

New Methods for the Synthesis of Aromatic Compounds

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by

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Declaration

The work described in this thesis is entirely my own, except where I have acknowledged help from co-workers or given reference to a published source in the literature.

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Abstract

New Methods for the Synthesis of Aromatic Compounds

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Introduction

The introduction describes the importance of arylamine compounds to society and provides a brief overview of the methods available for their synthesis. The application of metathesis catalysis to the *de novo* synthesis of heteroaromatic compounds is also described.

Results and discussion

The first section describes efforts towards the *de novo* synthesis of arylamines using a cross metathesis/oxidation protocol to form a 1,5-unsaturated dicarbonyl followed by an amine mediated cyclisation. The scope with respect to the 1,5-unsaturated dicarbonyl and amine is covered as well as the utility of some of the products. The section concludes with a modification of the Bohlmann Rahtz pyridine synthesis to furnish arylamines.

The next section describes the applications of our methodology to the synthesis of naphthylamines, specifically using the palladium catalysed α-arylation reaction. A discussion of the α-arylation reaction is included as well as our efforts to explore the scope of the reaction.

The third section follows our efforts to apply this methodologyy to the synthesis of five benzo[*c*]phenanthridine alkaloids including the first reported synthesis of maclekarpine B and C.

The final section concludes with a discussion of our efforts towards the *de novo* synthesis of furans bearing a benzylic stereocentre.

Abbreviations

Ac	Acetyl
AIBN	Azobisisobutyronitrile
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
br.	Broad
C	Celsius
c./conc.	Concentrated
Ar	Aromatic carbon atom
Cbz	Carboxybenzyl
cm^{-1}	Wavenumber
COSY	Correlated spectroscopy
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DCE	Dichloroethane
DCM	Dichloromethane
de novo	Latin: beginning again
DMA	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
D*t*BPF	1,1'-Bis(di-*tert*-butylphosphino)ferrocene
equiv.	Equivalent(s)
ESI^+	Electrospray ionisation (positive ion detection)
Et	Ethyl
et al.	*et alii* (Latin: and others)

FI^+	Field ionisation (positive ion detection)
g	Gram(s)
h	Hour(s)
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMDS	Hexamethyldisilazide
Hz	Hertz
I	*Iso*
IHAS	intramolecular homolytic aromatic substitution
in situ	Latin: in position
in vacuo	Latin: in a vacuum
IR	Infrared
J	Coupling constant (Hz)
LDA	Lithium diisopropylamide
M	Molar
Me	Methyl
mg	Milligram(s)
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
mol%	Molar percent
m.p.	Melting point
MVK	Methyl vinyl ketone
m/z	Mass to charge ratio
N	*Normal*
NHC	N-heterocyclic carbene
NMO	*N*-Methylmorpholine N-oxide
NMR	Nuclear magnetic resonance

nOe	Nuclear Overhauser effect
p	*para*
Ph	Phenyl
Phth	Phthalimide
pH	$-\log_{10}[H_3O^+]$
pK_a	$-\log_{10}[K_a]$
ppm	Parts per million
PPTS	Pyridinium p-toluenesulfonate
pr	Propyl
R	Generic alkyl group
RCM	Ring Closing Metathesis
rr	Regioisomer ratio
rt	Room temperature
RSM	Recovered starting material
S_EAr	Electrophilic aromatic substitution
sept.	Septet
S_NAr	Nucleophilic aromatic substitution
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
$S_{RN}1$	Radical-nucleophilic aromatic substitution
t/tert	*tertiary*
Tf/Triflate	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl

Ts	Toluene-4-sulfonyl
UV	Ultraviolet
via	Latin: by way of
X	Generic heteroatom substituent, often a halogen/*pseudo*halogen
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-tri*iso*propylbiphenyl
Δ	reflux
λ_{max}	Wavelength of maximum ultraviolet intensity
μW	Microwave
υ_{max}	Infrared absorption maximum

Chapter 1: Introduction

1.1 Arylamines

Arylamines can be found in a wide range of compounds, from medicines to materials to natural products and because of this, new methods for their efficient and selective synthesis is of continued interest.

Figure 1 displays some examples illustrating not only the importance of arylamines but also the breadth of their utility. Lavendamycin (**1**) is isolated from *Streptomyces lavendulae* and has demonstrated antibacterial and anticancer activity.[1,2] Dihydrosanguinarine (**2**) comes from a family of alkaloids collectively known as the benzo[c]phenanthridines and is discussed further in the thesis (Chapter 2.3). Bicalutamide (**3**) is used in the treatment of prostate cancer[3] and had grossed over $840 million sales by 2009.[4] Erlotinib (**4**) is used to treat non-small cell lung cancer, pancreatic cancer and several other types of cancer and had grossed over $1080 million sales by 2009.[4] Spironapthooxazine (**5**) is an example of a photochromic material which exists in two different forms based on the level of its exposure to UV radiation.[5]

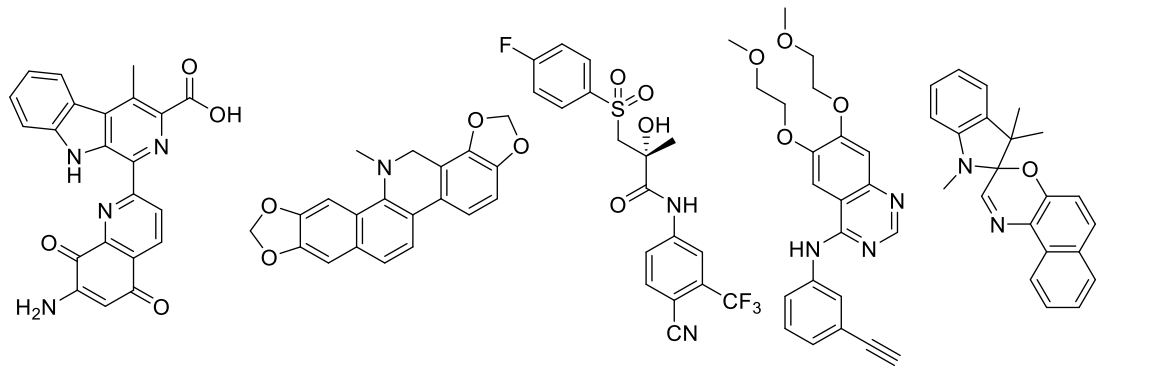
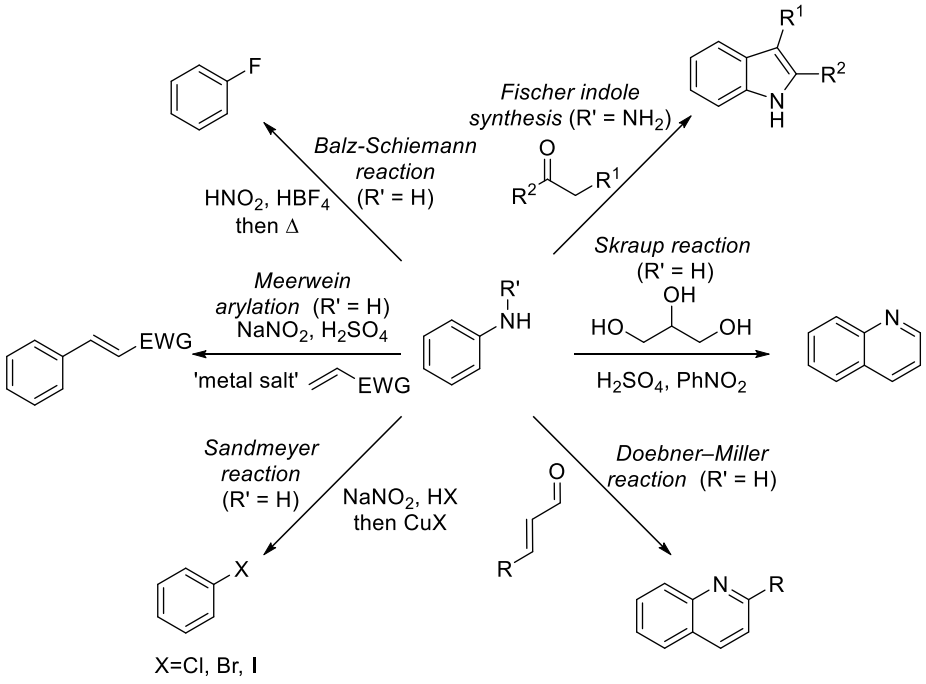


Figure 1 *Selected important arylamines.*

Not only are arylamines found in a wide range of materials and biologically important compounds they are also valuable intermediates in the synthesis of a range of heterocycles and offer a useful handle for further manipulation. They are key intermediates in the Skraup and Doebner-Miller quinoline synthesis and in many indole synthesise including the

classical Fisher indole synthesis. Using reactions such as the Sandmeyer reaction, Balz-Schiemann reaction and the Meerwien arylation, they can be transformed, through their diazonium salt, to a whole range of useful compounds (**Scheme 1**).



Scheme 1 *Some examples of arylamines as intermediates.*

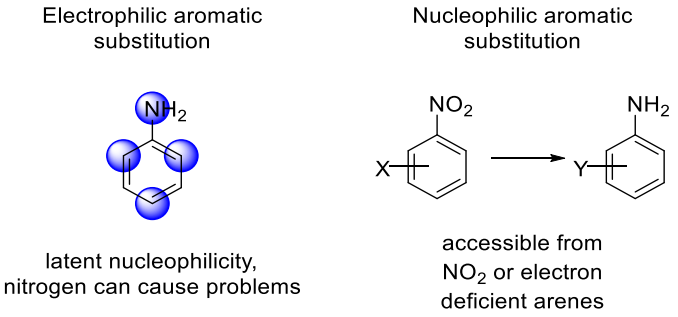
1.2 Current approaches

Due to the importance of arylamines, *vide supra*, they have received a large amount of interest from the synthetic community, and as such there are a number of useful methods for their synthesis.

1.2.1 Classical Methods

One method to access functionalised arylamines is to take advantage of the latent nucleophilicity of aniline. The nitrogen is *ortho*/*para*-directing, however problems can occur as the nitrogen itself is also nucleophilic. An alternative strategy is to acylate the nitrogen which reduces its nucleophilicity. Regioselectivity is also a problem and the system's substitution pattern is dictated by the substituents on the ring, making some patterns difficult to access (**Scheme 2**).

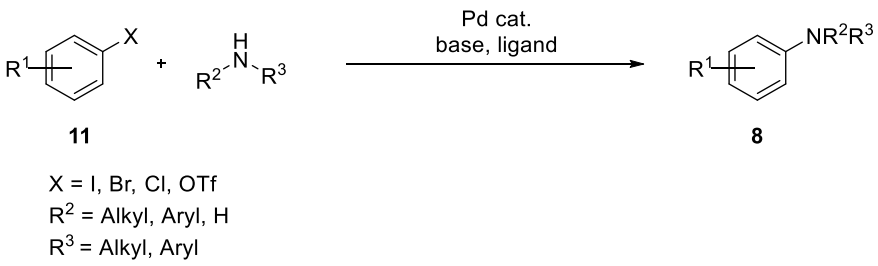
Synthesis of arylamines *via* electrophilic aromatic substitution, which involves a nitration and a reduction, are incompatible with many functional groups due to the harsh nitration and reductive conditions required. In addition, the synthesis can often require several protection/deprotection steps and it relies upon the desirable arene ring with a suitable leaving group attached being accessible (**Scheme 2**).



Scheme 2 *Functionalization of arylamines using classical chemistry.*

1.2.2 Buchwald Hartwig reaction

Since the discovery of the amination of aryl halides in 1994 by the groups of John Hartwig[6] and Stephen Buchwald,[7] the synthesis of arylamines has undergone a paradigm shift from classical methods to palladium-catalysed methods. The procedure involves the coupling of aryl halides **11** and amines **8** and boasts high yields and excellent substrate scope and regioselectivities. Furthermore, the reaction has found uses in natural product synthesis, drug candidate synthesis and materials chemistry (**Scheme 3**).[8]



Scheme 3 *Buchwald-Hartwig amination reaction.*

The mechanism has been studied intensively and a unified theory was published from the labs of Buchwald and Hartwig in 2006.[9] The order of steps was determined when using

2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) as the ligand. The first step of the catalytic cycle is the oxidative insertion of the palladium(0) species, formed by the dissociation of one BINAP ligand, to the aryl halide to form aryl palladium species **6**; this is also the rate determining step for this catalytic cycle. The second step is the formation of the palladium(II) aryl amide intermediate **7** *via* displacement of the halide by an amine. The final step is the reductive elimination which results in the formation of the desired arylamine **8** and regeneration of the palladium(0) catalyst. (**Figure 2**).

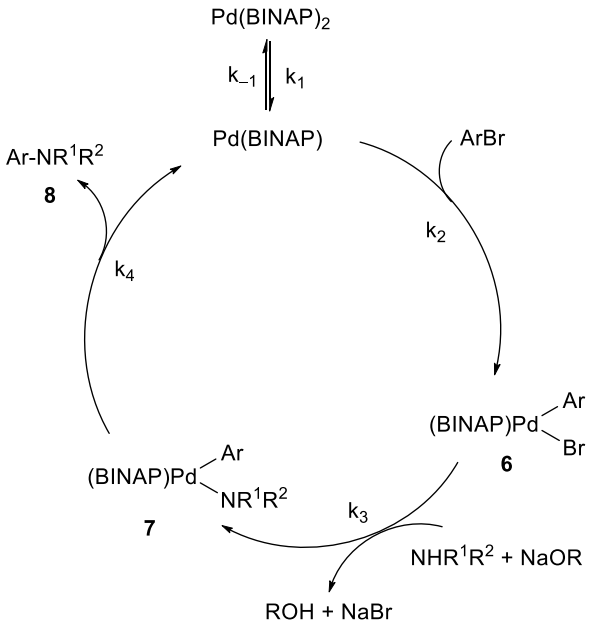


Figure 2 *Catalytic cycle of the Buchwald-Hartwig reaction.*

The first report of palladium catalysed C-N bond formation was reported by Migita and co-workers in 1983 required the use of heat and moisture sensitive tributyltin amides.[10] It was not until Buchwald and Hartwig employed the use of strong base to deprotonate the amine and form the corresponding amide that the method became synthetically viable. This was because the method now avoided the use of sensitive tributyltin amides. Since this discovery, most developments have been achieved by implementing new classes of ligands including BINAP,[11] 1,1'-bis(diphenylphosphino)ferrocene (dppf),[12] Xantphos,[13] more electron-rich chelating phosphines such as Josiphos,[14,15] dialkylbiaryl phosphines such as

Davephos,[16] N-heterocyclic carbenes[17] and trialkylphosphines.[18] However, their discovery and effects are beyond the scope of this report (**Figure 3**).

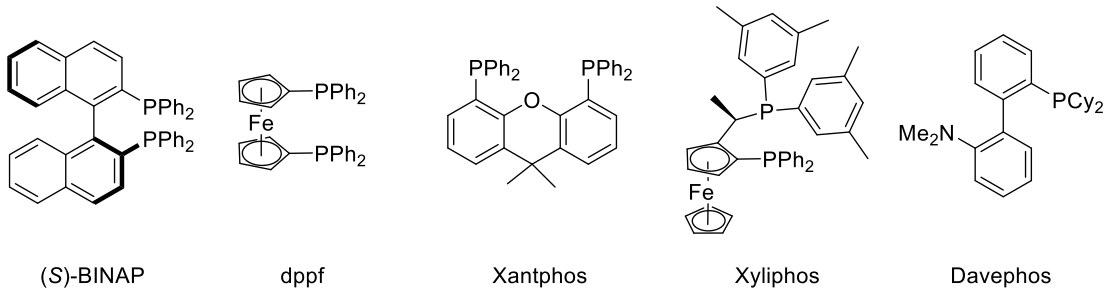
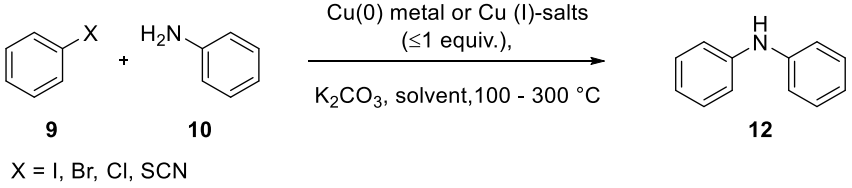


Figure 3 *Selected examples of common ligands used in the Buchwald-Hartwig amination reaction.*

The scope of the reaction has expanded over its development to include the coupling of aryl chlorides, electron deficient arenes as well as sterically demanding aryl halides with various amines, including ammonia equivalents and chiral amines.[8]

1.2.3 Ullmann biarylamine synthesis

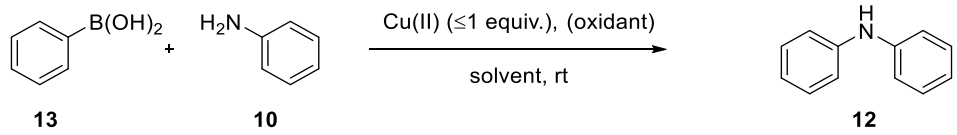
The copper-catalysed Ullmann biarylamine synthesis is also a useful strategy for the synthesis of substituted arylamines. First reported for the synthesis of biaryl ethers by Ullmann[19] it was quickly expanded to include the synthesis of biarylamines by Goldberg.[20] The coupling is between an aryl halide or aryl thiocyanate **9** and an arylamine **10** and the products are biarylamines **12**. Typical conditions require high temperatures (between 100 °C and 300 °C), K_2CO_3 as a base, a copper catalyst, inert reaction conditions (due to oxidation of intermediates) and a solvent with a lone pair to stabilise the intermediates (**Scheme 4**).[21]



Scheme 4 *Ullmann biarylamine synthesis.*

1.2.4 Chan-Lam coupling

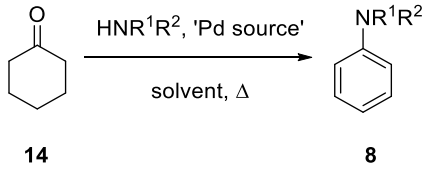
Some of the drawbacks of the Ullmann biarylamine synthesis have been addressed in the Chan-Lam coupling.[22] Here, a boronic acid **13** is used in place of the aryl halide and coupled with an arylamine **10** to give a biarylamine **12**. One of the advantages of the Chan-Lam coupling is that it can be performed at room temperature under an atmosphere of air. As the reaction uses a boronic acid, the copper species is not oxidised during the reaction and so must be used stoichiometrically or the reaction performed in the presence of a suitable oxidant, which can be oxygen (**Scheme 5**). The scope of the reaction has since been improved to include aliphatic amines still under mild conditions.[23]



Scheme 5 *Cham-Lam coupling.*

1.2.5 Dehydrogenative aromatisation

First reported between cyclohexanone and a nitroarene by Makosza,[24] dehydrogenative aromatization provides another useful synthesis of arylamines (**Scheme 6**).



Scheme 6 *Dehydrogenative aromatisation.*

Since its inception, the method has been expanded to using amines with stoichiometric metals, TiCl[25] or palladium acetate.[26] Catalytic methods have been developed but require higher temperatures. Cossy and co-workers employed catalytic palladium on carbon with a nitrobenzene oxidant to perfom the transformation.[27] Yoshikai and co-workers described the transformation using palladium acetate as the catalyst and an oxygen atmosphere for the

reoxidant; they also found the addition of Bu_4NBr significantly increased the rate of reaction.[28] Li and co-workers found success with similar aerobic conditions, using a $[(PMePh_2)_2PdCl_2]$ catalyst with a benzoic acid additive.[29] Access to anilines was also reported by Stahl and co-workers under a modification of the Semmler−Wolff reaction which proceeded under mild conditions.[30]

1.2.6 *De novo* methods

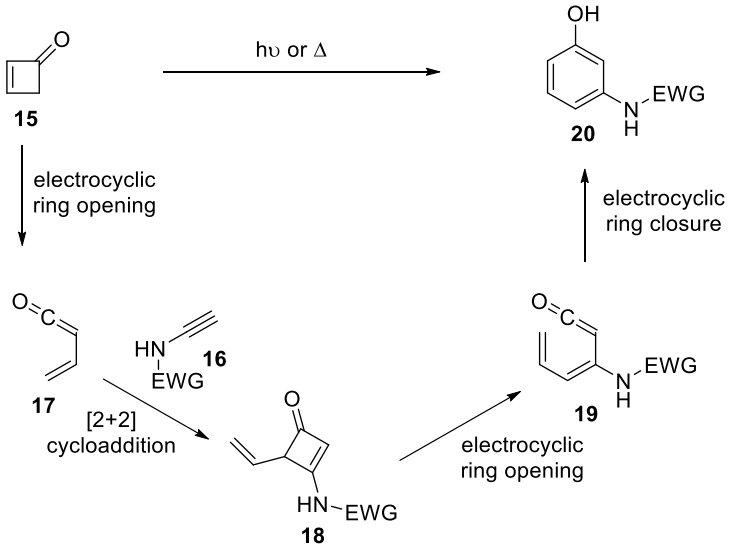
One of the challenges facing the previously described strategies is the need for a preformed, substituted ring system and apart from the dehydrogenative aromatization method, the ring also needs to be aromatic. This means that the arylamines that can be synthesised are limited by the availability of the aromatic precursors. Although there are many commercially available arenes, the desired precursors might not be available or easily accessed. One solution is to prepare the arylamine from an acyclic precursor. Here, it is possible to programme in substitution by choice of building blocks and take advantage of the regioselective and predictable chemistry of acyclic molecules which is sometimes difficult in aromatic chemistry.

There have been a number of strategies reported using a *de novo* approach for the synthesis of arylamines and these are described below. It should be noted that these approaches are encompassed by a larger body of work, the *de novo* synthesis of arene rings which is beyond the scope of this report.[31]

1.2.6.1 Tandem Ynamide Benzannulation/Ring-Closing Metathesis Strategy

Danheiser and co-workers reported the synthesis of arylamines from ynamide **16** and cyclobutenone **15**. The authors propose a cascade of four electrocyclic reactions, an electrocyclic ring-opening of the cyclobutenone **15** to generate a vinylketene **17**, followed by a [2 + 2] cycloaddition of vinylketene **17** with alkyne **16** to afford a vinylcyclobutenone intermediate **18**. This undergoes a 4-electron electrocyclic ring opening to generate

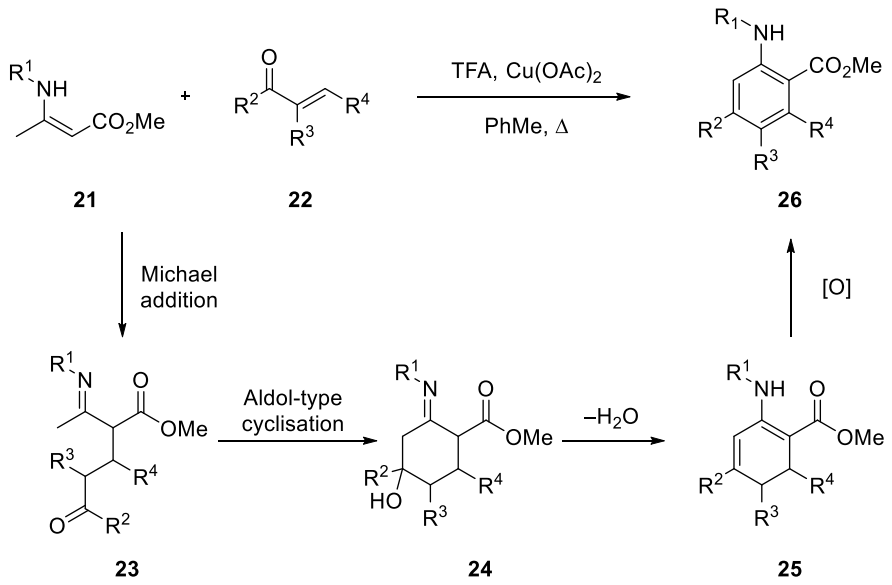
dienylketene **19** which cyclises *via* 6π-electrocyclic ring closure to give the arylamine **20** following a final tautomerization. The authors report good yields and explored the scope with respect to the starting materials. They also report the suitability of flow chemistry to the procedure and the formal synthesis of a drug candidate, (+)-FR900482. The authors also showed how the resulting arylamine can be used in the synthesis of other heterocycles (**Scheme 7**).[32]



Scheme 7 *Arylamine synthesis by Danheiser and co-workers.*

1.2.6.2 Formal (3 + 3) Cycloaddition/Oxidation of Enamines and Enones

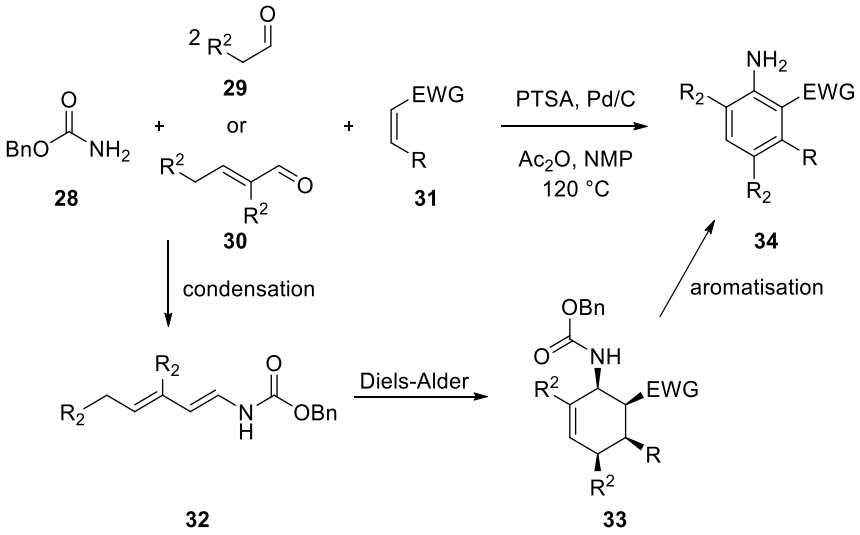
The synthesis of arylamines from an enamine and an α,β-unsaturated ketone was reported by Guan and co-workers. The authors compared their work to the Hantzsch pyridine synthesis. The mechanism is believed to commence with Michael addition of enamine **21** and enone **22** yielding adduct product **23** which undergoes an intramolecular cyclisation to yield intermediate **24**. Tautomerisation and elimination yield cyclohexadienamine **25** which is then oxidised by the $Cu(OAc)_2$ to yield arylamine **26**. The authors reported good yields and found the reaction tolerates alkyl groups at the R^1, aryl groups at R^2 and alkyl or aryl groups at R^3 (**Scheme 8**).[33]



Scheme 8 *Synthesis of arylamines by Guan and co-workers.*

1.2.6.3 Three component coupling of *O*-benzyl carbamates, aldehydes, and dienophiles

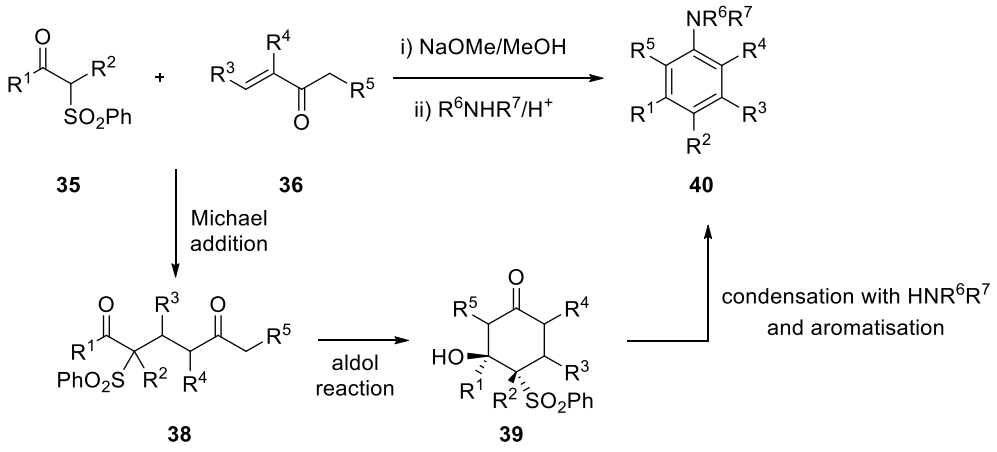
Beller and co-workers reported the *de novo* synthesis of arylamines *via* a multicomponent, Diels-Alder, aromatization/CBz cleavage reaction. They employed an *O*-benzyl carbamate **28**, either an α,β-unsaturated ketone **30** or two equivalents of an aldehyde **29,** and an electron deficient diene **31**. Highly substituted arylamines could be accessed in high yields with excellent regioselectivities and good scope. The reaction is believed to proceed *via* an acid-catalysed condensation to form diene **32**, which undergoes a Diels-Alder reaction with dienophile **31**. The resulting cyclohexene **33** can then be dehydrogenated in the presence of a palladium-on-carbon catalyst with concomitant *N*-CBz cleavage to furnish aniline **34** (**Scheme 9**).[34]



Scheme 9 *Multicomponent synthesis of arylamines by Beller and co-workers.*

1.2.6.4 Michael-Aldol reaction of β-keto sulfones

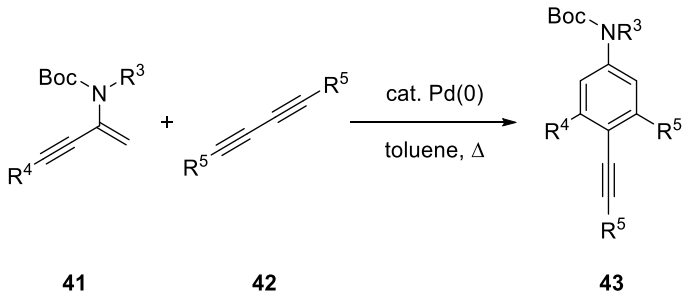
Padwa and co-workers described the synthesis of arylamines from a condensation of unsaturated ketone **36** and β-keto sulfones **35** followed by a condensation with an amine. The reaction is proposed to take place *via* the Michael reaction of the enolate formed by treatment of ketone **35** with sodium methoxide with α,β-unsaturated ketone **36**. The resulting dicarbonyl **38** undergoes an intramolecular aldol reaction to form cyclohexanone **39**. Treatment with an amine forms an enamine, which undergoes elimination of benzenesulfonic acid and water to give arylamine **40**.The authors report high yields and demonstrated alkyl groups could be installed at all positions on the aryl ring. They also demonstrated an extension of the methodology to include the synthesis of aryl substituted sulphides and ethers (**Scheme 10**).[35]



Scheme 10 *Synthesis of arylamines by Padwa and co-workers.*

1.2.6.5 Palladium-catalyzed cross-benzannulation of aminoenynes with diynes

Yamamoto and co-workers described an extension of their palladium-catalysed *homo*-benzannulation of conjugated enynes to include the synthesis of arylamines. Here a conjugated aminoenyne **41** is treated with diyne **42** and in the presence of a palladium catalyst, a cross-benzannulation takes place to furnish arylamine **43**. The reactions proceeded with high regioselectivities and in moderate yields (**Scheme 11**).[36]



41 **42** **43**

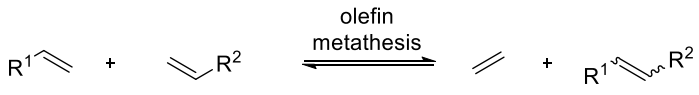
Scheme 11 *Synthesis of arylamines by Yamamoto and co-workers.*

1.3 Donohoe approach to heterocycles

De novo synthesis of aromatic compounds has been a theme in the Donohoe group whereby modern catalytic reactions are utilised, particularly the olefin metathesis reaction.

1.3.1 Olefin metathesis

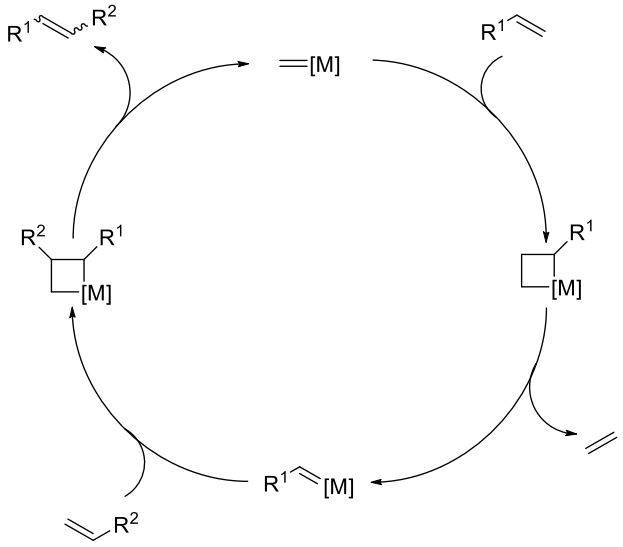
The olefin metathesis reaction is a powerful tool for the synthesis of alkene bonds and has added a new disconnection to the synthetic chemist's tool box. The term olefin metathesis was coined by Calderon and co-workers whilst studying the effects of transition metals in the synthesis of new polymers (**Scheme 12**).[37]



Scheme 12 *Olefin cross metathesis reaction.*

Chauvin is credited with the derivation of the mechanism for olefin cross metathesis. Based on experimental evidence, it was proposed that the reversible interconversion of an olefin and metal alkylidene *via* an alternating [2+2] cycloaddition and retro [2+2] cycloaddition

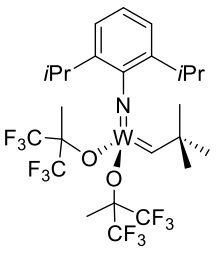
was responsible for the olefin metathesis phenomenon. The expulsion of ethylene gas is the driving force for the reaction (**Scheme 13**).[38]



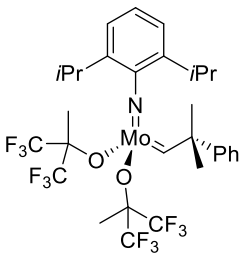
Scheme 13 *Olefin metathesis reaction mechanism.*

1.3.1.1 Early catalysts

The first highly popular, commercially available catalysts were reported by Schrock and co-workers who used Molybdenum carbenes **44** and **45** (**Figure 4**).[39] Molybdenum catalysts are defined by their high reactivity but generally have less functional group tolerance and are more sensitive towards moisture and air compared to their late transition metal contemporaries.



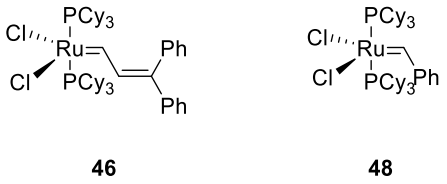
44



45

Figure 4 *Schrock's metathesis catalysts.*

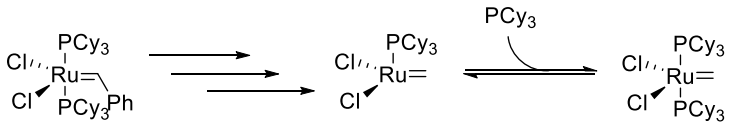
Ruthenium catalysts such as **46** and **48** were utilised by Grubbs and co-workers who reported relatively air and moisture stable complexes with excellent functional group tolerance and good activities.[40]



46 **48**

Figure 5 *Grubbs' first generation catalysts.*

Mechanistic studies showed that a phosphine ligand first dissociates to form a 14-electron species **49** to which an alkene can associate and the resulting complex can enter the catalytic cycle (**Scheme 13**). It is also reported that if complex **49** reassociates with another phosphine ligand the resulting complex, **50**, is relatively unstable with a half-life of 40 minutes at 55 °C, compared to the half-life of complex **48**, which is 8 days at the same temperature (**Scheme 14**).[41]



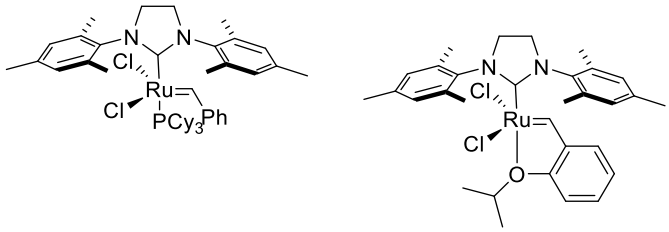
48 **49** **50**

Scheme 14 *Mechanism of catalyst **48** degradation.*

1.3.1.2 Recent catalysts for the olefin-metathesis reaction

The degradation of complex **48** was addressed in part by the use of N-heterocyclic carbene (NHC) ligands first reported by Nolan[42] and Grubbs[43] such as in catalyst **51**. Not only does the use of the NHC ligand improve the stability of the catalytic complexes, through a preference of the complex to coordinate an olefinic substrate compared to a phosphine ligand,[44] it also increases the scope to highly substituted and electron deficient alkenes.

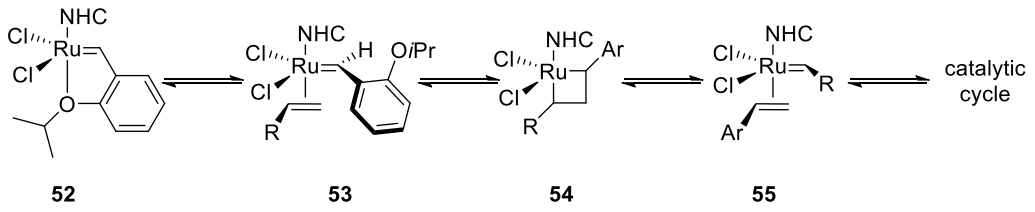
A further development was reported by Hoveyda and co-workers who used an isopropoxystyrene carbene, as in catalyst **52**, where the oxygen ligand is both tethered and chelated to the carbene. High yields and catalyst stability were reported.[45,46]



51 **52**

Figure 6 *Grubbs' second generation catalyst **51** and Hoveyda-Grubbs' second generation catalyst **52**.*

The mechanism for the Hovedya-Grubbs' second generation catalyst was studied in detail by Vorfalt and Wannowius who proposed that the initiation step is no longer the disassociation of a ligand but an associative/interchange step which involves the association of an alkene and the disassociation of the chelated oxygen to form complex **53**. This complex then undergoes a [2 + 2] cycloaddition to form complex **54**. [2 + 2] cycloaddition to form complex **55** is followed by alkene dissociation, at which point the catalyst enters the catalytic cycle.[47]

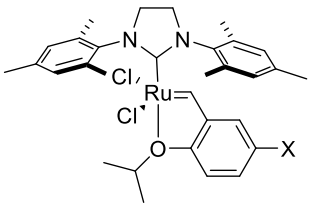


52 **53** **54** **55**

Scheme 15 *Proposed mechanism for the formation of the active metathesis complex from **52**.*

Several groups have developed catalysts to accelerate the formation of the active metathesis complex and have realised some significant improvements in activity. The inclusion of an electron withdrawing group at the aromatic C-4 position of the isoproxy 'ligand' has had the most significant effect. Grela and co-workers reported that the catalyst **56** employing a nitro group exhibited higher rates of reactivity compared to the Hovedya Grubbs' type catalyst. They hypothesised the quicker formation of the active complex, as well as a reduced affinity of the isoproxy 'ligand' for the ruthenium complex, was responsible for the increased activity.[48] Zhan prepared the aryl sulfonamide carbene **57** which also exhibited higher rates

,of reactivity.[49] Maudit and co-workers also observed higher rates of activity with complex **58,** which utilizes a trifluoroacetamide as the electron-withdrawing group.[50]



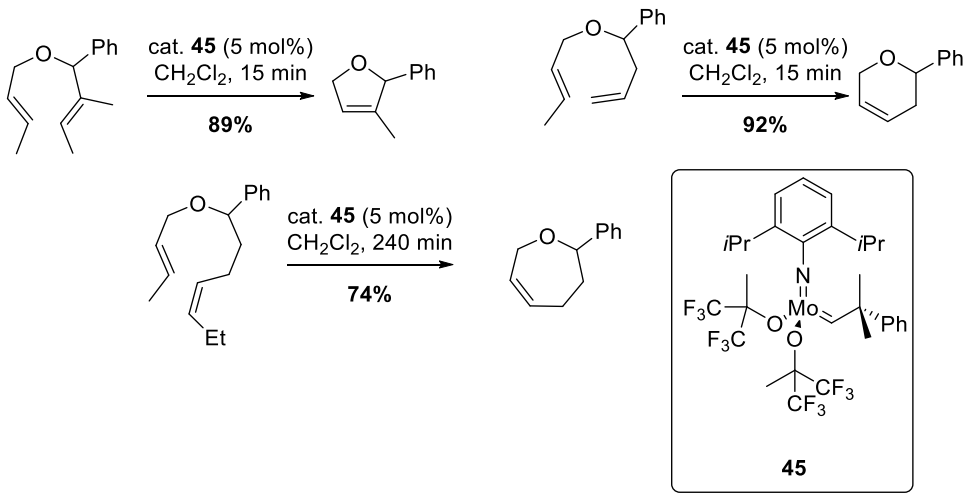
X = NO_2 **56**
X = SO_2NMe **57**
X = $NHCOCF_3$ **58**

Scheme 16 *Examples of Hoveyda-Grubbs' type catalysts with higher rates of activity.*

1.3.2 The application of the ring closing metathesis reaction to the synthesis of heterocycles

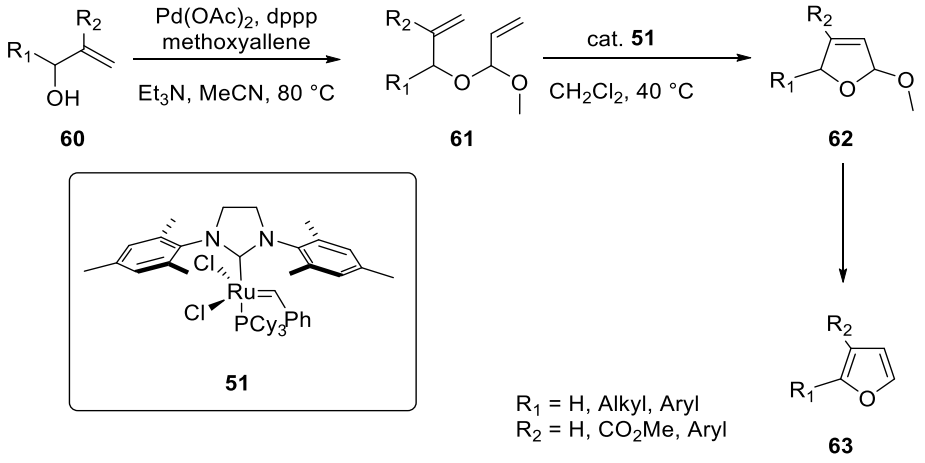
The development of well defined, highly active catalysts is one reason why the olefin metathesis reaction has become such a useful tool in the synthesis of heterocycles. The first reaction to be applied to the synthesis of heterocycles was the ring closing metathesis reaction.

In 1992, Grubbs described the synthesis of five, six and seven membered oxygen containing heterocycles using Schrock's catalyst **45**[51] and later reported the use of the Grubbs' first generation catalyst (**48**).[52] These examples demonstrated the power of the ring closing metathesis reaction in the synthesis of cyclic structures and started a whole new field in heterocycle synthesis.



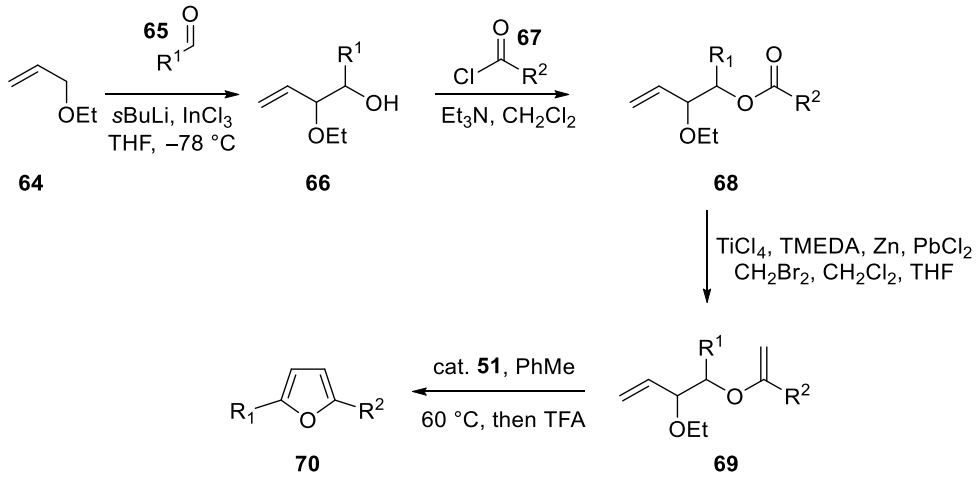
Scheme 17 *Synthesis of heterocycles by ring closing metathesis by Grubbs and co-workers.*

The Donohoe group entered the field in 2005 when they reported general and mild conditions for the synthesis of 2,3-substituted furans in good yields from acetal **61**.[53] Acetal **61** was easily accessed *via* a palladium-catalysed coupling reaction of an allylic alcohol **60** and methoxyallene. A ring closing metathesis reaction of acetal **61** yielded dihydrofuran **62** which aromatised under treatment with trifluoroacetic acid to yield furan **63**. The scope of the methodology tolerated aryl, alkyl and carbonyl functional groups and was expanded to include linked biaryl compounds, an important motif in organic semiconducting materials (**Scheme 18**).[53]



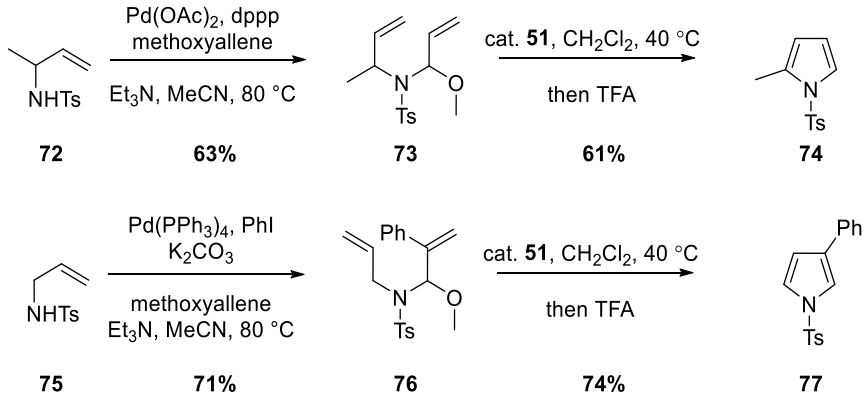
Scheme 18 *Synthesis of 1,2-substituted furans by Donohoe and co-workers.*

An alternate disconnection was also explored by the Donohoe group. Here the metathesis precursor was diene **69**. This compound was accessed *via* an indium-mediated addition of allyl ether **64** to aldehyde **65**, followed by a coupling with acid chloride **67.** Finally, an olefination under Takai-Utimoto conditions[54] gave diene **69**. Ring closing metathesis yielded 2,5-substituted furan **70** in good yields (**Scheme 19**).[55]



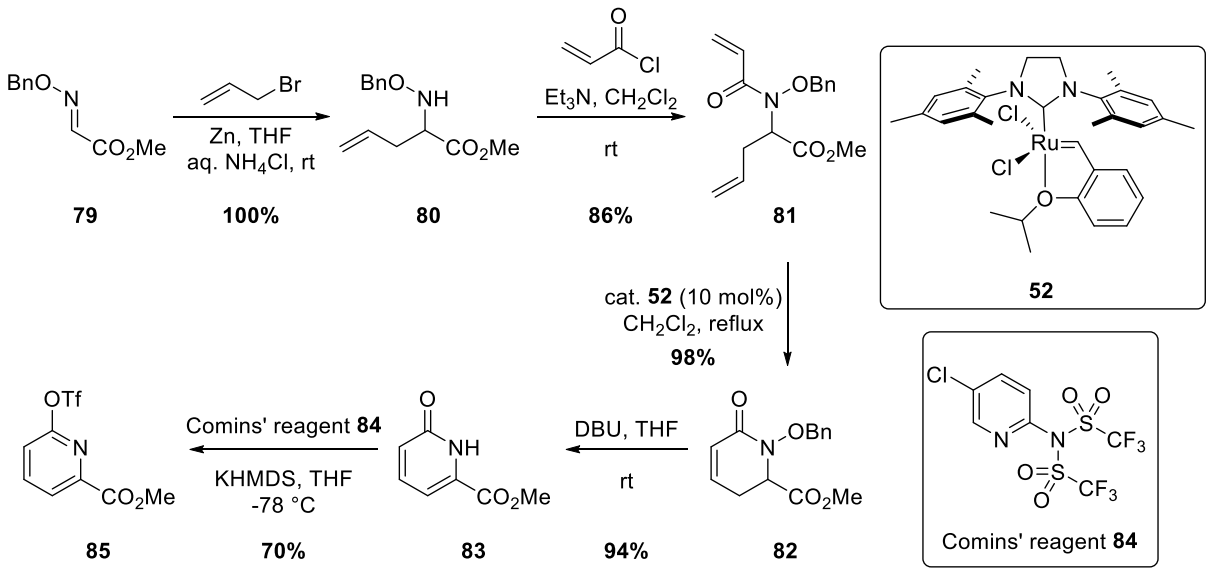
Scheme 19 *Synthesis of 1,4-substituted furans by Donohoe and co-workers.*

The methodology was also expanded to include the synthesis of *N*-substituted pyrroles. Using analogous chemistry as above to prepare *N*,*O*-acetal **72** and the similar ring closing metathesis reaction conditions, 2-substitued pyrrole **74** could be accessed. The scope was broadened by performing a palladium-coupling with iodobenzene in the presence of methoxyallene to give access to 3-substituted pyrrole **77** (**Scheme 20**).[53]



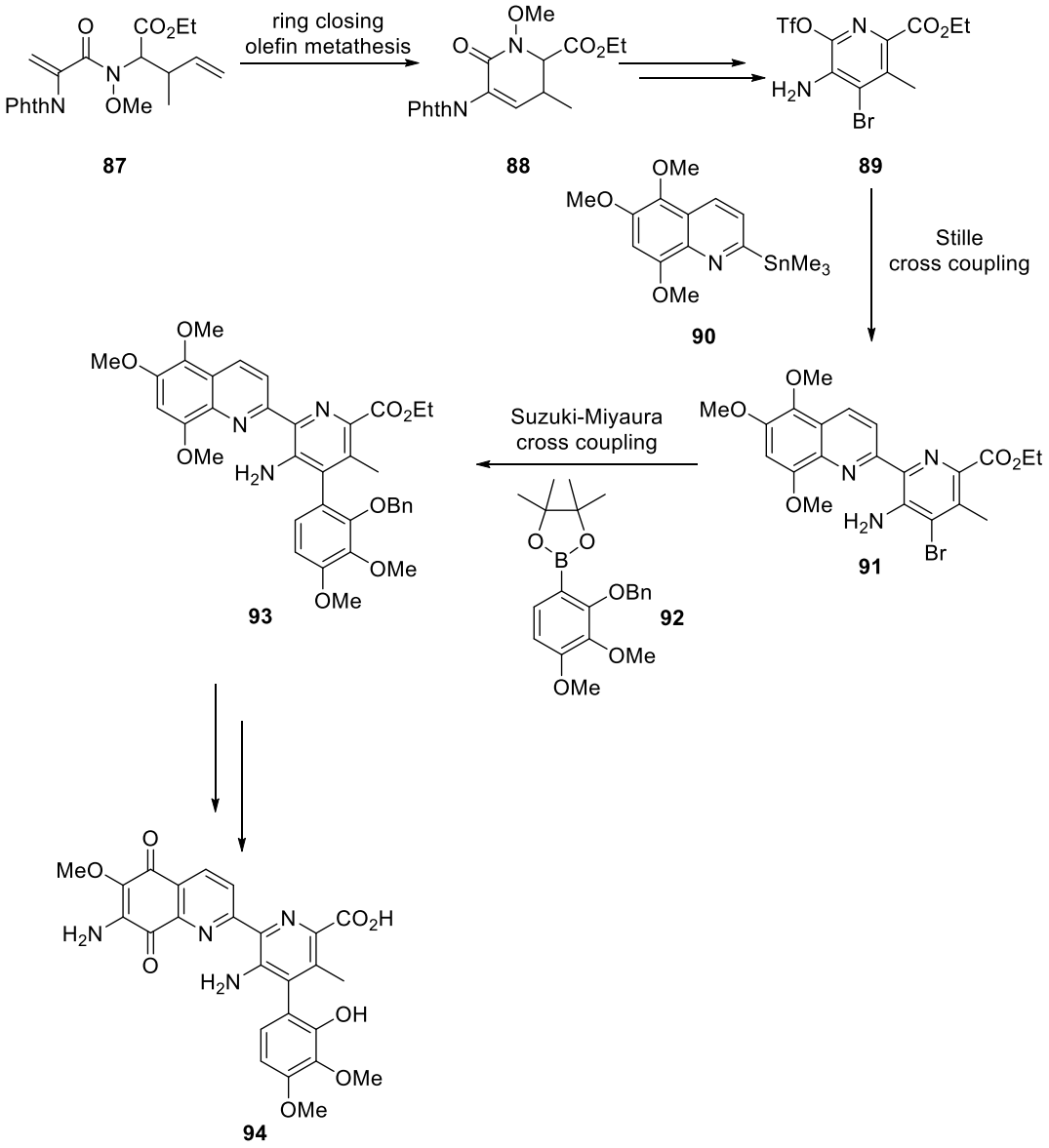
Scheme 20 *Donohoe and co-workers synthesis of substituted pyrroles.*

The ring closing metathesis strategy was then employed in the synthesis of pyridines. Imine **79** was subjected to zinc-mediated allylation conditions to give amine **80** in quantitative yield. Acylation of amine **80** with acryloyl chloride gave amide **81** in 86% yield which was subjected to ring closing metathesis conditions to give dihydropyridone **82** in 98% yield. Aromatisation, followed by formation of the aryl triflate using Comins' reagent **84**, gave pyridine **85** in a 66% yield over two steps (**Scheme 21**).[56]



Scheme 21 *Donohoe's ring closing metathesis synthesis of pyridine **85**.*

The ring closing metathesis strategy is best exemplified in the Donohoe synthesis of (±)-streptonigrin **94**. This synthesis also demonstrates the synergy between *de novo* synthesis and metal-catalysed cross-coupling reactions. Donohoe and co-workers synthesised metathesis precursor **87** in four steps. Ring closing metathesis of diene **87** gave dihydropyridone **88** in good yield and a further three steps gave pyridine **89** with all the correct functionality for the natural product. Pyridine **89** was then subjected to a Stille coupling with organostannane **90** to give biaryl **91.** A Suzuki–Miyaura coupling with boronate ester **92** complete the core of streptonigrin **93**. The natural product **94** was completed in 14 linear steps and 11% overall yield, representing a significant improvement on previous syntheses and demonstrating the power of *de novo* synthesis coupled with cross coupling chemistry (**Scheme 22**).[57]



Scheme 22 *Synthesis of (±)-streptonigrin (**94**)by Donohoe and co-workers.*

1.3.5 The application of the olefin cross metathesis reaction to the synthesis of heterocycles

The olefin cross-metathesis reaction arguably provides an even more powerful route to heterocycles as the starting materials are readily available and there is no requirement for design or synthesis of tethered metathesis precursors.

In 2003, Grubbs' and co-workers reported a general model for selectivity in cross-metathesis reactions.[58] In this report, they rated olefins on their ability to homodimerize in

the presence of different metathesis catalysts; this provided a guide to whether a selective cross-metathesis will take place.

Olefins were separated into four categories based on their reactivities with different catalysts. Type I olefins undergo rapid dimerisation in the presence of the metathesis catalyst and the resulting homodimers are also consumable. Type II olefins are less reactive, however still undergo slow homodimerisation and the homodimers are only sparingly consumed. Type III olefins do not undergo homodimerisation and type IV olefins are inert to cross-metathesis, however do not deactivate the catalyst (**Table 1**).[58]

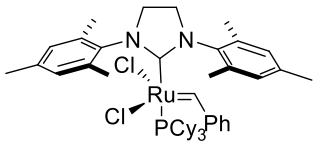
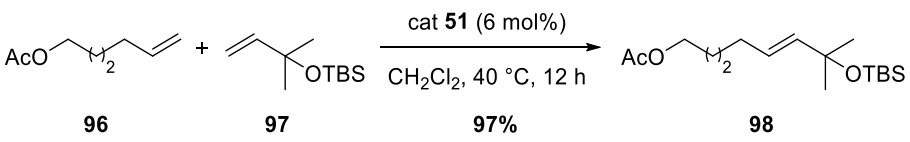
Type 1 (fast homodimerization)	**Type II (slow homodimerization)**	**Type III (no homodimerization**	**Type IV (spectators to CM)**
terminal olefins, 1° allylic alcohols, esters, allyl boronate esters, allyl halides, styrene (no large ortho substit.), allyl phosphonates, allyl silanes, allyl phosphine oxides, allyl sulfides, protected allyl amines	styrenes (large ortho substit.), acrylates, acrylamides, acrylic acid, acrolein, vinyl ketones, unprotected 3°allylic alcohols, vinyl epoxides, 2° allylic alcohols, perfluorinated alkene olefins	1,1-disubstituted olefins, non-bulky trisub. olefins, vinyl phosphonates, phenyl vinyl sulfone, 4° allylic carbons (all alkyl substit.) 3° allylic alcohols (protected)	vinyl nitro olefins, trisubstituted allyl alcohols (protected)  **51**

Table 1 *An example of Grubbs' substrate classification for Grubbs' second generation catalyst **51**.*

With these guidelines, it is possible to design a selective cross metathesis reaction. For example, the terminal alkene **96**, a type I olefin, and the protected tertiary allylic alcohol **97**, a type III olefin, undergo a selective cross metathesis. Although rapid dimerisation occurs with alkene **96**, the homodimer is also rapidly consumed. Only a metathesis that results in heterodimer **98** is irreversible because olefin **98** does not participate in metathesis reactions. Thus heterodimer **98** was isolated in 97% yield (**Scheme 23**).[58]

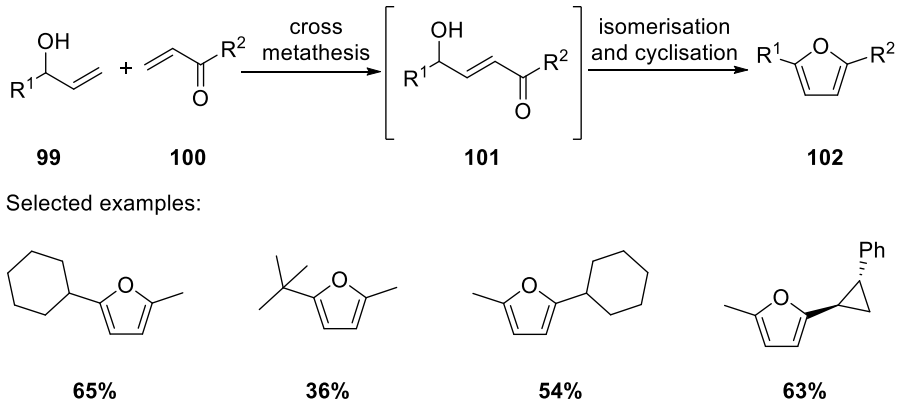


96 **97** **97%** **98**

Scheme 23 *Example of a selective cross metathesis.*

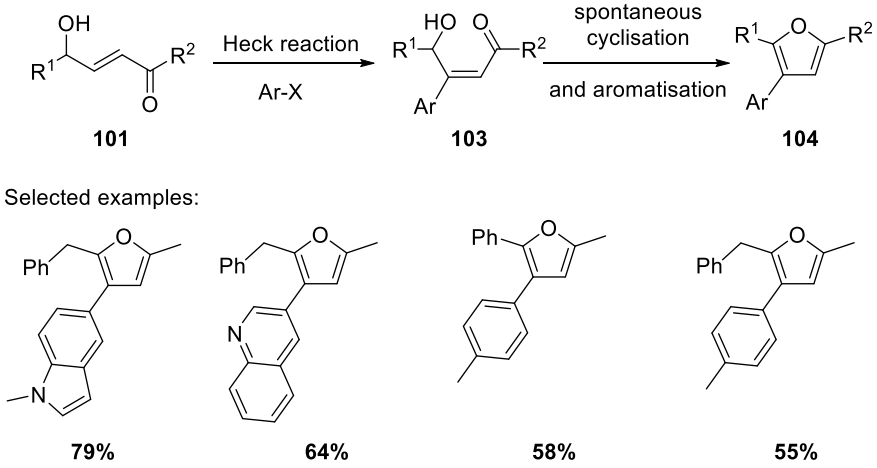
With this model for selectivity available, it was now possible to employ the cross metathesis for the selective synthesis of olefins.

