions, all benzyne precursor being consumed in 1.5 hours. Their corresponding *iso*-indolinones **9c** and **9d** were also readily synthesised.

5.4.4 Rearrangement Reactions of α-Nitro Ketones

It was assumed that changing the ester group in the nitroacetate to a ketone would favour the rearrangement reaction over α-arylation, again due to increased electrophilicity. Out of interest and due to the lack of any literature evidence, it was thought it would be beneficial to test this theory. To this end, nitropropanone **(430)** was synthesised as its dicyclohexylamine salt by reaction of phenolacetate **(428)** with potassium methanenitronate **(431)** and then treatment with dicyclohexylamine[221] (Scheme 144). In its crystalline form it is more stable and hence can be stored and then freshly converted on demand to nitropropanone by treatment with acid.



428 **429** **430** **431**

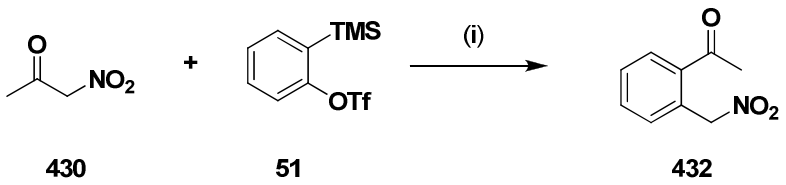
Reagents and Conditions: (i) **431**, DMSO, 5 ºC to rt, 18 h; (ii) $HNCy_2$, 49%; (iii) 2M HCl, 1 h, quant..

Scheme 144: Synthesis of nitropropanone

Nitropropanone **(430)** was reacted with benzyne precursor **51** in the usual manner to investigate its reactivity in the α-arylation reaction (Scheme 145, Table 16).

It was noted that using cesium fluoride in acetonitrile at 80 ºC (Table 16, Entries 2 and 4) gave desired ketone **432** only, and no α-arylation product. The modest yields are attributed to aromatic impurities that were difficult to separate *via* chromatography thus lowering the yield of clean product.

Use of alternative fluoride sources (Entries 1 and 7), lower reaction temperatures (Entry 2), different solvents (Entry 6) and increased pressure (Entry 5) were unsuccessful for this reaction.



430 51 432

Reagents and Conditions: see Table 16.

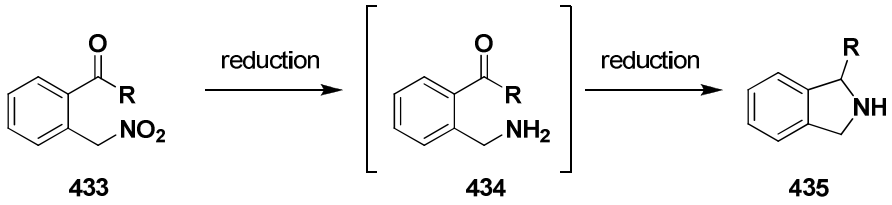
Scheme 145: Reaction of nitropropanone with benzyne

Table 16: Optimisation of C-C insertion reaction of benzyne into nitropropanone

Entry[a]	No. of equiv. of 51	Conditions	Yield of 432[b] / %
1	1.25	KF/18-crown-6, THF, rt	No product[c]
2	1.25	CsF, MeCN, 80 °C, 2 h	40
3	1.25	CsF, MeCN, 60 °C	No reaction
4	0.9	CsF, MeCN, 80 °C, 2 h	42
5	1.25	CsF, MeCN, 80 °C, 2 h, sealed tube	No product[c]
6	1.25	CsF, DME, 90 °C	No reaction
7	1.25	TBAT, MeCN, 80 °C	No reaction

[a]Typical reactions were carried out on a 1 mmol scale at a 0.2 M concentration. [b]Isolated yield after column chromatography. [c]A intractable mixture of products was formed.

As in the case of the nitroacetates, the ability to synthesise such ketones **433** could enable a facile synthesis of *iso*-indolines **435** after a nitro-reduction/reductive-amination (Scheme 146).



433 434 435

Scheme 146: Proposed reduction to form *iso*-indolines **435**

Due to time constraints, and deviation from the main α-arylation research topic, this project is to be continued by a co-worker.

5.5 Conclusions and Future Work

Unsubstituted nitroacetates undergo C-C insertion reactions with benzyne as well the desired α-arylation reaction. Optimisation studies were conducted but were unable to increase the amount of desired product by a significant amount to make the reaction viable. Neither the use of nitromalonates nor nitroamides provided a satisfactory solution.

α-Arylation was possible for methyl substituted ethyl nitroacetate with no unwelcome rearrangement product, but only in low isolated yields.

A novel silylaryl triflate benzyne precursor, **390**, was successfully synthesised, and proved to undergo benzyne formation at lower temperatures than its corresponding trimethylsilyl analogue, **51**.

The C-C insertion reaction was further optimised and shown to be a useful method for the synthesis of substituted *iso*-indolinones **9** in reasonable yields after a reduction/lactamisation sequence.

Nitropropanone **(430)** was also shown to undergo the same C-C insertion reaction, and in future work this will be expanded upon to make it general for a range of nitroketones and a reduction sequence should be a straightforward method to afford *iso*-indolines **435**.

Chapter 6: Results and Discussion: Investigations into the Addition of Schöllkopf Bis-Lactim Ethers to Arynes

6.1 Introduction

Based on the results in the previous two Chapters regarding the reactivity of glycine enolates towards arynes an alternative strategy was conceived. A glycine equivalent was required which has neither nucleophilic nitrogen lone pairs, nor electrophilic carbonyl moieties. This led us to consider the use of a classical auxiliary-based glycine equivalent in α-arylation reactions. Such molecules have been widely used in the diastereoselective synthesis of α-amino acids (Figure 21).[149,150,155]

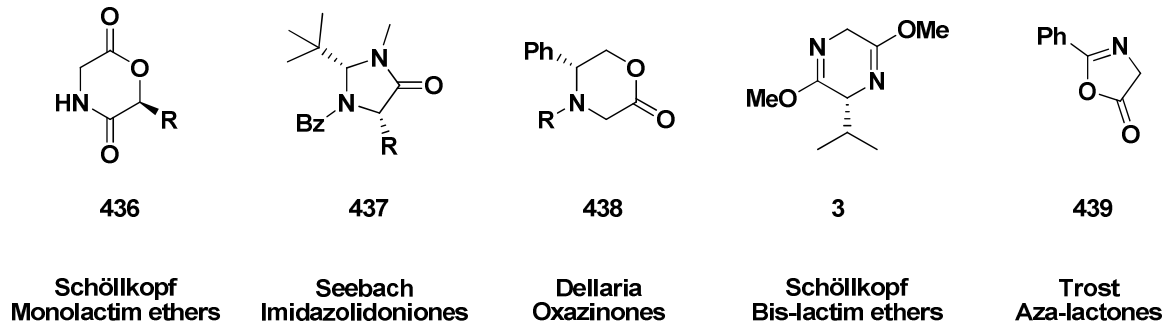


Figure 21: Examples of auxiliary-based glycine equivalents used in the synthesis of asymmetric, α-amino acids by Schöllkopf,[222,223] Seebach,[224] Dellaria[225] and Trost[226]

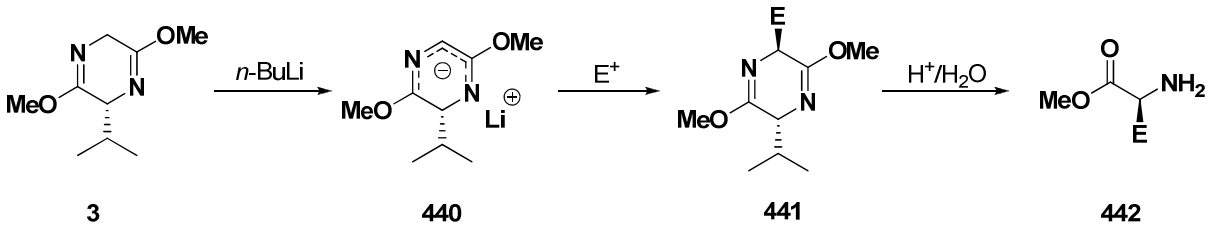
Not only would the use of a chiral auxiliary control the stereochemical outcome of the arylation, but the carbonyl and nitrogen functionalities would be tied up in a heterocyclic ring, minimising side reactions.

It was decided to explore the use of Schöllkopf's bis-lactim ether **3** in the first instance as the protected glycine equivalent, due to its complete lack of electrophilic carbonyl groups and the reduced nucleophilicity of the ring nitrogen atoms. It has also been successfully used by Pearson[227,228] in arylation reactions employing arene-manganese tricarbonyl complexes as the electrophilic arylating reagent.

6.1.1 Schöllkopf's Bis-Lactim Ether

In the 1980's Schöllkopf [223,229] developed methodology for the enantioselective synthesis of unnatural amino acids by the use of a chiral glycine enolate equivalent, the bis-lactim ether **3**. Deprotonation with alkyllithium bases occurs at the unsubstituted carbon to generate anion

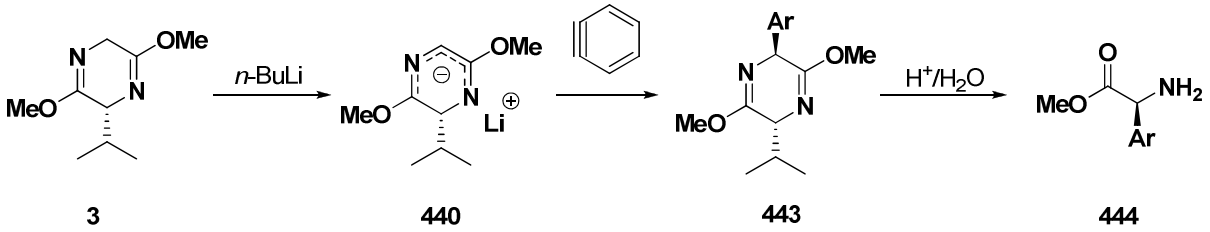
440, followed by diastereoselective nucleophilic attack on an electrophile on the opposite face to the *iso*-propyl group to give *anti* adduct **441**. A wide range of electrophiles have been employed such as alkylhalides, epoxides and aldhehydes.[229,230] Acidic hydrolysis of the bis-lactim ether releases the enantio-enriched new α–amino acid, **442** (Scheme 147).



3 440 441 442

Scheme 147: Schöllkopf's bis-lactim ether **3** used for the formation of optically pure amino acids **442**

It was hoped that the same strategy could be utilised for the formation of aryl amino acids **444**, by employing arynes as the electrophilic arylation reagent (Scheme 148).



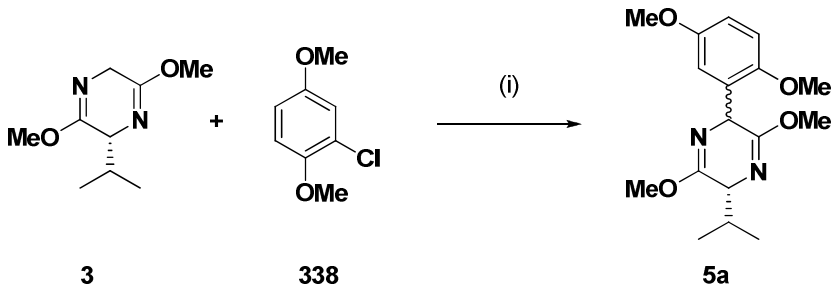
3 440 443 444

Scheme 148: Potential use of Schöllkopf's bis-lactim ethers in α-arylation reactions employing benzyne

6.2 Developing α-Arylation Methodology

6.2.1 Initial Observations

Deprotonation of a mixture of bis-lactim **3** and dimethoxyaryne precursor **338**[195] at −95 ºC using *sec*-butyllithium, followed by warming to room temperature overnight and quenching with water, afforded arylated adduct **5a** as an inseparable mixture of diastereoisomers (88 : 12 ratio) in a combined 45% yield (Scheme 149). The order of addition was crucial. If either of the starting materials were lithiated separately and then combined, no desired reaction occurred.



3 **338** **5a**

Reagents and Conditions: (i) 2 equiv. *s*-BuLi, THF, − 95 ºC to rt, 18 h, then H_2O, 45%, 88 : 12 dr.

Scheme 149: Arylation of bis-lactim ether **3** with dimethoxybenzyne

The data suggested the major diastereoisomer was the *syn*-adduct by observation of a larger H_1-H_4 coupling constant (J = 6.3 Hz) than that for the minor, *anti*-isomer (J = 3.1 Hz) (See Appendix 1). nOe analyses also confirmed this (Figure 22). This is also consistent with data reported for similar compounds.[228] This was an interesting result as the expected major diastereoisomer was the *anti*-adduct as would be expected for arylation on the opposite face to the *iso*-propyl group.

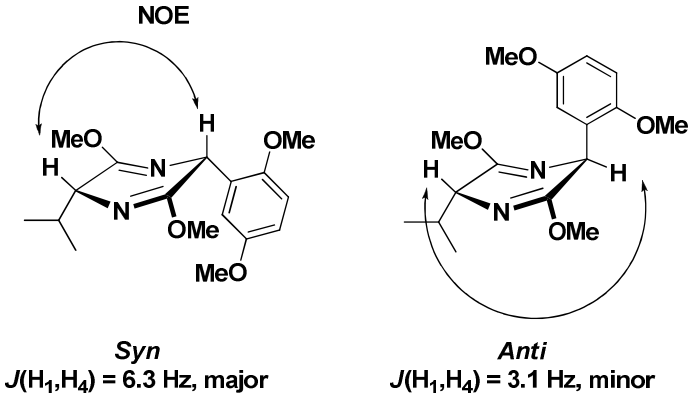


Figure 22: *J* values and nOes for *syn*- and *anti*-diastereoisomers of **5a**

To confirm this theory, a crystal was grown suitable for X-ray analysis, and this did indeed prove that the major diastereoisomer was of *syn* geometry (Figure 23).

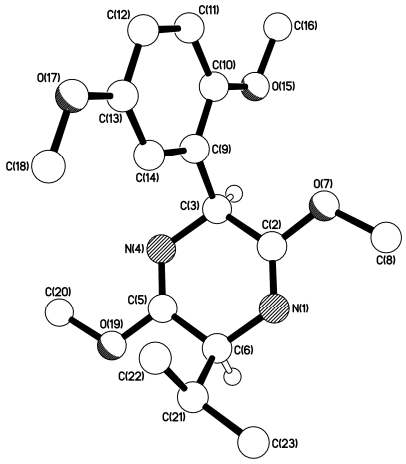
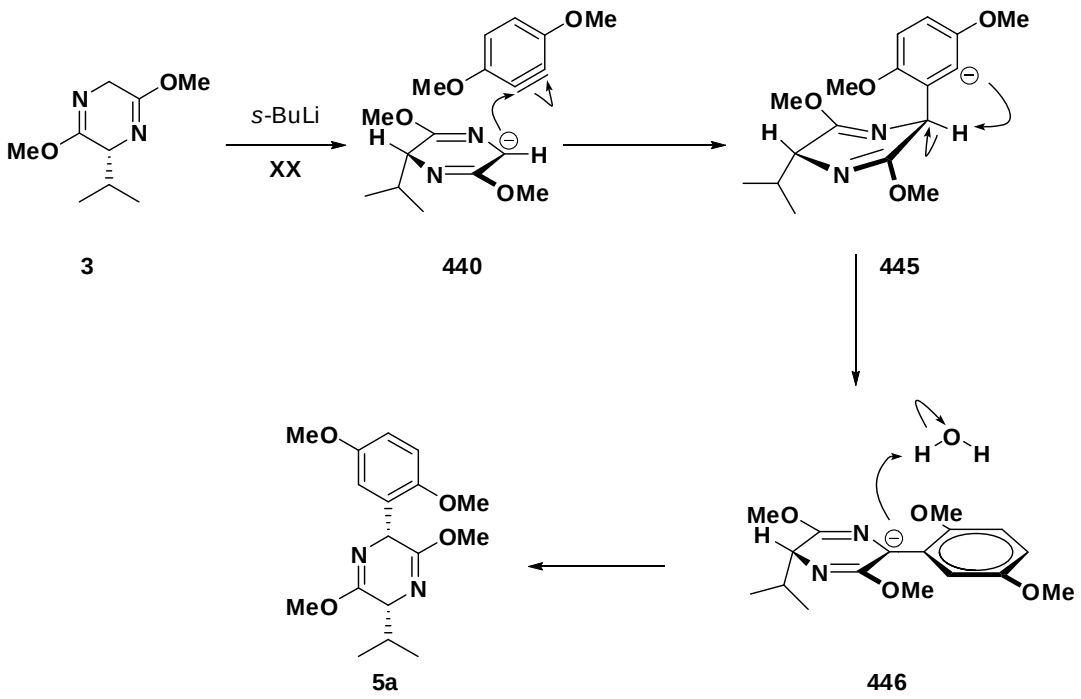


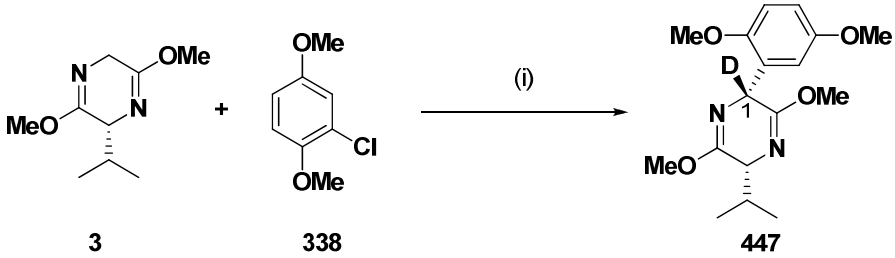
Figure 23: X-ray structure of *syn*-diastereoisomer **5a**

To rationalise this stereochemical outcome, a mechanism was proposed in which initial attack of lithiated **440** onto the aryne occurred as expected, on the opposite face to the *iso*-propyl group. Subsequent inter- or intra-molecular proton transfer to the α-aryl position with the newly formed carbanion **445** gave planar species **446**. Subsequent diastereoselective kinetic protonation occurred on the less hindered face to give *syn* adduct **5a** (Scheme 150).



Scheme 150: Proposed mechanism for *syn* diastereoisomer **5a** formation

To support this hypothesis, a deuterium-labelling experiment was undertaken. Quenching the reaction with D_2O as opposed to H_2O gave deuterium incorporation only in the C_1 position to give **447**, indicating that the second deprotonation had occurred as suggested (Scheme 151).



3 **338** **447**

Reagents and Conditions: (i) 2 equiv. *s*-BuLi, THF, −95 ºC to rt, 18 h then D_2O, 52%, 89 : 11 dr.

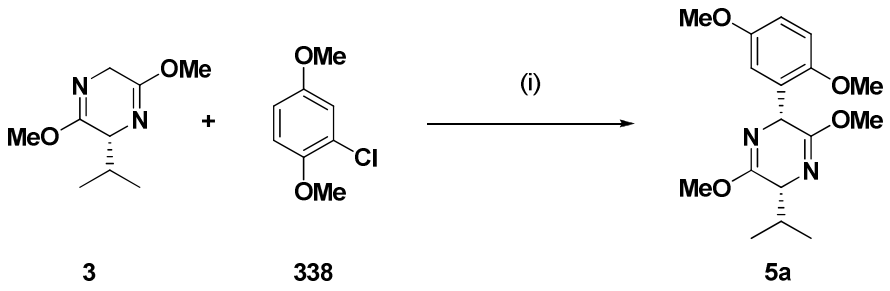
Scheme 151: Deuterium-labelling experiment

6.2.2 Optimisation of α-Arylation Reaction

With the aim of optimising both the yield and the dr, a series of conditions were applied to this reaction (Scheme 152, Table 17). Increasing the number of equivalents of chloride **338** to 1.75 and base to 3.0 (Entries 2 and 3) resulted in an improved yield of adduct **5a** to 63%.

Due to the mechanistic hypothesis, it was necessary to examine bulkier weak acids, with the aim of improving the dr. Gratifyingly it was observed that the use of 2,6-di-*tert*-butyl-4-methylphenol (BHT)[231] at room temperature gave an improved dr of 94 : 6 (Entry 6) and an increased yield of 75%. Quenching at −78 ºC (Entry 7) or the use of other bulkier proton sources such as *tert*-butanol or citric acid (Entries 4 and 5) did not further improve the dr or yield.

It was discovered that a single recrystallisation of **5a** from ethanol gave the product in a >99 : 1 dr.



3 338 5a

Reagents and Conditions: (i) *s*-BuLi, THF, −95 ºC to rt, 18 h then source of H^+, See Table 17.

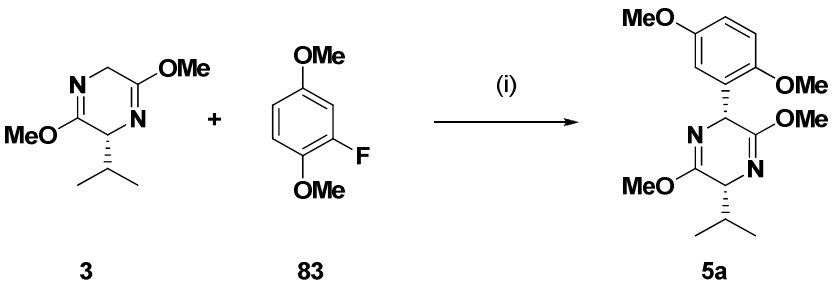
Scheme 152: Optimisation of arylation reaction

Table 17: Optimisation conditions for arylation reaction

Entry[a]	Equiv. 338	Equiv. *s*-BuLi	Proton Source	Temperature of proton quench	Yield[c] %	dr[d]
1	1	2.1	H_2O	rt	45	88 : 12
2	1.25	2.5	H_2O	rt	38	91 : 9
3	1.75	3.0	H_2O	rt	63	89 : 11
4	1.75	3.0	citric acid	rt	69	89 : 11
5	1.75	3.0	*t*-BuOH	rt	60	92 : 8
6	1.75	3.0	BHT[b]	rt	75	94 : 6
7	1.75	3.0	BHT	−78 ºC	57	91 : 9

[a]Typical reactions carried out on 1-2 mmol scale in anhydrous THF. Deprotonation occurs at −95 ºC for 30 mins followed by overnight warming to room temperature. [b]BHT = 2,6-di-*tert*-butyl-4-methylphenol. [c]Combined yield of both diastereoisomers after column chromatography. [d]As determined by integration of ^{1}H NMR spectra.

The use of fluoride precursor **83** was also investigated under the optimised conditions, as this did not require such low temperatures as **338** and could be generated with *n*-BuLi rather than *s*-BuLi (Scheme 153).[81]



3 **83** **5a**

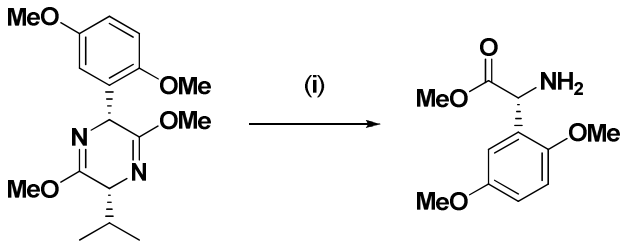
Reagents and Conditions: (i) 3 equiv. *n*-BuLi, THF, − 78 ºC to rt, 18 h then BHT, 56%, 96 : 4 dr.

Scheme 153: Arylation of bis-lactim ether **3** using benzyne derived from precursor **83**

Adduct **5a** was afforded and although the dr was the same, the yield was slightly reduced to 56%.

6.2.3 Hydrolysis of Adducts

The next process was to investigate the hydrolysis of bis-lactim ether adduct **5a** to the amino acid methyl ester **448**. Subjection to standard, mild acidic conditions (0.5 M HCl, THF, room temperature)[223] provided the expected amine **448** in 81% yield (Scheme 154).



5a **448**

Reagents and Conditions: (i) 0.5 M HCl, THF, rt, 18 h, 81 %, 83 : 17 er.

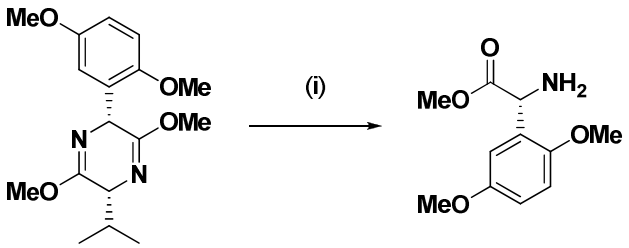
Scheme 154: Hydrolysis to methyl ester **448**

However, when the enantiomeric ratio of **448** was determined by chiral HPLC, it was discovered that some epimerisation had occurred during hydrolysis. The er of **448** was 83 : 17 as compared to the 93 : 7 dr of the adduct **5a**.

None of the literature examples indicate any epimerisation during hydrolysis; however, this could be explained by the fact that all of the literature examples start from the *anti*-adducts compared to the *syn*-adduct **5a**. During the hydrolysis process, tautomerisation, and hence epimerisation of the chiral centre is possible, but the *anti*-adducts are already in the most thermodynamically favourable state, and any tautomerisation before hydrolysis is complete

will return the adduct to this diastereoisomer. In this case, any tautomerisation is going to favour conversion to the thermodynamically more stable *anti*-adduct, hence decreasing the enantiomeric ratio once hydrolysis is complete. As a proof of concept, the hydrolysis was again attempted, but this time the reaction was quenched before it had gone to completion. ^{1}H NMR analysis of the crude material demonstrated that the remaining starting material had decreased its diastereomeric ratio from 93 : 7 to 89 : 1, indicating that epimerisation was occurring before hydrolysis took place.

To try to combat this undesirable degradation of chirality, a range of different conditions were examined, in which the acid, temperature, concentration and solvent were varied and in each case chiral HPLC analysis was used to determine whether epimerisation had occurred (Scheme 155, Table 18).



5a

93 : 7 dr

448

Reagents and Conditions: (i) See Table 18.

Scheme 155: Optimisation of hydrolysis reaction to reduce epimerisation

Table 18: Optimisation of hydrolysis reaction

Entry[a]	Acid	Solvent	Temperature / °C	Yield[c] / %	er[e]
1	0.5 M HCl	THF	rt	81	83 : 17
2	0.1 M HCl	THF	rt	73	71 : 29
3	0.5 M AcOH	THF	rt	no reaction[d]	/
4	0.5 M citric acid	THF	rt	56	/
5	0.5 M HCl	THF	0	69	79 : 21
6	2 M HCl	THF	rt	66	73 : 27
7	0.5 M CSA	THF	rt	64	78 : 22
8	2 M citric acid	THF	rt	42	72 : 28
9	0.1 M HCl	THF	0	66	91 : 9
10	0.5 M HCl	THF[b]	0	67	91 : 9
11	0.5 M HCl	MeCN	0	89	93 : 7
12	0.5 M CSA	THF	0	63	93 : 7

[a]Reactions were carried out on a 50 mg scale at a 0.15 M concentration and were allowed to stir overnight at the stated temperature. [b]Carried out at 0.03 M. [c]Isolated yield after column chromatography. [d]The dr of unreacted **5a** had decreased to 79 : 21. [e]As determined by chiral HPLC.

It was found that the use of either 0.5 M HCl in acetonitrile (Entry 11) or 0.5 M CSA in THF (Entry 12), both at 0 °C, did not result in any loss of optical purity. The yield was better for the HCl hydrolysis, and these were the conditions used in future experiments. This result was also shown to be reproducible and scalable to at least 1 gram.

It was interesting to observe that although conducting the reaction in acetic acid did not result in any hydrolysis (Table 18, Entry 3), considerable epimerisation of the starting

material was observed. A test reaction was carried out in which **5a** was treated with an excess of glacial acetic acid and allowed to stir at room temperature for 5 days. As expected, epimerisation had occurred and the dr of **5a** was now 12 : 82 in favour of the thermodynamically more stable *anti*-diastereoisomer. This would be useful in order to obtain, after hydrolysis, the opposite enantiomer of the α-aryl amino acid.

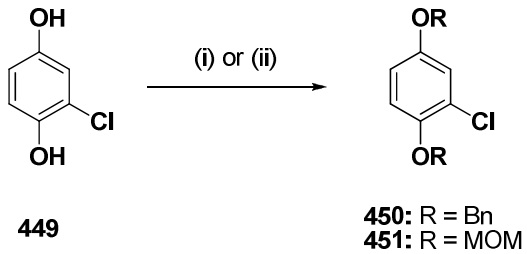
6.2.4 Scope of Reaction

The scope of the reaction was then investigated to ascertain which substitution patterns and functionality could be tolerated on the aryl unit. A range of benzyne precursors were employed, all containing *ortho*-directing groups (ODGs) and either a chloride or fluoride leaving group.

6.2.4.1 Synthesis of Benzyne Precursors

Although some of the benzyne precursors to be used in this reaction are commercially available, several needed to be synthesised. A combination of previously known benzyne precursors were synthesised along with novel ones.

Both the di-benzyl and di-MOM ethers **450** and **451** were prepared from chlorohydroquinone **(449)** using benzyl bromide and MOMCl respectively (Scheme 156).



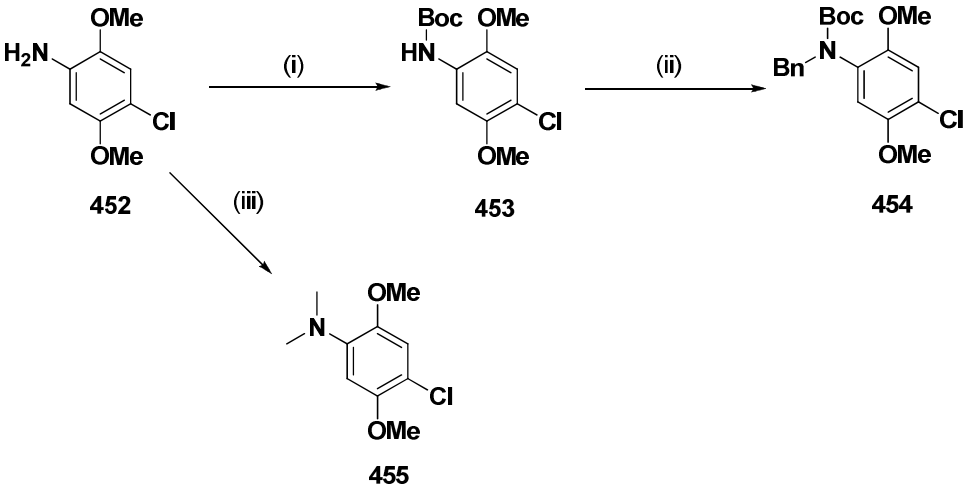
449

450: R = Bn
451: R = MOM

Reagents and Conditions: (i) BnBr, K_2CO_3, acetone, reflux, 18 h, 65% **450**; (ii) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt, 18 h, 71% **451**.

Scheme 156: Synthesis of di-benzyl and di-MOM ethers, **450** and **451**

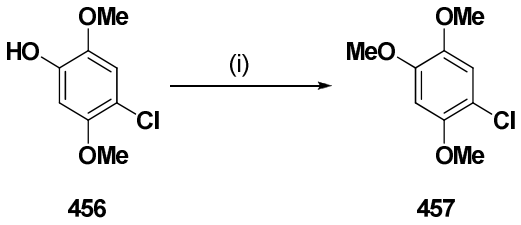
Dimethoxyaniline **452** was functionalised in two different manners (Scheme 157). First protection of the nitrogen as the *tert*-butyl carbamate gave **453** followed by a standard benzylation to give the benzyl, Boc-protected aniline **454**. Secondly a reductive amination employing formaldehyde and sodium cyanoborohydride gave dimethylaniline **455** in a good yield.



Reagents and Conditions: (i) Boc_2O, DMAP, THF, rt, 48 h, 49%; (ii) BnBr, NaH, DMF, 0 ^oC to rt, 3 h, 87%; (iii) HCHO, $NaCNBH_3$, AcOH, H_2O, MeOH, rt, 6 h, 75%.

Scheme 157: Functionalisation of aniline **452**

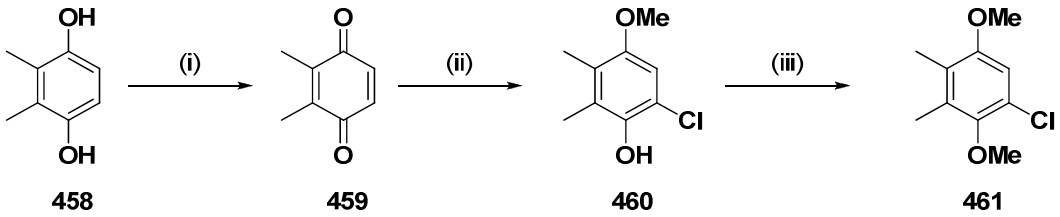
A trimethoxy precursor **457** was synthesised *via* methylation of 4-chloro-2,5-dimethoxyphenol **(456)** employing iodomethane (Scheme 158).



Reagents and Conditions: (i) MeI, NaH, CH_2Cl_2, rt, 48 h, 65%.

Scheme 158: Formation of trimethoxy benzyne precursor **457**

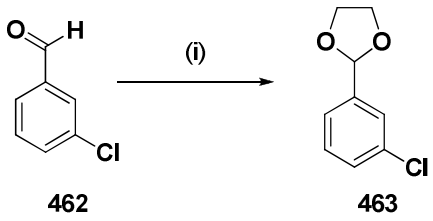
Dimethyl compound **461** was synthesised according to a three step literature procedure.[232,233] Oxidation of hydroquinone **458** with manganese dioxide gave quinone **459** in good yield. Chlorination was achieved through addition of anhydrous HCl to give **460** which was methylated under phase-transfer conditions to give precursor **461** (Scheme 159).



Reagents and Conditions: (i) MnO_2, Et_2O, rt, 30 min, 73%; (ii) AcCl, MeOH, 0 ^oC to rt, 18 h, 96%; (iii) Me_2SO_4, TBAB, KOH, CH_2Cl_2, H_2O, rt, 48 h, 76%.

Scheme 159: Synthesis of dimethyl precursor **461**

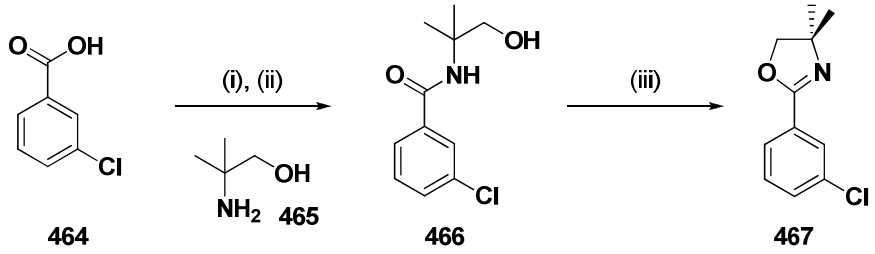
An alternative precursor containing an acetal directing group **463** was prepared from aldehyde **462** and ethylene glycol under Dean-Stark conditions (Scheme 160).



Reagents and Conditions: (i) $HOCH_2CH_2OH$, $PTSA{\cdot}H_2O$ cat., PhMe, reflux, Dean-Stark, 24 h, 50%.

Scheme 160: Acetal protection of **462**

Oxazoline **467** was synthesised from acid **464** according to a procedure by Meyers.[77] Amide formation with amino alcohol **465** and thionyl chloride promoted ring closure gave **467** in 71% over three steps (Scheme 161).

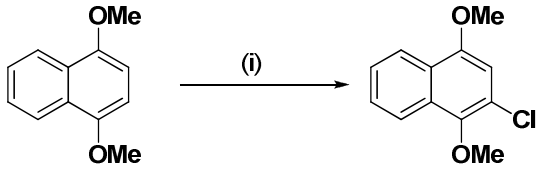


Reagents and Conditions: (i) $SOCl_2$, 100 ^oC, 1 h; (ii) **465**, CH_2Cl_2, 0 ^oC to rt, 18 h; (iii) $SOCl_2$, CH_2Cl_2/PhMe (3 : 1), reflux, 30 min then rt, 2 h, 71% over 3 steps.

Scheme 161: Synthesis of oxazoline precursor **467**

Two naphthalene aryne precursors were also synthesised. A modified literature procedure by Evans[234] was carried out to give chloro precursor **469** using a hypervalent iodine mediated chlorination of **468** employing iodosobenzene diacetate and chlorotrimethylsilane. Over-

chlorination was an issue; fortunately this could be resolved by the addition of stable free radical TEMPO to the reaction to give a clean mono-chlorination in 10 minutes (Scheme 162).

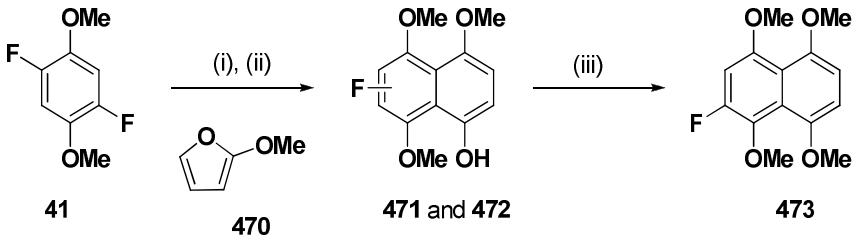


468 **469**

Reagents and Conditions: (i) $PhI(OAc)_2$, TMSCl, CH_2Cl_2, 0 °C, 1 h then **468**, TEMPO, CH_2Cl_2, 0 °C, 10 min, 43%.

Scheme 162: Chlorination of dimethoxynaphthalene **468**

Using methodology developed within the Barrett group,[36] a benzyne Diels-Alder reaction using 1,4-difluoro-2,5-dimethoxybenzene **(41)** and 2-methoxyfuran **(470)** generated regioisomeric species **471** and **472** after acid catalysed ring opening with 6 M HCl. Methylation with iodomethane gave fluoro-naphthalene precursor **473** (Scheme 163).



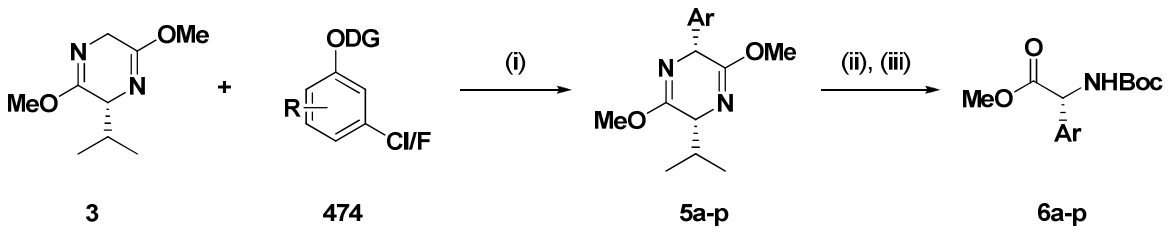
41 **470** **471** and **472** **473**

Reagents and Conditions: (i) *n*-BuLi, THF, −78 °C, 15 min then **470**, −78 °C to 0 °C, 3 h; (ii) 6 M HCl, MeOH, reflux, 3 h, 53% over 2 steps, 1 : 1.5 **471** : **472**; (iii) MeI, NaH, DMF, rt, 20 h, 41%.

Scheme 163: Synthesis of precursor **473**

6.2.4.2 α-Arylation Reactions

With the benzyne precursors in hand, examination of the scope of the optimised α-arylation was undertaken (Scheme 164, Table 19). Bislactim **3** was mixed with the required benzyne precursor **474** in THF at either −95 °C or −78 °C. Then either *sec*-butyllithium or *n*-butyllithium, depending on the nature of the benzyne precursor, was added dropwise and the reaction allowed to warm to room temperature overnight before being quenched with BHT. Following hydrolysis the amines were immediately protected as the corresponding *tert*-butyl carbamates **6** for ease of handling.

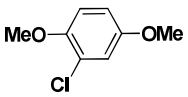
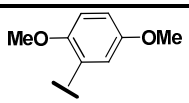
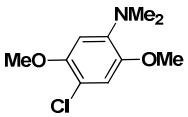
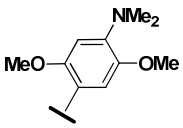
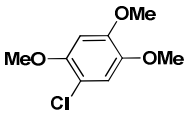
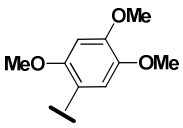
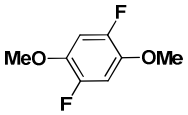
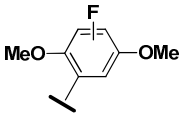
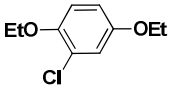
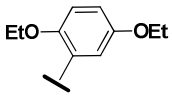
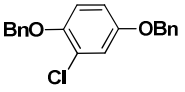
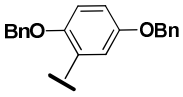
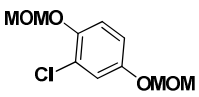
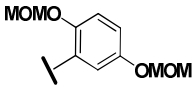


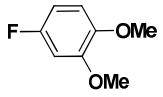
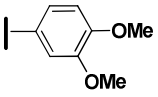
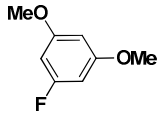
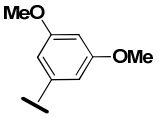
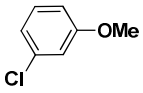
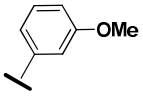
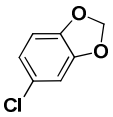
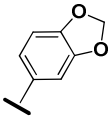
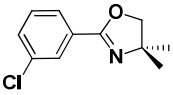
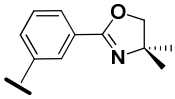
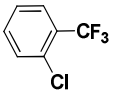
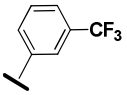
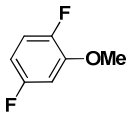
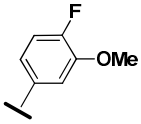
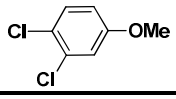
3 474 5a-p 6a-p

Reagents and Conditions: (i) *n*-BuLi, −78 ºC to rt or *s*-BuLi, −95 ºC to rt, THF then BHT, rt; (ii) 0.5 M HCl, MeCN, 0 ºC, 18 h; (iii) Boc_2O, *i*-Pr_2NEt, CH_2Cl_2, rt, 12 h, See Table 19.

Scheme 164: Scope of aryne α-arylation reaction

Table 19: Scope of α–arylation reaction with different benzyne precursors

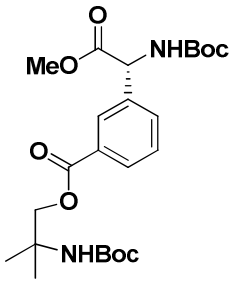
Entry	Benzyne precursor		Base[a]	Ar product		Yield 5[b] /%	dr[c]	Yield 6[b,d] /%	
1		**338**	*s*-BuLi		**5a**	75	94:6	89	**6a**
2		**455**	*s*-BuLi		**5b**	41	92:8	96	**6b**
3		**457**	*s*-BuLi		**5c**	37	94:6	59	**6c**
4		**41**	*n*-BuLi		**5d**	57[e]	91:9	48 + 46[f]	**6d + 6e**
5		**475**	*s*-BuLi		**5f**	72	92:8	98	**6f**
6		**450**	*s*-BuLi		**5g**	33	90:10	79	**6g**
7		**451**	*s*-BuLi		**5h**	52	89:11	66	**6h**

Entry	Benzyne precursor		Base[a]	Ar product		Yield 5[b] /%	dr[c]	Yield 6[b,d] /%	
8		**476**	*n*-BuLi		**5i**	62	76:24	92	**6i**
9		**88**	*n*-BuLi		**5j**	72	74:26	70	**6j**
10		**477**	*s*-BuLi		**5k**	67	70:30	67	**6k**
11		**478**	*s*-BuLi		**5l**	17	76:24	/	**/**
12		**467**	*n*-BuLi		**5m**	55	71:29	41	**6m**
13		**479**	*n*-BuLi		**5n**	61	50:50 >99:1[g]	93	**6n**
14		**480**	*n*-BuLi		**5o**	53	73:27	62	**6o**
15		**481**	*s*-BuLi	/	**5p**	/	/	/	**/**

[a]Reactions were carried out on a 1 mmol scale, employing benzyne precursor (1.75 equiv.) and base (3.0 equiv.) in THF (0.2 M) at either −78 ºC (for *n*-BuLi) or −95 ºC (for *s*-BuLi). After stirring for 1 h at low temperature, the reaction was allowed to warm to room temperature overnight and BHT (4 equiv.) was added. [b]Isolated yield. [c]Determined by ^{1}H NMR integration. [d]HPLC analysis of a representative number of compounds **5** determined that they undergo negligible racemisation upon hydrolysis to the corresponding amine; this indicates that the er of **6** should be the same as the dr of **5**. See Appendix 2. [e]Isolated as a mixture of regioisomers. [f]Separable by chromatography. [g]After separation by chromatography.