The approach was first demonstrated by Donohoe and co-workers with the synthesis of 2,5-substituted furan **102**.[59] Homoallylic alcohols undergo rapid homodimerization, however the homodimer also undergoes rapid cross metathesis too. Enones are slower in the cross metathesis and for Grubbs' second generation catalyst (**51**), they are type II substrates. Thus, a selective cross metathesis can be achieved between enone **100** and allylic alcohol **99**; the product of the cross metathesis is γ-hydroxyenone intermediate **101**. In the case where the cross metathesis was performed in the presence of catalytic amounts of pyridinium *p*-toluenesulfonate, an isomerisation to the *Z*-alkene followed by a cyclisation to form furan **102** was observed *in situ*. This approach proved successful, with a range of furans isolated in good yields and with excellent regioselectivity (**Scheme 24**).[59]



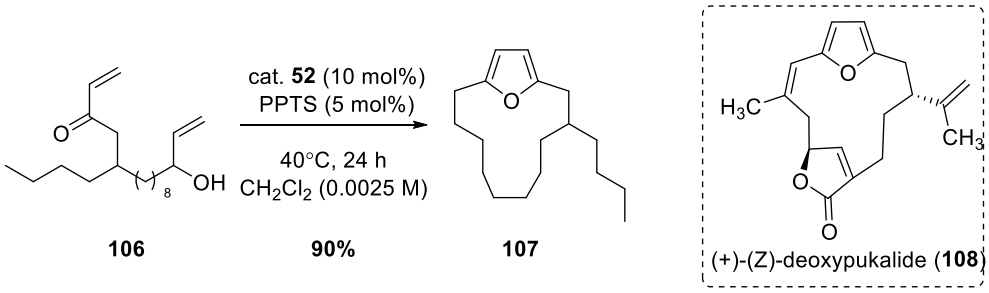
Scheme 24 *Synthesis of 2,5-substituted furans by Donohoe and co-workers.*

Perhaps a more profitable method for the double bond isomerisation was to utilise the Heck reaction for this puprose. Here, as a result of the mechanistic requirements of the reaction, a *cis*-γ-hydroxyenone **103** is formed along with the arylation and the intermediate **103** spontaneously cyclising to give a tri-substituted furan **104** (**Scheme 25**).[59]



Scheme 25 *Synthesis of 2,3,5-substituted furans by Donohoe and co-workers.*

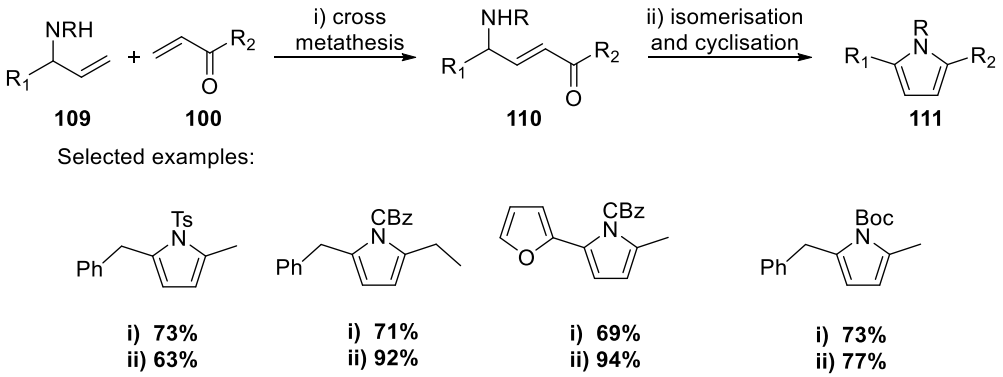
The power of the method was demonstrated in the synthesis of the (+)-(*Z*)-deoxypukalide core **107**. Diene **106** was synthesised in four steps from commercially available materials and the intramolecular cross metathesis and cyclisation, which constructed a 13-membered ring, furnished furan **107** in an excellent yield of 90% (**Scheme 26**).[59]



Scheme 26 *Synthesis of (+)-(Z)-deoxypukalide core **107** by Donohoe and co-workers.*

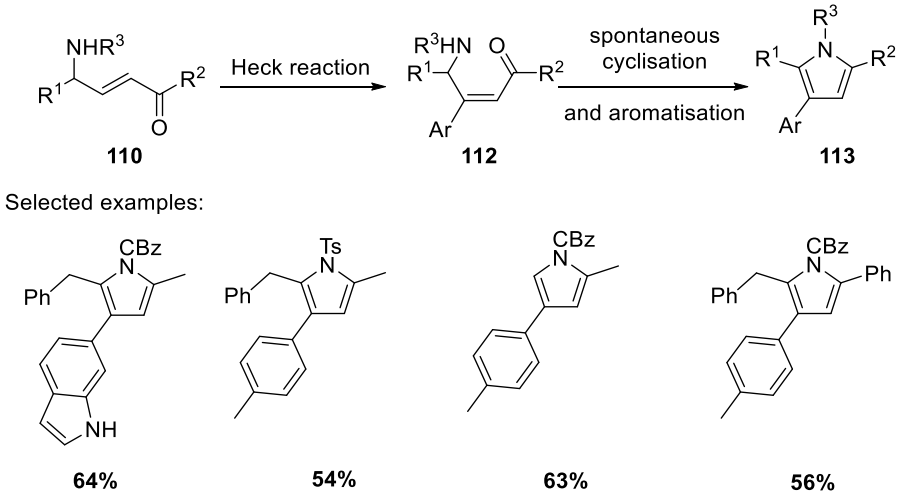
An analogous approach was then applied to the synthesis of pyrroles, utilising an allylic amine **109** and vinyl ketone **100**. Both the cross-metathesis and cyclisation of intermediate **110** were found to require more forcing conditions, *p*-toluenesulfonic acid instead of pyridinium *p*-toluenesulfonate and 48 h instead of 24 h, and a one-pot cyclisation was not found to be possible under acidic conditions. However it was later shown by Grela and co-workers that the addition of a Lewis acid did allow for a one-pot pyrrole-forming

protocol.[60] The procedure was shown to tolerate a range of functional groups attached to the nitrogen and showed good tolerance of substituents in the cyclisation (**Scheme 27**).[61]



Scheme 27 *Synthesis of 2,5-substituted pyrroles by Donohoe and co-workers.*

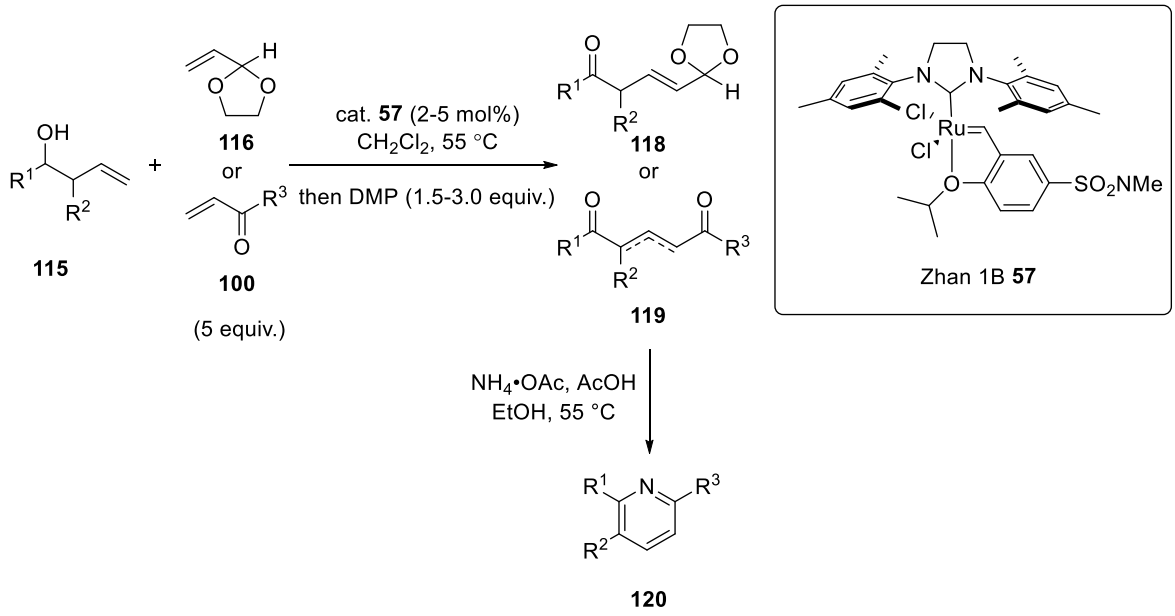
Furthermore, the Heck reaction/cyclisation protocol could be applied to the synthesis of 2,3,5-substituted pyrroles **111** and again good yields and excellent regioselectivities were observed (**Scheme 28**).[61]



Scheme 28 *Synthesis of 2,3,5-substituted pyrroles by Donohoe and co-workers.*

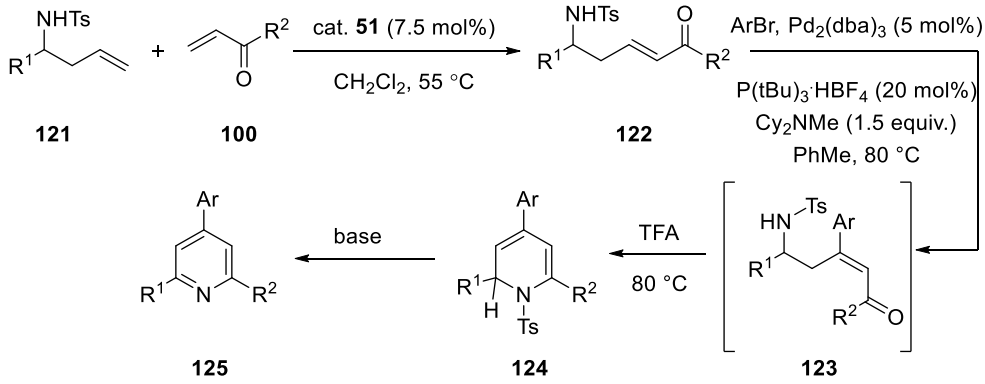
A natural extension of this methodology was to include the synthesis of pyridines. With the appropriate coupling partners, catalysts and conditions, this methodology allowed access to mono-, di-, 2,3,6-tri-, 2,4,6-tri-, and 2,3,5,6-tetrasubstituted pyridines. A cross metathesis reaction between enone **100** and homoallylic alcohol **115** followed by an oxidation by Dess-Martin periodinane yielded 1,5-dicarbonyl **119**. Optimisation studies showed that the most

efficient catalyst for this reaction was the Zhan 1B catalyst **57** and that the best yields were obtained using 5 equivalent of methyl vinyl ketone. A cyclisation of 1,5-dicarbonyl **119** in the presence of ammonium acetate allowed access to di- and 2,3,6-tri-substituted pyridines **120**. The analogous cross metathesis reaction using the homoallylic ketone proved to give inferior yields and in general, it hypothesised that homoallylic alcohols are privileged substrates in cross metathesis reactions.[62] Substituting the enone for the acetal **116** gave access to mono- and di-substituted pyridines (**Scheme 29**).



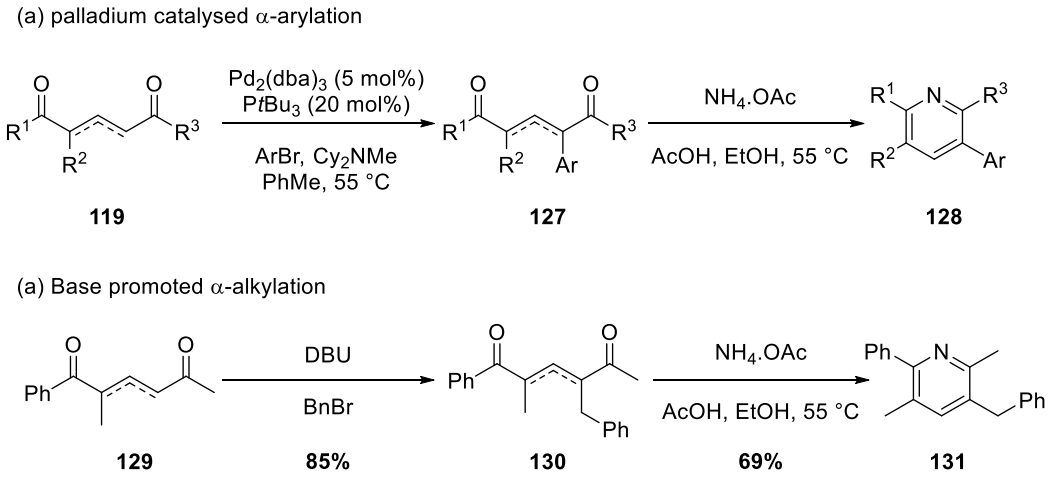
Scheme 29 *Synthesis of substituted pyridines by Donohoe and co-workers.*

By substituting the homoallylic alcohol for a homoallylic sulphonamide, 2,4,6-substituted pyridines could now be accessed. A cross metathesis between the sulphonamide **121** and vinyl ketone **100** gave δ-aminoenone intermediate **122** which could then be subjected to a one-pot Heck arylation, inverting the olefin geometry, an acidic cyclisation, and an elimination to yield 2,4,6-pyridines **125** in good yields (**Scheme 30**).



Scheme 30 *Synthesis of 2,4,6-substituted pyridines by Donohoe and co-workers.*

Higher-substituted pyridines could be accessed by modification of the 1,5-dicarbonyl intermediate **119** *via* either palladium-catalysed α-arylation or base promoted alkylation. The authors reported access to 2,3,5,6-substituted pyridines **128** & **131** with excellent regioselectivity and high yields (**Scheme 31**).



Scheme 31 *Synthesis of 2,3,5,6-substituted pyridines by Donohoe and co-workers.*

1.4 Outlook

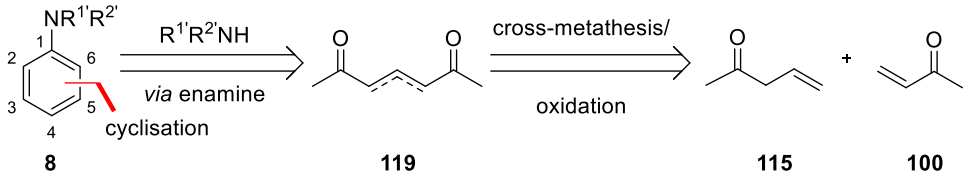
The methods available for the synthesis of arylamines are impressive. However, each method has its own advantages and challenges. The development of new methods which offer different substrate scope and functional group tolerance is still of importance. With the advent of new procedures for the synthesis of heteroaromatics *via de novo* synthesis, an interesting opportunity for the synthesis of arylamines has arisen; specifically *via* the use of 1,5-dicarbonyls **119**, **127** & **130** used in **Scheme 29** and **Scheme 31**.

Chapter 2: Results and Discussion

2.1 *De novo* synthesis of multi-substituted arylamines using alkene cross metathesis

2.1.1 Our approach

Due to the attractive features of a *de novo* synthesis of aromatic heterocycles, we planned to expand the methodology to include the synthesis of aromatic hydrocarbon systems. Moreover, some of the intermediates used in the *de novo* synthesis of heteroaryls could be used for such a synthesis which could be performed through enamine chemistry to form an arylamine **8** (**Scheme 32**). In the first instance, the 1,5-dicarbonyl intermediate **119** used to synthesise pyridines[63] would be a suitable intermediate to test our hypothesis.



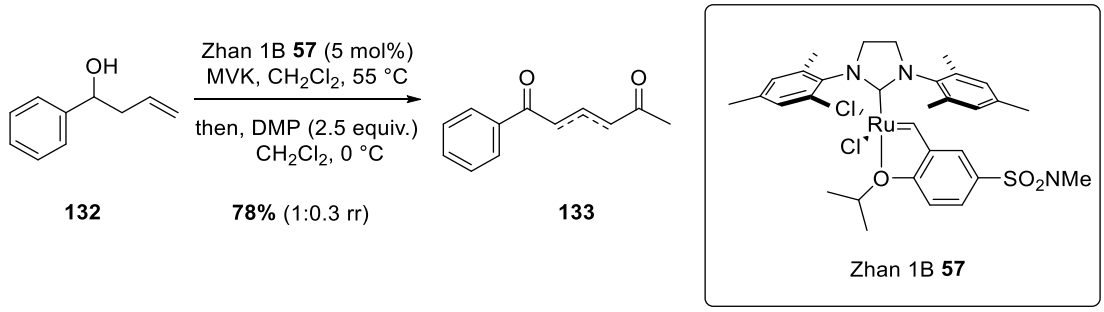
Scheme 32: *Arylamine retrosynthesis via a 1,5-dicarbonyl.*

Previous studies in the Donohoe group had already developed an efficient route to 1,5-unsaturated dicarbonyl **119** using a cross-metathesis/oxidation protocol and this was discussed in the Introduction. The cross metathesis reaction between homoallylic alcohol **115** and vinyl ketone **100** yielded a γ-hydroxy-α,β-unsaturated ketone which could be oxidised with Dess-Martin periodinane to the required unsaturated-1,5-dicarbonyl **119** as a mixture of regioisomers. Our hypothesis was that treatment of this 1,5-dicarbonyl **119** with an amine would result in the formation of arylamine **8** and so a research programme exploring the required conditions for high conversions was initiated.

2.1.2 Optimisation of the cyclisation

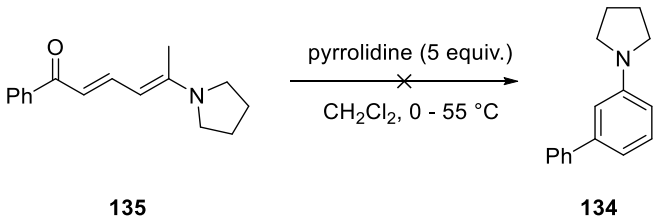
It was planned to use 1,5-dicarbonyl **133** and pyrrolidine for the optimisation studies. 1,5-Dicarbonyl **133** was accessed *via* a cross metathesis reaction of homoallylic alcohol **132**

and 5 equivalents of methyl vinyl ketone in the presence of Zhan 1B catalyst **57**. The resulting γ-hydroxy-α,β-unsaturated ketone was then treated with Dess-Martin periodininone to yield 1,5-dicarbonyl **133** in a 78% yield (**Scheme 33**).



Scheme 33 ***Synthesis of 1,5-dicarbonyl*** *133***.**

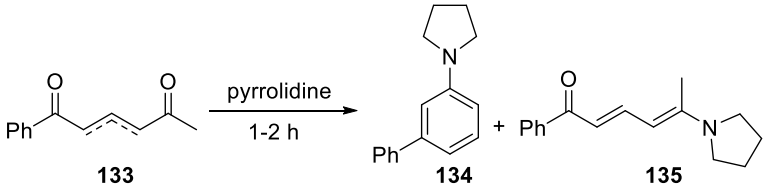
The optimisation studies began with the treatment of 1,5-dicarbonyl **133** with 2 equivalents of pyrrolidine in dichloromethane at a range of temperatures between −78 °C and 55 °C and pleasingly arylamine **134** was formed in good yields (**Table 2**, entries 1-4). In each case, the only other major component in the reaction mixture was enamine **135**. Re-subjection of enamine **135** to the cyclisation conditions, 5 equivalents amine, dichloromethane at a range of temperatures between 0 and 55 °C gave only unreacted starting material (**Scheme 34**). However, reducing the reaction temperature was clearly effective at minimizing this compound and optimising the cyclisation.



Scheme 34 *Resubjecting enamine* ***135*** *to the reaction conditions did not give arylamine.*

Next, variation in the equivalents of amine was investigated. Reducing the amount of amine used favoured the formation of unwanted enamine **135** (entry 5) while increasing the

equivalents of amine gave more of the desired product **134**; with 5 equivalents, nearly complete conversion to arylamine **134** was observed at 0 °C (83% isolated yield, entry 8).



133 **134** **135**

	Equiv. of Amine	Temperature (°C)	Solvent	Conversion (%)[c] 134	135
1	2.0	55	CH_2Cl_2	31	59
2	2.0	23	CH_2Cl_2	57 (50[a])	43
3	2.0	0	CH_2Cl_2	71	29
4	2.0	-78	CH_2Cl_2	74 (63[a])	26
5	1.5	0	CH_2Cl_2	53	47
6	3.0	0	CH_2Cl_2	79	21
7	5.0	0	CH_2Cl_2	86 (73[a])	14
8	5.0	0	CH_2Cl_2	89 (83[a])	11
9	5.0	0	PhMe	49	-
10	5.0	0	EtOH	71	-
11	5.0	0	THF	67	-
12	5.0	0	MeCN	56	-
13	5.0	0	*t*BuOH/H_2O	56	-
14	5.0	55	CH_2Cl_2	70	30
15	5.0	0	CH_2Cl_2	67[b]	23

[a]isolated yield, [b]$ZnCl_2$ (1 equiv.)
[c]based on ^{1}H NMR spectroscopy

Table 2 *Optimisation studies for 1,5-dicarbonyl **133** cyclisation.*

Investigating the effect of different solvents on the reaction showed that CH_2Cl_2 gave the best conversion, with other polar solvents working well and toluene giving the poorest conversions (entries 8 - 13). It is also worth noting that, with 5 equivalents of amine, it was possible to increase the reaction temperature and still achieve high yields. Also the reaction tolerated the presence of Lewis acid, $ZnCl_2$ in this case, which was an important discovery for more demanding cyclisations.

2.1.3 Mechanism

Clearly the mechanism of the reaction was of interest and although an unequivocal picture of the reaction pathway could not be proven, some progress was made. The investigation began by monitoring the reaction of 2 equivalents of pyrrolidine with 1,5-dicarbonyl **133** by ^{1}H NMR spectroscopy, since this reaction was sufficiently slow to allow the observation of the formation of intermediates. With the reaction being run in CD_2Cl_2 at room temperature, a ^{1}H NMR spectrum was obtained every 5 minutes and a picture of the reaction accumulated. The first observation made was the rapid formation of adduct **136** (**Figure 7**) which was formed before the first scan could be performed (less than three minutes). Adduct **136** could be identified by its characteristic ABX coupling, however the intermediate was short-lived and a sample for full characterisation could not be isolated (**Figure 7**).

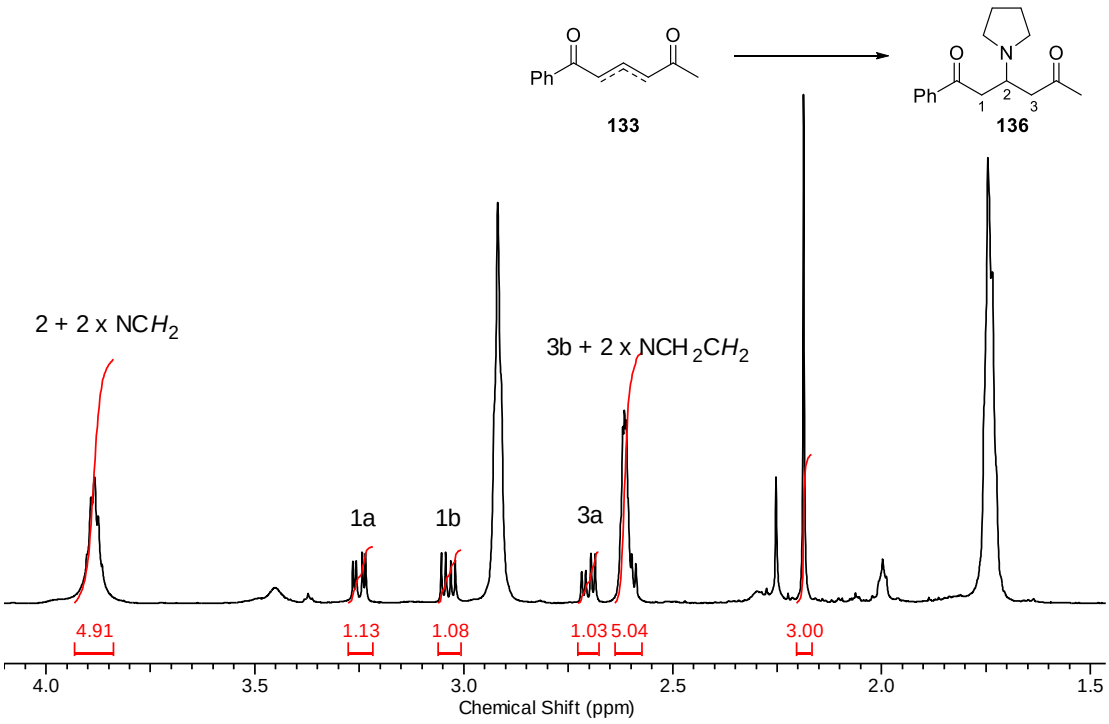
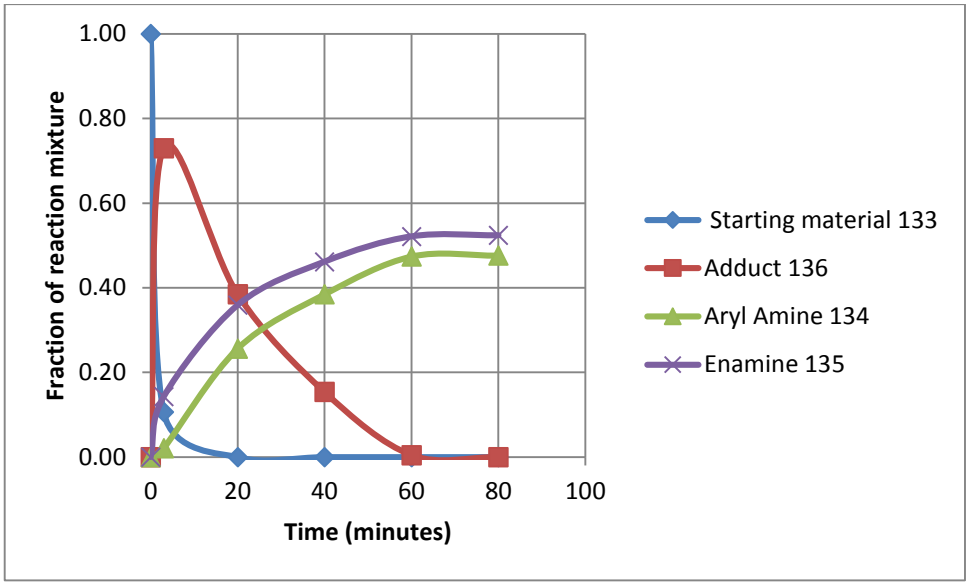


Figure 7 *Spectra of in situ adduct **136**.*

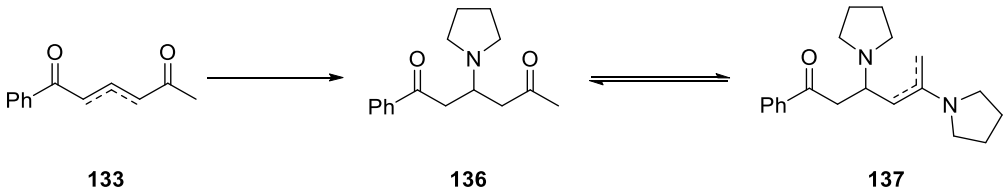
This observation agreed with observations that the position and geometry of the double bond did not affect the cyclisation reaction. Pyrrolidine adduct **136** was shown to be an

intermediate in the formation of both the desired arylamine and unwanted enamine side product. The disappearance of adduct **136** was concomitant with the formation of these two products. This is illustrated in **Graph 1** which shows the change in constitution of the reaction mixture over time.



Graph 1 *Proportion of the four major components in the reaction versus time.*

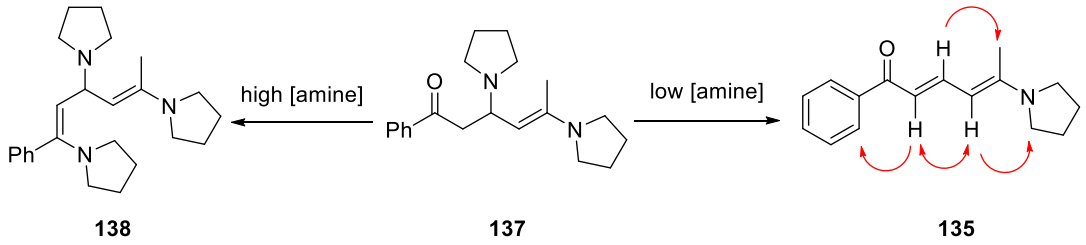
It was hypothesised that the next step in the reaction was the formation of an enamine at the methyl ketone to give enamine **137**. Although intermediate **137** was not observed by ^{1}H NMR analysis of the reaction mixture, it is a reasonable intermediate in the formtation of both the arylamine product **134** and the enamine side product **135**. One plausible explanation is that enamine **137** is either short lived or in rapid equilibrium with adduct **136** and thus only present in small quantities (**Scheme 35**).



133 **136** **137**

Scheme 35 *Proposed formation of enamine **137**.*

It is proposed that enamine **137** is the final common intermediate in the formation of the unwanted side product **135** and the desired arylamine **134**. It was clear from the optimisation studies that high equivalents of amine favoured the formation of arylamine **134** and low equivalents favoured production of enamine **135**. We hypothesise that at low equivalents, intermediate **137** undergoes an elimination reaction to give the most thermodynamically stable conjugated enamine **135** (**Scheme 36**). The structure of extended enamine was confirmed by doublets at 8.05 ppm, 6.61 ppm and 5.36 ppm in the ^{1}H NMR spectrum corresponding to the alkene protons. The geometry these double bonds was proven through nOe enhancements which were consistent with extended enamine **135**.



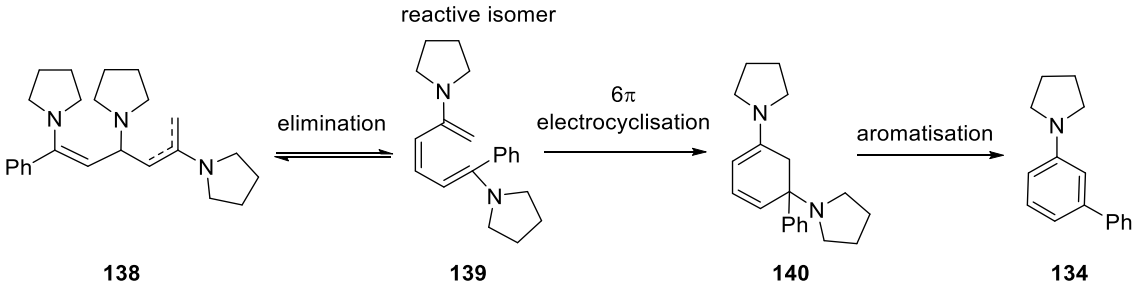
Scheme 36 *Formation of enamine side product* **135**.

At higher concentrations of amine, our hypothesis was that a second pyrrolidine attack takes place on intermediate **137** to give *bis*-enamine **138**. It is proposed there are two possible routes to the desired arylamine **134** from this intermediate, between which we are currently unable to distinguish.

2.1.3.1 Proposed pericyclic mode of cyclisation

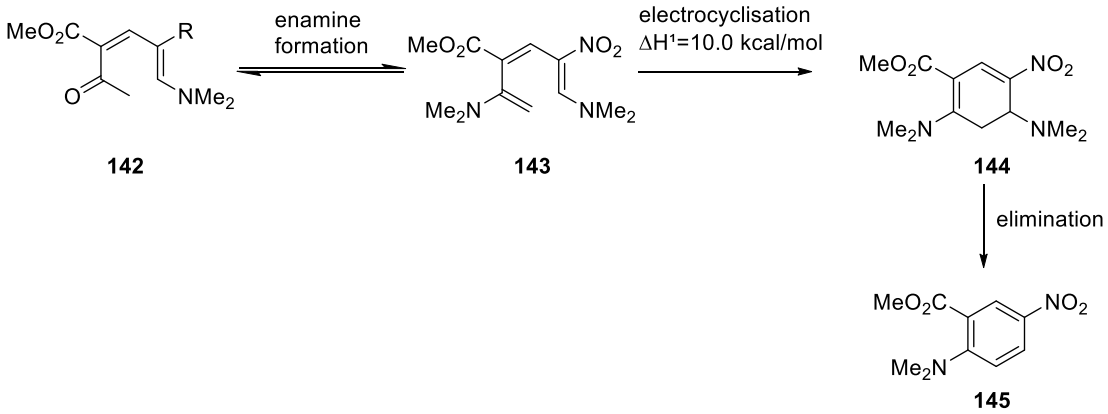
Firstly, elimination of the original pyrrolidine from enamine **138** would give triene **139**. It is unclear why the less favoured *Z*-configuaration is formed. One possibility is that *Z*-product **139** is the only reactive isomer and reversible addition of the pyrrolidine would set up an equilibrium. Any *Z*-product formed would be quickly converted to the arylamine product and although the majority of the material is the *E*-isomer, this cannot perform a cyclisation; so the

only pathway would be conversion back to enamine **138** and eventually to the reactive *Z*-isomer. This would be consistent with the Curtin–Hammett principle. Electrocyclisation of triene **139** would result in diene **140** which would rapidly eliminate pyrrolidine and aromatise to give arylamine **134**.



Scheme 37 *Key electrocyclisation.*

Although 6π electrocyclisations are generally energetically demanding and require high temperatures, there are some systems where the process is known to take place at lower temperatures. Davies and co-workers reported the synthesis of arylamine **145** from vinamidinium salts and methylacetoacetate *via* a dienone intermediate **142** under mild conditions.[64] They proposed that a key electrocyclisation is required to form the aryl ring. Their claims are supported by strong computational evidence and they show that appropriate electronics can drastically lower activation energies (**Scheme 38**).[65]



Scheme 38 *Davies and co-workers proposed mechanism base on computational studies.*

Yu and co-workers also carried out computational studies on the activation barrier of substituted trienes and found that particular substitution patterns of electron-donating and/or

electron-accepting groups can dramatically lower the activation energy of a 6π-electrocyclisation (**Figure 8**).[66] On of these patterns was a good match with the proposed cyclisationm precursor **139**

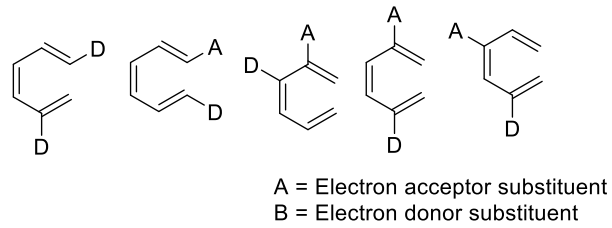
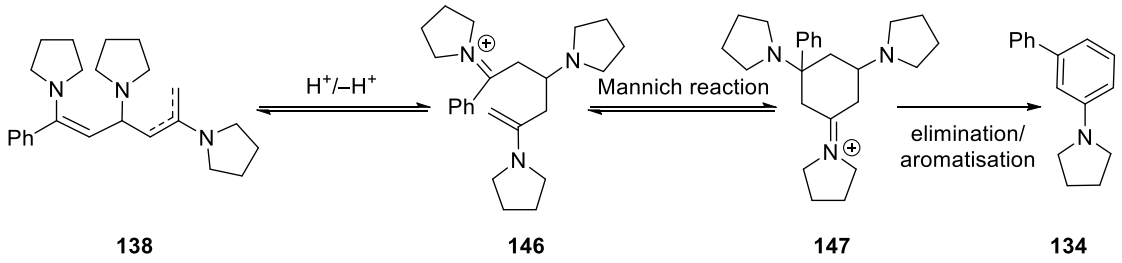


Figure 8 *Some substitution pattens Yu and co-workers calculated would require drastically reduced activation energys for a 6π electrocyclisation.*

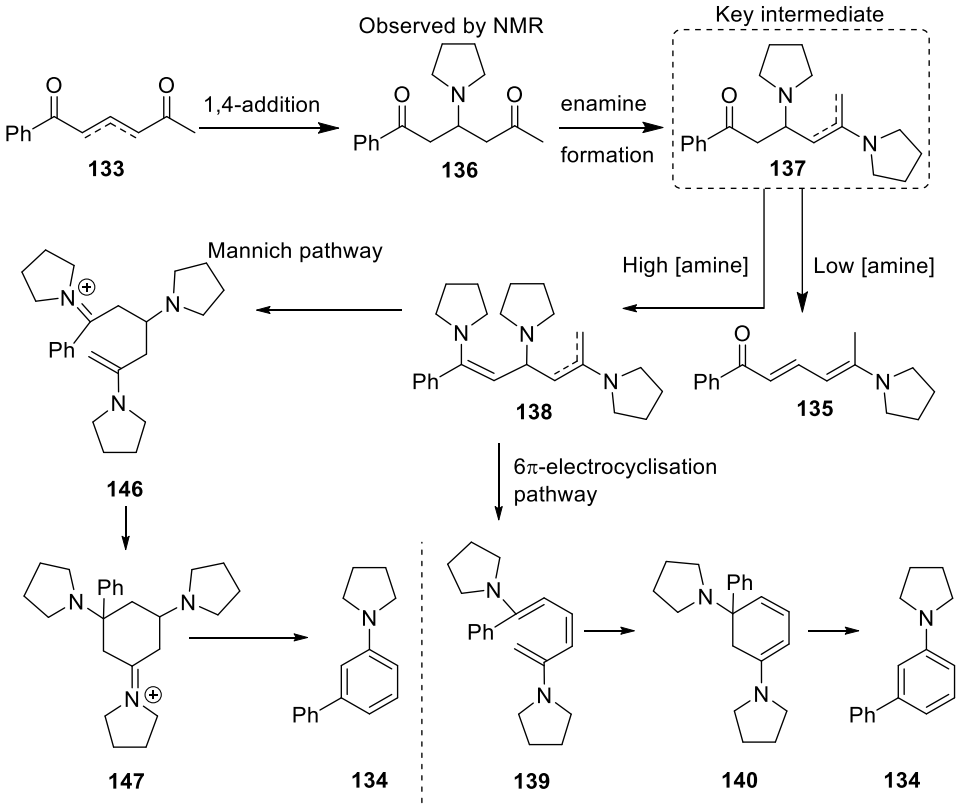
2.1.3.2 Proposed Mannich-type cyclisation

Another plausible mechanism is a Mannich-type reaction. The appeal of such a mechanism is we no longer need to explain the formation of a *Z* alkene but would still explain the cyclisation's dependence on a high equivalents of amine for good conversions to the arylamine product. Tautomer **146** of the *bis*-enamine could undergo a favourable 6-*exo*-trig cyclisation to give cyclohexanone **147**. Subsequent elimination of two molecules of pyrrolidine and tautomerization would result in formation of arylamine **134** (**Scheme 39**).



Scheme 39 *Proposed formation of arylamine **134** via Mannich pathway.*

Our proposed complete mechanism, including both the electrocyclisation and Mannich pathways, is shown below (**Scheme 40**).



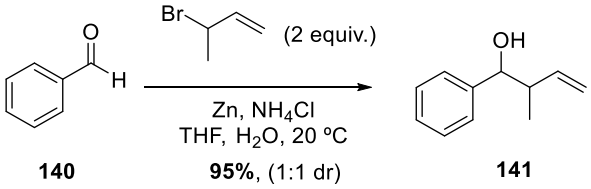
Scheme 40 *Proposed mechanism for arylamine formation.*

2.1.4 Ring substitution

With a good understanding of the effect the conditions had on the cyclisation, the effect that different substituents on the 1,5-dicarbonyl had on the cyclisation was explored.

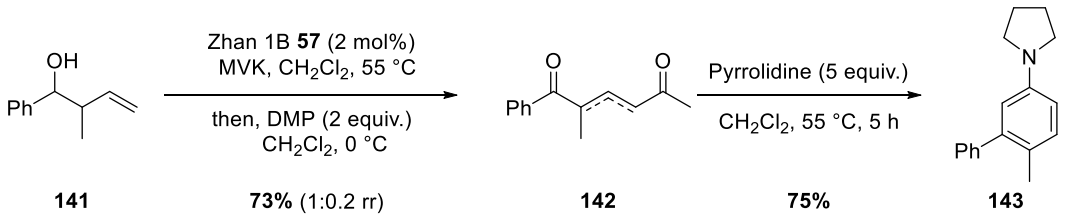
2.1.4.1 Substitution at C-4

The C-4 position on the aryl ring is accessed through substitution at the allylic position of the homoallylic alcohol coupling partner in the cross metathesis reaction. An efficient preparation of homoallylic alcohols *via* a zinc-mediated allylation of an aldehyde was utilised in the synthesis of homoallylic alcohol **141** (**Scheme 41**).



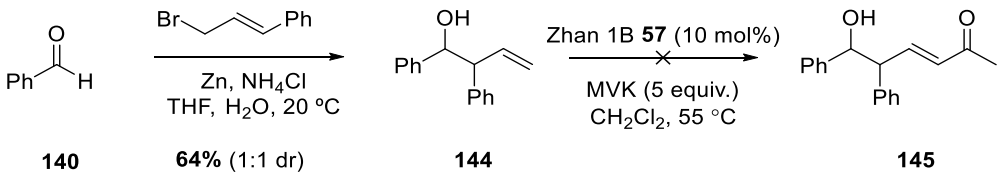
Scheme 41 *Synthesis of homoallylic alcohol **141**.*

Subjecting homoallylic alcohol **141** to the cross metathesis/oxidation protocol gave 1,5-dicarbonyl **142** in 73% yield. The 1,5-dicarbonyl **142** was isolated as a 1:0.2 mixture of regioisomers and the ^{1}H and ^{13}C NMR spectra were a good match to those reported in the literature.[67] The dicarbonyl was then subjected to the cyclisation conditions; in a slight modification to the optimised cyclisation conditions, the reaction was performed at room temperature as it was found to be sluggish at lower temperatures. The reaction was monitored by TLC where the appearance of a non-polar strong blue fluorescent spot was consistent with the formation of an electron rich conjugated system. The formation of arylamine **143** was confirmed by a doublet at 6.56 ppm and a singlet at 6.52 ppm in the ^{1}H NMR spectrum, corresponding to the electron rich aromatic protons *ortho* and *para* to the nitrogen on the arylamine ring. Pleasingly arylamine **143** was isolated in good yield (73%) (**Scheme 42**).



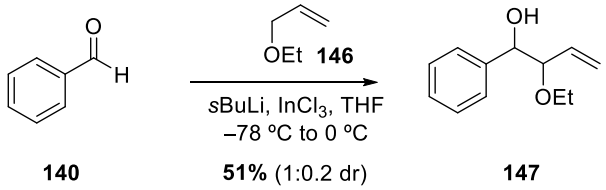
Scheme 42 *Synthesis of arylamine **143**.*

In order to test the tolerance of bulky groups at the C-3 position the synthesis of γ-hydroxy-α,β-unsaturated ketone **145** was undertaken. Treatment of benzylaldehyde (**140**) with 3-bromo-1-phenyl-1-propene under the zinc mediated allylation conditions yielded alcohol **144** in a good 64% yield as a single diastereomer. Subjecting homoallylic alcohol **144** to the cross-metathesis conditions however yielded mostly recovered starting material. This inferred that the cross metathesis reaction was sensitive to large allylic groups on the homoallylic alcohol which was consistent with previous observations made by a co-worker in the group.



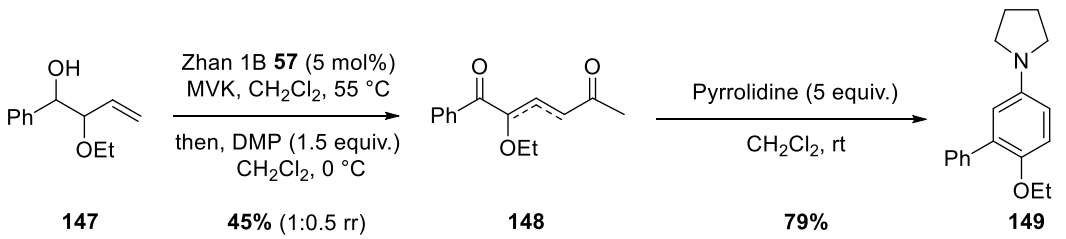
Scheme 43 *Attempted synthesis of γ-hydroxy-α,β-unsaturated ketone **145**.*

In order to test the effect that an extra heteroatom on the 1,5-dicarbonyl would have on the cyclisation, homoallylic alcohol **147** was synthesised from benzylaldehyde (**140**) and enol ether **146** *via* an indium-mediated allylation. The structure of homoallylic alcohol **147** was confirmed by comparison of ^{1}H and ^{13}C NMR spectra to those reported in the literature (**Scheme 44**).[55]



Scheme 44 *Synthesis of homoallylic alcohol **147**.*

Homoallylic alcohol **147** was then subjected to the cross metathesis/oxidation protocol which yielded α,β-unsaturated ketone **148** in moderate yields as a 1:0.5 mixture of regioisomers. This compound was then subjected to the cyclisation conditions; a doublet at 6.97 ppm and a mulitplet 6.68 ppm (intergrating to two protons) in the ^{1}H NMR spectrum were consistent with the formation of arylamine **149** and corresponded to the electron rich aromatic protons on the arylamine ring. Pleasingly arylamine **149** was isolated in a high yield of 79%. (**Scheme 45**).



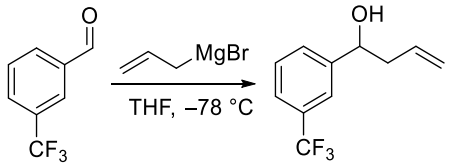
Scheme 45 *Synthesis of arylamine **149**.*

2.1.4.2 Substitution at C-3

It was next decided to investigate the effect of different groups at the C-3 position. Substitution at this position was particularly interesting since this would complement the nucleophilc reactivity of arylamines.

The C-3 position was accessed by changing the group α to the ketone on the homoallylic alcohol partner in the cross metathesis reaction. The α-position in turn came from an aldehyde, thus allowing an easy method to modify the C-3 position with a variety of different groups.

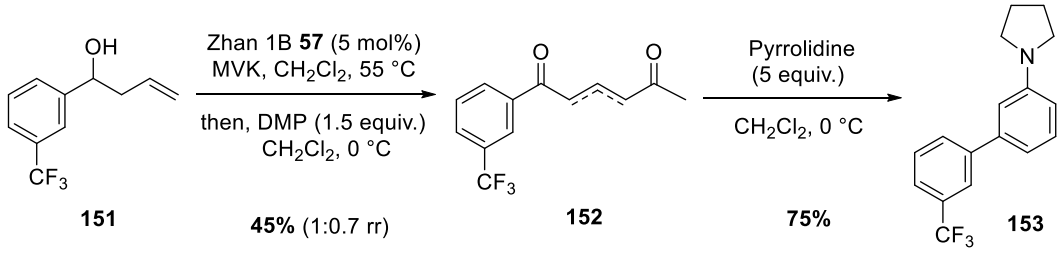
Firstly, it was decided to investigate the effect of different electron donating and electron withdrawing groups. Commercially available benzylaldehyde **150** was treated with allyl magnesium bromide to give homoallylic alcohol **151** in an excellent yield of 90% (**Scheme 46**).



Scheme 46 *Allylation of benzaldehyde **150**.*

Alcohol **151** was then subjected to the cross metathesis/oxidation protocol to give dicarbonyl **152** in a moderate yield of 45%. Subjection of this to the cyclisation conditions gave arylamine **153** in a good yield of 75% and the reaction was also found to proceed in under 2 hours at 0 °C; the product was clearly identified by a singlet at 6.75 ppm and two doublets at 6.89 ppm and 6.63 ppm in ^{1}H NMR spectrum which corresponded to the electron rich aromatic protons *ortho* and *para* to the nitrogen on the arylamine (**Scheme 47**). This result was consistent with our picture of the mechanism, since the trifluoromethyl group inductively increases the electrophilicity of the carbon adjacent to the carbonyl, making the second enamine formation more favourable and increasing the rate of arene formation. The

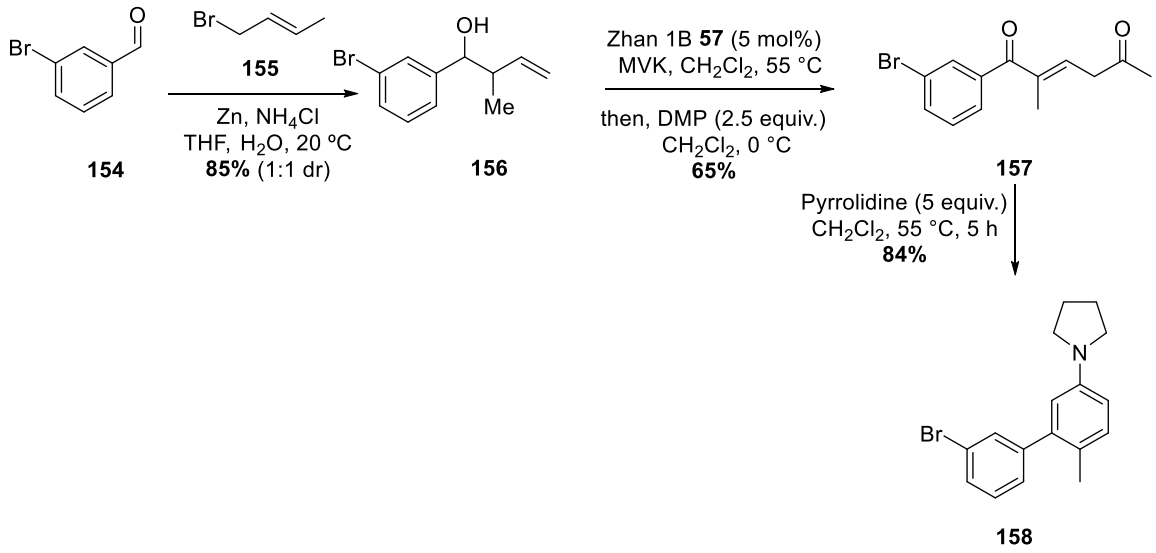
trifluoromethyl group is also an important motif in medicinal chemistry and the inclusion of this group into the scope of our reaction strengthened its utility.



Scheme 47 *Synthesis of arylamine **153**.*

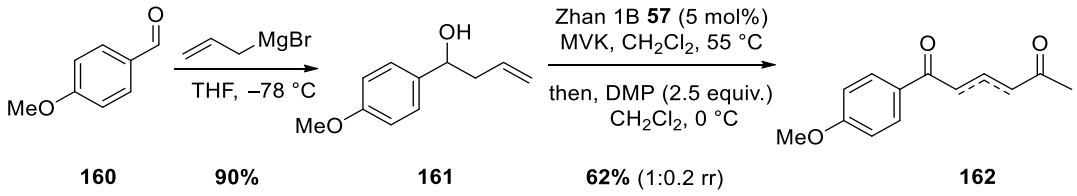
Arylamine **158** was also of interest. The aryl ring at the C-3 position is electron poor and so was relevant to our studies on the electronic effects of the sequence. Also from a synthetic point, the inclusion of a halogen atom offers an opportunity to further diversify the arylamines through metal catalysis and is an example of a product which might be difficult to synthesise by palladium-catalysed methodologies due to the presence of another carbon halogen bond which could present regioselectivity issues.

Benzaldehyde **154** was treated with bromide **155** under zinc-mediated allylation conditions to give homoallylic alcohol **156** in an excellent yield of 85%. Alcohol **156** was then subjected to the cross metathesis/oxidation procedure to give 1,5-dicarbonyl **157** in 60% yield as a single regioisomer. Treatment of dicarbonyl **157** with 5 equivalents of pyrrolidine at room temperature gave arylamine **158** in an excellent 84% yield. The formation of arylamine **158** was confirmed by a singlet at 6.44 ppm and a doublet at 6.56 ppm in the ^{1}H NMR spectrum which corresponded to the electron rich aromatic protons *ortho* and *para* to the nitrogen on the arylamine (**Scheme 48**).



Scheme 48 *Synthesis of arylamine **158**.*

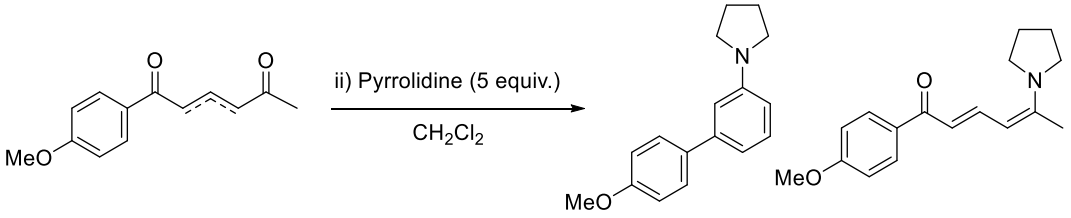
To investigate the effects of an electron rich group, it was decided next to synthesise arylamine **163** from benzaldehyde **160**. Treatment of benzaldehyde **160** with allyl Grignard gave alcohol **161** in 90% yield. Alcohol **161** was then subjected to the cross metathesis/oxidation procedure to give dicarbonyl **162** in good yield as a 1:0.2 mixture of regioisomers and was clearly identified by two sets of carbonyl peaks at 203.6 ppm, 197.3 ppm, 193.6 ppm and 187.5 ppm in the ^{13}C NMR spectrum (**Scheme 49**).



Scheme 49 *Synthesis of dicarbonyl **162**.*

1,5-Dicarbonyl **162** was subjected to the cyclisation conditions. Interestingly, when the reaction was performed at 0 °C, enamine **164** was isolated in 40% yield as the major product with the arylamine **163** being isolated in 26% yield. We hypothesised that the electron donating effect of the *para*-methoxy group deactivated the adjacent carbonyl, making nucleophilic attack from pyrrolidine less favourable; this was consistent with our mechanistic proposal. Pleasingly, heating the reaction was enough to overcome the reduced reactivity and

at 55 °C, arylamine **163** was isolated in 63% yield with only trace amounts of enamine **164** observed (**Scheme 50**).



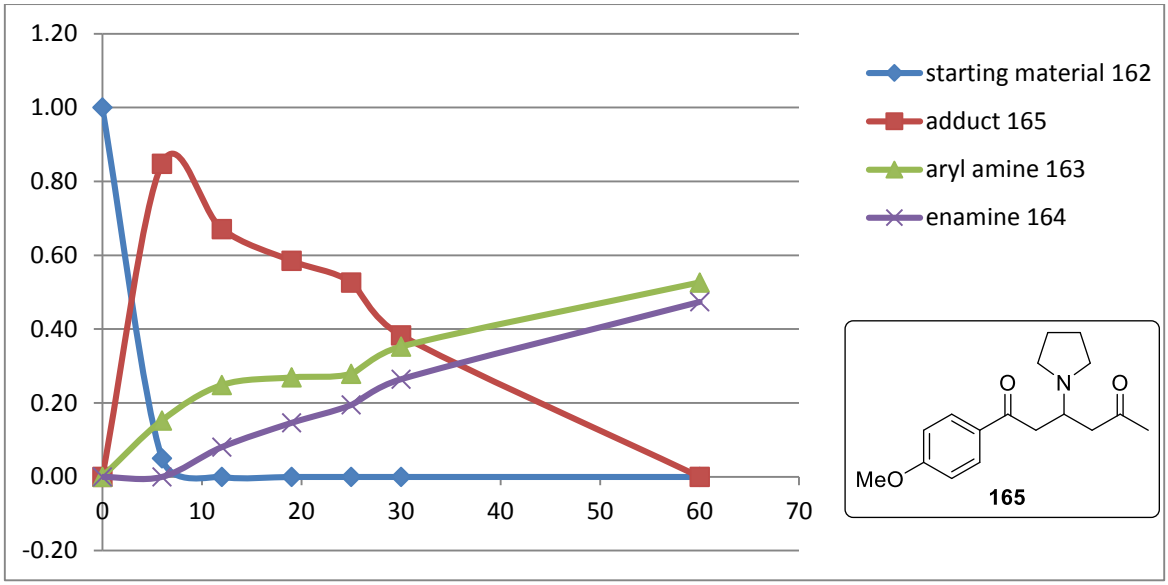
162 **163** **164**

Temperature	**163**	**164**
0 °C	26%	40%
rt	53%[a]	47%[a]
55 °C	63%	0%

[a] conversion based on ^{1}H NMR spectroscopy

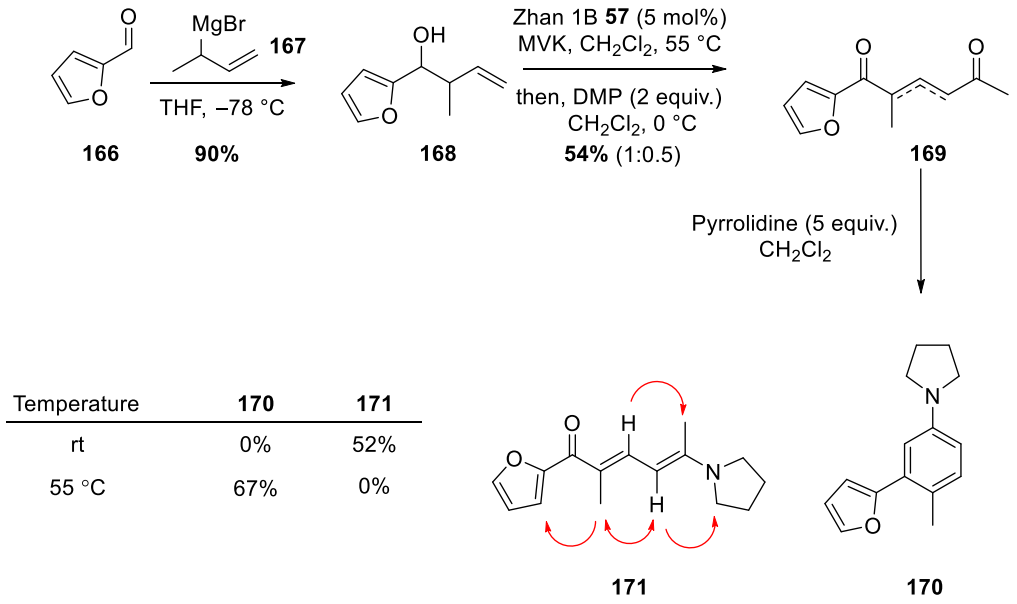
Scheme 50 *Effect of temperature on the formation of arylamine **163** and enamine **164**.*

It was decided to monitor the rate of formation and disappearance of the different components in the reaction over time by ^{1}H NMR analysis (**Graph 2**). Dicarbonyl **162** was treated with 5 equivalents of pyrrolidine at room temperature in an NMR tube and scans were taken at approximately every 5 minutes for 30 minutes and a final scan was recorded at 60 minutes. It was clear that the initial product was the pyrrolidine adduct **165** which was then consumed to give either the arylamine **163** or enamine **164**. The experiment highlighted that the reaction went through the same intermediates observed in the earlier mechanistic studies (**Graph 1**) which suggested that both cyclisations proceeded *via* the same mechanism. It also demonstrated that the reactivity of 1,5-dicarbonyl **162** was much much lower than 1,5-dicarbonyl **133**, which under the same conditions (5 equivalents of pyrrolidine, room temperature) gave near complete conversion to arylamine **134** in under 3 minutes. It was proposed that the electron donating effect of the *para*-methoxy group deactivated the adjacent carbonyl.



Graph 2 *Proportion of the four major components in the synthesis of arylamine **163** versus time.*

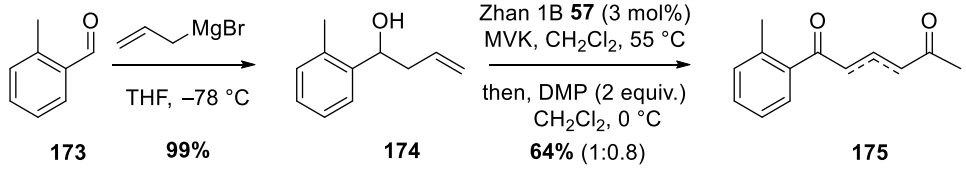
The same approach was then applied to the synthesis of arylamine **170** with a heterocycle, furan, at the C-3 position. Homoallylic alcohol **168** was accessed in good yields *via* treatment of furfural (**166**) with Grignard reagent **167**. This homoallylic alcohol was then subjected to the cross-metathesis/oxidation protocol to yield 1,5-dicarbonyl **169** in a good yield of 54%. Treatment of 1,5-dicarbonyl **169** with 5 equivalents of pyrrolidine at room temperature yielded exclusively enamine **171**, which was characterised by doublets in the ^{1}H NMR spectrum at 7.87 ppm and 5.12 ppm, corresponding to the alkene protons; the geometry of the double bonds was confirmed by n.O.e. studies which supported the proposed structure **171**. Again it is believed that the electron donating furan deactivated the adjacent carbonyl, thus disfavouring the formation of a second enamine and resulting in high conversions to enamine **171**. Pleasingly, heating the reaction to 55 °C gave arylamine **170** in a good yield of 67% (**Scheme 51**).