Dimethylamino, methoxy, and fluoride analogues gave adducts **5b-d** (Entries 2-4) with excellent diasteroselectivities and as single regioisomers except for **5d** which exhibited no regioselectivity and gave fluoride adduct **5d** as a 1 : 1 mixture of regioisomers. Fortunately

upon hydrolysis and *N*-Boc protection, the two isomeric carbamates **6d** and **6e** were separable. The low yield for **5c** can be rationalised by competing lithiation at the 5-position.[235] Changing the nature of the protecting groups to ethyl, benzyl, or MOM ethers (Entries 5-7) gave adducts **5f-h**, again in good diasteroselectivities and yields except for in the case of the sterically demanding benzyl precursor **450**. It was worth noting that under the mild hydrolysis conditions, no deprotection of the MOM ether in adduct **5h** was observed. Altering the position of the *para*-methoxy groups in **338** to the *ortho*-**476** and *meta*-**88** dimethoxy precursors provided adducts **5i** and **5j** in good yields (Entries 8-9), again with complete arene regioselectivity.[71] The diastereoselectivity for formation of these adducts was dramatically reduced to around 75 : 25. Although similar dioxole precursor **478** did participate in the α-arylation reaction, the yield was so low, that hydrolysis was not attempted (Entry 11). The reaction of 3-Chloroanisole **(477)** proceeded without incident to give adduct **5k** (Entry 10). The nature of this single directing group was varied from an ether to oxazoline precursor[236] **467** and 1-chloro-2-(trifluoromethyl)benzene[38] **(479)**, affording their respective adducts, **5m** and **5n** in respectable yields (Entries 12-13). The oxazoline ring in **5m** partially hydrolysed under the mild, acidic hydrolysis conditions, and as well as desired ester **6m**, ester **482** was also isolated in 12% yield (Figure 24).



482

Figure 24: Side-product of **5m** hydrolysis

Although there was no diastereoselectivity in the formation of adduct **5n**, the two diastereoisomers were easily separable, and hence the methyl ester **5n** was obtained in high enantiopurity. A fluoride on the anisole ring was also tolerated, giving adduct **5o** (Entry 14), however dichloride precursor **481** gave a large mixture of unidentifiable regioisomeric products (Entry 15). In all cases regiochemistry was confirmed by using a mixture of 1D and 2D NMR analyses.

It is clear that, for all aryne precursors without a chelating substituent in the *ortho* position to the Schöllkopf glycine (Entries 8-15), the diastereoselectivity of the reaction noticeably decreased. It was possible that without this substituent, there is twisting of the linked 6-membered rings out of plane, hence decreasing facial selectivity for the proton quench.

Purification of several adducts **5a-p** proved difficult, however it was found that after initial column chromatography with an ethyl acetate/hexanes solvent system, further chromatography using a toluene/acetone solvent system was successful in separating the products from the starting material **3**.

Hydrolysis and *N*-Boc protection were high yielding in all cases, except for oxazoline **5m**. Chiral HPLC analysis of a representative number of compounds **6** indicated that no racemisation had occurred on hydrolysis to the corresponding amine under the optimised low temperature conditions (See Appendix 2).

Several of the commercially available and synthesised aryne precursors did not work in the α-arylation reaction (Figure 25).

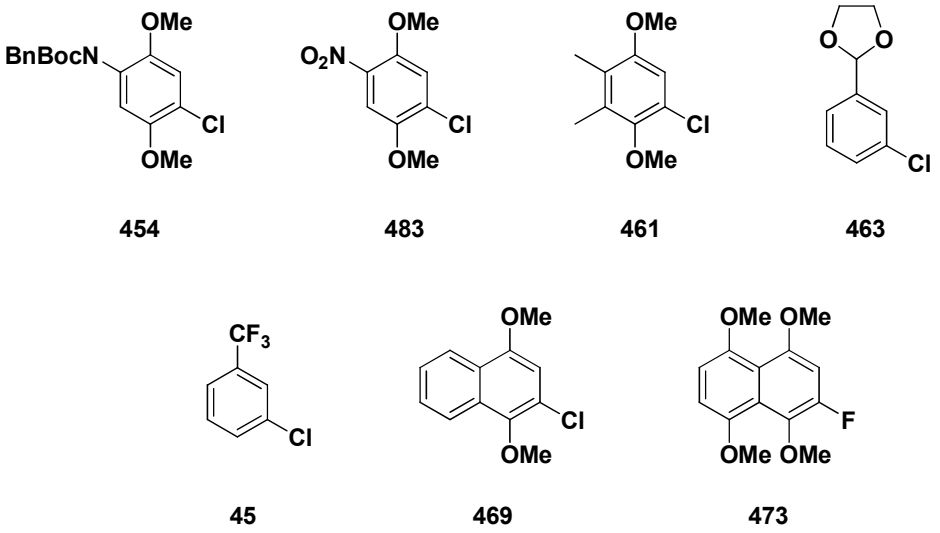


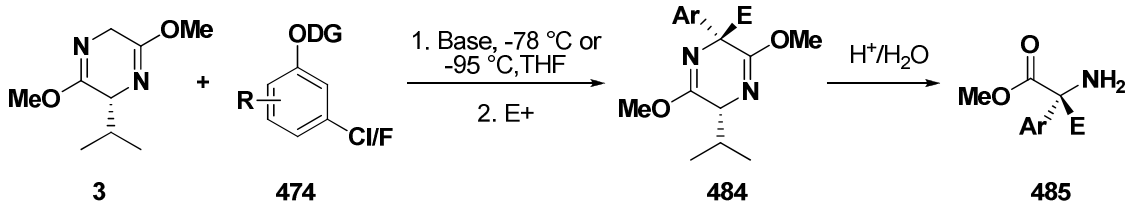
Figure 25: Benzyne precursors which were unsuccessful in the α-arylation reaction

Protected aniline **454** failed to react in the desired manner. GC-MS analysis indicated a possible Boc-transfer to the lithiated species. Reaction of nitro precursor **483** gave a complex mixture of unidentifiable products, possibly due to competing S_NAr side reactions. Dimethyl precursor **461** remained unchanged under the reaction conditions. Deuterium quenching experiments were undertaken, which showed Li/Cl exchange and methyl deprotonation were competing with *ortho* lithiation. Lithiated acetal **463** failed to collapse to benzyne at room temperature and starting materials were recovered. Trifluoromethyl precursor **45** underwent lithium/chlorine exchange rather than deprotonation to give trifluorotoluene by GC-MS. Both naphthalene precursors, **469** and **473** failed to collapse to benzyne under the reaction conditions.

6.3 Developing the Synthesis of Quaternary Aryl Amino Acids

6.3.1 Introduction

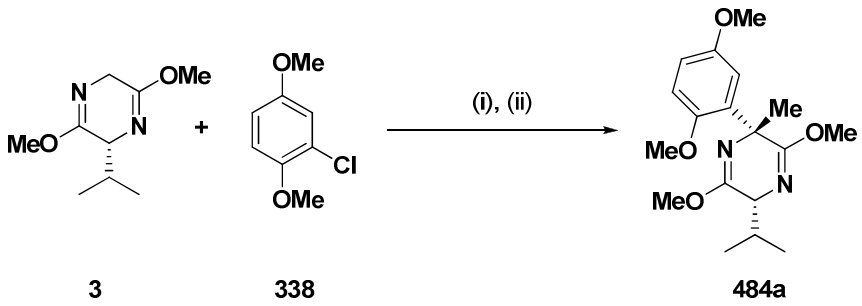
To extend this methodology for use in multi-component reactions, it was considered that quenching the key aza-enolate intermediate **446** with an electrophile rather than a proton source should provide quaternary Schöllkopf adducts **484** and hence quaternary aryl amino acids **485** upon auxiliary cleavage (Scheme 165).



Scheme 165: Proposed extension of the α-arylation methodology to synthesise quaternary adducts

6.3.2 Initial Observations and Optimisation

Carrying out the same procedure as for the α-arylation reactions; benzyne precursor **338** and Schöllkopf's bis-lactim ether **3** were allowed to react with 2.5 equivalents of *sec*-butyllithium at −95 ºC to carry out the required *ortho* lithiation for benzyne formation from **338** and deprotonation of bis-lactim **3**. After warming to room temperature, four equivalents of iodomethane were added and after stirring for 1 hour gave, gratifyingly, the desired quaternary species **484a** in a 88% yield and a dr of 85 : 15 (Scheme 166, Table 20, Entry 1).



3 338 484a

Reagents and Conditions: (i) *s*-BuLi, THF, −95 ºC to rt; (ii) See Table 20.

Scheme 166: Formation of α-methyl, α-aryl adduct **484a**

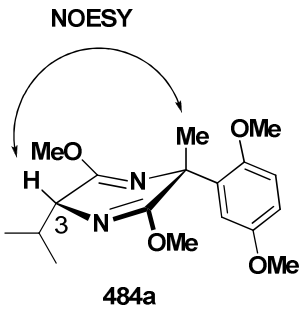
Table 20: Methylation conditions tested for formation of **484a**

Entry[a]	Methylating reagent	Temperature / ºC	Yield of 484a / %[c]	dr[d]
1	MeI	rt	88	85 : 15
2	MeI	0	-	86 : 14
3	MeI	−78	92	96 : 4
4	Me_2SO_4	−78 to rt	-	93 : 7

[a]Reactions were carried out on a 1 mmol scale. [b]Methylating reagents were added at the stated temperature and stirred for 1 hour further at that temperature. [c]Isolated yield. [d]As determined by integration of the ^{1}H NMR spectra

Lowering the temperature of iodomethane addition to 0 ºC did not improve the diastereoselectivity (Entry 2), but addition at − 78 ºC increased the dr to 96 : 14 and the yield to 92 % (Entry 3). The use of dimethylsulphate as an alternative methylating reagent did not increase the dr (Entry 4), and provided a range of undesirable side-products.

The major diastereoisomer was confirmed to have the *iso*-propyl and aryl moieties in a *syn* relationship by ^{1}H NMR NOESY analysis; a clear NOESY correlation could be observed between the methyl group and the proton at C-3 (Figure 26).

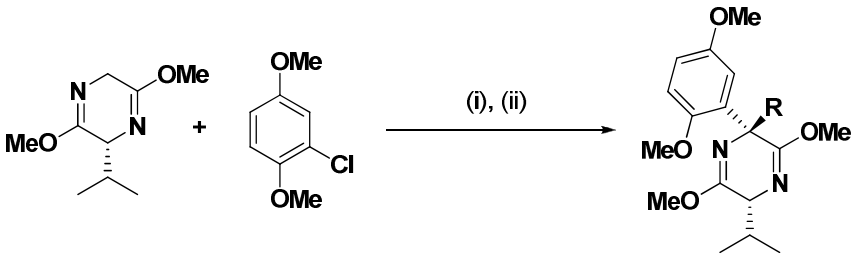


484a

Figure 26: NOESY correlation observed for **484a**

6.3.3 Scope of Reaction

The scope of the reaction was then examined to determine the nature of the electrophiles that could be introduced at C-6 (Scheme 167, Table 21).

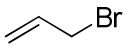
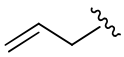
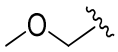
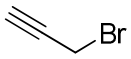
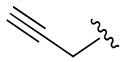
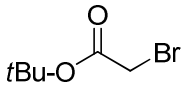
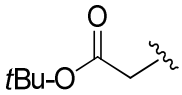
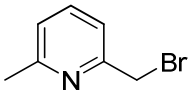
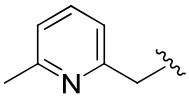
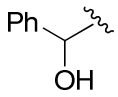
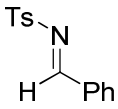
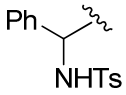
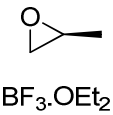
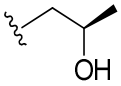


3 **338** **484**

Reagents and Conditions: (i) *s*-BuLi, THF, −95 ºC to rt; (ii) See Table 21.

Scheme 167: Formation of quaternary Schöllkopf adducts employing a range of electrophiles

Table 21: Different electrophiles employed in multi-component reaction

Entry[a]	Electrophile	R	Time /h[b]	Product	Yield /%[c]	dr at C-6[d]
1	MeI	Me	1	**484a**	92	96 : 4
2	BnBr	Bn	6	**484b**	88	>98 : 2
3			1	**484c**	85	>98 : 2
4	MOMCl		1	**484d**	53	95 : 5
5			1	**484e**	80	>98 : 2
6			3	**484f**	51	>98 : 2
7	AcCl	Ac	6	**484g**	59	89 : 11
8			5	**484h**	71	>98 : 2
9	PhCHO		12	**484i**[e]	69	>98 : 2[f]
10			12	**484j**	71	>98 : 2[g]
11			1	**484k**	50	>98 : 2

[a]Reactions were carried out on a 1 mmol scale in THF (0.2 M) using 1.5 equiv. of halide **338** and 2.75 equiv. *s*-BuLi at −95 ºC, followed by warming to room temperature over 18 h, re-cooling to −78 ºC and the addition of 4 equiv. of electrophile. [b]Reactions were monitored by GC-MS. [c]Isolated yield. [d]Determined by ^{1}H NMR integration. [e]**484i** was converted to its benzoyl ester for isolation purposes. [f]The adduct **484i** was obtained as a mixture of epimeric alcohols (50 : 50). [g]Adduct **484j** was obtained as a mixture of epimeric amines (87 : 13).

Alkylations employing benzyl bromide, allyl bromide and propargyl bromide (Entries 2,3 and 5) proceeded smoothly, furnishing the desired products **484b**, **484c** and **484e** in excellent yields and high diastereoselectivity. Interestingly, adduct **484b** displays a large upfield shift (around 2 ppm) at the C-3 proton compared to other analogues. This indicates that the product has adopted what Schöllkopf describes as an "aryl inside" conformation in which the C-3 proton is situated in the shielding cone of the aromatic ring.[237] A single crystal X-ray crystallographic analysis confirmed the presence of this conformation in the crystal lattice (Figure 27).

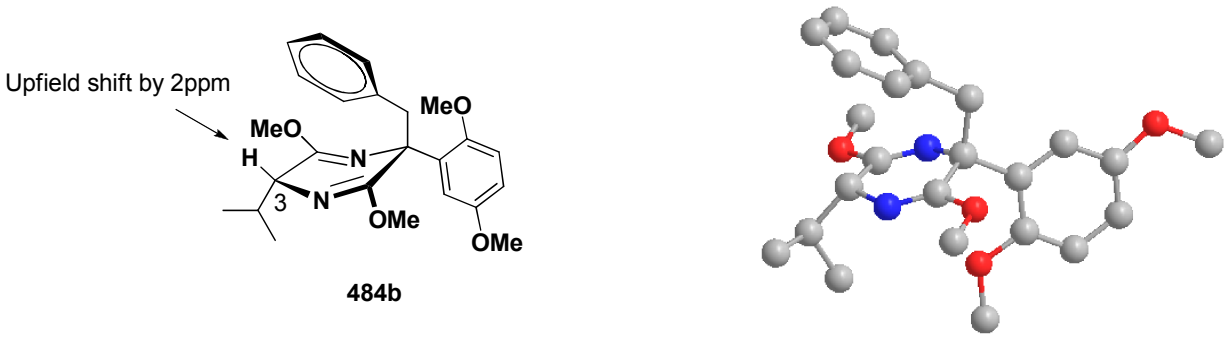


Figure 27: X-ray crystal structure of **484b** showing "aryl inside" conformation

Further alkylations with methyl chloromethyl ether, *tert*-butyl bromoacetate and 2-(bromomethyl)-6-methylpyridine (Entries 4, 6 and 8) provided adducts **484d**, **484f** and **484h** respectively, also with high diastereoselectivity, but with more modest yields. Acylation with acetyl chloride (Entry 7) afforded ketone **484g** in 59% yield, with a lower dr of 89 : 11, most likely due to the less sterically hindered nature of this electrophile. Replacing acetyl chloride with its corresponding Weinreb amide gave none of the required product. An aldol type reaction with benzaldehyde (Entry 9), afforded alcohol **484i** in good yield, which had to be protected as its benzoyl ester before purification, due to problematic retro-aldol reactivity of this alcohol.[229] There was complete diastereoselectivity at C-6, but no selectivity at the alcohol stereocentre (50 : 50). This was not the case for the similar Mannich type reaction with tosyl imine (Entry 10), where there was considerable stereoselectivity at the amine stereocentre (87 : 13). A possible explanation for this observed selectivity can be derived by examining the two possible Zimmerman-Traxler type transition states for such reactions, as proposed by Schöllkopf.[229] For the reaction with benzaldehyde (Figure 28), in $TS^{\neq}$ A, with the phenyl group axial, is consistent with there being an unfavourable 1,3-diaxial interaction with the methoxy group. However, there is an equally unfavourable interaction in $TS^{\neq}$ B where the phenyl group now occupies the equatorial position, as there is now a 1, 2-gauche interaction with the bulky dimethoxyaryl group

adjacent to it. It was considered that neither of these transition states was lower in energy, which would be consistent with the lack of diastereoselectivity.

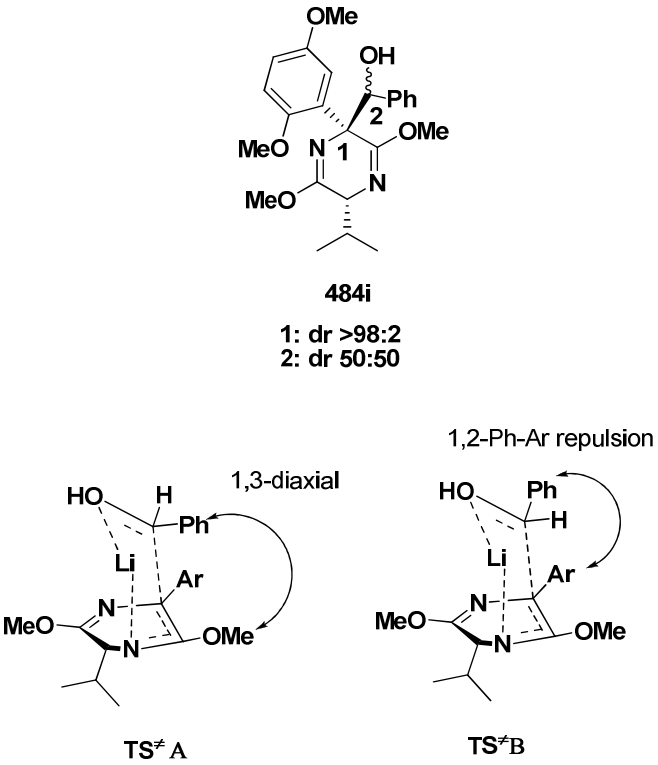


Figure 28: Transition state analysis to explain lack of diastereoselectivity at alcohol stereocentre

On the other hand, in the case of the Mannich reaction with the tosyl imine (Figure 29), it was postulated that with the tosyl group occupying an equatorial position, there is a large steric clash with the equatorial phenyl group in $TS^{\neq}$ B. Therefore the prediction is that the major diastereoisomer is derived from $TS^{\neq}$ A. However, this has not been proved, due to the inability to separate the two diastereoisomers despite much effort, and hence the inability to determine their absolute configuration.

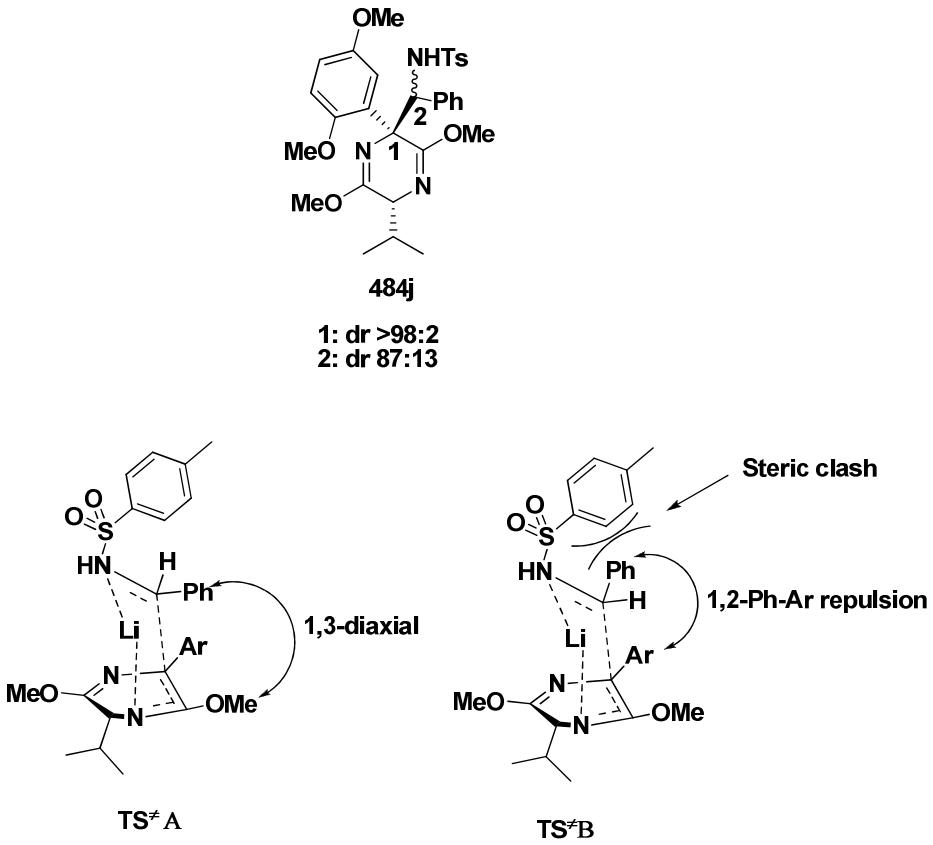
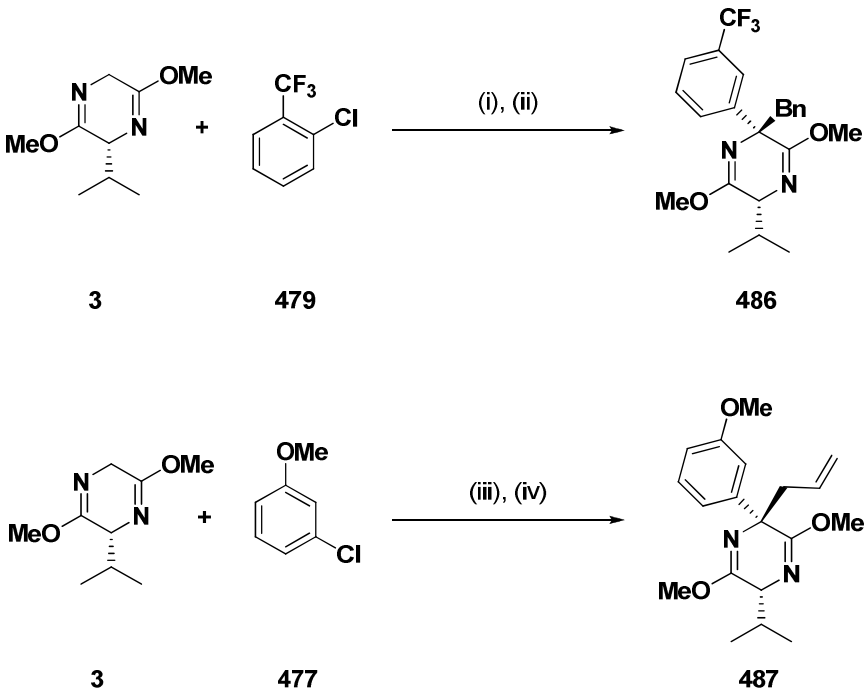


Figure 29: Transition state analysis to explain stereochemistry at C-2 of **484j**

Finally, addition of (*R*)-propylene oxide as the electrophile in the presence of boron trifluoride etherate (Table 21, Entry 11) gave alcohol **484k**. If (*S*)-propylene oxide is used instead, there was no reaction and indeed Schöllkopf noted significant levels of kinetic resolution when such reactions were performed with racemic oxiranes.[230]

In section 6.2, the scope of the methodology was demonstrated over a range of *ortho*-lithiation benzyne precursors. To establish that any of these precursors could be used to form quaternary adducts, precursor **479** was subjected to the benzylation conditions and precursor **477** to the allylation conditions, affording adducts **486** and **487** respectively, again in good yields and drs and with complete regioselectivity for these unsymmetrical benzynes. This time the lack of a chelating *ortho* substituent to the bis-lactim was no longer required to maintain high diastereoselectivity (Scheme 168).

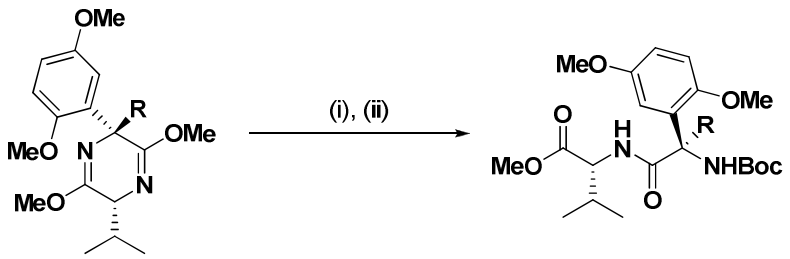


Reagents and Conditions: (i) *n*-BuLi, THF, −78 ºC to rt; (ii) BnBr, −78 ºC, 6 h, 67%, >98 : 2 dr; (iii) *s*-BuLi, THF, −95 ºC to rt; (iv) allyl bromide, −78 ºC, 1 h, 76%, 95 : 5 dr.

Scheme 168: Formation of quaternary adducts from different benzyne precursors

6.3.4 Hydrolysis of Quaternary Adducts

With the success of the multi-component reaction established, the hydrolysis of the sterically encumbered quaternary bis-lactim ethers was then examined. **484a**, **484d** and **484e**, containing relatively less sterically demanding substituents at the quaternary centre, were subjected to standard, mild hydrolysis conditions, employing 0.5 M HCl in THF at room temperature. The low temperature conditions in acetonitrile, which were used for the standard α-arylation reactions in Section 6.2 were no longer required, as there was no longer the problem of racemisation at the quaternary centre. Rather than revealing the amino acid esters, the quaternary methyl esters were isolated as their corresponding valine dipeptides, **488a**, **488d** and **488e** in good yields (Scheme 169). These hydrolysis reactions were also slow, taking on average 36-48 hours. The less-shielded imidate group had undergone complete hydrolysis, but the imidate functional group α to the quaternary centre had undergone incomplete cleavage to the peptide bond, a trend which is common in the literature for quaternary adducts.[237-240] When some of the bulkier adducts, e.g. **488b** were subjected to the same conditions, hydrolysis to the dipeptide was not complete after 1 week of stirring at room temperature.



484a: R = Me
484d: R = CH_2OMe
484e: R = $CH_2C{\equiv}CH$

488a: 75%, 96 : 4 dr
488d: 61%, 95 : 5 dr
488e: 72%, >98 : 2 dr

Reagents and Conditions: (i) 0.5 M HCl, THF, rt, 36 - 48 h; (ii) Boc_2O, *i*-Pr_2NEt, CH_2Cl_2, rt, 48 h.

Scheme 169: Hydrolysis of quaternary adducts to valine dipeptides

Possible mechanistic explanations for formation of this peptide bond are shown in Figure 30. Either a Krapcho-style elimination could occur, where the chloride anion could attack the less hindered imidate methyl group (Pathway A), or elimination of methanol *via* nitronium formation to relieve strain could provide the amide bond upon hydrolysis (Pathway B).

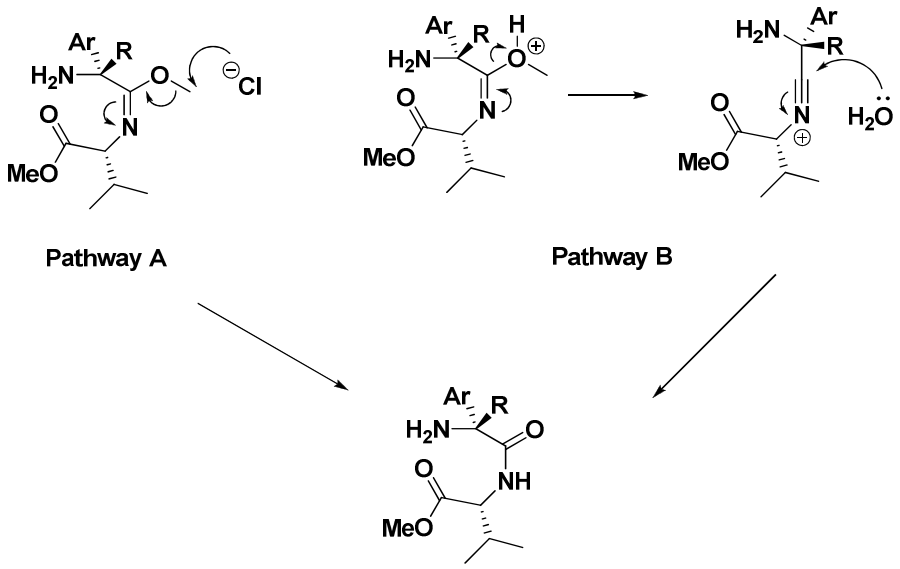
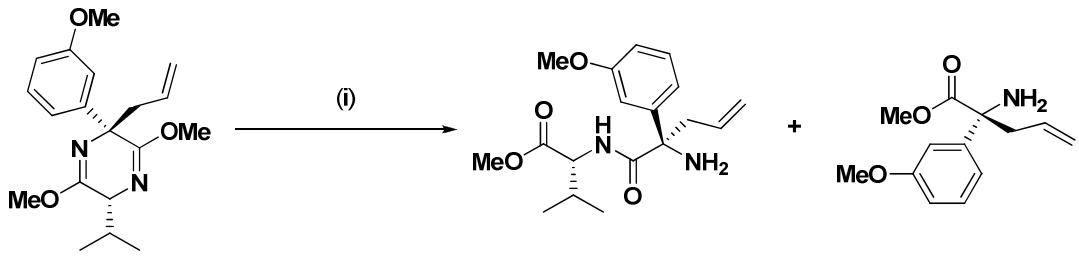


Figure 30: Possible mechanistic pathways for peptide formation

When analogue **487**, with a single methoxy group on the aromatic ring, was subjected to the same reaction conditions that gave the dipeptide for **484a**, a 1 : 1 separable mixture of dipeptide **489** and methyl ester **490** was afforded (Scheme 170). This is attributed to there being less steric congestion at the quaternary centre.

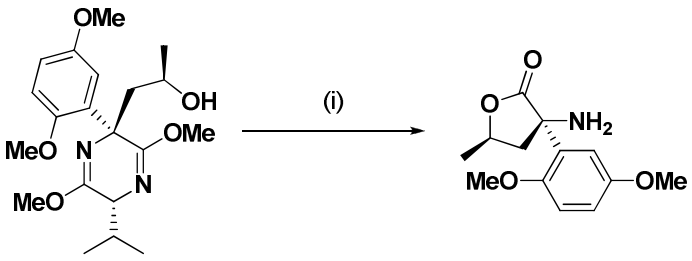


487 489 490

Reagents and Conditions: (i) 0.5 M HCl, THF, rt, 36 h, 80%

Scheme 170: Hydrolysis of less sterically hindered adduct **487**

The only example where the use of standard hydrolysis conditions resulted principally in the formation of the amino acid monomer was in the case of alcohol **484k**. Mild acidic hydrolysis gave lactone **491** in 80% yield and 96% ee (Scheme 171). The ability of the alcohol to undergo lactonisation under the reaction conditions clearly aided the hydrolysis of this imidate.

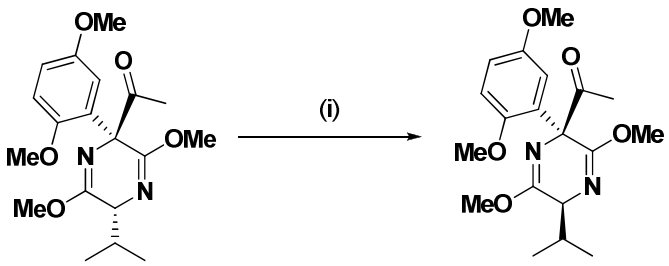


484k 491

Reagents and Conditions: (i) 0.5 M HCl, THF, rt, 48 h, 80%, 96% ee.

Scheme 171: Hydrolysis of analogue **484k**

It was also assumed that ketone **484g** would undergo hydrolysis, due to its non-sterically encumbered nature. However, upon exposure to 0.5 M HCl, epimerisation of the *iso*-propyl group at C-3 occurs in near quantitative yield, giving *anti* adduct **492** (Scheme 172). The electron withdrawing effect of the carbonyl moiety presumably increases the acidity of the C-3 proton to such an extent that under acidic conditions epimerisation at this centre occurs to afford the more thermodynamically stable *anti*-adduct.



484g **492**

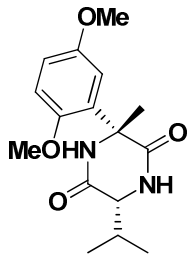
Reagents and Conditions: (i) 0.5 M HCl, THF, rt, 36 h, 95%, 88 : 12 dr.

Scheme 172: Epimerisation at C-3 of **484g**

There are several examples in the literature, where hydrolysis of quaternary Schöllkopf adducts to their corresponding amino acids has been achieved.[238,239,241-243] It was important to test these conditions on methyl adduct **484a** to see if any are successful in the arylated system (Scheme 173, Table 22, Entries 1-6). In all cases a mixture of dipeptide **494** and desired product **495** was observed, but these two compounds were inseparable.

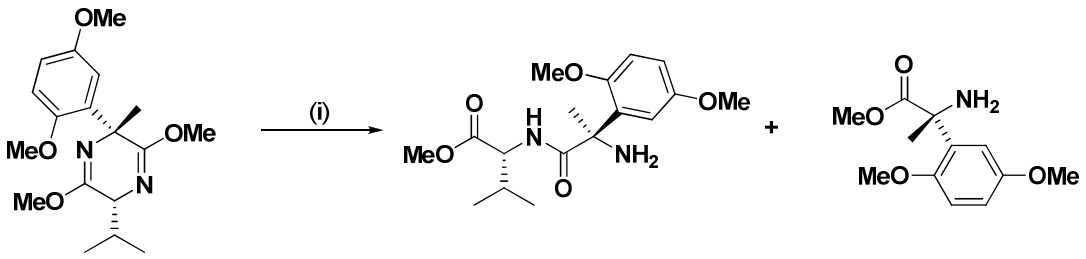
The best result was found employing 0.25 M HCl as solvent (Entry 2), which gave a 1 : 1 inseparable mixture of dipeptide **494** and desired methyl ester **495**. Other combinations of HCl and TFA in various solvents and at various temperatures (Entries 1 and 3-6) gave poorer ratios.

Schöllkopf reported that the use of high concentrations of acid in such hydrolysis reactions, resulted in the formation of 2,5-dioxohexahydropyrazines. It was also found to be the case for this compound as treatment of **484a** with 6 M HCl (Entry 7) gave predominantly **493** (Figure 31). The use of anhydrous HCl (generated *in situ*) also gave **493** as the major product (Entry 8). It was also attempted to use a Lewis acid to promote auxiliary cleavage (Entry 9), but with no success.



493

Figure 31: 2,5-dioxohexahydropyrazine **493** produced under strongly acidic conditions



484a **494** **495**

Reagents and Conditions: (i) See Table 22.

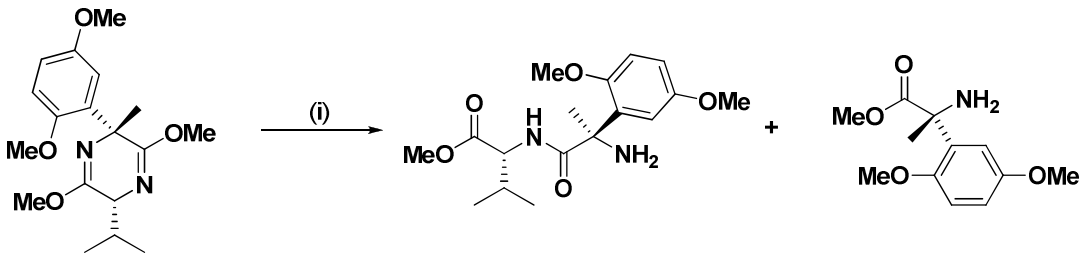
Scheme 173: Different hydrolysis conditions for bis-lactim **485a**

Table 22: Hydrolysis of adduct **484a**

Entry[a]	Conditions	Ratio[b] 494 : 495	Other result
1	0.25 M HCl, THF, rt, 48 h	5 : 1	
2	0.25 M HCl, rt, 48 h	1 : 1	
3	0.2 M TFA, MeCN, rt, 72 h	2 : 1	
4	0.5 M HCl, dioxane, rt, 72 h	1.3 : 1	
5	0.1 M TFA, H_2O: MeCN (1 : 3), 40 ˚C, 48 h	3 : 1	
6	TFA, MeCN : H_2O (1 : 1), 60 ˚C (μw), 20 min	2 : 1	
7	6 M HCl, THF, rt, 12 h	-	**493**
8	TMSCl, MeOH, rt, 36 h	-	**493** major product
9	$Sc(OTf)_3$, H_2O, THF, rt, 4 days	-	Complex mixture

[a]Reactions were carried out on a 20 mg scale. [b]As determined by integration of the ^{1}H NMR spectra

At this point it was sensible to do a thorough screen of various acidic conditions, as the only two acids applied so far were HCl and TFA. As the best result in Table 22 (Entry 2) involved the use of neat, aqueous acid at room temperature, the screen was started by stirring **484a** in an excess of a variety of 0.25 M acids of varying acidity and bulkiness for 48 hours (Scheme 174, Table 23, Entries 1-11). The Lewis acid, boron trifluoride etherate, was also utilised (Entries 12-13) as well as the acid cation exchange resin, Amberlite® 15 (Entry 14).



484a **494** **495**

Reagents and Conditions: (i) See Table 23.

Scheme 174: Acid screen for hydrolysis of **484a**

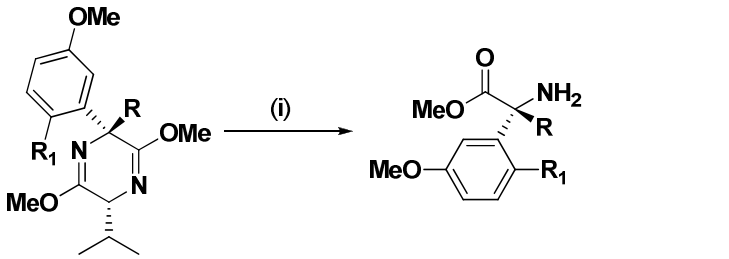
Table 23: Acid screen

Entry[a]	Aqueous acid	pK_a	Concentration / M	Solvent	equiv. of acid	Ratio[b] 494 : 495
1	$HClO_4$	−10	0.25	-	excess	1 : 1.4
2	HBr	−9	0.25	-	excess	1 : 1
3	HCl	−8	0.25	-	excess	1 : 1
4	H_2SO_4	−3	0.25	-	excess	1 : 1.85
5	PTSA	−2.6	0.25	-	excess	1 : 1.2
6	HNO_3	−1.3	0.25	-	excess	1.1 : 1
7	HBF_4	−0.4	0.25	-	excess	2 : 1
8	TFA	−0.25	0.25	-	excess	1 : 1.4
9	CSA	1.2	0.25	-	excess	1 : 1.1
10	citric acid	3.09	0.25	-	excess	incomplete
11	HCOOH	3.77	0.25	-	excess	incomplete
12	$BF_3{\cdot}OEt_2$		0.25	THF	2.25	1 : 1.4
13	$BF_3{\cdot}OEt_2$		0.25	H_2O	2.25	1 : 1.5
14	Amberlite 15		0.25	H_2O	2.25	1.2 :1
15	H_2SO_4		0.25	MeOH	2.25	3 : 1
16	H_2SO_4		0.25	THF	2.25	3 : 1
17	H_2SO_4		0.25	MeCN	2.25	1.5 : 1
18	H_2SO_4		0.25	PhMe	2.25	no reaction
19	H_2SO_4		0.5	-	excess	1 : 1.3
20	H_2SO_4		1	-	excess	1 : 3
21	H_2SO_4		3	-	excess	1 : 7.4
22	H_2SO_4		5	-	excess	1 : 7.7
23	H_2SO_4		6	-	excess	1 : 11
24	H_2SO_4		9	-	excess	complex mixture

[a]Reactions were performed on a 20 mg scale. [b]As determined by integration of the ^{1}H NMR

It is apparent from Table 23 (Entries 1-11) that the trend in reactivity bears no correlation to the pK_a of the acid in question. This indicates that it is either the nucleophilicity or the steric bulk of the conjugate base that may be important in these reactions. The best result from the initial screen was employing 0.25 M sulfuric acid (Entry 4), in which 1 : 1.85 ratio of dipeptide **494** to desired ester **495** was obtained. This superior acid was then tested in a assortment of co-solvents (Entries 15-18) to see if this could enhance selectivity, but provided far inferior results to the neat reaction. Another series of reactions was then carried out at different concentrations of sulfuric acid (Entries 19-24). Satisfyingly, the use of 6 M sulfuric acid (Entry 23) resulted in a 1 : 11 ratio in favour of desired **495**.

This reaction was reproducible, and methyl ester **495** was isolated in a 56% yield (Scheme 175). If the same conditions were also applied to the sterically least hindered analogue **487**, the same result was obtained and **490** was afforded in 58% yield. Chiral HPLC analysis confirmed the expected high enantioselectivities of these esters.



484a: R = Me, R^1 = OMe
487: R = $CH_2CH{=}CH_2$, R^1 = H

495: R = Me, R^1 = OMe, 56%, 90% ee
490: R = $CH_2CH{=}CH_2$, R^1 = H, 58%, 90% ee

Reagents and Conditions: (i) 6 M H_2SO_4, rt, 72 h.

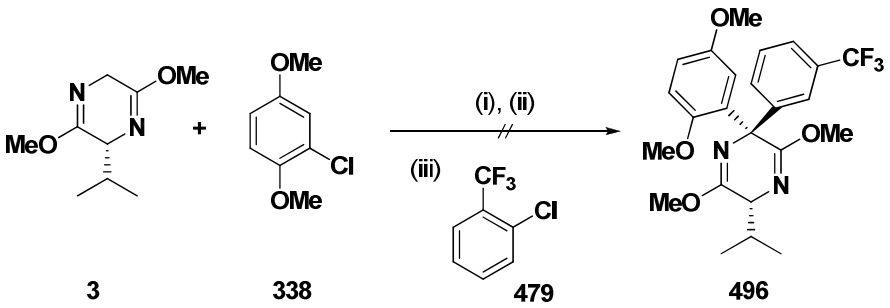
Scheme 175: Hydrolysis of adducts **485a** and **487** to their quaternary amino acids

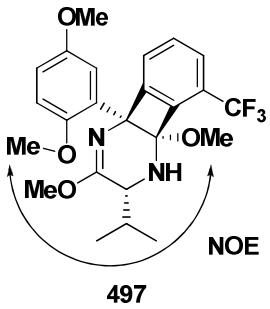
Unfortunately, when these conditions were again tested on some of the bulkier analogues, they remained resistant to hydrolysis, or in some cases decomposition was observed under the strong, acidic conditions.

Due to the successful hydrolysis of analogue **487**, with only one methoxy group, this suggests that if the aryl group is derived from a less sterically hindered benzyne precursor, then hydrolysis would be more facile, as was observed by Lee[243] for unsubstituted aryl quaternary bis-lactim ethers.

6.3.5 Double Aryne Addition

As part of the studies into quaternary Schöllkopf bis-lactims, it was thought interesting to see whether the benzylic carbanion generated after addition of the bis-lactim aza-enolate to the first aryne could react further with a different aryne, hence generating a quaternary biaryl system. To investigate this theory, standard α-arylation conditions were employed with dimethoxybenzyne. The resultant anion was then cooled to −78 ºC and the least sterically hindered benzyne precursor, 1-chloro-2-(trifluoromethyl)benzene **(479)** added followed by an equivalent of *n*-butyllithium and then allowed to slowly warm to room temperature (Scheme 176).





Reagents and Conditions: (i) *s*-BuLi, THF, −95 ºC to rt; (ii) **479**, −78 ºC; (iii) *n*-BuLi, −78 ºC to rt, 20%.

Scheme 176: Attempted double aryne addition

Although the reaction produced a very complex mixture of products, it was possible to isolate a compound assumed to be diaryl **496** in 20% yield. The reaction was attempted several times in which the order of addition was changed, and the number of equivalents of various reagents slightly altered, but the yield of this compound did not increase. Although the mass was correct, NMR analysis revealed that the isolated compound was aminal **497**, generated by attack of the aryl carbanion onto the imidate in close proximity. ^{1}H NMR showed only six aromatic protons, as opposed to the seven required for **496**, and the ^{13}C NMR chemical shift for the hemiaminal ether quaternary centre is observed at a lower chemical shift than is usual

for imidate carbons. One of the imidate IR stretching frequencies is also missing from **496**. An nOe correlation can be observed between the hemiaminal ether methyl group and one of the methoxy groups on the aryl group (Scheme 173).

6.4 Conclusions and Future Work

A general approach has been developed for the synthesis of enantiomerically enriched α-arylglycines, using arynes as electrophilic arylation reagents. The arynes were generated *via* an *ortho*-lithiation approach and Schöllkopf's bis-lactim ether **3** was employed as the protected glycine equivalent. Diastereoselective addition, afforded *syn* adducts in up to 96 : 4 dr and with moderate to good yields and excellent regioselectivities. Hydrolysis provided a variety of substituted arylglycines containing a range of functional groups without racemisation. This work was published in 2011 in Organic Letters.[244]

In an extension to this methodology, quaternary aryl bis-lactim ethers were synthesised in good to excellent yields and high diastereoselectivity *via* a three-component coupling reaction in which reaction of an electrophile with the intermediate benzylic anion gave a range of C-alkyl and hydroxyalkyl derivatives. Hydrolysis of these quaternary acids gave the constituent amino acid methyl esters in high enantioselectivity for less substituted compounds. Adducts with two methyl ethers on the aryl unit tended to undergo hydrolysis to the corresponding valine dipeptides. This work has been submitted for publication in the Belstein Journal of Organic Chemistry. Future work with less substituted aryl components, could allow the formation of a whole range of substituted quaternary aryl amino acids with the possibility of excellent enantioselectivities after hydrolysis.

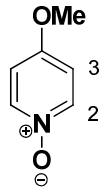
Some preliminary experiments showed that it was possible to generate a diaryl Schöllkopf adduct, but cyclisation to hemiaminal ether **497** ensued. Future work could develop the utility of this reaction towards synthesising quaternary biaryl amino acids, compounds which are traditionally difficult to prepare.

Chapter 7: Experimental Procedures

General methods

All manipulations and reactions of air or moisture sensitive materials were carried out in oven-dried glassware under an inert atmosphere of nitrogen. Solvents were distilled from CaH_2 (CH_2Cl_2, PhMe, triethylamine, pyridine, *n*-hexanes), Na/Ph_2CO (tetrahydrofuran, diethyl ether), or obtained as dry or anhydrous from Aldrich Chemical Company (*N*, *N*-dimethylformamide, acetonitrile, dimethysulfoxide). Other solvents and all reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Thin layer chromatography was performed on pre-coated silica gel F_{254} glass plates with visualization under UV light or by staining with potassium permanganate solution, ninhydrin or Dragendorff's reagent. Flash column chromatography was either performed using silica gel, particle size 40-63 μm or on pre-packed Redisep cartridges (eluants are given in parenthesis). Melting points were determined using a hot-stage apparatus and are uncorrected. IR spectra were recorded as thin films. The absorption bands are reported in wave number (cm^{-1}). Optical rotations were recorded at 25 ºC on a Perkin-Elmer 241 polarimeter with a path length of 1 dm, using the 589.3 nm D-line of sodium. Concentrations (c) are quoted in g/100 mL. Elemental analyses were determined by the University of North London Analytical Service. ^1H NMR spectra were recorded at 400 and 500 MHz and referenced to the residual solvent peak at 7.26 ppm ($CDCl_3$) and are quoted in ppm to 2 decimal places with coupling constants (*J*) to the nearest 0.1 Hz. ^{13}C NMR were recorded at 100 and 125 MHz and referenced to the solvent at 77.0 ppm ($CDCl_3$) and are quoted in ppm to 1 decimal place. High resolution mass spectrometry (CI, EI, ESI) was carried out by the Imperial College London Department of Chemistry Mass Spectrometry Service.

4-Methoxypyridine *N*-oxide (172)[128]

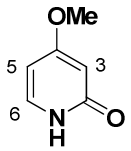


172

172 was prepared according to a literature procedure.[128] Sodium (2.46 g, 107 mmol) was added portion-wise to anhydrous MeOH (100 mL) at 0 ºC. When liberation of hydrogen gas ceased the ensuing mixture was allowed to warm to room temperature and then added quickly to a suspension of 4-nitropyridine-*N*-oxide **(171)** (10.0 g, 71.0 mmol) in anhydrous MeOH (50 mL) and then heated to reflux overnight. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* to give a cream solid which was treated with boiling CH_2Cl_2 (100 mL). The resulting mixture was filtered and the filtrate concentrated *in vacuo* to provide a yellow solid. Recrystallisation from acetone afforded **172** (6.15 g, 69%) as off-white needles.

M.p. (acetone) 100-102 ºC [lit.[128] 103-106 ºC]; R_f 0.29 (CH_2Cl_2 : MeOH 9 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, 2H, *J* = 7.7 Hz, H^2), 6.80 (d, 2H, *J* = 7.7 Hz, H^3), 3.85 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 140.1, 111.7, 56.1.

4-Methoxypyridin-2(1*H*)-one (174)[245]



174

Method A:

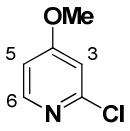
174 was prepared according to a literature procedure.[245] A solution of 4-methoxypyridine-*N*-oxide **(172)** (1.00 g, 8.00 mmol) in acetic anhydride (33 mL) was heated to reflux for 6 hours. After cooling to room temperature the solvent was removed *in vacuo* and the resulting intermediate 2-acetoxy-4-methoxypyridine was isolated using a Kugelrohr distillation apparatus (110 ºC, 0.3 mmHg). The intermediate was dissolved in a MeOH/H_2O mixture (1:1 v/v, 10 mL) and stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was recrystallised from acetonitrile to yield **174** (0.59 g, 59%) as a white crystalline solid.

Method B:

K_2CO_3 (1.24 g, 9.00 mmol) and MeI (0.560 mL, 9.00 mmol) were added sequentially to a solution of 2,4-dihydroxypyridine **(176)** (1.00 g, 9.00 mmol) in anhydrous DMF (160 mL) and stirred at room temperature. After 12 hours K_2CO_3 (0.620 g, 4.50 mmol) and MeI (0.280 mL, 4.50 mmol) were added and the ensuing mixture stirred for 18 hours. Concentration of the reaction mixture *in vacuo* gave a residue which was taken up in EtOAc (50 mL) and washed with saturated aqueous NH_4Cl solution (5 x 20 mL). The combined aqueous layers were extracted with $CHCl_3$/*i*-PrOH (3 x 50 mL of a 3 : 1 v/v mixture). The combined organic layers were concentrated *in vacuo* to give **174** (0.60 g, 60%).

M.p. (acetonitrile) 138-140 ºC; R_f 0.78 (CH_2Cl_2 : MeOH 10 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, 1H, *J* = 7.3 Hz, H^6), 5.97 (dd, 1H, *J* = 7.3, 2.5 Hz, H^5), 5.88 (d, 1H, *J* = 2.4 Hz, H^3), 3.79 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 167.2, 134.4, 101.3, 97.1, 55.4.

2-Chloro-4-methoxypyridine (169)[128]

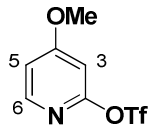


169

169 was prepared according to a literature procedure.[128] A solution of 4-methoxy-2-pyridone **(174)** (0.06 g, 0.48 mmol) in phosphorus oxychloride (2 mL) was heated at 95 ºC for 16 hours. Removal of excess phosphorus oxychloride *in vacuo* provided a yellow oil which was cooled to 0 ºC and carefully treated with saturated aqueous $NaHCO_3$ to pH 7. The resulting mixture was extracted with EtOAc (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **169** (0.03 g, 45%) as a colourless oil which was used in subsequent reactions without further purification.

R_f 0.68 (hexanes : EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, 1H, J = 5.8 Hz, H^6), 6.84 (d, 1H, J = 2.3 Hz, H^3), 6.76 (dd, 1H, J = 5.8, 2.3 Hz, H^5), 3.86 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 152.6, 150.2, 109.7, 109.4, 55.6.

4-Methoxypyridin-2-yl trifluoromethanesulfonate (175)

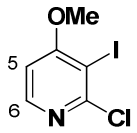


175

Trifluormethanesulfonic anhydride (2.19 mL, 13.0 mmol) was added drop-wise to a stirring solution of 4-methoxy-2-pyridone **(174)** (1.48 g, 11.8 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (2.67 g, 13.0 mmol) in CH_2Cl_2 (60 mL) at room temperature, then stirred at that temperature for 1 hour, after which a white precipitate had formed. The solvent was removed *in vacuo* and the residue was washed with pentane, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 10) to yield **175** (2.83 g, 93%) as a pale brown oil.

R_f 0.80 (EtOAc : hexanes 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, 1H, J = 5.8 Hz, H^6), 6.89 (dd, 1H, J = 5.8, 2.1 Hz, H^5), 6.64 (d, 1H, J = 2.1 Hz, H^3), 3.91 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 157.3, 149.0, 118.5 (q, $J_{C\text{-}F}$ 320 Hz), 111.1, 100.4, 55.9; IR 2950, 1608, 1567, 1492, 1421, 1320, 1138 cm^{-1}; *m/z* HRMS (CI) calcd. $C_7H_7F_3NO_4S$: $[M+H]^+$ 258.0061; found: $[M+H]^+$ 258.0054; Microanalysis calcd. for $C_7H_6F_3NO_4S$; C 32.69, H 2.35, N 5.45; found C 32.76, H 2.19, N 5.39.

2-Chloro-3-iodo-4-methoxypyridine (1)

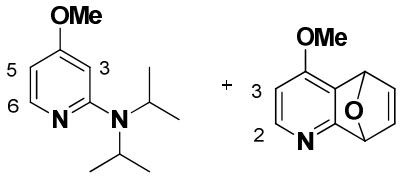


1

A solution of anhydrous di-*iso*-propylamine (0.06 mL, 0.39 mmol) in THF (1 mL) was cooled to −78 ºC before *n*-BuLi (0.24 mL of a 1.6 M solution in hexanes, 0.39 mmol) was added and the resulting mixture stirred for a further 20 minutes at that temperature. A solution of 2-chloro-4-methoxy pyridine **(169)** (0.04 mL, 0.35 mmol) in THF (1 mL) was added and stirred for 1 hour at −78 ºC before a solution of iodine (0.11 g, 0.42 mmol) in THF (1 mL) was added drop-wise and stirred for a further 1 hour. The reaction was allowed to warm to room temperature. After being quenched with H_2O (5 mL) the reaction mixture was extracted with Et_2O (3 x 5 mL) and the combined organic layers were washed with saturated sodium thiosulphate solution (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 2) to afford **1** (0.07 g, 75%) as white crystals.

M.p. (EtOAc/hexanes) 114-117 ºC; R_f 0.10 (EtOAc : hexanes 1 : 10); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, 1H, J = 5.7 Hz, H^6), 6.63 (d, 1H, J = 5.7 Hz, H^5), 3.97 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 156.1, 149.8, 105.1, 86.9, 57.0; IR 1565, 1538, 1454 cm^{-1}; HRMS (CI) calcd. C_6H_5ClNO: $[M+H]^+$, 269.9182; found $[M+H]^+$, 269.9184; Microanalysis calcd. for C_6H_4ClNO; C 26.74, H 1.87, N 5.20; found C 26.76, H 1.85, N 5.18.

***N,N*-Di-*iso*-propyl-4-methoxypyridin-2-amine (180a) and 5,8-Dihydro-5,8-epoxy-4-methoxyquinoline (182)**[122]



180a **182**

n-BuLi (0.48 mL of a 1.6 M solution in hexanes, 0.77 mmol) was added drop-wise to a stirring solution of di-*iso*-propylamine (0.11 mL, 0.77mmol) in THF (0.75 mL) at −78 ºC and the resulting mixture allowed to stir for a further 30 minutes at that temperature. Furan (1.02 mL, 14.00 mmol) and a solution of 2-chloro-4-methoxypyridine **(169)** (0.08 mL, 0.70 mmol) in THF (0.5 mL) were added simultaneously and the reaction allowed to warm to room temperature overnight. The reaction mixture was concentrated *in vacuo* before being taken up in $CHCl_3$ (10 mL) and washed with 10% $NaHCO_3$ solution (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a 2.7 : 1.5 : 1 mixture of **169**, **180a** and **182** (0.078 g).

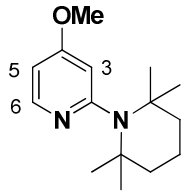
The compounds were separated by flash column chromatography (EtOAc : hexanes 1 : 4 to EtOAc : hexanes 3 : 1) for analytical purposes to afford **180a** as an amber oil.

R_f 0.81 (EtOAc : hexanes 3 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, 1H, *J* = 6.2 Hz, H^6), 6.11 (dd, 1H, *J* = 5.7, 2.1 Hz, H^5), 6.00 (d, 1H, *J* = 2.1 Hz, H^3), 4.25 (sept, 2H, *J* = 6.9 Hz, *i*-Pr), 3.76 (s, 3H, OMe), 1.28 (d, 12H, *J* = 6.9 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 159.4, 148.7, 98.9, 93.1, 52.1, 45.5, 20.7; HRMS (CI) calcd. $C_{12}H_{20}N_2O$: $[M+H]^+$, 209.1654; found: $[M+H]^+$ 209.1663.

Further elution gave **182** as a pale brown oil.

R_f 0.10 (EtOAc : $CHCl_3$ 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, 1H, *J* = 6.0 Hz, H^2), 7.11 (m, 2H, 2 x =CH), 6.48 (d, 1H, *J* = 6.0 Hz, H^3), 5.98 (s, 1H, CH), 5.59 (s, 1H, CH), 3.87 (s, 3H, OMe); δ_c (100 MHz, $CDCl_3$): 175.2, 157.8, 146.5, 143.8, 142.2, 106.1, 83.0, 80.0, 56.4, 55.7.

4-Methoxy-2-(2,2,6,6-tetramethylpiperidin-1-yl)pyridine (180b)[122]

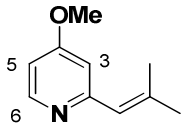


180b

n-BuLi (0.32 mL of a 1.6 M solution in hexanes, 0.51 mmol) was added drop-wise to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.09 mL, 0.51 mmol) in THF (0.75 mL) at −78 ºC and the resulting mixture allowed to stir for a further 30 minutes at that temperature. Furan (0.70 mL, 9.2 mmol) and a solution of 4-methoxypyridin-2-yl trifluoromethanesulfonate **(175)** (0.12 g, 0.46 mmol) in THF (0.5 mL) were added simultaneously and the reaction allowed to stir at −78 ºC for a further 3 hours. The reaction mixture was concentrated *in vacuo* before being taken up in $CHCl_3$ (10 mL) and washed with 10% $NaHCO_3$ solution (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield a 1 : 1 : 1 mixture of **175, 180b** and **182**, (0.09 g). Flash column chromatography (EtOAc : hexanes 1 : 10) provided a sample of **180b** as an amber oil for analytical purposes.

R_f 0.88 (EtOAc : hexanes 3 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, 1H, *J* = 5.7 Hz, H^6), 6.68 (dd, 1H, *J* = 5.7, 2.5 Hz, H^5), 6.60 (d, 1H, *J* = 2.4 Hz, H^3), 3.84 (s, 3H, OMe), 1.76 (m, 2H, CH_2), 1.56 (t, 4H, *J* = 6.2 Hz, 2 x CH_2), 1.13 (s, 12H, 4 x CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 162.6, 148.5, 114.0, 107.5, 55.0, 54.3, 41.7, 29.3, 18.3; IR 2967, 2927, 1589, 1562, 1465, 1440, 1253, 1162 cm^{-1}; HRMS (CI) calcd. $C_{15}H_{24}N_2O$: $[M+H]^+$, 249.1967; found $[M+H]^+$, 249.1962.

4-Methoxy-2-(2-methylprop-1-enyl)pyridine (184)

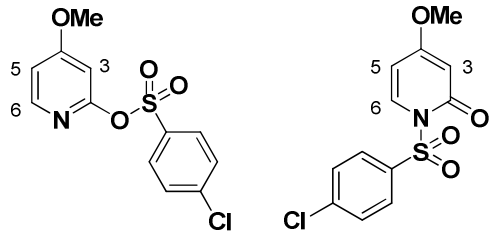


184

A solution of di-*iso*-propylamine (0.16 mL, 1.16 mmol) in THF (1.25 mL) was stirred at −78 °C for 15 minutes before *n*-BuLi (0.72 mL of a 1.6 M solution in hexanes, 1.16 mmol) was added and the resulting mixture stirred for a further 20 minutes at that temperature. A solution of 2-chloro-4-methoxy pyridine **169** (0.12 mL, 1.05 mmol) in THF (0.75 mL) was added and stirred for 1 hour at −78 ºC before 2-methylallyl magnesium chloride **(185)** (4.2 mL of a 0.5 M solution in THF, 2.10 mmol) was added drop-wise and the reaction warmed to room temperature overnight. The reaction was quenched with H_2O (10 mL), extracted with Et_2O (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 4) to yield **184** (0.005 g, 3%) as a yellow oil.

R_f 0.20 (EtOAc : hexanes 1 : 4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, 1H, *J* = 5.8 Hz, H^6), 6.73 (d, 1H, *J* = 2.4 Hz, H^3), 6.65 (dd, 1H, *J* = 5.8, 2.5 Hz, H^5), 6.32 (s, 1H, =CH), 3.87 (s, 3H, OMe), 2.08 (s, 3H, CH_3), 1.96 (s, 3H, CH_3); ^{13}C (100 MHz, $CDCl_3$) δ 165.7, 150.2, 125.1, 109.5, 106.9, 55.0, 29.7, 27.3, 19.8; HRMS (CI) calcd. $C_{10}H_{13}NO$: $[M+H]^+$, 164.1075; found $[M+H]^+$, 164.1074.

4-Methoxypyridin-2-yl 4-chlorobenzenesulfonate (189) and
1-(4-Chlorophenylsulfonyl)-4-methoxypyridin-2(1H)-one (191)



189 **191**

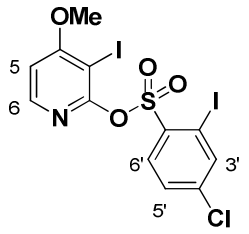
4-Chlorobenzenesulfonylchloride (0.18 g, 0.84 mmol) was added to a room temperature solution of 4-methoxy-2(1H)pyridone **(174)** (0.10 g, 0.76 mmol), NEt_3 (0.12 mL, 0.84 mmol) and DMAP (0.01 g, 0.08 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred at room temperature for 3 hours after which saturated aqueous NH_4Cl solution (10 mL) was added and the aqueous phase extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 4) to yield **189** (0.14 g, 59%) as a colourless oil.

R_f 0.81 (EtOAc : hexanes 3 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, 1H, *J* = 5.8 Hz, H^6), 8.00 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.55 (d, 2H, *J* = 8.7 Hz, Ar-H), 6.77 (dd, 1H, *J* = 5.8, 2.2 Hz, H^5), 6.23 (d, 1H, *J* = 2.1 Hz, H^3), 3.88 (s, 3H, OMe); ^{13}C (100 MHz, $CDCl_3$) δ 168.7, 158.4, 148.6, 140.8, 135.3, 130.1, 129.4, 110.3, 100.8, 55.8; IR 3095, 3023, 2944, 2846, 1062, 1565, 1488, 1438, 1376 cm^{-1}; HRMS (CI) calcd. $C_{12}H_{11}ClNO_4S$: $[M+H]^+$, 300.0097; found $[M+H]^+$, 300.0093.

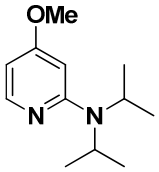
Further elution (EtOAc : hexanes 1 : 1) gave **191** (0.02 g, 9%) as a white solid.

M.p. (EtOAc/hexanes) 149-150 ºC; Rf 0.65 (EtOAc : hexanes 3 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.97 (d, 1H, *J* = 8.2 Hz, H^6), 7.54 (d, 2H, *J* = 8.7 Hz, Ar-H), 6.04 (dd, 1H, *J* = 8.2, 2.5 Hz, H^5), 5.67 (d, 1H, *J* = 2.5 Hz, H^3), 3.77 (s, 3H, OMe); ^{13}C (100 MHz, $CDCl_3$) δ 169.4, 161.5, 141.5, 135.3, 131.5, 131.1, 129.1, 103.2, 97.6, 56.0; IR 3459, 1644 (C=O) cm^{-1}; HRMS (CI) calcd. $C_7H_6F_3INO_4S$: $[M+H]^+$, 300.0097; found $[M+H]^+$, 300.0093.

3-Iodo-4-methoxypyridin-2-yl 4-chloro-2-iodobenzenesulfonate (192)



192

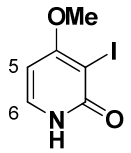


180a

n-BuLi (0.05 mL of a 1.6 M solution in hexanes, 0.08 mmol) was added drop-wise to a stirred solution of di-*iso*-propylamine (0.01 mL, 0.08 mmol) in THF (0.5 mL) at −78 ºC and the resulting mixture allowed to stir for a further 45 minutes at that temperature. A solution of 4-methoxypyridin-2-yl 4-chlorobenzenesulfonate **(189)** (0.021 g, 0.07 mmol) in THF (0.5 mL) was added drop-wise and the reaction stirred at −78 ºC for 1 hour before a solution of iodine (0.02 g, 0.08 mmol) in THF (0.5 mL) was added drop-wise and the reaction mixture allowed to stir for a further hour at that temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with 10% sodium thiosulphate solution (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 8) to yield **180a** (0.003 g, 21%) as an amber oil. Further elution (EtOAc : hexanes 1 : 1) gave **192** (0.016 g, 43%) as a white solid.

M.p. (EtOAc/hexanes) 113-136 ºC; R_f 0.54 (EtOAc : hexanes 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 1H, *J* = 2.0 Hz, $H^{3'}$), 8.11 (d, 1H, *J* = 8.6 Hz, $H^{6'}$), 7.94 (d, 1H, *J* = 5.6 Hz, H^6), 7.52 (dd, 1H, *J* = 8.5, 2.0 Hz, $H^{5'}$), 6.63 (d, 1H, *J* = 5.7 Hz, H^5), 3.98 (s, 3H, OMe); ^{13}C (100 MHz, $CDCl_3$) δ 167.8, 158.7, 148.4, 142.1, 140.1, 132.8, 130.3, 129.3, 128.4, 105.6, 93.1, 57.1; IR 2985, 2944, 2879, 1579, 1560, 1475, 1382, 1186, 1068 cm^{-1}; HRMS(CI) calcd. $C_{12}H_9ClI_2NO_4S$: $[M+H]^+$, 551.8030; found $[M+H]^+$, 551.8016.

3-Iodo-4-methoxypyridin-2(1H)-one (193)

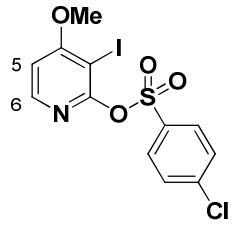


193

Sodium iodide (0.02 g, 0.13 mmol) was added portion-wise to a cooled solution of *N*-chlorosuccinimide (0.017 g, 0.13 mmol) in trifluoroacetic acid (1 mL) at 0 ºC and then allowed to warm to room temperature. A solution of 4-methoxy-2-pyridone **(174)** (0.014 g, 0.11 mmol) in AcOH (3 mL) was added drop-wise and the solution stirred at room temperature overnight. The reaction was quenched with H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with 10% sodium thiosulfate solution (5 mL) and H_2O (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography (CH_2Cl_2 : MeOH 10 : 1) to afford **193 (**0.011 g, 40%) as a dark yellow oil.

R_f 0.10 (EtOAc : hexanes 3 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 1H, *J* = 7.3 Hz, H^6), 6.13 (d, 1H, *J* = 7.3 Hz, H^5), 4.00 (s, 3H, OMe); ^{13}C (100 MHz, $CDCl_3$) δ 168.9, 164.4, 136.2, 94.8, 57.1, 29.7; IR 2921, 1623 (C=O), 1473, 1427, 1259, 1228, 1078 cm^{-1}; HRMS (CI) calcd. $C_6H_7INO_2$: $[M+H]^+$, 251.9522; found $[M+H]^+$, 251.9514.

3-Iodo-4-methoxypyridin-2-yl 4-chlorobenzenesulfonate (190)

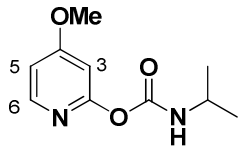


190

Para-chlorosulfonyl chloride (0.06 g, 0.29 mmol) was added portion-wise to a stirring solution of 3-iodo-4-methoxypyridin-2(1H)-one **(193)** (0.07 g, 0.26 mmol), NEt_3 (0.04 mL, 0.29 mmol) and DMAP (0.003 g, 0.026 mmol) in CH_2Cl_2 (10 mL) at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for a further 3 hours. Saturated aqueous NH_4Cl solution (10 mL) was added to the resulting orange solution and then the aqueous layer extracted was with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 2) to yield **190** (0.02 g, 19%) as a colourless oil.

R_f 0.65 (EtOAc : hexanes 3 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, 2H, *J* = 8.7 Hz, Ar-H), 8.08 (d, 1H, *J* = 5.4 Hz, H^6), 7.58 (d, 2H, *J* = 8.7 Hz, Ar-H), 6.67 (d, 1H, *J* = 5.6 Hz, H^5), 4.00 (s, 3H, OMe); ^{13}C (100 MHz, $CDCl_3$) δ 167.8, 148.5, 135.7, 130.9, 130.3, 129.3, 128.8, 105.7, 68.2, 57.1; IR 3095, 2958, 2927, 2858, 1727, 1631, 1479, 1288, 1087, 1004 cm^{-1}; MS(CI) calcd. $C_{12}H_{10}ClINO_4S$: $[M+H]^+$, 425.9064; found $[M+H]^+$, 426; $[M+NH_4]^+$, 443.

4-Methoxypyridin-2-yl isopropylcarbamate (194)

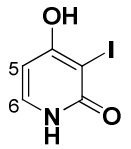


194

Iso-propyl *iso*cyanate (0.47 mL, 4.8 mmol) was added slowly to a solution of 4-methoxy-2-pyridone **(174)** (0.2 g, 1.6 mmol) and DMAP (0.06 g, 0.5 mmol) in THF (20 mL) at 0 ºC before the reaction mixture was heated at reflux for 72 hours. The reaction was quenched with 2 M HCl (2 mL) and Et_2O (20 mL) was added before the layers were separated. The aqueous layer was extracted with Et_2O (20 mL) and then the combined organic layers washed with saturated aqueous $NaHCO_3$ solution before being dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield **194** (0.32 g, 96%) as a white solid which was used in subsequent reactions without further purification.

M.p. (Et_2O) 164-166 ºC; R_f 0.82 (EtOAc : hexanes 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H, NH), 8.40 (d, 1H, *J* = 8.3 Hz, H^6), 6.07 (dd, 1H, *J* = 8.2, 2.5 Hz, H^5), 5.87 (d, 1H, *J* = 2.6 Hz, H^3), 4.11 (sept, 1H, *J* = 6.6 Hz, *i*-Pr), 3.84 (s, 3H, OMe), 1.31 (s, 3H, *i*-Pr), 1.29 (s, 3H, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 166.3, 151.2, 132.7, 102.6, 97.6, 55.9, 43.2, 22.5. IR 3361 (NH), 2921, 2850, 1731 (C=O), 1648, 1486, 1213 cm^{-1}; HRMS (CI) calcd. $C_{10}H_{15}N_2O_3$: $[M+H]^+$, 211.1083; found $[M+H]^+$, 211.1082.

4-Hydroxy-3-iodopyridine-2(1*H*)-one (197)

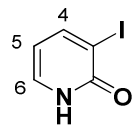


XX

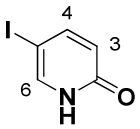
A solution of iodine (2.51 g, 9.90 mmol) in warm dioxane (14 mL) was added portion-wise over 5 minutes to a refluxing solution of 2,4-dihydroxypyridine **(196)** (1.00 g, 9.00 mmol) and sodium carbonate (1.91 g, 18.0 mmol) in H_2O (35 mL) and the resulting solution heated at reflux for 20 hours. After being allowed to cool to room temperature and then to 5 ºC the solution was acidified with glacial AcOH to pH 4-5. A cream precipitate was formed instantly which was filtered and dried over P_2O_5 for 48 hours to give **197** (0.89 g, 42%) which was used in subsequent reactions without further purification.

M.p. (H_2O) 230 ºC (decomp.); R_f 0.50 (CH_2Cl_2 : MeOH 3 : 1); ^{1}H NMR (400 MHz, DMSO) δ 7.23 (d, 1H, *J* = 7.1 Hz, H^6), 7.18 (d, 1H, *J* = 7.2 Hz, H^5); ^{13}C NMR (100 MHz, DMSO) δ 167.7, 162.3, 135.7, 98.4, 73.6; IR 3253, 3104, 1630, 1530, 1322, 1289, 1042, 1020, 874, 779 cm^{-1}; HRMS (CI) calcd. $C_5H_5INO_2$: $[M+H]^+$, 237.9365; found $[M+H]^+$, 237.9371; Microanalysis calcd. for $C_5H_4INO_2$; C 25.34, H 1.70, N 5.91; found C 25.26, H 1.69, N 5.98.

3-Iodopyridin-2(1H)-one (201)[246] **and 5-Iodopyridin-2(1H)-one (202)**



201



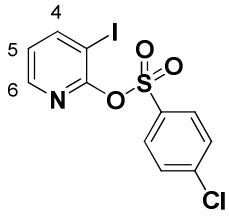
202

A mixture of 2-hydroxypyridine **(200)** (5.00 g, 52.6 mmol) and *N*-iodosuccinimide (13.0 g, 57.8 mmol) in acetonitrile (250 mL) was heated to reflux overnight. The reaction mixture was allowed to cool to room temperature before a white precipitate of 3,5-diiodopyridin-2(1H)-one was removed by filtration and the filtrate concentrated *in vacuo*. The residue was taken up in EtOAc (400 mL) and washed successively with saturated sodium thiosulphate solution (200 mL), H_2O (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes : Et_2O 5 : 1 to 0 : 1) to give a 1 : 0.7 mixture of **201** and **202** (2.84 g, 25%) as a yellow solid.

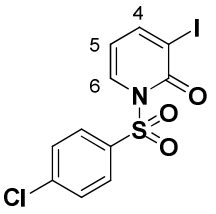
201: R_f 0.53 ($CHCl_3$: MeOH 20 : 1); ^{1}H NMR (400 MHz, DMSO): 8.10 (dd, 1H, *J* = 7.2, 1.9 Hz, H^6), 7.45 (dd, 1H, *J* = 6.4, 1.9 Hz, H^4), 5.99 (t, 1H, *J* = 6.7 Hz, H^5); ^{13}C NMR (100 MHz, DMSO) δ 160.1, 150.2, 136.5, 107.0, 93.2.

202: R_f 0.53 ($CHCl_3$: MeOH 20 : 1); ^{1}H NMR (400 MHz, DMSO) δ 7.66 (d, 1H, *J* = 2.5 Hz, H^6), 7.57 (dd, 1H, *J* = 9.6, 2.6 Hz, H^4), 6.23 (d, 1H, *J* = 9.4 Hz, H^3); ^{13}C NMR (100 MHz, DMSO) δ 161.6, 148.3, 142.3, 121.8, 66.4.

3-Iodopyridin-2-yl 4-chlorobenzenefulfonate (203) and 1-(4-Chlorophenylsulfonyl)-3-iodopyridin-2-(1H)-one (204)



203



204

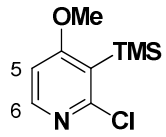
To a solution of 3-iodopyridin-2(1H)-one **(201)** and 5-iodopyridin-2(1H)-one **(202)** (2.41 g, 11.4 mmol) in anhydrous CH_2Cl_2 (80 mL) was added NEt_3 (1.75 mL, 12.5 mmol) and DMAP (0.140 g, 1.14 mmol), followed by 4-chlorobenzene-1-sulfonyl chloride (2.63 g, 12.5 mmol) and the reaction stirred at room temperature overnight. The reaction mixture was washed with saturated aqueous NH_4Cl solution (50 mL) and H_2O (50 mL). The aqueous layers were back extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes : Et_2O 20 : 1 to 5 : 1) to give **203** (0.55 g, 12%) as a white solid.

M.p. (hexanes/Et_2O) 74-76 ºC; R_f 0.13 (hexanes : Et_2O 20 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, 1H, *J* = 4.7, 1.7 Hz, H^6), 8.18 (dd, 1H, *J* = 7.8, 1.8 Hz, H^4), 8.07 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.56 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.00 (dd, 1H, *J* = 7.7, 4.8 Hz, H^5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 149.9, 147.3, 141.0, 135.6, 130.3, 129.4, 123.6, 83.3; IR 3442, 1571, 1477, 1407, 1381, 1181 cm^{-1}; HRMS (CI) calcd. $C_{11}H_8ClINO_3S$: $[M+H]^+$, 395.8958; found $[M+H]^+$, 395.8951.

Further elution gave **204** as a pale yellow oil for characterisation purposes:

R_f 0.08 (hexanes : Et_2O 20 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, 1H, *J* = 7.4, 1.8 Hz, H^6), 8.07 (d, 2H, *J* = 8.7 Hz, Ar-H), 7.99 (dd, 1H, *J* = 6.9, 1.7 Hz, H^4), 7.53 (d, 2H, *J* = 8.8 Hz, Ar-H), 6.07 (t, 1H, *J* = 7.1 Hz, H^5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 150.5, 142.2, 134.2, 132.1, 131.7, 129.4, 107.8, 95.0; IR 3107, 1672 (C=O), 1604, 1515, 1333, 1253, 1186, 1087 cm^{-1}; HRMS (CI) calcd. $C_{11}H_8ClINO_3S$: $[M+H]^+$, 395.8958; found $[M+H]^+$, 395.8969.

2-Chloro-4-methoxy-3-(trimethylsilyl)pyridine (206)[122]

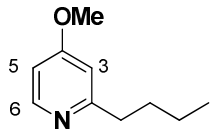


206

Iso-propylmagnesium chloride (0.028 mL of a 2 M solution in THF, 0.056 mmol) was added drop-wise to a stirring solution of 2-chloro-3-iodo-4-methoxypyridine **(1)** (0.015 g, 0.056 mmol) in THF (1 mL) at room temperature and the resulting solution stirred for 30 minutes. Chlorotrimethylsilane (0.029 mL, 0.224 mmol) was added to the pale yellow solution and stirred for a further 16 hours. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) and then extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* **206** (0.010 g, 80%) was identified as the sole product from ^{1}H NMR spectroscopic analysis of the crude material. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 3) for characterisation purposes to yield **206** as a pale yellow oil.

R_f 0.30 (hexanes : Et_2O 4 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, 1H, J = 5.8 Hz, H^6), 6.71 (d, 1H, J = 5.8 Hz, H^5), 3.85 (s, 3H, OMe), 0.41 (s, 9H, TMS); ^{13}C NMR (100 MHz, $CDCl_3$): 172.3, 157.5, 151.2, 121.6, 105.2, 55.5, 1.5.

2-Butyl-4-methoxypyridine (209)

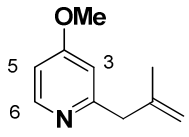


209

tert-BuLi (0.24 mL of a 1.7 M solution in pentane, 0.4 mmol) was added drop-wise to a solution of 2-chloro-3-iodo-4-methoxypyridine **(1)** (0.054 g, 0.2 mmol) in THF (2 mL) at −78 ºC and then stirred for 30 minutes at that temperature. *n*-BuLi (0.19 mL of a 1.6 M solution in hexanes, 0.3 mmol) was added and the reaction allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl solution (2 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 4 to 1 : 1) to give **209** (0.0035 g, 13%) as pale yellow oil.

R_f 0.11 (EtOAc : hexanes 1 : 4); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.34 (d, 1H, J = 5.6 Hz, H^6), 7.26 (m, 1H, H^5), 6.67 (d, 1H, J = 2.2 Hz, H^3), 3.83 (s, 3H, OMe), 2.74 (t, 2H, J = 7.6 Hz, CH_2), 1.72 (m, 2H, CH_2), 1.39 (m, 2H, CH_2), 0.94 (t, 3H, J = 7.4 Hz, CH_3); HRMS (CI) calcd. $C_{10}H_{16}NO$: $[M^+H]^+$, 166.1232; found $[M^+H]^+$, 166.1228.

4-Methoxy-2-(2-methylallyl)pyridine (208)

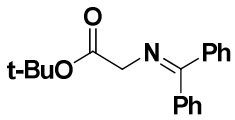


208

tert-BuLi (0.24 mL of a 1.7 M solution in pentane, 0.4 mmol) was added drop-wise to a solution of 2-chloro-3-iodo-4-methoxypyridine **(1)** (0.054 g, 0.2 mmol) in THF (2 mL) at −78 ºC and then stirred for 30 minutes at that temperature. 2-methylallylmagnesium chloride (0.6 mL of a 0.5 M solution in THF, 0.3 mmol) was added and the reaction allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl solution (2 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 10 to 1 : 1) to give **208** (0.005 g, 15%) as pale yellow oil.

R_f 0.06 (EtOAc : hexanes 1 : 10); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.37 (d, 1H, J = 5.8 Hz, H^6), 6.72 (d, 1H, J = 2.4 Hz, H^3), 6.67 (dd, 1H, J = 5.6, 2.5 Hz, H^5), 4.88 (s, 1H, =CH), 4.79 (s, 1H, =CH), 3.84 (s, 3H, OMe), 3.50 (s, 2H, CH_2), 1.72 (s, 3H, CH_3); ^{13}C NMR (100MHz, $CDCl_3$) δ 166.2, 161.5, 150.4, 143.6. 113.0, 108.9, 107.6, 55.0, 47.1, 29.7, 22.2; IR 2932 (C-H), 1611 cm^{-1}; HRMS (CI) calcd. $C_{10}H_{14}NO$: $[M^+H]^+$, 164.2243; found $[M^+H]^+$, 164.1075.

***tert*-Butyl 2-(diphenylmethyleneamino)acetate (290)[180]**

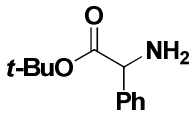


290

290 was prepared according to a literature procedure.[180] A solution of *t*-butyl 2-bromoacetate **(288)** (0.50 mL, 3.4 mmol) in acetonitrile (5 mL) was treated with benzophenonimine **(289)** (0.57 mL, 3.4 mmol) and di-*iso*-propylethylamine (0.59 mL, 3.4 mmol) and the resulting mixture heated to reflux for 12 hours. The reaction was allowed to cool to room temperature and most of the solvent removed *in vacuo*. The residue was partitioned between H_2O (10 mL) and Et_2O (20 mL) and the organic layer dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield **290** (0.99 g, 99%) as an off-white solid which was used in subsequent reactions without further purification.

M.p. (acetonitrile) 95-99 ºC [lit[247] 111-112 ºC]; R_f 0.81 (EtOAc : hexanes 3 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.82 (m, 10H, Ar-H), 4.12 (s, 2H, CH_2), 1.46 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.9, 139.4, 137.6, 136.2, 132.4, 130.4, 130.1, 128.8, 128.6, 128.3, 128.0, 127.7, 81.1, 56.3, 28.1; IR 2975, 1735 (C=O), 1623, 1446, 1367, 1216, 1149, 694 cm^{-1}.

$_{DL}$-Phenylglycine *tert*-butyl ester (300)[248]

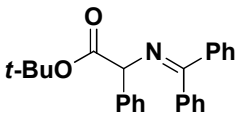


300

300 was prepared according to a literature procedure.[248] Perchloric acid (1.7 mL of a 70% wt solution in H_2O, 19.8 mmol) was added slowly to a solution of $_{DL}$-α-phenylglycine **(299)** (2.0 g, 13.2 mmol) in *tert*-butyl acetate (30 mL) at 0 ºC and then the reaction stirred at room temperature for 12 hours. The reaction mixture was washed with H_2O (80 mL) and 1 M HCl (50 mL). The combined aqueous layers were adjusted to pH 9 with 10% aqueous NaOH solution and then extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield **300** (2.0 g, 72%) as a pale yellow oil which was used in the subsequent reaction without further purification.

R_f 0.48 (CH_2Cl_2 : MeOH 10 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H, Ar-H), 4.50 (s, 1H, CH), 1.93 (s, 2H, NH_2), 1.41 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 140.9, 128.6, 127.7, 126.7, 81.5, 59.3, 27.9.

***tert*-Butyl 2-(diphenylmethyleneamino)-2-phenylacetate (296)**

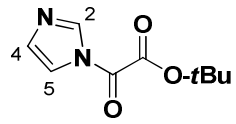


296

Benzophenonimine **(289)** (0.48 mL, 2.90 mmol) was added to a solution of phenylglycine *tert*-butyl ester **(300)** (0.30 g, 1.45 mmol) in CH_2Cl_2 (5 mL) and the reaction stirred at room temperature for 36 hours. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with saturated aqueous NH_4Cl solution (3 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes/Et_2O 20:1) to remove most of the remaining benzophenonimine. On standing at room temperature colourless crystals formed, which were filtered and washed with *n*-pentane to yield **296** (0.05 g, 10%) as colourless crystals for analytical purposes.

M.p. (hexanes/EtOAc) 78-80 ºC; R_f 0.52 (EtOAc : hexanes 1 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.47 (m, 5H, Ar-H), 7.34 (m. 6H, Ar-H), 7.13 (dd, 2H, *J* = 6.4, 2.9 Hz, Ar-H), 5.03 (s, 1H, CH), 1.39 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 169.7, 139.7, 139.6, 136.4, 130.3, 130.1, 129.0, 128.6, 128.5, 128.3, 128.0, 127.8, 127.5, 81.3, 70.2, 28.0; IR 2977, 1736 (C=O), 1623 (C=N), 1575, 1490, 1446, 1367, 1143; HRMS (CI) calcd. $C_{25}H_{26}NO_2$: $[M+H]^+$, 372.1964; found $[M+H]^+$, 372.1966.