Scheme 51 *Effect of temperature on formation of arylamine **170** and enamine **171**. nOe enhancements are shown by red arrows.*

With an understanding of the effect that electronics had at the C-3 position, it was decided to explore the influence of steric hindrance at the same position.

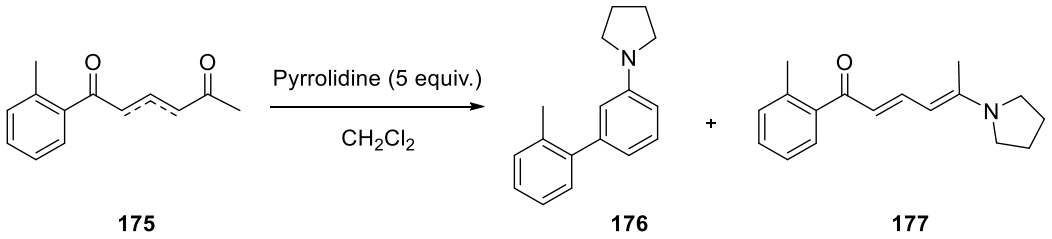
Our studies into the effect of steric hindrance began with homoallylic alcohol **174** which was synthesised from a Grignard reaction between aldehyde **173** and allyl magnesiumbromide. This reaction proceeded smoothly and homoallylic alcohol **174** was furnished in an excellent yield of 99%. Subjecting this olefin to a cross metathesis/oxidation protocol gave 1,5-dicarbonyl **175** in a good yield of 64% (**Scheme 52**).



Scheme 52 *Synthesis of dicarbonyl **175**.*

1,5-Dicarbonyl **175** was then treated with 5 equivalents of pyrrolidine at room temperature. The two major products in the crude reaction mixture were arylamine **176**, characterised by proton shifts between 6.37 - 6.65 ppm, corresponding to the electron rich aromatic protons *ortho* and *para* to the nitrogen on the arylamine ring, and enamine **177** which was not

isolated but exhibited characteristic doublets at 6.15 ppm and 5.25 ppm, which corresponded to the olefin protons and confirmed its presence. By varying the temperature, it was possible to vary the ratio of these two products and room temperature was found give best conversions to arylamine **176**. It was presumed that at lower temperatures, there was not enough energy to either form a second enamine or perform the arylamine forming cyclisation and thus formation of enamine **177** was favoured. The observation that higher temperatures favoured the formation of enamine **177** was consistent with our optimisation studies (**Table 2**, entries 1 - 4). Performing the reaction at room temperature gave arylamine **176** in a moderate yield of 39%.



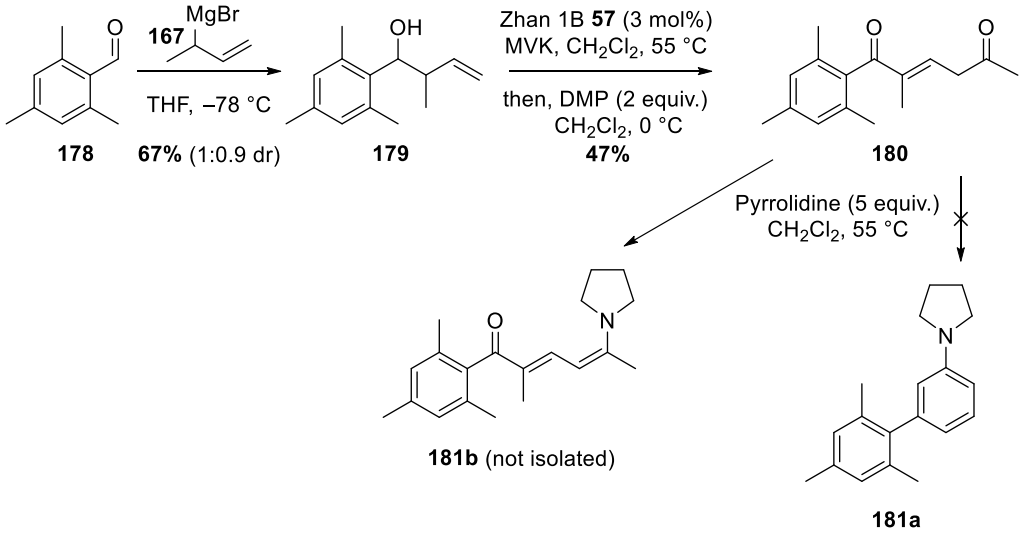
175 **176** **177**

Temperature (°C)	Yield of **176** (%)	Conversion **176/177**
0	16	38:62
rt	39	50:50
40	-	10:90

Scheme 53 *Effect of temperature on formation of arylamine **166** and enamine **177**.*

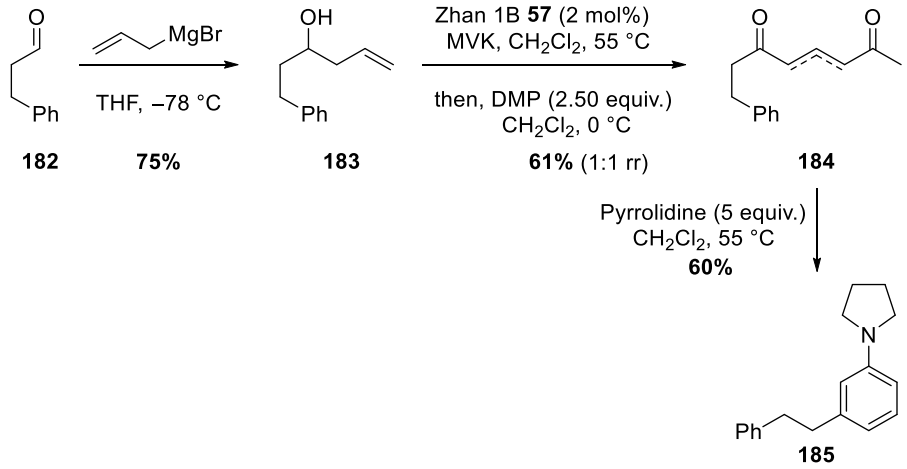
This result demonstrated that it was possible to install an aryl group with an *ortho* substituent at the C-3 position, albeit with a reduced yield. To further test the tolerance of bulky groups at this position, it was decided to synthesise 1,5-dicarbonyl **180** and test this substrate in the cyclisation. Mesitaldehyde (**178**) was allylated with Grignard reagent **167** to give homoallylic alcohol **179** in a good 67% yield as a 1:0.9 mixture of diastereomers. Treatment of this compound with the cross metathesis/oxidation protocol gave 1,5-dicarbonyl **180** as a single regioisomer. Unfortunately using the conditions optimised for the cyclisation of 1,5-dicarbonyl **175**, the reaction could not be encouraged to take place. Analysis of the crude

material suggested the enamine side product **181b** was the major product but it was not isolated.



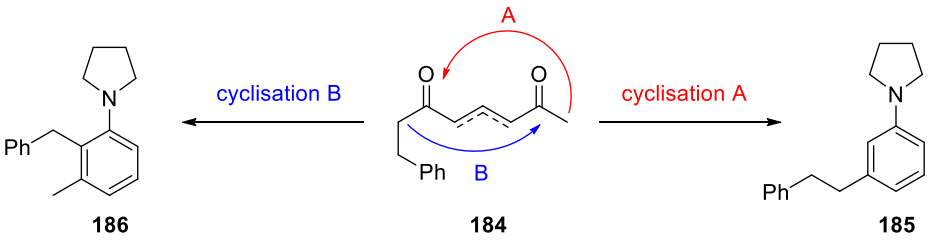
Scheme 54 *Attempted synthesis of arylamine **181**.*

We next attempted to install an alkyl group at the C-3 position. Homoallylic alcohol **183** was synthesised by the addition of allyl magnesiumbromide to hydrocinnamaldehyde (**182**) to give the desired homoallylic alcohol **183** in 75% yield. Subjecting this compound to a cross metathesis/oxidation protocol gave 1,5-dicarbonyl **184** in a good 61% yield. Pleasingly, treatment of 1,5-dicarbonyl **184** with the cyclisation conditions gave arylamine **185** in 60% yield (**Scheme 55**).



Scheme 55 *Synthesis of arylamine **185**.*

This reaction not only expanded the scope of the methodology to include an alkyl group at C-3 but was interesting because it is conceivable that a cyclisation could take place at either end of the dicarbonyl **184**, due to the presence of two enolisable centres. Each cyclisation would result in a different arylamine, **185** and **186**, however only one was observed. It was important to distinguish between the two possible products. The product was characterised as arylamine **185** due to two methylene signals in the ^{1}H NMR which were consistent with arylamine **185** and the lack of a CH_3 signal in the ^{1}H NMR required for arylamine **186**. This evidence supports a cyclisation of type A taking place (**Scheme 56**).

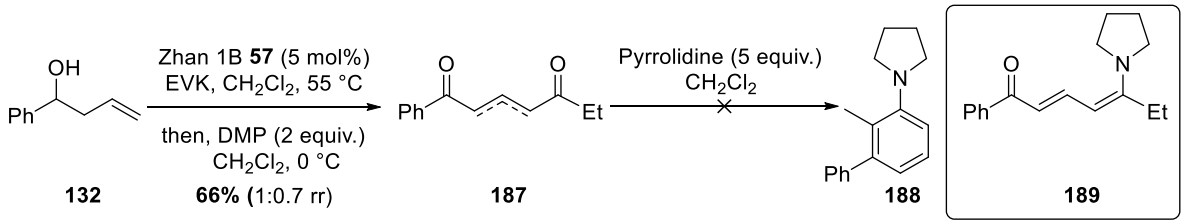


Scheme 56 *Two possible products from the cyclisation of 1,5-dicarbonyl **184** with pyrrolidine.*

2.1.4.3 Substitution at C-2

The C-2 position of the arylamine can be accessed *via* the use of different of vinyl ketones in the cross metathesis reaction, and the expected products would be 1,2,3-trisubstituted arylamines. Firstly, we tried to install a methyl at the C-2 position. Ethyl vinyl ketone was used in the cross metathesis reaction with homoallylic alcohol **132**. Oxidation of the resulting homoallylic alcohol gave 1,5-dicarbonyl **187** in a good yield of 66%. Treatment of this 1,5-dicarbonyl with 5 equivalents of pyrrolidine at room temperature gave a characteristic non-polar, light blue spot by TLC analysis and a ^{1}H NMR spectrum of the crude reaction mixture showed desired product **188** peaks, however there also appeared to be signals correlating to an extended enamine side product **189**, which was analogous to the side products observed with previous 1,5-dicarbonyls. Purification of the reaction mixture yielded approximately 5% of a compound with a ^{1}H NMR spectrum which was consistent with that

of arylamine **188**.[68] The addition of $ZnCl_2$ was ineffective, as well as heating the reaction to 55 °C and mostly decomposition was observed (**Scheme 57**).



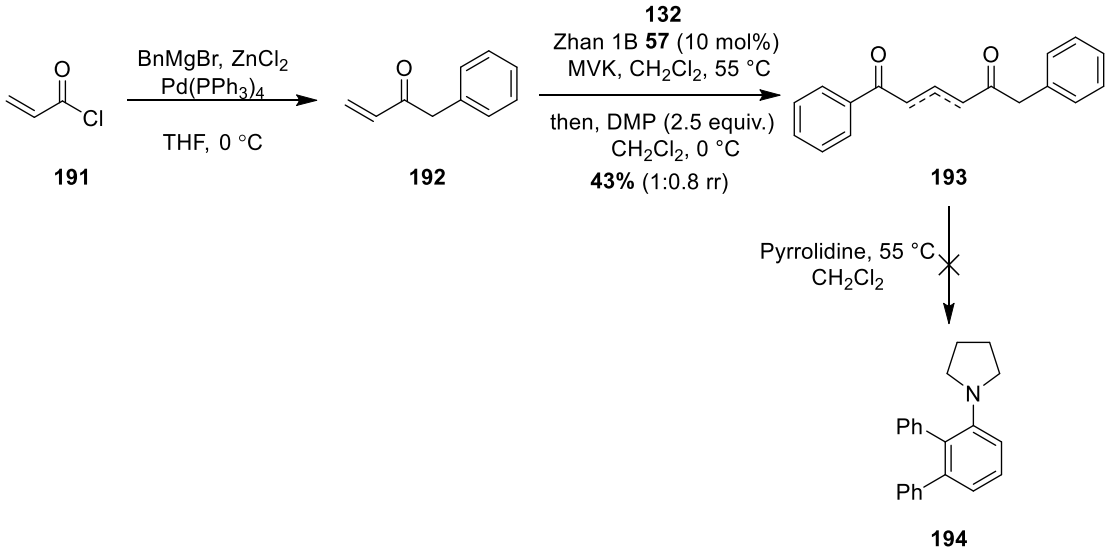
132 **66%** (1:0.7 rr) **187** **188** **189**

Temperature	**188**
rt	trace
rt	trace[a]
55 °C	trace[a]

[a] $ZnCl_2$ (1 equiv. added)

Scheme 57 *Attempted synthesis of arylamine **188**.*

We hypothesised that the electronic donating ethyl group might exert an electronic effect on the cyclisation and perhaps a different substituent may favour the cyclisation. Hence, we set about synthesising unsaturated 1,5-dicarbonyl **193**. Acryloyl chloride was subjected to a Negishi coupling with the zinc reagent resulting from the transmetalation of phenyl magnesium bromide with $ZnCl_2$ to yield unsaturated ketone **192** in 48% yield. A cross metathesis of the vinyl ketone **192** with allylic alcohol **132**, followed by an oxidation gave 1,5-dicarbonyl **193** in 43% yield. Unfortunately, subjecting 1,5-dicarbonyl **193** to the cyclisation conditions at 55 °C with or without $ZnCl_2$ did not give arylamine **194** and analysis of the ^1H NMR spectrum of the crude material showed decomposition (**Scheme 58**).



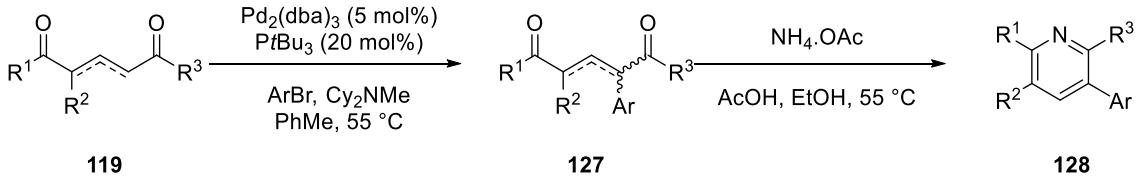
Scheme 58 *Attempted synthesis of arylamine **194**.*

Since efforts to increase the yields of the reaction with a substituent at C-2 to a reasonable level were unsuccessful, it was hypothesised that the increased bulk at the reaction centre was responsible for the lack of reactivity. This is consistent with our observations of complete regioselectivity of 1,5-dicarbonyl **184** (**Scheme 55**) where two possible cyclisations could take place. In that case, only the formation of an arylamine **185** was observed which was the product of a cyclisation from the less hindered side of the dicarbonyl (**Scheme 56)**.

2.1.4.4 Substitution at C-6

The C-6 position could be accessed *via* substituents at the α-position of the carbonyl which comes from the vinyl ketone partner in the cross metathesis reaction. Unfortunately, the cross metathesis of 1,1-disubstituteted vinyl ketones is known to be a difficult transformation[69] and previous studies in the Donohoe group had shown it not to be an amenable strategy for their synthesis. One of the advantages of a *de novo* synthesis of aromatic compounds is the option of functionalising the intermediates and taking advantage of the regioselective chemistry available for non-aromatic systems. Previous work in the Donohoe group had shown that treatment of 1,5-dicarbonyl **119** with $Pd_2(dba)_3$ and tBu$_3$P·HBF$_4$ under conditions developed by Fu[70] and co-workers gave the product of the α-arylation reaction **127**.[63] The arylation

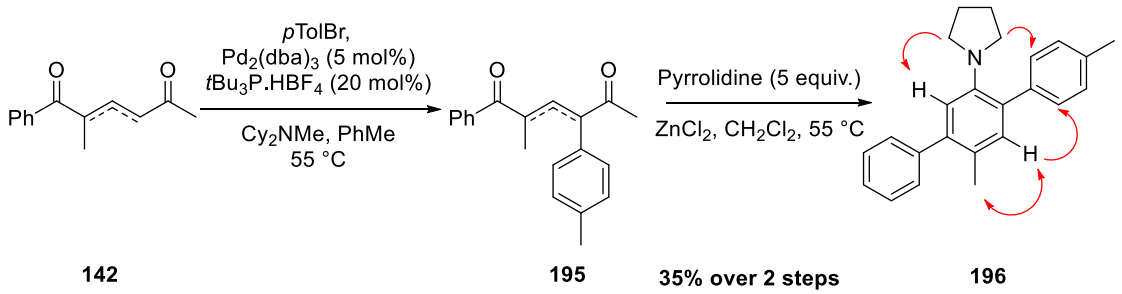
product was a complex mixture of isomers; however, treatment of this mixture with NH_4Cl in ethanol resulted in the formation of a pyridine **128** in good yield over two steps.



119 **127** **128**

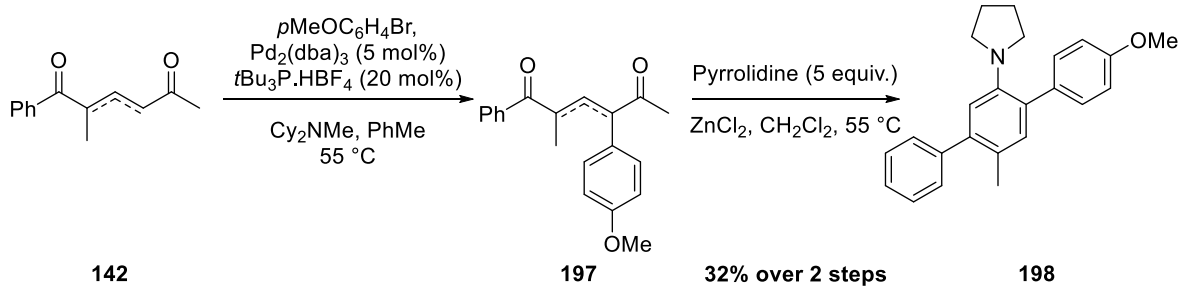
Scheme 59 *Synthesis of 2,3,5,6-substituted pyridines.*

The same modification to the 1,5-dicarbonyl would give access to the C-6 position of the arylamines and was therefore investigated. 1,5-Dicarbonyl **142** was treated with *p*-tolyl bromide, $Pd_2(dba)_3$ and $P(tBu_3)\cdot HBF_4$ in toluene and heated to 55 °C for 12 hours to give the arylation product **195** as a mixture of stereoisomers. A ^1H NMR spectrum of the product confirmed the formation of dicarbonyl **195** by the disappearance of doublets at 3.39 ppm and 6.11 ppm corresponding to the CH_2 and CH of the starting material and the appearance of a singlet at 2.40 ppm corresponding to the tolyl group. Treatment of the resulting mixture with 5 equivalents of pyrrolidine and $ZnCl_2$ at 55 °C resulted in smooth conversion to arylamine **196** in 35% yield over two steps. The structure of arylamine **196** was confirmed by diagnostic singlets at 7.01 ppm and 6.70 ppm in the ^1H NMR spectra corresponding to the protons on the arylamine ring. The substitution pattern of arylamine **196** was confirmed by n.O.e. studies which were consistent with structure **196**. Arylamine **196** was found to be particularly sensitive to air; we hypothesise that the extra electron donating effect of the tolyl group makes the arylamine very susceptible to oxidation. As a result, a good quality ^{13}C NMR spectrum could not be obtained for this arylamine (**Scheme 60**).



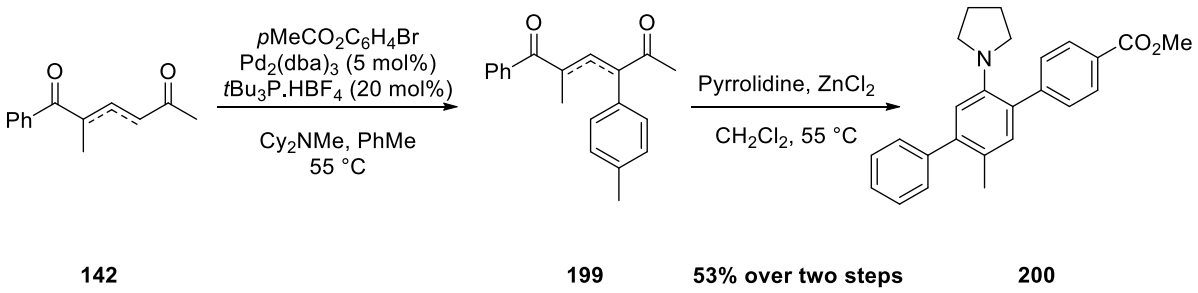
Scheme 60 *Synthesis of arylamine **196**. nOe enhancements are shown by red arrows.*

We then explored the effect of both electron rich and electron deficient aryl bromides in the α-arylation/cyclisation protocol. Pleasingly, the α-arylation using 4-bromoanisole worked well and a ^{1}H NMR spectrum of the crude material suggested good conversion (~70%) to product **197**. Pleasingly, treatment of this mixture with the same cyclisation conditions used in **Scheme 60** gave arylamine **198** in a moderate yield of 32% over two steps. Again arylamine **198** proved sensitive to oxidation and a good quality ^{13}C spectrum could not be obtained (**Scheme 61**).



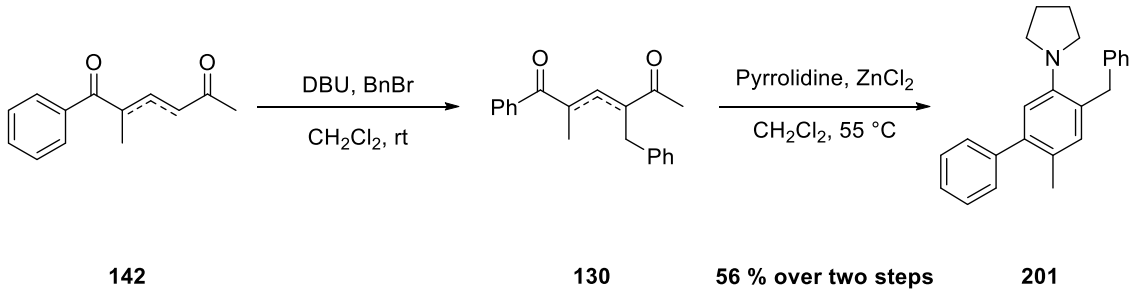
Scheme 61 *Synthesis of arylamine **198**.*

Finally, electron an deficient aryl bromide was subjected to the α-arylation/cyclisation protocol. The arylation proceeded smoothly and the mixture obtained was subjected to the cyclisation conditions. Pleasingly, arylamine **200** was furnished in a good 53% yield over two steps and full characterisation data could be obtained. This is in agreement with the hypothesis that oxidation is the main decomposition pathway for these arylamines, as the electron withdrawing ester lowers the susceptibility of this aryl system to oxidation.



Scheme 62 *Synthesis of arylamine **200**.*

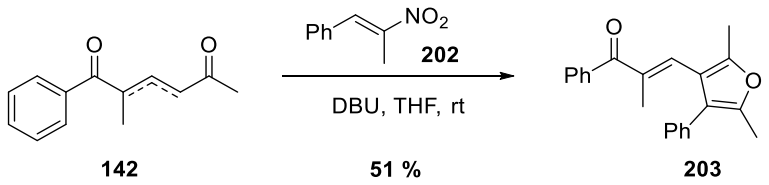
Having successfully demonstrated our ability to install a range of aryl groups at the C-6 position, it was next decided to explore the installation of an alkyl group. One approach to synthesising the prerequisite 1,5-dicarbonyl would be deprotonation of 1,5-dicarbonyl **142** at the internal α-position followed by alkylation with a suitable alkyl halide. This method had previously been explored in the Donohoe group and it was found that 1,8-diazabicycloundec-7-ene (DBU) was the most effective base for the deprotonation.[63] Deprotonation of 1,5-dicarbonyl **142** with DBU in CH_2Cl_2 followed by electrophilic attack of benzyl bromide gave substituted 1,5-dicarbonyl **130** after 3 hours. Thus was purified through a pad of SiO_2 and the mixture subjected to the cyclisation conditions. Pleasingly, arylamine **201** was furnished in a good 56% yield over two steps and its structure confirmed by a singlet at 4.06 ppm in the ^1H NMR spectrum corresponding to the benzyl protons. Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 328.2064 (Δ − 2.1 ppm), which corresponded to the $[M+H]^+$ ion of arylamine **201**. However, the product proved sensitive to oxidation and a good quality ^{13}C NMR spectrum could not be obtained (**Scheme 63**).



Scheme 63 *Synthesis of arylamine **201**.*

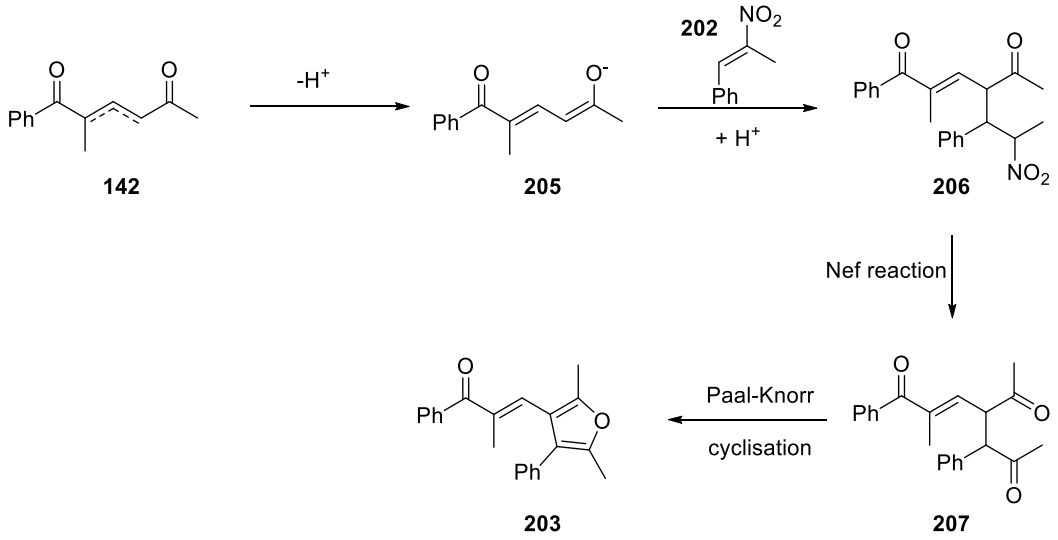
We then decided to explore the effect of Michael acceptors as the alkylating agents. The Michael addition of *trans*-β-methyl-β-nitrostyrene (**202**) would yield an interesting product with an intramolecular source of nitrogen for the cyclisation that might give access to indole

frameworks. Treatment of 1,5-dicarbonyl **142** with styrene **202** and DBU at room temperature, however, gave an unexpected product which we propose to be structure **203** (**Scheme 64**). Structure **203** is supported by a singlet in the ^{1}H NMR spectrum at 6.75 ppm which is a good match for the β-proton of an unsaturated ketone. Three other singlets at 2.25 ppm, 2.17 ppm and 1.84 ppm correspond to the three methyl groups. A singlet at 199.0 ppm in the ^{13}C NMR spectrum and stretching at 1647 cm^{-1} in the IR spectra are consistent with an aryl ketone.



Scheme 64 *Unexpected reaction of styrene **202** and dicarbonyl **142** and proposed product **203.***

Of course the formation of this product is of interest and the following mechanism is proposed for its formation (**Scheme 65**). Deprotonation of dicarbonyl **142** gives enolate **205** which performs a conjugate addition with styrene **202** to yield adduct **206**. Adduct **206** then undergoes a Nef reaction, which has been reported to take place in the presence of DBU,[71] followed by Paal-Knorr furan cyclisation, which may take place upon an acid workup to yield furan **203**.



Scheme 65 *Proposed mechanism of furan **203** formation.*

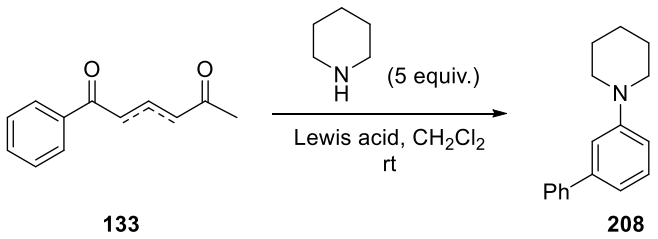
2.1.5 Amine Scope

After exploring the effect that 1,5-dicarbonyls had on cyclisation, we next investigated the range of amines that might be successful in orchestrating the cyclisation. This would greatly increase the utility of method and could provide some more insights into the mechanism. It was decided to use 1,5-dicarbonyl **133** to study the amine scope, as the substrate was reactive at low temperatures with pyrrolidine and by keeping this part constant, the relative reactivity of amines could be compared.

2.1.5.1 Secondary amines

We first decided to investigate which other secondary amines would be tolerated in the cyclisation.

Firstly the effect of changing from pyrrolidine to piperidine was explored. 1,5-Dicarbonyl **133** and 5 equivalents of piperidine were subjected to the best cyclisation conditions from the optimisation studies (CH_2Cl_2, room temperature). However, under extended reaction times arylamine **208** was formed in poor conversions. Arylamine **208** could be easily distinguished by a singlet at 7.18 ppm and doublets at 7.07 ppm and 6.97 ppm in the ^{1}H NMR spectrum which corresponded to the electron rich aromatic protons, *ortho* and *para* to the nitrogen on the arylamine ring. As piperidine is less nucleophilic than pyrrolidine, we thought that the addition of a Lewis acid might increase the electrophilicity of dicarbonyl **133**. Thus, the effect of different Lewis acids on the cyclisation was explored. Pleasingly, we noticed an immediate improvement in yield and the use of $ZnCl_2$ gave nearly complete conversion at room temperature, furnishing arylamine **208** in an isolated yield of 74% (**Scheme 66**).

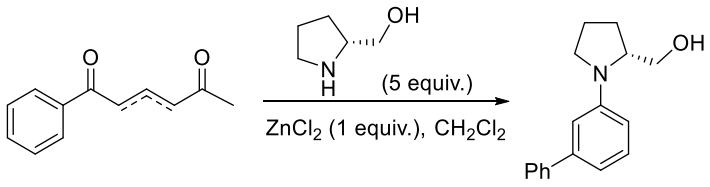


133 **208**

Additive	Time (h)	Yield
-	72	10%
$TiCl_4$	12	54%
BF_3•OEt_2	12	54%
$ZnCl_2$	12	74%

Scheme 66 *Effect of Lewis acid on the formation of arylamine **208***

These conditions were then applied in the synthesis of arylamine **209**. Arylamine **209** was clearly identified by doublets at 6.98 ppm and 6.78 ppm and a singlet at 6.92 ppm in the ^{1}H NMR spectrum which corresponded to the electron rich aromatic protons *ortho* and *para* to the nitrogen on the arylamine ring and was isolated in 66% yield (**Scheme 67**). Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 254.1539, which corresponded to the $[M+H]^+$ ion of arylamine **209**. The enantiomeric excess of compound **209** was also measured and found to have undergone no erosion during the cyclisation. Racemisation of chiral starting materials has been reported in the Buchwald-Hartwig amination reaction so this result strengthens the methodology.[72]

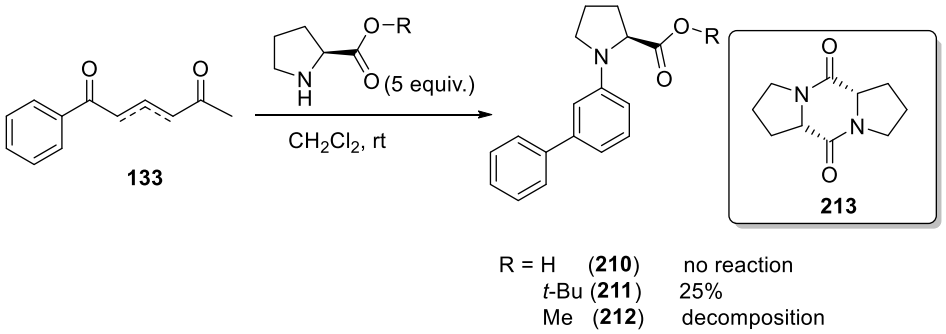


133 **66%** **209**, >99% ee

Scheme 67 *Synthesis of arylamine **209***

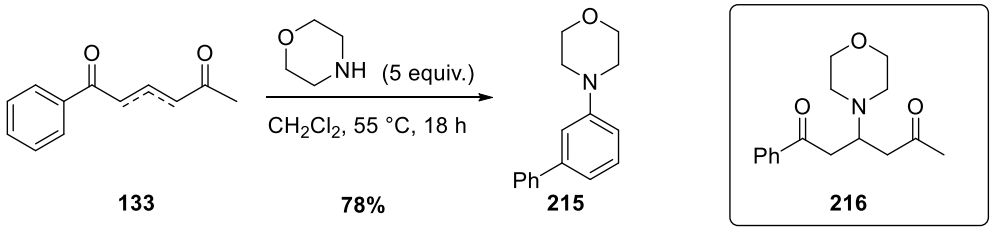
The next amine studied in the cyclisation was L-proline. This would be an interesting arylamine to access as the acidic proton at the chiral centre is readily racemised under the influence of strong base, commonly used for the Buchwald-Hartwig amination. Treatment of

1,5-dicarbonyl **133** with proline gave no formation of product **210** and analysis of the crude material showed mainly unreacted starting material. Pleasingly, some conversion to arylamine **211** was observed using the *t*-butyl ester of L-proline and this was confirmed by the formation of a compound with characteristic doublets at 6.93 ppm and 6.56 ppm and a singlet at 6.77 ppm in the ^{1}H NMR spectrum which corresponded to the electron rich aromatic protons *ortho* and *para* to the nitrogen on the arylamine ring; however the isolated yield was only 25%. The addition of $ZnCl_2$ reduced the presence of this compound to only trace amounts in the ^{1}H NMR spectrum of the crude reaction mixture. We hypothesised that the *t*-butyl ester was too bulky to form a *bis*-enamine. Unfortunately, attempts to synthesise the methyl ester resulted in the isolation of a compound which had data which matched that of dimer **213**, and also attempts at using the HCl salt of the methyl ester of proline in the cyclisation resulted in no product being formed (**Scheme 68**).



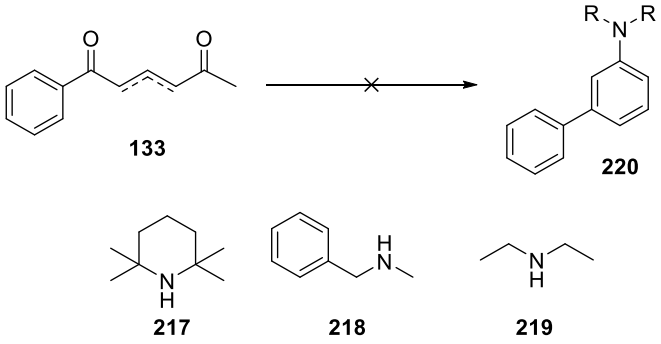
Scheme 68 *Attempted synthesis of proline based arylamines.*

We next investigated the use of morpholine in the cyclisation. However, when subjecting morpholine to $ZnCl_2$, a white precipitant formed, and low yields were observed in the cyclisation. Pleasingly, warming the reaction to 55 °C without the addition of $ZnCl_2$ was enough to give enhanced reactivity and arylamine **215** was isolated in 78% yield. Interestingly, the reaction of 1,5-dicarbonyl **133** and one equivalent of morpholine produced the 1,5-adduct **216** which was isolated and fully characterised (**Scheme 69**).



Scheme 69 *Synthesis of arylamine **215** and adduct **216**.*

In order to explore the tolerance of bulky amines, tetramethyl piperidine **217** and diethylamine **219** were subjected to the cyclisation conditions. However, neither substrate resulted in a successful cyclisation under our conditions. This was perhaps unsurprising since our proposed mechanism involves the formation of two enamines and it is well known that these amines are poor nucleophiles. Treatment of 1,5-dicarbonyl **133** with *N*-methyl benzyl amine (**218**) did show some conversion by ^{1}H NMR analysis, however even with optimisation, this could not be increased to an acceptable yield (**Scheme 70**).



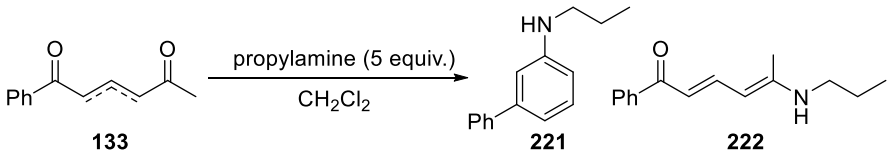
Scheme 70 *Bulky amines which failed in the cyclisation.*

2.1.5.2 Primary amines

2.1.5.2.1 Optimisation of the cyclisation

It was decided to determine whether this methodology could be expanded to include primary amines as substrates for the cyclisation. Again, the unsaturated 1,5 dicarbonyl **133** was chosen for the initial studies and *n*-propyl amine as the primary amine. The original conditions (5 equivalents amine, 0 °C, CH_2Cl_2, 2 hours) gave only moderate conversions to arylamine **221** (**Table 3,** entry 1). Similar to the pyrrolidine optimisation, a ^{1}H NMR

spectrum of the crude reaction mixture looked clean with the major product being the desired arylamine **221**, characterised by doublets at 6.95 ppm and 6.64 ppm and a singlet at 6.84 ppm which corresponded to the electron rich aromatic protons *ortho* and *para* to the nitrogen on the aryl ring. Doublets at 6.32 ppm and 3.81 ppm in the ^{1}H NMR spectra were consistent with an enamine **222**, analogous to the side product observed in the experiments with pyrrolidine (**Table 2**), however the side product was not isolated. We set about investigating different conditions for the cyclisation using propyl amine (**Table 3**).



133 **221** **222**

	Temperature (°C)	Additive	Concentration (M)	Time (h)	Conversion to **221**[a] (isolated yield)
1	0	-	0.10	2	33%
2	0	-	0.10	4	54% (38%)
3	rt	-	0.10	4	71% (50%)
4	rt	-	0.10	12	90%
5	rt	-	0.25	12	90%
6	rt	-	0.05	12	92%
7	rt	-	0.01	12	89%
8	**rt**	**-**	**0.10**	**72**	**100% (69%)**
9	rt	$Sc(OTf)_3$	0.10	12	79%
10	rt	$Ti(OEt)_4$	0.10	12	85%
11	rt	$ZnCl_2$	0.10	12	77% (42%)
12	40	-	0.10	12	90%
13	**55**	**-**	**0.10**	**12**	**100% (73%)**

[a] by ^{1}H NMR analysis

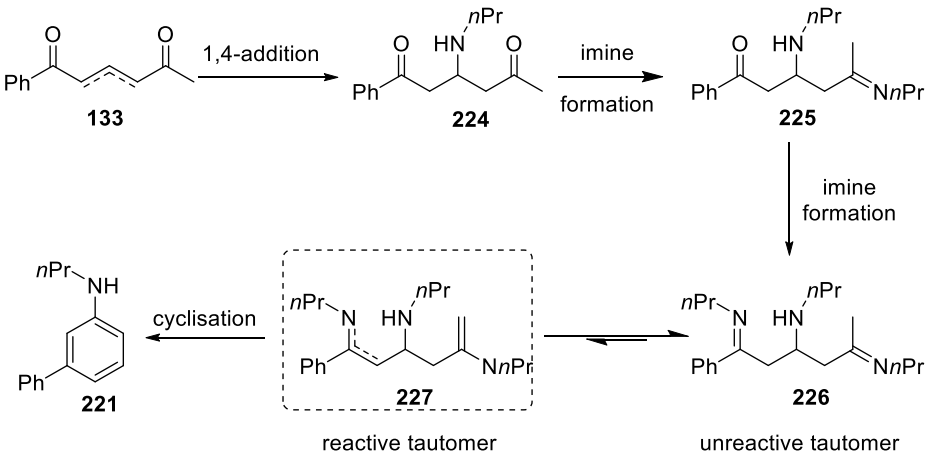
Table 3 *Optimisation of arylamine **221** formation.*

Firstly, the effect of temperature and time on the reaction was investigated. By increasing the reaction time from 2 hours to 4 hours, an improved conversion of 20% was realised (**Table 3**, entry 2). A further increase in conversion was observed when the reaction was carried out at room temperature (entry 3). Changes in concentration had little effect on the conversions to

arylamine **221** (entries 5-7). Pleasingly, increasing the reaction time to 72 hours gave near-complete conversion to the desired product with an isolated yield of 69% (entry 8). Moreover, the addition of different Lewis acids had little effect (entries 9-11). Increasing the temperature to 55 °C also led to complete conversion after 12 hours with arylamine **221** being obtained in an isolated yield of 73% (entry 13).

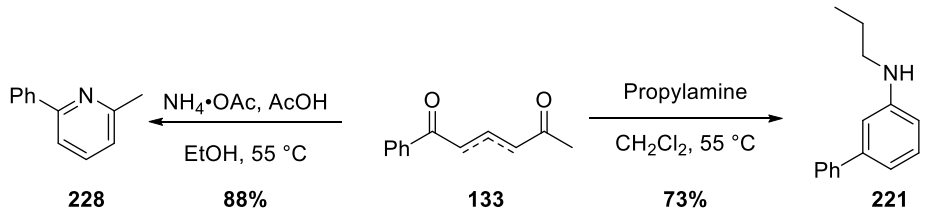
2.1.5.2.2 Pyridine versus arene formation - mechanisic studies

At this point we decided to reflect on the mechanism of the arylamine formation with primary amines. The results were consistent with our current mechanistic hypothesis (**Scheme 40,** page 42); primary amines form less stable enamines and thus the equilibrium lies to the side of the imine; *i.e.* there is less of the reactive tautomer **227** present and so the formation of arylamine **221** takes longer or requires more forcing conditions (**Scheme 71**).



Scheme 71 Proposed mechanism for arylamine **221** formation.

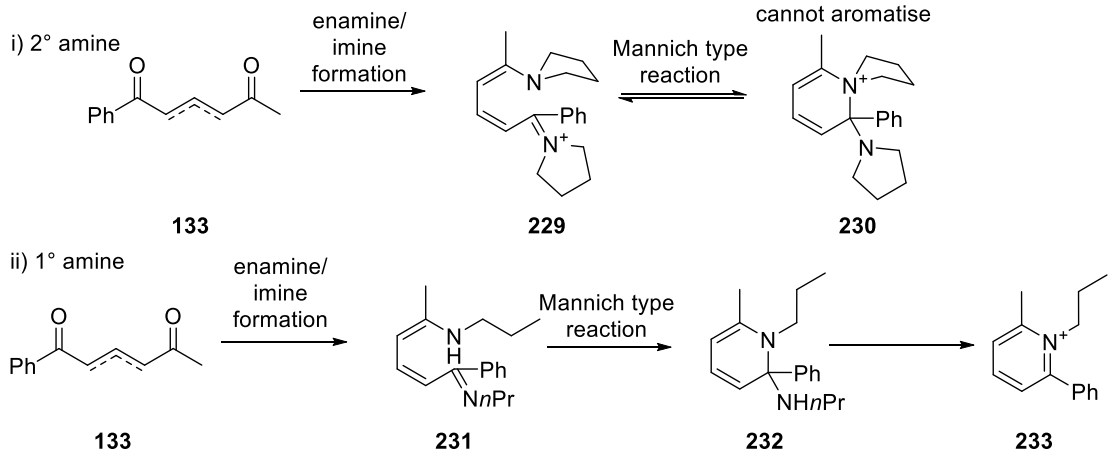
It was interesting to think about why arylamines were formed when a 1,5-dicarbonyl **133** was treated with a primary or secondary amine but in previous studies, reactions of 1,5-dicarbonyl **133** with ammonia formed the pyridine as the favoured product (**Scheme 72**).[63] The difference between the two reactions were twofold, i) the conditions and ii) the nitrogen source used. Thus, a programme of study was set up to investigate which of these factors was the cause of the change in selectivity of the reaction.



Scheme 72 *Two different reactions of 1,5-dicarbonyl **133** with different nitrogen sources.*

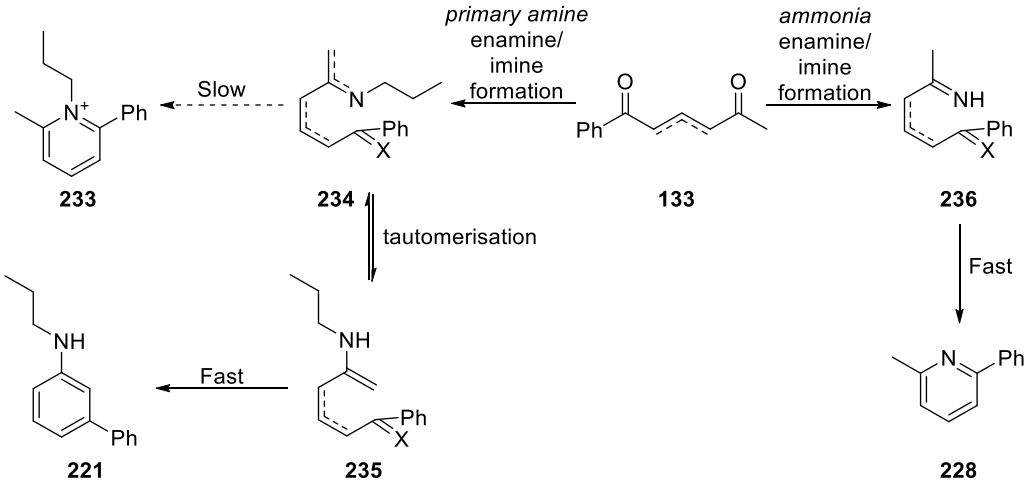
With secondary amines, the nucleophilic carbon of the enamine is the only site where the cyclisation will lead to a stable product. If intermediate **229** were to cyclise then a quaternary nitrogen (**230**) would be formed which cannot aromatise to a pyridine (**Scheme 73**, i). Thus, for secondary amines, it is the amine source which dictates the selectivitity of the cyclisation.

However, with primary amines, it is conceivable that the nitrogen of enamine **231** could cyclise and aromatise to give a pyridinium salt **233** (**Scheme 73**, ii). An electrocyclisation mechanism could be equally conceived.



Scheme 73 Formation of pyridine structure.

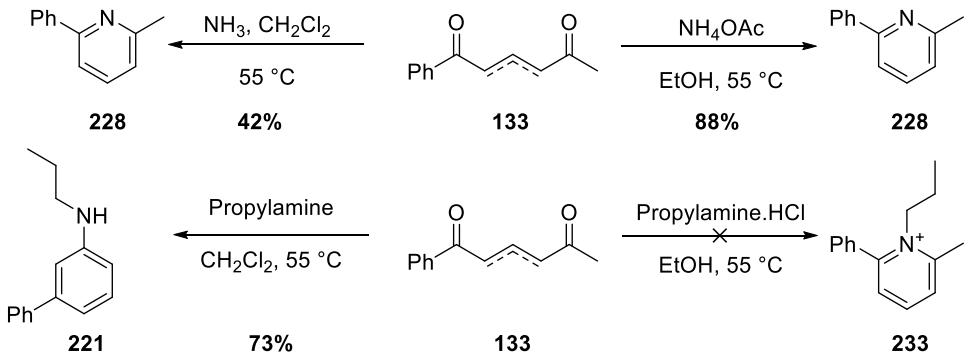
However, pyridinium salt **233** was not observed during the reaction. It is hypothesised that the reaction site is very sensitive to steric hindrance and the smaller nucleophilic carbon of enamine **235** is the preferred site of reaction (**Scheme 74**). This is supported by our earlier experiments, where we found that increasing the steric bulk at C-2 dramatically hindered the cyclisation (**Scheme 57,** page 54).



Scheme 74 *Proposed explanation for the different reactivities of a primary amine and ammonia.*

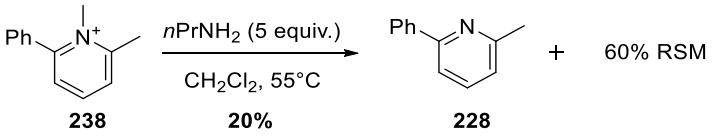
The formation of pyridines from 1,5-dicarbonyl **133** is also performed under acidic conditions (NH_4·OAc, AcOH) and it was possible that under basic conditions, an arylamine would be formed. Thus the reaction between 1,5-dicarbonyl **133** and ammonia was performed under basic conditions. Also, it is possible that if the reaction between *n*-propyl amine and 1,5-dicarbonyl **133** was performed under acidic conditions and pyridine product would be isolated (**Scheme 75**).

In order to make sure that differing reaction conditions were not an influence on the product outcome, 1,5-dicarbonyl **133** was treated with ammonia in dichloromethane and the reaction gave pyridine **228** in 42% yield. The same product was also isolated when treating 1,5-dicarbonyl **133** with ammonium formate and acetic acid. Treatment of 1,5-dicarbonyl **133** with propylamine·HCl salt gave a complex mixture with no trace of the pyridine product. These reactions supported our hypothesis that the nature of the aromatic product was based on the amine rather than the conditions (**Scheme 75**).



Scheme 75 *Subjection of 1,5-dicarbonyl **133** to different conditions and the different products formed.*

As another possibility, it was conceivable that pyridinium salt **233** does form reversibly and the reaction is under thermodynamic control with arylamine **221** being the thermodynamic product. Pyridinium salts are known to undergo rearrangement reactions in the presences of amines, specifically the Zincke reaction.[73] In order to test whether a pyridinium salt was being formed reversibly, compound **238** was synthesised and subjected to the arylamine forming conditions. After 24 hours the major component in the reaction mixture was the original pyridinium salt **238**; about 20% of the dealkylated product **228** was isolated but no arylamine was observed (**Scheme 76**).



Scheme 76 *Mechanistic experiment to determine the fate of pyridine **238** in our reaction conditions.*

With these results, it was concluded that the nature of the aromatic product formed from the cyclisation of 1,5-dicarbonyl **133** was determined by the type of nitrogen source used. Ammonia furnished pyridine structures and primary and secondary amines yielded arylamine products.

2.1.5.2.3 Scope of the primary amine

We next set about exploring the scope of other primary amines in the cyclisation and began by investigating the effect of steric bulk in the cyclisation. 1,5-Dicarbonyl **133** was treated

with a range of primary amines under the optimised conditions (5 equivalents of amine, dichloromethane, 55 °C, 12 hours) and a picture emerged with a clear boundary of where the steric tolerance lay.

Benzyl amine proved to be an excellent substrate for the cyclisation, with arylamine **239** isolated in a very good 81% yield. Cyclopentylamine also proved successful in the cyclisations with arylamine **240** being isolated in a good yield of 69%. Isopropylamine gave arylamine **241** in a moderate yield of 55% in the cyclisation. Increasing the size of the amine to *tert*-butyl amine proved unsuccessful in the cyclisation and it is hypothesised that, because of its size, it was not nucleophilic enough to participate in the cyclisation (**Table 4**).

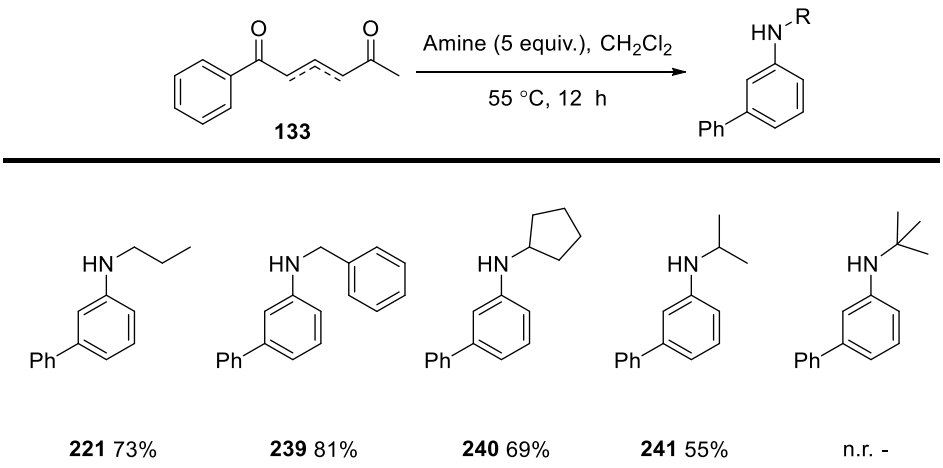
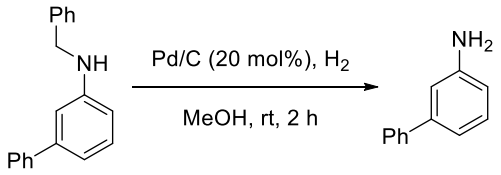


Table 4 *Study into the scope of steric bulk of primary amines.*

As shown in **Scheme 75**, the use of ammonia in the arylamine forming cyclisation resulted in the formation of a pyridine and not an aniline. However, anilines are an important class of molecule and it would significantly improve this methodology if it could be expanded to include anilines. Pleasing, benzyl amine was an excellent substrate for the cyclisation and yielded an *N*-benzyl arylamine. Benzyl groups can be easily cleaved under hydrogenolysis conditions and we demonstrated this by treating arylamine **239** with a palladium on carbon catalyst under an atmosphere of hydrogen to furnish aniline **242** in an excellent 92% yield.



239 **92%** **242**

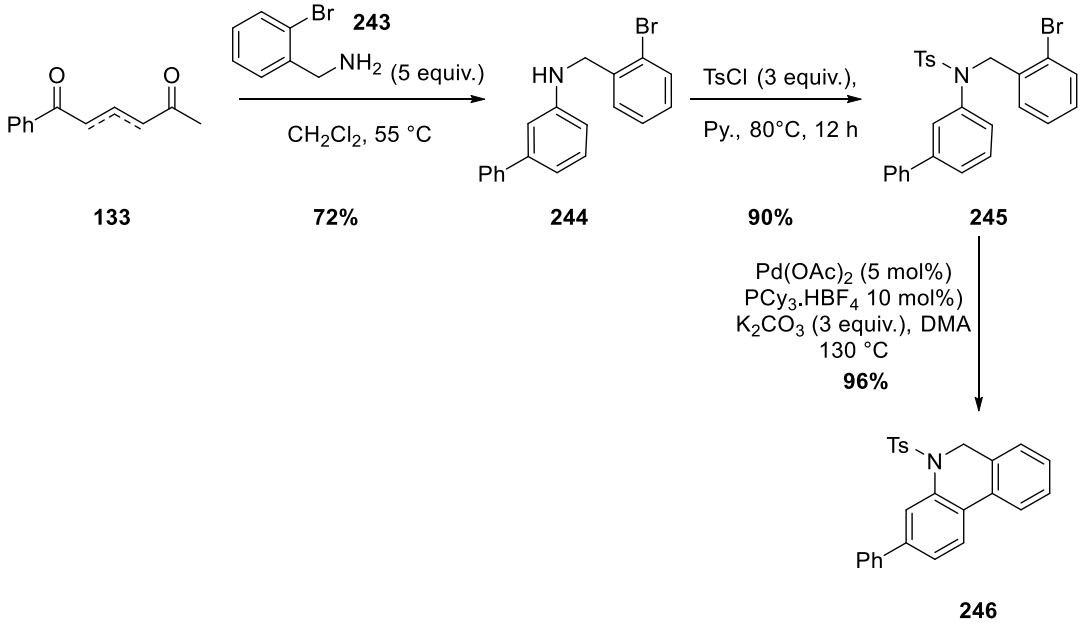
Scheme 77 *Deprotection of benzyl amine **239** to give aniline **242**.*

We were also interested in the synthesis of arylamine **244**, which would come from a cyclisation of 1,5-dicarbonyl **133** with 2-bromobenzylamine (**243**). This compound would not only be a difficult target for palladium catalysis, due to regioselectivity issues caused by the presence of a bromide group, but also provides a useful group for further manipulation with transition-metal catalysis. This complementary strategy is an advantage of the *de novo* synthesis approach.

Thus, 1,5-dicarbonyl **133** and 2-bromobenzylamine (**243**) were treated under the cyclisation conditions to give arylamine **244** in excellent yield. Arylamine **244** could be characterised by the loss of absorption at 1601 cm^{-1} in the IR spectrum corresponding to ketone stretching. Further evidence confirming the structure of arylamine **244** was the characteristic doublets at 6.92 ppm and 6.54 ppm and a singlet at 6.79 ppm corresponding to electron rich aromatic protons, *ortho* and *para* to the nitrogen of the arylamine (**Scheme 78**).

It was decided to use the C-H functionalization methodology, developed by Fagnou and co-workers, to demonstrate the use of arylamine **244** as an intermediate in the synthesis of more complex structures. However, treatment of arylamine **244** with Fagnou and co-workers' cyclisation conditions ($Pd(OAc)_2$ (5 mol%), $PCy_3.HBF_4$ (10 mol%), K_2CO_3 (3 equivalents), DMA, 130 °C) resulted in isolation of starting material.[74] Further investigation of Fagnou and co-workers' results revealed that an additional electron withdrawing group on the nitrogen should be required, presumably to reduce unwanted coordination of the substrate to the catalyst. Thus arylamine **244** was treated with tosyl chloride in pyridine to give *N*-tosyl

arylamine **245** in an excellent 90% yield (**Scheme 78**). Pleasingly *N*-tosyl arylamine **245** underwent smooth cyclisation under the Fagnou conditions to give tricycle **246** in an excellent 96% yield. The product of this reaction was solid and a single crystal of a suitable quality for single crystal X-ray diffraction was grown confirming the structure of tricycle **246** (**Figure 9**).



Scheme 78 *Synthesis of arylamine **244** and cyclisation to give tricycle **246**.*

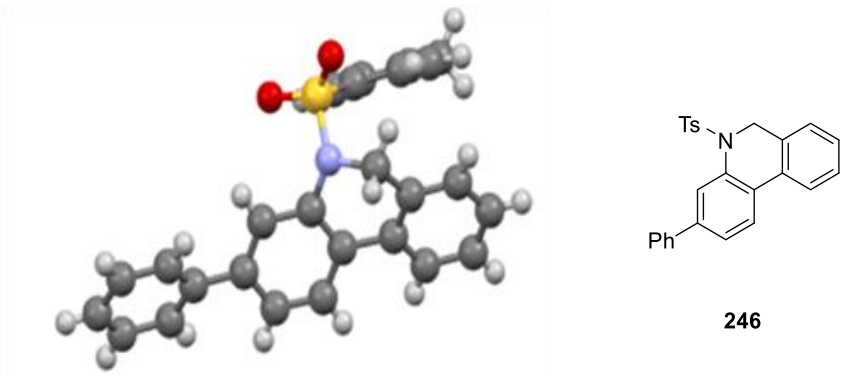
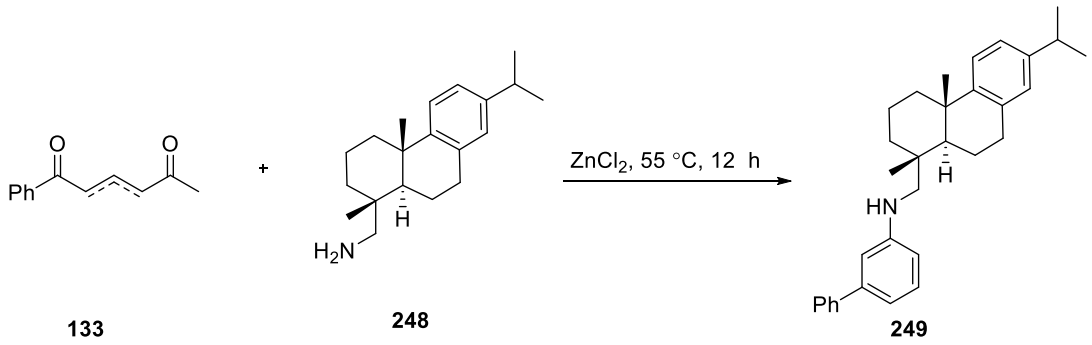


Figure 9 *Representation of the X-ray structure of arylamine **246**.*

It would also be beneficial to test our method on a more complicated amine such as steroid **248.** Steriod **248** was commercially available and would be a particularly challenging molecule due to its size and the presence of a neopentyl centre next to the nitrogen.

Subjecting dicarbonyl **133** and steroid **248** to the arylamine forming cyclisation conditions (5 equivalents of amine, $ZnCl_2$, 55 °C, 18 hours) furnished arylamine **249** in a good 63% yield. Arylamine **249** could be characterised by doublets at 6.93 ppm and 6.51 ppm and a singlet at 6.72 ppm in the ^1H NMR spectrum corresponding to the electron rich aromatic protons, *ortho* and *para* to the nitrogen of the arylamine. Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 438.3146, which corresponded to the $[M+H]^+$ ion of arylamine **249**.

It was apparent that the use of 5 equivalents of a precious amine was not an ideal set of conditions. Therefore, it was decided to investigate other strategies to reduce the number of amine equivalents required. It was postulated in the proposed mechanism that high equivalents of amine favoured the formation of a second enamine which allowed a cyclisation to take place; *i.e.* formation of an arylamine (**Scheme 40,** page 42). It was hypothesised that a high concentration of amine with respect to the carbonyl would have the same effect. This could be achieved by slow addition of the 1,5-dicarbonyl to the amine *via* a syringe pump. The reactions were performed in a sealed microwave vial. So, being mindful that piercing the sealed microwave vial with a needle for the syringe pump addition may result in loss of volatile dichloromethane at elevated temperatures, it was decided to change solvent to the higher boiling dichloroethane. We also knew that addition of $ZnCl_2$ was beneficial to the reaction. Pleasingly, after a 12 hour addition of 1,5-dicarbonyl **133** and a further 6 hours stirring at 55 °C, arylamine **249** was isolated in a moderate yield of 35%. When the $ZnCl_2$ used in the reaction was lowered to 20 mol%, which would give the same ratio of $ZnCl_2$ to amine as in our original cyclisation conditions, an improved yield of 56% was observed which was comparable to the reaction with 5 equivalents of amine.



133 **248** **249**

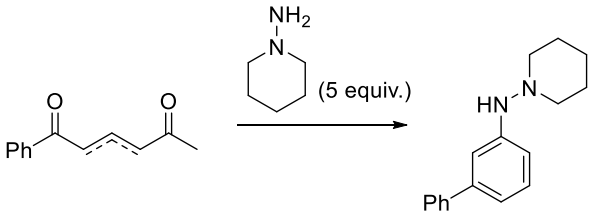
Amine (equivalents)	$ZnCl_2$ (equivalents)	Solvent	Isolated yield
5.0	1.0	CH_2Cl_2	63%
1.5	1.0	$C_2H_4Cl_2$	35%
1.5	0.2	$C_2H_4Cl_2$	56%

Scheme 79 *Investigation into the synthesis of arylamine **249**.*

2.1.5.3 Hydrazines

Another useful, related class of compounds are aryl hydrazines. They have interesting biological activities[75] as well as being important intermediates in the synthesis of indoles, *via* the Fisher indole synthesis.[76] We wondered if it would be possible to expand the scope of our reaction in include this important class of compounds.

Because of the documented difficulty in forming enamine type compounds from hydrazine,[77] it was decided to increase the temperature further, from 55 °C to 80 °C. Pleasingly with piperidine-1-amine the desired cyclisation took place. It was also noted that the addition of $ZnCl_2$ significantly increased the reaction yield. After purification of the reaction mixture, aryl hydrazine **250** was isolated in an excellent 83% yield. The characterisation of arylamine **250** was supported by diagnostic doublets at 7.16 ppm and 6.91 ppm and a singlet at 7.03 ppm which corresponded to the electron rich aromatic protons *ortho* and *para* to the nitrogen of the aryl hydrazine (**Scheme 80**).



133 **250**

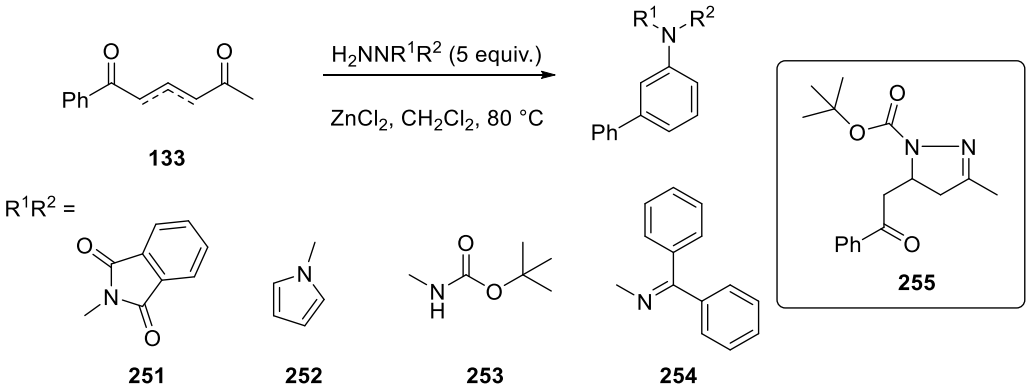
conditions	Yield
$ZnCl_2$, 55 °C	no reaction
80 °C, no $ZnCl_2$	54%
$ZnCl_2$, 80 °C	81%

Scheme 80 *Synthesis of aryl hydrazine **250**.*

The inclusion of aryl hydrazine **250** was an important extension to the methodology. However, access to an unsubstituted aryl hydrazine would be synthetically more important, giving access to Fischer indole reaction precursors. Subjecting hydrazine hydrate or hydrazine salts to the cyclisation gave no desired product. Therefore, we decided to explore protected hydrazine precursors in the cyclisation with our conditions developed for aryl hydrazine **250**.

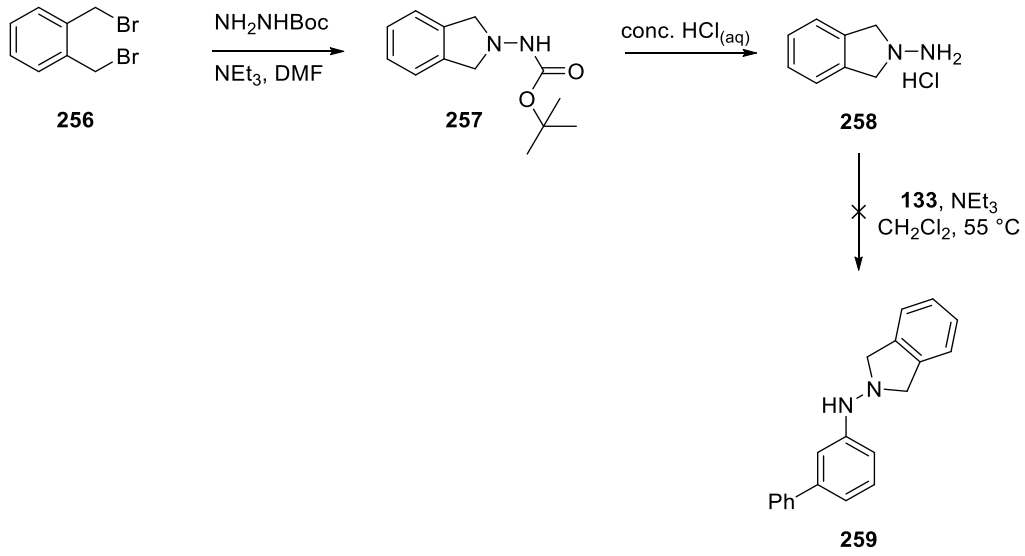
We tried a number of different protected hydrazines in the cyclisation reaction. Interestingly, using *tert*-butyl carbazate, as the amine source gave a side product in 24 % yield which we tentatively assigned the structure as dihydropyrazole **255**. Chemical shifts at 198.4 ppm and 155.6 ppm in the ^{13}C NMR spectrum corresponded to an aryl ketone and an imine carbon and their position was determined by HMBC studies. A multiplet at 3.86 ppm and doublet of doublets at 3.19 ppm, 3.04 ppm and 2.54 corresponded to two pairs of diastereotopic methylene protons and COSY studies showed they all coupled to a multiplet at 4.72 ppm which corresponded to the proton adjacent to the *N*Boc group. Side product **255** could result from the formation of an enamine followed by the second nitrogen acting as a nucleophile to perform another, undesirable cyclisation; however the remainder of the material was decomposition. The side product **255** proved unreactive under the reaction conditions which led us to investigate di-*N*-substituted hydrazines (**Scheme 81**).

Both hydrazine **252**, a modification of an amine protecting group and imine **254**, used as a hydrazine substitute[78] in the Buchwald-Hartwig reaction, gave no desired product. Trace amounts of product-like peaks of compound **251** were observed in a ^{1}H NMR spectrum for the phthlalimide protected hydrazine but it was hypothesised that the nitrogen was not nucleophilic enough to take part in the cyclisation. It was thought that the reduced hydrazine **258** could be successful in the synthesis of hydrazine **259** as it would be more nucleophilic (**Scheme 81**).



Scheme 81 *Failed attempts at the synthesis of a protected aryl hydrazine.*

Bis-bromo compound **256** was treated with NH_2NHboc and triethylamine at 50 °C and stirred for 12 hours at room temperature. After the addition of water, a white solid was isolated with a ^{1}H NMR spectrum matching that of *N*-boc-hydrazine **257**. This solid was then added to a concentrated solution of HCl to give hydrazine **258** as its HCl salt. Efforts to isolated the free hydrazine compound were unsuccessful in our hands and resulted in formation of a complex mixture. Thus we decided to generate the free hydrazine *in situ*. Consequently, 1,5-dicarbonyl **133** was treated with HCl salt **258** and triethylamine at 80 °C. Analysis of the crude mixture by ^{1}H NMR analysis showed only decomposition and no desired product like signals (**Scheme 82**).

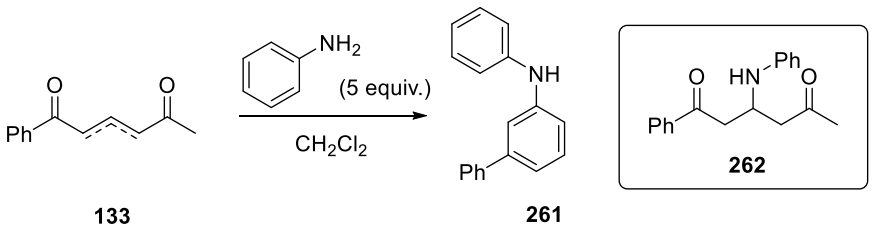


Scheme 82 *Attempted synthesis of arylamine **259.***

We successfully expanded the methodology to include hydrazines by increasing the reaction temperature however, were unable to include a hydrazine which could be easily deprotected to give a free hydrazine.

2.1.5.4 Anilines

The synthesis of diphenylamine **261** would be an important extension of the ring closing methodology as similar motifs are common in drug molecules.[79] Treatment of dicarbonyl **133** with 5 equivalents of aniline in the presence of $ZnCl_2$ at 55 °C produced an insoluble white precipitate and analysis of the reaction mixture showed that no desired product had formed. Repeating the reaction without the addition of $ZnCl_2$ yielded adduct **262** in 33% yield. We wondered whether the addition of different Lewis acids might encourage the formation of an enamine and not form an insoluble precipitate. Thus, the reaction was carried out in the presence of $BF_3{\cdot}OEt_2$ and $TiCl_4$. Both produced a dark solution upon addition but after heating for 12 hours at 55 °C no product was isolated and only decomposition was observed. We wondered whether increasing the reaction to 80 °C may offer a similar improvement as in the hydrazine case, however only trace amounts of desired product were observed (**Scheme 83**).



133 **261**

Temperature	Additive	Yield
55 °C	$ZnCl_2$	decomposition
55 °C	-	**262** 33%
80 °C	-	trace product

Scheme 83 *Attempted synthesis of bis-aniline **261**.*

Unfortunately, from these studies it appears that aniline is too poor a nucleophile to participate in the cyclisation.

2.1.6 Conclusion

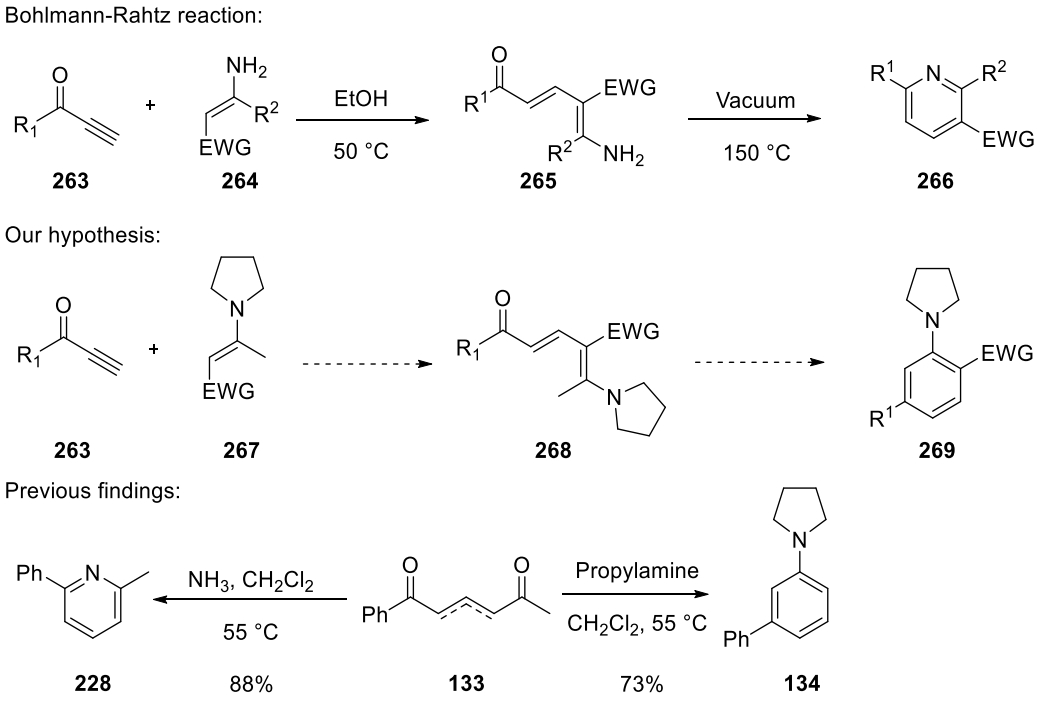
A useful, modular synthesis of arylamines has been developed, which is experimentally simple to perform and allows access to a diverse range of substrates. The scope has been explored with respect to both the amine and 1,5-dicarbonyl components and will hopefully find itself useful in a number of applications. A mechanism has been proposed based on some experimental observations and has allowed us to successfully alter the conditions to expand the scope to include more difficult substrates.

2.1.7 Bohlmann-Rahtz type synthesis of arylamines

2.1.7.1 Introduction

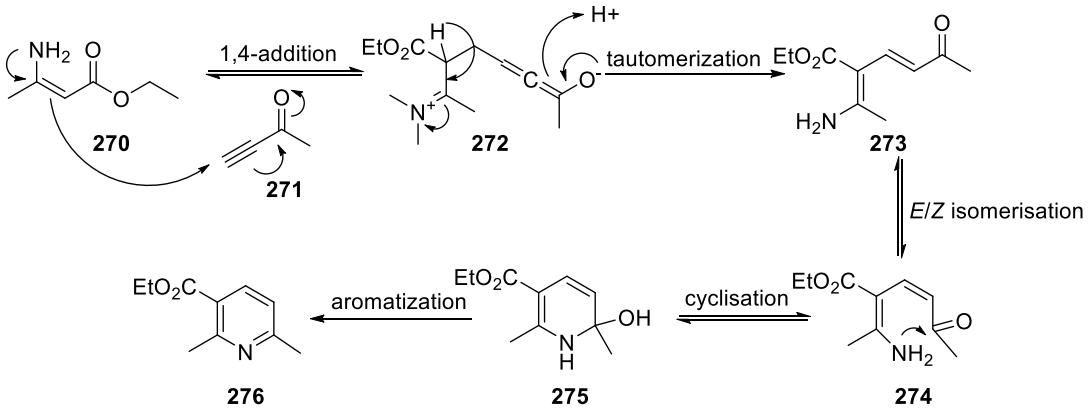
To further expand the scope and utility of the arylamine synthesis, other routes to α,β-unsaturated-1,5-dicarbonyl compounds were examined. We were aware that the Bohlmann-Rahtz reaction also utilised a 1,5-dicarbonyl type molecule **265** as an intermediate towards the synthesis of pyridines **266**. From our earlier studies with 1,5-dicarbonyl **133**, a cyclisation with ammonia formed pyridine **228** whilst a cyclisation with a primary or secondary amine gave arylamine **134** (see *section 2.1.5.2.2*). It was hypothesised that substituting primary

enamine **265** for a secondary or tertiary enamine **268** would have the same effect (**Scheme 84**).



Scheme 84 *Proposed synthesis of arylamines via Bohlmann-Rhatz type intermediate.*

The Bohlmann-Rahtz reaction was first reported in 1957 in laboratories of Bohlmann.[80] The first step was the conjugate addition of enamine **270** to alkynyl ketone **271** to yield aminodiene **273** which could be isolated in high yields. Aminodiene **273** was resistant to cyclisation due to the *E*-geometry of the enone double bond however at 150 °C *cis*/*trans* isomerisation was observed, followed by spontaneous cyclisation to yield pyridine **276** in high yields and excellent regioselectivity (**Scheme 85**).



Scheme 85 *Mechanism of the Bohlmann-Rahtz reaction.*

Although the advantages of this method are apparent: since it is a modular, rapid synthesis, with complete regiocontrol, it remained under-utilised for over 40 years, possibly due to some drawbacks including, multi-pot synthesis, high reaction temperatures, and poor scope.

Since the initial report, much work has been carried out address some of the original drawbacks of the procedure, and there have resulted in some synthetically useful procedures that have been utilised in the synthesis of natural products[81] and pyridine libraries.[82] The use of Lewis acid and Bronsted acid catalysts has significantly lowered the reaction temperature of the cyclisation to 50 °C and also allowed useful one-pot protocols to be developed.[83] The scope has now been extended to the synthesis of *tetra*-substituted pyridines still with complete regiocontrol.[84] The use of microwave[85] and flow reactors[86] has also significantly improved the applications of the methodology.

As discussed, we wanted to know whether we could utilise some of these recent developments to expand the scope of the reaction to a new range of substrates, arylamines. We also wished to retain some of the features that make the Bohlmann-Rahtz synthesis such a powerful tool, such as excellent regiocontrol, simple procedures and a highly modular approach.

2.1.7.2 Arylamine synthesis

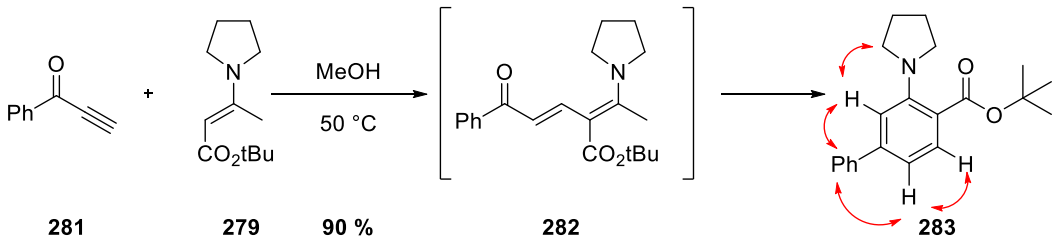
To test our hypothesis, it was decided to use enamine **279** which was synthesised easily in an excellent 87% yield, by the condensation of pyrrolidine and ketone **278** in toluene using catalytic *p*-toluene sulfonic acid. Enamine **279** could be characterised by the loss of a carbonyl signal in the ^{13}C NMR spectrum and the presence of a singlet at 4.40 ppm in the ^{1}H NMR spectrum corresponding to the vinylic proton. Alkynyl ketone **281** could be accessed *via* the oxidation of propargyl alcohol **280** with 2-iodoxybenzoic acid (IBX) in dimethyl sulfoxide. Ketone **281** was accessed in excellent yield and could be characterised by the shift at 177.4 ppm in ^{13}C NMR spectrum corresponding to the ketone carbon (**Scheme 86**).



278 **87%** **279** **280** **74%** **281**

Scheme 86 *Synthesis of enamine **279** and propargyl ketone **281**.*

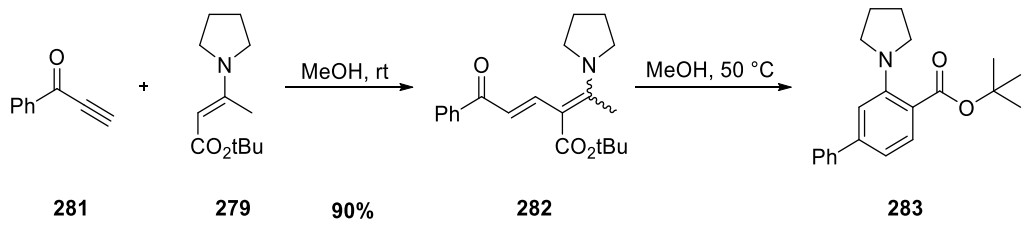
With enamine **279** and ketone **281** in hand, we set about investigating the conditions to form aminodiene **282**. Surprisingly, subjecting ketone **281** and enamine **279** to the Bohlmann-Rahtz conditions (methanol, 50 °C) did not yield aminodiene **282** but gave spontaneous cyclisation to form arylamine **283**. The structure of arylamine **283** was confirmed by a singlet at 6.97 ppm and doublet at 6.93 ppm in the ^{1}H NMR corresponding to the electron rich aromatic protons, *ortho* and *para* to the nitrogen of the arylamine. Further evidence was obtained by n.O.e. studies which showed enhancements between the arylamine signals and between the protons adjacent to the pyrrolidine and the *t*-butyl group (**Scheme 87**).



Scheme 87 *Synthesis of arylamine **283**. nOe enhancements are shown by red arrows.*

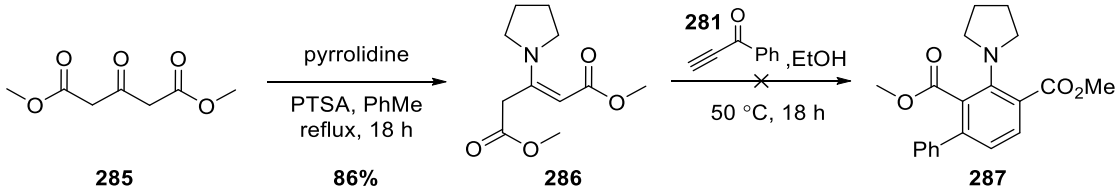
This reduction in the temperature required for the cyclisation was remarkable and greatly improved the applications of this procedure. Although the reason for the mild conditions required for the cyclisation is not clear, we hypothesise that it is due to the presence of a tertiary amine or trace pyrrolidine. Reversible 1,4-addition to the enone offers an easier pathway for the isomerisation of the double bond and thus negates the need for harsh conditions or extra additives.

We were able to isolate aminoenone **282** by performing the reaction at room temperature and demonstrate that, upon heating, aminoenone did cyclise to form arylamine **283**, demonstrating it to be a likely intermediate. Aminodiene **282** could be characterised by doublets at 7.93 ppm and 6.74 ppm in the ^{1}H NMR spectrum with a coupling constant of 14.7 Hz corresponding to a *trans*-coupling of the alkene protons. A shift at 190.0 ppm in the ^{13}C NMR spectrum, corresponding to the aryl ketone provided further evidence. Unfortunately nOe studies were unable to distinguish the geometry of the second alkene. It is noteworthy that the cyclisation of aminoenone **282** was observed in $CDCl_3$ at room temperature over one month.



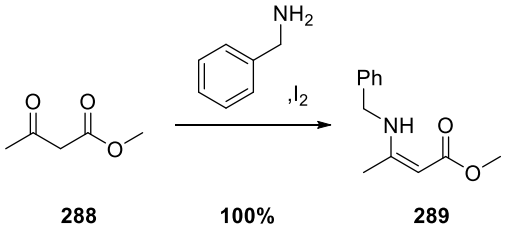
Scheme 88 *Isolation of aminoenone **282** and its cyclisation to arylamine **283**.*

The scope of this arylamine forming reaction was next explored. Firstly the scope at the C-6 position was investigated. Using dimethyl-1,3-acetonedicarboxylate **285** in the reaction sequence would result in an arylamine with an ester at the C-6 position. Treatment of ketone **285** with pyrrolidine furnished enamine **286** in 86% yield. Subjecting this enamine to our cyclisation conditions however yielded no product and gave a complex mixture by ^{1}H NMR analysis. It appeared that the new cyclisation was also sensitive to steric bulk at the reaction centre (**Scheme 89**).



Scheme 89 *Attempted synthesis of arylamine **287**.*

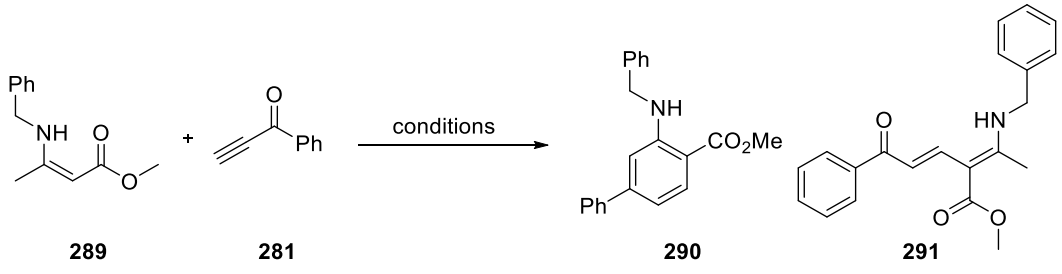
It was also of interest to examine whether this method could be expanded to include the use of primary amines. Firstly, we decided to investigate the use benzyl amine. Enamine **289** could be isolated in one step by the treatment of ketone **288** with benzyl amine in a quantitative yield.



Scheme 90 *Synthesis of enamine **289**.*

With enamine **289** in hand, cyclisation conditions were tried. Subjecting enamine **289** and propargyl ketone **281** to heating in methanol yielded aminodiene **291** in a quantitative yield and not the expected arylamine product. It had been shown by Bagely and co-workers that the addition of acid favours the formation of pyridines in the Bohlmann-Rhatz reaction and it was

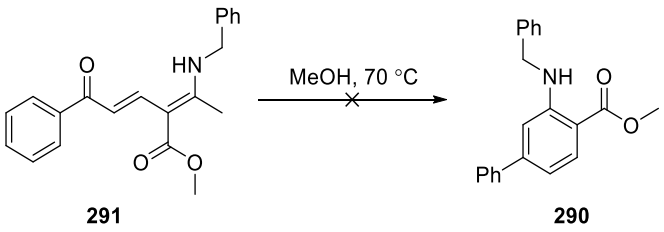
wondered whether it would favour the formation of arylamines in this cyclisation. The addition of trifluoroacetic acid to the cyclisation reaction gave a complex ^{1}H NMR spectrum. Interestingly, performing the reaction in a mixture of toluene and acetic acid gave high conversions to an unknown product which was not fully assigned (**Scheme 91**).



conditions	result
MeOH, 50 °C	isolated **291** in quant. yield
TFA (1 equiv.), MeOH, 50 °C	complex mixture
AcOH/Toluene (5:1)	unknown product

Scheme 91 *Investigation into the synthesis arylamine **290**.*

It was next decided to see if aminodiene **291** would cyclise to an arylamine under higher temperatures. However at 70 °C, only starting material was recovered. (**Scheme 92**).



Scheme 92 *Reaction of aminodiene **291** at higher temperature.*

2.1.7.2 Conclusion

The expansion of the Bohlmann-Rahtz reaction to include the synthesis of arylamines is a major milestone in the history of the reaction, however further research needs to build upon this work to fully explore the reaction and expand its scope to include the use of primary amines and develop a one-pot synthesis. This work is currently being carried out in the Donohoe group.

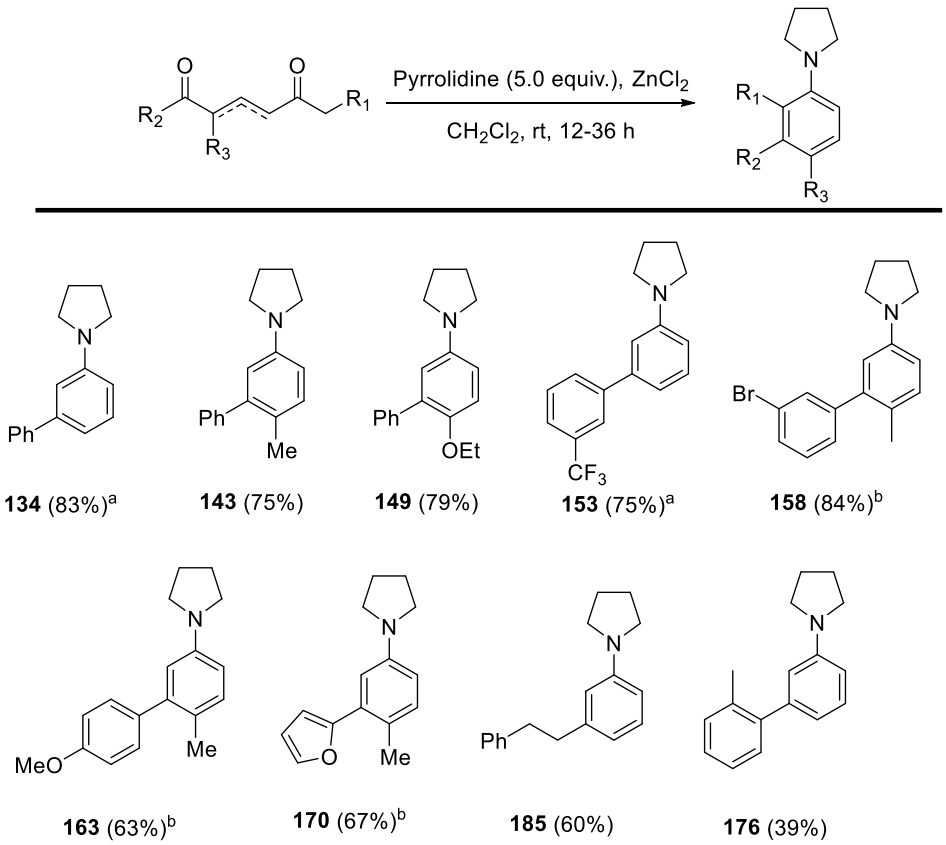
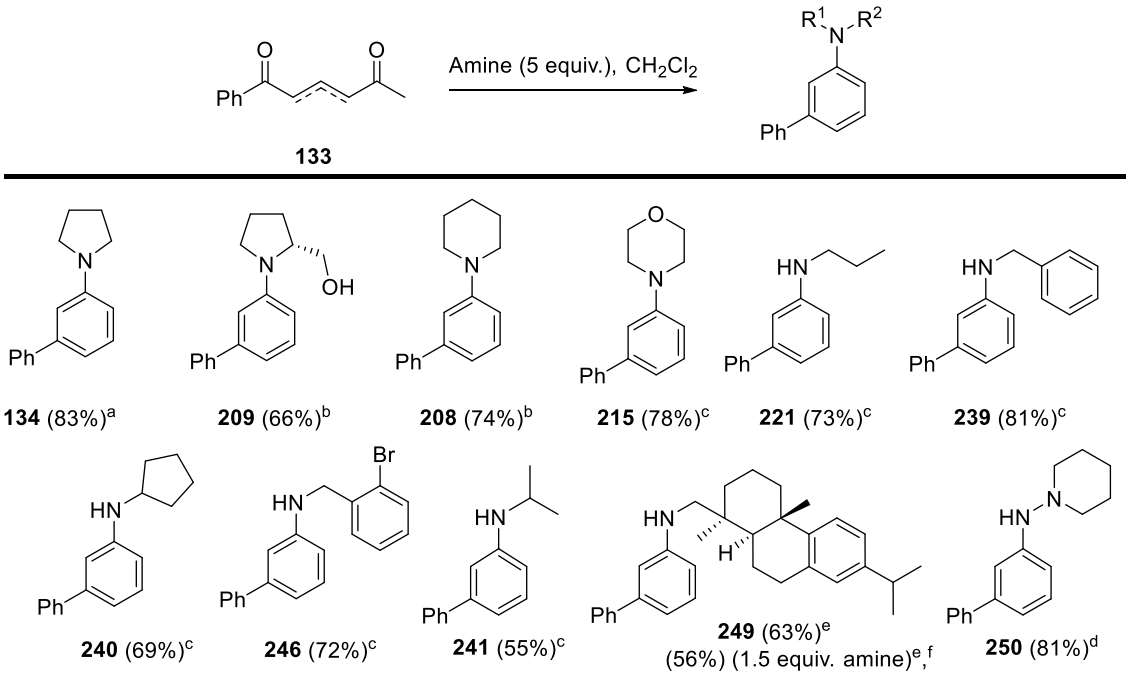


Table 5 *Summary table of ring substitution.*



[a] Reaction carried out 0 °C; [b] Reaction carried out at rt with 1 equiv. $ZnCl_2$; [c] Reaction carried out 55 °C; [d] Reaction carried out 85 °C; [e] Reaction carried out 55 °C with 1 equiv. $ZnCl_2$; [f] Reaction carried out in CH_4Cl_2 and **133** added over 12 h.

Table 6 *Summary table of amine scope.*

2.2 New methods for the synthesis of naphthylamines

2.2.1 Introduction

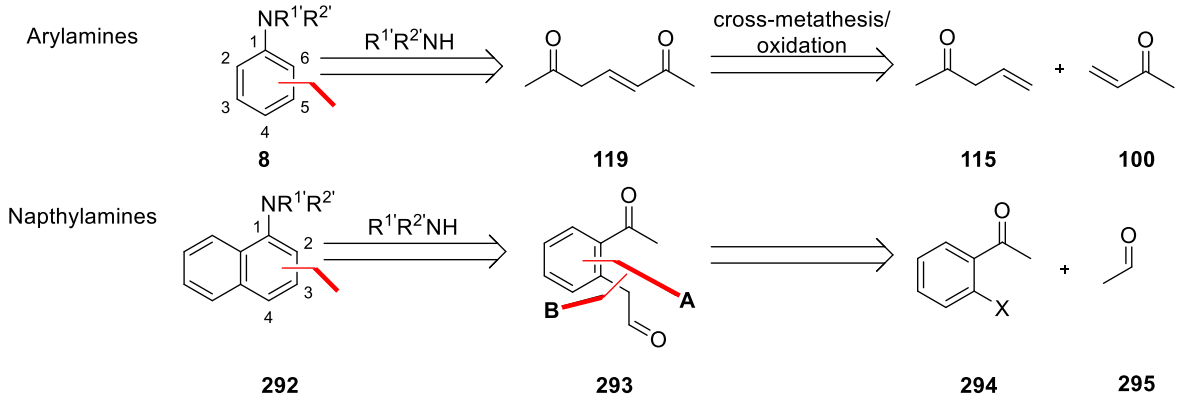
After exploring the scope of arylamine synthesis, we turned our attention to the synthesis of naphthylamines. This important core is found in a number natural products,[87] pharmaceuticals [79, 88] and in material science.[89]

Most methods discussed in the Introduction can be applied to naphthylamine synthesis. However as there are many fewer commercially available suitable naphthylamine starting materials, an efficient, robust method for their synthesis from simple starting materials with access to a diverse range of substituents would be highly desirable.

2.2.1.1 Our Approach

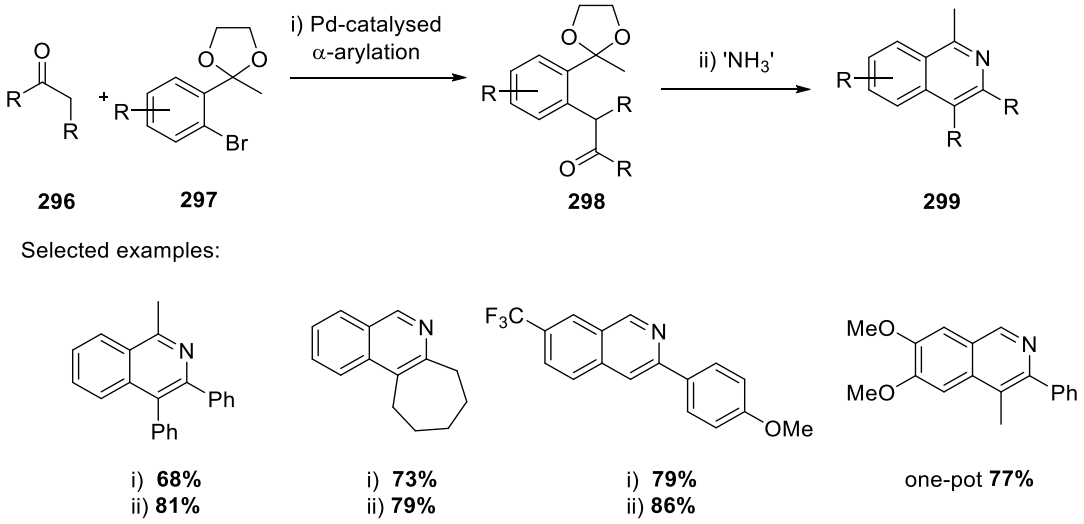
The disconnection **A** used for the synthesis of arylamine **292**, was unsuitable for the synthesis of naphthylamines as it would require the formation of a bond in the aryl ring which is

difficult using current technologies. A more suitable disconnection would be **B**, the bond between the aryl ring and the carbon α to the carbonyl (**Scheme 93**).



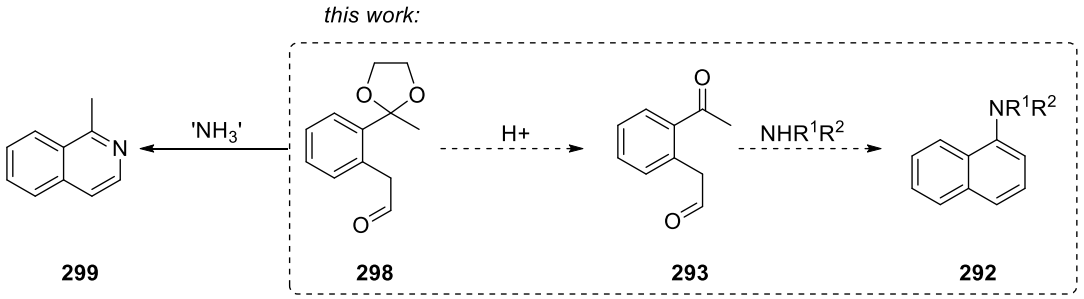
Scheme 93 *Proposed disconnection of naphthylamine **292**.*

Recently the Donohoe group published a paper describing the *de novo* synthesis of isoquinolines *via* formation of a masked 1,5 dicarbonyl. [90] The method gives access to a range of substituted isoquinolines and is a simple and efficient procedure which utilises the palladium(0) catalysed α-arylation reaction as a key step. The work describes how *ortho*-acetal aryl bromides **297** were coupled with ketones **296** to give masked 1,5-dicarbonyls **298**. These molecules were then treated with an acidic ammonia source, and then in the presence of water, were deprotected and cyclised to give isoquinolines **299** (**Scheme 94**).



Scheme 94 *Synthesis of isoquinolines via an α-arylation/cyclisation protocol.*

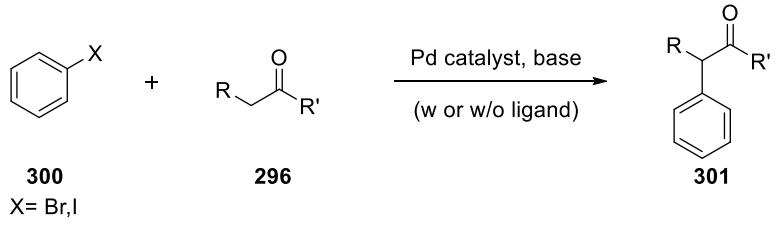
The product of α-arylation was a masked 1,5-dicarbonyl **298**. If the acetal was deprotected the resulting 1,5-dicarbonyl product **293** may be a successful substrate for an arylamine forming cyclisation and would give access to naphthylamine **292** (**Scheme 95**).



Scheme 95 *Planned approach to the synthesis of naphthylamine **292**.*

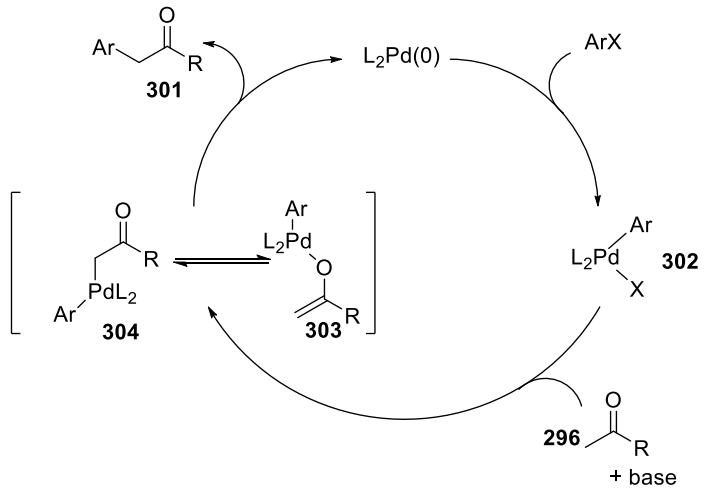
2.2.1.2 The palladium catalysed α-arylation reaction

The palladium catalysed α-arylation reaction is a powerful tool for the synthesis α-aryl carbonyl motifs. It was first discovered in 1997 by the groups of Buchwald,[91] Hartwig[92] and Miura[93] who reported the coupling of aryl halides **300** with a range of ketones **296** in the presence of palladium and a strong base. Both Buchwald and Hartwig reported the use of a ligand and palladium(0) (**Scheme 96**).



Scheme 96 *General scheme for the α-arylation reaction.*

Buchwald and Hartwig reported similar mechanistic postulations for the α-arylation reaction. The first step is oxidative addition of the palladium(0) catalyst with the aryl halide to form organometallic species **302**. Ligand exchange between the enolate, formed by deprotonation of ketone **296**, and a halide gives palladium enolate **303** or **304**. Reductive elimination yields aryl ketone **301** and regenerates the catalyst (**Scheme 97**).



Scheme 97 *Mechanism of the α-arylation reaction.*

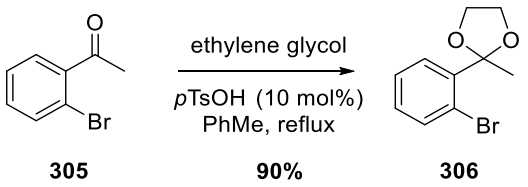
Since its discovery, the palladium catalysed α-arylation reaction has received a lot of attention from the synthetic community. Through the use of new ligands and modifications to the procedure, huge leaps have been made to expand the scope and develop mild conditions. These developments are beyond the scope of this report however an excellent review covering the area is available.[94]

2.2.2 Results and discussion

It was decided to test our naphthylamine-forming hypothesis on 1,5-dicarbonyl **309** which could be synthesised from an α-arylation reaction between aryl bromide **306** and propiophenone (**307**) (**Scheme 99**).

2.2.2.1 Synthesis of 1,5-dicarbonyl

Acetal **306** was accessed by an acetal protection of commercially available benzaldehyde **305** with ethylene glycol and *p*-toluenesulfonic acid with heating using Dean-Stark apparatus. The product was characterised by the complete disappearance of the aldehyde signal at 10.35 ppm and the emergence of a signal at 6.11 ppm, which was consistent with the methylene protons of the acetal (**Scheme 98**).

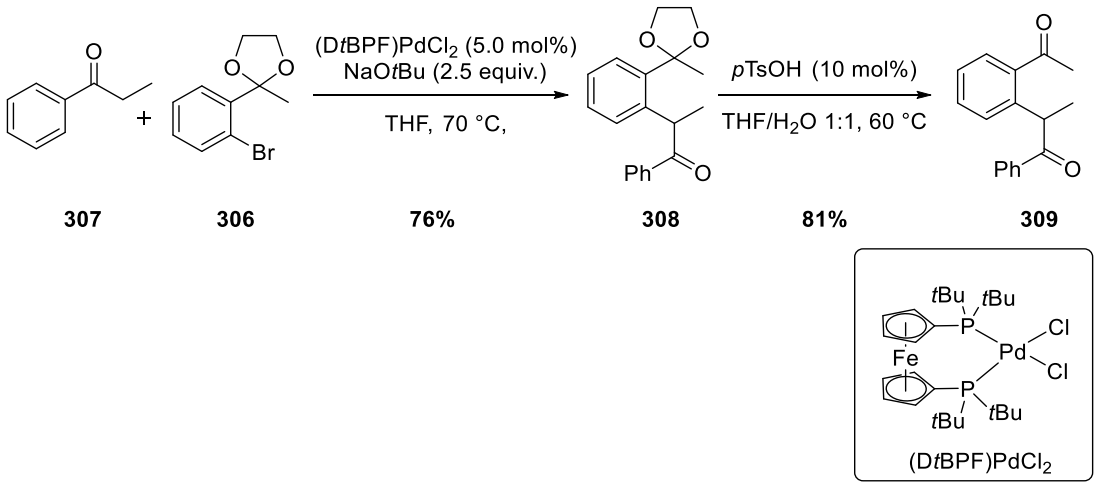


305 **90%** **306**

Scheme 98 *Synthesis of acetal **306**.*

The α-arylation reaction had previously been optimised by another member of the Donohoe group. It was found that sterically hindered bidentate ligands worked well, with D*t*BPF[95] performing the best in optimisation studies. It was also found that the use of a palladium(II) complex, (D*t*BPF)$PdCl_2$, which was first reported by Colacot[96]gave the best and most reliable results, with high yields reported with low catalyst loadings. It is believed that the active palladium(0) species is formed either by displacement of the two chlorides on the palladium species by two enolate molecules followed by a reductive elimination, or by displacement of one chloride ligand by an enolate molecule followed by β-hydride elimination and reductive elimination of HCl. The optimum amount of base was found to be 2.5 equivalents of *t*BuONa and the use of 1.2 equivalents of the ketone partner gave best conversions.[90]

Aryl bromide **306** was subjected to these optimised conditions furnishing masked 1,5-dicarbonyl **308** in a 76% yield. Treatment of the α-arylation product **308** with *p*-toluenesulfonic acid in a 1:1 mixture of THF and water yielded 1,5-dicarbonyl **309** in an excellent, 81%, yield. The structure of dicarbonyl **309** was characterised by two signals at 202.3 ppm and 201.3 ppm in the ^{13}C NMR spectrum which corresponded to the two carbonyl carbons (**Scheme 99**).

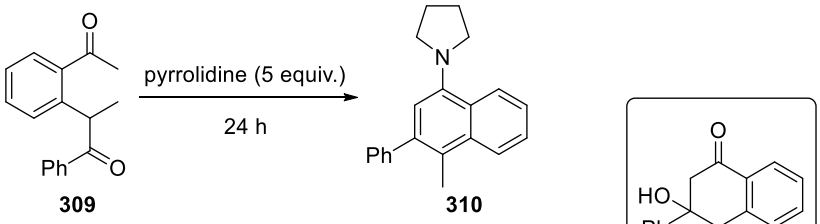


Scheme 99 *Synthesis of dicarbonyl **309**.*

2.2.2.2 Optimisation of the cyclisation

With dicarbonyl **309** in hand, the cyclisation to naphthylamine **310** using pyrrolidine was explored (**Table 7**). Applying the original arylamine-forming conditions gave low conversions to the product. However, better conversions were observed with the addition of $ZnCl_2$ and at higher temperatures. The reactions were stirred for 24 hours at the specified temperature. Analysis of the reaction mixture suggested that the reaction to form naphthylamines was not as clean as the analogous reaction forming arylamines. The formation of naphthylamine **310** was confirmed by a singlet at 6.98 ppm in the ^{1}H NMR spectrum corresponding to the electron rich proton *ortho* to the nitrogen on the naphthylamine ring. Further confirmation was obtained by the presence of a signal in the high-resolution mass spectrum at 288.1740, which corresponded to the $[M+H]^+$ ion of naphthylamine **310**. One side product, observed in varying yields, was bicycle **311**; the structure was confirmed from the ^{1}H NMR spectrum, by a quartet at 3.27 ppm corresponding to the proton next to the methyl group and two doublets at 3.27 ppm and 3.05 ppm corresponding to the AB system of the diastereotopic methylene protons. The side product proved to be a solid and pleasingly a crystal structure was obtained to prove its structure (**Figure 10**). Resubjecting bicycle **311** to the reaction conditions give a conversion to the

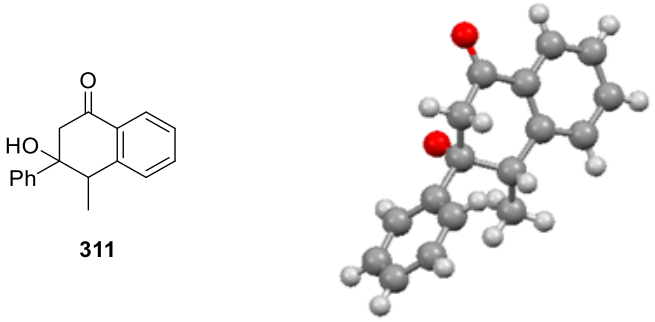
desired naphthylamine in high yields, so it is possible that bicycle **311** is an intermediate in the reaction.



309 **310** **311**

Temperature (°C)	Solvent	Additive	Yield of **310**
40	CH_2Cl_2	-	26%
40	CH_2Cl_2	$ZnCl_2$	30%
55	CH_2Cl_2	$ZnCl_2$	55%

Table 7 *Optimisation of naphthylamine **310** forming cyclisation.*

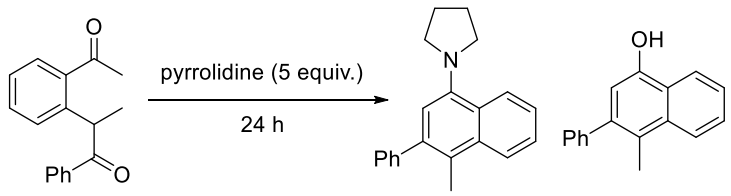


311

Figure 10 *Representation of the crystal structure of bicycle **311**.*

A mild, Lewis acid facilitated procedure, based upon the arylamine forming reaction in the previous section had therefore been developed. However, given the moderate yields and the differences observed in reactivity of the dicarbonyls **133** and **309** (i.e. the lack of reactivity at lower temperatures and the isolation of intermediate **311**), it was possible that the formation of naphthylamines occured *via* a different mechanism to the formation of arylamines. Therefore an optimisation study into the cyclisation to form naphthylamine **310** which was not based upon the arylamine forming reaction conditions was initiated.

The effects of solvent and temperature and the reaction between 1,5-dicarbonyl **309** and pyrrolidine were first investigated (**Table 8**). The use of higher boiling solvents allowed the temperature to be increased to 80 °C; however, under basic conditions conversions were poor with mostly decomposition observed (entries 1, 2 & 4). The reaction in methanol did yield some desired arylamine product, however the major observed product was phenol **312**, which was not isolated (entry 3). The addition of a Brønsted acid did favour the formation of naphthylamine, however the major observed product was still phenol **312** (entry 6). Willis and co-workers had previously observed the formation of a naphthylamine in high yields at 110 °C when using 10 equivalents of bulky amines in their isoquinoline synthesis.[97] Further increasing the temperature to 110 °C gave product **310** in 24% yield in toluene (entry 10), and in a 3:1 mixture of toluene/acetic acid an excellent yield of 76% was achieved (entry 8). Switching the solvent to ethanol gave phenol **312** in an excellent 90% yield (entry 9). The use of the HCl salt of pyrrolidine gave poor conversions (entry 11).



309 **310** **312**

Entry	Temperature (°C)	Solvent	Conversion[a] **310 (312)**
1	80	PhMe	decomp
2	80	THF	decomp
3	80	MeOH	28% (71%)
4	80	DCE	low conversion
5	80	PhMe/AcOH	26% (-)
6	80	MeOH/AcOH	37% (63%)
7	80	MeOH[b]	23% (77%)
8	110	PhMe/AcOH	76%[c] (-)
9	110	Ethanol	- (90%[c])
10	110	PhMe	24% (-)
11[d]	110	PhMe	decomp.

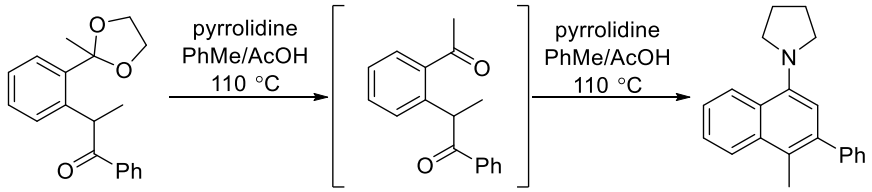
[a]by $_1$H NMR [b]1 equiv $ZnCl_2$ [c]isolated yield [d]Pyrrolidine.HCl

Table 8 *Optimisation of cyclisation to form naphthylamine **312**.*

With optimised naphthylamine-forming reaction conditions in hand (**Table 8**, entry 8), a one-pot protocol for the synthesis of naphthylamine **310** from protected 1,5-dicarbonyl **308**

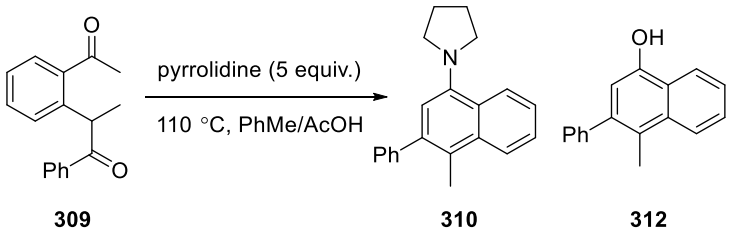
was targeted. It was hoped that the tolerance of both Lewis acid and Brønsted acid would allow for a successful one-pot protocol.

We subjected acetal **308** to the naphthylamine-forming conditions (**Table 8**, entry 8), anticipating that at elevated temperatures and under acidic conditions a deprotection of acetal **308** might occur and the resultant 1,5-dicarbonyl **309** would then perform the cyclisation. However, poor conversions, even after extended reaction times, were observed and mostly unreacted starting material was reisolated (**Scheme 100**).



Scheme 100 *Attempted one-pot synthesis of naphthylamine **310**.*

We reassessed that the addition of water might be needed for efficient deprotection of acetal **308**; so its effect on the final cyclisation was assessed. However, it was found that the presence of water reduced the overall yield of the cyclisation and favoured the formation of the naphthol side product **312** (**Table 9**). Therefore, we continued with our two-pot protocol.



Conditions	Conversion[a]	
	310	**312**
Anhydrous	73%	-
2.5 equiv. water	36%	19%
25 equiv. water	23%	18%

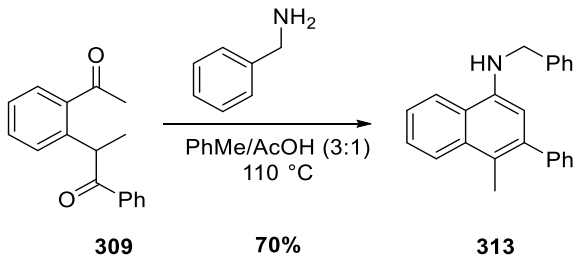
[a]by ^{1}H NMR

Table 9 *Effect of water on the naphthylamine-forming cyclisation.*

2.2.2.3 Exploration of the scope of the naphthylamine-forming cyclisation

With two sets of conditions for the cyclisation of 1,5-dicarbonyls to naphthylamines in hand, the scope of the reaction was explored with respect to the substitution patterns tolerated on the 1,5-dicarbonyl substrate and the range of amines.

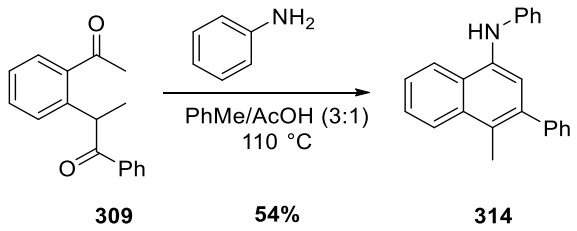
Our studies had already shown the cyclisation of dicarbonyl **309** worked well with a secondary amine, pyrrolidine, and thus we decided to see if the conditions were also amenable to a successful cyclisation with a primary amine, benzylamine. Treatment of 1,5-dicabonyl **309** with benzylamine in toluene/acetic acid yielded naphthylamine **313** in a good 70% yield. The formation of naphthylamine **313** was confirmed by the appearance of a singlet at 6.48 ppm in the ^{1}H NMR spectrum corresponding to the electron rich aromatic proton *ortho* to the nitrogen of the naphthylamine and a singlet at 4.30 ppm which was a diagnostic of benzylic protons next to an electron withdrawing group (**Scheme 101**).



Scheme 101 *Synthesis of naphthylamine **313**.*

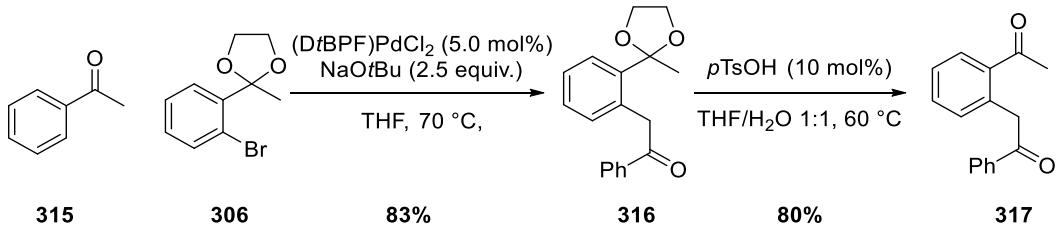
It was also desirable to study an amine which did not work in the arylamine synthesis to examine if the scope of the naphthylamine-forming cyclisation was any broader than the arylamine. Hence, dicarbonyl **309** was subjected to the acidic cyclisation conditions in the presence of aniline which had been previously unsuccessful (anilines, page 76). Pleasingly naphthylamine **314** was isolated in 54% yield. This highlighted the difference between the aryl and naphthylamine cyclisations and showed that the naphthylamine cyclisation could tolerate less nucleophilic amines. The formation of naphthylamine **314** was confirmed by a doublet integrating to two protons at 6.84 ppm and a triplet at 6.76 ppm corresponding to the electron rich protons *ortho* and *para* to the aniline. Further confirmation was obtained by the

presence of a signal in the high-resolution mass spectrum at 332.1398, which corresponded to the $[M+H]^+$ ion of naphthylamine **314** (**Scheme 102**).



Scheme 102 *Synthesis of naphthylamine **314**.*

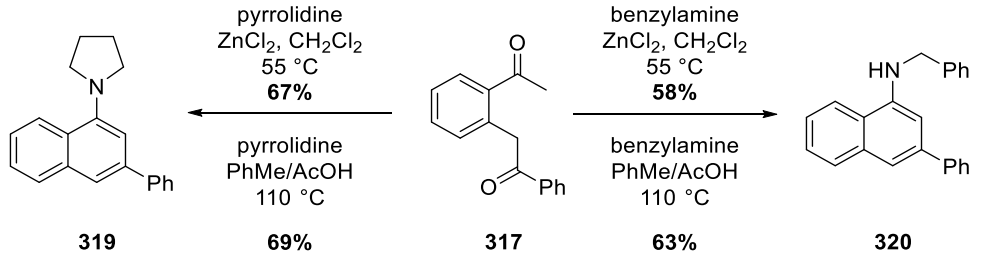
The scope of the ketone partner in the α-arylation reaction was next explored. Propiophenone (**307**) was known to be a reliable partner in the α-arylation reaction and resulted in the installation of a methyl group at the C-4 position; we also investigated acetophenone which would result in a hydrogen being present at the C-4 position. Thus 1,5-dicarbonyl **316** was synthesised from acetal **306** and acetophenone (**315**) *via* the α-arylation reaction ((D*t*BPF)$PdCl_2$, NaO*t*Bu in THF at 70 °C) to give acetal **316** in 83% yield. Dicarbonyl **317** was then synthesised in 80% yield by treating α-arylation product **316** with *p*-toluenesulfonic acid (**Scheme 103**).



Scheme 103 *Synthesis of 1,5-dicarbonyl **317**.*

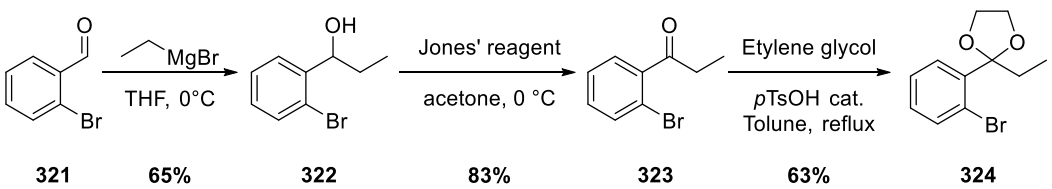
With dicarbonyl **317** in hand, it was subjected to Lewis acid cyclisation conditions with pyrrolidine. Pleasingly, naphthylamine **319** was isolated in 67% yield. The spectroscopic data for naphthylamine **319** was an excellent match to that reported in the literature.[98] The same conditions were then applied to the synthesis of naphthylamine **320** using benzylamine. Pleasingly, naphthylamine **320** was isolated in 58% yield. The formation of naphthylamine **320** was confirmed by the appearance of a singlet at 6.87 ppm in the ^1H NMR spectrum

corresponding to the electron rich proton *ortho* to the nitrogen on the naphthylamine and a singlet at 4.53 ppm which was a consistent with a pair of benzylic protons next to an electron withdrawing group. Dicarbonyl **317** was then subjected to the acidic cyclisation conditions developed earlier. Pleasingly naphthylamines **319** and **320** were isolated in slightly improved yields of 69% and 63% respectively (**Scheme 104**).