***tert*-Butyl 2-(1H-imidazole-1-yl)-2-oxoacetate (302)[186]**

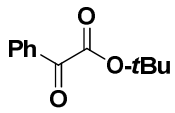


302

302 was prepared according to a literature procedure.[186] *tert*-Butyl alcohol (10.8 mL, 115 mmol) was added in one batch to a stirred solution of oxalyl chloride (10.0 mL, 115 mmol) in THF (200 mL) at 0 ºC. After 1 hour a solution of imidazole (23.5 g, 345 mmol) in THF (100 mL) was added *via* dropping funnel over 30 minutes. After stirring for a further 15 minutes the reaction mixture was filtered and the imidazole hydrochloride precipitate washed with THF (100 mL). The filtrate was concentrated *in vacuo* to give **302** (20.0 g, 89%) as a yellow/orange oil which was used in subsequent reactions without further purification.

R_f 0.10 (hexanes : EtOAc 20 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H, H^2), 7.62 (s, 1H, H^5), 7.13 (s, 1H, H^4), 1.64 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 163.5, 137.9, 131.6, 116.8, 87.3, 27.7.

***tert*-Butyl 2-oxo-2-phenylacetate (303)**[249]

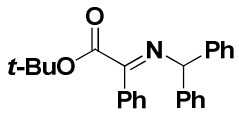


303

303 was prepared according to a literature procedure.[249] To a solution of *tert*-butyl 2-(1H-imidazole-1-yl)-2-oxoacetate **(302)** (4.71 g, 24.0 mmol) in THF (75 mL) at −50 ºC was added phenylmagnesium bromide solution (24.0 mL of a 1 M solution in THF, 24.0 mmol) in THF (25 mL) *via* dropping funnel over 1 hour with stirring. The solution was allowed to warm to room temperature over 3 hours and then poured into ice-H_2O (200 mL). The reaction mixture was extracted with Et_2O (2 x 100 mL), the organic layers washed with brine (50 mL), dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by vacuum distillation to give **303** (4.00 g, 81%) as a colourless oil.

b.p. 100 ºC/0.4 Torr; R_f 0.42 (hexanes : EtOAc 40 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.65 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.51 (t, 2H, *J* = 7.7 Hz, Ar-H), 1.64 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.8, 163.7, 134.6, 132.5, 129.9, 128.8, 84.7, 28.1.

(*E*)-*tert*-Butyl 2-(benzhydrylimino)-2-phenylacetate (304)

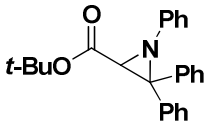


304

A mixture of diphenylmethanamine (0.44 mL, 2.54 mmol), *tert*-butyl 2-oxo-2-phenylacetate **(303)** (0.50 g, 2.42 mmol) and *para*-toluene sulfonic acid monohydrate (0.02 g, 0.12 mmol) was heated to 100 ºC overnight in the presence of 4 Å molecular sieves. After cooling to room temperature the residue was purified by flash column chromatography (hexanes : Et_2O 40 : 1) to give **304** (0.24 g, 27%) as an off-white solid.

M. p. (hexanes/Et_2O) 124-126 ºC; R_f 0.60 (hexanes : EtOAc 10 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, 2H, *J* = 7.8, 1.5 Hz, Ar-H), 7.25-7.48 (m, 13H, Ar-H), 5.84 (s, 1H, C<u>H</u>$(Ph)_2$), 1.62 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 159.3, 143.3, 134.6, 134.5, 130.9, 128.5, 128.4, 127.6, 127.0, 84.1, 70.9, 28.2; IR 3061, 3027, 2979, 2931, 1724, 1631, 1493, 1450, 1369, 1220, 1150, 1044 cm^{-1}; HRMS (CI) calcd. $C_{25}H_{26}NO_2$: $[M+H]^+$, 372.1964; found $[M+H]^+$, 372.1963.

***tert*-Butyl 1,3,3-triphenylaziridine-2-carboxylate (305)**

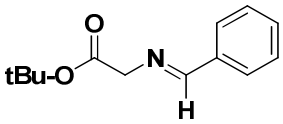


305

To a solution of cesium fluoride (0.62 g, 4.08 mmol) and *tert*-butyl 2-(diphenylmethyleneamino)acetate **(290)** (0.41 g, 1.36 mmol) in acetonitrile (25 mL) was added drop-wise 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **(51)** (0.41 mL, 1.70 mmol). The reaction was heated to 80 ºC for 1 hour 45 minutes before being allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue partitioned between Et_2O (20 mL) and H_2O (20 mL) and the layers separated. The aqueous phase was extracted with Et_2O (2 x 10 mL), then the combined organic layers dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes : EtOAc 30 : 1) to give **305** (0.40 g, 63%) as a yellow oil.

R_f 0.26 (hexanes : EtOAc 30 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2H, *J* = 6.9 Hz, Ar-H), 7.29-7.37 (m, 3H, Ar-H), 7.14 (m, 7H, Ar-H), 6.82-6.86 (m, 3H, Ar-H), 4.01 (s, 1H, C<u>H</u>CO_2*t*Bu), 1.19 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 147.4, 139.0, 135.7, 130.1, 129.9, 129.3, 128.4, 128.3, 127.8, 127.8, 127.5, 122.4, 120.8, 81.6, 57.9, 48.1, 27.6; IR 3060, 2976, 2930, 1746, 1710, 1595, 1491, 1448, 1367, 1306, 1273, 1154, 1029, 764, 697; HRMS (CI) calcd. $C_{25}H_{26}NO_2$: $[M+H]^+$, 372.1964; found $[M+H]^+$, 372.1975.

***(E)*-*tert*-Butyl 2-(benzylideneamino)acetate (308a)**[250]

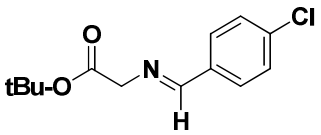


308a

A mixture of *tert*-butyl aminoacetate hydrochloride **(307)** (1.0 g, 6.0 mmol), NEt_3 (0.84 mL, 6.0 mmol) and $MgSO_4$ (4.3 g, 30 mmol) in anhydrous CH_2Cl_2 (25 mL) was stirred at room temperature for 1 hour before benzaldehyde (0.61 mL, 6.0 mmol) was added and the suspension stirred for a further 12 hours at room temperature. The reaction mixture was filtered, the filtrate washed with brine (2 x 10 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to give **308a** (1.24 g, 93%) as a pale yellow oil which was used in subsequent reactions without further purification.

R_f 0.50 (EtOAc : hexanes 1 : 10); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.27 (s, 1H, HC=N), 7.78 (dd, 2H, *J* = 7.6, 1.8 Hz, Ar-H), 7.43 (m, 3H, Ar-H), 4.31 (d, 2H, *J* = 1.1 Hz, CH_2), 1.50 (s, 9H, *t*-Bu); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.4, 165.2, 135.8, 129.7, 129.0, 128.5, 81.4, 62.7, 28.1.

(*E*)-*tert*-Butyl 2-(4-chlorobenzylideneamino)acetate (308b)[251]

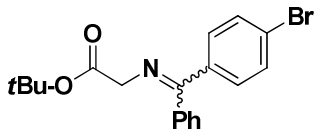


308b

A mixture of *tert*-butyl aminoacetate hydrochloride **(307)** (1.0 g, 6.0 mmol), NEt_3 (0.84 mL, 6.0 mmol) and $MgSO_4$ (4.3 g, 30 mmol) in anhydrous CH_2Cl_2 (25 mL) was stirred at room temperature for 1 hour before 4-chloro-benzaldehyde (0.84 g, 6.0 mmol) was added and the suspension stirred for a further 12 hours at room temperature. The reaction mixture was filtered, the filtrate washed with brine (2 x 10 mL) and dried over $MgSO_4$ before being concentrated *in vacuo* to give **308b** (1.36 g, 90%) as a pale yellow oil which solidified on standing to give an off-white solid which was used in subsequent reactions without further purification.

M.p. (CH_2Cl_2) 34-36 ºC; R_f 0.76 (EtOAc : hexanes 1 : 6); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.22 (s, 1H, HC=N), 7.71 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.38 (d, 2H, *J* = 8.5 Hz, Ar-H), 4.30 (d, 2H, *J* = 1.1 Hz, CH_2), 1.49 (s, 9H, *t*-Bu); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.2, 163.8, 137.1, 134.2, 129.5, 128.9, 81.6, 62.5, 28.1.

***tert*-Butyl 2-((4-bromophenyl)(phenyl)methyleneamino)acetate (312)**

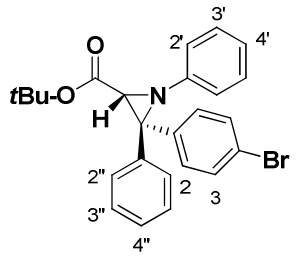


312

Perchloric acid (12.1 mL of a 70% wt. solution in H_2O, 200 mmol) was added to a solution of glycine **(310)** (10 g, 133 mmol) in *tert*-butylacetate (150 mL) at 0 ºC and then the reaction stirred at room temperature overnight. The reaction mixture was washed with H_2O (200 mL) and 1 M HCl solution (150 mL) and then combined aqueous layers adjusted to pH 9 with 1 M NaOH solution before being extracted with CH_2Cl_2 (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a pale yellow oil. The residue was purified by vacuum distillation (80 ºC/2 mmHg) to give *tert*-butyl 2-aminoacetate **(311)** as a colourless oil. A mixture of 4-bromobenzophenone (9.46 g, 36.2 mmol), *tert*-butyl 2-aminoacetate **(311)** (4.85 g, 37.0 mmol) and camphor sulfonic acid (0.17 g, 0.74 mmol) in benzene (8 mL) was heated to 90 ºC in the presence of 4 Å molecular sieves for 3 days. The reaction mixture was allowed to cool to room temperature, filtered and washed with Et_2O (2 x 10 mL). The resulting solution was washed with saturated aqueous $NaHCO_3$ solution (20 mL), the organic layer dried over $MgSO_4$, filtered, and concentrate *in vacuo* to give a brown semi-solid residue. Recrystallisation from petroleum ether 40-60 gave **312** (0.45 g, 3%) as a pale pink solid and a 3 : 1 mixture of isomers.

R_f 0.32 (EtOAc : hexanes 1 : 6); ^{1}H NMR (400MHz, benzene-d^6) δ 6.53-7.81 (m, 9H, Ar-H), 4.15 (s, 2H, CH_2), 4.10 (s, 2H, CH_2), 1.34 (s, 9H, *t*-Bu), 1.33 (s, 9H, *t*-Bu); ^{13}C NMR (100MHz, benzene-d^6) δ 170.0, 169.7, 169.1, 169.1, 139.8, 138.7, 136.0, 135.0, 132.3, 131.9, 131.7, 131.6, 131.5, 130.7, 130.6, 130.0, 129.7, 129.0, 128.9, 128.7, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.2, 126.9, 125.3, 122.9, 80.8, 80.6, 56.4, 28.0, 27.5; HRMS (CI) calcd. $C_{19}H_{21}BrNO_2$: $[M^+H]^+$, 374.0756; found $[M^+H]^+$, 374.0753.

(2*R,3*R**)-*tert*-Butyl 3-(4-bromophenyl)-1,3-diphenylaziridine-2-carboxylate (313)**

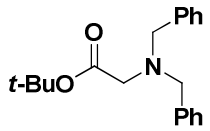


313

To a solution of the 2 isomers (3 : 1 ratio) of *tert*-butyl 2-((4-bromophenyl)(phenyl)methyleneamino)acetate **(312)** (0.033 g, 0.09 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **(51)** (0.03 mL, 0.11 mmol) in acetonitrile (1 mL) was added cesium fluoride (0.040 g, 0.27 mmol) and the reaction stirred at room temperature under nitrogen overnight. The reaction mixture was washed with saturated aqueous NH_4Cl solution (5 mL) and H_2O (5 mL). The aqueous layers were extracted with Et_2O (3 x 5 mL) and the combined organic layers dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 60) to give **313** (0.016 g, 92 : 8 dr, 40%) as a yellow oil.

R_f 0.15 (EtOAc : hexanes 1 : 60); ^{1}H NMR (400MHz, $CDCl_3$) *major diastereoisomer* δ 7.48 (d, 2H, *J* = 8.7 Hz, H^2), 7.45 (d, 2H, *J* = 8.7 Hz, H^3), 7.13 (m, 3H, $H^{3''+4''}$), 7.07 (m, 2H, $H^{2'}$), 7.01 (m, 2H, $H^{2''}$), 6.84 (m, 1H, $H^{4'}$), 6.80 (dd, 2H, *J* = 8.5, 1.0 Hz, $H^{3'}$), 3.99 (s, 1H, CH), 1.22 (s, 9H, *t*-Bu); ^{13}C NMR (100MHz, $CDCl_3$) *major diastereoisomer* δ 166.9, 147.0, 138.3, 135.0, 132.7, 131.6, 131.5, 130.9, 128.5, 128.0, 122.6, 121.5, 120.8, 81.8, 57.4, 48.0, 27.7; HRMS (CI) calcd. $C_{25}H_{25}BrNO_2$: $[M^+H]^+$, 450.1069; found $[M^+H]^+$, 450.1055.

***tert*-Butyl 2-(dibenzylamino)acetate (314)[190]**

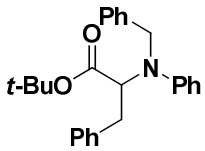


314

314 was prepared according to a literature procedure.[190] A mixture of freshly distilled dibenzylamine (13.0 mL, 67.7 mmol) and *tert*-butyl bromoacetate **(288)** (5.0 mL, 33.9 mmol) in a mixture of EtOH and 1, 4 dioxane (20 mL: 20 mL) was heated at reflux for 4 hours. The reaction mixture was allowed to cool to room temperature before the solvents were removed *in vacuo*. The residue was treated with 1 M KOH solution (50 mL), extracted with Et_2O (3 x 50 mL), the organic layers washed with brine (50 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Et_2O : hexanes 1 : 10) to give **314** (9.52 g, 90%) as a white solid.

M.p. (hexanes/Et_2O) 68-69 ºC; R_f 0.90 (hexanes : EtOAc 1 : 2); ^{1}H NMR (400 MHz, DMSO) δ 7.22-7.36 (m, 10H, Ar-H), 3.73 (s, 4H, CH_2Ph), 3.10 (s, 2H, CH_2CO_2tBu), 1.41 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, DMSO) δ 169.8, 138.8, 128.5, 128.2, 126.9, 80.1, 56.8, 53.8, 27.7; HRMS (ESI) calcd. $C_{20}H_{26}NO_2$: $[M+H]^+$, 312.1964; found $[M+H]^+$, 312.1965.

***tert*-Butyl 2-(benzyl(phenyl)amino)-3-phenylpropanoate (315)**

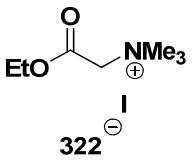


315

To a solution of cesium fluoride (0.62 g, 4.08 mmol) and *tert*-butyl 2-(dibenzylamino)acetate **(314)** (0.42 g, 1.36 mmol) in anhydrous acetonitrile (35 mL) was added drop-wise 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **(51)** (0.41 mL, 1.70 mmol) and then the reaction mixture heated at 80 ºC for 45 minutes. The reaction mixture was cooled to room temperature and the acetonitrile removed *in vacuo*. The residue was partitioned between H_2O (20 mL) and Et_2O (20 mL) and separated. The aqueous layer was further extracted with Et_2O (2 x 20 mL) and then the combined organic layers dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes : Et_2O 100 : 1) to give **315** (0.25 g, 47%) as a colourless oil.

R_f 0.27 (CH_2Cl_2 : hexanes 1 : 5); ^{1}H NMR (400 MHz, DMSO) δ 7.07-7.25 (m, 12H, Ar-H), 6.63-6.69 (m, 3H, Ar-H), 4.74 (t, 1H, *J* = 7.7 Hz, C<u>H</u>CO$_2$*t*Bu), 4.57 (d, 1H, *J* = 17.4 Hz, NC<u>H$_2$</u>Ph), 4.45 (d, 1H, *J* = 17.5 Hz, NC<u>H$_2$</u>Ph), 3.23 (dd, 1H, *J* = 13.9, 7.8 Hz, CHC<u>H$_2$</u>Ph), 3.11 (dd, 1H, *J* = 13.8, 7.6 Hz, CHC<u>H$_2$</u>Ph), 1.25 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, DMSO) δ 170.8, 148.3, 139.5, 137.8, 129.3, 128.7, 128.1, 128.1, 126.5, 126.3, 117.6, 114.5, 80.9, 64.5, 51.4, 35.4, 27.5; IR 3062, 3028, 2977, 2931, 1726 (C=O), 1599, 1503, 1453, 1367, 1147 cm^{-1}; HRMS (CI) calcd. $C_{26}H_{30}NO_2$: $[M+H]^+$, 388.2277; found $[M+H]^+$, 388.2268.

2-Ethoxy-*N*,*N*,*N*-trimethyl-2-oxoethanaminium iodide (322)[191]

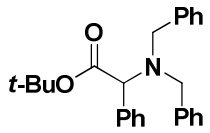


322

322 was prepared according to a literature procedure.[191] MeI (4.4 mL, 70 mmol) was added to a solution of ethyl 2-(dimethylamino)acetate **(321)** (6.7 mL, 50 mmol) in CH_2Cl_2 (100 mL) at −15 ºC, and then left at room temperature for 48 hours without stirring. White crystals were precipitated which were filtered and washed with acetone (5 x 25 mL), before being dried under vacuum to give **322** (11.1 g, 81%) as white crystals which was used in subsequent reactions without further purification.

M.p. (CH_2Cl_2) 179-180 ºC [lit.[191] 180-181 ºC]; ^{1}H NMR (400MHz, DMSO) δ 4.42 (s, 2H, CH_2), 4.24 (q, 2H, *J* = 7.1 Hz, OCH_2), 3.22 (s, 9H, NMe_3), 1.25 (t, 3H, *J* = 7.1 Hz, $OCH_2\underline{CH_3}$); ^{13}C NMR (100MHz, DMSO) δ 165.3, 63.1, 62.4, 53.7, 14.3; MS (EI) calcd. $C_7H_{17}INO_2$: $[M+H]^+$, 146; found $[M+H]^+$, 146.

***tert*-Butyl 2-(dibenzylamino)-2-phenylacetate (324)**

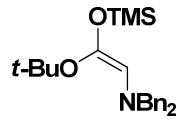


324

Cesium carbonate (0.81 g, 2.5 mmol), tetrabutylammoniumiodide (0.92 g, 2.5 mmol) and BnBr (0.30 mL, 2.5 mmol) were added sequentially to a solution of phenylglycine *tert*-butyl ester **(300)** (0.21 g, 1.0 mmol) in anhydrous DMF (10 mL) at room temperature. The reaction was then heated at 100 ºC overnight before being quenched with saturated aqueous NH_4Cl solution (10 mL) and then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated NH_4Cl solution (5 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 100 to 1 : 80) to give **324** (0.10 g, 25%) as a colourless oil.

R_f 0.29 (EtOAc : hexanes 1 : 100); ^{1}H NMR (400 MHz, DMSO) δ 7.44-7.26 (m, 15H, Ar-H), 4.32 (s, 1H, CH), 3.68 (s, 4H, NC$\underline{H_2}$Ph), 1.49 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, DMSO) δ 170.5, 139.1, 136.7, 128.5, 128.3, 128.3, 127.8, 127.1, 81.2, 65.6, 53.6, 27.8; IR 2976, 2930, 1727 (C=O), 1494, 1453, 1367, 1130 cm^{-1}; HRMS (CI) calcd. $C_{26}H_{30}NO_2$: $[M+H]^+$, 388.2277; found $[M+H]^+$, 388.2285.

(*E*)-*N*,*N*-Dibenzyl-2-*tert*-butoxy-2-(trimethylsilyloxy)ethenamine (331)[193]

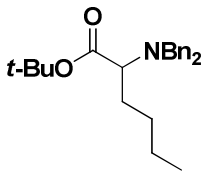


331

331 was prepared according to a literature procedure.[193] *n*-BuLi (4.4 mL of a 1.6 M solution in hexanes, 7.0 mmol) was added drop-wise to a solution of di-*iso*-propylamine (1.1 mL, 7.7 mmol) in cyclopentylmethyl ether (5 mL) at 0 to 5 ºC under argon and stirred for 30 minutes at this temperature. A solution of *tert*-butyl 2-(dibenzylamino)acetate **(314)** (2.0 g, 6.4 mmol) in cyclopentylmethyl ether (3.5 mL) was added to the reaction mixture at the same temperature over 5 minutes and stirred for a further 30 minutes. Chlorotrimethylsilane (0.98 mL, 7.7 mmol) was added drop-wise to the reaction mixture at 0 to 5 ºC and stirred for 30 minutes at that temperature before being stirred at room temperature for a further 1.5 hours. The reaction mixture was poured into a mixture of ice water and hexanes (20 mL:20 mL), separated and the aqueous phase extracted with hexanes (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* before being dried under high vacuum (0.2 mmHg) for 30 minutes to give **331** (2.2 g, 89%) as a yellow oil which was used in subsequent reactions without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.19 (m, 10H, Ar-H), 4.55 (s, 1H, CH), 3.80 (s, 4H, NC$\underline{H_2}$Ph), 1.31 (s, 9H, *t*-Bu), 0.08 (s, 9H, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 139.9, 128.0, 126.6, 108.0, 79.6, 58.6, 29.2, -0.2.

***tert*-Butyl 2-(dibenzylamino)hexanoate (334)**

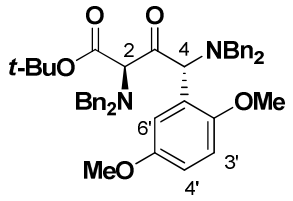


334

Methyllithium (0.97 mL of a 1.6 M solution in Et_2O, 1.55 mmol) was added drop-wise to a solution of (*E*)-*N*,*N*-dibenzyl-2-tert-butoxy-2-(trimethylsilyloxy)ethenamine **(331)** (0.60 g, 1.55 mmol) in THF (8 mL) at −78 ºC in an oven-dried Schlenk flask under nitrogen. The solution was stirred at −15 to −10 ºC for 1 hour before being re-cooled to −78 ºC. *n*-BuLi (1.06 mL of a 1.6 M solution in hexanes, 1.70 mmol) was added drop-wise at that temperature followed by 3-bromoanisole **(40)** (0.20 mL, 1.55 mmol) and the reaction allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL), extracted with EtOAc (2 x 20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes : Et_2O 100 : 1 to 60 : 1) to give **334** (0.14 g, 25%) as a yellow oil.

R_f 0.56 (EtOAc : hexanes 1 : 10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.25 (m, 10H, Ar-H), 3.97 (d, 2H, *J* = 13.9 Hz, NC$\underline{H_2}$Ph), 3.59 (d, 2H, *J* = 13.9 Hz, NC$\underline{H_2}$Ph), 3.20 (t, 1H, *J* = 7.5 Hz, CH), 1.70 (m, 2H, CH_2), 1.55 (s, 9H, *t*-Bu), 1.42 (m, 2H, CH_2), 1.23 (m, 2H, CH_2), 0.87 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 140.0, 128.8, 128.2, 126.8, 80.7, 61.3, 54.5, 29.3, 28.4, 28.3, 22.4, 14.0; IR 2985, 1724 (C=O), 1494, 1454, 1390, 1253, 1139 cm^{-1}; HRMS (CI) calcd. $C_{24}H_{34}NO_2$: $[M+H]^+$, 368.2590; found $[M+H]^+$, 368.2579.

(2R*,4R*)-*tert*-Butyl 2,4-bis(dibenzylamino)-4-(2,5-dimethoxyphenyl)-3-oxobutanoate (337)

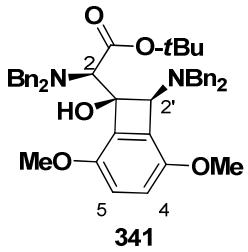


337

Methyllithium (1.34 mL of a 1.6 M solution in Et_2O, 2.14 mmol) was added drop-wise to a solution of (*E*)-*N*,*N*-dibenzyl-2-tert-butoxy-2-(trimethylsilyloxy)ethenamine **(331)** (0.82 g, 2.14 mmol) in THF (21 mL) at −78 ºC in an oven-dried Schlenk flask under nitrogen. The solution was stirred at −15 to −10 ºC for 1 hour before being re-cooled to −95 ºC. 1-chloro-2,5-dimethoxy benzene **(338)** (0.15 mL, 1.07 mmol) was added to the reaction and stirred for 15 minutes at that temperature before *sec*-BuLi (0.89 mL of a 1.26 M solution in cyclohexane, 1.12 mmol) was added drop-wise at −95 ºC, stirred for 15 minutes and the reaction allowed to warm to room temperature overnight. The reaction was quenched with H_2O (20 mL), extracted with Et_2O (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 20), followed by trituration with hexanes to give **337** (0.17 g, 0.25 mmol, 12%) as a white solid.

M.p. (hexanes/EtOAc) 122-124 ºC; R_f 0.31 (hexanes : EtOAc 20 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, 4H, *J* = 7.2 Hz, Ar-H), 7.11-6.87 (m, 16H, Ar-H), 6.85 (dd, 1H, *J* = 9.0, 3.0 Hz, $H^{4'}$), 6.73 (d, 1H, *J* = 3.0 Hz, $H^{6'}$), 6.66 (d, 1H, *J* = 9.0 Hz, $H^{3'}$), 4.97 (s, 1H, H^4), 3.98 (d, 2H, *J* = 14.0 Hz, $N^2C\underline{H_2}Ph$), 3.98 (s, 1H, H^2), 3.83 (s, 3H, OMe), 3.65 (s(br), 4H, $N^4\underline{CH_2}Ph$), 3.50 (s, 3H, OMe), 3.35 (d, 2H, *J* = 14.0 Hz, $N^2\underline{CH_2}Ph$), 1.53 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 168.9, 153.2, 140.3, 138.3, 129.0, 128.7, 128.7, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 126.7, 126.6, 126.4, 126.2, 123.9, 118.1, 114.4, 111.9, 81.4, 70.0, 65.2, 55.6, 55.0, 54.7, 54.2, 28.3; IR 1735, 1718, 1496, 1454, 1367, 1224, 1139 cm^{-1}; HRMS (ESI) calcd. $C_{44}H_{49}N_2O_5$: $[M+H]^+$, 685.3641; found $[M+H]^+$, 685.3625. Microanalysis calcd. for $C_{44}H_{48}N_2O_5$; C 77.16, H 7.06, N 4.09; found C 77.0, H 7.13, N 4.13; X-ray crystal data $C_{44}H_{48}N_2O_5$, M = 684.84, Monoclinic, P2(1), a=9.34676(10) Å, b = 30.1319(3) Å, c = 13.86705(18) Å, α = 90°, β = 103.1165(12)°, γ = 90°, V= 3803.59(8) $Å^3$, Z= 4, D_c= 1.196 Mg/m^3, μ(Cu-Kα) = 0.616 mm^{-1}, T = 173 K, colourless blocky needles, 18283 independent measured reflections, 3638 independent observed reflections [F>4σ(F)], 329 parameters.

(R*)-*tert*-Butyl 2-(dibenzylamino)-2-((1R*,2S*)-2-(dibenzylamino)-1-hydroxy-3,6-dimethoxy-1,2-dihydrocyclobutabenzen-1-yl)acetate (341)

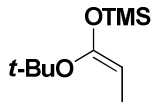


341

Methyllithium (1.07 mL of a 1.6 M solution in Et_2O, 1.71 mmol) was added drop-wise to a solution of (*E*)-*N*,*N*-dibenzyl-2-tert-butoxy-2-(trimethylsilyloxy)ethenamine **(331)** (0.66 g, 1.71 mmol) in THF (17 mL) at −78 ºC in an oven-dried Schlenk flask under nitrogen. The solution was stirred at −15 to −10 ºC for 1 hour before being re-cooled to −95 ºC. 1-chloro-2,5-dimethoxy benzene **(338)** (0.24 mL, 1.71 mmol) was added to the reaction and stirred for 15 minutes at that temperature before *sec*-BuLi (1.20 mL of a 1.34 M solution in cyclohexane, 1.171 mmol) was added drop-wise at −95 ºC, stirred for 15 minutes and the reaction allowed to warm to −40 ºC. After stirring for 2 hours at that temperature the reaction was quenched with H_2O (20 mL), extracted with Et_2O (2 x 50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 20 to 1 : 10) to give **341** (0.28 g, 24%) as a pale yellow oil.

R_f 0.42 (hexanes : EtOAc 10 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.44 (m, 20H, Ar-H), 6.77 (d, 1H, *J* = 8.8 Hz, H^5), 6.67 (d, 1H, *J* = 8.8 Hz, H^4), 5.45 (s, 1H, OH), 4.61 (s, 1H, $H^{2'}$), 4.14 (s(br), 2H, $N^{2'}C\underline{H_2}Ph$), 3.90 (s(br), 2H, $N^2C\underline{H_2}Ph$), 3.90 (s, 3H, OMe), 3.85 (s, 1H, H^2), 3.49 (d, 2H, *J* = 13.5 Hz, $N^2\underline{CH_2}Ph$), 3.41 (s(br), 2H, $N^{2'}\underline{CH_2}Ph$), 3.38 (s, 3H, OMe), 1.09 (s, 9H, *t*-Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 149.5, 149.5, 139.0, 134.2, 133.9, 129.4, 129.2, 128.9, 128.8, 128.5, 128.4, 128.1, 128.0, 127.9, 127.9, 127.3, 127.2, 126.6, 126.4, 115.5, 112.4, 81.0, 80.8, 67.5, 67.0, 57.4, 56.9, 55.9, 54.4, 27.6; IR 1727, 1494, 1527, 750 cm^{-1}; HRMS (ESI) calcd. $C_{44}H_{49}N_2O_5$: $[M+H]^+$, 685.3641; found $[M+H]^+$, 685.3623.

(*E*)-(1-*tert*-Butoxyprop-1-enyloxy)trimethylsilane (343)[193]

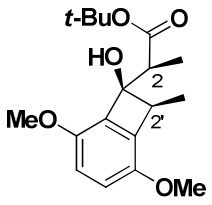


343

343 was prepared according to a literature procedure.[193] *n*-BuLi (15.9 mL of a 1.6 M solution in hexanes, 25.5 mmol) was added drop-wise to a solution of di-*iso*-propylamine (3.9 mL, 27.8 mmol) in cyclopentylmethyl ether (17 mL) at 0-5 ºC under argon and the resulting solution stirred for 30 minutes at that temperature. A solution of *tert*-butyl propanoate (3.5 mL, 23.2 mmol) in cyclopentylmethyl ether (6 mL) was added to the reaction mixture at the same temperature over 15 minutes and then stirred for a further 30 minutes. Chlorotrimethylsilane (3.6 mL, 27.8 mmol) was added at the same temperature over 5 minutes followed by stirring for 1.5 hours. The cloudy reaction mixture was poured into ice water/hexanes (20 mL/20 mL) and extracted with hexanes (2 x 20 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by vacuum distillation to give **343** (1.4 g, 30%) as a colourless oil.

b.p. 68-72 ºC/0.8 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (q, 1H, *J* = 6.6 Hz, CH), 1.49 (d, 3H, *J* = 6.5 Hz, CH_3), 1.32 (s, 9H, *t*-Bu), 0.20 (s, 9H, TMS); ^{13}C NMR (100 MHZ, $CDCl_3$) δ 152.0, 85.4, 78.1, 29.0, 10.7, -0.1.

(S*)-*tert*-Butyl2-((1R*,2S*)-1-hydroxy-3,6-dimethoxy-2-methyl-1,2-dihydrocyclobutabenzen-1-yl)propanoate (346)

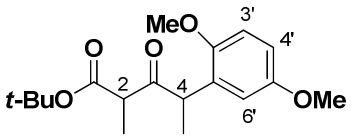


346

To a solution of (*E*)-(1-*tert*-butoxyprop-1-enyloxy) trimethylsilane **(343)** (0.22 g, 1.00 mmol) in anhydrous THF (11 mL) at −78 ºC in an oven dried Schlenk flask under nitrogen was added drop-wise methyllithium (0.63 mL of a 1.6 M solution in Et_2O, 1.00 mmol), the solution was then warmed to −15 ºC and stirred at that temperature for 1 hour. The reaction was cooled to −78 ºC and 1-fluoro-3, 5-dimethoxy benzene **(83)** (0.13 mL, 1.00 mmol) was added drop-wise and stirred for 15 minutes at that temperature before *n*-BuLi (0.66 mL of a 1.6 M solution in hexanes, 1.05 mmol) was added drop-wise and stirred for 1 hour at −78 ºC before the reaction was allowed to warm to room temperature overnight. The reaction was quenched with H_2O (20 mL), extracted with Et_2O (2 x 20 mL) and the combined organic layers dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 30 to 1 : 15) to give **346** (0.09 g, 27%) as an off white solid.

M.p. (EtOAc/hexanes) 42-47 ºC; R_f 0.61 (hexanes : EtOAc 10 : 1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, 1H, *J* = 8.8 Hz, Ar-H), 6.63 (d, 1H, *J* = 8.8 Hz, Ar-H), 4.05 (s, 1H, OH), 3.79 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.59 (q, 1H, *J* = 6.8 Hz, $H^{2'}$), 2.95 (s, 1H, *J* = 7.3 Hz, H^2), 1.49 (s, 9H, *t*-Bu), 1.38 (d, 3H, *J* = 7.0 Hz, $CH_3{}^{2'}$), 1.05 (d, 3H, *J* = 7.3 Hz, $CH_3{}^2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 148.7, 148.5, 133.6, 133.1, 114.8, 112.4, 81.5, 80.7, 56.4, 56.2, 47.4, 44.7, 28.1, 14.8, 13.1; IR 3471 (br, OH), 2975, 1725 (C=O), 1496, 1461, 1369, 1257, 1155 cm^{-1}; HRMS (CI) calcd. $C_{18}H_{30}NO_5$: $[M+NH_4]^+$, 340.2124; found $[M+NH_4]^+$, 340.2126.

***tert*-Butyl 4-(2,5-dimethoxyphenyl)-2-methyl-3-oxopentanoate (345)**



345

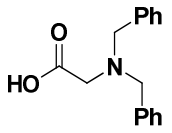
To a solution of (*E*)-(1-*tert*-butoxyprop-1-enyloxy) trimethylsilane **(343)** (0.33 g, 1.60 mmol) in anhydrous THF (16 mL) at −78 ºC in an oven dried Schlenk flask under nitrogen was added drop-wise methyllithium (0.09 mL of a 1.47 M solution in Et_2O, 1.60 mmol), the solution was then warmed to −15 ºC and stirred at that temperature for 1 hour. The reaction was cooled to −78 ºC and 1-fluoro-3, 5-dimethoxy benzene **(83)** (0.12 mL, 0.80 mmol) was added drop-wise and stirred for 15 minutes at that temperature before *n*-BuLi (0.53 mL of a 1.6 M solution in hexanes, 0.84 mmol) was added drop-wise and stirred for 1 hour at −78 ºC before the reaction was allowed to warm to 0 ºC. The reaction was quenched with H_2O (20 mL), extracted with Et_2O (2 x 20 mL) and the combined organic layers dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 20) to give **345** (0.06 g, 22%, 1 : 2 mixture of unassigned diastereoisomers).

R_f 0.30 (hexanes : EtOAc 20 : 1); IR 2979, 1739 (C=O), 1714 (C=O), 1502, 1457, 1369, 1240, 1220, 1159, 1049; HRMS (CI) calcd. $C_{18}H_{30}NO_5$: $[M+NH_4]^+$, 340.2124; found $[M+NH_4]^+$, 340.2123.

Major Diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H, Ar-H$^{6'}$), 6.76 (d, 1H, *J* = 2.9 Hz, Ar-H$^{4'}$), 6.66 (d, 1H, *J* = 2.9 Hz, Ar-H$^{3'}$), 4.39 (q, 1H, *J* = 6.9 Hz, CH^4), 3.78 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.59 (q, 1H, *J* = 6.8 Hz, CH^2), 1.44 (s, 9H, *t*-Bu), 1.35 (d, 3H, *J* = 6.8 Hz, CH_3), 1.15 (d, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 170.0, 153.8, 129.7, 115.0, 112.6, 111.7, 81.5, 55.7, 51.2, 45.8, 27.9, 16.1, 12.9.

Minor Diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 1H, Ar-H$^{6'}$), 6.74 (d, 1H, *J* = 2.9 Hz, Ar-H$^{4'}$), 6.73 (d, 1H, *J* = 2.9 Hz, Ar-H$^{3'}$), 4.29 (q, 1H, *J* = 7.0 Hz, CH^4), 3.79 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.49 (q, 1H, *J* = 6.8 Hz, CH^2), 1.35 (s, 9H, *t*-Bu), 1.36 (d, 3H, *J* = 6.8 Hz, CH_3), 1.23 (d, 3H, *J* = 7.3 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 169.8, 150.9, 129.5, 114.9, 112.5, 111.5, 81.0, 55.9, 51.5, 44.2, 27.8, 16.5, 13.8.

2-(Dibenzylamino)acetic acid (353)[197]

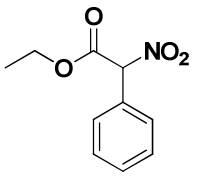


353

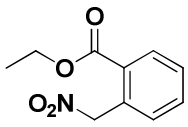
353 was prepared according to a literature procedure.[197] To a solution of glycine **(310)** (5.0 g, 66.6 mmol) in H_2O (40 mL) was added KOH (13.3 g, 237 mmol) and EtOH (40 mL). BnBr (15.8 mL, 133.2 mmol) was added to the resulting solution slowly *via* dropping funnel and the reaction stirred at room temperature overnight and then refluxed for 30 minutes. The solution was allowed to cool to room temperature and then concentrated by about 50% *in vacuo* before being acidified to pH 6 with glacial AcOH. A white solid precipitated immediately which was collected by filtration and dried over P_2O_5 for 48 hours to give **353** (8.9 g, 34.9 mmol, 52%) as a white solid which was used in subsequent reactions without further purification.

M.p. (EtOH) 200-203 ºC; R_f 0.12 (hexanes : EtOAc 20 : 1); ^{1}H NMR (400 MHz, DMSO) δ 7.22-7.36 (m, 10H, Ar-H), 3.73 (s, 4H, CH_2Ph), 3.11 (s, 2H, CH_2 gly); ^{13}C NMR (100 MHz, DMSO) δ 172.4, 139.1, 128.5, 128.2, 126.9, 56.7, 53.3.

Ethyl 2-nitro-2-phenylacetate (369)[252] and Ethyl 2-(nitromethyl)benzoate (370)



369

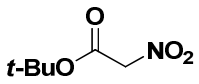


370

To a solution of ethylnitroacetate **(368)** (0.11 mL, 1.0 mmol), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate **(51)** (0.30 mL, 1.25 mmol) and 18-crown-6 (0.79 g, 3 mmol) in THF (5 mL) at 0 ºC was added potassium fluoride (0.17 g, 3 mmol) and the reaction stirred at 0 ºC for 6 hours before warming to room temperature overnight. A further batch of potassium fluoride (0.11 g, 2 mmol) was added and the reaction stirred at room temperature for a further 24 hours. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with EtOAc (2 x 10 mL). The organic layer was washed with saturated KCl solution (4 x 10 mL) and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 20) to give a 1 : 2.8 mixture of **369** and **370** (0.14 g, 67%) as a pale yellow oil.

R_f 0.17 (EtOAc : hexanes 1 : 6); ^{1}H NMR (400MHz, $CDCl_3$) *both isomers* δ 8.16 (dd, 1H, *J* = 7.6, 1.4 Hz, Ar-H), 7.38-7.63 (m, 8H, Ar-H), 6.17 (s, 1H, CH), 5.85 (s, 2H, CH_2NO_2), 4.28-4.40 (m, 4H, 2 x OCH_2), 1.38 (t, 3H, *J* = 7.2 Hz, CH_3), 1.30 (t, 3H, *J* = 7.1 Hz, CH_3); ^{13}C NMR (100MHz, $CDCl_3$) *both isomers* δ 166.2, 164.0, 133.1, 132.8, 131.6, 130.8, 130.4, 130.2, 129.9, 129.1, 128.9, 90.8, 77.6, 63.4, 61.6, 14.2, 13.9; IR 2931 (C-H), 1731 (C=O), 1530 (NO_2), 1348 (NO_2) cm^{-1}; HRMS (CI) calcd. $C_{10}H_{15}N_2O_4$: $[M+NH_4]^+$, 227.1032; found $[M+NH_4]^+$, 227.1037.

***tert*-Butyl 2-nitroacetate (376)**[208]

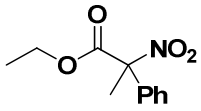


376

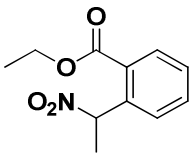
376 was prepared according to a literature procedure.[208] Polymer supported nitrite resin (0.5 g of *ca.* 4 mmol/g resin, 2 mmol) was dried under vacuum overnight before acetonitrile (5 mL) was added and the suspension stirred at room temperature for 30 minutes. The mixture was cooled to −15 ºC and *tert*-butyl bromoacetate **(288)** (0.15 mL, 1 mmol) was added drop-wise and the reaction stirred at −15 ºC for 8 hours. The reaction was filtered through a sinter whilst still cold and washed with small portions of CH_2Cl_2 (5 x 1 mL). The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 10) to give **376** (0.085 g, 53%) as a colourless oil.

R_f 0.50 (EtOAc : hexanes 1 : 10); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.07 (s, 2H, CH_2), 1.52 (s, 9H, *t*-Bu); ^{1}H NMR (100MHz, $CDCl_3$) δ 160.7, 85.2, 76.8, 27.8.

Ethyl 2-nitro-2-phenylpropanoate (382)[253] and Ethyl 2-(1-nitroethyl)benzoate (383)



382



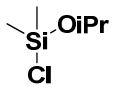
383

2-(trimethylsilyl)phenyl trifluoromethanesulfonate **(51)** (0.30 mL, 1.25 mmol) was added to a solution of ethyl 2-nitropropanoate **(381)** (0.13 mL, 1 mmol), potassium fluoride (0.17 g, 3 mmol) and 18-crown-6 (0.79 g, 3 mmol) in THF (5 mL) and stirred at room temperature for 1.5 hours. The reaction was quenched with H_2O (5 mL), extracted with EtOAc (2 x 10 mL) and the combined organic layers dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 40) to give a 1 : 3.5 mixture of **382** and **383** (0.15 g, 66%) as a yellow oil.

382: R_f 0.76 (EtOAc : hexanes 1 : 6); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.43-7.47 (m, 5H, Ar-H), 4.34 (q, 2H, *J* = 7.1 Hz, OCH_2), 2.27 (s, 3H, CH_3), 1.31 (t, 3H, *J* = 7.1 Hz, $OCH_2\underline{CH_3}$); ^{13}C NMR (100MHz, $CDCl_3$) δ 167.2, 134.1, 129.9, 128.6, 127.5, 95.1, 63.2, 23.2, 10.1; IR 2931 (C-H), 1744 (C=O), 1554 (NO_2), 1342 (NO_2) cm^{-1}; HRMS (CI) calcd. $C_{11}H_{17}N_2O_4$: $[M+NH_4]^+$, 241.1188; found $[M+NH_4]^+$, 241.1185.

383: R_f 0.76 (EtOAc : hexanes 1 : 6); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.02 (dd, 1H, *J* = 7.8, 1.3 Hz, Ar-H), 7.59 (dt, 1H, *J* = 7.9, 1.4 Hz, Ar-H), 7.49 (m, 2H, Ar-H), 6.69 (q, 1H, *J* = 6.9 Hz, CH), 4.39 (q, 2H, *J* = 7.3 Hz, OCH_2), 1.92 (d, 3H, *J* = 6.9 Hz, CH_3), 1.41 (t, 3H, *J* = 7.1 Hz, $OCH_2C\underline{H_3}$); ^{13}C NMR (100MHz, $CDCl_3$) δ 166.6, 137.1, 132.8, 131.0, 129.6, 129.1, 127.0; HRMS (CI) calcd. $C_{11}H_{17}N_2O_4$: $[M+NH_4]^+$, 241.1188; found $[M+NH_4]^+$, 241.1185.

Chloro(*iso*-propoxy)dimethylsilane (386)[210]

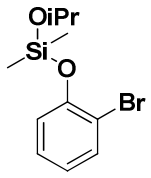


386

To a solution of urea (30 g, 500 mmol) in *i*-PrOH (38 mL), was added drop-wise *via* syringe-pump at room temperature dichlorodimethylsilane **(385)** (60 mL, 500 mmol) and then the reaction allowed to stir at room temperature overnight. The solution was filtered *via* cannula under nitrogen and then purified by distillation to give **386** (50 g, 66%) as a colourless oil.

B.p. 103-105 ºC [lit.[210] 108-109 ºC]; ^{1}H NMR (400MHz, $CDCl_3$) δ 4.23 (sept, 1H, *J* = 6.2 Hz, *i*-Pr), 1.21 (d, 6H, *J* = 6.2 Hz, *i*-Pr), 0.46 (s, 6H, $SiMe_2$);^{13}C NMR (100MHz, $CDCl_3$) δ 66.4, 25.2, 2.5.

(2-Bromophenoxy)(*iso*-propoxy)dimethylsilane (388)



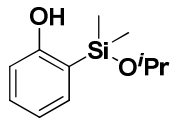
388

2-bromophenol **(387)** (2 mL, 17.2 mmol) was added drop-wise *via* syringe pump over 4 hours under argon to chloro(*iso*-propoxy)dimethylsilane **(386)** (2.6 g, 17.2 mmol) at room temperature. The resulting mixture was purified by vacuum distillation to give **388** (1.56 g, 31%) as a colourless oil.

B.p. 65-70 ºC/0.15 mbar; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.55-7.51 (m, 1H, Ar-H), 7.20-7.18 (m, 1H, Ar-H), 7.02 (dd, 1H, *J* = 8.1, 1.4 Hz, Ar-H), 6.85 (dt, 1H, *J* = 7.7, 1.4 Hz, Ar-H), 4.29 (sept, 1H, *J* = 6.1 Hz, *i*-Pr), 1.21 (d, 6H, *J* = 6.1 Hz, *i*-Pr), 0.30 (s, 6H, $SiMe_2$).

Due to the instability of the compound, no further characterisation was possible and it was carried on to the next stage.

2-(*iso*-Propoxydimethylsilyl)phenol (389)

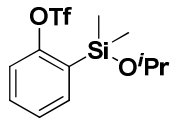


389

To an oven dried Schlenk flask containing a solution of (2-bromophenoxy)(iso-propoxy)dimethylsilane **(388)** (13 g, 45 mmol) in anhydrous THF (100 mL) at −78 ºC was added drop-wise *tert*-BuLi (53 mL of a 1.7 M solution in pentane, 90 mmol) *via* syringe pump over 10 minutes. The resulting solution was allowed to warm to room temperature overnight before being quenched with saturated aqueous NH_4Cl solution (100 mL). The ensuing mixture was extracted with Et_2O (3 x 100 mL), the combined organic layers washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by vacuum distillation to afford **389** (5.52g, 58%) as a colourless oil.

B.p. 68-70 ºC/ 0.23 mbar; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.75 (s, 1H, Ar-OH), 7.30-7.26 (m, 1H, Ar-H), 7.15 (dd, 1H, *J* = 7.3, 1.7 Hz, Ar-H), 6.87 (dt, 1H, *J* = 7.3, 0.8 Hz, Ar-H), 6.82 (d, 1H, *J* = 8.1 Hz, Ar-H), 4.22 (sept, 1H, *J* = 6.1 Hz, *i*-Pr), 1.29 (d, 6H, *J* = 6.1 Hz, *i*-Pr), 0.42 (s, 6H, $SiMe_2$); ^{13}C NMR (100MHz, $CDCl_3$) δ 162.2, 133.5, 131.6, 129.6, 119.5, 115.8, 66.9, 25.5, 0.0; IR 3331 (OH), 1595, 1438, 1277, 1252, 1223 cm^{-1}; HRMS (ESI) calcd. $C_{11}H_{19}O_2Si$: $[M+H]^+$, 211.1154; found $[M+H]^+$, 211.1159.

2-(*iso*-Propoxydimethylsilyl)phenyl trifluoromethanesulfonate (390)

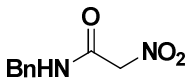


390

Di-*iso*-propylethylamine (5.4 mL, 31.2 mmol) and triflic anhydride (5.3 mL, 31.2 mmol) were added sequentially to a Schlenk flask containing a solution of 2-(isopropoxydimethylsilyl)phenol **(389)** (5.5 g, 26 mmol) in anhydrous CH_2Cl_2 (150 mL) at −78 ºC and then stirred for a further 30 minutes at that temperature. The solvent was removed *in vacuo* before anhydrous hexane (50 mL) was added to the residue. The solution was filtered *via* a filter cannula under nitrogen and then concentrated *in vacuo*. The residue was purified by vacuum distillation to give **390** (7.5 g, 84%) as a colourless oil.

B. p. 125 ºC/2 mbar; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.70 (dd, 1H, *J* = 7.3, 1.9 Hz, Ar-H), 7.49-7.44 (m, 1H, Ar-H), 7.37 (dt, 1H, *J* = 7.3, 0.7 Hz, Ar-H), 7.32 (d, 1H, *J* = 8.4 Hz, Ar-H), 4.09 (sept, 1H, *J* = 6.2 Hz, *i*-Pr), 1.19 (d, 6H, *J* = 6.0 Hz, *i*-Pr), 0.47 (s, 6H, $SiMe_2$); ^{13}C NMR (100MHz, $CDCl_3$) δ 154.6, 136.6, 131.7, 131.4, 127.5, 119.6, 118.5 (q, $J_{C\text{-}F}$ 320), 65.8, 25.6, -0.3; IR 2974, 1599, 1420, 1247, 1205, 1134, 1026 cm^{-1}; HRMS (ESI) calcd. $C_{12}H_{21}NO_4SSi$: $[M+NH_4]^+$, 360.0913; found $[M+NH_4]^+$, 360.0916.

***N*-Benzyl-2-nitroacetamide (397)**[211]

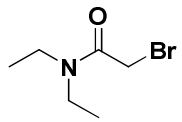


397

397 was prepared according to a literature procedure.[211] Benzylamine (8.2 mL, 75 mmol) was added drop-wise *via* dropping funnel to a solution of methyl nitroacetate **(396)** (1.38 mL, 15 mmol) in MeOH (20 mL) and stirred at room temperature for 3 days. The reaction mixture was then concentrated *in vacuo*, and acidified to pH 4 with 1 M HCl solution, before being extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2) to give **397** (1.31 g, 45%) as a white solid.

M.p. (CH_2Cl_2) 84-86 ºC [lit.[211] 87-89 ºC]; R_f 0.24 (CH_2Cl_2); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.39-7.28 (m, 5H, Ar-H), 6.73 (s(br), 1H, NH), 5.14 (s, 2H, CH_2NO_2), 4.52 (d, 2H, *J* =5.7 Hz, CH_2Ph); ^{13}C NMR (100MHz, $CDCl_3$) δ 160.3, 136.6, 128.9, 128.0, 127.8, 77.7, 44.1.

2-Bromo-*N*,*N*-diethylacetamide (400)[212]

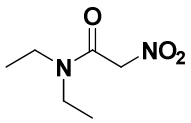


400

400 was prepared according to a literature procedure.[212] A solution of bromo acetyl bromide **(399)** (0.87 mL, 10mmol) in CH_2Cl_2 (1 mL) was added drop-wise to a solution of diethylamine (2.08 mL, 20 mmol) in CH_2Cl_2 (9 mL) at 0 ºC and then stirred for a further 15 minutes at this temperature before being allowed to stir at room temperature for 1 hour. The reaction mixture was poured into H_2O (10 mL), extracted with CH_2Cl_2 (2 x 10 mL) and then $CHCl_3$ (2 x 10 mL) before the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **400** (1.65 g, 85%) as an orange oil which was used in subsequent reactions without further purification.

R_f 0.33 (CH_2Cl_2); ^{1}H NMR (400MHz, $CDCl_3$) δ 3.84 (s, 2H, CH_2Br), 3.38 (m, 4H, $C\underline{H}_2CH_3$), 1.25 (t, 3H, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.13 (t, 3H, *J* = 7.2 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (100MHz, $CDCl_3$) δ 166.1, 43.0, 40.6, 26.3, 14.4, 12.5.

***N*,*N*-Diethyl-2-nitroacetamide (401)**[254]

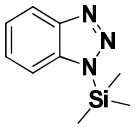


401

Polymer supported nitrite (4.04 g of 4mmol/g resin, 16.2 mmol) was dried under vacuum over night before acetonitrile (35 mL) was added and the resultant suspension stirred at room temperature for 30 minutes before being cooled to −15 ºC. A solution of 2-bromo-*N*,*N*-diethylacetamide **(400)** (1.57 g, 8.1 mmol) in acetonitrile (5 mL) was added drop-wise and then the reaction stirred for 48 hours at −15 ºC. The reaction was filtered whilst still cold through a sinter and washed with CH_2Cl_2 (5 x 5 mL) before the filtrate was concentrated *in vacuo*. The residue was purified twice by flash column chromatography (EtOAc : hexanes 1 : 5 then CH_2Cl_2) to give **401** (0.13g, 10%) as a colourless oil.

R_f 0.23 (CH_2Cl_2); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.27 (s, 2H, CH_2NO_2), 3.45 (q, 2H, *J* = 7.1 Hz, C$\underline{H}_2$CH$_3$), 3.25 (q, 2H, *J* = 7.2 Hz, C$\underline{H}_2$CH$_3$), 1.24 (t, 3H, *J* = 7.2 Hz, CH$_2$C$\underline{H}_3$), 1.18 (t, 3H, *J* = 7.2 Hz, CH$_2$C$\underline{H}_3$); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.1, 75.2, 42.2, 12.8.

1-(Trimethylsilyl)-*1H*-benzo[d][1,2,3]triazole (408)[216]

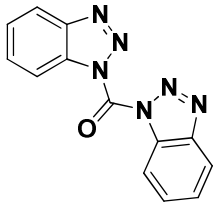


408

408 was prepared according to a literature procedure.[216] Hexamethyldisilazane (21 mL, 100 mmol) was added to a solution of benzotriazole **(407)** (5.96 g, 50 mmol) in THF (100 mL) and heated to reflux overnight. Concentration *in vacuo* afforded **408** (9.12 g, 95%) as a colourless oil which was used in subsequent reactions without further purification.

^{1}H NMR (400MHz, $CDCl_3$) δ 8.14 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.04 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.47 (m, 1H, Ar-H), 7.36 (m, 1H, Ar-H), 0.71 (s, 9H, TMS); ^{13}C NMR (100MHz, $CDCl_3$) δ 146.7, 127.2, 125.9, 123.6, 119.9, 111.2, 0.34.

***1,1*-Carbonyldibenzontriazole (409)**[216]

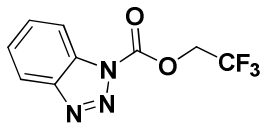


409

409 was prepared according to a literature procedure.[216] Phosgene (11.9 mL of a 20% soln. in PhMe, 23.8 mmol) was added slowly to a solution of 1-(trimethylsilyl)-1H-benzo[d][1,2,3]triazole **(408)** (9.12 g, 47.7 mmol) in CH_2Cl_2 (14 mL) at 0 ºC and then stirred at room temperature for 1 hour. The reaction mixture was filtered to removed the precipitate formed, and the filter cake was washed with anhydrous CH_2Cl_2. The white solid was recrystallised from PhMe to give **409** (4.21 g, 67%) as white needles.

M.p. (PhMe) 201-203 ºC [lit.[216] 182-183 ºC]; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.24 (m, 2H, Ar-H), 7.79 (m, 1H, Ar-H), 7.63 (m, 1H, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ 145.8, 145.0, 132.6, 130.9, 126.8, 121.0, 113.5.

***2,2,2*-Trifluoroethyl 1H-benzo[d][1,2,3]triazole-1-carboxylate (410)**

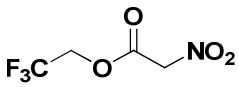


410

1,1-carbonyldibenzontriazole **(409)** (3.5 g, 13.2 mmol) was stirred in 2,2,2-trifluoroethanol (15 mL, 137 mmol) overnight at room temperature until all the solid had dissolved. Excess alcohol was removed *in vacuo* and the residue dissolved in CH_2Cl_2 (20 mL) before being washed with 3% KOH solution (15 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The solid remaining was purified by recrystallisation from PhMe to give **410** (2.15 g, 66%) as white crystals.

M.p. (PhMe) 89-91 ºC; ^{1}H NMR (400MHz, $CDCl_3$) δ 8.17 (d, 1H, *J* = 8.3 Hz, Ar-H), 8.08 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.71 (m, 1H, Ar-H), 7.55 (m, 1H, Ar-H), 4.98 (q, 2H, *J* = 7.9 Hz, CH_2CF_3); ^{13}C NMR (100MHz, $CDCl_3$) δ 147.7, 145.9, 131.5, 130.8, 126.3, 122.3 (q, $J_{C\text{-}F}$ = 278 Hz), 120.7, 113.2, 63.3 (q, $J_{C\text{-}F}$ = 38 Hz); IR 1768 (C=O), 1454, 1413, 1332, 1211 cm^{-1}; HRMS (ESI) calcd. $C_9H_7F_3N_3O_2$: $[M+H]^+$, 246.0490; found $[M+H]^+$, 246.0482.

***2,2,2*-Trifluoroethyl 2-nitroacetate (411)**

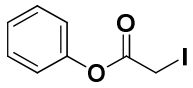


411

To a solution of potassium *tert*-butoxide (1.12 g, 10 mmol) in DMSO (25 mL) at 10 ºC was slowly added nitromethane (0.54 mL, 10mmol) and then stirred at 10 ºC for a further 10 minutes. 2,2,2-trifluoroethyl 1H-benzo[d][1,2,3]triazole-1-carboxylate **(410)** (1.23 g, 5 mmol) in DMSO (25 mL) was added drop-wise *via* syringe pump and then the resulting solution stirred for 2 hours at 10 ºC before being allowed to stir at room temperature overnight. The reaction mixture was poured into H_2O (100 mL) and acidified to pH 3-4 with 10% AcOH solution. The solution was extracted with CH_2Cl_2 (3 x 75 mL) and then the combined organic layers washed with H_2O (75 mL) and pH 9 buffer (Aldrich) (50 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated *in vacuo* using a low temperature water bath and low pressure. Vacuum distillation of the crude material gave **411** alongside some residual DMSO. The mixture was taken up in Et_2O (20 mL) and washed with H_2O (3 x 10 mL). The ethereal layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* using a low temperature water bath and low pressure to give pure **411** (0.29g, 31%) as a colourless oil.

B.p. 65-70 ºC/0.10 mbar; ^{1}H NMR (400MHz, $CDCl_3$) δ 5.29 (s, 2H, CH_2NO_2), 4.64 (q, 2H, *J* = 8.0 Hz, CH_2CF_3); ^{13}C NMR (100MHz, $CDCl_3$) δ 160.5, 122.1 (q, J_{C-F} = 277 Hz), 75.4, 61.9 (q, J_{C-F} = 38 Hz); IR 1780 (C=O), 1572 (NO_2), 1410, 1349 (NO_2), 1284 cm^{-1}; MS (CI) calcd. $C_4H_8F_3N_2O_4$: $[M+NH_4]^+$, 205; found $[M+NH_4]^+$, 205.

Phenyl 2-iodoacetate (415) [255]

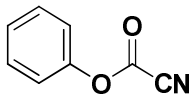


415

A mixture of phenyl bromoacetate **(414)** (1.43 mL, 10 mmol) and NaI (1.92 g, 12.8 mmol) in acetone (7 mL) was stirred at room temperature overnight and then heated to reflux for 4 hours. The reaction was allowed to cool to room temperature, before being filtered and washed with Et_2O (3 x 10 mL). The filtrate was concentrated *in vacuo* before being taken up in Et_2O (20 mL) and washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by recrystallisation from H_2O to give **415** (1.93 g, 74%) as a pale brown solid.

M.p. (H_2O) 68-69 ºC [lit.[255] 75-77 ºC]; R_f 0.78 (EtOAc : hexanes 1 : 10); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.44 (t, 2H, *J* = 7.9 Hz, Ar-H), 7.29 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.15 (dd, 2H, *J* = 8.2, 1.3 Hz, Ar-H), 3.94 (s, 2H, CH_2I); ^{13}C NMR (100MHz, $CDCl_3$) δ 167.5, 150.6, 129.5, 126.3, 121.0, -6.0.

Phenyl carbonocyanidate (418)[219]

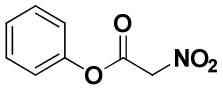


418

418 was prepared according to a literature procedure.[219] Trimethylsilyl cyanide (1.25 mL, 10 mmol) was added slowly to a mixture of phenyl chloroformate **(417)** (1.25 mL, 10 mmol) and 1,4-diazabicyclo[2.2.2]octane (0.006 g, 0.06 mmol) and the reaction allowed to stir at room temperature overnight. TMSCl was removed by vacuum distillation and the remaining solid was dried under vacuum to give **418** (1.3 g, 88%) as an off white solid which was used in subsequent reactions without further purification.

M.p. (CH_2Cl_2) 49-51ºC [lit.[219] 48-50 ºC]; R_f 0.6 (CH_2Cl_2); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.46 (t, 2H, *J* = 7.5 Hz, Ar-H), 7.36 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.20 (dd, 2H, *J* = 7.4, 1.1 Hz, Ar-H); ^{13}C NMR (100MHz, $CDCl_3$) δ 149.1, 142.5, 130.1, 127.8, 120.5, 109.1; IR 2251 (CN), 1762 (C=O), 1725, 1481, 1234, 1215 cm^{-1}.

Phenyl 2-nitroacetate (416)



416

Method A:

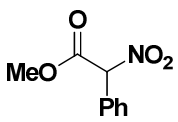
A solution of silver nitrite (1.81 g, 11.8 mmol) in Et_2O (5 mL) was cooled to 0 ºC, before a solution of phenyl 2-iodoacetate **(415)** (1.54 g, 5.88 mmol) in Et_2O (11 mL) was added drop-wise *via* syringe pump. The solution was then stirred at room temperature for 5 days. The reaction mixture was filtered and washed with Et_2O (3 x 10 mL) and then the filtrate concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 10) to give **416** (0.10 g, 10%) as a colourless oil.

Method B:

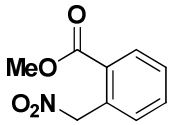
To a solution of NaH (0.12 g, 3 mmol) in anhydrous THF (3 mL) was added drop-wise nitromethane (0.16 mL, 3 mmol) at room temperature and then stirred for a further 15 minutes. A solution of phenyl carbonocyanidate **(418)** (0.44 g, 3 mmol) in THF (4.5 mL) was added drop-wise to the reaction mixture and then stirred at room temperature for 48 hours. The reaction was acidified to pH 3 with 1 M HCl solution, before being extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 10) to give **416** (0.027 g, 5%) as a colourless oil.

R_f 0.23 (EtOAc : hexanes 1 : 10); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 (t, 2H, J = 7.9 Hz, Ar-H), 7.31 (t, 1H, J = 7.4 Hz, Ar-H), 7.17 (m, 2H, Ar-H), 5.40 (s, 2H, CH_2NO_2); ^{13}C NMR (100MHz, $CDCl_3$) δ 160.2, 149.7, 129.7, 127.0, 120.9, 76.2; IR 1768 (C=O), 1560 (NO_2), 1492, 1339, 1186 (NO_2) cm^{-1}; HRMS (CI) calcd. $C_8H_{11}N_2O_4$: $[M+NH_4]^+$, 199.0719; found $[M+NH_4]^+$, 119.0719.

Methyl 2-nitro-2-phenylacetate (422)[256] and Methyl 2-(nitromethyl)benzoate (423)



422

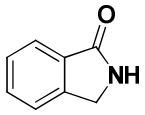


423

2-(trimethylsilyl)phenyl trifluoromethanesulfonate **(51)** (0.42 mL, 1.75 mmol) was added to a solution of methyl nitroacetate **(396)** (0.09 mL, 1 mmol), potassium fluoride (0.23 g, 4 mmol) and 18-crown-6 (1.06 g, 4 mmol) in THF (4 mL) in a sealed tube and stirred at room temperature for 48 hours. The reaction was diluted with EtOAc (10 mL) and washed with saturated aqueous KCl solution (4 x 5 mL), before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1:30) to give a 1 : 5.3 mixture of **422** and **423** (0.12 g, 62%) as a yellow oil.

423: R_f 0.38 (EtOAc : hexanes 1 : 5); ^{1}H NMR (400MHz, $CDCl_3$) *both isomers* δ 8.17 (dd, 1H, *J* = 7.7, 1.4 Hz, Ar-H), 7.65 (td, 1H, *J* = 7.5, 1.5 Hz, Ar-H), 7.58 (td, 1H, *J* = 7.6, 1.4 Hz, Ar-H), 7.42 (dd, 1H, *J* = 7.5, 1.2 Hz, Ar-H), 5.88 (s, 2H, CH_2NO_2), 3.93 (s, 3H, OMe); ^{13}C NMR (100MHz, $CDCl_3$) *both isomers* δ 166.6, 133.1, 133.0, 131.6, 130.6, 130.2, 130.0, 90.7, 52.4; IR 1711 (C=O), 1558 (NO_2), 1272 (NO_2), 1082 cm^{-1}: HRMS (CI) calcd. $C_9H_{13}N_2O_4$: $[M+NH_4]^+$, 213.0875; found $[M+NH_4]^+$, 213.0877.

Isoindolin-*1*-one (9a)[257]

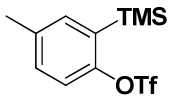


9a

Nickel(II)chloride hexahydrate (0.12 g, 0.51 mmol) was added to a solution of **422** and **423** (0.10 g, 0.51 mmol, 1 : 8.5 **422** : **423**) in MeOH (5 mL) at 0 ºC, followed by the slow addition of sodium borohydride (0.096 g, 2.6 mmol) at the same temperature. The reaction was stirred for 15 minutes at 0 ºC and then stirred at room temperature for 4 hours. The reaction was quenched by drop-wise addition of 1 M HCl until pH 5. Solid $NaHCO_3$ was then added portion-wise until pH 9, followed by the removal of the MeOH *in vacuo*. The remaining aqueous layer was extracted with EtOAc (3 x 5 mL), then the organic layers washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid. The residue was purified by flash column chromatography (CH_2Cl_2 : MeOH 30 : 1) to give **9a** (0.052 g, 77%) as a white solid.

M.p. (CH_2Cl_2/MeOH) 152-154 ºC [lit.[257] 149-151 ºC]; R_f 0.17 (EtOAc : hexanes 1 : 10); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.89 (dd, 1H, *J* = 8.3, 1.2 Hz, Ar-H), 7.58 (dt, 1H, *J* = 7.6, 1.1 Hz, Ar-H), 7.49 (t, 2H, *J* = 7.2 Hz, Ar-H), 6.36 (s(br), 1H, NH), 4.47 (s, 2H, CH_2); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.3, 143.7, 132.2, 131.7, 128.0, 123.7, 123.2, 45.8.

4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (426)[258]

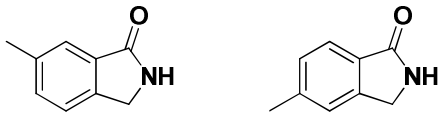


426

Hexamethyldisilazane (2.1 mL, 10 mmol) was added to a solution of 2-bromo-4-methylphenol **(424)** (0.6 mL, 5 mmol) in THF (100 mL) and the mixture heated to reflux overnight. The reaction was allowed to cool to room temperature before the solvent was removed *in vacuo*. The crude material was re-dissolved in anhydrous THF (50 mL) and cooled to −78 ºC, before *n*-BuLi (3.45 mL of a 1.45 M solution in hexanes, 5 mmol) was added drop-wise. The resultant solution was stirred for 30 minutes at −78 ºC and then at room temperature for 30 minutes. The reaction was re-cooled to −78 ºC and triflic anhydride (1.26 mL, 7.5 mmol) was added drop-wise. After 20 minutes of stirring at −78 ºC, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes) to give **426** (1.21 g, 76%) as a colourless oil.

R_f 0.89 (hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H, Ar-H), 7.21 (m, 2H, Ar-H), 2.36 (s, 3H, CH_3), 0.36 (s, 9H, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 137.2, 136.7, 132.2, 131.7, 119.3, 118.5 (q, $J_{C\text{-}F}$ = 320 Hz), 20.8, -0.8.

6-methyl*iso*indolin-1-one[259] **and 5-methyl*iso*indolin-1-one (9b)**[260]



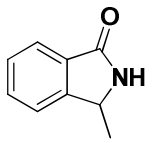
9b

4-methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate **(426)** (0.39 g, 1.25 mmol) was added to a solution of methyl nitroacetate **(396)** (0.092 mL, 1 mmol), potassium fluoride (0.17 g, 3 mmol) and 18-crown-6 (0.79 g, 3 mmol) in THF (4 mL) and stirred at room temperature for 48 hours. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL), extracted with EtOAc (2 x 10 mL) and the combined organic layers washed with saturated KCl solution (5 x 5 mL) before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was subjected flash column chromatography (EtOAc : hexanes 1:10) to give an inseparable mixture of methyl 5-methyl-2-(nitromethyl)benzoate, methyl 2-nitro-2-m-tolylacetate, methyl 4-methyl-2-(nitromethyl)benzoate, methyl 2-nitro-2-p-tolylacetate and some other impurities as a yellow oil (110 mg) which was carried on to the reduction stage without further purification.

Nickel(II)chloride hexahydrate (0.12 g, 0.50 mmol) was added to the residue of the first step (0.11 g) in MeOH (2.5 mL) at 0 ºC, followed by the portion-wise addition of sodium borohydride (0.095 g, 2.95 mmol) at the same temperature. The reaction was stirred for 15 minutes at 0 ºC and then stirred at room temperature for 4 hours. The reaction was quenched by drop-wise addition of 1 M HCl until pH 5. Solid $NaHCO_3$ was then added portion-wise until pH 9, followed by the removal of the MeOH *in vacuo*. The remaining aqueous layer was extracted with EtOAc (3 x 5 mL), then the organic layers washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid. The residue was purified by flash column chromatography (CH_2Cl_2 : MeOH 30 : 1) to give a 1 : 1.2 mixture of the two regioisomers of **9b** (0.019 g, 13% over 2 steps) as a white solid.

R_f 0.72 (CH_2Cl_2 : MeOH 1 : 10); ^{1}H NMR (400MHz, $CDCl_3$) *both isomers* δ 7.87 (s(br), 1H, NH), 7.84 (s(br), 1H, NH), 7.74 (d, 1H, *J* = 8.3 Hz, Ar-H), 7.66 (s, 1H, Ar-H), 7.35 (m, 2H, Ar-H), 7.28 (m, 2H, Ar-H), 4.41 (s, 4H, 2 x CH_2), 2.45 (s, 3H, CH_3), 2.44 (s, 3H, CH_3);^{13}C NMR (100MHz, $CDCl_3$) *both isomers* δ 172.3. 172.3, 144.2, 142.4, 141.0, 138.0, 132.8, 132.3, 129.7, 129.0, 123.9, 123.6, 123.4, 122.9.

3-methyl*iso*indolin-1-one (9c)[261]

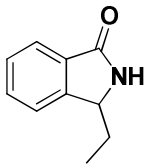


9c

Nickel(II)chloride hexahydrate (0.086 g, 0.36 mmol) was added to a solution of **382** and **383** (0.083 g, 0.36 mmol, 1 : 3.5 **382** : **383**) in MeOH (2 mL) at 0 ºC, followed by the slow addition of sodium borohydride (0.068 g, 1.8 mmol) at the same temperature. The reaction was stirred for 15 minutes at 0 ºC and then stirred at room temperature for 3 hours. The reaction was quenched by drop-wise addition of 1 M HCl until pH 5. Solid $NaHCO_3$ was then added portion-wise until pH 9, followed by the removal of the MeOH *in vacuo*. The remaining aqueous layer was extracted with EtOAc (3 x 5 mL), then the organic layers washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid. The residue was purified by flash column chromatography (CH_2Cl_2 : MeOH 30 : 1) to give **9c** (0.037 g, 70%) as a white solid.

M.p. (CH_2Cl_2/MeOH) 110 ºC [lit.[262] 112-114 ºC]; R_f 0.23 (EtOAc : hexanes 1 : 10); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.03 (s(br), 1H, NH), 7.84 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.56 (dt, 1H, *J* = 7.4, 0.9 Hz, Ar-H), 7.46 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.43 (dd, 1H, *J* = 7.4, 0.6 Hz, Ar-H), 4.70 (q, 1H, *J* = 6.7 Hz, NCHAr), 1.50 (d, 3H, *J* = 6.7 Hz, CH_3); ^{13}C NMR (100MHz, $CDCl_3$) δ 171.2, 149.0, 131.8, 131.7, 128.0, 123.7, 122.2, 52.7, 20.3.

3-Ethyl*iso*indolin-1-one (9d)[261]



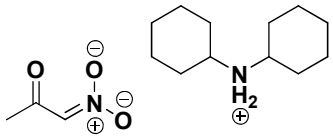
9d

2-(trimethylsilyl)phenyl trifluoromethanesulfonate **(51)** (0.42 mL, 1.75 mmol) was added to a solution of ethyl 2-nitrobutanoate (0.15 mL, 1 mmol), potassium fluoride (0.23 g, 4 mmol) and 18-crown-6 (1.06 g, 4 mmol) in THF (4 mL) and stirred at room temperature for 1 hour. The reaction was quenched with saturated aqueous NH_4Cl solution (5 mL), extracted with EtOAc (2 x 10 mL) and the combined organic layers washed with saturated KCl solution (5 x 5 mL) before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was subjected flash column chromatography (EtOAc : hexanes 1:20) to give an inseparable mixture of ethyl 2-(1-nitropropyl)benzoate and ethyl 2-nitro-2-phenylbutanoate and some other impurities as a yellow oil (0.14 g) which was carried on to the reduction stage without further purification.

Nickel(II)chloride hexahydrate (0.14 g, 0.59 mmol) was added to the residue of the first step (0.14 g) in MeOH (3 mL) at 0 ºC, followed by the portion-wise addition of sodium borohydride (0.11 g, 2.95 mmol) at the same temperature. The reaction was stirred for 15 minutes at 0 ºC and then stirred at room temperature for 4 hours. The reaction was quenched by drop-wise addition of 1 M HCl until pH 5. Solid $NaHCO_3$ was then added portion-wise until pH 9, followed by the removal of the MeOH *in vacuo*. The remaining aqueous layer was extracted with EtOAc (3 x 5 mL), then the organic layers washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow solid. The residue was purified by flash column chromatography (CH_2Cl_2 : MeOH 30 : 1) to give **9d** (0.040 g, 25% over 2 steps) as a white solid.

M.p. (CH_2Cl_2/MeOH) 102 ºC [lit.[263] 103-105 ºC]; R_f 0.56 (CH_2Cl_2 : MeOH 1 : 10); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.19 (s(br), 1H, NH), 7.84 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.54 (dt, 1H, *J* = 7.4, 1.1 Hz, Ar-H), 7.45 (d, 1H, *J* = 7.4 Hz, Ar-H), 7.42 (dd, 1H, *J* = 7.4, 0.7 Hz, Ar-H), 4.60 (dd, 1H, *J* = 6.8, 4.8 Hz, NCHAr), 2.02 (ddq, 1H, *J* = 14.8, 7.4, 4.6 Hz, AB CH_2), 1.71 (ddq, 1H, *J* = 14.4, 7.3, 7.3 Hz, AB CH_2), 0.96 (t, 3H, *J* = 7.4 Hz, CH_3); ^{13}C NMR (100MHz, $CDCl_3$) δ 171.6, 147.5, 132.3, 131.7, 128.0, 123.7, 122.4, 58.2, 27.4, 9.5.

Dicyclohexylammonium 2-oxopropylideneazinate (429)[221]

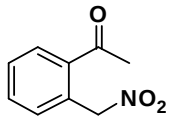


XX

429 was prepared according to a literature procedure.[221] A solution of potassium *tert*-butoxide (6.73 g, 60 mmol) in DMSO (38 mL) was cooled to 15 ºC. Nitromethane (3.66 mL, 60 mmol) was added at a rate so that the internal temperature did not rise above 25 ºC and then the reaction cooled to 5 ºC. Phenylacetate (3.79 mL, 30 mmol) was added and the reaction allowed to warm to room temperature overnight. The reaction mixture was poured into ice (18 g) and then diluted with brine (20 mL) before being neutralised to pH 7 with 1M HCl solution. The mixture was extracted with CH_2Cl_2 (2 x 40 mL), and the resulting aqueous layer acidified to pH 1 with 1M HCl solution. This aqueous solution was extracted with Et_2O (3 x 40 mL) and the combined ethereal layers dried over $MgSO_4$ and filtered. Dicyclohexylamine (6.00 mL, 30 mmol) was added to the solution which was then concentrated *in vacuo* to around 100 mL. On cooling a solid precipitated which was recrystallised from acetonitrile to give **429** (4.2 g, 49%) as pale yellow crystals.

M.p. (acetonitrile) 152-154 ºC [lit.[221] 135-139 ºC]; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.84 (s, 1H, $CH{=}NO_2$), 3.15 (m, 2H, 2 x CHN^+), 2.00 (s, 3H, $COCH_3$), 1.99 (m, 4H, cyclohexyl-H), 1.76 (d, 4H, *J* = 13.2 Hz, cyclohexyl-H), 1.61 (d, 2H, *J* = 12.2 Hz, cyclohexyl-H), 1.42 (m, 4H, cyclohexyl-H), 1.21 (m, 6H, cyclohexyl-H); ^{13}C NMR (100MHz, $CDCl_3$) δ 187.0, 112.5, 53.0, 29.1, 28.5, 25.2, 24.8.

1-(2-(Nitromethyl)phenyl)ethanone (432)



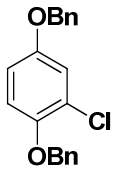
432

Nitropropanone **(430)** was prepared from its dicyclohexylamine salt **429**, by treatment with 2M HCl solution for 1 hour and subsequent extraction with CH_2Cl_2 (x 3), drying over $MgSO_4$ and concentration *in vacuo* to give a white solid: ^{1}H NMR (400MHz, $CDCl_3$) δ 5.27 (s, 2H, CH_2NO_2), 2.33 (s, 3H, $COCH_3$).

2-(trimethylsilyl)phenyl trifluoromethanesulfonate **(51)** (0.49 mL, 2.0 mmol) was added to a solution of nitropropanone **(430)** (0.21 g, 2.2 mmol) and cesium fluoride (0.91 g, 6 mmol) in acetonitrile (15 mL) and heated to 80 ºC for 1 hour followed by cooling to room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL), before being extracted with CH_2Cl_2 (3 x 10 mL) and then the organic phases dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 25) to give **432** (0.15 g, 42%) as a pale yellow solid.

M.p. (EtOAc/hexanes) 82-84 ºC; R_f 0.50 (EtOAc : hexanes 1 : 25); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.95 (m, 1H, Ar-H), 7.60 (m, 2H, Ar-H), 7.39 (m, 1H, Ar-H), 5.78 (s, 2H, CH_2NO_2), 2.65 (s, 3H, $COCH_3$); ^{13}C NMR (100MHz, $CDCl_3$) δ 200.4, 137.0, 133.3, 132.6, 130.6, 130.2, 129.1, 77.4, 28.5; IR 1673 (C=O), 1550 (NO_2), 1421, 1378, 1359, 1256 (NO_2) cm^{-1}; HRMS (CI) calcd. $C_9H_{13}N_2O_3$: $[M+NH_4]^+$, 197.0926; found $[M+NH_4]^+$, 197.0926.

(2-Chloro-1,4-phenylene)bis(oxy)bis(methylene)dibenzene (450)

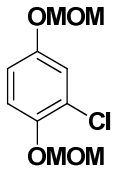


450

K_2CO_3 (9.5 g, 69.0 mmol) was added to 2-chloro-1,4-benzenediol **(449)** (2.0 g, 13.8 mmol) in acetone (25 mL). BnBr (4.1 mL, 34.5 mmol) was added and the mixture heated to reflux overnight. The mixture was allowed to cool to room temperature and was filtered, concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes 1 : 50 to 1 : 20) to give **450** (2.9 g, 65%) as a white solid.

M.p. (EtOAc : hexanes) 68-69 ºC; R_f 0.27 (EtOAc : hexanes 1 : 10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 - 7.35 (m, 10H, Ar-H (Bn)), 7.08 (d, 1H, *J* = 3.0 Hz, Ar-H), 6.92 (d, 1H, *J* = 9.0 Hz, Ar-H), 6.81 (dd, 1H, *J* = 8.9, 3.0 Hz, Ar-H), 5.12 (s, 2H, CH_2Ph), 5.03 (s, 2H, CH_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 148.9, 137.1, 136.9, 128.9, 128.8, 128.3, 128.2, 127.7, 127.5, 124.4, 117.5, 116.1, 114.1, 72.1, 71.0; IR 1498, 1453, 1381, 1207, 1014 cm^{-1}; HRMS (ESI) calcd. $C_{20}H_{17}ClNaO_2$: $[M + Na]^+$, 347.0815; found $[M + Na]^+$, 347.0809. Microanalysis calcd. for $C_{20}H_{17}ClO_2$: C, 73.96; H, 5.28. Found: C, 74.19; H, 5.39.

2-Chloro-1,4-bis(methoxymethoxy)benzene (451)

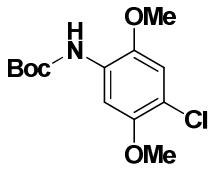


451

MOMCl (5.25 mL, 69.2 mmol) was added drop-wise to a solution of 1,4-dihydroxy-2-chlorobenzene **(449)** (2.00 g, 13.8 mmol) and di-*iso*-propylethylamine (14.5 mL, 83.0 mmol) in CH_2Cl_2 (30 mL) at 0 ºC. After the addition was complete, the mixture was stirred at room temperature overnight, filtered, washed with CH_2Cl_2 and concentrated *in vacuo.* The residue was purified by flash column chromatography (Redisep (120g), CH_2Cl_2) to give **451** (2.28 g, 71%) as a colourless oil.

R_f 0.76 (EtOAc : hexanes 1 : 10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, 1H, *J* = 2.9 Hz, Ar-H), 7.09 (d, 1H, *J* = 8.8 Hz, Ar-H), 6.89 (dd, 1H, *J* = 9.0, 2.9 Hz, Ar-H), 5.17 (s, 2H, C<u>H</u>$_2$OMe), 5.10 (s, 2H, C<u>H</u>$_2$OMe), 3.53 (s, 3H, OMe), 3.47 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 148.1, 124.6, 118.8, 118.2, 115.9, 96.2, 95.3, 56.6, 56.2; IR 1492, 1218, 1190 cm^{-1}; HRMS (ESI) calcd. $C_{10}H_{13}ClNaO_4$: $[M + Na]^+$, 255.0400; found $[M + Na]^+$, 255.0397. Microanalysis calcd. for $C_{20}H_{13}ClO_4$: C, 51.62; H, 5.63. Found: C, 51.58; H, 5.62.

***tert*-Butyl 4-chloro-2,5-dimethoxyphenylcarbamate (453)**

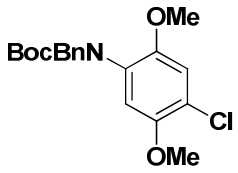


453

Boc_2O (2.56 g, 11.73 mmol) was added to a solution of 4-chloro-2,5-dimethoxyaniline **(452)** (2.0 g, 10.66 mmol) and DMAP (0.39 g, 3.20 mmol) in THF (25 mL). The mixture was stirred at room temperature for 48 hours and then poured in to H_2O (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL) and then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 20) to give **453** (1.5 g, 49%) as a white solid.

M.p. (EtOAc/hexanes) 102-103 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s (br), 1H, NH), 7.09 (s (br), 1H, Ar-H), 6.89 (s, 1H, Ar-H), 3.92 (s, 3H, OMe), 3.86 (s, 3H, OMe), 1.56 (s, 9H, Boc); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 149.4, 141.7, 127.8, 114.3, 112.4, 103.6, 80.8, 56.9, 56.5, 28.5; IR 3440 (N-H), 1720 (C=O), 1520, 1483, 1402, 1150 cm^{-1}; HRMS (ESI) calcd. $C_{13}H_{18}ClNNaO_4$: $[M+Na]^+$, 310.0822; found $[M+Na]^+$, 310.0827.

***tert*-Butyl benzyl(4-chloro-2,5-dimethoxyphenyl)carbamate (454)**

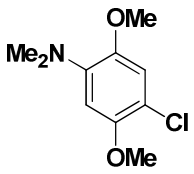


454

tert-butyl 4-chloro-2,5-dimethoxyphenylcarbamate **(453)** (0.50 g, 1.73 mmol) was dissolved in DMF (8 mL). BnBr (0.26 mL, 2.21 mmol) was added and the mixture cooled to 0 ºC before NaH (0.09 g of a 60% dispersion in mineral oil, 2.21 mmol) was added portion-wise. The reaction was stirred for 45 minutes at 0 ºC before the ice bath was removed and the reaction stirred room temperature for a further 3 hours. The reaction was quenched by pouring onto ice/H_2O (25 mL) and then the mixture was extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL) before being dried over $MgSO_4$, filtered and concentrate *in vacuo*. The residue was purified by flash column chromatography (Redisep (40 g) heptane to EtOAc : heptane 1 : 5) to give **454** (0.57 g, 87%) as a white solid.

M.p. (EtOAc/heptane) 79-80 ºC; R_f 0.33 (EtOAc : heptane 1 : 5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.41 (m, 5H, Ar-H (Bn)), 6.88 (s(br) , 1H, Ar-H), 6.34 (s(br), 1H, Ar-H), 5.10 (s(br), 1H, CH_2Ph), 4.62 (s(br), 1H, CH_2Ph), 3.72 (s, 3H, OMe), 3.61 (s, 3H, OMe), 1.51 and 1.36 (2 x s, 9H, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 149.6, 148.6, 138.5, 130.2, 129.0, 128.4, 127.5, 121.0, 114.7, 113.9, 80.2, 56.8, 56.2, 52.9, 28.5; IR 1686 (C=O), 1505, 1377, 1164 cm^{-1}; HRMS (ESI) calcd. $C_{20}H_{24}ClNNaO_4$: $[M+Na]^+$, 400.1292; found $[M+Na]^+$, 400.1300.

4-Chloro-2,5-dimethoxy-*N*,*N*-dimethylaniline (455)

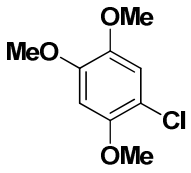


455

Sodium cyanoborohydride (1.5 g, 24.0 mmol) was added with stirring at room temperature to a solution of 4-chloro-2,5-dimethoxyaniline **(452)** (1.0 g, 5.3 mmol), glacial AcOH (1 mL) and formaldehyde (50 mL of a 37% aqueous solution) in MeOH (150 mL). After 6 h at room temperature, the mixture was quenched with 1M HCl (5 mL) and diluted with EtOAc (200 mL). The solution was washed with saturated aqueous $NaHCO_3$ (100 mL) and the organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2) to give chloride **455** (0.85 g, 75%) as an orange oil.