Scheme 104 *Synthesis of naphthylamine **319** and **320**.*

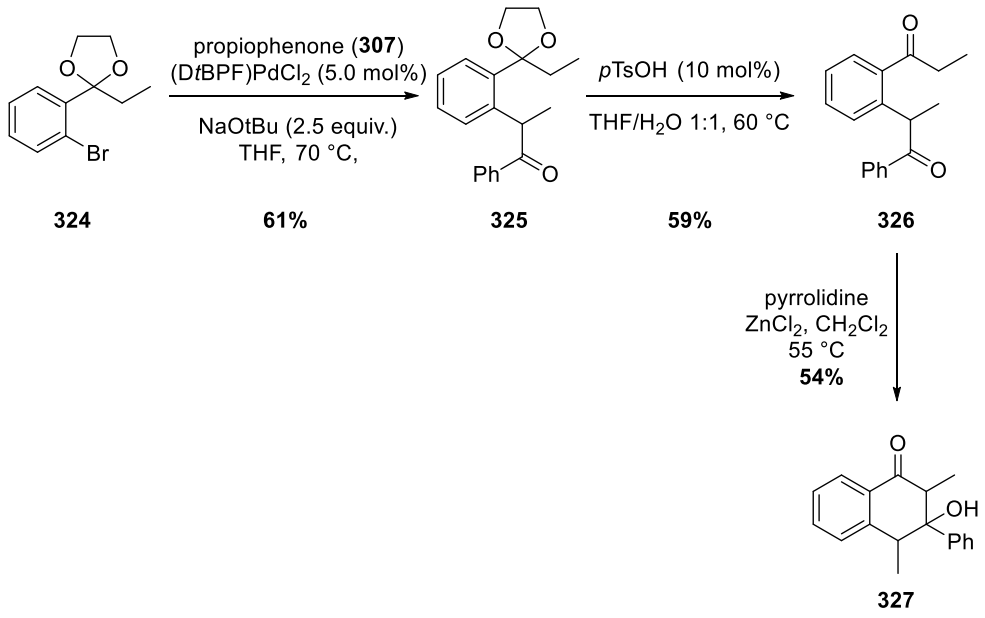
In the earlier synthesis of arylamines, substitution at the C-2 position of the 1,5-dicarbonyl prevented the cyclisation (**Scheme 57**, page 54). It was of interest to see if substitution at this position would have the same effect in the naphthylamine series; consequently, 1,5-dicarbonyl **326** was prepared. Aryl bromide **321** was treated with ethyl magnesium bromide to yield alcohol **322** in 65% yield. Oxidation using Jones' reagent gave ketone **323** in 83% yield which could be protected using ethylene glycol to give acetal **324** in 63% yield, characterised by multiplets between 3.96 - 4.11 ppm and 3.69 - 3.86 ppm in the ^{1}H NMR spectrum corresponding to the diastereotopic methylene protons of the acetal group (**Scheme 105**).



Scheme 105 *Synthesis of acetal **324**.*

Acetal **324** was then used as the coupling partner in the arylation of propiophenone **307** under α-arylation conditions. Cyclisation intermediate **325** was isolated in 61% yield and was then

treated with *p*-toluenesulfonic acid to remove the acetal protecting group thus furnishing dicarbonyl **326** in 59% yield. Subjecting intermediate **326** to both sets of cyclisation conditions did not yield any naphthylamine product. Under the Lewis acid conditions, cyclohexanone **327** was isolated in 54% yield; however, resubjecting this compound to the cyclisation conditions did not yield any naphthylamine product and only cyclohexanone **327** was recovered. Cyclohexanone **327** could be characterised by a pair of quartets at 3.61 ppm and 3.12 ppm in the ^{1}H NMR spectrum, corresponding to the CH protons next to the methyl groups. Strong stretching in the FTIR spectrum at 1683 cm^{-1} was indicative of an aromatic ketone and a chemical shift of 198.5 ppm in the ^{13}C NMR spectra also supported this. Treatment of diketone **326** with the acidic cyclisation conditions gave a complex mixture (**Scheme 106**).

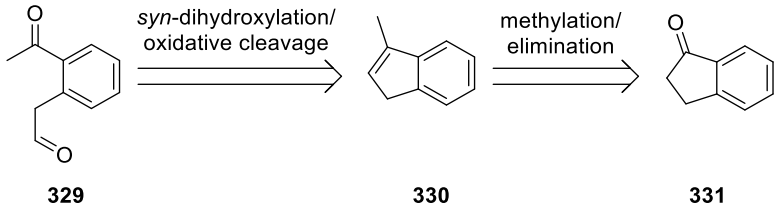


Scheme 106 *Synthesis of cyclohexanone **327**.*

At this point all naphthylamines that had been investigated contained an aryl group at the C-3 position because this allows regioselective enolisation in the α-arylation reaction. To continue our efforts in exploring the scope of substitution on the naphthylamine ring, the synthesis of a naphthylamine lacking substitution at the C-3 position was investigated. The synthesis of the prerequisite 1,5-dicarbonyl *via* α-arylation would require acetaldehyde as a coupling partner which is a difficult reaction to accomplish – note that the α-arylation of acetone was only

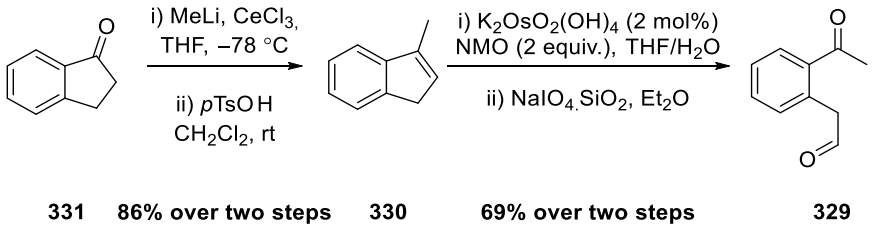
recently reported[99] and the arylation of aldehydes is still a challenging reaction due to competing aldol reactions.

Therefore, an alternative route to the keto-aldehyde substrate **329** was devised which began from a cyclic alkene **330** and involved a *syn*-dihydroxylation followed by an oxidative cleavage. The cyclic alkene **330** could be, prepared from indanone **331** *via* an alkylation/elimination sequence (**Scheme 107**).



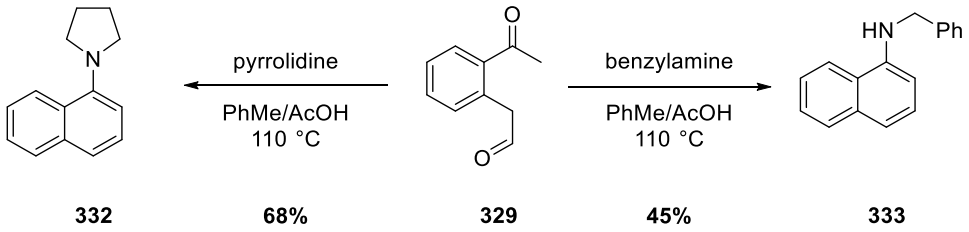
Scheme 107 *Retrosynthetic analysis of dicarbonyl **329**.*

Consequently, indanone **331** was treated with an organocerium complex generated from the transmetalation of methyl lithium with $CeCl_3$. Treatment of the resulting tertiary alcohol with *para*-toluenesulfonic acid resulted in the elimination of the alcohol to furnish indene **330** in an 86% yield. Dihydroxylation under Upjohn conditions[100] gave a *syn*-diol, which was then treated with silica-supported sodium periodate to accomplish an oxidative cleavage, yielding dicarbonyl **329** in 69% yield over two steps (**Scheme 108**). Dicarbonyl **329** was easily distinguished by a singlet at 9.76 ppm in the ^{1}H NMR spectrum corresponding to the aldehyde proton and two singlets at 200.8 ppm and 199.0 ppm in the ^{13}C NMR corresponding to the carbonyl signals.



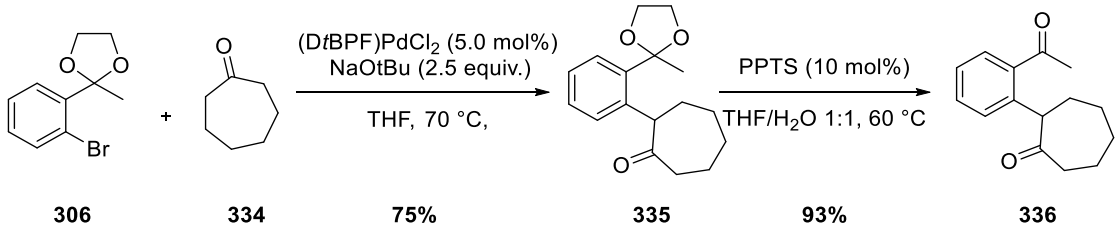
Scheme 108 *Synthesis of dicarbonyl **329**.*

Dicarbonyl **329** and pyrrolidine were then subjected to our acidic cyclisation conditions. Pleasingly, the desired cyclisation took place and naphthylamine **332** was isolated in 68% yield. The spectroscopic data for **332** were consistent with those previously reported.[101] Dicarbonyl **329** was then treated with benzylamine under acidic cyclisation conditions to yield naphthylamine **333** in a 45%, yield. Again, the data was an excellent match to that reported in the literature (**Scheme 109**).[102]



Scheme 109 *Synthesis of naphthylamines **332** and **333**.*

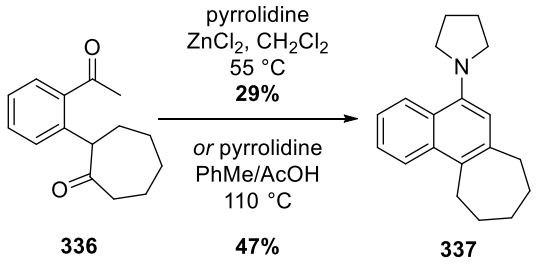
In a continuation of our interest into the scope of the naphthyl ring formation, it was decided to investigate the use of cyclic ketones as coupling partners in the α-arylation reaction. Hence, acetal **306** and cyclohexanone (**334**) were subjected to the previous α-arylation conditions, to furnish intermediate **335** in a good 75% yield. Deprotection of acetal **335** with *p*-toluenesulfonic acid yielded a complex mixture; however, use of the less acidic pyridinium *p*-toluenesulfonate gave clean conversion and dicarbonyl **336** was isolated in an excellent yield of 93% (**Scheme 110**).



Scheme 110 *Synthesis of dicarbonyl **336**.*

1,5-Dicarbonyl **336** and pyrrolidine were then subjected to Lewis acid cyclisation conditions. The reaction appeared to show a number of different products by TLC analysis and upon

purification naphthylamine **337** was isolated in 29% yield. The formation of naphthylamine **337** was confirmed by the presence of a singlet at 6.88 ppm in the ^{1}H NMR spectrum and a peak in the high-resolution mass spectrum at 266.1908, which corresponded to the $[M+H]^{+}$ ion of naphthylamine **337**. Dicarbonyl **336** was then subjected to acidic naphthylamine formation conditions; pleasingly an improved isolated yield of 47% of naphthylamine **337** was realised (**Scheme 111**).

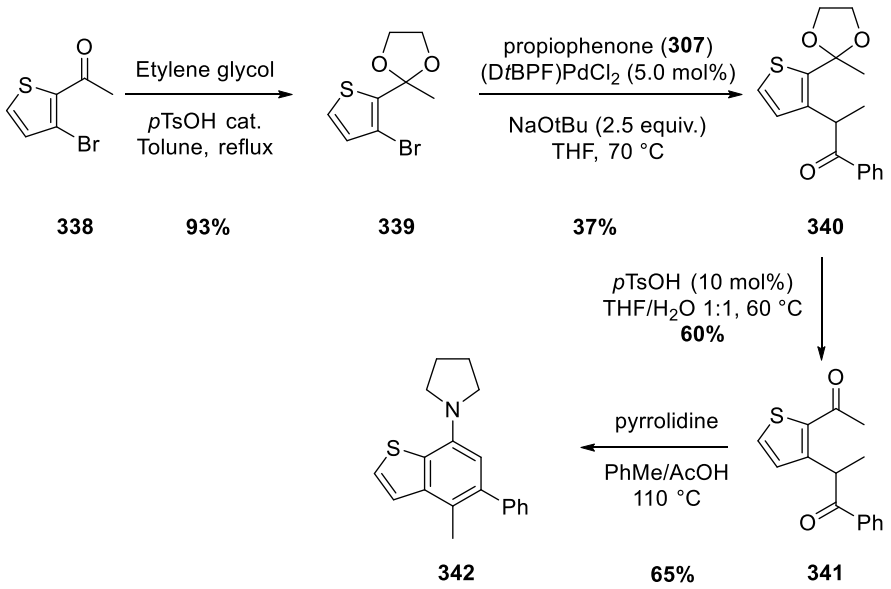


Scheme 111 *Synthesis of naphthylamine **337**.*

An interesting application of this methodology would be the synthesis of polycyclic heterocycles containing indole or benzothiophene units. To test this theory, we set about the synthesis of benzothiophene **342** which could be synthesised from commercially available ketone **338**.

Acetal protection of ketone **338** gave acetal **339** in a 93% yield. Coupling of aryl bromide **339** and propiophenone (**307**) under α-arylation conditions furnished ketone **340** in 37% yield. The ketone was then unmasked with *p*-toluenesulfonic acid to give dicarbonyl **341** in a good 60% yield. Dicarbonyl **341** could clearly be distinguished by strong stretching in the IR spectrum at 1683 cm^{-1} and 1661 cm^{-1} and chemical shifts at 200.8 ppm and 191.5 ppm in the ^{13}C NMR spectrum corresponding to the carbons of an aryl ketone. Treatment of dicarbonyl **341** and pyrrolidine with naphthylamine cyclisation conditions yielded benzothiophene **342** in a good 65% yield. The singlet at 6.54 ppm in the ^{1}H NMR spectrum is characteristic of aromatic proton *ortho* to the nitrogen. Further confirmation was provided by a peak in the

high-resolution mass spectrum at 316.1130, which corresponded to the $[M+Na]^+$ ion of naphthylamine **342** (**Scheme 112**).



Scheme 112 *Synthesis of naphthylamine **342**.*

2.3 Synthesis of benzo[*c*]phenanthridine natural products

2.3.1 Introduction

To further exemplify the ring closing methodology and demonstrate its ability to simplify the synthesis of aryl and naphthylamines, it was decided to test it in the area of natural product synthesis. Naphthylamines are a common core in natural products with over 12,000 found when searched in the Reaxys™ database. Within the family of arylamine containing natural products, the benzo[*c*]phenanthridine alkaloids presented themselves as an attractive target due to their biological importance and their structural features which could be accessed through our methodology, coupled with C-H activation chemistry such as that demonstrated in the synthesis of tricycle **246** (**Scheme 78**, page 71). This combination would provide a powerful and flexible route into this class of alkaloids.

The benzo[*c*]phenanthridine alkaloids are secondary metabolites found in *Papaveraceous* and *Rutaceous* plants. They are separated into three broad classes based on the oxidation state of the B-ring. **Table 10** shows some of the O_4-base alkaloids; there are also O_5-bases such as chelirubine **355** and O_6-bases such as macarpine **356**. A number of partially hydrogenated benzo[*c*]phenanthridine alkaloids have also been isolated such as chelidonine **354** (**Table 10**).

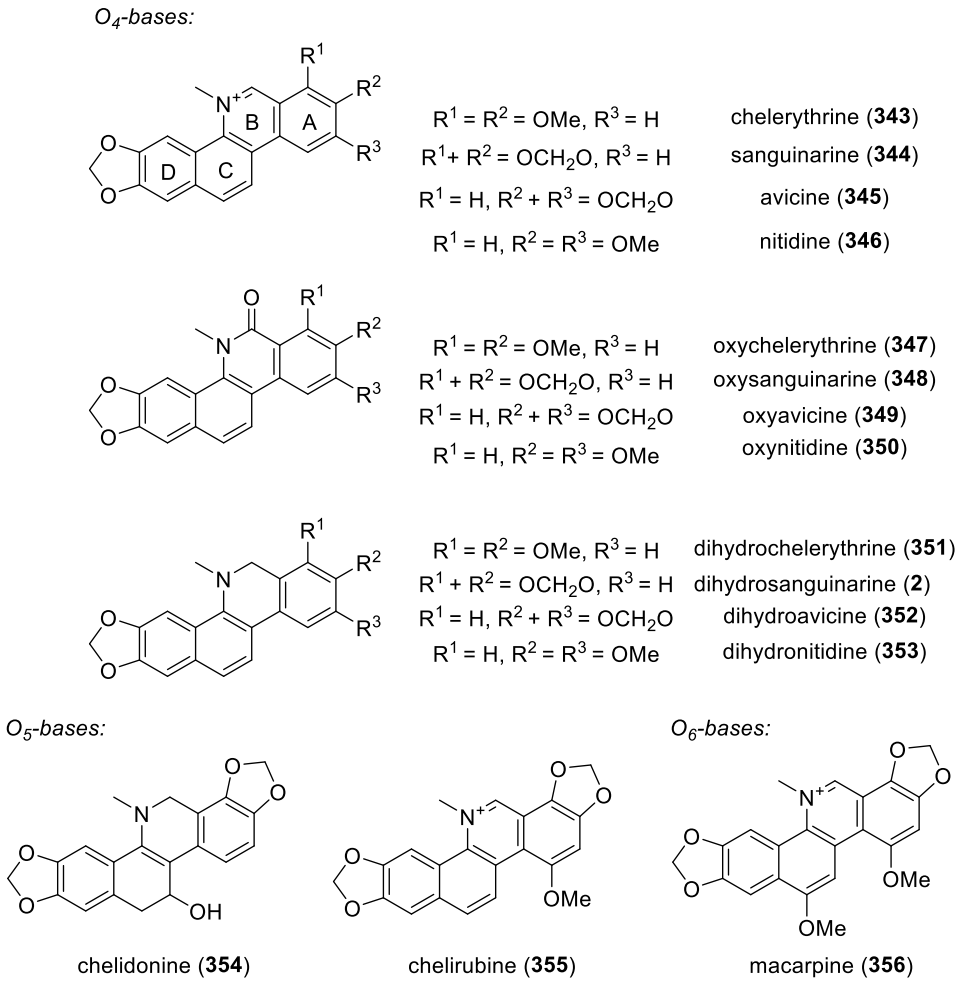


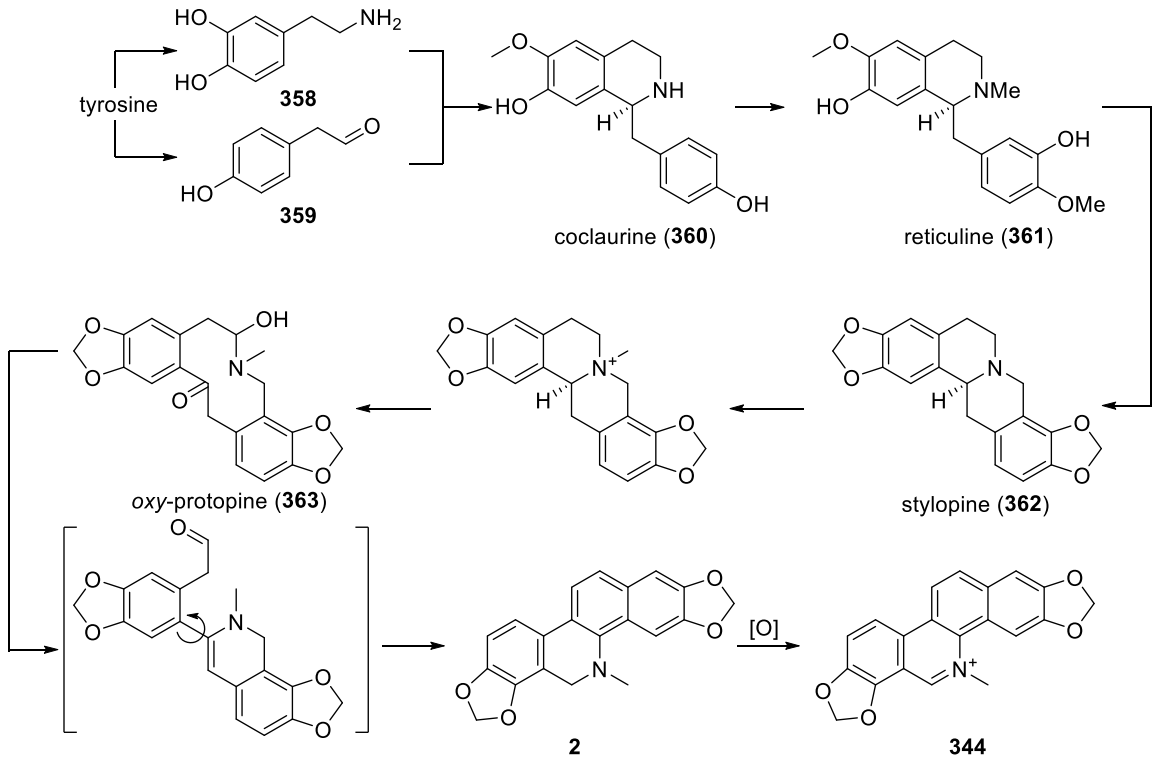
Table 10 *Benzo[c]phenanthridine alkaloids.*

The benzo[c]phenanthridines have also exhibited some interesting biological properties. For example, oxyavicine (**349)** can be used to treat ophthalmic disorders[103] and has demonstrated analgesic and anti-inflammatory effects.[104] Sanguinarine (**344**) inhibits lipoxygenase and mediates chemical defences against microorganisms, virus and herbivores in plants.[105] Chelerythrine (**343**) and nitidine (**346**) have been shown to inhibit protein kinase C and DNA topoisomerase 1.[106]

2.3.2 Biosynthesis

Benzo[*c*]phenanthridines are biosynthesised from tyrosine *via* a benzylisoquinoline.[107] It is proposed that the initial synthesis is the same as for the alkaloid berberine and is described by Dewick.[108] Coclaurine (**360**) is formed from *via* Pictet–Spengler reaction between two

molecules of tyrosine, one which has been decarboxylated and oxidised to form dopamine (**358**) and the other which undergoes transamination to the pyruvic acid derivative and then decarboxylated to form aldehyde **359**, followed by a methylation. Coclaurine (**360**) then undergoes a series of hydroxylations and methylations to form reticuline (**361**). It was found that labelled (*s*)-reticuline (**361**) had much higher conversions to benzo[c]phenanthridine products than its enantiomer. It is then hypothesised that reticuline (**361**) cyclises to form stylopine (**362**) *via* a Mannich type cyclisation. This molecule undergoes a methylation and oxidation to oxy-portopine **363** which undergoes a rearrangement to give the benzo[c]phenanthridine (**2**) framework (**Scheme 113**).[109]



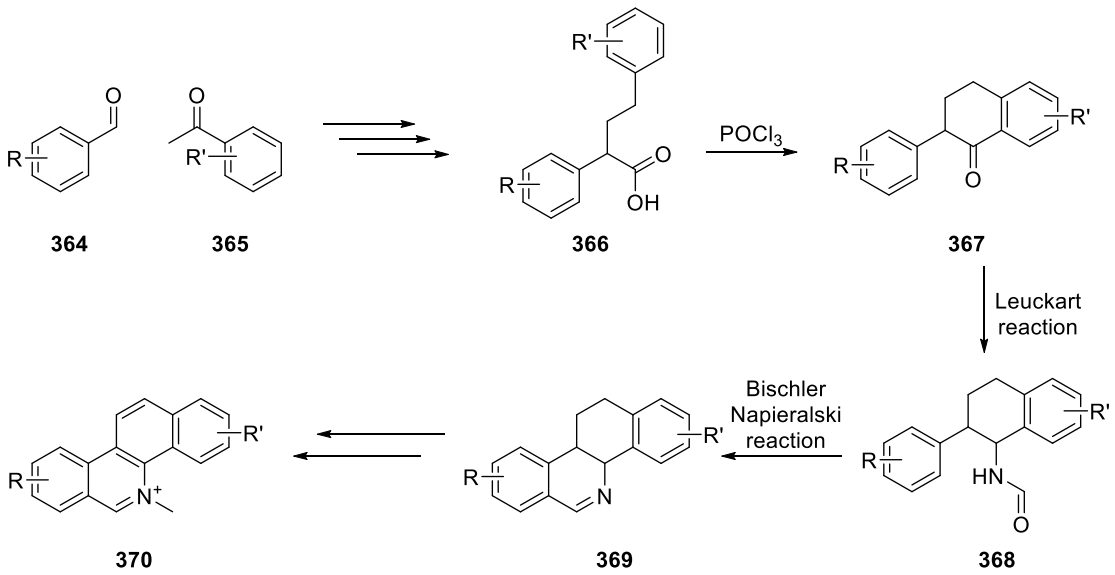
Scheme 113 *Biosynthesis of dihydrosanguianine (**2**) and sanguinanine (**344**).*

2.3.3 Previous Synthesises

As an important class of compounds, the benzo[c]phenanthridine have attracted some attention from the synthetic community. The following is a brief summary of some of the strategies that have been employed in the synthesis of benzo[*c*]phenanthridines.

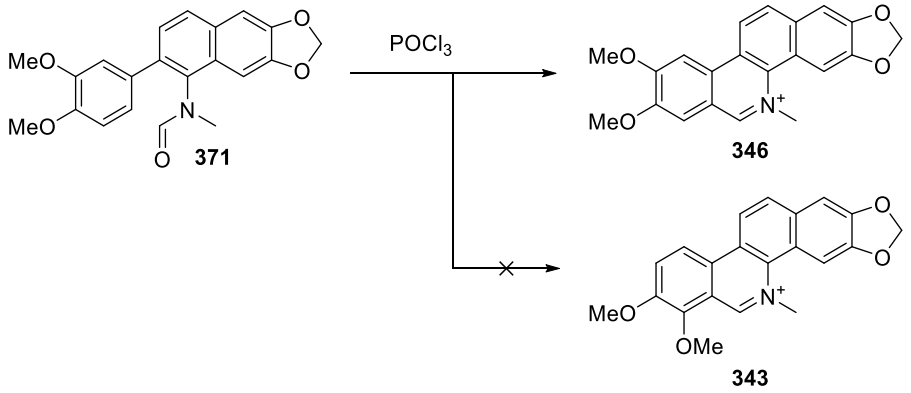
2.3.3.1 Robinson and Bailey synthesis – Bischler-Napieralski approach and key Friedel-Craft reaction

The first synthetic route was described by Robinson and co-workers and is based on a key Bischler-Napieralski reaction to from the isoquinoline fragment **369**. Acid **366** could be accessed in five steps from benzyl aldehyde **364** and acetophenone **365**. Treated of acid **366** with phosphoryl chloride formed the acid chloride which underwent a spontaneous Friedel-Crafts acylation to yield cyclohexanone **367**. This was transformed into Bischler-Napieralski precursor **368** by treatment with ammonium formate. A subsequent Bischler-Napieralski reaction yielded dihydroisoquinoline **369** which could be oxidised by a palladium on carbon catalyst and methylated to give the benzo[*c*]phenanthridine framework **370** (**Scheme 114**).[110]



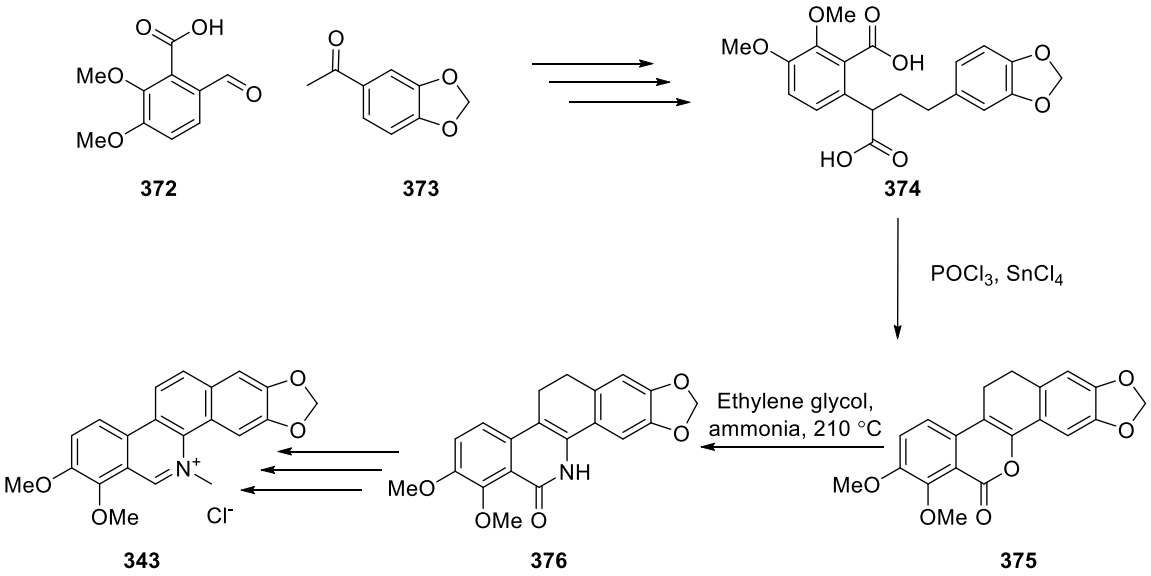
Scheme 114 *Synthesis of benzo[c]phenanthridine by Robinson and co-workers.*

One of the limitations of this approach is that due to steric and electronic effects, a cyclisation that results in structures of type **343** (where substitution has taken place in the *ortho* and *meta* positions to the methoxy groups) is not possible as substitution at the position *meta* and *para* to the methoxy groups is preferred. Thus, this method cannot access chelerythine (**343**) or sanguanine (**344**) (**Scheme 115**).



Scheme 115 *Limitation of the Bischler-Napieralski approach.*

Bailey and co-workers later continued the work and published the synthesis of chelerythrine chloride (**343**) *via* a key Friedel-Crafts reaction. Acid **374** was accessed *via* the same approach as in **Scheme 114**. Heating acid **374** with polyphosphoric acid followed by cooling and treatment with stannic(IV) chloride furnished lactone **375** which could be converted to lactam **376** by heat in the presence of ammonia. Conversion of lactam **376** to its chloride, reduction and methylation yielded chelerythrine chloride (**343)** (**Scheme 116**).[111]

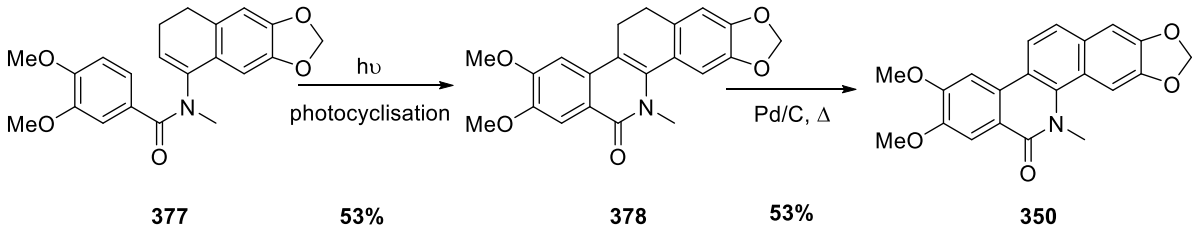


Scheme 116 *Synthesis of chelerythrine chloride **343** by Bailey and co-workers*

2.3.3.2 Niomya Synthesis – Photocyclisation

Niomya reported the synthesis of four benzo[*c*]phenanthridine alkaloids, demonstrating the power of his photocyclisation methodology. The key step was an enamide photocyclisation of

enamide **377** to form lactam **378** in 53% yield. Dehydrogenation of the product gave oxynitidine (**350**). The author also synthesised oxyavicine (**349**) and demonstrated that the reduction with lithium aluminium hydride furnished dihydronitidine (**353**) and dihydroavicine (**352**) (**Scheme 117**).[112]



377 **53%** **378** **53%** **350**

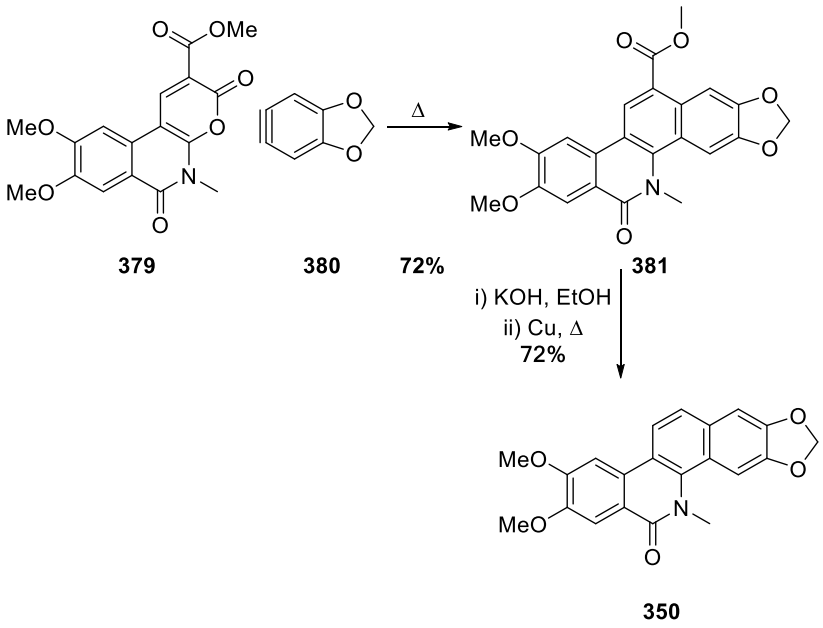
Scheme 117 *Synthesis of oxynitidine (**350**) by Niomya and co-workers.*

2.3.3.3 Cycloaddition

A key reaction for the synthesis of cyclic compounds is the cycloaddition reaction and this has been explored by a number of groups in the synthesis of benzo[*c*]phenanthridine alkaloids.

2.3.3.3.1 Guitian synthesis

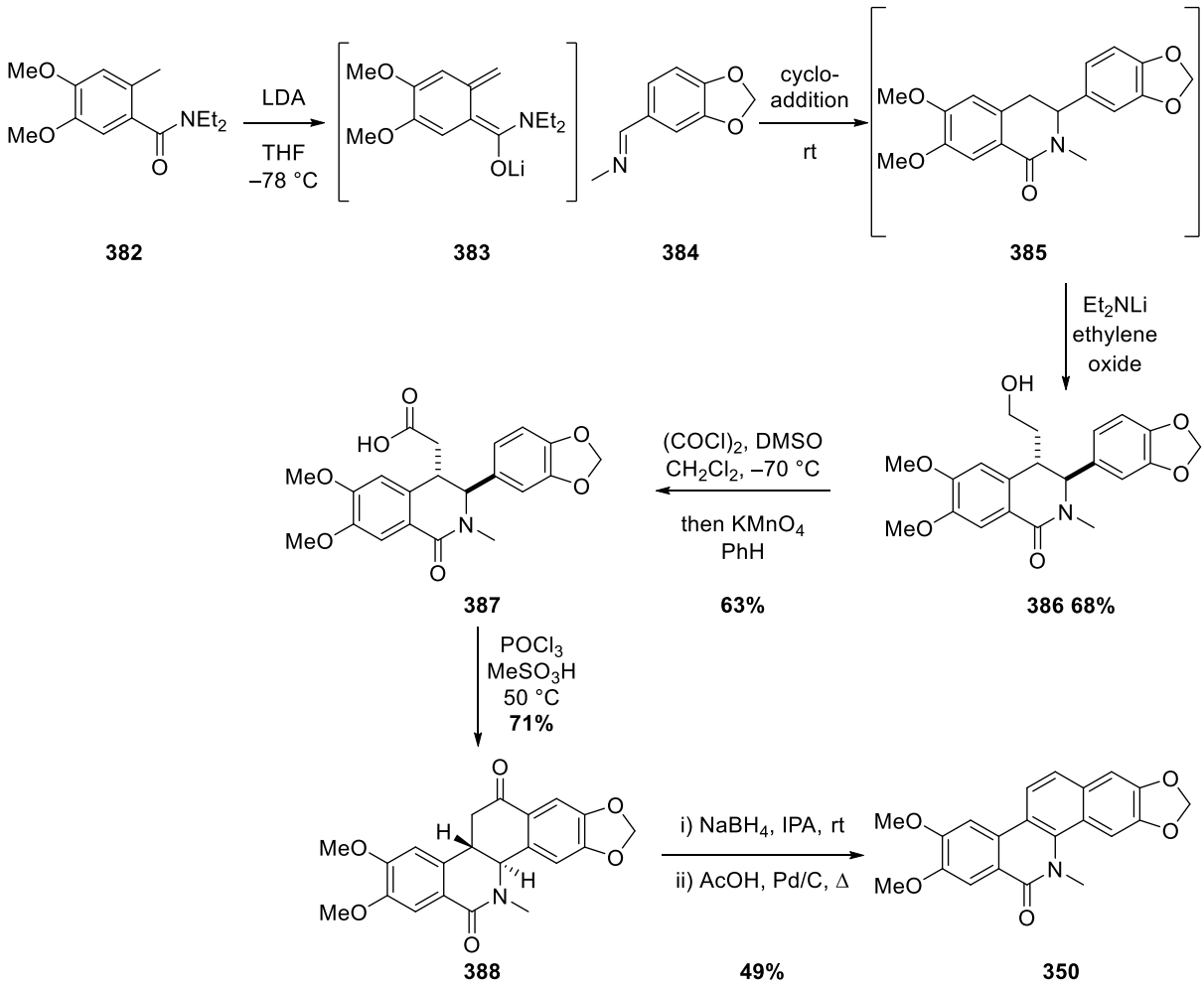
Guitian and co-workers exploited a cycloaddition reaction between pyrone **379** and benzyne **380** followed by the elimination of carbon dioxide. Ester **381** could then be transformed into oxynitidine **350** by hydrolysis and decarboxylation. The transformation of oxynitidine (**350**) to nitidine (**346**) is a known procedure and so this constitutes a formal synthesis of nitidine (**346**). This method was then used to synthesise a number of other benzo[*c*]phenanthridine alkaloids (**Scheme 118**).[113]



Scheme 118 *Synthesis of oxynitidine (**350**) by Guitian and co-workers.*

2.3.3.3.2 Clark Synthesis

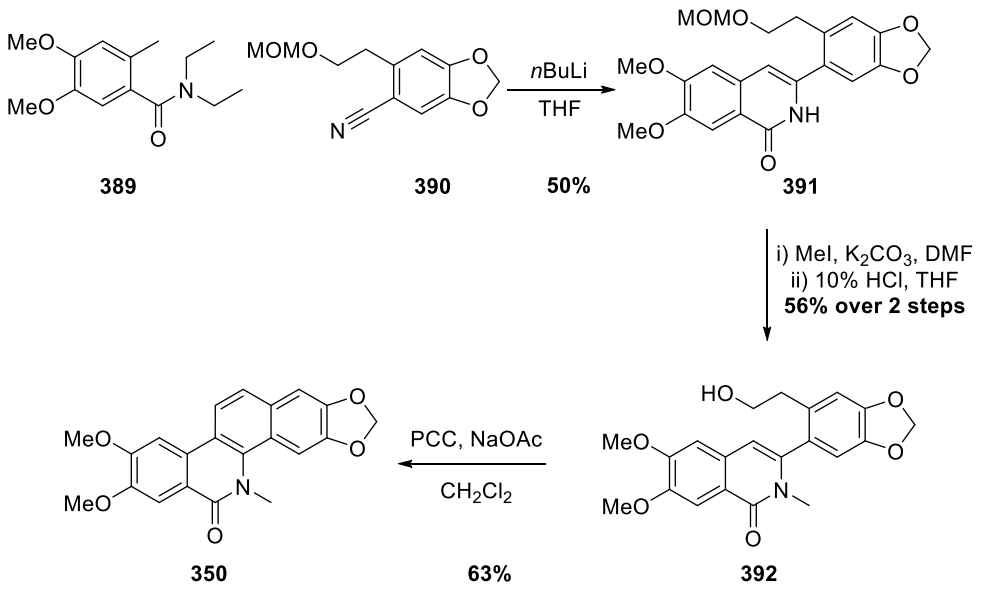
A cycloaddition reaction was also used as the key step in Clark and co-worker's total synthesis of oxynitidine (**350**). Treatment of toluene **382** with lithium diisopropylamide (LDA) gave diene **383** which underwent a cycloaddition reaction with imine **384**. After elimination of diethylamide, lactam **385** was generated and under the basic conditions was alkylated with ethylene oxide to give alcohol **386**. Subsequent oxidation to acid **387** followed by an intramolecular acylation completed the benzo[*c*]phenanthridine framework **388**. To finish the synthesis, ketone **388** was reduced with sodium borohydride and dehydrogenated by palladium on carbon to yield oxynitidine (**350**) in six steps and 17% overall yield (**Scheme 119**).[114]



Scheme 119 *Synthesis of oxynitidine (**350**) by Clark and co-workers.*

2.3.3.3.3 Cho Synthesis

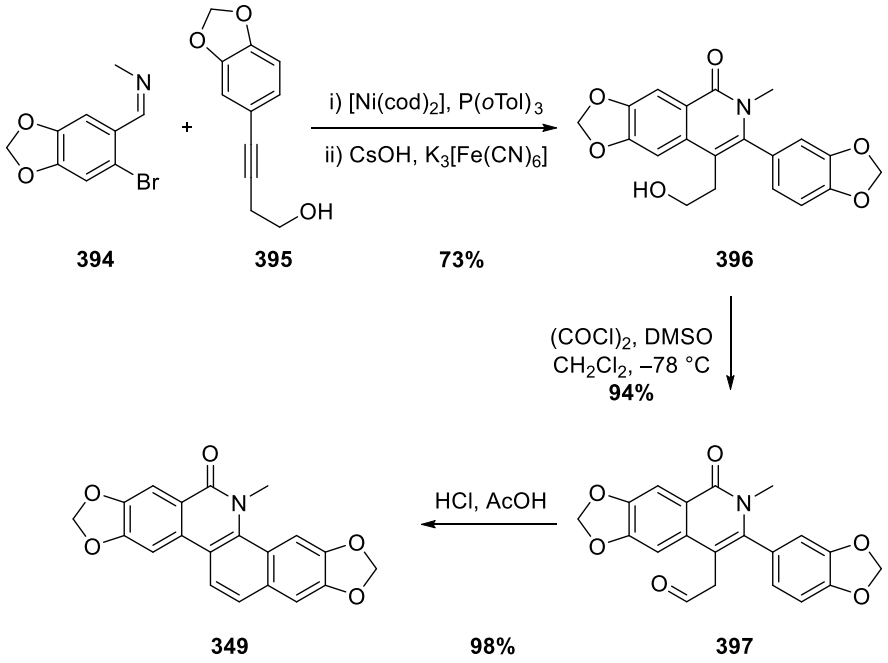
This approach was then modified by Cho and co-workers to allow access to a number of extra benzo[*c*]phenanthridines and protoberberines. In this strategy, the imine was replace by nitrile **390**. The diene was generated by treatment of toluamide **389** with *n*BuLi and treatment with nitrile **390** resulted in smooth conversion to pyridone **391** in good yield. Methylation followed by deprotection of the methoxymethyl ether group yielded alcohol **392** which was oxidised to the aldehyde. Spontaneous cyclisation formed the final ring and completed the synthesis of oxynitidine (**350**) (**Scheme 120**).[115]



Scheme 120 *Synthesis of oxynitidine (**350**) by Cho and co-workers.*

2.3.3.6 Cheng Synthesis – Alkyne cyclisation

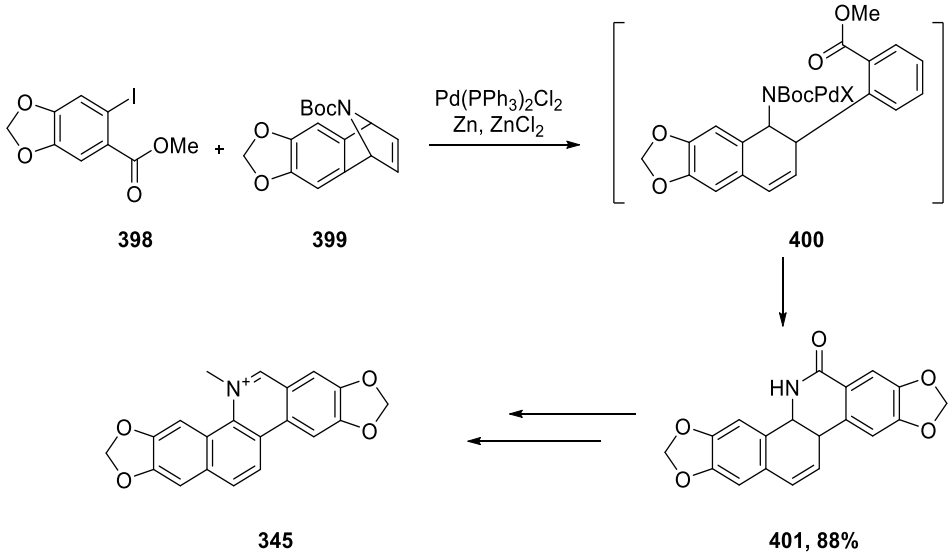
Cheng and co-workers reported the use of their nickel-catalyzed regioselective cyclisation of *o*-halobenzaldimine with alkynes as the key step in the synthesis of several benzo[*c*]phenanthridine alkaloids. Treatment of imine **394** and alkyne **395** with a nickel(0) catalyst, followed by the addition of caesium hydroxide and $K_3[Fe(CN)_6]$ gave pyridone **396** in good yields. The final ring was constructed by oxidation under Swern conditions followed by treatment with acid to catalyse the final cyclisation and elimination to yield oxyavicine (**349**) in 5 steps with an overall yield of 67% (**Scheme 121**).[116]



Scheme 121 *Synthesis of oxyavicine (**349**) by Cheng and co-workers.*

2.3.3.7 Xu Synthesis – Palladium ring-opening reaction

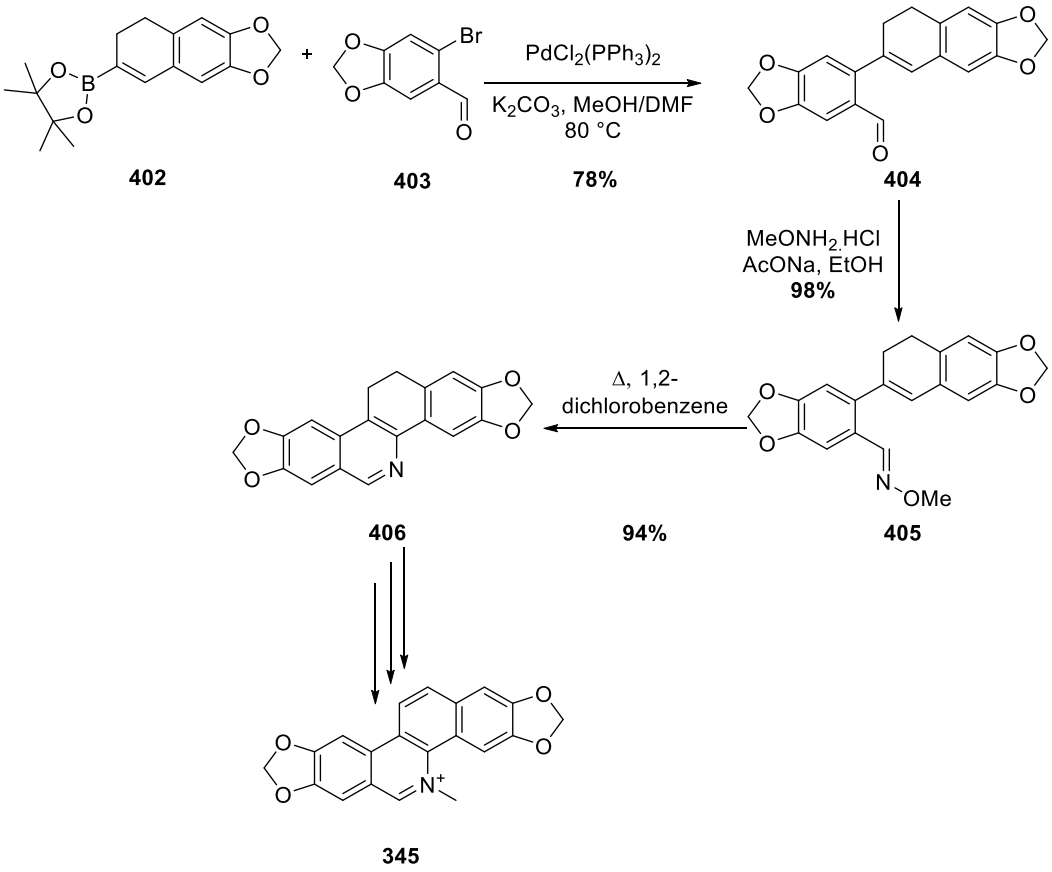
Xu and co-workers completed their alkaloid synthesis using a palladium-catalyzed ring-opening coupling reaction between azabicyclic alkene **399** and *o*-iodobenzoate **398** via intermediate **400** followed by an intramolecular cyclisation. The resulting pyridone **401** was then furnished appropriately to yield avicine chloride (**345**) (**Scheme 122**). The approach was also used to synthesise a number of other alkaloids.[117]



Scheme 122 *Synthesis of benzo[c]phenanthridine alkaloids by Xu and co-workers.*

2.3.3.8 Hibino – 6π-electrocylisation

Hibino constructed the *aza*-triene moiety **405** *via* a Suzuki coupling of bronic acid **402** and aryl bromide **403** followed by a condensation with hydroxylamine. The *aza*-triene **405** then underwent a microwave assisted 6π-electrocylisation to give the core scaffold **406** which could be further manipulated to yield avicine (**345**) (**Scheme 123**). The authors also demonstrate the power of this method with the synthesis of several other alkaloids.[118]

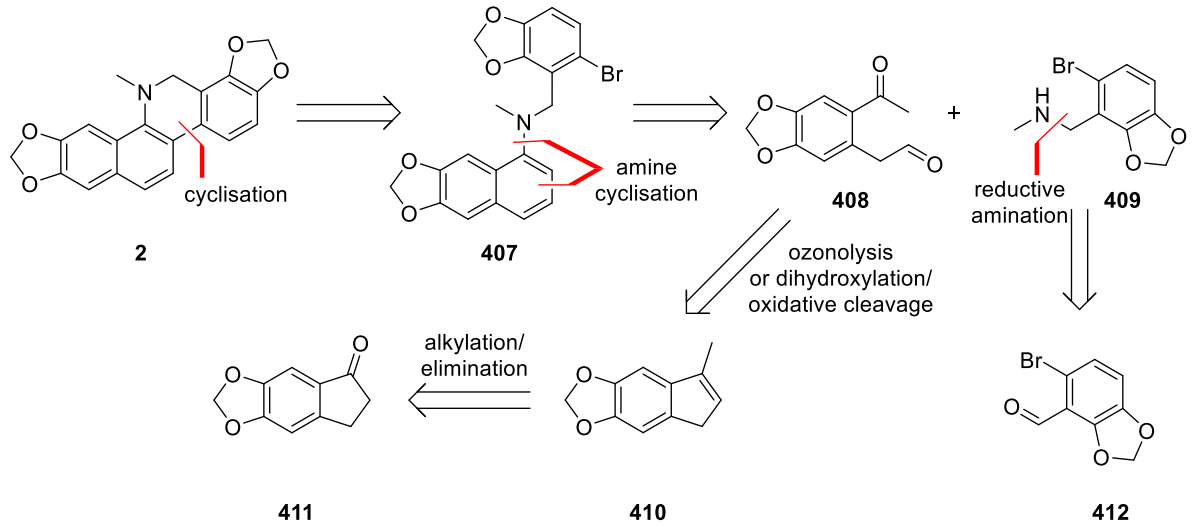


Scheme 123 *Synthesis of benzo[c]phenanthridine alkaloids by Hibino and co-workers.*

2.3.4 Our disconnection

In the first instance, our methodology was targeted at the synthesis of dihydrosanguinarine (**2**). It was decided to leave the formation of the B ring until the end as this disconnection could be achieved using either C-H activation chemistry such as that used in the synthesis of tricycle **246** (**Scheme 78,** page 71) or *via* an intramolecular homolytic aromatic substitution (IHAS) reaction. Naphthylamine **407** would come from our naphthylamine forming

cyclisation between dicarbonyl **408** and benzyl amine **409**. Benzyl amine **409** could be accessed *via* a reductive amination between benzaldehyde **412** and methyl amine. Dicarbonyl **408** could be accessed by either through ozonolysis or a dihydroxylation/oxidative cleavage procedure upon indene **410** which could in turn be accessed by an alkylation/elimination sequence from indanone **411** (**Scheme 124**).

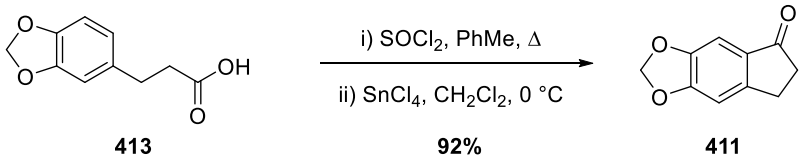


Scheme 124 *Retrosynthetic analysis of dihydrosanguinarine (2).*

2.3.5 Results and discussion

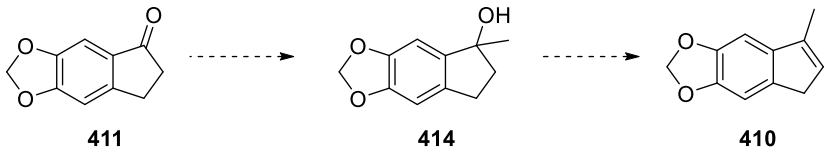
2.3.5.1 Synthesis of indene 410

Although indanone **410** was commercially available, it could be more economically synthesised from acid **143** by an intramolecular Friedel-Crafts acylation. As such, indanone **411** could be synthesised by refluxing acid **413** with thionyl chloride in toluene for 12 hours, followed by a solvent swap to dichloromethane and treatment with tin(IV) chloride. Indanone **411** was isolated as a tan solid in 92% yield (**Scheme 125**).



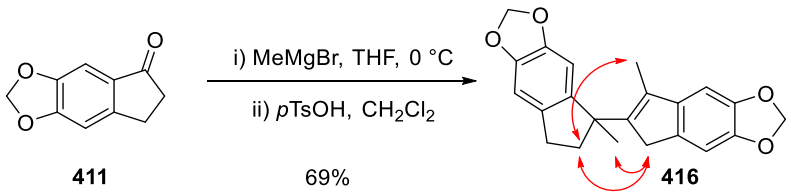
Scheme 125 *Synthesis of indanone **411**.*

It was next planned to synthesise indene **410** by the addition of a methyl nucleophile to the carbonyl of indanone **411** followed by elimination of the resulting tertiary alcohol **414** (**Scheme 126**).



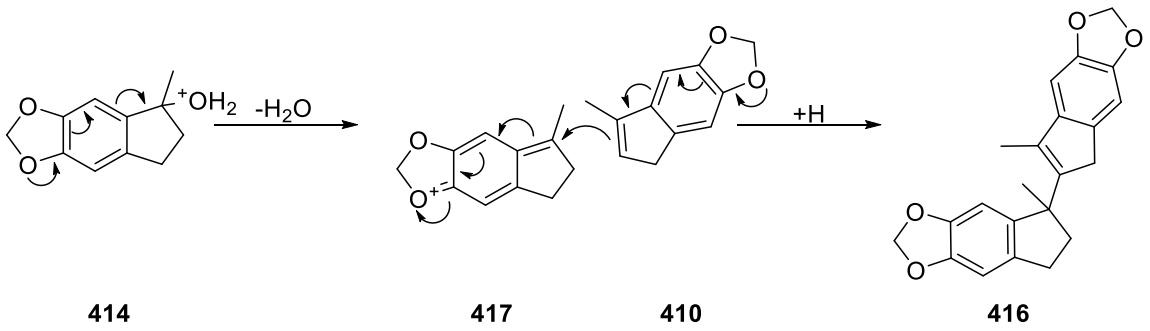
Scheme 126 *Planned synthesis of indene **410**.*

Treatment of indanone **411** with methylmagnesium bromide gave good conversions to tertiary alcohol **414**, but an attempt to purify the reaction mixture by flash column chromatography resulted in concomitant elimination to yield indene **410** and so it was decided to carry out the elimination on the crude tertiary alcohol. Attempted elimination of crude alcohol **414** with *p*-toluenesulfonic acid resulted in formation of an unexpected product which was assigned as dimer **416** (**Scheme 127**). Dimer **416** was characterised by a doublet of doublets at 3.29 ppm corresponding to an allylic pair of protons and a doublet of doublet of doublets at 2.14 ppm corresponding to one of a pair of diastereotopic protons in the ^{1}H NMR spectrum; this assignment was supported by n.O.e. enhancements.



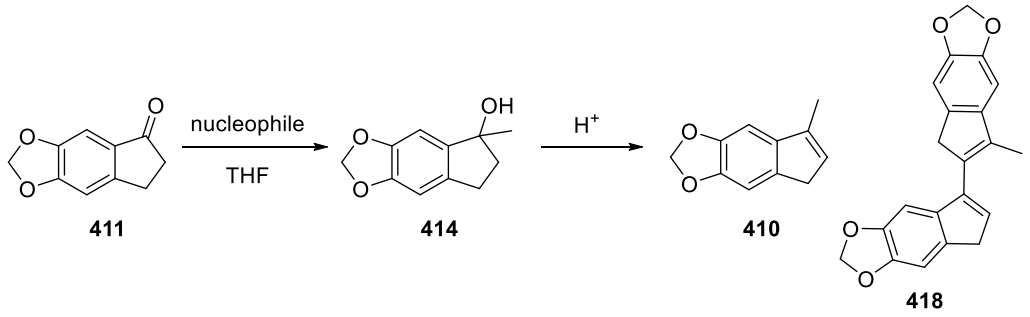
Scheme 127 Synthesis of dimer **416 (***key n.O.e. enhancement shown in red***)**.

The mechanism of formation of dimer **416** is of interest and it is proposed that the dimerisation could come from nucleophilic attack of indene **410**, on cation **417** formed from the elimination of alcohol **414** (**Scheme 128**).



Scheme 128 *Proposed mechanism for the formation of dimer **416**.*

It was decided to use the less acidic pyridinium *p*-toluenesulfonate for the elimination. We hypothesised that the conjugate base, pyridine, would be able deprotonate cation **417** faster than indene **410** could attack and pleasingly good conversions were observed from crude alcohol **414** to indene **410** (**Table 11**, entry 1). Indene **410** was easily characterised by signals at 6.15 ppm, 3.26 ppm and 2.15 ppm in the ^{1}H NMR spectrum corresponding to the vinylic proton, the allylic methylene group and the allylic methyl group.



	Nucleophile	Temperature (°C)	Elimination	Isolated Yield 410	418	414	416
1[c]	MeMgBr	0°C	PPTS, CH_2Cl_2	70%	-	-	-
2[b]	MeMgBr	0°C	sat. $NH_4Cl_{(aq)}$	-	-	100%[a]	-
3[b]	MeMgBr	0°C	1M $HCl_{(aq)}$	65%	5%	-	-
4[b]	MeMgCl	0°C	HCl (1M)	40%	20%	-	-
5[b]	MeLi, $CeCl_3$	–78 °C	1M HCl	-	-	-	100%[a]
6[c]	**MeLi, $CeCl_3$**	**–78 °C**	**PPTS, CH_2Cl_2**	**77%**	**-**	**-**	**-**

[a] conversion by ^{1}H NMR analysis
[b] one-pot procedure [c] two-pot procedure

Table 11 *Optimisation of the synthesis of indene **410**.*

The ease with which alcohol **414** was eliminated put forward the possibility that the process could be telescoped or that the elimination could take place upon an acidic work-up. A work-up using a saturated solution of NH_4Cl was not enough to induce the elimination (entry 2), however a 1.0 M aqueous HCl wash was successful in generating indene **410** (entry 3). However, the process proved to be capricious and yielded varying amounts of side product **418** which was believed to result from an undesired reaction of the product **410** with any unreacted starting material **411** (entry 3 and 4). Side product **418** proved to be a solid and the structure was confirmed with a crystal structure (**Figure 11**).