R_f 0.22 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H, Ar-H), 6.61 (s, 1H, Ar-H), 3.89 (s, 3H, OMe), 3.86 (s, 3H, OMe), 2.82 (s, 6H, NMe_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 146.9, 142.1, 114.8, 113.6, 104.7, 57.3, 56.2, 43.4; IR 1507, 1448, 1380, 1209, 1132, 1032 cm^{-1}; HRMS (ESI) calcd. $C_{10}H_{15}ClNO_2$: $[M + H]^+$, 216.0791; found $[M + H]^+$, 216.0785. Microanalysis calcd. for $C_{10}H_{14}ClNO_2$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.53; H, 6.59; N, 6.44.

1-Chloro-2,4,5-trimethoxybenzene (457)

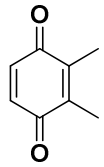


457

MeI (0.50 mL, 8.00 mmol) and NaH (0.32 g of a 60% dispersion in mineral oil, 8.00 mmol) were added at 0 ºC to a solution of 4-chloro-2,5-dimethoxyphenol **(456)** (1.0 g, 5.3 mmol) in DMF (20 mL) and the mixture was stirred at room temperature for 48 h. The reaction was quenched with H_2O (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 4) to give **457** (0.95 g, 88%) as a colourless oil.

R_f 0.75 (EtOAc : hexanes 1 : 3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H, Ar-H), 6.54 (s, 1H, Ar-H), 3.84 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.79 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 148.6, 143.7, 114.0, 113.2, 99.3, 57.3, 56.8, 56.5; IR 1508, 1465, 1438, 1206, 1169 cm^{-1}; HRMS (ESI) calcd. $C_9H_{11}ClNaO_3$: $[M + Na]^+$, 225.0294; found $[M + Na]^+$, 225.0277. Microanalysis calcd. for $C_9H_{11}ClO_3$: C, 53.35; H, 5.47. Found: C, 53.41; H, 5.59.

2,3-Dimethylcyclohexa-2,5-diene-1,4-dione (459)[264]

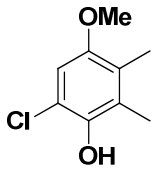


459

459 was prepared according to a literature procedure.[232] 2,3-dimethylbenzene-1,4-diol **(458)** (0.90 g, 6.51 mmol) was dissolved in anhydrous Et_2O (100 mL) and then manganese dioxide (4.53 g, 52.1 mmol) was added and the reaction stirred at room temperature. After 30 minutes the reaction was stopped, filtered through celite®, and washed with Et_2O (50 mL). The filtrate was concentrated *in vacuo* and the residue purified by recrystallisation from hexane to give **459** (0.65 g, 73%) as a bright yellow solid.

M.p. (hexane) 51-52 ºC [lit.[264] 55 ºC]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 2H, 2 x =CH), 2.03 (s, 6H, 2xCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 114.2, 136.5, 12.4.

6-Chloro-4-methoxy-2,3-dimethylphenol (460)[233]

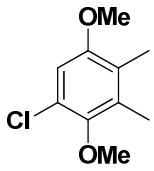


460

460 was prepared according to a literature procedure.[233] Anhydrous MeOH (25 mL) was cooled to 0 ºC, before acetyl chloride (2.79 mL, 39.2 mmol) was added and then the mixture stirred at the same temperature for 30 minutes. **459** (0.534 g, 3.92 mmol) was added in one portion, and once all the solid had dissolved, the cooling bath was removed and the reaction stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* to give **460** (0.71 g, 96%) as a yellow-brown solid which was used in subsequent reactions without further purification.

M.p. (MeOH) 42-43 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 1H, Ar-H), 5.20 (s, 1H, OH), 3.75 (s, 3H, OMe), 2.21 (s, 3H, CH_3), 2.12 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 143.8, 126.0, 125.6, 116.1, 108.5, 56.4, 12.9, 12.1.

1-Chloro-2,5-dimethoxy-3,4-dimethylbenzene (461)[233]

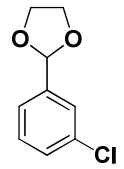


461

461 was prepared according to a literature procedure.[233] **460** (0.67 g, 3.6 mmol) was dissolved in CH_2Cl_2 (12 mL), before tetrabutylammonium bromide (0.35 g, 1.08 mmol) was added, followed by a solution of KOH (0.60 g, 10.8 mmol) in H_2O (12 mL). The mixture was stirred vigorously at room temperature and dimethylsulfate was added in 3 portions at hour intervals (0.4 mL, 0.4 mL, 0.22 mL, 10.8 mmol). The reaction was stirred for a further 3 hours and then a 2 M NaOH solution (5 mL) was added and then stirred for 48 hours. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10mL). The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Redisep (12 g) EtOAc : heptane 1 : 10) to give **461** (0.55 g, 76%) as a colourless oil.

R_f 0.47 (EtOAc : heptanes 1 : 10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (s, 1H, Ar-H), 3.77 (s, 3H, OMe), 3.75 (s, 3H, OMe), 2.22 (s, 3H, CH_3), 2.10 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 148.2, 132.6, 125.4, 124.6, 109.7, 60.7, 56.1, 13.2, 12.2.

2-(3-Chlorophenyl)-1,3-dioxolane (463)[265]

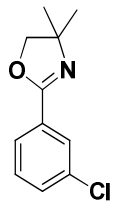


463

A solution of 3-Chlorobenzaldeyde **(462)** (1.0 mL, 8.8 mmol), *p*-toluenesulfonic acid monohydrate (0.05g, 0.27 mmol) and ethylene glycol (0.59 mL, 10.6 mmol) in PhMe was heated to reflux for 24 hours under Dean-Stark conditions. The reaction was allowed to cool to room temperature and was then diluted with EtOAc (300 mL) before being washed with 1M NaOH solution (30 mL), H_2O (100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Redisep (120 g) EtOAc : heptane 1 : 10) to give **463** (0.81 g, 50%) as a colourless oil.

R_f 0.73 (EtOAc : heptanes 1 : 8); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 1H, Ar-H), 7.34 (m, 3H, Ar-H), 5.80 (s, 1H, CH acetal), 4.12 (m, 2H, CH_2), 4.04 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 134.6, 129.9, 129.5, 126.8, 124.9, 103.1, 65.6.

2-(3-Chlorophenyl)-4,4-dimethyl-4,5-dihydrooxazole (467)[77]

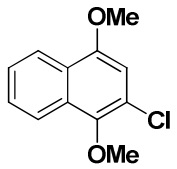


467

467 was prepared according to a literature procedure.[77] 3-Chlorobenzoic acid **(464)** (2.00 g, 12.8 mmol) was dissolved in thionyl chloride (2.8 mL, 38 mmol) and heated to 100 ºC for one hour. After being allowed to cool to room temperature, the excess thionyl chloride was removed *in vacuo*. The crude acid chloride was dissolved in CH_2Cl_2 (6 mL) and this solution was added drop-wise to a solution of 2-amino-2-methylpropan-1-ol **(465)** (2.44 mL, 25.5 mmol) in CH_2Cl_2 (6 mL) at 0 ºC. After the addition was complete, the reaction was allowed to stir at room temperature overnight. The reaction was filtered to remove the white precipitate and washed with CH_2Cl_2, before being concentrated *in vacuo*. The crude alcohol was dissolved in CH_2Cl_2 (10 mL) and PhMe (3.5 mL), before thionyl chloride (2.8 mL, 38 mmol) was added and the reaction heated to reflux. As soon as reflux had been obtained the reaction was allowed to cool to room temperature and then stirred for 2 further hours. H_2O was added carefully to destroy excess thionyl chloride (around 20 mL) and then 1 M NaOH solution was added until the pH = 11. The mixture was extracted with EtOAc (2 x 100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Redisep (120 g) EtOAc : heptanes 1 : 20 to 1 : 5) to give **467** (1.9 g, 71%) as a colourless oil.

R_f 0.69 (EtOAc : heptane 1 : 4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (m, 1H, Ar-H), 7.81 (ddd, 1H, *J* = 7.8, 0.9, 0.9 Hz, Ar-H), 7.42 (m, 1H, Ar-H), 7.33 (m, 1H, Ar-H), 4.11 (s, 2H, OCH_2), 1.38 (s, 6H, $2xCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 134.6, 131.4, 130.1, 129.8, 128.6, 126.5, 79.5, 68.0, 28.6.

2-Chloro-1,4-dimethoxynaphthalene (469)[234]

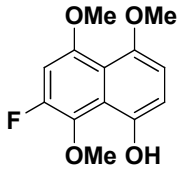


469

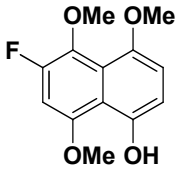
A solution of iodosobenzene diacetate (0.38 g, 1.10 mmol) in anhydrous CH_2Cl_2 (5 mL) was cooled to 0 ºC before TMSCl (0.30 mL, 2.21 mmol) was added drop-wise. The reaction was stirred for a further hour at 0 ºC before a solution of 1,4-dimethoxynapthalene **(468)** (0.20 g, 1.04 mmol) and TEMPO (0.016 g, 0.10 mmol) in anhydrous CH_2Cl_2 (2 mL) was added drop-wise to the reaction mixture. After 15 minutes the reaction was complete and the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (Redisep (12 g) heptane to EtOAc : heptanes 1 : 5) to give **469** (0.10 g, 43%) as a white solid.

M.p. (EtOAc/heptanes) 80-81 ºC [lit.[234] 76-80 ºC]; R_f 0.42 (EtOAc : heptane 1 : 3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, 1H, *J* = 8.4 Hz, Ar-H), 8.06 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.57 (ddd, 1H, *J* = 8.2, 6.9, 1.3 Hz, Ar-H), 7.49 (m, 1H, Ar-H), 6.75 (s, 1H, Ar-H), 3.98 (s, 3H, OMe), 3.97 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 145.6, 129.3, 127.7, 125.9, 125.6, 122.8, 122.7, 121.9, 105.8, 61.6, 56.1.

7-Fluoro-4,5,8-trimethoxynaphthalen-1-ol (471)[36] **and 6-Fluoro-4,5,8-trimethoxynaphthalen-1-ol (472)**[36]



471

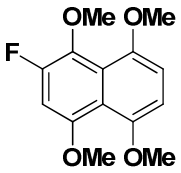


472

471 and **472** were prepared according to a literature procedure.[36] 1,4-difluoro-2,5-dimethoxybenzene **(41)** (0.522 g, 3.0 mmol) was dissolved in THF (10 mL) and cooled to −78 ºC. *n*-BuLi (1.88 mL of a 1.6 M solution in hexanes, 3.0 mmol) was added drop-wise and the reaction stirred at −78 ºC for a further 15 minutes. 2-methoxyfuran **(470)** (0.42 mL, 4.5 mmol) was added in one portion and then the reaction stirred at −78 ºC for 1 hour and then at 0 ºC for 2 hours. The reaction was then quenched with H_2O and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in MeOH (20 mL) and 6 M HCl solution (5 mL), and the reaction heated to reflux for three hours. After allowing the reaction to cool to room temperature, the mixture was concentrated *in vacuo* and then taken up in CH_2Cl_2 (30 mL). The solution was washed with H_2O (20 mL) and then brine (20 mL), before being dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Redisep (40 g) heptane to CH_2Cl2 : heptanes 10 : 1) to give a 1 : 1.5 mixture of **471** and **472** (0.4 g, 53% over 2 steps) as a colourless oil.

R_f 0.52 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) *both isomers* δ 9.31 (s, 1H, OH), 9.05 (s, 1H, OH), 6.86 (m, 2H, Ar-H), 6.77 (m, 2H, Ar-H), 6.69 (d, 1H, J_{H-F} = 11.5 Hz, Ar-H), 6.64 (d, 1H, J_{H-F} = 13.3 Hz, Ar-H), 4.07 (s, 3H, OMe), 4.03 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.90 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.87 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$) *both isomers* δ 97.8 (d, J_{C-F} = 25.7 Hz), 97.1 (d, J_{C-F} = 27.9 Hz), 63.3 (d, J_{C-F} = 6.6 Hz), 63.0 (d, J_{C-F} = 2.9 Hz), 58.1, 58.1, 57.1 ,56.9.

2-Fluoro-1,4,5,8-tetramethoxynaphthalene (473)[36]

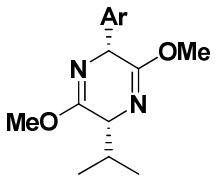


473

473 was prepared according to a literature procedure.[36] **471** and **472** (0.37 g, 1.5 mmol) were dissolved in DMF (3.5 mL) and then NaH (0.073 g of a 60% dispersion in mineral oil, 1.8 mmol) was added, followed by MeI (0.11 mL, 1.8 mmol) and then stirred at room temperature for 20 hours. The reaction was quenched with H_2O (5 mL), extracted with EtOAc (3 x 10 mL), and the combined organic layers dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Redisep (12 g) CH_2Cl_2) to give **473** (0.16 g, 41%) as an off-white solid.

M.p. (CH_2Cl_2) 119-121 ºC [lit.[36] 116-117 ºC]; R_f 0.27 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, 1H, J = 8.6 Hz, Ar-H), 6.76 (d, 1H, J = 9.2 Hz, Ar-H), 6.73 (d, 1H, $J_{H\text{-}F}$ = 12.7 Hz, Ar-H), 3.93 (s, 3H, OMe), 3.92 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.87 (s, 3H, OMe);^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0 (d, $J_{C\text{-}F}$ = 242.7 Hz), 154.1 (d, $J_{C\text{-}F}$ = 11 Hz), 151.8 (d, $J_{C\text{-}F}$ = 2.2 Hz), 150.8 (d, $J_{C\text{-}F}$ = 5.9 Hz), 136.2 (d, $J_{C\text{-}F}$ = 13.2 Hz), 124.3 (d, $J_{C\text{-}F}$ = 2.9 Hz), 117.3, 109.2, 107.2, 98.7 (d, $J_{C\text{-}F}$ = 26.5 Hz), 62.9 (d, $J_{C\text{-}F}$ = 2.9 Hz), 57.8, 57.7, 57.2.

General Procedures for α-Arylation Reactions

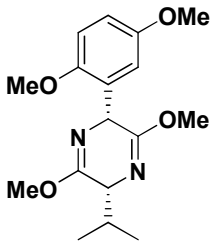


5

General Procedure A: *sec*-BuLi (in cyclohexane, 3.0 equiv) was added drop-wise to imidate **3** (1 equiv) and benzyne precursor **474** (1.75 equiv) in THF (0.2 M) at −95 ºC. The mixture was maintained at −95 ºC for 30 min, before being allowed to warm to room temperature overnight. 2,6-Di-tert-butyl-4-methylphenol (4 equiv) in THF (0.5 M) was added to the reaction mixture which was stirred for 1 h further at room temperature. H_2O was added and the mixture was extracted with EtOAc (x 3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*.

General Procedure B: *n*-BuLi (in hexanes, 3.0 equiv) was added drop-wise to imidate **3** (1 equiv) and benzyne precursor **474** (1.75 equiv) in THF (0.2 M) at −78 ºC. The mixture was maintained at −78 ºC for 30 min, before being allowed to warm to room temperature overnight. 2,6-Di-tert-butyl-4-methylphenol (4 equiv) in THF (0.5 M) was added and the mixture stirred at room temperature for 1 h. H_2O was added and the mixture was extracted with EtOAc (x 3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*.

(2*R*,5*R*)-2-(2,5-Dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine (5a)

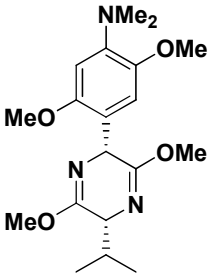


5a

Imidate **5a** was prepared according to general procedure A, starting from imidate **3** (0.18 mL, 1.00 mmol), 2-chloro-1,4-dimethoxybenzene (**388**) (0.25 mL, 1.75 mmol) and *s*-BuLi (2.14 mL of a 1.4 M solution in cyclohexane, 3.00 mmol). Purification by flash column chromatography (hexanes to EtOAc : hexanes 1 : 10) gave **5a** (0.24 g, 94 : 6 dr, 75%) as an off-white solid: M.p. (EtOAc/hexanes) 111-113 ºC; R_f 0.2 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −108 (*c* 1.0, $CHCl_3$); IR 1687, 1501, 1463, 1231, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 6.90 (d, 1H, *J* = 8.9 Hz, Ar-H), 6.81 (dd, 1H, *J* = 8.9, 3.1 Hz, Ar-H), 6.64 (d, 1H, *J* = 3.0 Hz, Ar-H), 5.64 (d, 1H, *J* = 6.1 Hz, CHAr), 4.05 (dd, 1H, *J* = 6.1, 3.7 Hz, CH*i*-Pr), 3.87 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.64 (s, 3H, OMe), 2.46 (m, 1H, *i*-Pr), 1.19 (d, 3H, *J* = 6.9 Hz, *i*-Pr), 0.91 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) *major isomer* δ 163.3, 161.9, 153.6, 151.7, 130.5, 114.2, 113.1, 112.8, 60.4, 56.7, 55.5, 53.4, 52.8, 52.6, 30.9, 20.7, 17.5; HRMS (CI) calcd. $C_{17}H_{25}N_2O_4$:[(M + H]$^+$, 321.1814; found [M + H]$^+$, 321.1824.

X-ray crystal data $C_{17}H_{24}N_2O_4$, M = 320.38, Monoclinic, P2(1)/c, a=12.43258(16) Å, b = 17.07734(17) Å, c = 8.35561(11) Å, α = 90°, β = 109.0094(14)°, γ = 90°, V= 1677.28(4) $Å^3$, Z= 4, D_c= 1.269 Mg/m^3, μ(Cu-Kα) = 0.091 mm^{-1}, T = 173 K, colourless tabular needles, 34557 independent measured reflections, 3892 independent observed reflections [F>4σ(F)], 208 parameters.

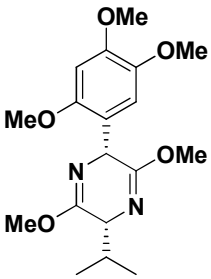
4-((2*R*,5*R*)-5-*iso*-Propyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)-2,5-dimethoxy-*N*,*N*-dimethylaniline (5b)



5b

Imidate **5b** was prepared according to general procedure A, starting from imidate **3** (0.18 mL, 1.00 mmol), 4-chloro-2,5-dimethoxy-*N*,*N*-dimethylaniline (**455**) (0.38 g, 1.75 mmol) and *s*-BuLi (2.14 mL of a 1.4 M solution in cyclohexane, 3.00 mmol). Purification by flash column chromatography (Redisep (12 g), heptane to EtOAc : heptane 1:20), followed by (Redisep (12 g), CH_2Cl_2 : heptane 1 : 1) gave **5b** (0.15 g, 92 : 8 dr, 41%) as a yellow oil: R_f 0.53 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −81.5 (*c* 0.1, $CHCl_3$); IR 1692, 1592, 1460, 1233, 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 6.40 (s, 1H, Ar-H), 6.12 (s, 1H, Ar-H), 5.63 (d, 1H, *J* = 6.1 Hz, CHAr), 4.02 (dd, 1H, *J* = 6.2, 3.6 Hz, CH*i*-Pr), 3.85 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.62 (s, 3H, OMe), 2.84 (s, 6H, NMe_2), 2.42 (m, 1H, *i*-Pr), 1.17 (d, 3H, *J* = 7.0 Hz, *i*-Pr), 0.88 (d, 3H, *J* = 7.6 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ 163.0, 162.2, 155.8, 146.7, 144.5, 135.0, 104.8, 103.6, 60.7, 55.5, 55.5, 54.2, 52.8, 52.8, 42.5, 31.1, 20.0, 17.7; HRMS (ESI) calcd. $C_{19}H_{30}N_3O_4$: $[M + H]^+$, 364.2236; found $[M + H]^+$, 364.2240. Microanalysis calcd. for $C_{19}H_{29}N_3O_4$: C, 62.79; H, 8.04; N, 11.56. Found: C, 62.83; H, 8.12; N, 11.44.

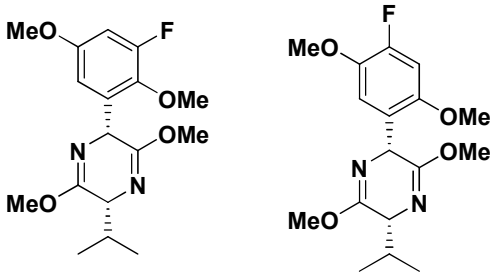
(2*R*,5*R*)-2-*iso*-Propyl-3,6-dimethoxy-5-(2,4,5-trimethoxyphenyl)-2,5-dihydropyrazine (5c)



5c

Imidate **5c** was prepared according to general procedure A, starting from imidate **3** (0.18 mL, 1.00 mmol), 1-chloro-2,4,5-trimethoxybenzene (**457**) (0.35 g, 1.75 mmol) and *s*-BuLi (2.14 mL of a 1.4 M solution in cyclohexane, 3.00 mmol). Purification by flash column chromatography (hexanes to EtOAc : hexanes 1:8) gave **5c** (0.13 g, 94 : 6 dr, 37%) as a yellow solid: M.p. (EtOAc : hexanes) 72-74 ºC; R_f 0.11 (EtOAc : hexanes 1:10); $[\alpha]_D^{25}$ = −35.6 (*c* 0.9, $CHCl_3$); IR 1693, 1519, 1436, 1231, 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 6.56 (s, 1H, Ar-H), 6.54 (s, 1H, Ar-H), 5.57 (d, 1H, *J* = 6.1 Hz, CHAr), 4.02 (dd, 1H, *J* = 6.1, 3.6 Hz, CH*i*-Pr), 3.88 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.60 (s, 3H, OMe), 2.42 (m, 1H, *i*-Pr), 1.16 (d, 3H, *J* = 6.9 Hz, *i*-Pr), 0.87 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ 163.1, 162.0, 151.5, 148.7, 143.2, 120.9, 111.6, 98.3, 60.3, 57.2, 56.2, 56.0, 53.0, 52.5, 52.5, 30.8, 19.6, 17.4; HRMS (CI) calcd. $C_{18}H_{27}N_2O_5$: $[M + H]^+$, 351.1920; found $[M + H]^+$, 351.1916. Microanalysis calcd. for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 7.99. Found: C, 61.79; H, 7.38; N, 7.87.

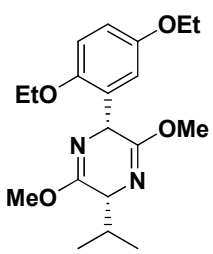
(2*R*,5*R*)-2-(3-Fluoro-2,5-dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine and (2*R*,5*R*)-2-(4-Fluoro-2,5-dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine (5d)



5d

Imidates **5d** was prepared according to general procedure B, starting from imidate **3** (0.18 mL, 1.00 mmol), 1,4-difluoro-2,5-dimethoxybenzene (**41**) (0.30 g, 1.75 mmol) and *n*-BuLi (1.88 mL of a 1.6 M solution in hexanes, 3.00 mmol). Purification by flash column chromatography (Redisep (12 g), heptane to EtOAc : heptane 1 : 10), followed by (Redisep (12 g), PhMe : acetone 50 : 1) gave **5d** (0.19 g, 56%, as a 1 : 1 mixture of regioisomers, 91 : 9 dr for each isomer) as a white solid: M.p. (EtOAc : hexanes) 54-56 ºC; R_f 0.62 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −108.8 (*c* 1.2, $CHCl_3$); IR 1691, 1519, 1497, 1232, 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomers* δ 6.73 (d, 1H, $J_{H\text{-}F}$ = 12.9 Hz, Ar-H), 6.67 (d, 1H, $J_{H\text{-}F}$ = 9.6 Hz, Ar-H), 6.60 (dd, 1H, $J_{H\text{-}F}$ = 12.8 Hz, *J* = 3 Hz, Ar-H), 6.34 (dd, 1H, $J_{H\text{-}F}$ = 1.6 Hz, *J* = 3.1 Hz, Ar-H), 5.56 (d, 1H, *J* = 5.1 Hz, CHAr), 5.56 (d, 1H, *J* = 6.2 Hz, CHAr), 4.02 (m, 2H, 2 x CH*i*-Pr), 3.81 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.60 (s, 3H, OMe), 2.43 (m, 2H, *i*-Pr), 1.16 (d, 3H, *J* = 7.4 Hz, *i*-Pr), 1.16 (d, 3H, *J* = 7.2 Hz, *i*-Pr), 0.86 (d, 3H, *J* = 7.0 Hz, *i*-Pr), 0.85 (d, 3H, *J* = 6.4 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomers* δ 163.7, 163.7, 161.9, 161.3, 155.7 (d, $J_{C\text{-}F}$ = 244.1 Hz), 155.6 (d, $J_{C\text{-}F}$ = 11.0 Hz), 151.9 (d, $J_{C\text{-}F}$ = 242.7 Hz), 151.7 (d, $J_{C\text{-}F}$ = 8.1 Hz), 141.5 (d, $J_{C\text{-}F}$ = 11.0 Hz), 140.1 (d, $J_{C\text{-}F}$ = 11.8 Hz), 136.0 (d, $J_{C\text{-}F}$ = 3.7 Hz), 125.0 (d, $J_{C\text{-}F}$ = 3.7 Hz), 114.4 (d, $J_{C\text{-}F}$ = 3.7 Hz), 108.4 (d, $J_{C\text{-}F}$ = 2.9 Hz), 102.4 (d, $J_{C\text{-}F}$ = 22.8 Hz), 101.6 (d, $J_{C\text{-}F}$ = 22.1 Hz), 62.1 (d, $J_{C\text{-}F}$ = 5.1 Hz), 60.6 (d, $J_{C\text{-}F}$ = 3.7 Hz), 57.0, 56.9, 55.7, 53.9 (d, $J_{C\text{-}F}$ = 4.4 Hz), 53.3, 52.8, 31.0, 19.9, 19.9, 17.6; ^{19}F NMR (200 MHz, $CDCl_3$) δ −128.5, −134.1; HRMS (ESI) calcd. $C_{17}H_{23}FN_2NaO_4$: $[M + Na]^+$, 361.1540; found $[M + Na]^+$, 361.1536. Microanalysis calcd. for $C_{17}H_{23}FN_2O_4$: C, 60.34; H, 6.85; N, 8.28. Found: C, 60.27; H, 6.93; N, 8.24.

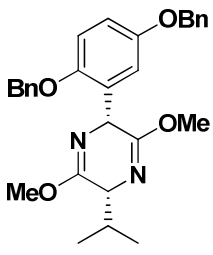
(2*R*,5*R*)-2-(2,5-Diethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine (5f)



5f

Imidate **5f** was prepared according to general procedure A, starting from imidate **3** (0.18 mL, 1.00 mmol), 2-chloro-1,4-diethoxybenzene (**475**) (0.31 mL, 1.75 mmol) and *s*-BuLi (2.30 mL of a 1.3 M solution in cyclohexane, 3.00 mmol). Purification by flash column chromatography (hexanes to EtOAc : hexanes 1 : 10), gave **5f** (0.25 g, 91 : 9 dr, 72%,) as an off-white solid: M.p. (MeOH) 68-70 ºC; R_f 0.58 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −125.3 (*c* 0.1, $CHCl_3$); IR 1689, 1500, 1433, 1232 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 6.77 (d, 1H, *J* = 8.8 Hz, Ar-H), 6.68 (dd, 1H, *J* = 9.4, 2.9 Hz, Ar-H), 6.49 (d, 1H, *J* = 3.1 Hz, Ar-H), 5.59 (d, 1H, *J* = 6.2 Hz, CHAr), 3.99 (q, 2H, *J* = 7.0 Hz, OEt), 3.93 (dd, 1H, *J* = 6.8, 3.5 Hz, CH*i*Pr), 3.84 (q, 2H, *J* = 7.0 Hz, OEt), 3.60 (s, 3H, OMe), 3.52 (s, 3H, OMe), 2.34 (m, 1H, *i*-Pr), 1.31 (t, 3H, *J* = 7.0 Hz, OEt), 1.27 (t, 3H, *J* = 7.0 Hz, OEt), 1.09 (d, 3H, *J* = 7.0 Hz, *i*-Pr), 0.80 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ 163.5, 162.3, 153.2, 151.2, 131.0, 114.6, 114.5, 114.5, 65.6, 64.0, 60.6, 53.5, 52.8, 52.7, 31.1, 20.0, 17.7, 15.3, 15.1; HRMS (ESI) calcd. $C_{19}H_{29}N_2O_4$: $[M + H]^+$, 349.2127; found $[M + H]^+$, 349.2121. Microanalysis calcd. for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.45; H, 8.18; N, 7.99.

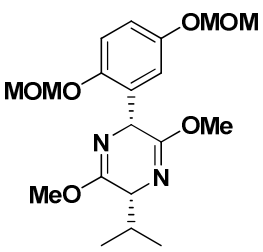
(2*R*,5*R*)-2-(2,5-Di(benzyloxy)phenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine (5g)



5g

Imidate **5g** was prepared according to general procedure A, starting from imidate **3** (0.18 mL, 1.00 mmol), benzyl precursor **450** (0.57 g, 1.75 mmol) and *s*-BuLi (2.14 mL of a 1.4 M solution in cyclohexane, 3.00 mmol). Purification by flash column chromatography (Redisep (12 g), heptane to EtOAc : heptane 1 : 10), followed by (Redisep (12 g), PhMe : acetone 50 : 1) gave **5g** (0.16 g, 90 : 10 dr, 33%) as a white solid: M.p. (EtOAc/hexanes) 53-55 ºC; R_f 0.54 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −75.9 (*c* 1.1, $CHCl_3$); IR 1688, 1500, 1453, 1231, 1194 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 7.26 - 7.49 (m, 10H, Ar-H (Bn)), 6.89 (d, 1H, *J* = 8.9 Hz, Ar-H), 6.83 (dd, 1H, *J* = 9.0, 2.7 Hz, Ar-H), 6.69 (d, 2H, *J* = 2.9 Hz, Ar-H), 5.76 (d, 1H, *J* = 6.2 Hz, CHAr), 5.13 (s, 2H, CH_2Ph), 4.97 (s, 2H, CH_2Ph), 4.02 (dd, 1H, *J* = 6.2, 3.7 Hz, CH*i*-Pr), 3.68 (s, 3H, OMe), 3.61 (s, 3H, OMe), 2.41 (td, 1H, *J* = 6.8, 3.7 Hz, *i*-Pr), 1.17 (d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.86 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ 163.7, 162.1, 153.3, 151.2, 138.0, 137.5, 131.1, 128.7, 128.7, 128.4, 127.8, 127.6, 127.3, 115.1, 114.8, 114.5, 71.5, 70.7, 60.7, 55.4, 53.7, 52.8, 52.7, 31.1, 20.0, 17.7; HRMS (ESI) calcd. $C_{29}H_{32}N_2NaO_4$: $[M + Na]^+$, 495.2259; found $[M + Na]^+$, 495.2260.

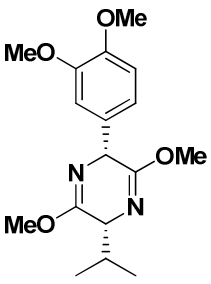
(2*R*,5*R*)-2-(2,5-Di(methoxymethoxy)phenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine (5h)



5h

Imidate **5h** was prepared according to general procedure A, starting from imidate **3** (0.18 mL, 1.00 mmol), MOM precursor **451** (0.41 g, 1.75 mmol) and *s*-BuLi (2.31 mL of a 1.3 M solution in cyclohexane, 3.00 mmol). Purification by flash column chromatography (Redisep (12 g), heptane to EtOAc : heptane 1 : 10) gave **5h** (0.20 g, 88 : 12 dr, 52%) as a yellow oil: R_f 0.38 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −121.0 (*c* 1.0, $CHCl_3$); IR 1691, 1497, 1435, 1232, 1147, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 7.08 (d, 1H, *J* = 9.0 Hz, Ar-H), 6.90 (dd, 1H, *J* = 8.9, 3.0 Hz, Ar-H), 6.76 (d, 1H, *J* = 2.9 Hz, Ar-H), 5.59 (d, 1H, *J* = 6.1 Hz, CHAr), 5.17 (m, 4H, 2 x CH_2O), 4.01 (dd, 1H, *J* = 6.2, 3.7 Hz, CH*i*-Pr), 3.68 (s, 3H, OMe), 3.60 (s, 3H, OMe), 3.51 (s, 3H, OMe), 3.44 (s, 3H, OMe), 2.40 (td, 1H, *J* = 6.8, 3.7 Hz, *i*-Pr), 1.15 (d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.86 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ 163.7, 161.8, 152.5, 150.5, 131.4, 117.0, 116.6, 116.5, 95.8, 95.4, 60.7, 56.1, 56.0, 54.0, 52.8, 52.7, 31.2, 20.0, 17.7; HRMS (ESI) calcd. $C_{19}H_{28}N_2NaO_6$: $[M + Na]^+$, 403.1845; found $[M + Na]^+$, 403.1848. Microanalysis calcd. for $C_{19}H_{28}N_2O_6$: C, 59.98; H, 7.42; N, 7.36. Found: C, 58.87; H, 7.50; N, 7.27.

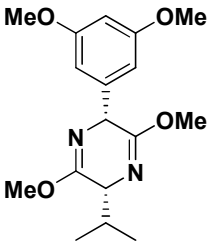
(2*R*,5*R*)-2-(3,4-Dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine (5i)



5i

Imidate **5i** was prepared according to general procedure B, starting from imidate **3** (0.18 mL, 1.00 mmol), 1-fluoro-3,4-dimethoxybenzene (**476**) (0.23 mL, 1.75 mmol) and *n*-BuLi (1.88 mL of a 1.6 M solution in hexane, 3.00 mmol). Purification by flash column chromatography (Redisep (12 g), heptane to EtOAc : heptane 1 : 5) gave **5i** (0.20 g, 76 : 24 dr, 62%) as a yellow oil: R_f 0.43 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −9.1 (*c* 0.1, $CHCl_3$); IR 1691, 1514, 1460, 1234 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 6.84 - 6.90 (m, 3H, Ar-H), 5.15 (d. 1H, *J* = 4.9 Hz, CHAr), 3.99 (t, 1H, *J* = 4.8 Hz, CH*i*-Pr), 3.86 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.66 (s, 3H, OMe), 2.22 (td, 1H, *J* = 6.8, 4.5 Hz, *i*-Pr), 1.09 (d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.82 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ 164.6, 162.1, 148.8, 148.4, 132.9, 120.1, 111.3, 111.0, 61.3, 59.5, 56.0, 56.0, 52.8, 52.8, 32.0, 20.0, 18.3; HRMS (ESI) calcd. $C_{17}H_{24}N_2NaO_4$: $[M + Na]^+$, 343.1634; found $[M + Na]^+$, 343.1639.

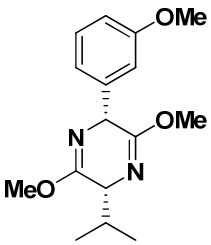
(2*R*,5*R*)-2-(3,5-Dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine (5j)



5j

Imidate **5j** was prepared according to general procedure B, starting from imidate **3** (0.18 mL, 1.00 mmol), 1-fluoro-3,5-dimethoxy benzene (**88**) (0.23 mL, 1.75 mmol) and *n*-BuLi (1.88 mL of a 1.6 M solution in hexane, 3.00 mmol). Purification by flash column chromatography (Redisep (12 g), heptane to EtOAc : heptane 1 : 20) gave **5j** (0.23 g, 81 : 19 dr, 72%) as a yellow oil: R_f 0.51 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −59 (*c* 1.0, $CHCl_3$); IR 1692, 1595, 1456, 1202, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 6.51 (d, 2H, *J* = 2.3 Hz, Ar-H), 6.37 (t, 1H, *J* = 2.3 Hz, Ar-H), 5.13 (d, 1H, *J* = 4.9 Hz, CHAr), 3.98 (t, 1H, *J* = 4.7 Hz, CH*i*-Pr), 3.77 (s, 6H, 2 x OMe), 3.74 (s, 3H, OMe), 3.66 (s, 3H, OMe), 2.20 (m, 1H, *i*-Pr), 1.09 (d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.82 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ 164.7, 161.8, 160.7, 142.5, 106.3, 99.5, 61.3, 59.9, 55.5, 55.4, 52.8, 32.1, 20.0, 18.3; HRMS (ESI) calcd. $C_{17}H_{24}N_2NaO_4$: $[M + Na]^+$, 343.1634; found $[M + Na]^+$, 343.1623.

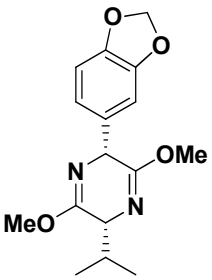
(2*R*,5*R*)-2-*iso*-Propyl-3,6-dimethoxy-5-(3-methoxyphenyl)-2,5-dihydropyrazine (5k)



5k

Imidate **5k** was prepared according to general procedure A, starting from imidate **3** (0.18 mL, 1.00 mmol), 3-chloroanisole **(477)** (0.21 mL, 1.75 mmol) and *s*-BuLi (2.14 mL of a 1.4 M solution in cyclohexane, 3.00 mmol). Purification by flash column chromatography (Redisep (12 g), heptane to EtOAc : heptane 1 : 10), followed by (Redisep (12 g), PhMe : acetone 50 : 1) gave **5k** (0.20 g, 70 : 30 dr, 76%) as a yellow oil: R_f 0.55 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −9.7 (*c* 1.3, $CHCl_3$); IR 1670, 1583, 1460, 1364, 1171, 1015 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 6.94 (m, 1H, Ar-H), 6.89 (m, 1H, Ar-H), 6.81 (m, 2H, Ar-H), 5.19 (d, 1H, *J* = 5.1 Hz, CHAr), 3.99 (t, 1H, *J* = 4.8 Hz, CH*i*-Pr), 3.79 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.67 (s, 3H, OMe), 2.20 (td, 1H, *J* = 6.8, 4.2 Hz, *i*-Pr), 1.08 (d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.81 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ 164.8, 161.9, 159.6, 141.7, 129.3, 120.5, 113.7, 112.9, 61.3, 59.8, 55.4, 52.9, 52.9, 32.1, 20.0, 18.3; HRMS (ESI) calcd. $C_{16}H_{22}N_2NaO_3$: $[M + Na]^+$, 313.1528; found $[M + Na]^+$, 313.1519.

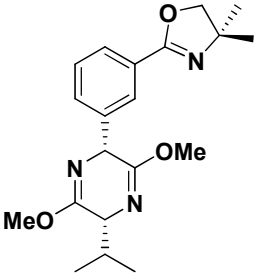
(2R,5R)-2-(Benzo[d][1,3]dioxol-5-yl)-5-*iso*propyl-3,6-dimethoxy-2,5-dihydropyrazine (5l)



5l

Imidate **5l** was prepared according to general procedure A, starting from imidate **3** (0.18 mL, 1.00 mmol), 5-chloro-1,3-benzodioxole **(478)** (0.15 mL, 1.25 mmol) and *sec*-BuLi (1.79 mL of a 1.4 M solution in cyclohexane, 2.50 mmol). Purification by flash column chromatography (Redisep (12 g), heptane to EtOAc : heptane 1 : 10), followed by (Redisep (12 g), PhMe : acetone 50 : 1) gave **5l** (0.052 g, 76 : 24 dr, 17%) as a yellow oil: R_f 0.48 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −11 (*c* 2.0, $CHCl_3$); IR 1691, 1515, 1462, 1237 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 6.83 (d, 1H, *J* = 1.8 Hz, Ar-H), 6.80 (dd, 1H, *J* = 1.8, 0.4 Hz, Ar-H), 6.77 (s, 1H, Ar-H), 5.94 (s, 2H, OCH_2O), 5.11 (d, 1H, *J* = 5.1 Hz, CHAr), 3.97 (t, 1H, *J* = 4.8 Hz, CH*i*-Pr), 3.74 (s, 3H, OMe), 3.66 (s, 3H, OMe), 2.21 (td, 1H, *J* = 6.8, 4.5 Hz, *i*-Pr), 1.08 (d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.79 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ 164.5, 161.9, 147.7, 146.9, 134.2, 121.3, 108.6, 108.5, 101.2, 61.4, 59.4, 53.0, 52.8, 32.1, 19.9, 18.1; HRMS (ESI) calcd. $C_{16}H_{21}N_2O_4$: $[M + H]^+$, 305.1501; found $[M + H]^+$, 305.1533.

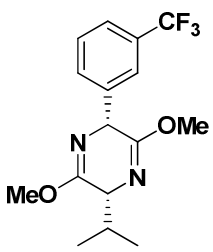
2-(3-((2*R*,5*R*)-5-*iso*-Propyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (5m)



5m

Imidate **5m** was prepared according to general procedure B, starting from imidate **3** (0.18 mL, 1.00 mmol), oxazoline precursor **467** (0.36 g, 1.75 mmol) and *n*-BuLi (1.88 mL of a 1.6 M solution in hexane, 3.00 mmol). Purification by flash column chromatography (Redisep (12 g), heptane to EtOAc : heptane 1 : 5) followed by (Redisep (12 g), PhMe : acetone 50 : 1) gave **5m** (0.20 g, 71 : 29 dr, 55%) as a yellow oil: R_f 0.32 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −19 (*c* 1.0, $CHCl_3$); IR 1691, 1648, 1303, 1237, 1193, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 7.97 (s, 1H, Ar-H), 7.91 - 7.82 (m, 1H, Ar-H), 7.41 - 7.34 (m, 2H, Ar-H), 5.25 (d, 1H, *J* = 5.1 Hz, CHAr), 4.11 (s, 2H, CH_2O), 4.03 (t, 1H, *J* = 4.7 Hz, CH*i*-Pr), 3.77 (s, 3H, OMe), 3.67 (s, 3H, OMe), 2.25 (td, 1H, *J* = 6.8, 4.5 Hz, *i*-Pr), 1.40 (s, 6H, 2 x CH_3) , 1.11 (d, 3H, *J* =6.9 Hz, *i*-Pr), 0.81 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ 164.8, 162.2, 161.5, 140.5, 130.3, 128.5, 128.3, 127.4, 79.3, 67.8, 61.2, 59.7, 52.9, 52.9, 31.9, 28.6, 20.0, 18.1; HRMS (CI) calcd. $C_{20}H_{28}N_3O_3$: $[M + H]^+$, 358.2131; found $[M + H]^+$, 358.2131.

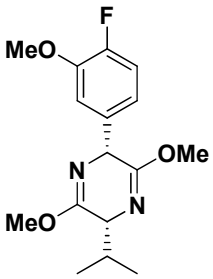
(2*R*,5*R*)-2-*iso*-Propyl-3,6-dimethoxy-5-(3-(trifluoromethyl)phenyl)-2,5-dihydropyrazine (5n)



5n

Imidate **5n** was prepared according to general procedure B, starting from imidate **3** (0.18 mL, 1.00 mmol), 1-chloro-2-(trifluoromethyl)benzene (**479**) (0.23 mL, 1.75 mmol) and *n*-BuLi (1.88 mL of a 1.6 M solution in hexane, 3.00 mmol). Purification by flash column chromatography (hexanes to EtOAc : hexanes 1 : 20) gave **5n** (0.20 g, 50 : 50 dr, 61%) as a yellow oil. Further chromatography (EtOAc : hexanes 1 : 10) gave **5n** as a single diastereoisomer: R_f 0.8 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −130.2 (*c* 0.45, $CHCl_3$); IR 1697, 1437, 1331, 1240, 1165, 1127 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 - 7.45 (m, 4H, Ar-H), 5.29 (d, 1H, *J* = 5.0 Hz, CHAr), 4.05 (t, 1H, *J* = 4.6 Hz, CH*i*-Pr), 3.80 (s, 3H, OMe), 3.69 (s, 3H, OMe), 2.26 (m, 1H, *i*-Pr), 1.11 (d, 3H, *J* =6.9 Hz, *i*-Pr), 0.79 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 160.8, 140.9, 131.2, 130.4 (q, $J_{C\text{-}F}$ = 32.4 Hz), 128.5, 124.6 (q, $J_{C\text{-}F}$ = 3.9 Hz), 124.2 (q, $J_{C\text{-}F}$ = 272.0 Hz), 124.0 (q, $J_{C\text{-}F}$ = 3.6 Hz), 61.0, 59.1, 52.7, 52.7, 31.7, 19.6, 17.7; ^{19}F NMR (200 MHz, $CDCl_3$) δ −62.6; HRMS (ESI) calcd. $C_{16}H_{21}F_3NO_2$: $[M + H]^+$, 329.1477; found $[M + H]^+$, 329.1478.

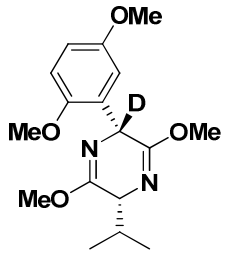
(2*R*,5*R*)-2-(4-Fluoro-3-methoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine (5o)



5o

Imidate **5o** was prepared according to general procedure B, starting from imidate **3** (0.18 mL, 1.00 mmol), 1,4-difluoro-2-methoxybenzene **(480)** (0.20 mL, 1.75 mmol) and *n*-BuLi (1.88 mL of a 1.6 M solution in hexane, 3.00 mmol). Purification by flash column chromatography (Redisep (12 g), heptane to EtOAc : heptane 1 : 10), followed by (Redisep (12 g), PhMe : acetone 50 : 1) gave **5o** (0.16 g, 73 : 27 dr, 53%) as a yellow oil: R_f 0.56 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −20.0 (*c* 1.0, $CHCl_3$); IR 1691, 1515, 1462, 1237 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 7.00 (m, 2H, Ar-H), 6.86 (m, 1H, Ar-H), 5.15 (d, 1H, *J* = 4.9 Hz, CHAr), 3.99 (t, 1H, *J* = 4.5 Hz, CH*i*-Pr), 3.85 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.66 (s, 3H, OMe), 2.22 (td, 1H, *J* = 6.8, 4.4 Hz, *i*-Pr), 1.08 (d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.79 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (100 MHz, $CDCl_3$) *major isomer* δ 164.9, 161.6, 151.5 (d, $J_{C\text{-}F}$ = 244.9 Hz), 147.4 (d, $J_{C\text{-}F}$ = 11.0 Hz), 136.5 (d, $J_{C\text{-}F}$ = 3.7 Hz), 120.3 (d, $J_{C\text{-}F}$ = 6.6 Hz), 116.0 (d, $J_{C\text{-}F}$ = 18.4 Hz), 113.3 (d, $J_{C\text{-}F}$ = 2.2 Hz), 61.2, 59.4, 56.4, 53.0, 52.9, 31.9, 19.9, 18.1; ^{19}F NMR (200 MHz, $CDCl_3$) δ −138.0; HRMS (ESI) calcd. $C_{16}H_{22}FN_2O_3$: $[M + H]^+$, 309.1614; found $[M + H]^+$, 309.1617.

(2*R*,5*R*)-2-(*D*,2,5-Dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine (447)

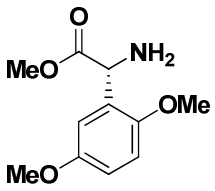


447

sec-BuLi (3.0 equiv) was added drop-wise to a solution of imidate **3** (0.36 mL, 2.0 mmol) and **388** (0.50 mL, 3.5 mmol) in THF (10 mL) at −95 ºC. The mixture was maintained at −95 ºC for 30 min, before being allowed to warm to room temperature overnight. D_2O (1 mL) was added and the mixture stirred for 1 hour further at room temperature. H_2O was added and the mixture extracted with EtOAc (x 3). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 10) to give **447** (0.33 g, 89 : 11 dr, 52%) as an off-white solid.

M.p. (EtOAc/hexanes) 62-63 ºC; R_f 0.2 (EtOAc : hexanes 1 : 10); $[\alpha]_D^{25}$ = −121.3 (*c* 1.0, $CHCl_3$); IR 1685, 1501, 1463, 1224 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 6.90 (d, 1H, *J* = 8.9 Hz, Ar-H), 6.81 (dd, 1H, *J* = 8.9, 3.1 Hz, Ar-H), 6.64 (d, 1H, *J* = 3.0 Hz, Ar-H), 4.04 (d, 1H, *J* = 3.4 Hz, CH*i*-Pr), 3.87 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.64 (s, 3H, OMe), 2.46 (m, 1H, *i*-Pr), 1.19 (d, 3H, *J* = 6.9 Hz, *i*-Pr), 0.91 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) *major isomer* δ 163.4, 161.8, 153.7, 151.7, 130.4, 114.1, 113.2, 112.9, 60.4, 56.8, 55.6, 52.7, 52.6, 30.9, 19.7, 17.5; HRMS (CI) calcd. $C_{17}H_{24}N_2O_4$: $[M + H]^+$, 322.1877; found: $[M + H]^+$, 322.1877.

(*R*)-Methyl 2-amino-2-(2,5-dimethoxyphenyl)acetate (448)

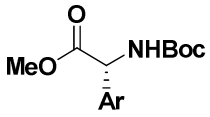


448

0.5 M HCl (0.92 mL, 0.46 mmol) was added to a solution of **5a** (0.066 g, 94 : 6 dr, 0.21 mmol) in MeCN (1 mL) and the mixture stirred at 0 ºC overnight. Saturated aqueous Na_2CO_3 was added to pH 8-9 and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was dried under vacuum for 5 h to remove the valine methyl ester, and purified by flash column chromatography (CH_2Cl_2 : MeOH (NH_3) 30 : 1) to give **448** (0.042 g, 89%, 86% ee) as an amber oil.

R_f 0.47 (CH_2Cl_2 : MeOH (NH_3) 30 : 1); $[\alpha]_D^{25}$ = −74 (*c* 1.0, $CHCl_3$); IR 3382, 1733, 1497, 1463, 1221, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 - 6.78 (m, 3H, Ar-H), 4.72 (s, 1H, CHAr), 3.79 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.70 (s, 3H, OMe), 2.09 (s(br), 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 153.7, 150.9, 129.8, 114.8, 113.5, 112.1, 56.1, 55.7, 54.8, 52.3; HRMS (CI) calcd. $C_{11}H_{16}NO_4$: $[M + H]^+$, 226.1079; found $[M + H]^+$, 226.1082. The enantiomeric excess was determined by HPLC. [CHIRALPACK® IC, 292 nm, hexane : *i*-PrOH = 60 : 40, 1.0 mL/min]: 14.999 min (major), 24.665 min (minor).

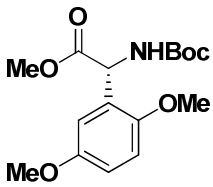
General Procedure for imidate hydrolysis and *N*-Boc protection



6

General Procedure: 0.5 M HCl (2.25 equiv) was added to bis-imidate **5** (1 equiv) in MeCN (0.1 M) and the mixture stirred at 0 ºC overnight. Saturated aqueous Na_2CO_3 was added to pH 8-9 and the mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (0.1 M) and di-*iso*-propylethylamine (2.1 equiv) and Boc_2O (2.2 equiv) were added and the mixture stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes 1 : 5) to give the desired carbamates **6**.

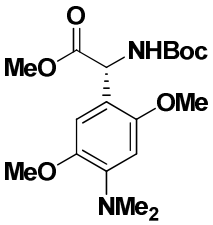
(*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-(2,5-dimethoxyphenyl)acetate (6a)



6a

Prepared according to the general procedure, starting from imidate **5a** (0.10 g, 0.32 mmol), carbamate **6a** (0.093 g, 89%) was obtained as a colourless oil: R_f 0.54 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −107.6 (*c* 1.04, $CHCl_3$); IR 3366, 1747, 1709, 1499, 1222, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (s(br), 1H, NH), 6.81 (d, 2H, *J* = 1.4 Hz, Ar-H), 5.66 (d, 1H, *J* = 8.8 Hz, Ar-H), 5.42 (d, 1H, *J* = 9.1 Hz, CHAr), 3.77 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.68 (s, 3H, OMe), 1.43 (s, 9H, Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 155.3, 153.6, 151.1, 126.7, 116.0, 114.2, 112.2, 79.9, 55.7, 55.6, 54.5, 52.5, 28.3; HRMS (ESI) calcd. $C_{16}H_{23}NNaO_6$: $[M + Na]^+$, 348.1423; found $[M + Na]^+$, 348.1415.

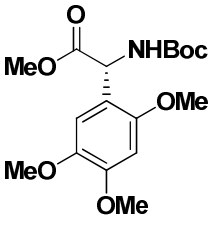
(*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-(4-(dimethylamino)-2,5-dimethoxyphenyl)acetate (6b)



6b

Prepared according to the general procedure, starting from imidate **5b** (0.035 g, 0.096 mmol), carbamate **6b** (0.034 g, 96%) was obtained as a yellow oil: R_f 0.51 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −83.2 (*c* 1.0, $CHCl_3$); IR 3374, 1746, 1712, 1487, 1457, 1215, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.46 (d, 1H, *J* = 2.9 Hz, Ar-H), 6.41 (d, 1H, *J* = 2.6 Hz, Ar-H), 5.64 (d, 1H, *J* = 8.5 Hz, NH), 5.51 (d, 1H, *J* = 8.7 Hz, CHAr), 3.79 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.74 (s, 3H, OMe), 2.82 (s, 6H, NMe_2), 1.47 (s, 9H, Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 155.8, 155.2, 146.6, 143.5, 131.3, 105.5, 104.5, 79.9, 58.3, 55.5, 54.1, 52.5, 42.0, 28.4; HRMS (ESI) calcd. $C_{18}H_{29}N_2O_6$: $[M + H]^+$, 369.2026; found $[M + H]^+$, 369.2025.

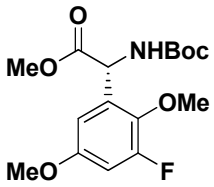
(R)-Methyl 2-(tert-butoxycarbonylamino)-2-(2,4,5-trimethoxyphenyl)acetate (6c)



6c

Prepared according to the general procedure, starting from imidate **5c** (0.041 g, 0.12 mmol), carbamate **6c** (0.025 g, 59%) was obtained as a colourless oil: R_f 0.52 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −52.0 (*c* 0.7, $CHCl_3$); IR 3366, 1746, 1708, 1512, 1464, 1206, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H, Ar-H), 6.54 (s, 1H, Ar-H), 5.63 (d, 1H, *J* = 8.5 Hz, NH), 5.41 (d, 1H, *J* = 8.8 Hz, CHAr), 3.91 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.72 (s, 3H, OMe), 1.47 (s, 9H. Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 155.3, 151.3, 149.7, 143.1, 117.1, 113.5, 97.7, 79.9, 56.5, 56.4, 56.1, 54.0, 52.5, 28.3; HRMS (ESI) calcd. $C_{17}H_{25}NNaO_7$: $[M + Na]^+$, 378.1529; found $[M + Na]^+$, 378.1521. Microanalysis calcd. for $C_{17}H_{25}NO_7$: C, 57.45; H, 7.09; N, 3.94. Found: C, 57.38; H, 6.95; N, 3.86.

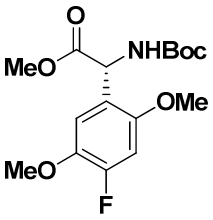
(*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-(3-fluoro-2,5-dimethoxyphenyl)acetate (6d)



6d

Prepared according to the general procedure, starting from imidate **5d** (0.051 g, 0.15 mmol), carbamate **6d** (0.025 g, 48%) was obtained as a colourless oil: R_f 0.71 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −50.1 (*c* 1.4, $CHCl_3$); IR 3380, 1747, 1712, 1497, 1435, 1231, 1158, 1142 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 - 6.64 (m, 2H, Ar-H), 5.68 (d, 1H, *J* = 8.1 Hz, NH), 5.51 (d, 1H, *J* = 8.4 Hz, CHAr), 3.89 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.75 (s, 3H, OMe), 1.46 (s, 9H. Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 155.7 (d, $J_{C\text{-}F}$ = 247.6 Hz), 155.5 (d, $J_{C\text{-}F}$ = 10.5 Hz), 155.0, 139.1 (d, $J_{C\text{-}F}$ = 11.9 Hz), 132.3 (d, $J_{C\text{-}F}$ = 3.5 Hz), 109.5, 103.4 (d, $J_{C\text{-}F}$ = 22.6 Hz), 80.1, 61.4, 55.8, 53.7, 52.8, 28.3; ^{19}F NMR (200 MHz, $CDCl_3$) δ −127.5; HRMS (ESI) calcd. $C_{16}H_{22}NNaO_6$: $[M + Na]^+$, 366.1329; found $[M + Na]^+$, 366.1332. Microanalysis calcd. for $C_{16}H_{22}NO_6$: C, 55.97; H, 6.46; N, 4.08. Found: C, 56.07; H, 6.54; N, 4.09.

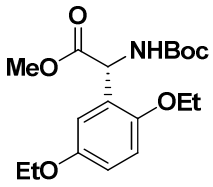
(*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-(4-fluoro-2,5-dimethoxyphenyl)acetate (6e)



6e

Prepared according to the general procedure, starting from imidate **5d** (0.051 g, 0.15 mmol), carbamate **6e** (0.024 g, 46%) was obtained as a colourless oil: R_f 0.53 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −74.5 (*c* 1.1, $CHCl_3$); IR 3382, 1747, 1709, 1510, 1315, 1217, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, 1H, $J_{H\text{-}F}$ = 9.2 Hz, Ar-H), 6.71 (d, 1H, $J_{H\text{-}F}$ = 12.5 Hz, Ar-H), 5.65 (d, 1H, *J* = 8.4 Hz, NH), 5.41 (d, 1H, *J* = 8.8 Hz, CHAr), 3.87 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.71 (s, 3H, OMe), 1.46 (s, 9H, Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 155.2, 152.6 (d, $J_{C\text{-}F}$ = 247.0 Hz), 151.1 (d, $J_{C\text{-}F}$ = 8.3 Hz), 141.3 (d, $J_{C\text{-}F}$ = 11.1 Hz), 121.2 (d, $J_{C\text{-}F}$ = 3.6 Hz), 116.1, 101.2 (d, $J_{C\text{-}F}$ = 22.5 Hz), 80.1, 57.1, 56.3, 54.1, 52.6, 28.3; ^{19}F NMR (200 MHz, $CDCl_3$) δ −130.7; HRMS (ESI) calcd. $C_{16}H_{22}NNaO_6$: $[M + Na]^+$, 366.1329; found $[M + Na]^+$, 366.1325. Microanalysis calcd. for $C_{16}H_{22}NO_6$: C, 55.97; H, 6.46; N, 4.08. Found: C, 56.05; H, 6.52; N, 3.92.

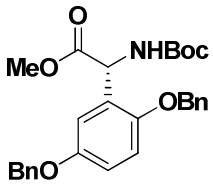
(*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-(2,5-diethoxyphenyl)acetate (6f)



6f

Prepared according to the general procedure, starting from imidate **5f** (0.033 g, 0.095 mmol), carbamate **6f** (0.033 g, 98%) was obtained as a colourless oil: R_f 0.55 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −72.4 (*c* 1.4, $CHCl_3$); IR 3459, 1748, 1712, 1498, 1476, 1214, 1159, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s(br), 1H, Ar-H), 6.81 (m, 2H, Ar-H), 5.67 (d, 1H, *J* = 9.0 Hz, NH), 5.43 (d, 1H, *J* = 9.1 Hz, CHAr), 4.11-3.89 (m, 4H, 2 x OEt), 3.71 (s, 3H, OMe), 1.47 (s, 9H, Boc), 1.40 (q, 6H, *J* = 6.8 Hz, 2 x OEt); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 155.3, 152.9, 150.3, 126.9, 116.7, 114.9, 113.0, 79.8, 64.4, 64.0, 54.8, 52.4, 28.3, 14.9, 14.7; HRMS (ESI) calcd. $C_{18}H_{27}NNaO_6$: $[M + Na]^+$, 376.1736; found $[M + Na]^+$, 376.1735. Microanalysis calcd. for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.21; H, 7.67; N, 3.87.

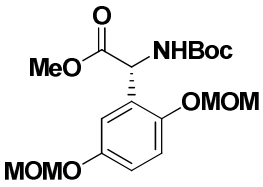
(*R*)-Methyl 2-(2,5-di(benzyloxy)phenyl)-2-(*tert*-butoxycarbonylamino)acetate (6g)



6g

Prepared according to the general procedure, starting from imidate **5g** (0.039 g, 0.08 mmol), carbamate **6g** (0.03 g, 79%) was obtained as a white solid: M.p. 88-90 ºC; R_f 0.58 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −71.4 (*c* 1.3, $CHCl_3$); IR 3747, 1736, 1698, 1499, 1453, 1217, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.33 (m, 10H, Ar-H (Bn)), 7.03 (s(br), 1H, Ar-H), 6.88 (m, 2H, Ar-H), 5.68 (d, 1H, *J* = 8.8 Hz, NH), 5.54 (d, 1H, *J* = 8.9 Hz, CHAr), 5.10 (s, 2H, CH_2Ph), 5.03 (s, 2H, CH_2Ph), 3.66 (s, 3H, OMe), 1.47 (s, 9H, Boc);^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 155.2, 153.0, 150.3, 137.0, 136.8, 128.6, 128.6, 128.0, 127.9, 127.5, 127.2, 127.1, 117.1, 115.2, 113.5, 79.9, 70.8, 70.6, 54.5, 52.5, 28.4; HRMS (ESI) calcd. $C_{28}H_{31}NNaO_6$: $[M + Na]^+$, 500.2049; found $[M + Na]^+$, 500.1983. Microanalysis calcd. for $C_{28}H_{31}NO_6$: C, 70.42; H, 6.54; N, 2.93. Found: C, 70.51; H, 6.51; N, 2.86.

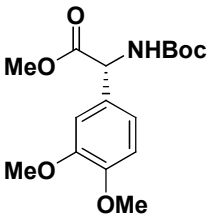
(*R*)-Methyl 2-(2,5-di(methoxymethoxy)phenyl)-2-(*tert*-butoxycarbonylamino)acetate (6h)



6h

Prepared according to the general procedure, starting from imidate **5h** (0.076 g, 0.20 mmol), carbamate **6h** (0.051 g, 66%) was obtained as a colourless oil: R_f 0.49 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −80.5 (*c* 1.1, $CHCl_3$); IR 3361, 1747, 1709, 1497, 1150, 992 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.08 - 6.97 (m, 3H, Ar-H), 5.68 (d, 1H, *J* = 8.8 Hz, NH), 5.51 (d, 1H, *J* = 8.9 Hz, CHAr), 5.19 - 5.12 (m, 4H, 2 x OCH_2), 3.72 (s, 3H, OMe), 3.50 (s, 3H, OMe), 3.59 (s, 3H, OMe), 1.47 (s, 9H, Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 155.2, 152.1, 149.6, 127.5, 118.5, 117.0, 115.7, 95.1, 94.9, 80.0, 56.1, 56.0, 54.2, 52.6, 28.3; HRMS (ESI) calcd. $C_{18}H_{27}NNaO_8$: $[M + Na]^+$, 408.1634; found $[M + Na]^+$, 408.1632.

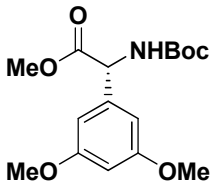
(*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-(3,4-dimethoxyphenyl)acetate (6i)



6i

Prepared according to the general procedure, starting from imidate **5i** (0.025 g, 0.08 mmol), carbamate **6i** (0.024 g, 92%) was obtained as a colourless oil: R_f 0.52 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −11.7 (*c* 1.4, $CHCl_3$); IR 3361, 1745, 1708, 1513, 1461, 1257, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93 - 6.84 (m, 3H, Ar-H), 5.51 (d (br), 1H, *J* = 6.0 Hz, NH), 5.25 (d, 1H, *J* = 7.1 Hz, CHAr), 3.90 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.75 (s, 3H, OMe), 1.46 (s, 9H, Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 154.8, 149.2, 149.2, 129.3, 119.5, 111.3, 110.2, 80.2, 57.3, 55.9, 53.4, 52.7, 28.3; HRMS (ESI) calcd. $C_{16}H_{23}NNaO_6$: $[M + Na]^+$, 348.1423; found $[M + Na]^+$, 348.1423. Microanalysis calcd. for $C_{16}H_{23}NO_6$: C, 59.09; H, 7.13; N, 4.31. Found: C, 58.91; H, 7.05; N, 4.29.

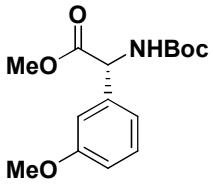
(*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-(3,5-dimethoxyphenyl)acetate (6j)



6j

Prepared according to the general procedure, starting from imidate **5j** (0.024 g, 0.07 mmol), carbamate **6j** (0.016 g, 70%) was obtained as a colourless oil: R_f 0.50 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −9.2 (*c* 0.3, $CHCl_3$); IR 3372, 1745, 1714, 1462, 1206, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.53 (d, 2H, *J* = 2.1 Hz, Ar-H), 6.43 (t, 1H, *J* = 2.1 Hz, Ar-H), 5.54 (br d, 1H, *J* = 5.9 Hz, NH), 5.26 (d, 1H, *J* = 7.3 Hz, CHAr), 3.81 (s, 6H, 2 x OMe), 3.76 (s, 3H, OMe), 1.47 (s, 9H, Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 161.1, 154.8, 139.0, 105.2, 100.4, 80.2, 57.6, 55.4, 52.7, 28.3; HRMS (ESI) calcd. $C_{16}H_{23}NNaO_6$: $[M + Na]^+$, 348.1423; found $[M + Na]^+$, 348.1435.

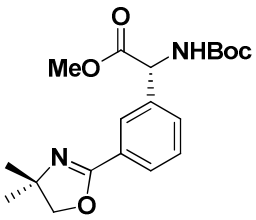
(R)-Methyl 2-(tert-butoxycarbonylamino)-2-(3-methoxyphenyl)acetate (6k)



6k

Prepared according to the general procedure, starting from imidate **5k** (0.082 g, 0.28 mmol), carbamate **6k** (0.055 g, 67%) was obtained as a colourless oil: R_f 0.47 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −32.6 (*c* 1.0, $CHCl_3$); IR 3370, 1743, 1705, 1489, 1253, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 - 7.28 (m, 1H, Ar-H), 6.98 - 6.88 (m, 3H, Ar-H), 5.56 (d, 1H, *J* = 6.4 Hz, NH), 5.32 (d, 1H, *J* = 7.5 Hz, CHAr), 3.83 (s, 3H, OMe), 3.75 (s, 3H, OMe), 1.46 (s, 9H, Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 159.9, 154.8, 138.3, 129.9, 119.4, 114.0, 112.8, 80.2, 57.5, 55.3, 52.7, 28.3; Microanalysis calcd. for $C_{15}H_{21}NO_5$: C, 61.0; H, 7.17; N, 4.74. Found: C, 60.89; H, 7.09; N, 4.71.

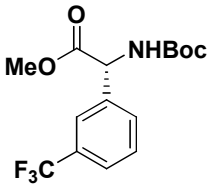
(*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-(3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)phenyl)acetate (6m)



6m

Prepared according to the general procedure, starting from imidate **5m** (0.058 g, 0.16 mmol), carbamate **6m** (0.024 g, 41%) was obtained as a colourless gum: R_f 0.36 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −13.7 (*c* 1.0, $CHCl_3$); IR 3444, 1745, 1708, 1649, 1354, 1202, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 - 7.90 (m, 2H, Ar-H), 7.49 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.40 (t, 1H, *J* = 7.7 Hz, Ar-H), 5.65 (d (br), 1H, *J* = 6.2 Hz, NH), 5.36 (d, 1H, *J* = 7.2 Hz, CHAr), 4.12 (s, 2H, CH_2O), 3.72 (s, 3H, OMe), 1.44 (s, 9H, Boc), 1.39 (s, 6H, 2 x CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 161.5, 154.7, 137.3, 130.1, 128.8, 128.8, 128.3, 126.8, 80.2, 79.1, 67.7, 57.4, 52.8, 28.4, 28.3; HRMS (ESI) calcd. $C_{19}H_{27}N_2O_5$: $[M + H]^+$, 363.1920; found $[M + Na]^+$, 363.1915.

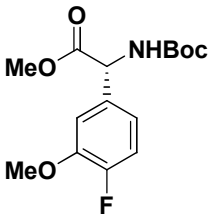
(*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-(3-(trifluoromethyl)phenyl)acetate (6n)



6n

Prepared according to the general procedure, starting from imidate **5n** (0.037 g, 0.11 mmol), carbamate **6n** (0.035 g, 93%) was obtained as a yellow oil: R_f 0.57 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −62.6 (*c* 1.1, $CHCl_3$); IR 3367, 1745, 1705, 1327, 1158, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 - 7.60 (m, 3H, Ar-H), 7.51 (t, 1H, *J* = 7.7 Hz, Ar-H), 5.74 (d (br), 1H, *J* = 5.3 Hz, NH), 5.42 (d, 1H, *J* = 6.9 Hz, CHAr), 3.76 (s, 3H, OMe), 1.46 (s, 9H, Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 154.7, 138.2, 131.2 (q, $J_{C\text{-}F}$ = 32.3 Hz), 130.6, 129.3, 125.3, 123.8 (q, $J_{C\text{-}F}$ = 272.4 Hz), 123.7, 80.5, 57.2, 53.0, 28.2; ^{19}F NMR (200 MHz, $CDCl_3$) δ −62.5; HRMS (ESI) calcd. $C_{15}H_{18}F_3NNaO_4$: $[M + Na]^+$, 356.1086; found $[M + Na]^+$, 356.1089.

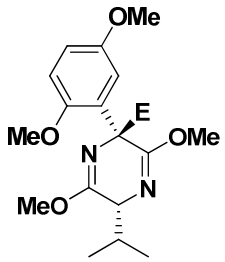
(*R*)-Methyl 2-(*tert*-butoxycarbonylamino)-2-(4-fluoro-3-methoxyphenyl)acetate (6o)



6o

Prepared according to the general procedure, starting from imidate **5o** (0.080 g, 0.26 mmol), carbamate **6o** (0.051 g, 62%) was obtained as a yellow oil: R_f 0.48 (EtOAc : hexanes 1 : 5); $[\alpha]_D^{25}$ = −5.3 (*c* 0.95, $CHCl_3$); IR 3386, 1743, 1707, 1515, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (dd, 1H, *J* = 10.9, 8.3 Hz, Ar-H), 6.99 (dd, 1H, *J* = 7.8, 1.5 Hz, Ar-H), 6.93 - 6.89 (m, 1H, Ar-H), 5.61 (d, 1H, *J* = 5.9 Hz, NH), 5.28 (d, 1H, *J* = 7.0 Hz, CHAr), 3.91 (s, 3H, OMe), 3.75 (s, 3H, OMe), 1.46 (s, 9H, Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 154.74, 152.3 (d, $J_{C\text{-}F}$ = 247.1 Hz), 147.9 (d, $J_{C\text{-}F}$ = 10.9 Hz), 133.3, 119.4 (d, $J_{C\text{-}F}$ = 6.8 Hz), 116.3 (d, $J_{C\text{-}F}$ = 18.6 Hz), 112.4, 80.4, 57.2, 56.3, 52.8, 28.3; ^{19}F NMR (200 MHz, $CDCl_3$) δ −135.3; HRMS (ESI) calcd. $C_{15}H_{20}FNNaO_5$: $[M + Na]^+$, 336.1223; found $[M + Na]^+$, 336.1220.

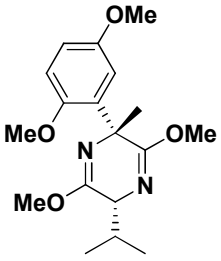
General Procedure for the synthesis of quaternary Schöllkopf adducts



484

General Procedure: *sec*-BuLi (2.15 mL of a 1.28 M solution in cyclohexane, 2.75 mmol) was added drop-wise with stirring to imidate **3** (0.18 mL, 1.00 mmol) and 2-chloro-1, 4-dimethoxybenzene (**388**) (0.21 mL, 1.50 mmol) in THF (5 mL) at −95 ºC. The mixture was maintained at −95 ºC for 30 min, before being allowed to warm to room temperature overnight. The mixture was re-cooled to −78 ˚C when the electrophile (4 equiv) was added and stirring was continued at −78 ˚C until GC-MS analysis indicated that the reaction was complete. The mixture was warmed to room temperature and H_2O (5 mL) was added and the mixture extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

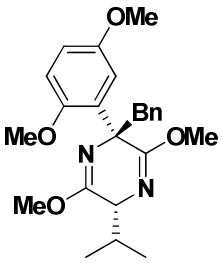
(2*R*,5*R*)-2-(2,5-Dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2-methyl-2,5-dihydropyrazine (484a)



484a

Imidate **484a** was prepared according to the general procedure, employing MeI (0.25 mL, 4.00 mmol) as the electrophile at −78 ˚C for 1 h. Purification by flash column chromatography (EtOAc : hexanes 1 : 15 to 1 : 8) gave **484a** (0.307 g, 94 : 6 dr, 92%) as an off-white solid: M.p. (EtOAc/hexanes) 32-34 ºC; R_f 0.55 (EtOAc : hexanes 1 : 4); $[\alpha]_D^{25}$ = −88.3 (*c* 1.2, $CHCl_3$); IR 1688 (C=N), 1671 (C=N), 1497, 1462, 1224, 1201 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 7.03 (d, 1H, *J* = 2.3 Hz, Ar-H), 6.80 (m, 2H, Ar-H), 3.95 (d, 1H, *J* = 3.2 Hz, C<u>H</u>-*i*Pr), 3.81 (s, 3H, OMe), 3.64 (s, 6H, 2 x OMe), 3.64 (s, 3H, OMe), 2.47 (dsept, 1H, *J* = 6.8, 3.2 Hz, *i*-Pr), 1.64 (s, 3H, CH_3), 1.20 (d, 3H, *J* = 6.9 Hz, *i*-Pr), 0.87 (d, 3H, *J* = 6.7 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) *major isomer* δ 166.5, 162.4, 153.2, 152.3, 133.9, 113.9, 112.6, 111.8, 59.9, 58.8, 56.0, 55.5, 52.7, 52.4, 30.0, 26.1, 19.8, 17.1; HRMS (ESI) calcd. $C_{18}H_{27}N_2O_4$: $[M + H]^+$, 335.1971; found $[M + H]^+$, 335.1979.

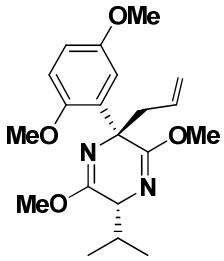
(2*R*,5*R*)-2-Benzyl-2-(2,5-dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine (484b)



484b

Imidate **484b** was prepared according to the general procedure, employing BnBr (0.48 mL, 4.00 mmol) as the electrophile at −78 ˚C for 6 h. Purification by flash column chromatography (EtOAc : hexanes 1 : 15 to 1 : 8) gave **484b** (0.360 g, >98 : 2 dr, 88%) as a yellow solid: M.p. (EtOAc/hexanes) 86-88 ºC; R_f 0.4 (EtOAc : hexanes 1 : 3); $[\alpha]_D^{25}$ = 9.6 (*c* 0.8, $CHCl_3$); IR 1692 (C=N), 1668 (C=N), 1497, 1461, 1299, 1230, 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, 3H, *J* = 5.1, 2.1 Hz, Ar-H), 7.19 (d, 1H, *J* = 2.7 Hz, Ar-H), 7.07 (m, 2H, Ar-H), 6.85 (m, 2H, Ar-H), 3.84 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.48 (AB, 2H, *J* = 12.2 Hz, CH_2Ph), 2.11 (d, 1H, *J* = 3.0 Hz, C<u>H</u>-*i*Pr), 2.08 (m, 1H, *i*-Pr), 0.89 (d, 3H, *J* = 6.7 Hz, *i*-Pr), 0.71 (d, 3H, *J* = 6.6 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 162.3, 153.2, 152.5, 136.3, 134.0, 131.3, 127.5, 126.5, 114.2, 113.1, 112.0, 63.3, 60.1, 56.1, 55.6, 52.6, 52.2, 44.3, 29.8, 19.5, 17.4; HRMS (ESI) calcd. $C_{24}H_{31}N_2O_4$: $[M + H]^+$, 411.2284; found $[M + H]^+$, 411.2272. X-ray crystal data $C_{24}H_{30}N_2O_4$, M = 410.50, Monoclinic, P2(1), a=9.97411(9) Å, b = 13.15260(10) Å, c = 17.19106(14) Å, α = 90°, β = 103.3454(9)°, γ = 90°, V= 2194.32(3) $Å^3$, Z= 4, D_c= 1.243 Mg/m^3, μ(Cu-Kα) = 0.682 mm^{-1}, T = 173 K, colourless blocks, 57518 / 8630 independent measured reflections, 8100 independent observed reflections [F>4σ(F)], 550 parameters.

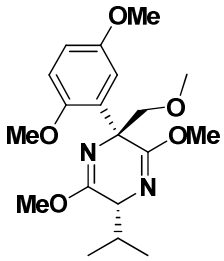
(2*R*,5*R*)-2-Allyl-2-(2,5-dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazine (484c)



484c

Imidate **484c** was prepared according to the general procedure, employing allyl bromide (0.35 mL, 4.00 mmol) as the electrophile at −78 ˚C for 1 h. Purification by flash column chromatography (EtOAc : hexanes 1 : 15 to 1 : 10) gave **484c** (0.305 g, >98 : 2 dr, 85%) as a colourless oil; R_f 0.52 (EtOAc : hexanes 1 : 3); $[\alpha]_D^{25}$ = -59.5 (*c* 1.0, $CHCl_3$); IR 1689 (C=N), 1670 (C=N), 1498, 1299, 1227, 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, 1H, *J* = 2.7 Hz, Ar-H), 6.81 (m, 2H, Ar-H), 5.73 (m, 1H, C<u>H</u>=CH_2), 5.11 (m, 2H, CH=C<u>H</u>$_2$), 3.88 (d, 1H, *J* = 3.5 Hz, C<u>H</u>-*i*Pr), 3.80 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.66 (s, 3H, OMe), 2.96 (dd, 1H, *J* = 13.1, 7.1 Hz, C<u>H</u>$_2$CH=CH_2), 2.91 (dd, 1H, *J* = 13.0, 7.7 Hz, C<u>H</u>$_2$CH=CH_2), 2.40 (dsept, 1H, *J* = 6.9, 3.7 Hz, *i*-Pr), 1.17 (d, 3H, *J* = 6.9 Hz, *i*-Pr), 0.86 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 163.2, 153.2, 152.4, 133.4, 133.3, 119.1, 114.4, 113.1, 112.2, 62.2, 61.2, 56.1, 55.6, 52.7, 52.4, 43.8, 30.5, 19.9, 17.7; HRMS (ESI) calcd. $C_{20}H_{29}N_2O_4$: $[M + H]^+$, 361.2127; found $[M + H]^+$, 361.2112.

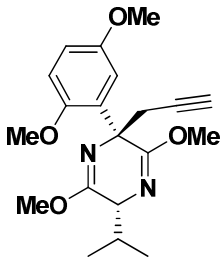
(2*S*,5*R*)-2-(2,5-Dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2-(methoxymethyl)-2,5-dihydropyrazine (484d)



484d

Imidate **484d** was prepared according to the general procedure, employing MOMCl (0.30 mL, 4.00 mmol) as the electrophile at −78 ˚C for 1 h. Purification by flash column chromatography (EtOAc : hexanes 1 : 15 to 1 : 5) gave **484d** (0.20 g, 95 : 5 dr, 53%) as an off-white solid: M.p. (EtOAc/hexanes) 48-50 º; R_f 0.29 (EtOAc : hexanes 1 : 4); $[\alpha]_D^{25}$ = −64.2 (*c* 1.1, $CHCl_3$); IR 1696 (C=N), 1501, 1464, 1230, 1136 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 6.81 (m, 3H, Ar-H), 4.11 (d, 1H, *J* = 8.9 Hz, C<u>H</u>$_2$OMe), 4.02 (d, 1H, *J* = 3.3 Hz, C<u>H</u>-*i*Pr), 3.86 (d, 1H, *J* = 8.9 Hz, C<u>H</u>$_2$OMe), 3.78 (s, 3H, OMe), 3.67 (s, 9H, 3 x OMe), 3.38 (s, 3H, $CH_2OC\underline{H}_3$), 2.43 (dsept, 1H, *J* = 6.8, 3.3 Hz, *i*-Pr), 1.18 (d, 3H, *J* = 6.9 Hz, *i*-Pr), 0.84 (d, 3H, *J* = 6.7 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) *major isomer* δ 164.4, 162.9, 153.2, 152.3, 131.5, 113.9, 113.2, 112.2, 77.8, 63.0, 61.0, 59.8, 56.3, 55.6, 52.7, 52.6, 30.3, 19.8, 17.4; HRMS (ESI) calcd. $C_{19}H_{29}N_2O_5$: $[M + H]^+$, 365.2076; found $[M + H]^+$, 365.2071.

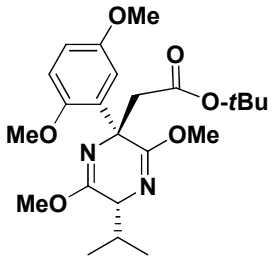
(2*R*,5*R*)-2-(2,5-Dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2-(prop-2-ynyl)-2,5-dihydropyrazine (484e)



484e

Imidate **484e** was prepared according to the general procedure, employing propargyl bromide (0.59 g of an 80% wt in PhMe solution, 4.00 mmol) as the electrophile at −78 ˚C for 1 h. Purification by flash column chromatography (EtOAc : hexanes 1 : 10 to 1 : 5) gave **484e** (0.285 g, >98 : 2 dr, 80%) as a white solid: M.p. (EtOAc/hexanes) 59-60 ˚C; R_f 0.38 (EtOAc : hexanes 1 : 4); $[\alpha]_D^{25}$ = −58.8 (*c* 1.3, $CHCl_3$); IR 1692 (C=N), 1667 (C=N), 1500, 1228, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (m, 3H, Ar-H), 4.16 (d, 1H, *J* = 3.6 Hz, C<u>H</u>-*i*Pr), 3.78 (s, 3H, OMe), 3.72 (s, 6H, 2 x OMe), 3.71 (s, 3H, OMe), 3.21 (dd, 1H, *J* = 16.1, 2.6 Hz, C<u>H</u>$_2$C≡CH), 3.16 (dd, 1H, *J* = 16.1, 2.6 Hz, C<u>H</u>$_2$C≡C), 2.39 (dsept, 1H, *J* = 6.8, 3.6 Hz, *i*-Pr), 1.97 (t, 1H, *J* = 2.6 Hz, C≡C<u>H</u>), 1.18 (d, 3H, *J* = 6.9 Hz, *i*-Pr), 0.84 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 163.0, 153.2, 152.3, 132.1, 144.5, 113.8, 112.6, 80.7, 70.7, 62.5, 61.3, 56.5, 55.6, 52.8, 52.7, 30.7, 19.9, 17.7; HRMS (ESI) calcd. $C_{20}H_{27}N_2O_4$: $[M + H]^+$, 359.1971; found $[M + H]^+$, 359.1967.

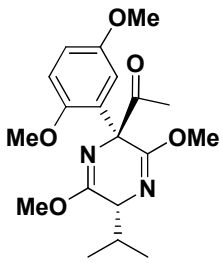
***tert*-Butyl 2-((2*R*,5*R*)-2-(2,5-Dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)acetate (484f)**



484f

Imidate **484f** was prepared according to the general procedure, employing *tert*-butyl bromoacetate (0.59 mL, 4.00 mmol) as the electrophile at −78 ˚C for 3 h. Purification by flash column chromatography (EtOAc : hexanes 1 : 10 to 1 : 5) gave **484f** (0.220 g, >98 : 2 dr, 51%) as a colourless oil; R_f 0.52 (EtOAc : hexanes 1 : 4); $[\alpha]_D^{25}$ = −43.3 (*c* 0.9, $CHCl_3$); IR 1728 (C=O),1691 (C=N),1498, 1356, 1230, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (m, 1H, Ar-H), 6.77 (m, 2H, Ar-H), 3.96 (d, 1H, *J* = 4.6 Hz, C<u>H</u>-*i*Pr), 3.78 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.72 (s, 6H, 2 x OMe), 3.32 (AB quartet, 2H, *J* = 14.1 Hz, CH_2Ph), 2.20 (m, 1H, *i*-Pr), 1.40 (s, 9H, *t*-Bu), 1.08 (d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.80 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 164.1, 162.6, 153.2, 152.4, 132.9, 114.8, 114.7, 113.0, 79.9, 62.2, 61.4, 57.0, 55.6, 52.6, 52.5, 45.1, 31.3, 27.9, 19.9, 18.4; HRMS (ESI) calcd. $C_{23}H_{35}N_2O_6$: $[M + H]^+$, 435.2495; found $[M + H]^+$, 435.2485.

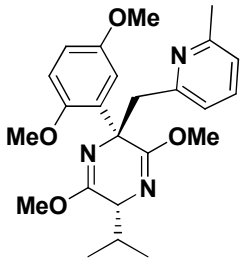
1-((2*R*,5*R*)-2-(2,5-Dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethanone (484g)



484g

Imidate **484g** was prepared according to the general procedure, employing acetyl chloride (0.29 mL, 4.00 mmol) as the electrophile at −78 ˚C for 3 h. Purification by flash column chromatography (EtOAc : hexanes 1 : 5) gave **484g** (0.215 g, 89 : 11 dr, 59%) as a yellow solid: M.p. (EtOAc/hexanes) 83-84 ˚C; R_f 0.33 (EtOAc : hexanes 1 : 4); $[\alpha]_D^{25}$ = −183.3 (*c* 0.9, $CHCl_3$); IR 1679 (C=N), 1630 (C=O), 1487, 1356, 1209, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 7.05 (d, 1H, *J* = 2.9 Hz, Ar-H), 6.87 (m, 2H, Ar-H), 4.80 (d, 1H, *J* = 10.3 Hz, C<u>H</u>-*i*Pr), 3.82 (s, 3H, OMe), 3.80 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.51 (s, 3H, OMe), 2.28 (s, 3H, C<u>H</u>$_3$), 2.39 (dsept, 1H, *J* = 10.3, 6.7 Hz, *i*-Pr), 1.01 (d, 6H, *J* = 6.7 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) *major isomer* δ 172.1, 160.5, 153.5, 151.5, 136.0, 126.3, 116.9, 115.7, 113.7, 112.5, 58.3, 57.2, 56.4, 55.8, 53.6, 26.9, 23.3, 19.3, 18.8; HRMS (ESI) calcd. $C_{19}H_{27}N_2O_5$: $[M + H]^+$, 363.1920; found $[M + H]^+$, 363.1912.

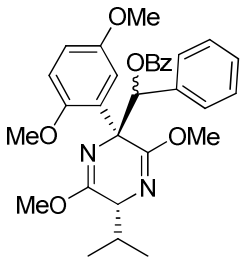
(2*R*,5*R*)-2-(2,5-Dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2-((6-methylpyridin-2-yl)methyl)-2,5-dihydropyrazine (484h)



484h

Imidate **484h** was prepared according to the general procedure, employing 2-(bromomethyl)-6-methylpyridine (0.74 g, 4.00 mmol) in THF (5 mL) as the electrophile at −78 ˚C for 5 h. Purification by flash column chromatography (EtOAc : hexanes 1 : 5 to 1 : 1) gave **484h** (0.300 g, >98 : 2 dr, 71%) as a yellow oil; R_f 0.17 (EtOAc : hexanes 1 : 4); $[\alpha]_D^{25}$ = 3.4 (*c* 1.0, $CHCl_3$); IR 1692 (C=N),1668 (C=N),1497, 1356, 1227, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.18 (d, 1H, *J* = 2.7 Hz, Ar-H), 7.01 (d, 1H, *J* = 7.6, Ar-H), 6.84 (m, 3H, Ar-H), 3.82 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.64 (AB quartet, 2H, *J* = 12.0 Hz, CH_2Ph), 2.51 (s, 3H, CH_3), 2.17 (d, 1H, *J* = 3.2 Hz, C<u>H</u>-*i*Pr), 2.13 (m, 1H, *i*-Pr), 0.93 (d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.73 (d, 3H, *J* = 6.7 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 162.5, 157.4, 156.6, 153.3, 152.5, 135.5, 133.8, 122.4, 120.6, 114.1, 113.3, 112.5, 63.2, 60.0, 56.2, 55.6, 52.6, 52.4, 46.5, 29.8, 24.4, 19.6, 17.4; HRMS (ESI) calcd. $C_{24}H_{32}N_3O_4$: $[M + H]^+$, 426.2393; found $[M + H]^+$, 426.2372.