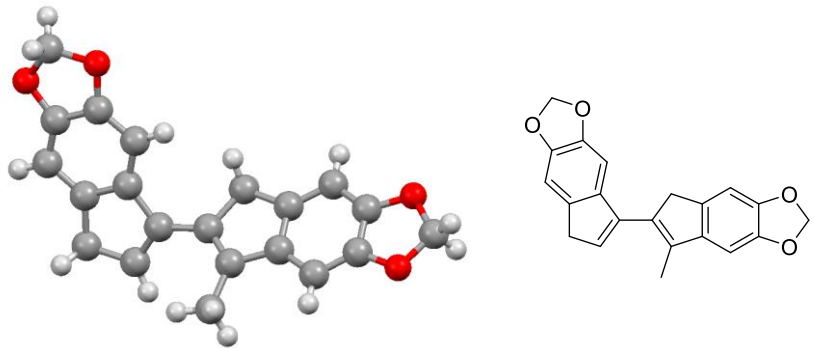


Figure 11 *Representation of the X-ray structure of dimer **418**.*

The use of a greater number of equivalents of methylmagnesium bromide did not result in a greater conversion to alcohol **414**. It was hypothesised that some of ketone **411** was deprotonated under the basic methylmagnesium bromide conditions to form its enolate which was not reactive and when quenched upon work-up was observed as recovered starting material. Thus, the methyl nucleophile was switched to the analogous organocerium reagent which is known to be less basic.[119]

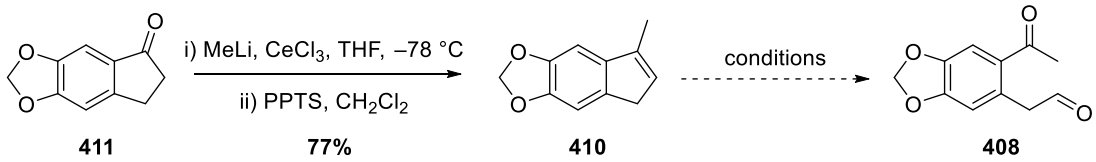
Pleasingly, the reaction of indanone **411** with an organocerium reagent gave complete conversion to tertiary alcohol **414**, however a 1.0 M aqueous HCl work-up yielded dimer **416** (entry 5). Due to the capricious nature of the HCl work-up, it was decided to switch to the

two-pot pyridinium *p*-toluenesulfonate procedure whereby indene **410** could be accessed reliably in high yields (entry 6).

It was decided that entry 6 gave the most reliable and high yielding results and so these conditions were used routinely in our synthesis.

2.3.5.2 Synthesis of dicarbonyl 408

With a reliable and high yielding route to indene **410** in hand, attention was turned to the synthesis of dicarbonyl **408** (**Scheme 129**).

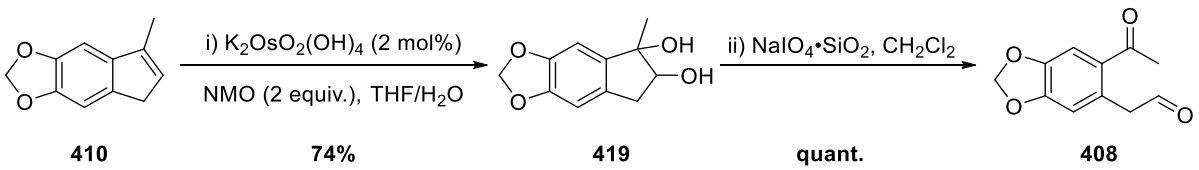


Scheme 129 *Summary of indene **410** and planned synthesis of dicarbonyl **408**.*

The first strategy investigated was a dihydroxylation and oxidative cleavage procedure. Pleasingly, treatment of indene **410** with Upjohn dihydroxylation conditions,[100] potassium osmate(VI) dihydrate (0.02 equivalents), *N*-methylmorpholine-*N*-oxide (NMO) (2 equivalents) and THF/H_2O, furnished diol **419** in an excellent isolated yield of 74%. Diol **419** was easily characterised by a triplet at 4.05 ppm, a good match for a proton next to an alcohol and a pair of doublet of doublets at 3.00 ppm and 2.70 ppm, corresponding to the two methylene protons next to the alcohol. Further evidence was found in the IR spectrum where broad stretching observed at 3257 cm^{-1} corresponded to the OH bond stretching of the two alcohols (**Scheme 130**).

Treatment of diol **419** with silica supported sodium periodate yielded dicarbonyl **408** in quantitative yield and in excellent purity; this was important as dicarbonyl **408** was found to be unstable and best used immediately after its synthesis. Dicarbonyl **408** could be easily characterised by a singlet at 9.64 ppm in the ^1H NMR spectrum corresponding to the

aldehyde proton as well as two singlets at 199.0 ppm and 198.4 ppm in the ^{13}C NMR spectrum corresponding to the carbonyl signals (**Scheme 130**).



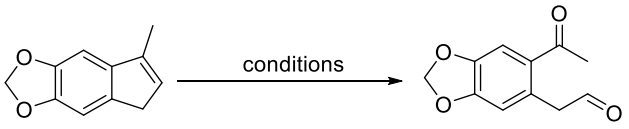
Scheme 130 *Synthesis of dicarbonyl **408**.*

A one-pot protocol for the synthesis of dicarbonyl **408** was investigated next; it would make this step operationally simpler and improve its utility. Using ozonolysis conditions developed by Gibbs and co-workers,[120] the synthesis of dicarbonyl **408** was attempted from indene **410**. Unfortunately ^1H NMR analysis of the crude reaction mixture showed only decomposition (**Table 12**, entry 1) and so alternative conditions were sought.

A one-pot dihydroxylation and oxidative cleavage was next attempted. Firstly, the effect of the two solvent systems on a one-pot reaction was investigated. Pleasingly, use of a dihydroxylation solvent system (*t*BuOH/THF/H_2O) as the solvent for both the dihydroxylation and oxidative cleavage in one-pot gave 50% conversion to the aldehyde product **408**, however upon purification by silica flash column chromatography only a 10% yield (entry 2). Water is essential to the dihydroxylation reaction so we tested a dichloromethane/water mix was tested with the hope that the oxidative cleavage might be more efficient in dichloromethane. However, this solvent system was not conducive to the dihydroxylation and only starting material was recovered (entry 3).

Further literature investigation uncovered some one-pot conditions published by Johnson and co-workers. Here, sodium periodate was used as both the reoxidant for osmium tetroxide and for the oxidative cleavage; the solvent used was dioxane and water.[121] Pleasingly, under these conditions, good conversions were observed to aldehyde **408** but isolated yields were

still poor (entry 4). It has been reported that tertiary amines and pyridines can significantly improve the rate of dihydroxylation reactions.[122] A further set of conditions found using $(n\text{Bu}_4\text{N})_2\text{IO}_4$, a more organic soluble periodate source, and a pyridine additive gave excellent conversions to aldehyde **408**.[123] Unfortunately, only poor isolated yields were observed (entry 5). Switching the solid phase of our purification protocol from slightly acidic silica to basic alumina immediately improved the isolated yield and now dicarbonyl **408** was isolated in 48% yield (entry 6).



410 **408**

Entry	Conditions	Result
1	O_3, CH_2Cl_2, –78 °C then Zn, AcOH, 0 °C	decomposition
2	i) $K_2OsO_2(OH)_4$ (2 mol%), NMO (2 equiv.), tBuOH/THF/H_2O 9/10/1 then $NaIO_4.SiO_2$	50%[a], 10%[b]
3	i) $K_2OsO_2(OH)_4$ (2 mol%), NMO (2 equiv.), CH_2Cl_2:H_2O 4:1	rsm
4	i) OsO_4 (2 mol%), $NaIO_4$ (2 equiv.), Dioxane:H_2O, 3:1	23%[b]
5	i) OsO_4 (10 mol%), $(n\text{Bu}_4\text{N})_2\text{IO}_4$ (4.4 equiv.), 2,6-lutidine (2.5 equiv.), acetone:H_2O, 3:1	95%[a] 17%[b]
6	**i) OsO_4 (10 mol%), $(n\text{Bu}_4\text{N})_2\text{IO}_4$ (4.4 equiv.), 2,6-lutidine (2.5 equiv.), acetone:H_2O, 3:1**	**48%[b,c]**

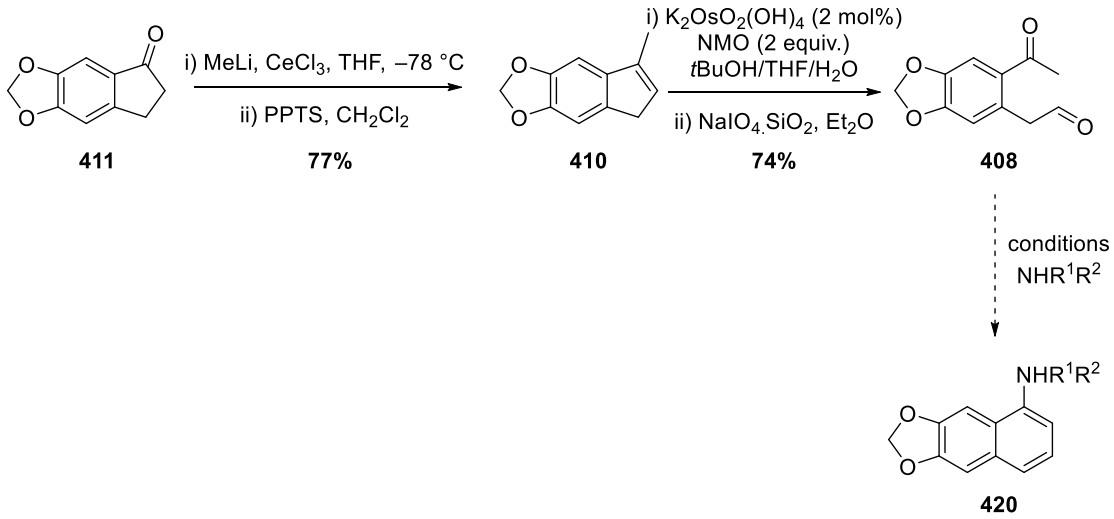
[a]conversion based on ^{1}H NMR [b]isolated yield [c] purified using alumina

Table 12 *Optimisation of a one-pot dicarbonyl **408** synthesis.*

Even though a one-pot procedure to form aldehyde **408** from indene **410** which gave acceptable yields had been found, it was decided to use the two-pot conditions (**Scheme 130**) in our synthesis as is was still operationally simple and gave a better overall yield.

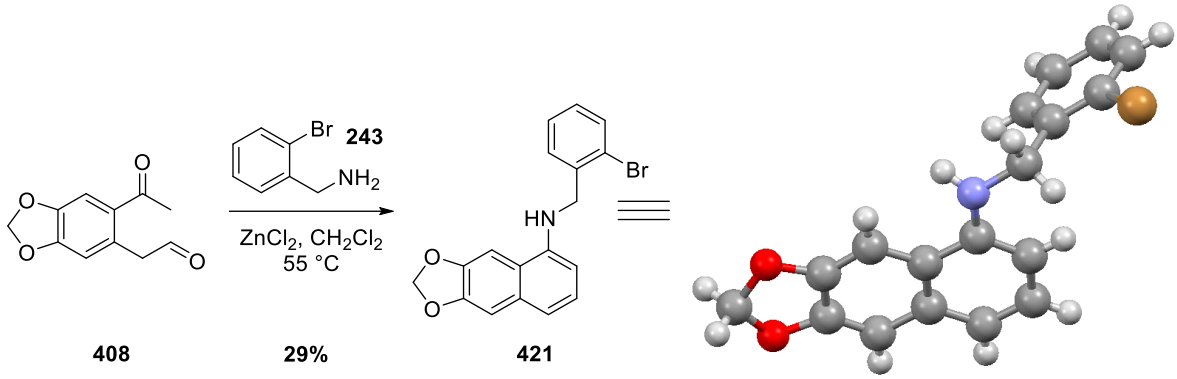
2.3.5.3 Naphthylamine formation

With dicarbonyl **408** in hand, we set about investigating the key cyclisation to form arylamine **420**. As the amine required for the cyclisation in the real system was precious, we decided to first investigate the cyclisation with a model system (**Scheme 131**).



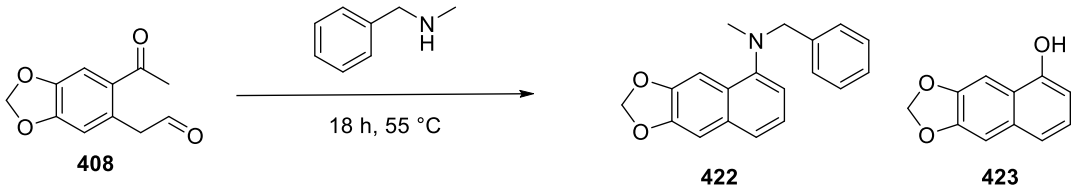
Scheme 131 *Synthesis dicarbonyl **408** and planned synthesis of arylamine **420**.*

The investigations begin with amine **243** to assess whether dicarbonyl **408** was a suitable substrate for the cyclisation. Dicarbonyl **408** and benzylamine **243** were heated in the presence of $ZnCl_2$ in dichloromethane at 55 °C for 12 hours. Pleasingly, arylamine **421** was observed and could be isolated in a 29% yield. Naphthylamine **421** proved to be a solid; thus, a crystal structure was acquired and proved the structure of this compound (**Scheme 132**). It was possible that the low yield may have been caused by decomposition of dicarbonyl **480** prior to use in the reaction; dicarbonyl **408** had previously been found to partially decompose when left in $CDCl_3$ over night (**Scheme 132**).



Scheme 132 *Synthesis of arylamine **421** and a representation its crystal structure.*

Happy that dicarbonyl **408** was a viable partner in the naphthylamine forming cyclisation, we set about investigating if a secondary amine would be a suitable substrate for the cyclisation. Thus, *N*-methyl benzylamine and dicarbonyl **408** were subjected to our optimised Lewis acid, naphthylamine-forming conditions to furnish arylamine **422** in a good 40% yield (**Table 13**, entry 1). The effects of the conditions on the reaction were explored. Changing from dichloromethane to dichloroethane gave a small improvement in the yield of the reaction. Other Lewis acids were also explored, however it was found that moderate/soft Lewis acids worked best, with $ZnCl_2$ giving the highest conversion (entry 2-6). We next began a programme of study to reduce the number equivalents of amine required for the cyclisation since, similar to arylamine **249**, the amine we would ultimately be using was precious. Thus, we optimised the process with a syringe pump addition protocol and we were able to reduce the amount of amine required to 1.5 equivalents with comparable yields (entries 7-9). A reduction in the amount of $ZnCl_2$ when using 1.5 equivalents of amine increased the yield to 37% (entry 10). A major side product that became apparent when using 1.5 equivalents of amine was napthol **423** which was presumably formed *via* a competing intramolecular aldol reaction.



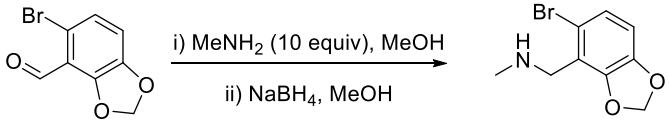
408 **422** **423**

Entry	Equivalents of amine	Solvent	Additivie	Addition time (h)	Conversion	
					422	**423**
1	5	CH_2Cl_2	$ZnCl_2$[a]	-	40%	-
2	5	$C_2H_4Cl_2$	$ZnCl_2$[a]	-	55%	-
3	5	$C_2H_4Cl_2$	CuCl[a]	-	43%	-
4	5	$C_2H_4Cl_2$	$TiCl_4$[a]	-	-	-
5	5	$C_2H_4Cl_2$	$SnCl_4$[a]	-	-	-
6	5	$C_2H_4Cl_2$	$AlMe_3$[a]	-	-	-
7	5	$C_2H_4Cl_2$	$ZnCl_2$[a]	1	49%	-
8	5	$C_2H_4Cl_2$	$ZnCl_2$[a]	12	45%	-
9	1.5	$C_2H_4Cl_2$	$ZnCl_2$[a]	12	31%	22%
10	**1.5**	**$C_2H_4Cl_2$**	**$ZnCl_2$[b]**	**12**	**37%**	**11%**

[a] 1.0 equivalents [b] 0.2 equivalents

Table 13 *Optimisation of naphthylamine **422** formation.*

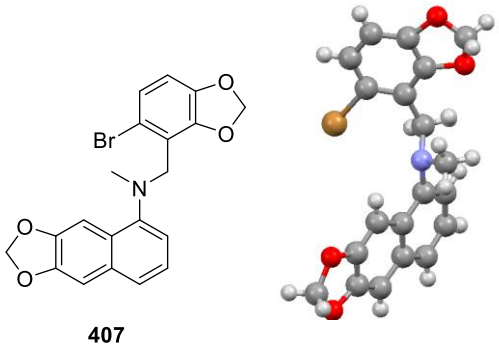
With conditions for a 1.5 equivalent amine addition in hand (**Table 13**, entry 10) and using our naphthylamine forming conditions from the previous chapter (**Table 8**, entry 8), we set about exploring the synthesis of naphthylamine **407**, which would be used in the total synthesis. The cyclisation would require the use of benzyl amine **409** which could be prepared *via* a reductive amination of commercially available benzylaldehyde **412** and methylamine. Accordingly, benzyl aldehyde **412** was treated with an excess of methylamine in methanol, this mixture was then concentrated, to remove the excess methylamine, dissolved in methanol and treated with sodium borohydride to give benzyl amine **409** in quantitative yield (**Scheme 133**).



412 **Quant.** **409**

Scheme 133 *Synthesis of benzyl amine **409**.*

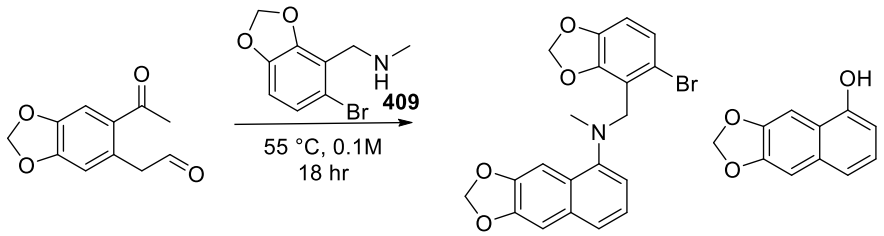
Benzyl amine **409** and dicarbonyl **408** were now subjected to the naphthyl ring forming cyclisation with 5 equivalents of amine and 1 equivalent of $ZnCl_2$. Pleasingly naphthylamine **407** was isolated in a high yield of 61% and 58% of the excess amine was recovered (**Table 14**, entry 1). Pleasing naphthylamine **407** proved to be solid and a crystal structure was obtained to confirm the structure (**Figure 12**).



407

Figure 12 Representation of the X-ray structure of naphthylamine **407**.

Using the procedure developed earlier which involved 1.5 equivalents of amine, compound **408** (**Table 13**, entry 10) treated with amine **409** to yield arylamine **407** in a good yield of 54% (entry 2). However the formation of phenol **423** was observed in significant quantities. We next set about trying to reduce the formation of phenol **423** and improve the overall yield. It was found that increasing the reaction temperature or increasing the addition time reduced the overall yield of naphthylamine **407** and favoured formation of phenol **423** (entry 3 & 4). Increasing the amount of $ZnCl_2$ hindered the formation of naphthylamine (entry 5) and lowering the amount of $ZnCl_2$ significantly reduced the isolated yield (entry 6). It was hypothesised that increasing the concentration of the reaction should favour the bimolecular reaction to form naphthylamine **407** over the unimolecular reaction to form phenol **423**; however, little difference was observed when the concentration was increased from 0.1 M to 0.5 M (entry 7). Earlier conditions developed for the synthesis of naphthylamines in the presences of acid were also tried however, only a 20% conversion was observed, suggesting that dicarbonyl **408** or the product **407** were unstable to acidic conditions (entry 8).



408 **407** **423**

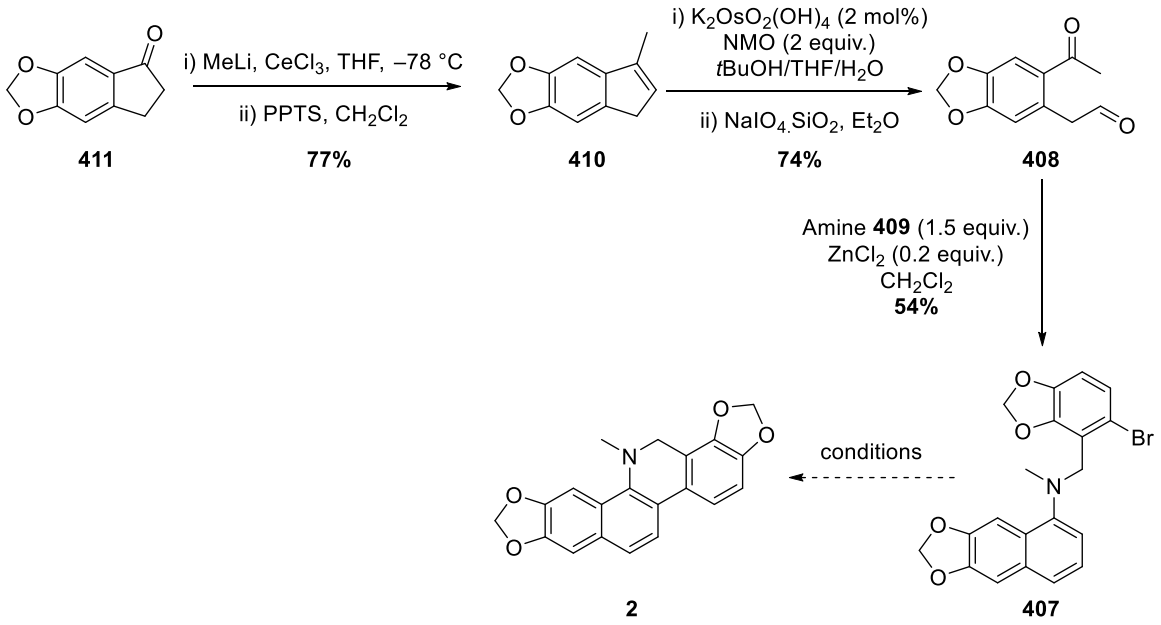
Entry	Equivalents of amine	Solvent	Equivalents of $ZnCl_2$	Addition time (h)	Isolated Yield (%)	
					407	**423**
1	**5**	**CH_2Cl_2**	**1**	**-**	**61**	**-**
2	**1.5**	**$C_2H_4Cl_2$**	**0.25**	**12**	**54**	**24**
3[a]	1.5	$C_2H_4Cl_2$	0.25	12	32	20
4	1.5	$C_2H_4Cl_2$	0.25	24	27	20
5	1.5	$C_2H_4Cl_2$	1	12	50	25
6	1.5	$C_2H_4Cl_2$	0.05	12	16	8
7[b]	1.5	$C_2H_4Cl_2$	0.25	12	46	21
8	5	PhMe/AcOH	-	-	20	-

[a]reaction performed at 80 °C [b]Reaction perfomred at 0.5 M concentration

Table 14 *Optimisation of the formation of naphthylamine **407**.*

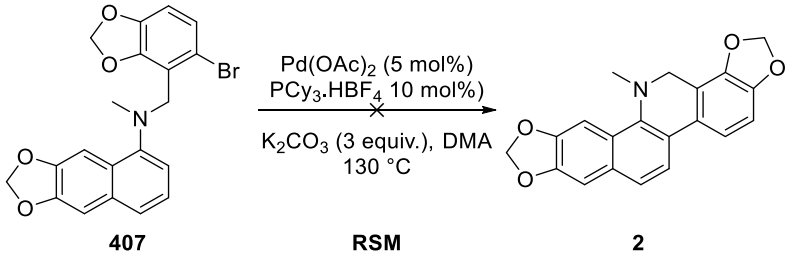
2.3.5.4 Final cyclisation

It was hoped that the final cyclisation of arylamine **407** would form the B ring and complete the synthesis of dihydrosanguinarine (**2**) (**Scheme 134**). Before discussing the completion of the synthesis of dihydrosanguinarine (**2**), it is worth noting that the natural product, dihydrosanguinarine (**2**), was found to be light sensitive and as such we took necessary precautions to reduce its exposure to light such as performing the reaction in the dark and performing purification in a darkened laboratory. This observation was consistent with findings reported by Howell and co-workers.[124]



Scheme 134 *Synthesis of arylamine **408** and planned final cyclisation.*

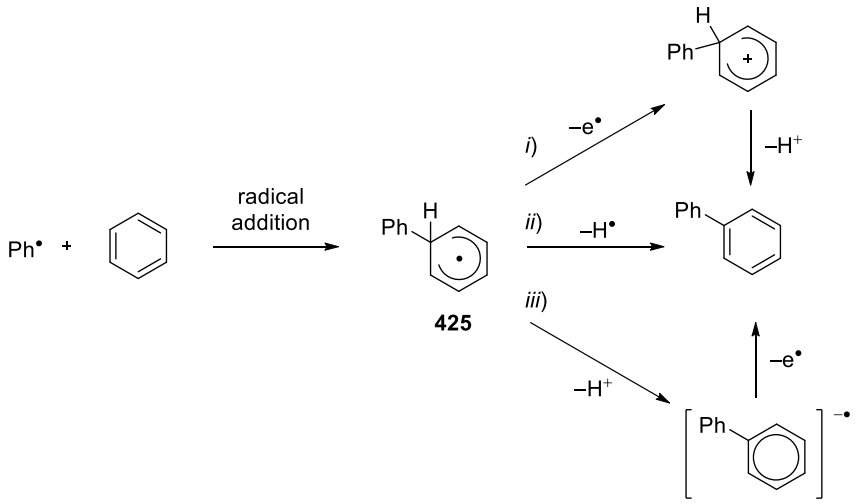
The required transformation was similar to the formation of tricycle **246** from arylamine **245** (**Scheme 78,** page 71). Thus, treating arylamine **407** with the same conditions ($Pd(OAc)_2$ (5 mol%), $PCy_3.HBF_4$ (10 mol%), K_2CO_3 (3 equivalents), DMA, 130 °C),[74] resulted in only recovered starting material (**Scheme 135**). This was unsurprising as our previous studies had established that an electron withdrawing group on the nitrogen was required for good conversions, presumably to stop the nucleophilic nitrongen of starting material **407** from poisoning the catalyst. We still believed it was worth attempting this reaction due to its success in the cyclisation of arylamine **245**. However, the prospect of developing a protecting group strategy to include and remove an electron withdrawing group on the nitrogen of arylamine **407**, led us to explore other cyclisation reactions.



Scheme 135 *Treatment of arylamine **407** to Fagnou's cyclisation conditions.*

2.3.5.4.1 The homolytic aromatic substitution reaction

Homolytic aromatic substitution (HAS) represents an alternative method to couple aryl rings. It is defined by Bowman as the replacement of a leaving group (usually H•) by the attack of a radical on an aromatic ring. This reaction forms a σ-radical complex **425** which then loses a leaving group to form an aromatic product. The final step is not well understood and there are different mechanisms proposed for different conditions used. Either the product is formed by loss of a hydrogen radical (**Scheme 136**, *i*), an oxidation to an aryl cation followed by loss of a proton (**Scheme 136**, *ii*) or under basic conditions, deprotonation, and then rapid oxidation (**Scheme 136**, *iii*).[125, 126]



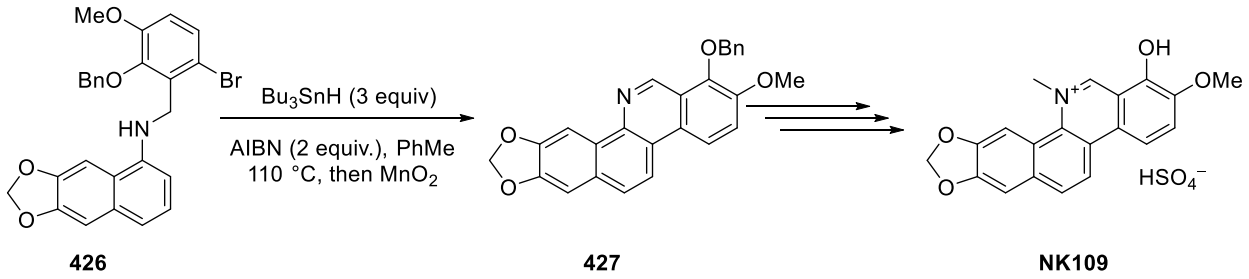
Scheme 136 *Proposed mechanism of the HAS reaction.*

HAS reactions have found few applications in natural product synthesis due to their poor regioselectivities in comparison with electrophilic and nucleophilic aromatic substitution reactions and the requirement of high equivalents of one coupling partners to stop radical dimerisation. However, utilizing aryl radicals does have the benefit of avoiding the use of the expensive, late stage transition metals.

The intramolecular homolytic aromatic substitution (IHAS) reaction however negates the need for an excess of one coupling partner and demonstrates excellent regioselectivities.

Using radical initiating systems such as *tri*-butyltin hydride and azobisisobutyronitrile (AIBN), the reaction has found its application in a number of natural product syntheses.[126]

Nakanishi and co-workers[127] used the IHAS reaction in their synthesis of NK 109, a benzo[c]phenanthridine alkaloid with reported anticancer properties. They established that portionwise addition of *tri*-butyltin hydride and AIBN and sub-stoichiometric amounts of AIBN both favoured decomposition; they also found 110 °C to be the optimal temperature. In their reactions, the cyclisation of arylamine **426** was followed by an *in situ* oxidation with manganese dioxide to yield the compound **427** (**Scheme 137**).

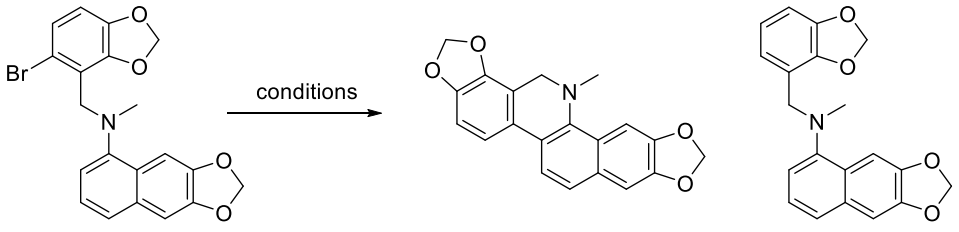


Scheme 137 *Key HAS reaction in the synthesis of NK 109 by Nakanishi and co-workers.*

Based on Nakanishi's results, naphthylamine **407** was subjected to three equivalents of *tri*-butyltin hydride and two equivalents of AIBN (**Table 16**, entry 1) and pleasingly dihydrosanguinarine (**2**) was isolated in a 32% yield. However a 56% yield of debromo compound **428** was also isolated, presumably formed from a side reaction of the aryl radical with *tri*-butyltin hydride. The ^{1}H and ^{13}C NMR spectra of dihydrosanguinarine (**2**) were an excellent match to those reported in the literature (see **Appendix 1**). Side product **428** could be distinguished by an extra aromatic proton in ^{1}H NMR spectrum compared to arylamine **407** and a peak in the HRMS of 336.1232 corresponding to $[M+H]^+$ of side product **428**.

To try to reduce the formation of side product **428**, fewer equivalents of *tri*-butyltin hydride were added. Using 1.2 equivalents of *tri*-butyltin hydride and 0.5 equivalents AIBN increased the conversion to dihydrosanguinarine (**2**), however incomplete conversion was observed

after 18 hours (entry 2). A higher conversion was observed using two equivalents of *tri*-butyltin hydride and 1.5 equivalents AIBN (entry 3); with the same conditions and a 1.5 hour addition of AIBN *via* a syringe pump, dihydrosanguinarine (**2**) was isolated in 42% yield alongside 36% of the debromo product **428** (entry 4). Due to formation of debromo side product **428**, it was decided to explore other radical forming conditions in an attempt to reduce its formation.



407 **2** **428**

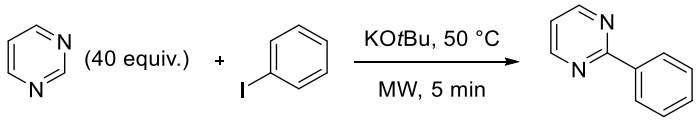
Entry	Conditions	Conversion[a] (%)		
		2	**428**	**407**
1	$HSnBu_3$ (3 equiv), AIBN (2 equiv.), PhMe, 110 °C, 0.02M 2 h	32[b]	56[b]	-
2	$HSnBu_3$ (1.2 equiv), AIBN (0.5 equiv.), PhMe, 110 °C, 0.01M 18 h	36	17	44
3	$HSnBu_3$ (2 equiv), AIBN (1.5 equiv.), PhMe, 110 °C, 0.01M 2 h	56	44	-
4	$HSnBu_3$ (2 equiv), AIBN (1.5 equiv.), PhMe, 110 °C, 0.01M, add. over 1.5 h, 2 h	67 (42[b])	33 (36[b])	-

[a]based on ^{1}H NMR analysis
[b]isolated yield

Table 15 *Optimisation of the final cyclisation with $HSnBu_3$ and AIBN to dihydrosanguinarine (2).*

2.3.5.4.2 Base catalysed HAS reaction

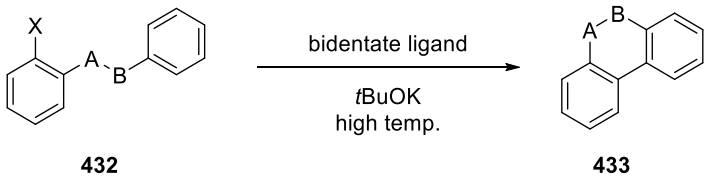
Itashi has reported the use of KO*t*Bu as radical promoter for the coupling of nitrogen containing electron deficient aromatics **429** and aryl iodides **430**. The reaction gives high conversions however requires the use of 40 equivalents of the electron deficient arene, presumably to reduce any undesired radical-radical couplings (**Scheme 138**).[128]



429 **430** 98% **431**

Scheme 138 *KOtBu promoted aryl coupling reported by Itashi and co-workers.*

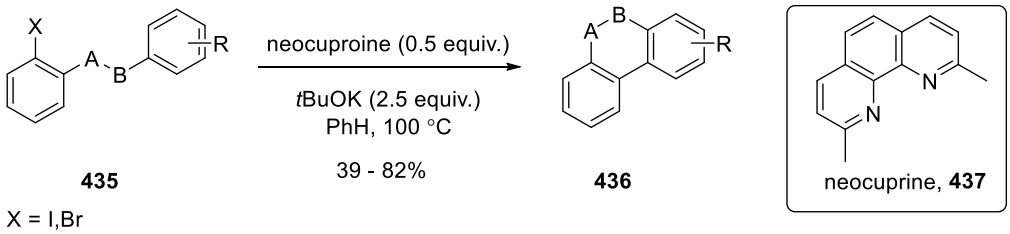
Since the initial discovery, several groups have developed the methodology into a useful synthetic tool. Most work has concentrated on the IHAS reaction. One of the major discoveries reported independently by Lei and co-workers,[129] Shi and co-workers[130] and Hayashi and co-workers[131] was that the addition of a bidentate nitrogen ligand improved overall efficiency (**Scheme 139**).[132]



432 **433**

Scheme 139 General scheme of the *IHAS using KOtBu promoter.*

Shi and co-workers reported the cyclisation of tethered diaryl **435** to tricyclic systems **436**. Their best yields were obtained using with 0.5 equivalents of the ligand neocuprine (**437**), 2.5 equivalents of KO*t*Bu in benzene at 100 °C. They exemplified the reaction with –O, –N and –C containing tethers and demonstrated that both aryl iodides and bromides could be used as the coupling partner, however aryl iodides gave superior yields.[133]

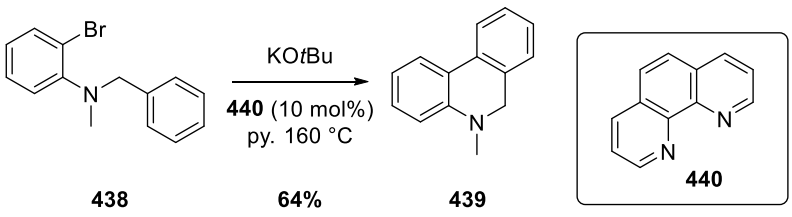


435
X = I,Br
A = CH_2, NMe, O
B = CH_2, NMe, O
R = alkyl, aryl, Cl, F

436

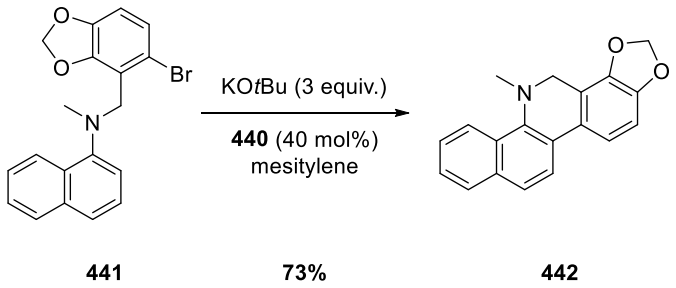
Scheme 140 *KOtBu promoted cyclisation reported by Shi and co-workers.*

Charette and co-workers reported high yields for the cyclisation of arylamines, amides and ethers. They found that performing the reaction in pyridine as the solvent in a microwave gave the best yields (**Scheme 141**).[134]



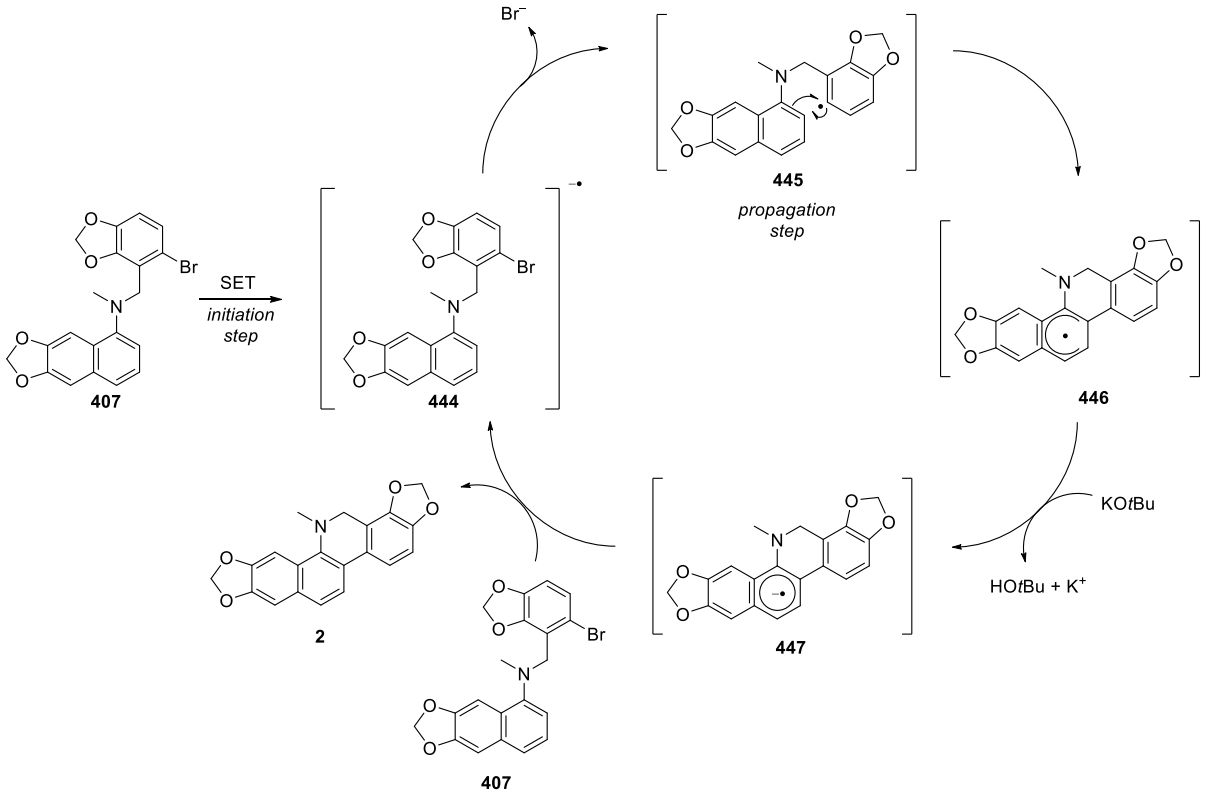
Scheme 141 *Cyclisation reported by Charette and co-workers.*

Bisai and co-workers reported on the cyclisation of arylamine **441** to form benzo[*c*]phenanthridine type structure **442**. Their research found that the addition of 40 mol% of phenanthroline (**440**) and KO*t*Bu gave best yields. They also observed better conversions using mesitylene as a solvent (**Scheme 142**).[135]



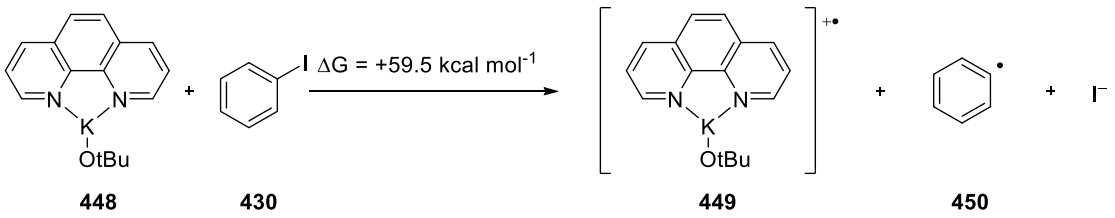
Scheme 142 *Synthesis of benzo[c]phenanthridine type structures by Bisai and co-workers.*

Bisai also proposed a mechanism based on the base-promoted HAS reaction reported earlier (**Scheme 136**). It was proposed that a single electron transfer (SET) from a KO*t*Bu-amine complex formed radical anion **444**. Loss of a bromide gave radical **445** which undergoes a cyclisation to form stabilised radical **446**. Removal of a proton gave radical anion **447** which is a highly reductive species due to its high conjugation. This species then transfers an electron to arylamine **407** which ensures propagation of the chain and also forms the product **2** (**Scheme 143**).



Scheme 143 *Proposed mechanism for base mediated IHAS cyclisation.*

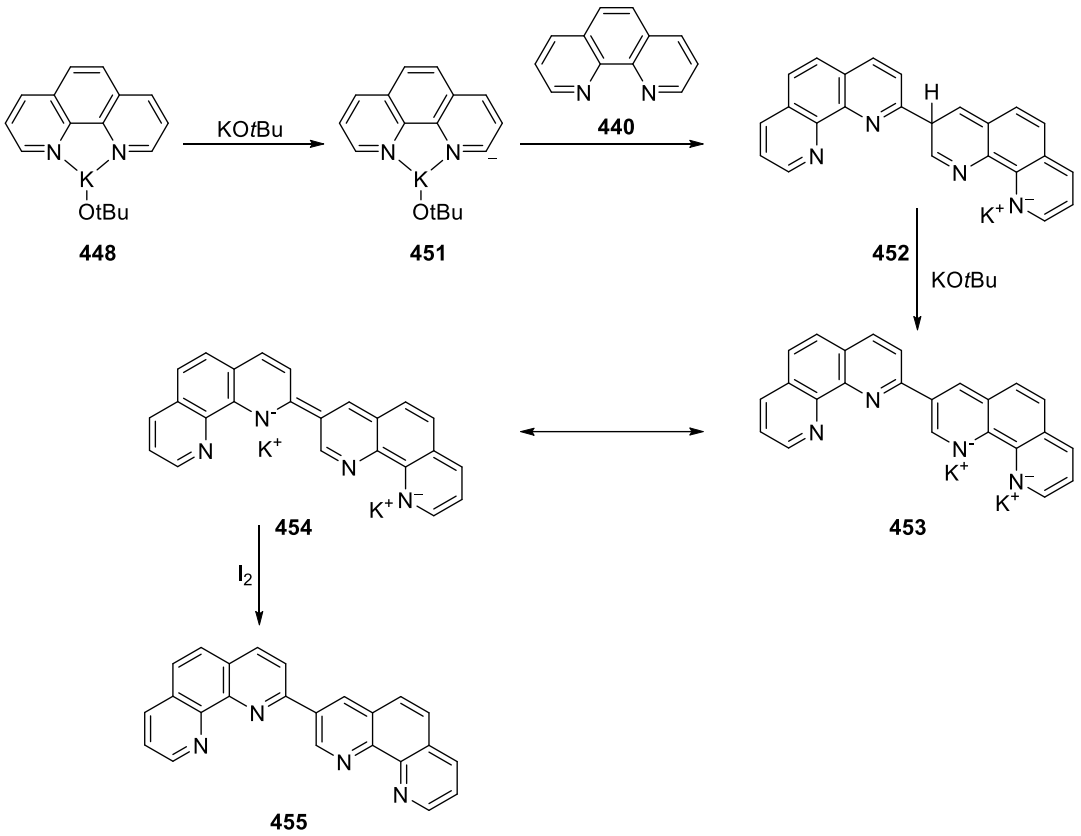
The mechanism for SET is not fully understood. In his seminal mechanistic studies Hayashi[131] proposes that a single electron transfer (SET) from a KO*t*Bu-phenanthroline complex forms radical anion **449**. This has been supported by several other authors who propose the same mechanism for SET.[133,135] Murphy and co-workers are sceptical of this mechanism due to high free energy change which they calculate to be $\Delta G = +59.5$ kcal mol^{-1} for the formation of compounds **449** and **450** from starting materials **448** and **430** (**Scheme 144**).[136]



Scheme 144 *Proposed SET from KOtBu-phenanthroline complex.*

Murphy proposed that intermediate organic super-electron-donors, formed by reaction of ligands with strong base, perform the SET. Organic super-electron-donors are typically characterised by electron rich heterocycles where loss of two electrons restores full aromaticity and are known to catalyse HAS reactions.[136] Murphy proposes that an organic super-electron-donor **454** is formed by deprotonation of a KO*t*Bu-phenanthroline complex to form anion **451**. Attack at the *meta*-position by another molecule of phenanthroline **440** forms dimer **452**, which, after a further deprotonation forms dianion **453** with the charge delocalised around the 6 rings. Analysis of canonical form **454** displays a resemblance to other super-electron donors. Murphy attempted to synthesise donor **454**, but when he tried to isolate the product, it proved to be highly pyrophoric, another trait of super-electron donors. Treatment of compound **454** with iodine, an electron acceptor, yielded *bis*-phenanthroline **455** in 36% yield supporting the formation of super-electron-donor **454**.[136]

Calculations on energy barriers also supported this being a viable pathway with the rate determining step being the deprotonation of phenanthroline at 15.8 kcal mol^{-1}. The overall transformation to compound **454** is strongly favoured with a reaction energy of −30 kcal mol^{-1} (**Scheme 145**).[136]



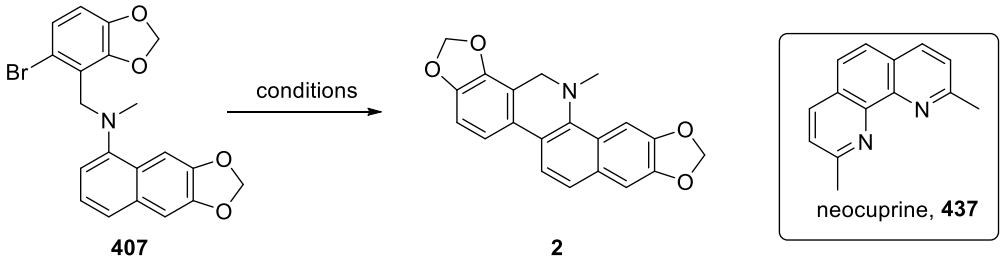
Scheme 145 *Proposed base mediated formation of organic super-electron-donor complex **454** from phenanthroline **440**.*

2.3.5.4.3 Application of the base mediated HAS reaction to the final cyclisation

With the studies above in mind, the application of the base mediated IHAS reaction was applied to the final cyclisation of arylamine **407**.

Pleasing, subjecting naphthylamine **407** to Shi's conditions[130] (0.5 equivalents neocuprine (**437**), 2.5 equivalents of KO*t*Bu in benzene at 100 °C) furnished dihydrosanguinarine (**2**) in 46% yield with 20% recovered starting material (**Table 16**, entry 1). Applying Charette and co-workers' conditions (**Scheme 141**)[134] where pyridine was used as the solvent and the reaction performed in a microwave gave only poor conversions in our hands (entry 2). The use of NaO*t*Bu or performing the reaction under air gave no conversion (entry 3 and 4). Bisai and co-workers report that the use of mesitylene as a solvent (**Scheme 142**)[135] gave improved yields and we observed moderate conversions in shorter times (entry 5). Increasing the

amount of ligand and base also gave a significant increase to the yield, with our best conditions furnishing dihydrosanguinarine (**2**) in 56% with complete conversion being observed (entry 6).



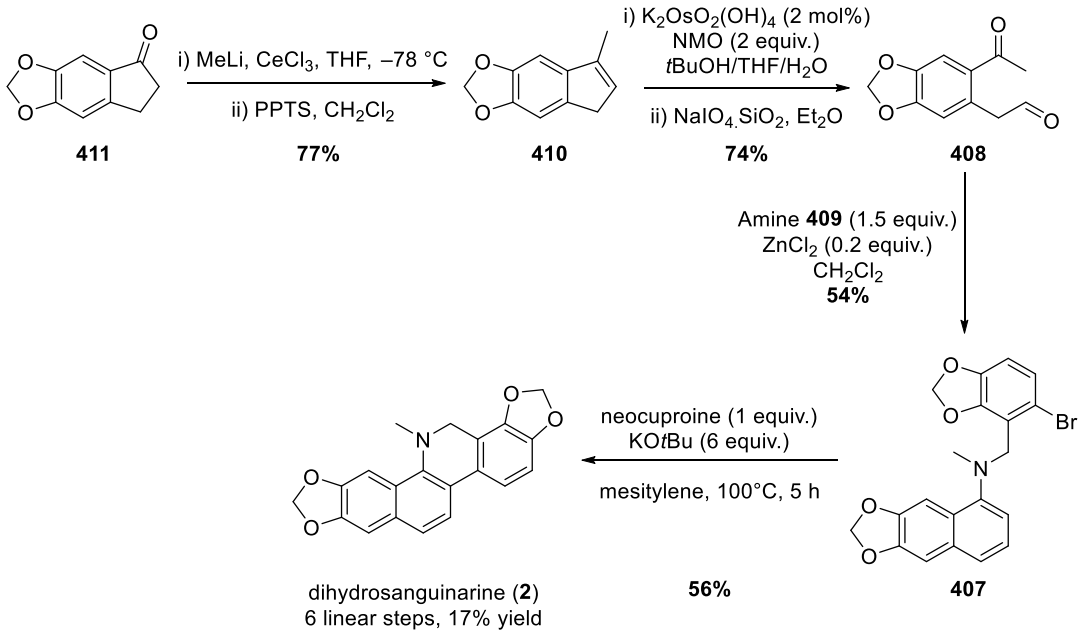
407 **2**

Entry	Conditions	Conversion[a]	
		2	**407**
1	neocuproine (0.5 equiv.), KO*t*Bu (2.5equiv.), PhH, 100°C, 12 h	46%[b]	20%[b]
2	KO*t*Bu (2.5 equiv.), pyridine (0.1M), MW 150°C, 20 min	20%	-
3	neocuproine (0.5 equiv.), NaO*t*Bu (2.5equiv.), PhH, 100°C, 12 h	-	100%
4	neocuproine (0.5 equiv.), KO*t*Bu (2.5equiv.), PhH, air, 100°C, 12 h	-	100%
5	neocuproine (0.5 equiv.), KO*t*Bu (2.5equiv.), mesitylene, 100°C 5 h	40%	-
6	**neocuproine (1 equiv.), KO*t*Bu (6 equiv.), mesitylene, 100°C 5 h**	**100% (56%[b])**	**-**

[a]based on NMR, [b]isolated yield

Table 16 *Optimisation of the final cyclisation to dihydrosanguinarine (**2**).*

Pleasingly this completed the synthesis of dihydrosanguinarine (**2**) in 6 linear steps with an overall yield of 17% (**Scheme 146**).



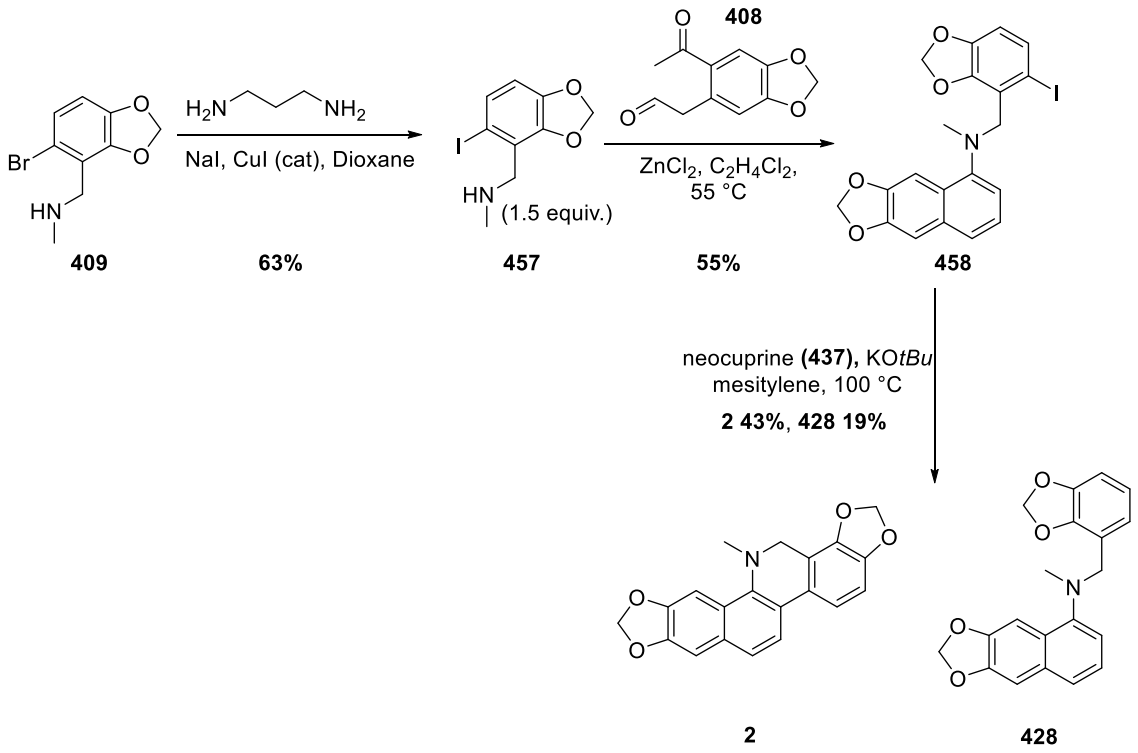
Scheme 146 Total *synthesis of dihydrosanguinarine (**2**).*

2.3.5.5 Synthesis and cyclisation of aryl iodide 458

Bowman and Storey state that aryl iodides are superior substrates for radical cyclisations than aryl bromides because the iodo group is abstracted faster.[125] In order to test the reactivity of an aryl iodide in our cyclisation, naphthylamine **458** was synthesised.

The prerequisite aryl iodide **457** was not available, however Buchwald and co-workers recently reported a modification to the Finkelstein reaction which includes the reaction of aryl halides.[137] Treatment of aryl bromide **409** with 1,3-diaminopropane and sodium iodide in the presence of a copper(I) iodide catalyst yielded aryl iodide **457** in a good 63% yield. The formation of aryl iodide **457** was supported by a peak at 291.9827 which corresponded to the $[M+H]^+$ ion. Aryl iodide **457** and 1,5-dicarbonyl **408** were then subjected to our optimised naphthyl ring forming conditions (**Table 14**, entry 2) to yield naphthylamine **458** in 55% yield. The formation of naphthylamine **458** was confirmed by comparison of the spectra with that obtained for arylamine **407**. Further confirmation was sought from the HRMS which showed a signal at 462.0186 which corresponded to the $[M+H]^+$ ion. Treatment of naphthylamine **458** to the optimised radical cyclisation conditions gave dihydrosanguinarine

(**2**) in 43% yield. Analysis of the rest of the reaction material revealed a significant quantity of the deiodo compound **428** had been formed (**Scheme 147**). It was hypothesised that the increased rate of aryl radical formation also increased the rate of formation of the dehalogenated side product in this system.



Scheme 147 *Synthesis of dihydrosanguinarine via arylamine **458**.*

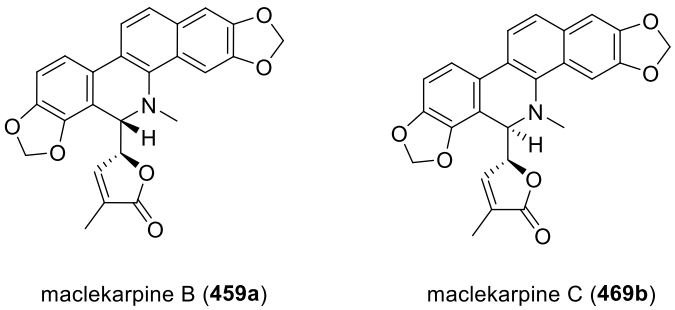
This completed the synthesis of dihydrosanguinarine in 13% over 6 linear steps. Unfortunately the use of aryl iodide **458** in the cyclisation did not represent an improvement over the use aryl bromide **407** in the final cyclisation (43% vs. 56%) and as such we continued to use the aryl bromide in our studies.

2.3.5.6 Synthesis of other benzo[c]phenanthridine natural products

With the efficient synthesis of dihydrosanguinarine completed, it was decided to investigate the synthesis of other, more complicated, natural products based on this route.

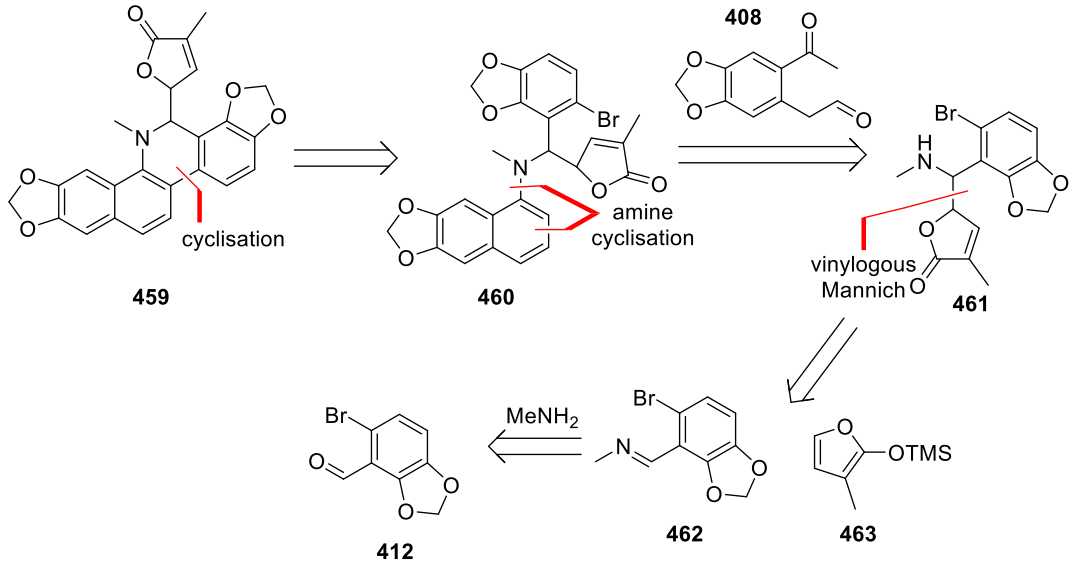
Recently, a number of O_4-base benzo[c]phenanthridine alkaloids with substitution on the B-ring have been reported including maclekarpine B (**459a**) and C (**459b**). Their isolation

from the roots of *Macleaya microcarpa* was described in 2010 by Qin and Deng. Maclekarpine C was also reported to have demonstrated cytotoxicity against several human cancer cell-lines (**Scheme 148)**[138]



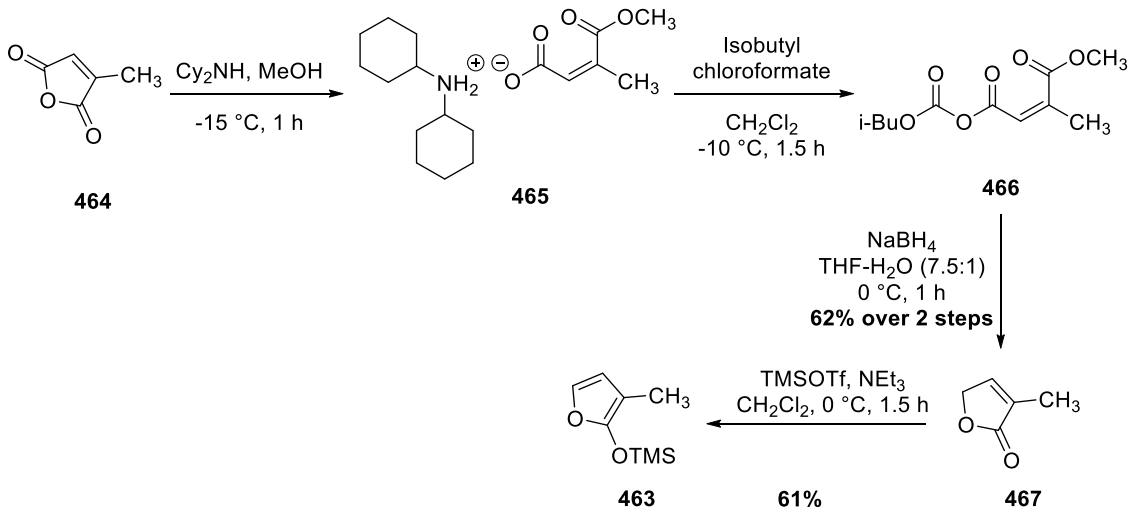
Scheme 148 *Structures of maclekarpine B (**459a**) and C (**460b**).*

Our original disconnection could easily be adapted to maclekarpine B and C by changing the amine used in the naphthylamine cyclisation to amine **461**. Pleasingly, this amine could be accessed *via* condensation between benzaldehyde **412** and methyl amine followed by a vinylogous Mannich reaction with trimethylsilyl-furan **463**. Hoveyda and co-workers have reported a method for synthesising such amines with high diastereo and enantio selectivities (**Scheme 149**).[139]



Scheme 149 *Retrosynthetic analysis of maclekarpine B (**459a**) and C (**459b**).*

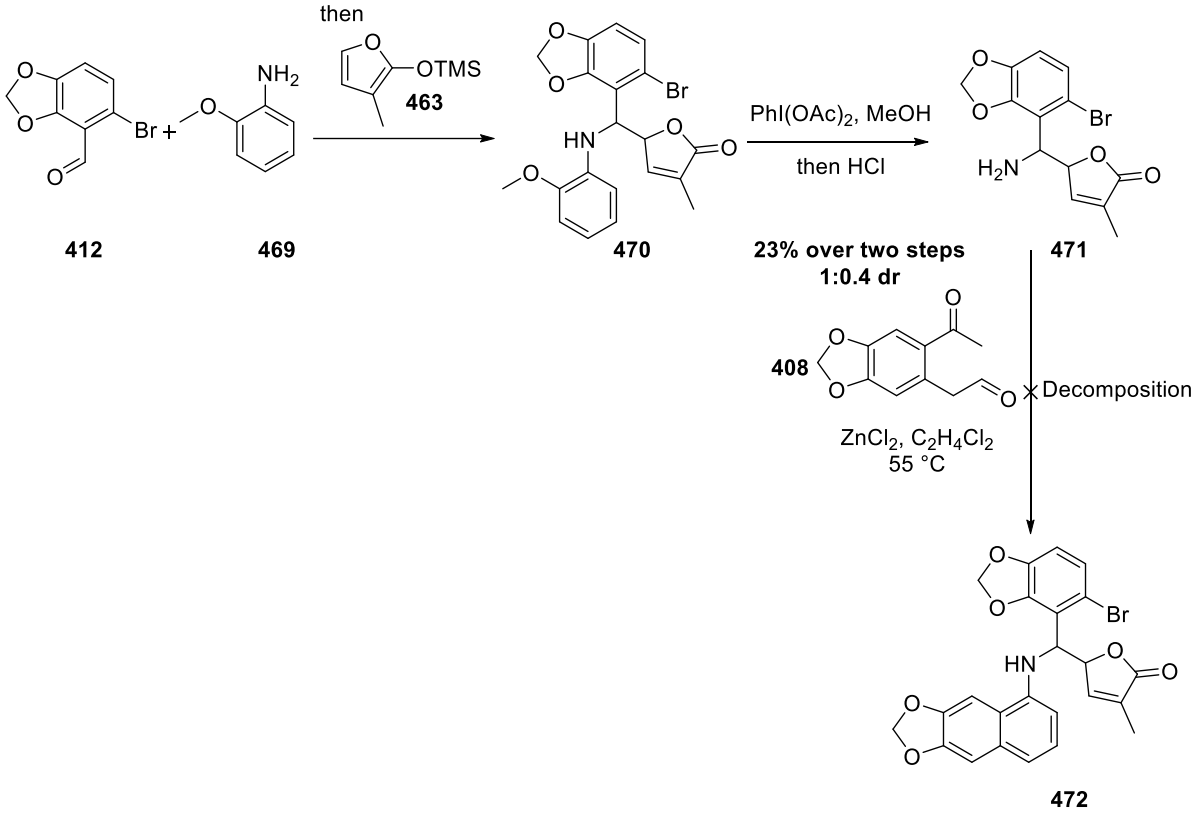
With this disconnection in mind, we set about the synthesis of amine **461**. Amine **461** would be accessed by a vinylogous Mannich reaction between imine trimethylsilyl-furan **463** and imine **462**. The synthesis of trimethylsilyl-furan **463** was achieved by treatment of anhydride **464** with selective solvolysis conditions, then isobutyl chloroformate to furnish mixed anhydride **466**. Selective reduction of anhydride **466** and cyclisation gave furanone **467**, which upon treatment with trimethylsilyl trifluoromethanesulfonate yielded furan **463** which was a good match to the data reported in the literature (**Scheme 150**).[140]



Scheme 150 *Synthesis of furan **463**.*

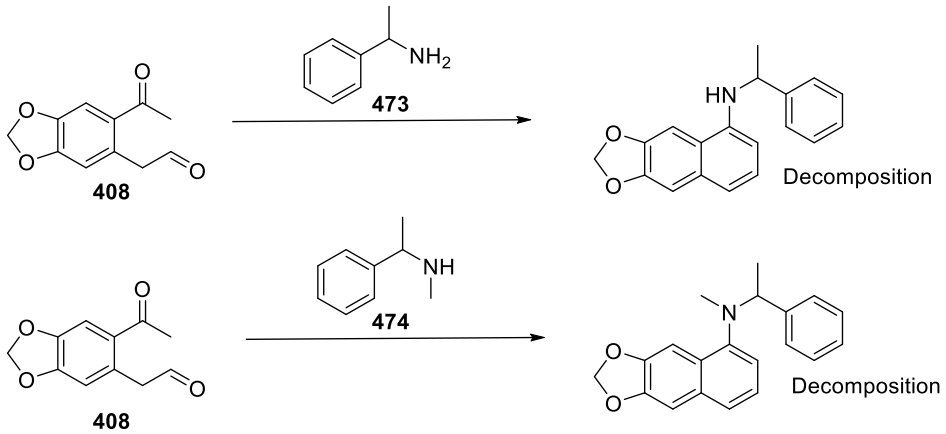
Using conditions developed by Levacher,[141] *o*-anisidine (**469**) was condensed with benzaldehyde **412**, and the resulting imine was treated with trimethylsilyl-furan **463** to yield amine **470** which could not be separated from an unknown side product. However treatment of amine **470** with oxidative deprotection conditions, reported by Hovedya and co-workers,[139] yielded benzyl amine **471** in a good purity and isolated yield of 23% yield as a 1:0.4 mixture of diastereomers. The structure of the amine was confirmed by multiplets at 7.15 ppm and 6.79 ppm in the ^{1}H NMR spectrum which corresponded to the alkene proton. A signal at 174.0 ppm in ^{13}C NMR spectrum corresponded to the carbonyl carbon of the lactone. Before optimising this reaction, benzyl amine **471** was treated with the arylamine forming conditions (1.5 equivalents amine, syringe pump addition of dicarbonyl, $ZnCl_2$, $C_2H_4Cl_2$) however a

complex mixture was observed by ^{1}H NMR analysis with no product-like peaks being observed (**Scheme 151**).



Scheme 151 *Attempted cyclisation of a complex amine towards a synthesis of maclekarpines B (**459a**) and C (**459b**).*

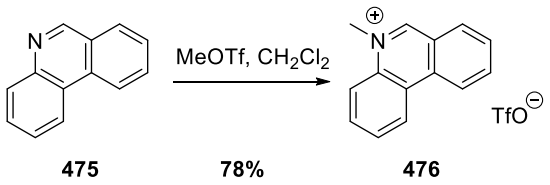
In order to further understand the tolerance of different amines in the naphthylamine cyclisation, benzyl amine **473** and **474** were subjected to the naphthylamine forming conditions with dicarbonyl **408**. However, decomposition was observed in both cases, suggesting that the cyclisation was sensitive to branched primary amines (**Scheme 152**).



Scheme 152 *Amines which failed in the cyclisation.*

With the discovery that the naphthylamine cyclisation was sensitive to branched amines, it was decided to alter the order of steps in the synthesis of maclekarpine B (**459a**) and C (**459b**) to avoid their use in the arylamine forming cyclisation. We planned to use our synthesis of dihydrosanguinanine (**2**) and then oxidise the product to sanguinanine (**344**) for which there were a number of available procedures. It would then be possible to treat the resulting imine with trimethylsilyl-furan **463**, or another nucleophilic source of lactone **467** to yield maclekarpine B (**459a**) and C (**459b**).

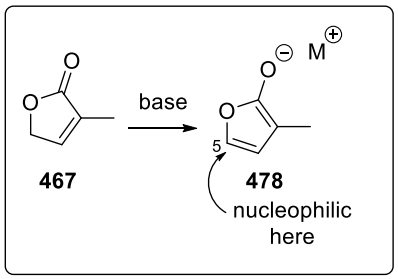
To test our planned synthesis, it was decided to use try some addition conditions on model isoquinolinium **476**. To the end, isoquinoline **475** was treated with methyl trifluoromethansulfonate in dichloromethane to yield isoquinolinium salt **476** in a good 78% yield which was a good match to the data reported in the literature. [142]

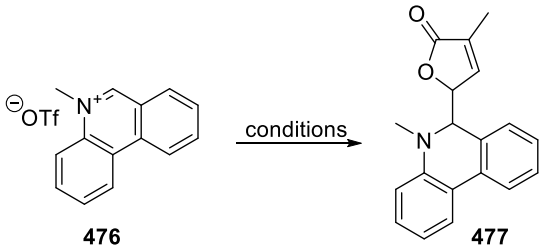


Scheme 153 *Synthesis of isoquinolinium salt **476**.*

Isoquinolinium salt **476** was then treated with several addition conditions with different nucleophiles. Treatment of isoquinolinium salt **476** with furanone **467** and sodium hydroxide gave dihydroisoquinoline **477** in a moderate 36% yield (**Table 17**, entry 1). Dihydroisoquinoline **477** could be characterised by multiplets at 4.96 ppm, 4.80 ppm and a doublet at 4.32 ppm in the ^{1}H NMR spectrum, which corresponded to the protons at the benzylic and allylic positions. High conversions were observed when trimethylsilyl-furan **463** was used in either dimethyl sulfoxide or acetonitrile, with 95% and 93% yield isolated in each case (entry 2 and 3). Lithium enolate **478** (where M = Li^{+}) was formed by treatment of

furanone **467** with lithium diisopropylamide. Treatment of isoquinolinium salt **476** with enolate **478** yielded the desired product **477** in a good 69% yield (entry 4).



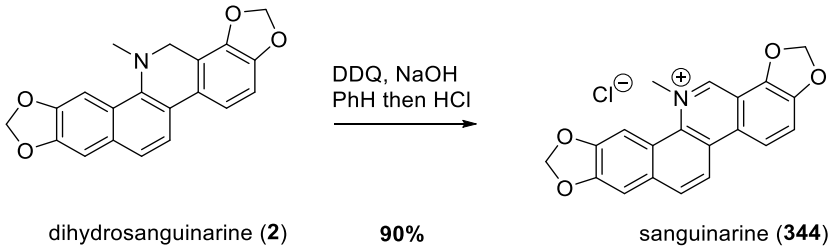


Entry	Conditions	Yield
1	furanone **467**, NaOH, H_2O,	38%
2	furan-TMS **463**, Et_3N, DMSO,	95% (1:0.75, dr)
3	furan-TMS **463**, Et_3N, MeCN,	93% (1:1, dr)
4	furanone **467**, LDA, THF,	69%, (3:1, dr)

Table 17 *Synthesis of dihydroisoquinoline 477.*

With a good precedent that for several different addition conditions in hand, we applied them to the synthesis of maclekarpine B and C.

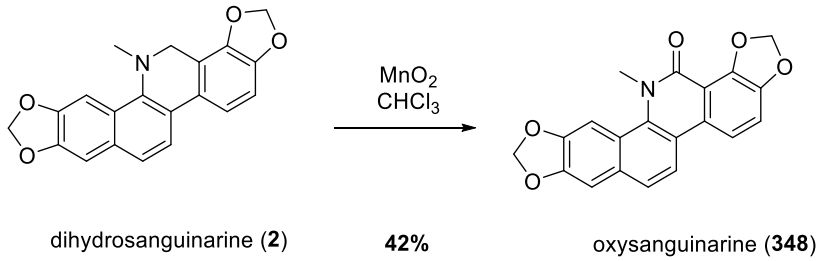
The isoquinolinium salt of dihydrosanguinarine (**2**) could be formed by treatment of the molecule with basic 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), followed by an acidic work-up. The product, sanguinarine (**344**), was isolated in a 90% yield and this represented the total synthesis of sanguinarine in 7 linear steps and 15% yield (**Scheme 154**) The data for sanguinarine (**344**) was a good match to that in the literature (see **Appendix 1**).



Scheme 154 *Synthesis of sanguinarine (**344**).*

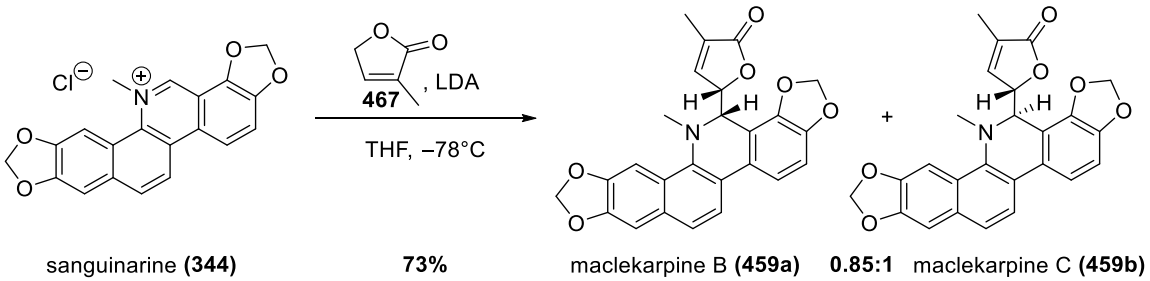
Dihydrosanguinarine was also treated with the oxidant manganese(II) oxide. However, a different natural product, oxysanguianirine (**348**) was isolated in 42% yield. This selectivity was similar to observations made by Dominguez and co-workers who reported a similar

oxidation under manganese(II) oxide oxidation conditions.[143] The data for oxysanguianirine (**348**) was well matched to that reported in the literature; this completed the synthesis of all three oxidation states of the benzo[c]phenanthridine alkaloids (**Scheme 155**).



Scheme 155 *Synthesis of oxysanguianirine (**348**).*

In continuation of our efforts towards maclekarpine B and C, sanguinarine (**344**) was subjected with our addition conditions. Trimethylsilyl-furan (**463**) proved to be unreactive with sanguinarine (**344**) even at elevated temperatures. Treatment of sanguinarine (**344**) with the lithium enolate of furanone **467** in tetrahydrofuran at −78 °C (**Table 17**, entry 4) proved successful, with a mixture of maclekarpine B **(459a)** and C **(459b)** being isolated in a 73% yield as a 0.85:1 inseparable mixture of diastereomers. Attempts to separate the two diastereomers were made with flash column chromatography and HPLC but both were unsuccessful. This represents the first total synthesis of maclekarpine B **(459a)** in 8 linear steps and 6% yield and maclekarpine C **(459b)** in 8 linear steps and an overall yield of 6%. The major peaks of the pair of diastereomers was an excellent match to that reported for maclekarpine C **(459b)** and the minor peaks of the pair of diastereomers was an excellent match to that reported for maclekarpine B **(459a)** (see **Appendix 1**).[138]



Scheme 156 *Synthesis of maclekarpine B and C.*

2.3.6 Summary

This work has demonstrated the utility of the naphthylamine forming cyclisation in the synthesis of benzo[*c*]phenanthridine natural products. The synthesis of dihydrosanguinarine (**2**) was completed in 6 linear steps with an overall yield of 17%.

A key intermediate in the synthesis, dicarbonyl **408**, could be accessed in four steps in an overall yield of 56%. Attempts to reduce the number of steps in this procedure led to reduced overall yields or capricious results. The naphthylamine forming cyclisation was achieved in 61% with five equivalents of amine. The amount of amine required for the cyclisation was successfully reduced to 1.5 equivalents using a syringe pump addition protocol. However, due to a competing intramolecular aldol reaction the yield of arylamine **407** could not be optimised above 54% of the desired arylamine.

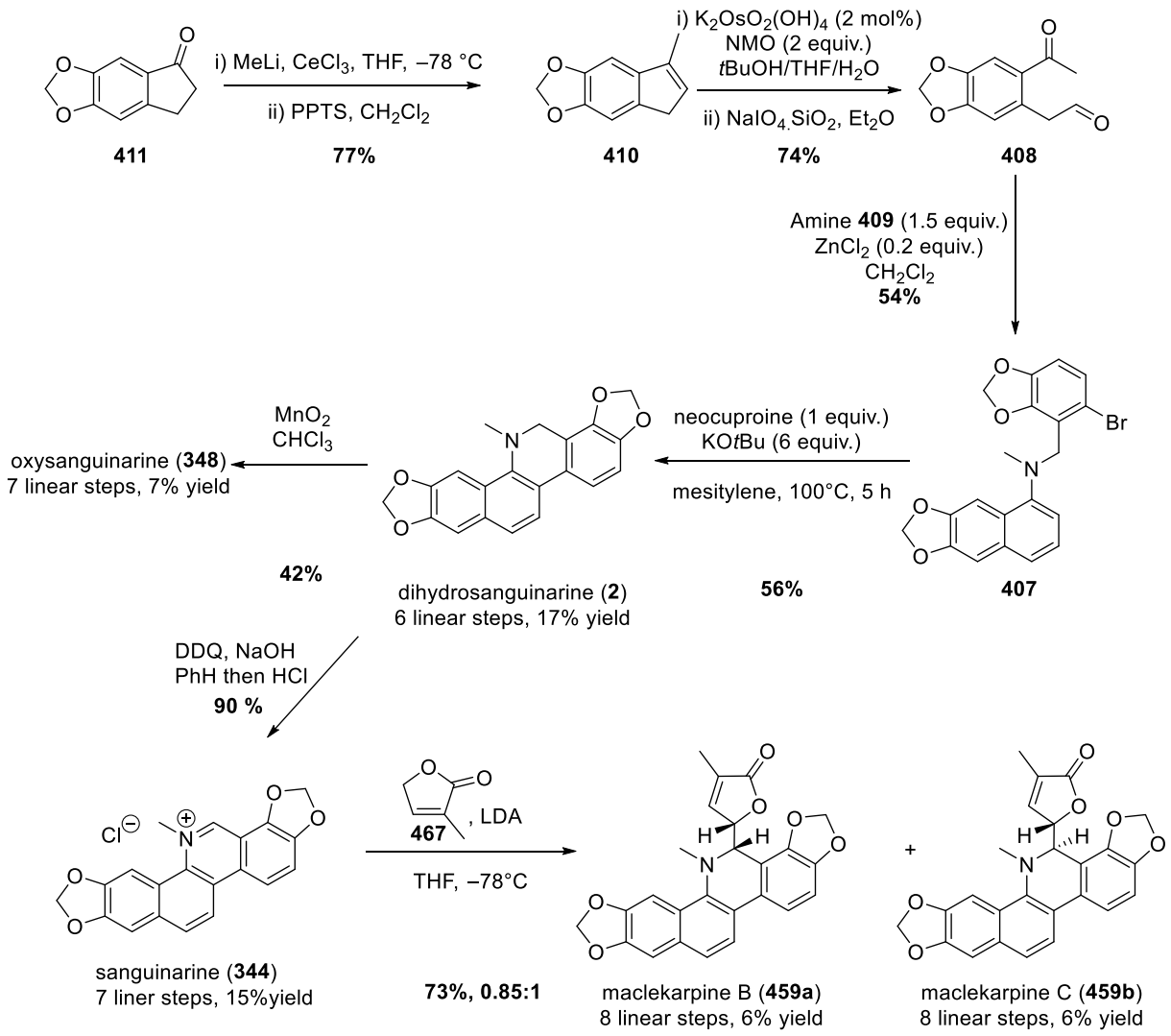
A base catalysed IHAS reaction was used for the final cyclisation. This procedure used KO*t*Bu and a phenanthroline catalyst to perform a single electron transfer. This procedure negated the use of the expensive late stage transition metals or the use of toxic tin hydride reagents. The final cyclisation to form dihydrosanguinarine (**2**) was achieved in a good 56% which is comparable to other IHAS reactions using an aryl bromide. Unfortunately the use of an aryl iodide, which is normally accompanied by an improved yield, led to the formation of a dehalogenated side product.

The approach was then applied to the synthesis of other members of the benzo[*c*]phenanthridine family. Using different oxidation conditions oxysanguianirine (**348**) and sanguinarine (**344**) were isolated in 7 linear steps and in 7% and 15% yield respectively. This completed the synthesis of the three different oxidation states of the benzo[*c*]phenanthridine alkaloid core.

The synthesis compares well with other reported syntheses of benzo[*c*]phenanthridine alkaloids, with a shorter overall step count than most syntheses and a competitive overall yield. This method could also be easily be applied to the synthesis of chelerythrine, avicine and nitidine and all related oxidation states by modifying the starting materials. All the required starting materials are available from Sigma Aldrich.

The method was finally used in the first total synthesis of maclekarpine B (**359a**) and C (**359b**). It was discovered that the naphthylamine forming cyclisation was sensitive to branched amines. However, using a vinylogous Mannich reaction of the enolate of furanone **467** and sanguinarine (**344**) the synthesis of maclekarpine B and C was completed in 8 linear steps and 6% yield for each natural product, although they could not be separated.

Further work will be aimed at trying to separate the two natural products and trying to improve the diastereoselectivity of this reaction. The development of an enantioselective vinylogous Mannich reaction to constitute an asymmetric synthesis of the two natural products would also be a target.



Scheme 157 *Summary of the synthesis of several benzo[c]phenanthridine natural products.*

2.4 *De novo* synthesis of chiral furans

2.4.1 Introduction

Heterocycles with an adjacent benzylic stereogenic centre are an important class of molecule found in a number of biologically active natural products, pharmaceutical targets and chiral catalysts (**Figure 13**). Bipinnatin J (**480**) is a member of a family of biologically active terpene natural products known as furanocembrenolides; it is structurally simpler than other members and is isolated from *Pseudopterogorgia bipinnata*.[144] Liphagal (**481**), isolated from the marine sponge *Aka coralliphaga*, was shown to be an inhibitor of PI3 Kinase α, a key kinase involved in several important biological pathways vital to cancer.[145] Nicotine (**482**) is a parasympathomimetic alkaloid found in the nightshade family of plants and is believed to be a major contributing factor to the dependence-forming properties of tobacco smoking. Epibatidine (**483**) is an alkaloid found on the back of the poison dart frog *Epipedobates anthonyi* and is known to have potent analgesic activity.[146]

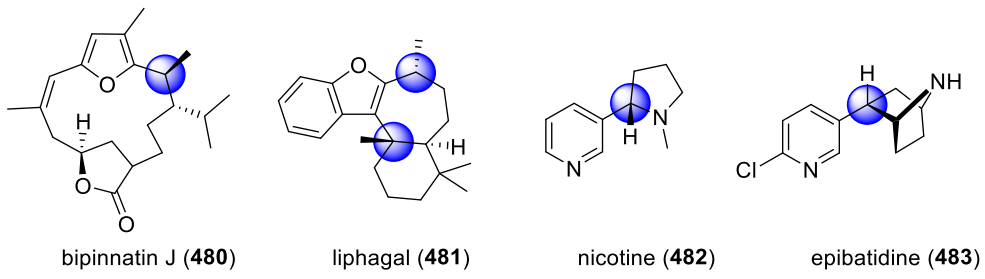
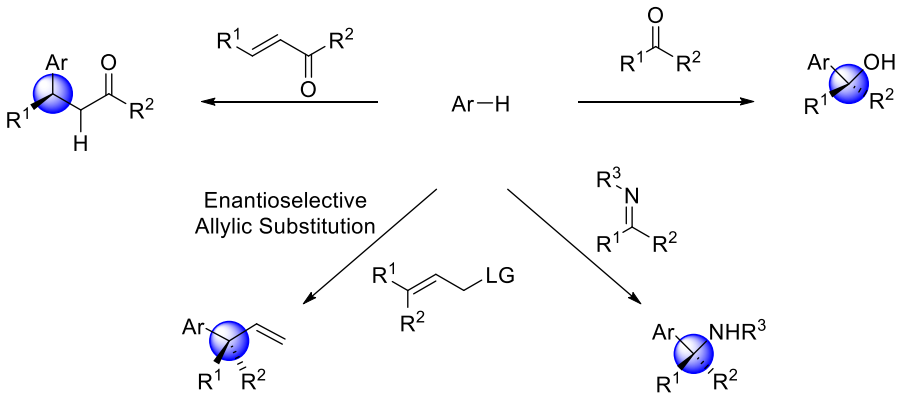


Figure 13 *Selected examples of heterocycles with an adjacent stereogenic centre (highlighted in blue).*

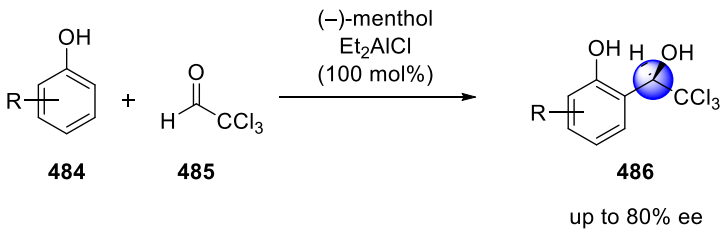
Due to their importance, methods for synthesising benzylic stereogenic centres have received much interest from the synthetic community. However, there are few general procedures for the synthesis of enantioenriched benzylic centres of electron deficient arenes and limited scope for the synthesis of quaternary benzylic chiral centres.

The most used strategy for the synthesis of benzylic stereogenic centres is electrophilic aromatic substitution epitomised by the enantioselective Friedel-Crafts alkylation reaction.[147] The reactions usually employ an electron rich arene, a suitable electrophile such as an aldehyde, imine, α,β-unsaturated carbonyl or allylic halide and an acid (**Scheme 158**).



Scheme 158 *Possible substrates for the electrophilic asymmetric alkylation of aromatic compounds to form benzylic stereogenic centres (highlighted in blue).*

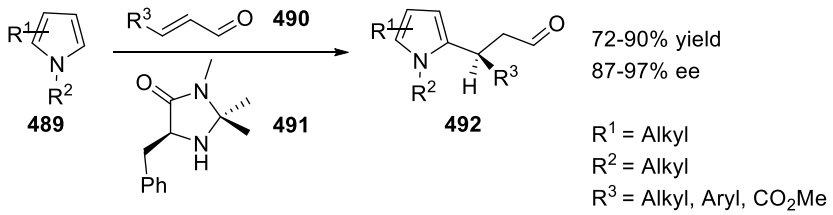
One successful strategy applied to the asymmetric synthesis of benzylic stereogenic centres is the use of a chiral Lewis acid, best demonstrated by Casiraghi and co-workers who used a menthol ligand in the asymmetric alkylation of phenol **484** in the presence of an aluminium Lewis acid and an aldehyde **485**. They were able to achieve up to 80% ee with this relatively simple procedure.[148]



Scheme 159 *Application of a chiral ligand to the asymmetric alkylation of phenol by Casiraghi and co-workers.*

Another strategy that has been successful in the asymmetric alkylation of aromatic compounds is the employment of a chiral organocatalyst. This is well demonstrated by Macmillan and co-workers' use of their imidazolidinone catalyst **491** in the alkylation of *N*-protected pyrroles **489** with an α,β-unsaturated aldehyde **490**, obtaining high yields and

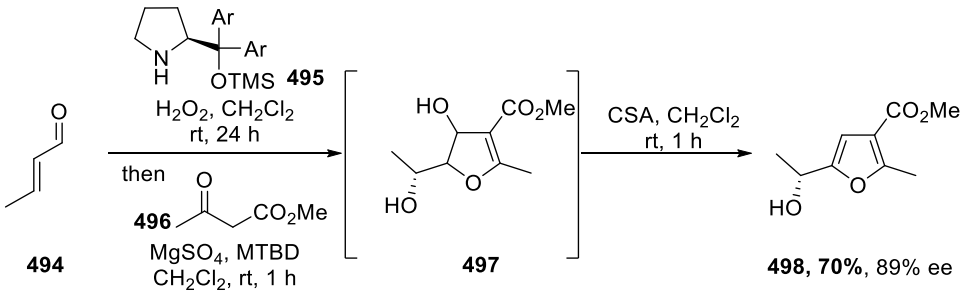
excellent enantioselectivity (**Scheme 160**). The author also exemplifies his work with indoles and arylamines.[149]



Scheme 160 *Macmillan's synthesis of chiral pyrroles.*

Other notable methods for the synthesis of benzylic chiral centres include Hoveyda and co-workers' application of the catalytic enantioselective allylic substitution reaction to the synthesis of quaternary benzylic stereogenic centres adjacent to electron rich heterocycles[150] and Aggarwal and co-workers' synthesis of furans with a benzylic stereogenic centre using a novel coupling of electron rich aromatic compounds with enantioenriched secondary and tertiary boronic esters.[151]

Jørgensen and co-workers demonstrated an elegant asymmetric variant of the Feist–Benary reaction, a base promoted reaction between 1,3-dicarbonyl **496** and unsaturated carbonyls **494** using their prolinol base catalyst **495**, for the synthesis of furans **498**. This method is noteworthy because it also includes electron deficient furans within its scope (**Scheme 161**).[152]

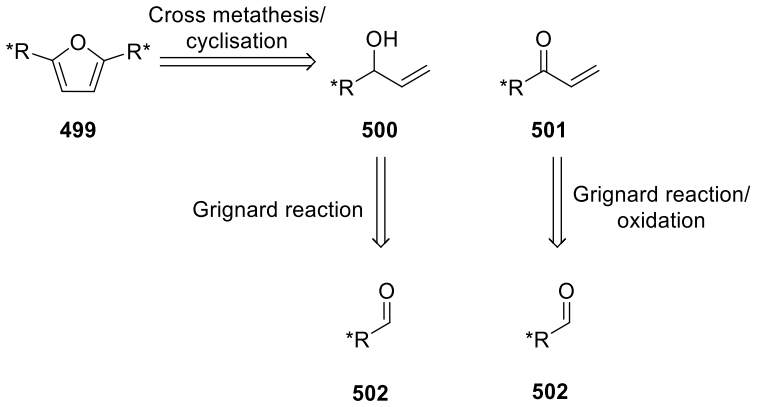


Scheme 161 *Asymmetric synthesis of furans by Jørgensen and co-workers.*

2.4.2 Our approach to the synthesis of benzylic stereogenic centres

Cross metathesis has emerged as a powerful tool for the *de novo* synthesis of heterocycles and the Donohoe group has explored the applications of this methodology in the synthesis of numerous heterocycles (see *section 1.3 Donohoe approach to heterocycles*). Recently, Donohoe and co-workers published a cross metathesis strategy in the synthesis of furans from allylic alcohols and vinyl ketones discussed in the introduction (**Scheme 24**, page 28).[59]

The good tolerance of sterically demanding groups was attractive and made it apparent that this methodology could be expanded to include the synthesis of furans with stereogenic benzylic centres. Donohoe and co-workers used similar methodology to construct pyrroles and pyridines, so any extension in scope for the synthesis of furans could similarly by applied to the synthesis of these heterocycles (**Scheme 162**).



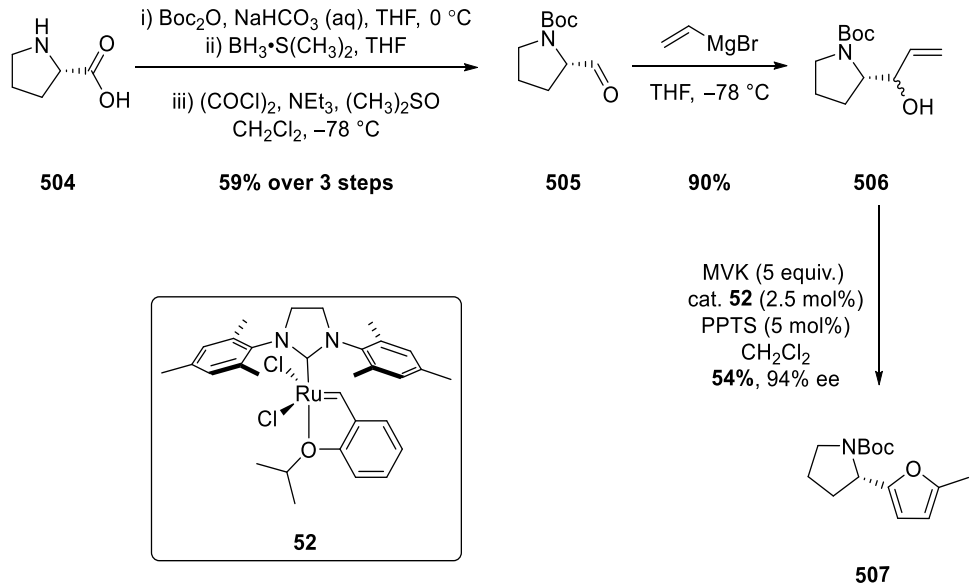
Scheme 162 *Retrosynthetic analysis for furnas with a benzylic stereogenic centre.*

It was proposed that, in an extension of the previous methodology the allylic alcohol **500** and the vinyl ketone **501** could both contain stereogenic components. These could ultimately be disconnected back to a stereogenic aldehyde **502**; thus it would be possible to install a stereogenic centre at either position on the furan from one stereogenic aldehyde (**Scheme 162**).

2.4.3 Synthesis of 2,5-substitued chiral furans

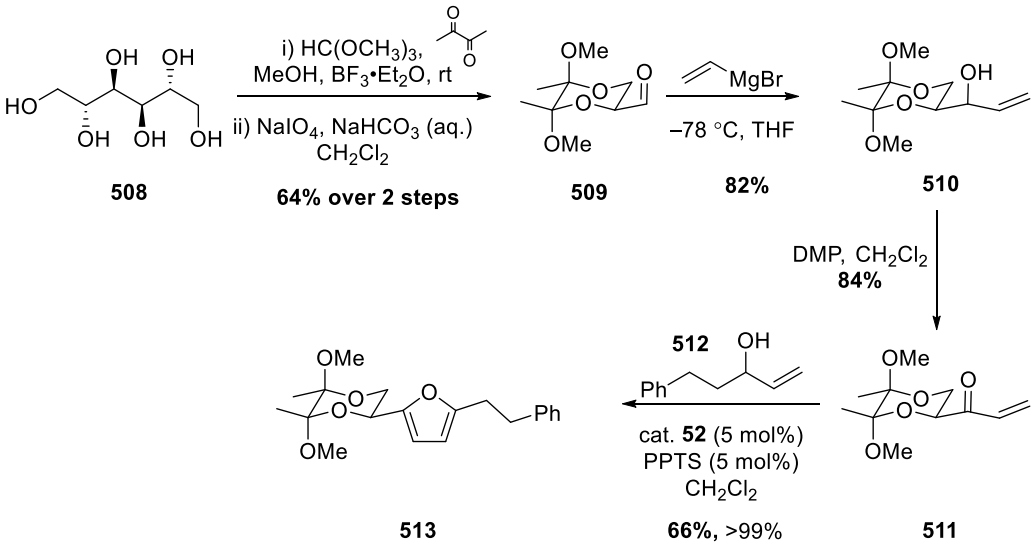
Amino acids offer access to a range of potential chiral aldehydes and are also known to possess biological activity so it was decided that proline would be an ideal starting point for the synthesis of furans containing a benzylic stereogenic centre.

Boc-Protected L-prolinal **505** was obtained by treatment of L-proline **504** with di-*tert*-butyl dicarbonate in a mixture of saturated aqueous sodium bicarbonate and tetrahydrofuran. The resulting protected amino acid was reduced with borane dimethyl sulfide complex to the alcohol which was oxidised under Swern oxidation conditions to furnish aldehyde **505** in 59% yield over three steps. Subsequent treatment of aldehyde **505** with vinyl magnesium bromide furnished allylic alcohol **506**. Treatment of allylic alcohol **506** with the optimised furan-forming conditions (five equivalents of methyl vinyl ketone, 2.5 mol% Hoveyda-Grubbs second generation catalyst **52** and pyridinium *p*-toluene sulfonate in dichloromethane) gave desired furan **507** in 54% yield. The opposite enantiomer was synthesised by the same method from D-proline. Analysis, by comparison to a racemate using chiral high-performance liquid chromatography (HPLC) showed only small erosion of enantiopurity in the transformation of proline to furan **507** (**Scheme 163**).



Scheme 163 *Synthesis of furan **507**.*

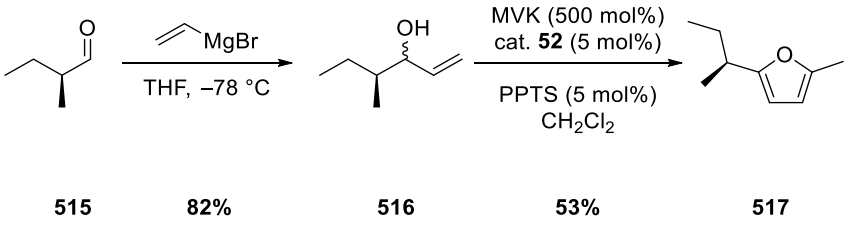
It was next investigated whether installation of a stereogenic centre from the enone component would be possible. Aldehyde **509** could be synthesised in 64% yield from the acetal protection of D-mannitol **508**, followed by oxidative cleavage using sodium periodate. It was decided to use acetal **509** as the protecting group due to its reported enhanced stability towards acid which was important due to the slightly acidic conditions of the final cyclisation.[153] Treatment of aldehyde **509** with vinyl magnesium bromide yielded allylic alcohol **510** in 82% yield. This was then oxidised using Dess–Martin periodinane reagent to give enone **511** in 84% yield. Subjecting enone **511** and allylic alcohol **510** to the tandem cross metathesis, cyclisation conditions yielded furan **513** in 66% yield. A racemic standard was synthesised from glycol. Analysis of furan **513** by comparison to the racemate using chiral HPLC analysis indicated an enantiomeric excess of >99% (**Scheme 164**).



Scheme 164 *Synthesis of furan **513**.*

So far the tertiary benzylic stereogenic centres incorporated only *O*- and *N*-bound substituents so it was decided to test an all-carbon tertiary centre in the cyclisation. Addition of vinyl magnesium bromide to aldehyde **515** furnished allylic alcohol **516** in 82% yield which, upon treatment with cross metathesis/cyclisation conditions yielded furan **517** in 53% yield. Unfortunately, we were unable to separate the two enantiomers using chiral HPLC so were

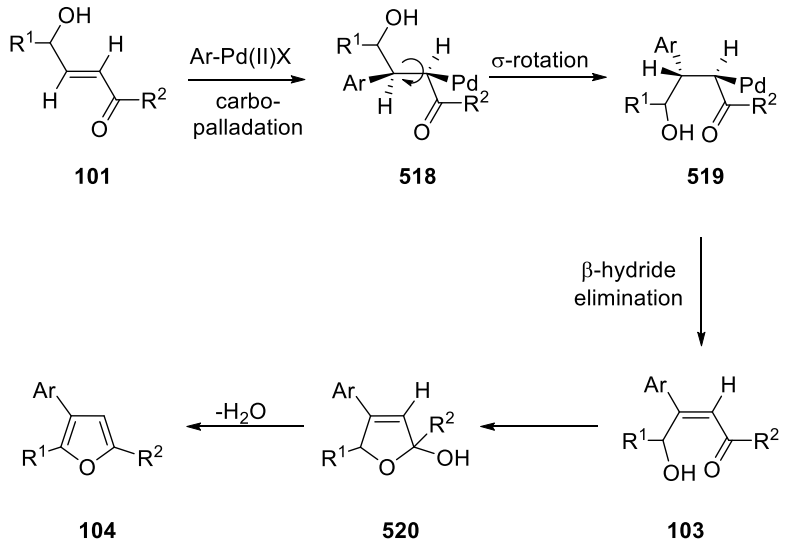
unable to determine the enantiomeric excess of furan **517**, however the molecule did demonstrate a specific rotation so some enantiopurity had clearly been retained (**Scheme 165**).



Scheme 165 *Synthesis of furan **517**.*

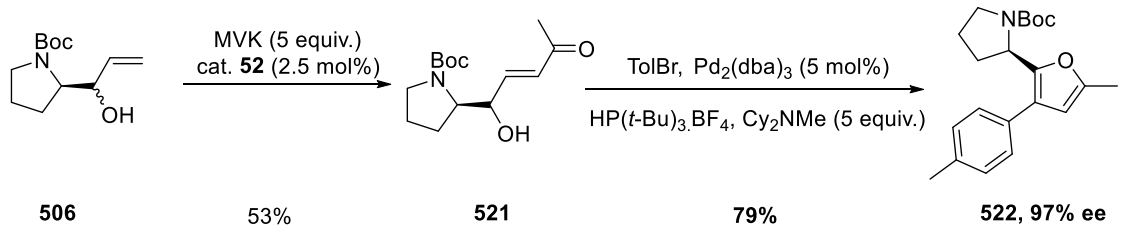
2.4.4 Synthesis of 2,3,5-substitued chiral furans

It had also been shown by the Donohoe group that 2,3,5-substitued furans **104** can be synthesised using a slight modification of the original methodology (**Scheme 25**, page 29). Instead of performing a one-pot cross metathesis/cyclisation, intermediate γ-hydroxy ketone **101** could be isolated, by performing the reaction without pyridinium *p*-toluene sulfonate. γ-Hydroxy ketone **101** is then subjected to a Heck reaction under conditions developed by Fu and co-workers.[70] Carbopalladation of the palladium species generated from oxidative insertion of the palladium(0) catalyst into the aryl halide gives intermediate **518**. Rotation of the σ-bond to align the palladium and hydrogen in a *syn* relationship, as is required for the β-hydride elimination step, yields **519**. This compound then undergoes β-hydride elimination to yield enone **103** where the ketone and hydroxyl are now *cis* to each other. Spontaneous cyclisation and aromatisation yields furan **520**.



Scheme 166 *Proposed mechanism for tandem Heck/cyclisation reaction.*

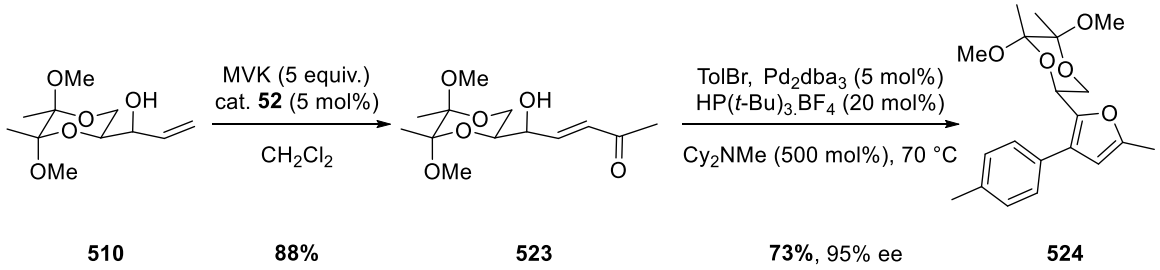
Again, it was first decided to investigate the application of this sequence to enantioenriched furans using proline. Vinyl alcohol **506** was synthesised as previously described (**Scheme 163**). Treatment of vinyl alcohol **506** and methyl vinyl ketone with Hoveyda-Grubbs second generation catalyst **52** yielded hydroxyl ketone **521** in 53% yield. Under Fu's Heck conditions with 4-tolyl bromide ($Pd_2(dba)_3$, HP(*t*-Bu)$_3$.BF_4 and Cy_2NMe), furan **522** was obtained in 79% yield. The opposite enantiomer was synthesised *via* the same route. Using chiral HPLC analysis against a racemic standard showed only small erosion in the enantiomeric excess (3 %).



Scheme 167 *Synthesis of furan **522**.*

Allylic alcohol **510** was then subjected to a cross metathesis with methyl vinyl ketone to give hydroxyl ketone **523**. This was subjected to the Heck/cyclisation procedure to give furan **524** in 78% yield. A racemic standard was also synthesised from glycerol and subsequent chiral

HPLC analysis against the racemate determined that furan **524** was highly enantioenriched (95 %).



510 **88%** **523** **73%**, 95% ee **524**

Scheme 168 *Synthesis of furan **524**.*

2.4.5 Summary

Five enantioenriched furans had been synthesised in good yields from commercially available starting materials. Three 2,5-disubstituted furans were synthesised in a one-pot procedure from readily available materials and two 2,3,5-trisubstituted furans were also synthesised using a cross methathesis/Heck reaction protocol. The enantioenriched furans all showed excellent retention of their enantiomeric excess and were isolated in good yields. The methodology compares well with that currently available as it negates the need for electron rich rings however further work needs to be applied to the synthesis of electron-deficient heterocycles as this will really increase the utility of the methodology.

Chapter 3: Experimental

5.1 General methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer (Bruker Avance AV400) at 400 MHz and 100 MHz respectively in $CDCl_3$, CD_2Cl_2, CD_3OD or DMSO-d_6 and referenced to residual solvent peaks or to $SiMe_4$ as an internal standard. Chemical shifts are quoted in ppm (parts per million) to the nearest 0.01 ppm with signal splittings recorded as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad singlet (br. s). Coupling constants, *J*, are measured in Hz to the nearest 0.1 Hz. ^{1}H and ^{13}C NMR spectra were recorded at room temperature. Assignments were based upon DEPT, COSY and HMQC experiments and by comparison of the spectral data with that of known compounds.

Infrared spectra were recorded as thin films of neat samples on a Bruker Tensor 27 FT-IR spectrometer equipped with Attenuated Total Reflectance sampling accessories. Absorption maxima are quoted in wavenumbers (cm^{-1}) for the range 3500-800 cm^{-1}.

High resolution mass spectra are given to four decimal places and were recorded on a Bruker MicroTof (resolution = 10000 FWHM) under conditions of electrospray ionisation (ESI) or field ionisation (FI). Calibration was *via* the lock-mass of tetraoctyl ammonium bromide for positive ions and sodium dodecyl sulfate for negative ions.

Melting points (m.p.) were obtained from recrystallised samples using a Lecia VMTG heated-stage microscope and are uncorrected. The solvent systems used for recrystallisation are quoted in parentheses. Optical rotations were recorded on a Perkin Elmer 241 Polarimeter (using the sodium D line, 589 nm) at room temperature. The $[\alpha]_D^{20}$ values are reported in ° (formal unit: deg dm^{-1} cm^3 g^{-1}). The concentration of the sample in g $(100\ mL)^{-1}$ and the solvent are given in brackets.

Flash column chromatography was performed using silica gel (60 Å, 0.033-0.070 mm, BDH)[255] for all compounds apart from the dicarbonyl **408** where it was performed using basic alumina (pH 9.5, 58 Å, 150 mesh, Sigma-Aldrich). TLC analyses were performed on Merck Kiesegel 60 F_{254} 0.25 mm precoated silica plates for all compounds. Product spots were visualized under UV light (λ_{max} = 254 nm) and/or by staining with potassium permanganate or vanillin solutions as deemed appropriate.

Reagents and catalysts were obtained from Sigma-Aldrich, Alfa, Fluorochem, TCI and Johnson Matthey and were used directly as supplied.

All anhydrous reactions were carried out in flame-dried glassware and under an inert atmosphere of argon provided by a balloon. All reactions were stirred with magnetic followers. Petrol refers to petroleum ether in the boiling range 40-60 °C. THF, toluene, CH_2Cl_2 and MeOH were dried by purification through two activated alumina purification columns.[256] Dry DMF and DMA were used directly from Sure/Seal® bottles from Sigma-Aldrich.

Crystal structure determination was carried out using X-ray diffraction data measured on an Enraf-Nonius Kappa CCD diffractometer. Intensity data were processed using the DENZO SMN package and further processing was carried out using the Crystals, Cameron and Mercury software.

5.2 General Procedures

Experimental Procedures for the Synthesis of Arylamines

General Procedure 1 for synthesis of allylic alcohols

A solution of aldehyde (1 equiv.) in THF (0.10 M with respect to aldehyde) was cooled to −78 °C and Grignard reagent (1.1 equiv.) added dropwise. The reaction was then monitored until full consumption of the aldehyde was observed by TLC. The reaction mixture was allowed to warm to room temperature and then quenched by the addition a saturated aqueous solution of NH_4Cl (3x). The mixture was extracted with EtOAc (3x). The organic layers were combined, dried ($MgSO_4$) and concentrated to give crude reaction mixture which was purified under the noted conditions.

General Procedure 2 for the cross metathesis of homoallylic alcohols

A resealable reaction tube, fitted with a magnetic follower, was charged with Zhan 1B catalyst (2 - 5 mol%). The tube was then sealed with a rubber septum and purged with argon. Argon sparged CH_2Cl_2 (0.10 M with respect to the homoallylic alcohol), the corresponding α,β-enone (500 mol%) and the corresponding homoallylic alcohol (1 equiv.) were added sequentially *via* syringe. The rubber septum was then replaced with a screw cap and the tube was heated at 55 °C for 24 to 48 hours. After cooling to 0 ºC, the reaction mixture was diluted with CH_2Cl_2 (0.10 M with respect to the homoallylic alcohol), water (100 μL/mmol of homoallylic alcohol) and Dess-Martin periodinane (1.5 equiv.) were added and the reaction was monitored by TLC until the cross metathesis product was consumed. The reaction mixture was filtered through a cartridge of SiO_2 (eluting with Et_2O) and solvent was removed *in vacuo*. Purification of the residue by flash column chromatography, under the conditions noted, afforded the corresponding α,β-unsaturated 1,5-dicarbonyl.

General Procedure 3 for the cross metathesis of homoallylic alcohols

A reaction tube, fitted with a magnetic follower, was charged with Zhan 1B catalyst (2 - 5 mol%). The tube was then sealed with a rubber septum and purged with argon. Argon sparged CH_2Cl_2 (0.10 M with respect to the homoallylic alcohol), methyl vinyl ketone (5 equiv.) and the corresponding homoallylic alcohol (1 equiv.) were added sequentially *via* syringe. The reaction mixture was heated at reflux under argon for 24 to 48 hours. After cooling to room temperature the reaction mixture was filtered through a cartridge of SiO_2. The fractions containing the target cross metathesis product were combined and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (0.10 M with respect to the homoallylic alcohol) and then cooled to 0 ºC. Water (100 μL/mmol of homoallylic alcohol) and Dess-Martin periodinane (200 - 300 mol%) were added sequentially and the reaction was monitored by TLC until the CM product was consumed. The reaction mixture was filtered through a cartridge of SiO_2 (eluting with Et_2O) and solvent was removed *in vacuo*. Purification of the residue by flash column chromatography, under the conditions noted, afforded the corresponding unsaturated 1,5-dicarbonyl.

General Procedure 4 for the formation of arylamines

A microwave vial fitted with a magnetic follower was charged with the corresponding α,β-unsaturated 1,5-dicarbonyl (100 mol%), dissolved in CH_2Cl_2 (0.10 M with respect to α,β-unsaturated 1,5-dicarbonyl) and the corresponding amine (5 equiv.) added. The reaction mixture was stirred at room temperature for 5-18 hours. The crude mixture was concentrated and purified by flash column chromatography, under the conditions noted to afford the corresponding arylamine.

General Procedure 5 for the formation of arylamines

A microwave vial fitted with a magnetic follower was charged with the corresponding α,β-unsaturated 1,5-dicarbonyl (1 equiv.), dissolved in CH_2Cl_2 (0.10 M with respect to α,β-unsaturated 1,5-dicarbonyl) and the corresponding amine (5 equiv.) added. The reaction mixture was heated at 55 °C for 18 hours and then cooled to room temperature. The crude

mixture was concentrated and purified by flash column chromatography, under the conditions noted to afford the corresponding arylamine.

General Procedure 6 for synthesis of allylic alcohols

To a mixture of the corresponding aldehyde (1 equiv.) in THF (0.5 M with respect to aldehyde) and saturated aqueous NH_4Cl (0.25 M with respect to aldehyde) was added zinc powder (300 mol%) and the corresponding allylic halide (1.5 - 2.0 equiv.) and the mixture was vigorously stirred at room temperature and monitored by TLC. After all of the aldehyde was consumed the reaction mixture was extracted with EtOAc (3×). The organic extracts were combined and extracted with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by flash column was performed under the conditions noted, to afford the corresponding allyl alcohol.

General Procedure 7 for the arylation of α,β-unsaturated 1,5-dicarbonyl intermediates

A reaction tube, fitted with magnetic follower, was charged with $Pd_2(dba)_3$ (5 mol%), P(*t*-Bu_3)HBF_4 (20 mol%), and (if solid) the corresponding aryl bromide (3 equiv.). The tube was sealed with a septum and purged with argon. Argon sparged, anhydrous toluene (0.10 M with respect to the enone component), the requisite α,β-unsaturated 1,5- dicarbonyl (equiv.), the corresponding aryl bromide (if liquid) (3 equiv.) and Cy_2NMe (3 equiv.) were added sequentially *via* syringe. The mixture was then heated at 55 °C for 16 hours. The mixture was cooled to room temperature, diluted with EtOAc and then filtered through Celite. Solvent was removed *in vacuo*, the residue was filtered through a cartridge of SiO_2 (under the conditions noted) and solvent was removed *in vacuo* to afford a crude product which was directly subjected to General Procedure 5.

General Procedure 8 for acetal protection of ketones

para-Toluenesulfonic acid monohydrate (2.0 mol%) was added to a solution of ketone (1 equiv.) and ethanediol (1.3 equiv.) in toluene (0.1 M with respect to ketone). The flask was equipped with a Dean-Stark apparatus and the solution heated to reflux for 18 hours. The

reaction mixture was cooled to room temperature and quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc (3×). The organic extracts were combined and extracted with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by flash column was performed under the conditions noted, to afford the corresponding acetal.

General Procedure 9 for palladium-catalysed α-arylation of ketones

(D*t*BPF)$PdCl_2$ (5 mol%) and NaO*t*Bu (2.5 equiv.) were sealed in a microwave vial and the vial sealed. Aryl halide (1 equiv.) was dissolved in THF (0.2 M with respect to ketone) and the resulting solution was added *via* syringe to the tube at room temperature. The ketone (2 equiv.) was then added *via* syringe to the tube. The tube was then heated to 70 °C for 18 hours. The reaction was then cooled to room temperature and quenched by the addition of water. The aqueous later was extracted with Et_2O and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product which was purified under the conditions noted.

General Procedure 10 for deprotection of acetal

para-Toluenesulfonic acid monohydrate (10 mol%) was added to a solution of the acetal substrate (1 equiv.) in THF/H_2O (1:1, 0.1 M with respect to acetal) in a microwave vial and the vial sealed. The tube was heated to 60 °C for 18 hours then cooled to room temperature. Saturated aqueous $NaHCO_3$ was added and the aqeous later extracted with EtOAc (3x) and the combined organics dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product, which was purified as specified.

General Procedure 11 for Lewis acid cyclisation to form naphthylamine

A microwave vial fitted with a magnetic follower was charged with the corresponding 1,5-dicarbonyl (1 equiv.) and $ZnCl_2$ (1.0 M in Et_2O, 1 equiv.), dissolved in CH_2Cl_2 (0.10 M with respect to 1,5-dicarbonyl) and the corresponding amine (5 equiv.) added. The reaction mixture was heated at 55 °C for 18 hours and then cooled to room temperature. The crude

mixture was concentrated and purified by flash column chromatography, under the conditions noted to afford the corresponding naphthylamine.

General Procedure 12 for acid cyclisation to form naphthylamine

A microwave vial fitted with a magnetic follower was charged with the corresponding 1,5-dicarbonyl (1 equiv.), dissolved in PhMe/AcOH 3:1 (0.10 M with respect to 1,5-dicarbonyl) and the corresponding amine (5 equiv.) added carefully. The reaction mixture was heated at 110 °C for 18 hours and then cooled to room temperature. The crude mixture was washed with 1.0 M NaOH and extracted into EtOAc (3x). The organic layers were combined, dried ($MgSO_4$) and concentrated. The crude product was purified by flash column chromatography, under the conditions noted to afford the corresponding naphthylamine.

General Procedure 13 for the vinylation of aldehyde

To a solution of aldehyde (1 equiv.) in THF (0.1 M) cooled to −78 ^oC was added dropwise a solution of vinyl magnesium bromide (1.1 equiv., 1.0 M in THF) over 15 min. The solution was then allowed to warm up to room temperature and stirred for 2 hours. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl and extracted with Et_2O (2x). The organic layers were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude product was then purified under the conditions noted.

General Procedure 14 for cross metathesis and cyclisation of vinyl alcohol and enone

A sealable tube fitted with a septum was charged with Hoveyda-Grubbs (II) catalyst (5 mol%) and pyridinium *p*-toluenesulfonate (2.5 mol%) and flushed with argon. CH_2Cl_2 (0.25 M with respect to allylic alcohol), allylic alcohol (1 equiv.) and enone (2.5 equiv.) were then added *via* a syringe and the septum replaced with a cap and left to stir for 12 hours at room temperature. The reaction mixture was passed through a short plug of silica and concentrated *in vacuo*. The crude mixture was purified under the conditions noted.

General Procedure 15 for cross metathesis of vinyl alcohol and enone

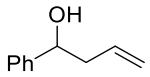
A sealable tube fitted with a septum was charged with Hoveyda-Grubbs (II) catalyst **52** (5 mol%) and flushed with argon. CH_2Cl_2 (0.25 M with respect to allylic alcohol), allylic alcohol (1 equiv.) and enone (2.5 equiv.) were then added *via* a syringe and the septum replaced with a cap and left to stir for 12 hours at room temperature. The reaction mixture was passed through a short plug of silica and concentrated *in vacuo*. The crude mixture was purified under the conditions noted.

General Procedure 16 for Heck coupling, cyclisation and aromatisation

A sealable tube fitted with a septum was charged with $Pd_2(dba)_3$ (5 mol%), tBu$_3$PHBF$_4$ (20 mol%), γ–hydroxy-α,β–unsaturated ketone (1 equiv.), aryl bromide (2.5 equiv.) and Cy_2MeN (2.5 equiv.), 1,4-Dioxane (0.1 M) and heated to 70 ^oC for 12 hours. The reaction mixture was passed through a short pad of silica and concentrated *in vacuo*. The crude mixture was purified under the conditions noted.