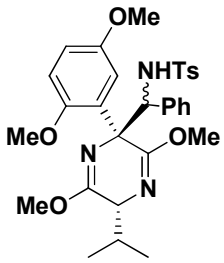
((2*S*,5*R*)-2-(2,5-Dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)(phenyl)methyl benzoate (484i)



484i

Imidate **484i** was prepared according to the general procedure, employing PhCHO (0.41 mL, 4.00 mmol) as the electrophile at −78 ˚C for 12 h. The residue was then taken up in CH_2Cl_2 (5 mL) and benzoyl chloride (0.23 mL, 2 mmol) and DMAP (0.61 g, 5 mmol) added, before the mixture was stirred at room temperature overnight. The mixture was quenched with H_2O (5 mL) and extracted with EtOAc (2 x 5 mL), before being dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography (PhMe) gave a 1 : 1 mixture of benzoyl protected alcohols **484i** (0.366 g, >98 : 2 dr, 69%) as a colourless oil; R_f 0.51(PhMe); $[\alpha]_D^{25}$ = - 103.8 (*c* 1.0, $CHCl_3$); IR 1722 (C=O), 1691(C=N), 1498, 1273, 1238, 1229 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *both isomers* δ 8.02 (d, 2H, *J* = 7.3 Hz, Ar-H), 7.94 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.51 (m, 2H, Ar-H), 7.38 (m, 4H, Ar-H), 7.36 (s, 1H, C<u>H</u>OBz), 7.33 (s, 1H, C<u>H</u>OBz), 7.27 (m, 6H, Ar-H), 7.19 (m, 4H, Ar-H), 6.95 (d, 1H, *J* = 3.0 Hz, Ar-H), 6.92 (d, 1H, *J* = 2.5 Hz, Ar-H), 6.80 (m, 4H, Ar-H), 3.91 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.81 (d, 1H, *J* = 3.8 Hz, CH*i*-Pr), 3.71 (s, 3H, OMe), 3.70 (s, 6H, 2 x OMe), 3.68 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.66 (s, 3H, OMe), 2.58 (d, 1H, *J* = 3.4 Hz, CH*i*-Pr), 2.17 (m, 1H, *i*-Pr), 2.06 (m, 1H, *i*-Pr), 0.94 (d, 3H, *J* = 6.9 Hz, *i*-Pr), 0.91(d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.71(d, 3H, *J* = 6.7 Hz, *i*-Pr), -0.14 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) *both isomers* δ 166.0, 165.9, 164.4, 164.3, 160.9, 159.6, 153.3, 153.0, 152.6, 152.6, 137.8, 137.7, 137.4, 132.7, 132.7, 130.8, 130.7, 129.8, 128.7, 129.1, 128.6, 128.3, 128.3, 128.0, 127.8, 127.8, 127.4, 125.3, 116.2, 114.5, 114.0, 113.7, 113.4, 113.3, 78.4, 77.1, 68.1, 66.7, 60.4, 59.6, 56.9, 56.4, 55.6, 55.5, 52.8, 52.6, 52.4, 52.3, 30.4, 29.8, 21.5, 19.5, 17.4, 15.5. HRMS (ESI) calcd. $C_{31}H_{35}N_2O_6$: $[M + H]^+$, 531.2495; found $[M + H]^+$, 531.2485.

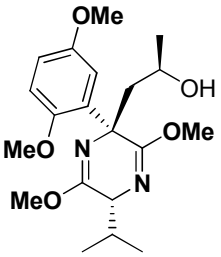
***N*-(((2*S*,5*R*)-2-(2,5-dimethoxyphenyl)-5-*iso*propyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)(phenyl)methyl)-4-methylbenzenesulfonamide (484j)**



484j

Imidate **484j** was prepared according to the general procedure, employing a solution of (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (1.04 g, 4.00 mmol) in THF (5 mL) as the electrophile at −78 ˚C for 12 hours. Purification by flash column chromatography (EtOAc : hexanes 1 : 20 to 1 : 8), followed by recrystallisation from EtOH gave a 87 : 13 unassigned mixture of tosyl amines **484j** (0.411 g, >98 : 2) as a white solid; M.p. (EtOH) 135-136 ºC; R_f 0.47 (EtOAc : hexanes 1 : 4); IR 1690 (C=N), 1498, 1234, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *both isomers* δ 7.32 (m, 3H, Ar-H), 7.09 (m, 7H, Ar-H), 6.94 (m, 10H, Ar-H), 6.82 (dd, 2H, *J* = 9.0, 2.8 Hz, Ar-H), 6.75 (dd, 2H, *J* = 8.9, 3.3 Hz, Ar-H), 6.28 (d, 1H, *J* = 8.1 Hz, C_2H), 5.81 (d, 1H, *J* = 8.6 Hz, NH), 5.78 (d, 1H, *J* = 8.3 Hz, NH), 5.61 (d, 1H, *J* = 8.4 Hz, C_2H), 3.86 (s, 6H, 2 x OMe), 3.80 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.67 (s, 6H, 2 x OMe), 3.51 (s, 3H, OMe), 2.58 (d, 1H, *J* = 3.7 Hz, C<u>H</u>-*i*Pr), 2.46 (d, 1H, *J* = 2.9 Hz, C<u>H</u>-*i*Pr), 2.34 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.07 (m, 1H, *i*-Pr), 1.94 (m, 1H, *i*-Pr), 0.85 (d, 3H, *J* = 7.2 Hz, *i*-Pr), 0.83 (d, 3H, *J* = 7.5 Hz, *i*-Pr), 0.61 (d, 3H, *J* = 6.7 Hz, *i*-Pr), 0.61 (d, 3H, *J* = 6.7 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) *both isomers* δ 165.3, 164.7, 160.7, 160.0, 152.9, 152.7, 152.0, 142.2, 141.9, 138.8, 138.3, 137.1, 136.1, 130.1, 129.2, 129.1, 128.8, 128.7, 128.4, 127.3, 127.0, 126.9, 126.9, 126.8, 126.7, 116.3, 114.8, 114.1, 113.8, 113.7, 113.0, 67.4, 66.7, 61.8, 60.4, 60.4, 60.0, 56.2, 55.9, 55.9, 55.7, 52.9, 52.6, 52.5, 52.5, 30.6, 30.3, 21.3, 21.3, 19.5, 19.5, 17.7, 17.5; HRMS (ESI) calcd. $C_{31}H_{38}N_3O_6S$: $[M + H]^+$, 580.2481; found $[M + H]^+$, 580.2463.

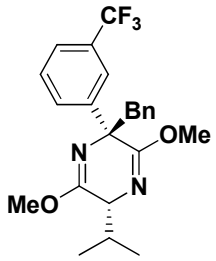
(*R*)-1-((2*R*,5*R*)-2-(2,5-Dimethoxyphenyl)-5-*iso*-propyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)propan-2-ol (484k)



484k

Imidate **484k** was prepared according to the general procedure, employing *R*-propylene oxide (0.28 mL, 4.00 mmol) and $BF_3.OEt_2$ (0.49 mL, 4.00 mmol) as the electrophile at −78 ˚C for 1 h. Purification by flash column chromatography (EtOAc : hexanes 1 : 5 to 1 : 1) gave **484k** (0.186 g, >98 : 2 dr, 50%) as a yellow oil; R_f 0.21 (EtOAc : hexanes 1 : 3); $[\alpha]_D^{25}$ = -61 ºC (*c* 0.7, $CHCl_3$); IR 3433 (OH), 1689 (C=N), 1670 (C=N),1498, 1229, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (m, 2H, Ar-H), 6.77 (dd, 1H, *J* = 8.9, 3.0 Hz, Ar-H), 4.07 (s(br), 1H, OH), 7.23 (d, 1H, *J* = 3.9 Hz, CH*i*-Pr), 3.80 (m, 1H, C<u>H</u>OH), 3.80 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.76 (s, 3H, OMe), 2.41 (m, 2H, CH_2), 1.62 (m, 1H, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 165.0, 153.2, 151.2, 134.5, 114.6, 113.9, 112.8, 66.1, 64.4, 63.1, 56.6, 55.7, 53.0, 52.8, 47.5, 31.5, 23.6, 20.1, 19.4; HRMS (ESI) calcd. $C_{20}H_{31}N_2O_5$: $[M + H]^+$, 379.2233; found $[M + H]^+$, 379.2217.

(2*R*,5*R*)-2-Benzyl-5-*iso*-propyl-3,6-dimethoxy-2-(3-(trifluoromethyl)phenyl)-2,5-dihydropyrazine (486)

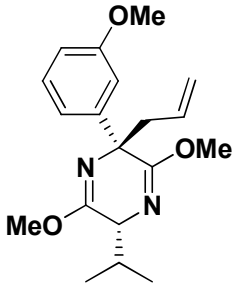


486

n-BuLi (2.14 mL of a 1.4 M solution in hexane, 3.00 mmol) was added drop-wise to imidate **3** (0.18 mL, 1.00 mmol) and 1-chloro-2-(trifluoromethyl)benzene (**479**) (0.23 mL, 1.75 mmol) in THF (5 mL) at −78 ºC. The mixture was maintained at −78 ºC for 30 min, before being allowed to warm to room temperature overnight. The mixture was re-cooled to −78 ˚C, BnBr (0.48 mL, 4.00 mmol) was added to the mixture and stirred at −78 ˚C for 6 h. The mixture was warmed to room temperature and H_2O (5 mL) was added and the mixture extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 20) to give **486** (0.220 g, >98 : 2 dr, 67%) as a yellow solid.

M.p. (EtOAc/hexanes) 31-33 ºC; R_f 0.71 (EtOAc : hexanes 1 : 3); $[\alpha]_D^{25}$ = -46.6 (*c* 1.5, $CHCl_3$); IR 1689 (C=N), 1436, 1328, 1117 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (m, 2H, Ar-H), 7.52 (m, 2H, Ar-H), 7.25 (m, 3H, Ar-H), 7.13 (m, 2H, Ar-H), 3.83 (s, 3H, OMe), 3.75 (d, 1H, *J* = 2.7 Hz, C<u>H</u>-*i*Pr), 3.72 (s, 3H, OMe), 3.15 (AB quartet, 2H, *J* = 8.1 Hz, CH_2Ph), 2.12 (m, 1H, *i*-Pr), 0.91 (d, 3H, *J* = 6.9 Hz, *i*-Pr), 0.54 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ163.8, 161.0, 158.8, 145.2, 136.5, 130.5, 130.4, 128.2, 127.7, 126.6, 125.8 (q, J_{C-F} = 245 Hz), 124.0, 123.8, 64.8, 60.4, 52.5, 52.3, 46.9, 31.1, 19.3, 17.0; ^{19}F NMR (200 MHz, $CDCl_3$) δ −62.8; HRMS (ESI) calcd. $C_{23}H_{26}F_3N_2O_2$: $[M + H]^+$, 419.1946; found $[M + H]^+$, 419.1942.

(2*R*,5*R*)-2-Allyl-5-*iso*-propyl-3,6-dimethoxy-2-(3-methoxyphenyl)-2,5-dihydropyrazine (487)

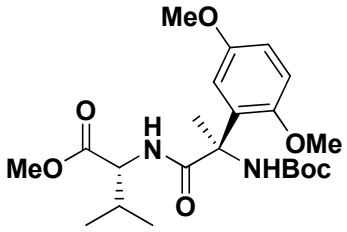


487

sec-BuLi (2.73 mL of a 1.1 M solution in cyclohexane, 3.00 mmol) was added drop-wise to imidate **3** (0.18 mL, 1.00 mmol) and 3-chloroanisole **(477)** (0.21 mL, 1.75 mmol) in THF (5 mL) at −95 ºC. The mixture was maintained at −95 ºC for 30 min, before being allowed to warm to room temperature overnight. The mixture was re-cooled to −78 ˚C before allyl bromide (0.35 mL, 4.00 mmol) was added to the mixture and stirred at −78 ˚C for 6 h. The mixture was warmed to room temperature and H_2O (5 mL) was added and the mixture extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2 : hexanes 1 : 1) to give **487** (0.240 g, >98 : 2 dr, 76%) as a colourless oil.

R_f 0.69 (EtOAc : hexanes 1 : 3); $[\alpha]_D^{25}$ = −101.6 (*c* 0.9, $CHCl_3$); IR 1689 (C=N), 1602, 1434, 1236, 1142 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (t, 1H, *J* = 8.0 Hz, Ar-H), 7.15 (dd, 1H, *J* = 7.9, 0.9 Hz, Ar-H), 7.11 (t, 1H, *J* = 2.0 Hz, Ar-H), 6.81 (dd, 1H, *J* = 8.1, 2.0 Hz, Ar-H), 5.64 (m, 1H, C<u>H</u>=CH_2), 5.09 (m, 2H, CH=C<u>H_2</u>), 3.96 (d, 1H, *J* = 4.1 Hz, C<u>H</u>-*i*Pr), 3.82 (s, 3H, OMe), 3.81 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.03 (dd, 1H, *J* = 13.2, 7.4 Hz, C<u>H_2</u>CH=CH_2), 2.64 (dd, 1H, *J* = 13.1, 7.1 Hz, C<u>H_2</u>CH=CH_2), 2.17 (m, 1H, *i*-Pr), 1.03 (d, 3H, *J* = 6.9 Hz, *i*-Pr), 0.66 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 162.8, 159.1, 145.7, 133.7, 128.7, 119.1, 118.4, 113.0, 111.9, 64.1, 61.2, 55.1, 52.5, 52.5, 46.0, 31.7, 19.6, 17.7; HRMS (ESI) calcd. $C_{19}H_{27}N_2O_3$: $[M + H]^+$, 331.2022; found: $[M + H]^+$, 331.2015.

(*R*)-Methyl 2-((*R*)-2-(*tert*-butoxycarbonylamino)-2-(2,5-dimethoxyphenyl)propanamido)-3-methylbutanoate (488a)

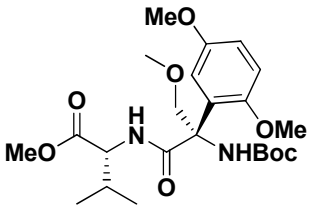


488a

0.5 M HCl (1.9 mL, 0.93 mmol) was added to imidate **484a** (0.138 g, 0.41 mmol) in THF (3 mL), and the resulting mixture stirred at room temperature for 36 h. Saturated aqueous Na_2CO_3 solution was added drop-wise until pH 9. The mixture was poured into H_2O (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (3 mL), and sequentially di-*iso*-propylethylamine (0.16 mL, 0.90 mmol) and Boc_2O (0.19 g, 0.86 mmol) were added. The mixture was stirred at room temperature for 48 h, after which the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2 : MeOH (NH_3) 30:1) to give **488a** (0.134 g, 75%, 96 : 4 dr) as a yellow gum.

R_f 0.74 (CH_2Cl_2 : MeOH 10 : 1); $[\alpha]_D^{25}$ = −12.2 (*c* 0.8, $CHCl_3$); IR 3429 (NH), 1731 (C=O), 1688 (C=O), 1464, 1223, 1168, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 7.11 (d, 1H, *J* = 2.3 Hz, Ar-H), 6.85 (m, 2H, Ar-H), 6.28 (s(br), 2H, 2 x NH), 4.52 (dd, 1H, *J* = 8.7, 5.1 Hz, C<u>H</u>-*i*Pr), 3.82 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.67 (s, 3H, OMe), 2.11 (m, 1H, *i*-Pr), 1.96 (s, 3H, CH_3), 1.35 (s, 9H, Boc), 0.92 (d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.82 (d, 3H, *J* = 6.9 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) *major isomer* δ 174.3, 172.0, 154.2, 153.1, 151.0, 129.6, 115.6, 113.2, 112.2, 79.1, 60.4, 57.2, 55.8, 55.6, 52.0, 31.4, 28.3, 24.3, 19.0, 17.6; HRMS (CI) calcd. $C_{22}H_{34}N_2O_7Na$: $[M + Na]^+$, 461.2264; found $[M + Na]^+$, 461.2204.

(*R*)-Methyl 2-((*S*)-2-(*tert*-Butoxycarbonylamino)-2-(2,5-dimethoxyphenyl)-3-methoxypropanamido)-3-methylbutanoate (488d)

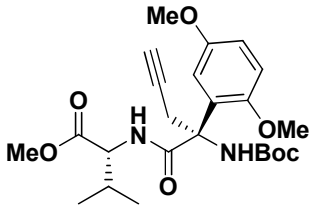


488d

0.5 M HCl (0.62 mL, 0.31 mmol) was added to imidate **484d** (0.050 g, 0.14 mmol) in THF (1 mL), and the resulting mixture stirred at room temperature for 36 h. Saturated aqueous Na_2CO_3 solution was added drop-wise until pH 9. The mixture was poured into H_2O (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (2 mL), and sequentially di-*iso*-propylethylamine (0.050 mL, 0.31 mmol) and Boc_2O (0.064 g, 0.29 mmol) were added. The mixture was stirred at room temperature for 48 h, after which the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2 : MeOH (NH_3) 50:1) to give **488d** (0.040 g, 61%, 95 : 5 dr) as a colourless oil.

R_f 0.19 (CH_2Cl_2 : MeOH 20 : 1); $[\alpha]_D^{25}$ = −1.3 (*c* 1.05, $CHCl_3$); IR 3412 (NH), 1743 (C=O), 1716 (C=O),1682 (C=O), 1496, 1467, 1229, 1169, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 7.05 (d, 1H, *J* = 2.52 Hz, Ar-H), 6.83 (m, 2H, Ar-H), 6.33 (s(br), 1H, NH), 4.56 (dd, 1H, *J* = 8.8, 5.0 Hz, CH*i*-Pr), 4.39 (d, 1H, *J* = 9.3 Hz, C$\underline{H}_2$OMe), 3.92 (s(br), 1H, C$\underline{H}_2$OMe), 3.80 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.42 (s, 3H, OMe), 2.13 (m, 1H, *i*-Pr), 1.37 (s, 9H, Boc), 0.93 (d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.84 (d, 3H, *J* = 6.9 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) *major isomer* δ 172.0, 171.4, 154.4, 153.1, 151.4, 126.7, 116.0, 113.5, 112.2, 79.2, 73.5, 63.3, 59.0, 57.6, 55.9, 55.5, 51.9, 31.3, 28.3, 18.9, 17.5; HRMS (ESI) calcd. $C_{23}H_{36}N_2O_8Na$: $[M + Na]^+$, 491.2369; found $[M + Na]^+$, 491.2351.

(*R*)-Methyl 2-((*R*)-2-(*tert*-Butoxycarbonylamino)-2-(2,5-dimethoxyphenyl)pent-4-ynamido)-3-methylbutanoate (488e)

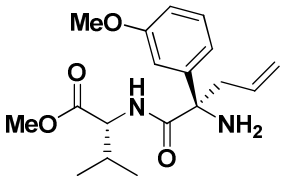


488e

0.5 M HCl (0.40 mL, 0.20 mmol) was added to imidate **484e** (0.032 g, 0.089 mmol) in THF (1 mL), and the resulting mixture stirred at room temperature for 36 h. Saturated aqueous Na_2CO_3 solution was added drop-wise until pH 9. The mixture was poured into H_2O (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (1.5 mL), and sequentially di-*iso*-propylethylamine (0.034 mL, 0.20 mmol) and Boc_2O (0.041 g, 0.19 mmol) were added. The mixture was stirred at room temperature for 48 h, after which the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2 : MeOH (NH_3) 50:1) to give **488e** (0.032 g, 72%, > 98 : 2 dr) as a colourless oil.

R_f 0.24 (CH_2Cl_2 : MeOH 20 : 1); $[\alpha]_D^{25}$ = −12.4 (*c* 0.7, $CHCl_3$); IR 3405 (NH), 1740 (C=O), 1712 (C=O),1682 (C=O), 1496, 1468, 1226 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H, Ar-H), 7.00 (s(br), 1H, NH), 6.86 (m, 2H, Ar-H), 6.48 (s(br), 1H, NH), 4.55 (dd, 1H, *J* = 8.3, 4.9 Hz, CH*i*-Pr), 3.80 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.60 (br d, 1H, *J* = 15.7 Hz, C$\underline{H}_2$C≡CH), 3.40 (br d, 1H, *J* = 14.8 Hz, C$\underline{H}_2$C≡CH), 2.15 (m, 1H, *i*-Pr), 2.08 (s, 1H, C≡C$\underline{H}$), 1.42 (s, 9H, Boc), 0.95 (d, 3H, *J* = 6.9 Hz, *i*-Pr), 0.87 (d, 3H, *J* = 6.9 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 171.3, 154.1, 153.2, 150.8, 127.1, 115.4, 114.1, 112.5, 79.9, 79.5, 72.0, 62.9, 57.7, 55.9, 55.6, 51.9, 31.4, 28.3, 26.2, 19.0, 17.5; HRMS (ESI) calcd. $C_{24}H_{34}N_2O_7Na$: $[M + Na]^+$, 485.2264; found $[M + Na]^+$, 485.2246.

(*R*)-Methyl 2-((*R*)-2-Amino-2-(3-methoxyphenyl)pent-4-enamido)-3-methylbutanoate (489)

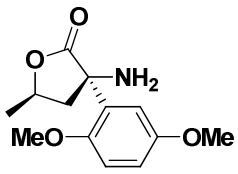


489

0.5 M HCl (0.69 mL, 0.34 mmol) was added to imidate **487** (0.051 g, 0.15 mmol) in THF (1.5 mL), and the resulting mixture stirred at room temperature for 36 h. Saturated aqueous Na_2CO_3 solution was added drop-wise until pH 9. The mixture was poured into H_2O (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 5) to give **489** (0.020 g, 40%, 95 : 5 dr) as a colourless oil.

R_f 0.54 (EtOAc : hexanes 1 : 1); $[\alpha]_D^{25}$ = 3.3 (*c* 1.6, $CHCl_3$); IR 3367 (NH), 1742 (C=O), 1675 (C=O), 1493, 1438, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 8.10 (d, 1H, *J* = 9.0 Hz, NH), 7.29 (m, 1H, Ar-H), 7.19 (dd, 2H, *J* = 7.8, 1.0 Hz, Ar-H), 6.84 (m, 1H, Ar-H), 5.70 (m, 1H, C<u>H</u>=CH_2), 5.22 (m, 2H, C<u>H</u>$_2$CH=CH_2), 4.45 (dd, 1H, *J* = 9.1, 4.9 Hz, C<u>H</u>*i*-Pr), 3.83 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.20 (dd, 1H, *J* = 13.5, 6.3 Hz, CH=C<u>H</u>$_2$), 2.71 (dd, 1H, *J* = 13.4, 8.3 Hz, CH=C<u>H</u>$_2$), 2.15 (m, 1H, *i*-Pr), 1.80 (s(br), 2H, NH_2), 0.83 (d, 3H, *J* 6.9 Hz, *i*-Pr), 0.80 (d, 3H, *J* = 6.9 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) *major isomer* δ 174.2, 172.5, 159.7, 144.5, 133.6, 129.4, 120.1, 117.8, 112.8, 111.6, 62.3, 57.0, 55.2, 52.0, 44.9, 31.2, 18.9, 17.5; HRMS (ESI) calcd. $C_{18}H_{27}N_2O_4$: $[M + H]^+$, 335.1971; found: $[M + H]^+$, 335.1960.

(3*R*,5*R*)-3-Amino-3-(2,5-dimethoxyphenyl)-5-methyldihydrofuran-2(3H)-one (491)

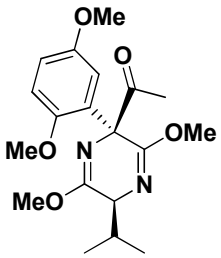


491

0.5 M HCl (0.23 mL, 0.11 mmol) was added to imidate **484k** (0.020 g, 0.050 mmol) in THF (0.5 mL), and the resulting mixture stirred at room temperature for 48 h. Saturated aqueous Na_2CO_3 solution was added drop-wise until pH 9. The mixture was poured into H_2O (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (CH_2Cl_2 : MeOH (NH_3) 40:1) to give **491** (0.010 g, 80%, 96% ee) as a colourless oil.

R_f 0.48 (CH_2Cl_2 : MeOH (NH_3) 20:1); $[\alpha]_D^{25}$ = -13.6 (*c* 1.4, $CHCl_3$); IR 2932(NH), 1760 (C=O), 1494, 1229 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, 1H, *J* = 2.9 Hz, Ar-H), 6.89 (d, 1H, *J* = 8.8 Hz, Ar-H), 6.83 (dd, 1H, *J* = 8.9, 2.9 Hz, Ar-H), 4.52 (m, 1H, C<u>H</u>CH_3), 3.86 (s, 3H, OMe), 3.80 (s, 3H, OMe), 2.90 (dd, 1H, *J* = 13.2, 6.4 Hz, C<u>H</u>$_2$), 2.04 (dd, 1H, *J* = 13.1, 8.4 Hz, C<u>H</u>$_2$), 1.84 (s(br), 2H, NH_2), 1.49 (d, 3H, *J* 6.2 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.5, 153.7, 150.4, 131.6, 113.3, 113.0, 112.5, 62.3, 60.4, 55.9, 55.8, 46.3, 14.2; HRMS (ESI) calcd. $C_{13}H_{18}NO_4$: $[M + H]^+$, 252.1236; found $[M + H]^+$, 252.1231. The enantiomeric excess was determined by HPLC. [CHIRALPACK® IC, 254 nm, hexane : *i*-PrOH = 60 : 40, 1.0 mL/min]: 11.146 min (major), 16.452 min (minor).

1-((2*R*,5*S*)-2-(2,5-Dimethoxyphenyl)-5-*iso*propyl-3,6-dimethoxy-2,5-dihydropyrazin-2-yl)ethanone (492)

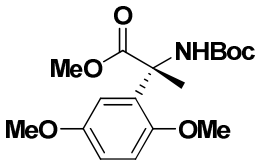


492

0.5 M HCl (0.55 mL, 0.27 mmol) was added to imidate **484g** (0.044 g, 0.12 mmol) in THF (2 mL), and the resulting mixture stirred at room temperature for 36 h. Saturated aqueous Na_2CO_3 solution was added drop-wise until pH 9. The mixture was poured into H_2O (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 8) to give **492** (0.042 g, 95%, 88 : 12 dr) as a yellow oil.

R_f 0.55 (EtOAc : hexanes 1 : 4); $[\alpha]_D^{25}$ = 13.7 (*c* 1.0, $CHCl_3$); IR 1747 (C=O), 1681 (C=N), 1503, 1416, 1223, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major isomer* δ 7.15 (d, 1H, *J* = 3.0 Hz, Ar-H), 6.87 (d, 1H, *J* = 8.9 Hz, Ar-H), 6.82 (dd, 1H, *J* = 8.9, 3.0 Hz, Ar-H), 4.30 (d, 1H, *J* = 10.5 Hz, C<u>H</u>-*i*Pr), 3.82 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.63 (s, 3H, OMe), 2.74 (m, 1H, *i*-Pr), 2.40 (s, 3H, C<u>H</u>$_3$), 1.16 (d, 3H, *J* = 6.5 Hz, *i*-Pr), 0.82 (d, 3H, *J* = 6.8 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) *major isomer* δ 169.7, 153.7, 151.2, 143.9, 137.4, 124.6, 116.3, 115.6, 113.9, 112.9, 62.4, 60.9, 56.6, 55.8, 52.4, 28.9, 20.9, 19.6, 19.0, 14.7; MS (ESI) calcd. $C_{19}H_{27}N_2O_5$: $[M + H]^+$, 363; found: $[M + H]^+$, 363.

(*R*)-Methyl 2-(*tert*-Butoxycarbonylamino)-2-(2,5-dimethoxyphenyl)propanoate (495)

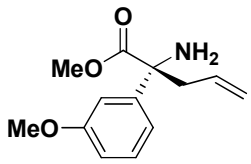


495

Imidate **484a** (0.10 g, 0.30 mmol) was stirred in 6 M H_2SO_4 (1 mL) at room temperature for 3 days. Saturated aqueous Na_2CO_3 solution was added drop-wise until pH 9. The mixture was poured into H_2O (5 mL), and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was re-dissolved in CH_2Cl_2 (2 mL), and sequentially di-*iso*-propylethylamine (0.11 mL, 0.66 mmol) and Boc_2O (0.14 g, 0.63 mmol) were added. The mixture was stirred at room temperature for 48 h, after which the mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 5) to give **495** (0.057 g, 56%, 90% ee) as a colourless oil.

R_f 0.54 (EtOAc : hexanes 1 : 3); $[\alpha]_D^{25}$ = -36.8 (*c* 0.6, $CHCl_3$); IR 3435 (NH), 1741 (C=O), 1717 (C=O), 1495, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H, Ar-H), 6.80 (s(br), 2H, Ar-H), 6.14 (s, 1H, NH), 3.80 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.71 (s, 3H, OMe), 1.97 (s, 3H, CH_3), 1.33 (s, 9H, Boc); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 154.0, 153.2, 150.7, 130.6, 115.4, 112.6, 112.2, 79.2, 59.4, 56.2, 55.6, 52.8, 28.3, 22.6; HRMS (ESI) calcd. $C_{17}H_{25}NO_6Na$: $[M + Na]^+$, 362.1580; found $[M + Na]^+$, 362.1563. The enantiomeric excess was determined by HPLC. [CHIRALPACK® IC, 254 nm, hexane : *i*-PrOH = 90 : 10, 1.0 mL/min]: 8.533 min (major), 10.813 min (minor).

(*R*)-Methyl 2-Amino-2-(3-methoxyphenyl)pent-4-enoate (490)

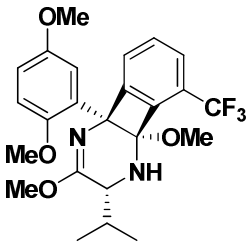


490

Imidate **487** (0.024 g, 0.073 mmol) was stirred in 6 M H_2SO_4 (1 mL) at room temperature for 3 days. Saturated aqueous Na_2CO_3 solution was added drop-wise until pH 9. The mixture was poured into H_2O (5 mL), and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 3) to give **490** (0.010 g, 58%, 90% ee) as a colourless oil.

R_f 0.65 (EtOAc : hexanes 1 : 1); $[\alpha]_D^{25}$ = 12.1 (*c* 1.4, $CHCl_3$); IR 2963 (NH), 1731 (C=O), 1493, 1438, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 1H, Ar-H), 7.14 (m, 2H, Ar-H), 6.89 (dd, 1H, *J* = 7.8, 2.3 Hz, Ar-H), 5.72 (m, 1H, C<u>H</u>=CH_2), 5.21 (m, 2H, C<u>H</u>$_2$CH=CH_2), 3.85 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.00 (dd, 1H, *J* = 13.6, 6.7 Hz, C=C<u>H</u>$_2$), 2.69 (dd, 1H, *J* = 13.7, 7.8 Hz, C=C<u>H</u>$_2$), 1.91 (s(br), 2H, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 159.7, 144.4, 132.9, 129.4, 120.0, 117.7, 112.7, 111.5, 63.1, 55.3, 52.6, 44.6; HRMS (ESI) calcd. $C_{13}H_{18}NO_3$: $[M + H]^+$, 236.1287; found $[M + H]^+$, 236.1285. The enantiomeric excess was determined by HPLC. [CHIRALPACK® IC, 254 nm, hexane : *i*-PrOH = 60 : 40, 1.0 mL/min]: 3.773 min (major), 15.399 min (minor).

Adduct 497



497

sec-BuLi (2.1 mL of a 1.3 M solution in cyclohexane, 2.75 mmol) was added drop-wise to imidate **3** (0.18 mL, 1.0 mmol) and 2-chloro-1, 4-dimethoxybenzene **(388)** (0.21 mL, 1.5 mmol) in THF (5 mL) at −95 ºC. The mixture was maintained at −95 ºC for 30 min, before being allowed to warm to room temperature overnight and then re-cooled to −78 ºC. A solution of 1-chloro-2-(trifluoromethyl)benzene **(379)** (0.23 mL, 1.75 mmol) in THF (2.5 mL) at −78 ºC was transferred *via* cannula to the reaction flask. *n*-BuLi (1.25 mL of a 1.6 M solution in hexane, 2 mmol) was added drop-wise to the reaction and stirred at −78 ºC for 30 minutes before the reaction was allowed to warm to room temperature. Saturated aqueous NH_4Cl solution (5 mL) was added and the mixture extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc : hexanes 1 : 10) to give **497** (0.093 g, 20%) as a yellow oil.

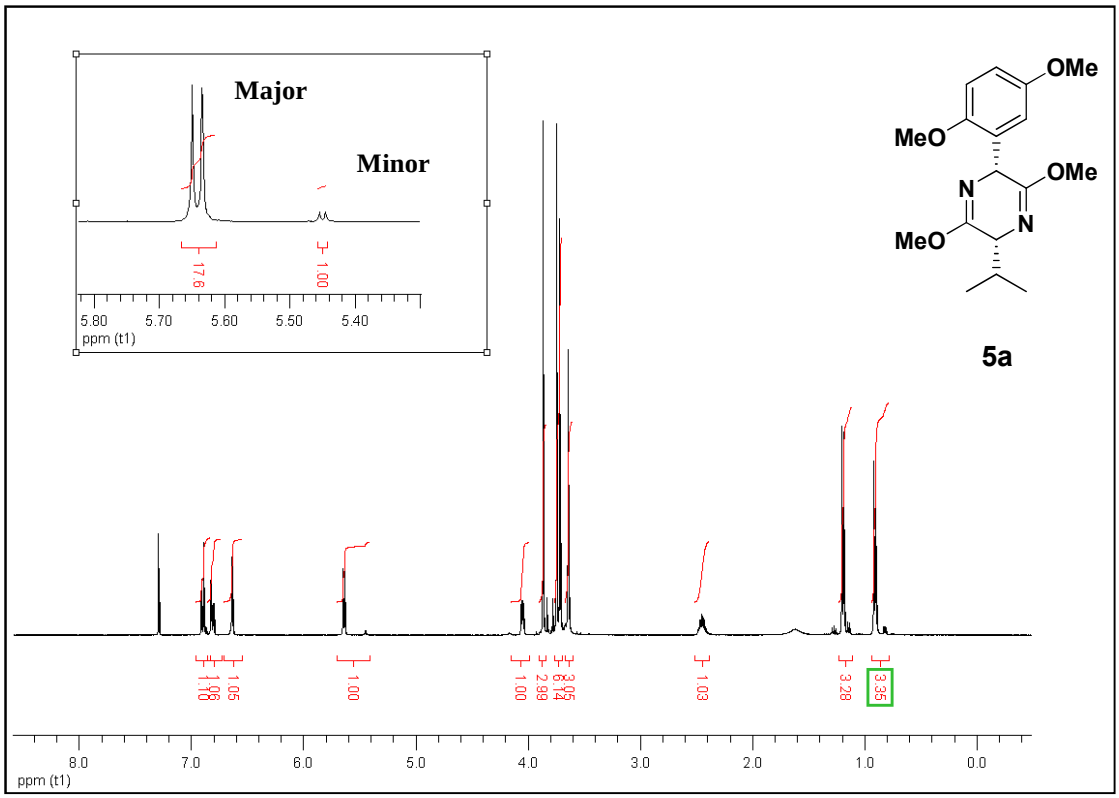
R_f 0.37 (EtOAc : hexane 1 : 5); $[\alpha]_D^{25}$ = 111.6 (*c* 0.3, $CHCl_3$); IR 2853, 1666 (C=N), 1498, 1220, 1130 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 1H, *J* = 7.5 Hz, Ar-H), 7.64 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.50 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.09 (d, 1H, *J* = 2.9 Hz, Ar-H), 6.94 (d, 1H, *J* = 8.9 Hz, Ar-H), 6.87 (dd, 1H, *J* = 8.9, 3.0 Hz, Ar-H), 3.84 (s, 3H, OMe), 3.75 (d, 1H, *J* = 3.5 Hz, CH*i*-Pr), 3.75 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.40 (s, 3H, OMe), 3.22 (s (br), 1H, NH), 2.32 (m, 1H, *i*-Pr), 1.10 (d, 3H, *J* = 6.8 Hz, *i*-Pr), 0.05 (d, 3H, *J* = 6.5 Hz, *i*-Pr); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 153.5, 152.3, 146.1, 137.2, 128.4, 127.9 (d, $J_{C\text{-}F}$ = 33.1 Hz), 127.3, 126.3 (d, $J_{C\text{-}F}$ = 5.5 Hz), 125.9, 123.7 (q, $J_{C\text{-}F}$ = 274.0 Hz), 114.4, 112.9, 112.5, 95.9, 69.2, 66.1, 56.2, 55.7, 53.1, 51.3, 26.0, 23.7, 15.3; ^{19}F NMR (200 MHz, $CDCl_3$) δ –57.6; HRMS (ESI) calcd. $C_{24}H_{28}F_3N_2O_4$: $[M + H]^+$, 465.2001; found $[M + H]^+$, 465.1989.

Appendices

Appendix 1

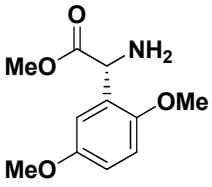
^{1}H NMR for **5a** showing major and minor diastereoisomer

$CDCl_3$, 400 MHz



Appendix 2

HPLC traces, showing lack of racemisation for compounds **5a**, **5f** and **5j**

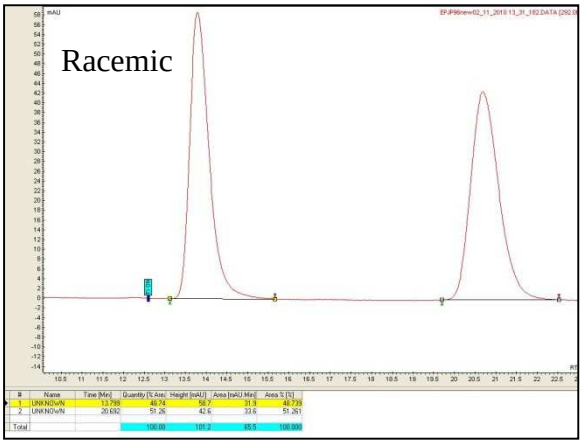


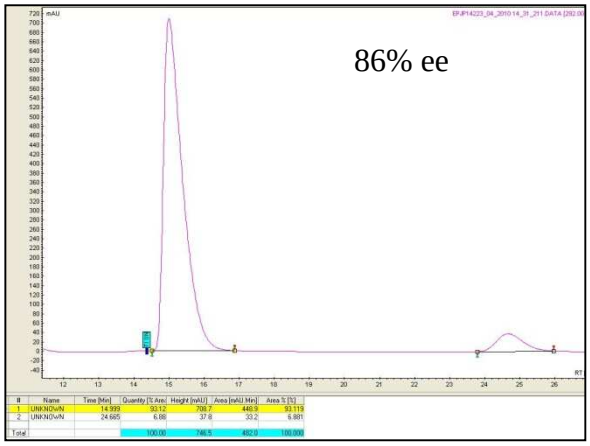
448

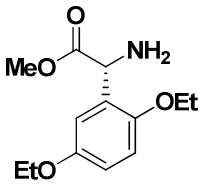
Derived from **5a**, 94 : 6 dr.

Peak	Time	Area
1	14.999	93.119
2	24.665	6.881

CHIRALPACK® IC, 292 nm, hexane : *iso*-propanol = 60 : 40, 1.0 mL/min



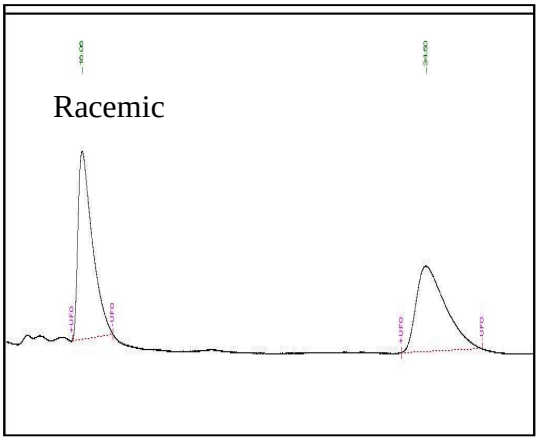


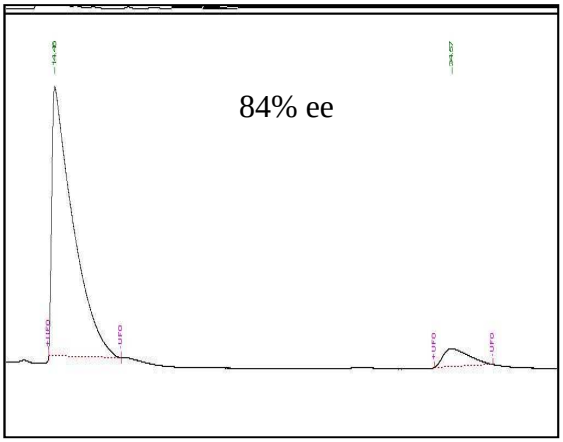


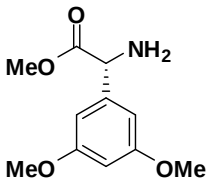
Derived from **5f**, 92 : 8 dr.

Peak	Time	Area
1	14.463	92.46
2	34.465	7.54

CHIRALPACK® IC, 254 nm, hexane : *iso*-propanol = 60 : 40, 1.0 mL/min



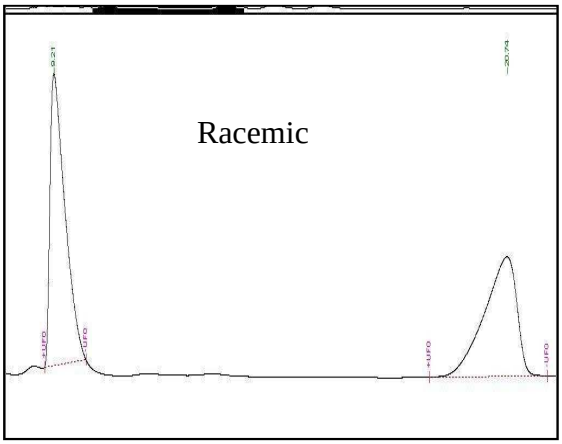


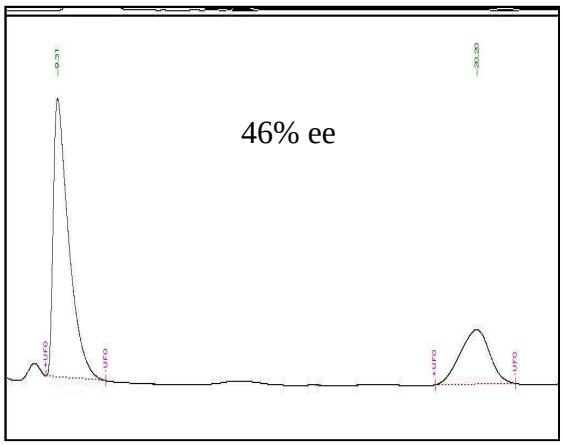


Derived from **5j**, 74 : 26 dr

Peak	Time	Area
1	9.312	72.76
2	20.203	27.24

CHIRALPACK® IC, 254 nm, hexane : *iso*-propanol = 60 : 40, 1.0 mL/min





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