5.3 Experimental details

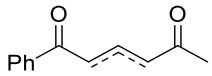
1-Phenylbut-3-en-1-ol, 132



Benzaldehyde (3.00 g, 28.3 mmol, 2.87 mL) and allyl magnesium bromide (2.0 M in hexanes, 31.1 mmol, 15.5 mL) were subjected to General Procedure 1. The crude mixture was purified by flash column chromatography (petrol-EtOAc, 4:1) to afford *allylic alcohol* **132** (2.92 g, 70%) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.34 - 7.46 (4 H, m), 7.22 - 7.34 (1 H, m), 5.85 (1 H, ddt, *J*=17.1, 10.0, 7.1, 7.1 Hz), 5.13 - 5.25 (2 H, m), 4.77 (1 H, dd, *J*=7.3, 5.4 Hz), 2.45 - 2.65 (2 H, m), 2.14 (1 H, br. s.); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 143.9, 134.5, 128.5, 127.6, 125.8, 118.5, 73.3, 43.9. Data were consistent with those previously reported.[154]

(*E*)-1-Phenylhex-3-ene-1,5-dione, 133

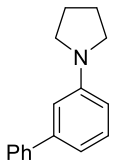


1-Phenylbut-3-en-1-ol **132** (100 mg, 0.746 mmol), Zhan 1B catalyst (5 mol%) and but-3-en-2-one were subjected to General Procedure 2. The reaction mixture was heated for 36 hours. Dess-Martin periodinane (200 mol%) was used for the oxidation step. The crude mixture was purified by flash column chromatography (petrol-EtOAc, 9:1 to 6:4) to afford *unsaturated dicarbonyl* **133** (109 mg, 78%, 1:0.3 rr) as a red oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.86 - 8.05 (2.6 H, m, Ar*H*), 7.54 - 7.66 (1.3 H, m, Ar*H*), 7.40 - 7.54 (2.6 H, m, Ar*H*), 7.01 - 7.15 (1.3 H, m, C=C*H*CH_2), 6.89 - 6.96 (0.3 H, m, C*H*=$CHCH_2$), 6.19 (1 H, dt, *J*=16.2, 1.4 Hz, C*H*=$CHCH_2$), 3.94 (2 H, dd, *J*=6.9,

1.4 Hz, C*H*$_2$), 3.39 - 3.51 (0.6 H, m, C*H*$_2$), 2.30 (3 H, s, C*H*$_3$), 2.19 - 2.27 (0.9 H, m, C*H*$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 198.2, 196.1, 139.9, 136.1, 134.3, 133.7, 132.9, 129.3, 128.8, 128.6 (2C), 128.2, 47.0, 41.6, 30.0, 26.7 (only 16 signals observed). Data were consistent with those previously reported.[155]

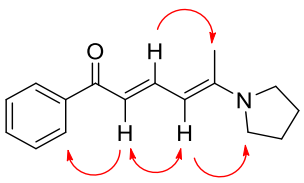
1-([1,1'-Biphenyl]-3-yl)pyrrolidine, 134



Unsaturated 1,5-dicarbonyl **133 (**40 mg, 0.22 mmol) and pyrrolidine were subjected to General Procedure 4. The reaction mixture was stirred for 2 hours. In a modification to the General Procedure the reaction was carried out at 0 °C. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **134** (39 mg, 83%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.65 (2 H, d, *J*=7.1 Hz, Ar*H*), 7.46 (2 H, t, *J*=7.5 Hz, Ar*H*), 7.34 - 7.39 (1 H, m, Ar*H*), 7.31 - 7.34 (1 H, m, Ar*H*), 6.92 (1 H, d, *J*=7.6 Hz, *H*C(6)), 6.80 (1 H, t, *J*=2.0 Hz, *H*C(2)), 6.61 (1 H, dd, *J*=8.2, 2.1 Hz, *H*C(4)), 3.38 (4 H, t, *J*=6.6 Hz, NC*H*$_2$), 2.05 (4 H, t, *J*=6.6 Hz, NCH$_2$C*H*$_2$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 148.3, 142.4, 142.4, 129.5, 128.6, 127.4, 127.0, 114.7, 110.7, 110.5, 47.7, 25.5. Data were consistent with those previously reported.[156]

(2*E*,4*E*)-1-Phenyl-5-(pyrrolidin-1-yl)hexa-2,4-dien-1-one, 135

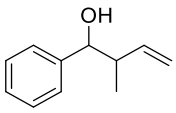


To a solution of (*E*)-1-phenylhex-2-ene-1,5-dione **133** (10 mg, 0.050 mmol) in CH_2Cl_2 (0.5 mL) in a round bottomed flask containing a magnetic follower was added pyrrolidine (5 µl,

0.05 mmol). The reaction mixture was stirred at room temperature for 24 h. The solvent was then removed *in vacuo* and purified by flash column chromatography (EtOAc) to give *enamine* **135** (5 mg, 39 %) as an orange oil.

^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.05 (1 H, dd, *J*=13.7, 12.5 Hz, CH=C*H*CH), 7.90 - 7.99 (2 H, m, Ar*H*), 7.36 - 7.51 (3 H, m, Ar*H*), 6.61 (1 H, d, *J*=13.9 Hz, C*H*=CHCH), 5.36 (1 H, d, *J*=12.6 Hz, CH=CHC*H*), 3.31 - 3.53 (4 H, m, NCH_2), 2.20 (3 H, s, CH_3), 1.92 - 2.01 (4 H, m, NCH$_2$CH_2). *NOE enhancements associated with enamine **135** are represented by red arrows on the compound structure.* **^{13}C NMR** (125 MHz, *CHLOROFORM-d*) δ ppm 189.1, 156.0, 146.0, 140.5, 130.9, 128.1, 127.8, 111.2, 98.0, 48.4, 25.1, 16.3; **FTIR** 2967, 1721, 1678, 1597, 1448, 1264, 1100, 729 cm^{-1}; **HRMS** m/z [$C_{16}H_{19}NO$+H]$^{+}$ cal.242.1539, found 242.1540 (Δ + 1.4).

2-Methyl-1-phenylbut-3-en-1-ol, 134

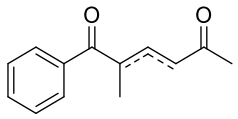


Benzaldehyde (0.930 g, 8.77 mmol, 0.894 mL) and crotyl bromide (2.37g, 17.5 mmol, 1.81 mL) were subjected to General Procedure 1. The crude mixture was purified by flash column chromatography (petrol-EtOAc, 19:1) to afford *allylic alcohol* **141** (1.42g, 95%, 1:1 dr) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.23 - 7.45 (10 H, m, Ar*H*), 5.70 - 5.90 (2 H, m, C*H*=CH_2), 5.15 - 5.27 (2 H, m, CH=CH_aH$_b$), 5.02 - 5.11 (2 H, m, CH=CH$_a$$H_b$), 4.59 (1 H, d, *J*=5.6 Hz, C*H*OH), 4.37 (1 H, d, *J*=7.8 Hz, C*H*OH), 2.55 - 2.64 (1 H, m, C*H*CH_3), 2.44 - 2.55 (1 H, m, C*H*CH_3), 2.28 (2 H, br. S, O*H*), 1.04 (3 H, d, *J*=6.8 Hz, CH_3), 0.90 (3 H, d, *J*=6.8 Hz, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 142.7, 142.5, 140.7,

140.4, 128.2, 128.1, 127.6, 127.3, 126.9, 126.6, 116.7, 115.5, 77.9, 76.8, 46.2, 44.7, 16.5, 14.1. Data were consistent with those previously reported.[157]

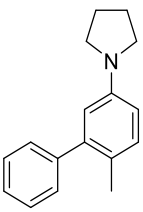
1-Phenyl-3-(phenylamino)hexane-1,5-dione, 142



2-Methyl-1-phenylbut-3-en-1-ol **141** (100 mg, 0.617 mmol), Zhan 1B catalyst (2 mol%) and but-3-en-2-one were subjected to General Procedure 3. The reaction mixture was heated for 24 hours. Dess-Martin periodinane (200 mol%) was used for the oxidation step. The crude mixture was purified by flash column chromatography (petrol-EtOAc 9:1 to 6:4) to afford unsaturated dicarbonyl **142** (91 mg, 73%, 1:0.2 rr) as a red oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.95 (0.4 H, d, *J*=7.3 Hz, Ar*H*), 7.68 (2 H, d, *J*=7.1 Hz, Ar*H*), 7.35 - 7.63 (3.6 H, m, ArH), 6.95 (0.2 H, dd, *J*=16.2, 7.8 Hz, CHC*H*=CH), 6.45 (1 H, td, *J*=7.0, 1.4 Hz, C*H*CH_2), 6.15 (0.2 H, d, *J*=16.2 Hz, C*H*=CHCH), 4.33 (0.2 H, q, *J*=6.9 Hz, CH_3C*H*), 3.43 (2 H, d, *J*=7.1 Hz, CH_2), 2.24 (0.6 H, s, CHCH_3), 2.20 (3 H, s, CCH_3), 1.95 (3 H, s, CH_3), 1.40 (0.6 H, d, *J*=7.1 Hz, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 204.3, 199.6, 198.3 (2C), 146.3, 138.7, 137.9, 135.9, 135.6, 133.6, 132.0, 131.8, 129.5, 128.8, 128.5, 128.2, 44.2, 43.4, 30.1, 26.9, 17.3, 13.1. Data were consistent with those previously reported.[155]

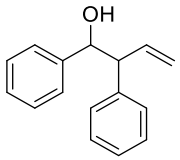
1-(6-Methyl-[1,1'-biphenyl]-3-yl)pyrrolidine, 143



Unsaturated 1,5-dicarbonyl **142 (**44 mg, 0.22 mmol) and pyrrolidine were subjected to General Procedure 4. The reaction mixture was stirred for 12 hours. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **143** (39 mg, 75%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.33 - 7.48 (5 H, m, Ar*H*), 7.16 (1 H, d, *J*=8.2 Hz, *H*C(5)), 6.56 (1 H, d, *J*=7.8 Hz, *H*C(6)), 6.52 (1 H, s, *H*C(2)), 3.26 - 3.39 (4 H, m, NCH_2), 2.19 (3 H, s, CH_3), 1.98 - 2.07 (4 H, m, NCH$_2$CH_2); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 146.2, 143.0, 142.5, 131.0, 129.2, 128.0, 126.6, 122.0, 113.4, 110.9, 47.9, 25.5, 19.3; **FTIR** 2965, 1613, 1562, 1509, 1488, 1460, 1420, 1369, 1282, 1180, 976, 847, 799, 773, 702, 630 cm^{-1}; **HRMS** m/z [$C_{17}H_{19}N$+H] $^{+}$ cal.238.1590, found 238.1587 (+ 1.2).

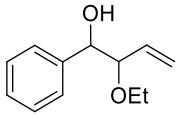
1,2-Diphenylbut-3-en-1-ol, 144



Benzaldehyde (1.06 g, 10.0 mmol, 1.01 mL) and 3-bromo-1-phenyl-1-propene (4.00 g, 20.0 mmol) were subjected to General Procedure 6. The crude mixture was purified by flash column chromatography (petrol-EtOAc, 19:1) to afford *allylic alcohol* **144** (1.44 g, 64%, 1:0.5 dr) as an oil.

^{1}H NMR *for major diastereomer* (200 MHz, *CHLOROFORM-d*) δ ppm 6.94 - 7.48 (13 H, m), 6.27 (1 H, ddd, *J*=16.7, 10.6, 9.6 Hz), 5.30 (1 H, d, *J*=4.1 Hz), 5.23 (1 H, d, *J*=11.3 Hz), 4.86 (1 H, d, *J*=7.5 Hz), 3.56 (1 H, t, *J*=8.4 Hz); **^{13}C NMR** (101 MHz, *CHLOROFORM-d*) δ ppm 141.9, 140.7, 137.9, 128.4 (2x), 127.9, 127.5, 126.7, 126.6, 118.5, 77.3, 59.2. Data were consistent with those previously reported.[158]

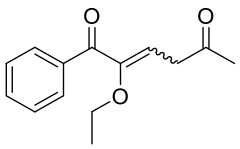
2-Ethoxy-1-phenylbut-3-en-1-ol, 147



To a stirred solution of allyl enol ether **146** (500 mg, 5.81 mmol) at −78 °C in THF (50 mL) was added *sec*-BuLi (2.5 M in hexanes, 5.81 mmol, 5.6 mL) and the reaction stirred for 1 hour. A solution of $InCl_3$ (427 mg, 1.93 mmol) in THF (10 mL) was added dropwise and the reaction stirred for 30 min. Benzyaldehyde was added dropwise and the reaction stirred for 1 hour, then quenched by the addition of aqueous HCl (1.0 M, 5 mL/mmol) and the product extracted in Et_2O (2 x). The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$, dried ($MgSO_4$), and concentrated. The crude product was purified by flash column chromatography (petrol-EtOAc, 19:1) to afford *alcohol* **147** (189 mg, 51%, 1:0.2 dr) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.25 - 7.40 (5 H, m), 5.57 (1 H, ddd, *J*=17.4, 10.4, 7.1 Hz), 5.02 - 5.28 (2 H, m), 4.49 (1 H, d, *J*=8.1 Hz), 3.53 - 3.81 (2 H, m), 3.34 - 3.47 (1 H, m), 1.16 - 1.29 (3 H, m); **^{13}C NMR** (*CHLOROFORM-d*) δ ppm 139.7, 134.7, 128.1, 127.9, 127.4, 119.0, 85.8, 76.8, 64.5, 15.3. Data were consistent with those previously reported. [159]

2-Ethoxy-1-phenylhex-2-ene-1,5-dione, 148

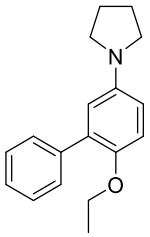


2-Ethoxy-1-phenylbut-3-en-1-ol (82 mg, 0.43 mmol), Zhan 1B catalyst (5 mol%) and but-3-en-2-one were subjected to General Procedure 3. The reaction mixture was heated for 48 hours and then filtered using petrol-Et_2O (1:1). Dess-Martin periodinane (200 mol%) was

used for the oxidation step. The crude mixture was purified by flash column chromatography (petrol-EtOAc, 9:1 to 6:4) to afford *unsaturated dicarbonyl* **148** (44 mg, 45%, 1:0.5 dr) as a red oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.82 - 7.93 (3.0 H, m, Ar*H*), 7.56 (1.5 H, t, *J*=7.5 Hz, Ar*H*), 7.45 (3.0 H, t, *J*=7.7 Hz, Ar*H*), 5.89 (1.0 H, t, *J*=7.1 Hz, C=C*H*), 5.27-5.32 (0.5, t, *J*=6.8 Hz, C=C*H*), 3.77 - 3.97 (3.0 H, m, CH_3CH_2), 3.45 - 3.51 (2.0 H, m, CCH_3), 3.36 (1.0 H, d, *J*=7.3 Hz, CH_2), 2.23 (3.0 H, s, CCH_3), 2.14 (1.5 H, s, CCH_3), 1.32 (1.5 H, t, *J*=6.9 Hz, CH_3CH_2), 1.25 (3.0 H, t, *J*=6.9 Hz, CH_3CH_2); **^{13}C NMR** (*CHLOROFORM-d*) δ ppm 205.1, 192.2, 153.6, 137.2, 133.3, 132.8, 129.9, 129.5, 128.4, 128.3, 119.7, 100.0, 66.6, 63.7, 41.0, 40.4, 30.0, 15.5, 14.4; **FTIR** 2979, 1716, 1657, 1597, 1448, 1359, 1253, 1160, 1047, 1017, 978, 717, 666 cm^{-1}; **HRMS** m/z $[C_{14}H_{16}O_3+Na]^+$ cal. 255.0992, found 255.0989 (δ + 1.1).

1-(6-Ethoxy-[1,1'-biphenyl]-3-yl)pyrrolidine, 149

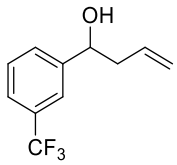


Unsaturated 1,5-dicarbonyl **148 (**24 mg, 0.10 mmol) and pyrrolidine were subjected to General Procedure 4. The reaction mixture was stirred for 5 hours. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **149** (22 mg, 79%) as a colourless oil.

^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.59 (2 H, m, Ar*H*), 7.41 (2 H, t, *J*=7.6 Hz, Ar*H*), 7.33 (1 H, m, Ar*H*), 6.97 (1 H, d, *J*=8.8 Hz, *H*C(5)), 6.68 (2 H, m, *H*C(2) & *H*C(6)), 3.89 (2 H, q, *J*=6.9 Hz, CH_3CH_2), 3.32 (4 H, m, NCH_2), 2.04 (4 H, m, NCH_2CH_2), 1.27 (3 H, t, J=6.9, CH_3); **^{13}C NMR** (125 MHz, *CHLOROFORM-d*) δ ppm 139.3, 132.6, 129.5,

129.3, 128.3, 127.9, 127.9, 126.8 (2C), 116.4, 65.9, 48.8, 25.4, 15.1; **FTIR** 2973, 2873, 1613, 1508, 1487, 1420, 1390, 1369, 1230, 1050, 699 cm^{-1}; **HRMS** m/z $[C_{18}H_{21}NO+H]^+$ cal. 268.1696, found 268.1697 (δ + 1.1).

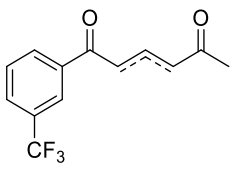
1-(3-(Trifluoromethyl)phenyl)but-3-en-1-ol, 151



3-(Trifluoromethyl)benzaldehyde (500 mg, 2.87 mmol, 0.384 mL) and allyl magnesium bromide (2.0 M in THF, 3.16 mmol, 1.58 mL) were subjected to General Procedure 1. The crude reaction mixture was purified by flash column chromatography (petrol-EtOAc, 9:1) to give *alcohol* **151** (560 mg, 90%).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.53 (1 H, s, Ar*H*), 7.40 - 7.46 (2 H, m, Ar*H*), 7.32 - 7.39 (1 H, m, *ArH*), 5.62 - 5.83 (1 H, m, C*H*=CH_2), 5.02 - 5.13 (2 H, m, CH=CH_2), 4.62 - 4.74 (1 H, m, C*H*OH), 2.27 - 2.50 (3 H, m, CH_2CHO*H*); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 144.8, 133.7, 130.7 (q, *J*=31.8 Hz), 129.2, 128.8, 124.3 (q, *J*=4.0 Hz), 122.6 (q, *J*=4.0 Hz), 124.2 (q, *J*=273.4 Hz), 119.1, 72.6, 43.9; **^{19}F NMR** (377 MHz, *CHLOROFORM-d*) δ ppm -62.6 (CF_3). Data were consistent with those previously reported. [160]

(*E*)-1-(3-(Trifluoromethyl)phenyl)hex-3-ene-1,5-dione, 152

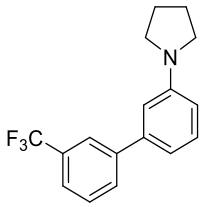


1-(3-(Trifluoromethyl)phenyl)but-3-en-1-ol **151** (150 mg, 0.694 mmol), Zhan 1B catalyst (5 mol%) and but-3-en-2-one were subjected to General Procedure 3. The reaction mixture was

heated for 24 hours and then filtered using Petrol-Et_2O (1:1). Dess-Martin periodinane (300 mol%) was used for the oxidation step. Purification by flash column chromatography (petrol-EtOAc, 8:2 to 7:3) afforded *unsaturated dicarbonyl* **152** (85 mg, 45%, 1:0.7 rr) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.06 - 8.28 (3.4 H, m, Ar*H*), 7.84 (1.7 H, dd, *J*=17.5, 7.7 Hz, Ar*H*), 7.54 - 7.71 (1.7 H, m, Ar*H*), 7.00 - 7.21 (1.7 H, m, C*H*CH_2), 6.92 (0.7 H, d, *J*=15.7 Hz, CH=C*H*), 6.21 (1.0 H, d, *J*=16.4 Hz, CH=C*H*), 3.98 (2 H, d, *J*=8.1 Hz, CH_2), 3.50 (1.4 H, d, *J*=7.1 Hz, CH_2), 2.31 (3.0 H, s, CH_3), 2.26 (2.1 H, s, CH_3); **^{13}C NMR** (125 MHz, *CHLOROFORM-d*) δ ppm 204.1, 198.0, 194.8, 188.9, 141.4, 138.9, 138.0, 136.6, 134.6, 131.7, 131.3, 131.5 (q, ^{2}J=33.4 Hz), 131.2 (q, ^{2}J=33.4 Hz), 130.1, 129.6, 129.3 (2C, m) 2 x C, 128.5, 125.4 (q, ^{3}J=3.8 Hz), 125.0 (q,^{3}J=3.8 Hz), 123.6 (q, ^{1}J=272.8 Hz), 123.5 (q, ^{1}J=272.8 Hz), 46.8, 41.5, 30.1, 26.8; **^{19}F NMR** (377 MHz, *CHLOROFORM-d*) δ ppm -62.8 (CF_3); **FTIR** 2360, 2342, 1674, 1331, 1168, 1127, 1073, 806, 695 cm^{-1}; **HRMS** m/z $[C_{13}H_{11}F_3O_2+Na]^+$ cal. 279.0603, found 279.0607 (Δ – 1.4).

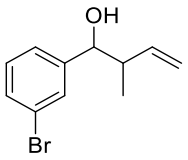
1-(3'-(Trifluoromethyl)-[1,1'-biphenyl]-3-yl)pyrrolidine, 153



Unsaturated 1,5-dicarbonyl **152 (**35 mg, 0.14 mmol) and pyrrolidine were subjected to General Procedure 4. The reaction mixture was heated for 5 hours. In a modification to the General Procedure the addition of amine took place at 0 °C then warmed to room temperature. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **153** (30 mg, 72%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.87 (1 H, s, Ar*H*), 7.80 (1 H, d, *J*=7.6 Hz, Ar*H*), 7.51 - 7.64 (2 H, m, Ar*H*), 7.34 (1 H, t, *J*=7.8 Hz, *H*C(5)), 6.89 (1 H, d, *J*=7.6 Hz, *H*C(6)), 6.75 (1 H, s, *H*C(2)), 6.63 (1 H, d, *J*=8.2 Hz, *H*C(4)), 3.38 (4 H, t, *J*=6.5 Hz, NC*H*$_2$), 1.99 - 2.13 (4 H, m, NCH$_2$C*H*$_2$); **^{13}C NMR** (126 MHz, *CHLOROFORM-d*) δ ppm 148.8, 143.6, 141.3, 131.0, 131.4 (q, ^{2}J=32.4 Hz), 130.1, 129.4, 124.5 (q, ^{3}J=3.7 Hz), 124.1 (q, ^{3}J=3.7 Hz), 124.8 (q, ^{1}J=272.8 Hz), 115.0, 111.9, 110.8, 48.2, 25.9; **^{19}F NMR** (377 MHz, *CHLOROFORM-d*) δ ppm -62.5 (CF$_3$); **FTIR** 2968, 1601, 1485, 1461, 1430, 1375, 1330, 1249, 1163, 1123, 1096, 1075, 997, 842, 803, 771, 700, 663 cm^{-1}; **HRMS** m/z [C$_{17}$H$_{16}$F$_3$N+H]$^+$ cal. 292.1308, found 292.1315 (Δ + 2.5).

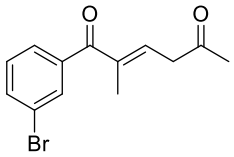
1-(3-Bromophenyl)-2-methylbut-3-en-1-ol, 156



3-Bromo-benzaldehyde (1.00 g, 5.41 mmol, 0.630 mL) and crotyl bromide (1.46 g, 10.8 mmol, 1.11 mL) were subjected to General Procedure 6. The crude mixture was purified by flash column chromatography (petrol-EtOAc, 9:1) to afford *allylic alcohol* **156** (1.10 g, 85%, 1:1 dr) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.34 - 7.58 (4 H, m, Ar*H*), 7.12 - 7.30 (4 H, m, Ar*H*), 5.66 - 5.87 (2 H, m, C*H*=CH$_2$), 5.16 - 5.25 (2 H, m, CH=C*H*$_a$H$_b$), 5.02 - 5.14 (2 H, m, CH=CH$_a$*H*$_b$), 4.54 - 4.68 (1 H, m, C*H*OH), 4.34 (1 H, d, *J*=7.6 Hz, C*H*OH), 2.51 - 2.60 (1 H, m, C*H*CH$_3$), 2.39 - 2.51 (1 H, m, C*H*CH$_3$), 2.18 - 2.25 (1 H, m, O*H*), 2.01 (1 H, d, *J*=2.8 Hz, O*H*), 0.99 (3 H, d, *J*=6.8 Hz, C*H*$_3$), 0.90 (3 H, d, *J*=6.8 Hz, C*H*$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 144.9, 144.8, 140.0, 139.8, 130.7, 130.4, 129.9, 129.8, 129.6, 129.5, 125.6, 125.1, 122.5, 122.3, 117.5, 116.1, 77.1, 76.4, 46.3, 44.5, 16.5, 13.6. Data were consistent with those previously reported. [161]

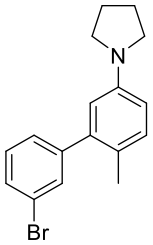
(*E*)-1-(3-Bromophenyl)-2-methylhex-2-ene-1,5-dione, 157



1-Phenylhex-5-en-3-one (85 mg, 0.35 mmol), Zhan 1B catalyst (2 mol%) and but-3-en-2-one were subjected to General Procedure 3. The reaction mixture was heated for 24 hours and then filtered using petrol-Et_2O (1:1). Dess-Martin periodinane (200 mol%) was used for the oxidation step. Purification by flash column chromatography (petrol-EtOAc, 9:1 to 1:1) afforded *unsaturated dicarbonyl* **157** (74 mg, 60%) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.78 (1 H, s, Ar*H*), 7.61 (1 H, d, *J*=8.1 Hz, Ar*H*), 7.57 (1 H, d, *J*=7.6 Hz, Ar*H*), 7.28 (1 H, t, *J*=7.8 Hz, Ar*H*), 6.44 (1 H, t, *J*=6.9 Hz, C*H*), 3.44 (2 H, d, *J*=6.8 Hz, CH_2), 2.20 (3 H, s, CH_3), 1.92 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 204.1, 196.6, 139.9, 137.8, 137.0, 134.7, 132.3, 129.8, 128.0, 122.4, 43.3, 30.1, 13.0; **FTIR** 1717, 1681, 1651, 1562, 1416, 1359, 1254, 1162, 1070, 1027, 900, 737, 672 cm^{-1}; **HRMS** m/z $[C_{13}H_{13}BrO_2+Na]^+$ cal.302.9991, found 302.9981 (Δ + 3.3).

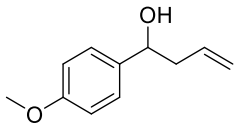
1-(3'-Bromo-6-methyl-[1,1'-biphenyl]-3-yl)pyrrolidine, 158



Unsaturated 1,5-dicarbonyl **157 (**50 mg, 0.18 mmol) and pyrrolidine were subjected to General Procedure 4. The reaction mixture was heated for 8 hours. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **158** (46 mg, 82%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.54 (1 H, s, Ar*H*), 7.49 (1 H, d, *J*=6.8 Hz, Ar*H*), 7.30 (2 H, m, Ar*H*), 7.14 (1 H, d, *J*=8.3 Hz, *H*C(5)), 6.56 (1 H, d, *J*=8.2 Hz, *H*C(6)), 6.44 (1 H, s, *H*C(2)), 3.30 (4 H, m, NC*H*$_2$), 2.71 (3 H, s, C*H*$_3$) 2.02 (4 H, m, NCH$_2$C*H*$_2$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 146.3, 145.1, 141.0, 132.1, 131.1, 129.6, 129.5, 127.9, 122.1, 121.7, 113.0, 111.4, 47.8, 25.5, 19.2; **FTIR** 2966, 1614, 1592, 1557, 1510, 1473, 1403, 1370, 1282, 1160, 1073, 996, 846, 788, 753 cm^{-1}; **HRMS** m/z $[C_{17}H_{18}BrN+H]^+$ cal. 316.0651, found 316.0655 (Δ + 1.4).

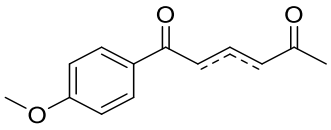
1-(4-Methoxyphenyl)but-3-en-1-ol, 161



p-Anisaldehyde (1.00 g, 7.35mmol, 0.893 mL) and allyl magnesium chloride (2.0 M in THF, 8.09 mmol, 4.45 mL) were subjected to General Procedure 1 to give *alcohol* **161** (1.18 g, 90%).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.29 (2 H, d, *J*=8.6 Hz, Ar*H*), 6.89 (2 H, d, *J*=8.6 Hz, Ar*H*), 5.68 - 5.90 (1 H, m, C*H*=CH$_2$), 5.05 - 5.21 (2 H, m, CH=C*H*$_2$), 4.69 (1 H, t, *J*=6.4 Hz, C*H*CO), 3.81 (3 H, s, OC*H*$_3$), 2.50 (2 H, t, *J*=6.8 Hz, C*H*$_2$), 2.07 (1 H, br. s, O*H*); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 159.0, 136.1, 134.7, 127.1, 118.2, 113.8, 73.0, 55.3, 43.8. Data were consistent with those previously reported.[162]

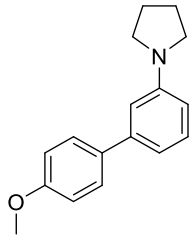
(*E*)-1-(4-Methoxyphenyl)hex-3-ene-1,5-dione, 162



1-(4-Methoxyphenyl)but-3-en-1-ol **161** (100 mg, 0.56 mmol), Zhan 1B catalyst (5 mol%) and but-3-en-2-one were subjected to General Procedure 3. The reaction mixture was heated for 48 hours and then filtered using petrol-Et_2O (1:1). Dess-Martin periodinane (250 mol%) was used for the oxidation step. Purification by flash column chromatography (petrol-EtOAc, 9:1 to 6:4) afforded *unsaturated dicarbonyl* **162** (77 mg, 62%, 1:0.2 rr) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.83 - 7.89 (2.4 H, m, Ar*H*), 6.94 - 7.03 (1.2 H, m, C*H*CH_2), 6.85 - 6.90 (2.6 H, m, Ar*H* & C*H*=$CHCH_2$), 6.10 (1.0 H, d, *J*=16.1 Hz, C*H*=$CHCH_2$), 3.78 - 3.83 (5.6 H, m, OCH_3, CH_2), 3.37 (0.4 H, d, *J*=7.1 Hz, CH_2), 2.22 (3.0 H, s, CCH_3), 2.16 (0.6 H, s, CCH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 203.6, 197.3, 193.6, 187.5, 162.9, 139.5, 137.8, 133.2, 130.0, 129.7, 129.6, 129.3, 128.1, 128.0 113.0, 112.8, 54.5, 54.5, 46.0, 40.3, 29.0., 25.6; **FTIR** 2963, 1671, 1598, 1511, 1511, 1421, 1314, 1258, 1171, 1026, 979, 839 cm^{-1}; **HRMS** m/z $[C_{13}H_{14}O_3+Na]^+$ cal. 241.0829, found 241.0835 (Δ + 2.1).

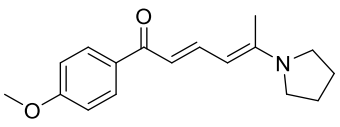
1-(4'-Methoxy-[1,1'-biphenyl]-3-yl)pyrrolidine, 163



Unsaturated 1,5-dicarbonyl **162 (**35 mg, 0.16 mmol) and pyrrolidine were subjected to General Procedure 5. Purification by flash column chromatography (petrol-EtOAc to 19:1) afforded *arylamine* **163** (25 mg, 63%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.53 - 7.63 (2 H, m, Ar*H*), 7.30 (1 H, t, *J*=7.8 Hz, *H*C(5)), 6.96 - 7.04 (2 H, m, Ar*H*), 6.88 (1 H, d, *J*=7.6 Hz, *H*C(6)), 6.75 (1 H, s, *H*C(2)), 6.57 (1 H, dd, *J*=8.2, 2.1 Hz, *H*C(4)), 3.88 (3 H, s OCH_3), 3.33 - 3.42 (4 H, m, NCH_2), 2.00 - 2.09 (4 H, m, NCH_2CH_2); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 159.0, 148.3, 141.9, 134.9, 129.5, 128.3, 114.4, 114.0, 110.3, 110.2, 55.4, 47.7, 25.5; **FTIR** 2967, 1597, 1573, 1508, 1423, 1381, 1359, 1328, 1304, 1250, 1196, 1163, 1111, 1017, 979, 909, 832, 728, 644 cm^{-1}; **HRMS** m/z $[C_{17}H_{19}NO+H]^+$ cal. 254.1539, found 254.1541 (Δ -0.7).

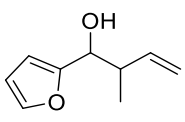
(2*E*,4*E*)-1-(4-Methoxyphenyl)-5-(pyrrolidin-1-yl)hexa-2,4-dien-1-one, 164



Enamine **164** (17 mg, 40%) was isolated as a side product of the above reaction performed at room temperature.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.95 (1 H, dd, *J*=13.4, 12.5 Hz, CH=C*H*CH), 7.88 (2 H, d, *J*=8.8 Hz, Ar*H*), 6.84 (2 H, d, *J*=8.8 Hz, Ar*H*), 6.54 (1 H, d, *J*=13.7 Hz, C=C*H*), 5.26 (1 H, d, *J*=12.5 Hz, C=C*H*), 3.78 (3 H, s, OCH_3), 3.32 (4 H, br. s., NCH_2), 2.13 (3 H, s, CCH_3), 1.88 (4 H, t, *J*=6.5 Hz, NCH_2CH_2); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 187.8, 162.0, 155.5, 145.3, 133.2, 129.8, 113.3, 111.0, 97.8, 55.4, 48.4, 25.2, 16.3; **FTIR** 2967, 1597, 1573, 1508, 1423, 1381, 1359, 1328, 1304, 1250, 1196, 1163, 1111, 1017, 979, 909, 832, 728, 644, 608 cm^{-1}; **HRMS** m/z $[C_{17}H_{22}NO_2]$ cal. 272.1645, found 272.1640 (Δ + 1.8).

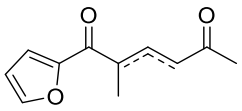
1-(Furan-2-yl)-2-methylbut-3-en-1-ol, 168



Furfural (1.00 g, 10.4 mmol, 0.862 mL) and 1-methyl-2-propenylmagnesium bromide (0.5 M in Et_2O, 11.4 mmol, 22.8 mL) were subjected to General Procedure 1 to give *alcohol* **168** (1.01 g, 78%, 1:1 dr).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.35 - 7.45 (2 H, m, Furan-*H*), 6.36 (2 H, td, *J*=3.8, 2.0 Hz, Furan-*H*), 6.29 (1 H, d, *J*=2.9 Hz, Furan-*H*), 6.25 (1 H, d, *J*=2.9 Hz, Furan-*H*), 5.69 - 5.89 (2 H, m, C*H*=CH_2), 5.04 - 5.29 (4 H, m, CH=CH_2), 4.59 (1 H, t, *J*=5.6 Hz, C*H*CO), 4.44 (1 H, dd, *J*=7.7, 3.5 Hz, C*H*CO), 2.67 - 2.80 (2 H, m, C*H*CH_3), 2.19 (1 H, br. s, O*H*), 2.12 (1 H, br. s, O*H*), 1.09 (3 H, d, *J*=6.8 Hz, CH_3), 0.97 (3 H, d, *J*=6.8 Hz, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 155.3, 155.0, 142.0, 141.8, 140.0, 139.6, 117.1, 116.0, 110.1, 110.1, 107.3, 106.9, 71.4, 71.4, 43.6, 43.1, 16.3, 15.1. Data were consistent with those previously reported.[163]

(*E*)-1-(Furan-2-yl)-2-methylhex-2-ene-1,5-dione, 169

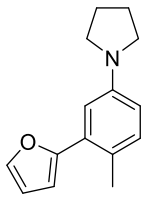


1-(Furan-2-yl)-2-methylbut-3-en-1-ol **168** (150 mg, 0.99 mmol), Zhan 1B catalyst (5 mol%) and but-3-en-2-one were subjected to General Procedure 3. The reaction mixture was heated for 24 hours and then filtered using Petrol-Et_2O (1:1). Dess-Martin periodinane (200 mol%) was used for the oxidation step. Purification by flash column chromatography (petrol-EtOAc, 8:2 to 7:3) afforded *unsaturated dicarbonyl* **169** (102 mg, 54%, 1:0.5 rr) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.53 - 7.60 (1.5 H, m, Furan-*H*), 7.20 (1.0 H, dd, *J*=3.7, 0.7 Hz, Furan-*H*), 7.12 (0.5 H, d, *J*=3.4 Hz, Furan-*H*), 6.84 (1.0 H, dd, *J*=16.1, 8.1 Hz, CH_2C*H*=CH), 6.69 - 6.76 (0.5 H, m, C*H*=C), 6.48 - 6.54 (1.0 H, m, Furan-*H*), 6.43 - 6.48 (0.5 H, m, Furan-*H*), 6.12 (1.0 H, d, *J*=16.1 Hz, C(O)C*H*), 3.97 - 4.15 (1.0 H, m,C*H*CH_3), 3.39 (1.0 H, d, *J*=7.1 Hz, CH_2), 2.14 - 2.23 (4.5 H, m, CHCH_3), 1.87 (1.5 H, t, *J*=1.0 Hz, C(O)CH_3), 1.33 (3.0 H, d, *J*=6.8 Hz, C(O)CH_3); **^{13}C NMR** (100 MHz,

CHLOROFORM-d) δ ppm 204.7, 198.4, 188.3, 184.3, 151.7 (2 signals), 147.0 (2 signals), 145.6, 137.9, 133.2, 132.3, 120.1, 118.3, 112.6, 111.9, 44.9, 43.2, 30.1, 26.9, 16.6, 13.2. Data were consistent with those previously reported.[155]

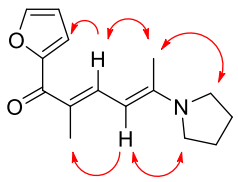
1-(3-(Furan-2-yl)-4-methylphenyl)pyrrolidine, 170



Unsaturated 1,5-dicarbonyl **169 (**40 mg, 0.26 mmol) and pyrrolidine were subjected to General Procedure 5. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded arylamine **170** (40 mg, 68%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.52 (1 H, dd, *J*=1.7, 0.7 Hz, Furan-*H*), 7.12 (1 H, d, *J*=8.6 Hz, *H*C(5)), 6.96 (1 H, d, *J*=2.7 Hz, Furan-*H*), 6.55 (1 H, dd, *J*=3.2, 0.7 Hz, Furan-*H*), 6.49 - 6.54 (2 H, m, *H*C(2) and *H*C(6)), 3.26 - 3.42 (4 H, m, NCH_2), 2.42 (3 H, s, CH_3), 1.95 - 2.09 (4 H, m, NCH$_2$CH_2); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 154.4, 146.4, 141.3, 131.8, 130.6, 121.6, 111.5, 111.2, 110.4, 108.2, 47.9, 25.5, 20.8; **FTIR** 2966, 1615, 1511, 1487, 1461, 1366, 1284, 1245, 1211, 1156, 1037, 1016, 908, 849, 799, 734 cm^{-1}; **HRMS** m/z [$C_{15}H_{17}NO$+H]$^{+}$ cal. 228.1383, found 228.1379 (Δ + 1.5).

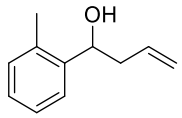
(2*E*,4*E*)-1-(Furan-2-yl)-2-methyl-5-(pyrrolidin-1-yl)hexa-2,4-dien-1-one, 171



Enamine **171** (56 mg, 52%) was isolated as a side product of the above reaction performed at room temperature.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.87 (1 H, d, *J*=12.0 Hz, C(O)C=C*H*), 7.54 (1 H, s, Furan-*H*), 6.87 (1 H, d, *J*=3.2 Hz, Furan-*H*), 6.41 - 6.48 (1 H, m, Furan-*H*), 5.12 (1 H, d, *J*=12.0 Hz, NC=C*H*), 3.33 - 3.48 (4 H, m, NCH_2), 2.12 (3 H, s, CH_3), 1.91 - 2.02 (4 H, m, NCH$_2$CH_2); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 182.3, 153.9, 153.7, 144.2, 143.8, 121.7, 115.4, 111.0, 95.4, 48.5, 25.2, 16.2, 12.1; **FTIR** 2970, 1523, 1467, 1435, 1379, 1342, 1316, 1276, 1221, 1179, 1153, 1064, 1021, 928, 873, 804, 754, 726 cm^{-1}; **HRMS** m/z [$C_{15}H_{19}NO_2$+H]$^+$ cal. 246.1489, found 246.1489 (Δ + 1.4).

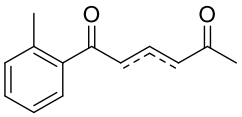
1-(*o*-tolyl)But-3-en-1-ol, 174



2-Methylbenzaldehyde (1.00g , 8.30 mmol) and allyl magnesium bromide (2.0 M in THF, 12.5 mmol, 6.25 mL) were subjected to General Procedure 1. The crude reaction mixture was purified by flash column chromatography (petrol-EtOAc, 19:1 to 9:1) to give *alcohol* **174** (1.31 g, 99%).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.40 (1 H, d, *J*=7.6 Hz, Ar*H*), 6.99 - 7.21 (3 H, m, Ar*H*), 5.67 - 5.89 (1 H, m, C*H*=CH$_2$), 5.11 (1 H, d, *J*=15.4 Hz, CH=CH_aH$_b$), 5.08 (1 H, d, *J*=8.6 Hz, CH=CH$_a$$H_b$), 4.89 (1 H, dd, *J*=8.2, 4.5 Hz, C*H*OH), 2.38 - 2.48 (1 H, m, CH_aH$_b$), 2.34 (1 H, dd, *J*=14.2, 8.2 Hz, CH$_a$$H_b$), 2.26 (3 H, s, C$H_3$), 1.88 (1 H, br. s., O*H*); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 142.0, 134.8, 134.4, 130.4, 127.3, 126.3, 125.2, 118.3, 69.7, 42.7, 19.1. Data were consistent with those previously reported. [164]

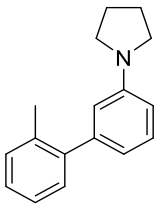
(*E*)-1-(o-tolyl)Hex-3-ene-1,5-dione, 175



1-(*o*-tolyl)But-3-en-1-ol (100 mg, 0.617 mmol), Zhan 1B catalyst (3 mol%) and but-3-en-2-one were subjected to General Procedure 3. The reaction mixture was heated for 24 hours and then filtered using Petrol-Et_2O (1:1). Dess-Martin periodinane (200 mol%) was used for the oxidation step. Purification by flash column chromatography (petrol-EtOAc, 7:3) afforded *unsaturated dicarbonyl* **175** (80 mg, 64%, 1:0.8 rr) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.61 (0.8 H, d, *J*=7.8 Hz, Ar*H*), 7.07 - 7.37 (6.4 H, m, Ar*H*), 6.98 (0.8 H, dt, *J*=16.1, 7.0 Hz, C*H*CH_2), 6.71 (1 H, dt, *J*=15.8, 7.3 Hz, C*H*CH_2), 6.47 (1 H, d, *J*=15.9 Hz, CH=C*H*), 6.10 (0.8 H, d, *J*=16.1 Hz, CH=C*H*), 3.81 (1.6 H, dd, *J*=6.8, 1.5 Hz, CH_2), 3.35 (2 H, d, *J*=7.1 Hz, CH_2), 2.45 (2.4 H, s, CH_3), 2.32 (3 H, s, CH_3), 2.24 (2.4 H, s, CH_3), 2.14 (3 H, s, CH_3); **^{13}C NMR** (101 MHz, *CHLOROFORM-d*) δ ppm 204.3, 199.5, 198.4, 196.2, 141.5, 140.3, 139.0, 138.2, 137.1, 136.5, 134.2, 133.6, 132.4, 132.1, 131.4, 130.7, 128.9, 128.3, 125.9, 125.4, 46.8, 44.3, 30.1, 26.7, 21.6, 20.3; **FTIR** 3370, 2964, 1994, 1718, 1676, 1601, 1457, 1358, 1263, 1016, 764, 629 cm^{-1}; **HRMS** m/z $[C_{13}H_{14}O_2+Na]^+$ cal. 225.0891, found 225.0886 (Δ − 2.9).

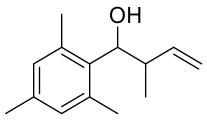
1-(2'-Methyl-[1,1'-biphenyl]-3-yl)pyrrolidine, 176



Unsaturated 1,5-dicarbonyl **175 (**26 mg, 0.13 mmol) and pyrrolidine were subjected to General Procedure 4. The reaction mixture was stirred for 3 hours. Purification by flash column chromatography (petrol-EtOAc, 49:1) afforded *arylamine* **176** (12 mg, 39%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.08 - 7.27 (5 H, m, Ar*H*), 6.37 - 6.65 (3 H, m, *H*C(2), *H*C(4) and *H*C(6)), 3.24 (4 H, m, NC*H*$_2$), 2.23 (3 H, s, C*H*$_3$), 1.89 - 1.98 (4 H, m, NCH$_2$C*H*$_2$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 147.7, 143.0, 142.9, 135.5, 130.2, 129.7, 128.8, 127.0, 125.6, 116.6, 112.6, 110.1, 47.7, 25.5, 20.5; **FTIR** 2965, 1596, 1571, 1478, 1438, 1370, 1259, 1172, 1032, 993, 847, 776, 755, 727, 702, 623 cm^{-1}; **HRMS** m/z [C$_{17}$H$_{19}$N+H]$^{+}$ cal. 238.1590, found 238.1590 (Δ + 0.3).

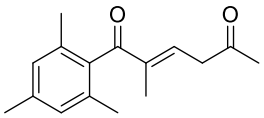
1-Mesityl-2-methylbut-3-en-1-ol, 179



Mesitaldehyde (1.00g, 6.79 mmol) and 1-methyl-2-propenylmagnesium bromide (0.5 M in Et$_2$O, 7.45 mmol, 14.9 mL) were subjected to General Procedure 1. The crude reaction mixture was purified by flash column chromatography (petrol-EtOAc, 9:1) to give *alcohol* **179** (0.930 g, 67%, 1:0.9 dr).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.85 (1.8 H, s, Ar*H*), 6.83 (2.0 H, s, Ar*H*), 5.92 (0.9 H, ddd, J=16.4, 10.0, 8.5 Hz, CH$_2$=C*H*), 5.56 (1.0 H, ddd, *J*=17.4, 10.5, 6.8 Hz, CH$_2$=C*H*), 5.29 (0.9 H, d, J=17.1 Hz, C*H*$_a$H$_b$=CH), 5.25 (0.9 H, d, J=10.3 Hz, C*H*$_a$H$_b$=CH), 4.96 (1.0 H, d, *J*=17.1 Hz, CH$_a$*H*$_b$=CH), 4.89-4.78 (2.9 H, m, C*H*OH & C*H*$_a$H$_b$=CH), 2.86 - 3.00 (1.9 H, m, C*H*CH$_3$), 2.46 (5.4 H, s, C*H*$_3$), 2.42 (6 H, s, C*H*$_3$), 2.24 (5.7 H, s, C*H*$_3$), 1.99 (0.9 H, br. s, O*H*), 1.78 (1 H, br. s, O*H*), 1.31 (3 H, d, *J*=6.6 Hz, CHC*H*$_3$), 0.83 (2.7 H, d, *J*=6.8 Hz, CHC*H*$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 142.2, 140.0, 136.9, 136.7, 136.6, 136.4, 135.8, 134.5, 130.3, 130.1, 116.5, 114.3, 75.4, 74.0, 43.9, 42.1, 21.1 (2C), 20.8 (2C), 16.8, 16.5. Data were consistent with those previously reported.[165]

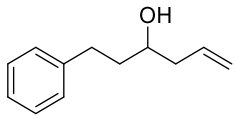
(*E*)-1-Mesityl-2-methylhex-2-ene-1,5-dione, 180



Alcohol **179** (170 mg, 0.833 mmol), Zhan 1B catalyst **57** (3 mol%) and but-3-en-2-one were subjected to General Procedure 3. The reaction mixture was heated for 24 hours and then filtered using Petrol-Et_2O (1:1). Dess-Martin periodinane (200 mol%) was used for the oxidation step. Purification by flash column chromatography (petrol-EtOAc, 9:1 to 3:1) afforded *unsaturated dicarbonyl* **180** (140 mg, 47%) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.66 - 6.83 (2 H, m, Ar*H*), 6.34 (1 H, tq, *J*=7.3, 1.4 Hz, C*H*), 3.30 (2 H, d, *J*=7.3 Hz, CH_2), 2.20 (3 H, s, C(O)CH_3), 2.07 (3 H, s, CH_3), 2.01 (6 H, s, CH_3), 1.83 - 1.88 (3 H, m, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 204.0, 202.5, 140.7, 138.2, 138.1, 136.9, 134.1, 128.2, 43.7, 30.1, 21.1, 19.2, 11.0; **FTIR** 2921, 1719, 1654, 1611, 1431, 1357, 1260, 1006, 895, 852, 731 cm^{-1}; **HRMS** m/z $[C_{16}H_{20}O_2+Na]^+$ cal. 267.1356, found 267.1364 (Δ − 3.1).

1-Phenylhex-5-en-3-ol, 183

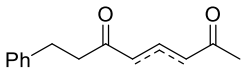


Hydrocinnamaldehyde (5.00 g, 37.3 mmol, 4.91 mL) and allyl magnesium bromide (1.0 M in Et_2O, 41.0 mmol, 41.0 mL) were subjected to General Procedure 1. The crude mixture was purified by flash column chromatography (petrol-EtOAc 9:1) to afford *allylic alcohol* **183** (4.90 g, 75%) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.15 - 7.40 (5 H, m, Ar*H*), 5.72 - 5.97 (1 H, m, C*H*=CH_2), 5.17 (2 H, d, *J*=13.6 Hz, CH=CH_2), 3.70 (1 H, br. s, O*H*), 2.79 - 2.91 (1 H, m, C*H*OH), 2.62 - 2.78 (1 H, m, CHC$H_a$$H_b$CH), 2.33 - 2.37 (1 H, m, CHC$H_a$$H_b$CH), 2.15 - 2.29 (1 H, m, CH_aCH_bCH_2), 1.66 - 1.90 (3 H, m, CH_aCH_bCH_2); **^{13}C NMR** (100 MHz,

CHLOROFORM-d) δ ppm 142.1, 134.7, 128.5, 128.4, 125.8, 118.3, 69.9, 42.1, 38.5, 32.1. Data were consistent with those previously reported.[166]

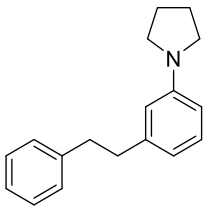
1-Phenylhex-5-en-3-one, 184



1-Phenylhex-5-en-3-one (97 mg, 0.46 mmol), Zhan 1B catalyst (2 mol%) and but-3-en-2-one were subjected to General Procedure 3. The reaction mixture was heated for 48 hours and then filtered using petrol-Et_2O (1:1). Dess-Martin periodinane (250 mol%) was used for the oxidation step. Purification by flash column chromatography (petrol-EtOAc, 9:1 to 6:4) afforded *unsaturated dicarbonyl* **184** (77 mg, 61%, 1:1 rr) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.21 - 7.33 (4 H, m, Ar*H*), 7.14 - 7.23 (6 H, m, Ar*H*), 6.79 - 6.95 (2 H, m, C*H*=CHCH$_2$), 6.01 - 6.19 (2 H, m, CH=C*H*CH$_2$), 3.33 (4 H, m, CHC*H*$_2$), 2.86 - 2.97 (6 H, m, C*H*$_2$C*H*$_a$H$_b$), 2.81 (2 H, d, *J*=7.3 Hz, CH$_2$CH$_a$*H*$_b$), 2.25 (3 H, s, C*H*$_3$), 2.19 (3 H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 205.7, 204.4, 199.0, 198.1, 141.0, 140.5, 139.0, 138.2, 134.2, 133.3, 128.6, 128.5, 128.4, 128.3, 126.3, 126.1, 46.5, 45.9, 44.4, 41.5, 30.0, 29.9, 29.6, 26.7. Data were consistent with those previously reported.[155]

1-(3-Phenethylphenyl)pyrrolidine, 185

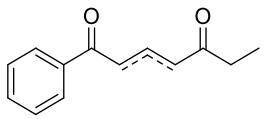


Unsaturated 1,5-dicarbonyl **184 (**50 mg, 0.23 mmol) and pyrrolidine were subjected to General Procedure 4. The reaction mixture was stirred for 18 hours. Purification by flash

column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **185** (35 mg, 60%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.31 - 7.38 (2 H, m, Ar*H*), 7.18 - 7.31 (4 H, m, Ar*H* & *H*C(5)), 6.60 (1 H, d, *J*=7.3 Hz, *H*C(6)), 6.44 - 6.54 (2 H, m, *H*C(2) & *H*C(4)), 3.29 - 3.38 (4 H, m, NCH_2), 2.89 - 3.04 (4 H, m, CCH_2CH_2), 2.01 - 2.10 (4 H, m, NCH$_2$CH_2); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 148.0, 142.9, 142.3, 129.2, 128.5, 128.3, 125.8, 115.8, 111.9, 109.6, 47.7, 38.5, 38.1, 25.5; **FTIR** 2925, 1600, 1578, 1497, 1453, 1370, 1174, 1015, 908, 839, 770, 695 cm^{-1}; **HRMS** m/z $[C_{18}H_{21}N+H]^+$ cal. 252.1747, found 252.1736 (Δ + 4.0).

1-Phenylheptane-1,5-dione, 187

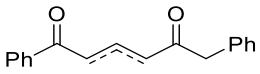


1-Phenylbut-3-en-1-ol (200 mg, 1.35 mmol), Zhan 1B catalyst (5 mol%) and 1-penten-3-one were subjected to General Procedure 3. The reaction mixture was heated for 24 h and then filtered using Petrol-Et$_2$O (1:1). Dess-Martin periodinane (200 mol%) was used for the oxidation step. Purification by flash column chromatography (petrol-EtOAc, 7:3) afforded *unsaturated dicarbonyl* **187** (199 mg, 66%, 1:0.7 rr) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.87 - 8.00 (3.4 H, m, Ar*H*), 7.53 - 7.63 (1.7 H, m, Ar*H*), 7.43 - 7.52 (3.4 H, m, Ar*H*), 7.03 - 7.14 (1.7 H, m, CH$_2$C*H*), 6.92 (0.7 H, dt, *J*=15.7, 1.3 Hz, C*H*C(O)), 6.21 (1 H, dt, *J*=16.2, 1.4 Hz, C*H*C(O)), 3.91 (2 H, dd, *J*=6.8, 1.5 Hz, CHCH_2), 3.43 (1.4 H, dd, *J*=7.3, 1.0 Hz, CHCH_2), 2.63 (2 H, q, *J*=7.3 Hz, CH_2CH$_3$), 2.53 (1.4 H, q, *J*=7.2 Hz, CH_2CH$_3$), 1.05 - 1.14 (5.1 H, m, CH_3); **^{13}C NMR** (100 MHz, CHLOROFORM-*d*) δ ppm 207.1, 200.6, 196.3, 190.4, 140.3, 138.5, 137.4, 136.1, 133.7, 133.3, 132.9, 129.2, 128.8, 128.6, 128.6, 128.2, 45.9, 41.7, 36.2, 32.9, 8.0, 7.6; **FTIR** 2977,

1672, 1622, 1597, 1579, 1448, 1341, 1269, 1202, 1111, 979, 753, 691 cm^{-1}; **HRMS** m/z $[C_{13}H_{14}O_2+Na]^+$ cal.225.0886, found 225.0880 (Δ + 2.7).

(*E*)-1,6-Diphenylhex-2-ene-1,5-dione, 193



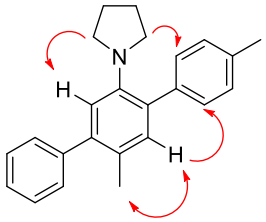
$ZnCl_2$ (11 mL, 1.0 M in Et_2O, 11 mmol) was added to a solution of $PhCH_2MgBr$ ((10 mL, 1.0 M in Et_2O, 10 mmol) at room temperature to give a white suspension of $PhCH_2ZnCl$. This suspension was then added to a solution of acrylolyl chloride (1.00 g, 11.0 mmol) and $Pd(PPh_3)_4$ (578 mg, 0.500 mmol) in THF (5 mL) cooled to 0 °C. The mixture was then stirred for 30 minutes at 0 °C, then quenched with a small amount of water. The mixture was diluted with hexane and filtered. The filtrate was concentrated and passed for a short plug of silica (9:1) to give 4-phenyl-1-buten-3-one **192**[167] which was used without further purification. **^{1}H NMR** (200 MHz, *CHLOROFORM-d*) δ ppm 7.07 - 7.60 (5 H, m, Ar*H*), 6.02 - 6.57 (2 H, m, CH=CH_2), 5.84 (1 H, dd, *J*=9.2, 2.4 Hz, C*H*=CH_2), 3.89 (2 H, s, CH_2).

1-Phenylbut-3-en-1-ol (100 mg, 0.676 mmol), Zhan 1B catalyst (10 mol%) and 4-phenyl-1-buten-3-one (500 mg, 3.37 mmol) were subjected to General Procedure 3. In a modification to the General Procedure a further portion of Zhan 1B catalyst (5 mol%) was added after 24 hours. The reaction mixture was heated for 48 hours and then filtered using Petrol-Et_2O (1:1). Dess-Martin periodinane (250 mol%) was used for the oxidation step. Purification by flash column chromatography (petrol-EtOAc, 7:3) afforded *unsaturated dicarbonyl* **193** (68 mg, 43 %, 1:0.8 rr) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.86 (2 H, d, *J*=7.3 Hz, Ar*H*), 7.81 (1.6 H, d, *J*=7.1 Hz, Ar*H*), 7.44 - 7.57 (1.8 H, m, Ar*H*), 7.38 (3.6 H, q, *J*=7.9 Hz, Ar*H*), 7.06 - 7.31 (9 H, m, Ar*H*), 6.87 - 7.02 (1.8 H, m, CH_2C*H*), 6.77 (0.8 H, d, *J*=15.4 Hz, CH=C*H*), 6.18 (1 H, d, *J*=16.1 Hz, CH=C*H*), 3.78 - 3.84 (3.6 H, m), 3.70 (1.6 H, s), 3.38 (2 H, d, *J*=7.1 Hz),

contains approximately 10% of unknown impurity; **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 204.2, 197.1, 196.2, 190.5, 140.0, 139.9, 137.5, 136.1, 134.2, 133.7, 132.9, 132.5, 129.5, 129.5, 129.4, 129.0, 128.8, 128.8, 128.7, 128.7, 128.6, 128.3, 127.4, 127.0, 50.2, 47.3, 45.1, 41.7; **FTIR** 3030, 1683, 1624, 1598, 1580, 1496, 1449, 1271, 1210, 983, 751, 699 cm^{-1}; **HRMS** m/z $[C_{18}H_{16}O_2+Na]^+$ cal.287.1043, found 287.1031 (Δ + 4.0).

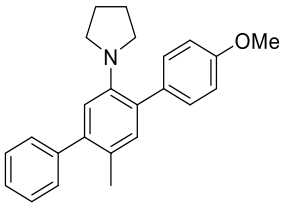
1-(4,5'-Dimethyl-[1,1':4',1''-terphenyl]-2'-yl)pyrrolidine, 196



Unsaturated 1,5-dicarbonyl **142** (42 mg, 0.21 mmol) and 4-bromotoluene were subjected to General Procedure 7. The crude material was filtered through a cartridge of SiO_2 (petrol-EtOAc 8:2) and then subjected to General Procedure 5. In a modification to the General Procedure $ZnCl_2$ (0.21 mL, 1.0 M in Et_2O, 0.21 mmol) was added Purification by flash column chromatography (petrol-EtOAc 1:0 to 19:1) afforded *arylamine* **196** (24 mg, 35%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.34 (6 H, m, ArH), 7.27 (1 H, m, ArH), 7.11 (2 H, m, ArH), 7.01 (1 H, s, C, *H*C(5)), 6.70 (1 H, s, *H*C(2)), 2.83 (4 H, br. s, NC*H*$_2$), 2.30 (3 H, m, TolC*H*$_3$), 2.14 (3 H, s, C*H*$_3$), 1.66 (4 H, br. s, NCH$_2$C*H*$_2$) *NOE enhancements associated with arylamine **196** are represented by red arrows on the compound structure; the product proved to be quite unstable and a satisfactory 13C spectra could not be obtained;* **FTIR**: 3019, 3029, 1599, 1573, 1488, 1452, 1418, 1327, 1232, 1074, 1026, 908, 856, 785, 755, 735, 697 cm^{-1}; **HRMS** m/z $[C_{24}H_{25}N+H]^+$ cal. 328.2060, found 328.2052 (Δ + 2.5).

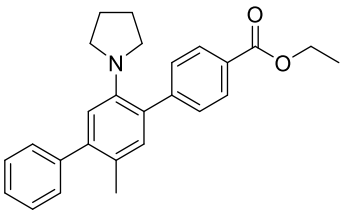
Ethyl 5'-methyl-2'-(pyrrolidin-1-yl)-[1,1':4',1''-terphenyl]-4-carboxylate, 198



Unsaturated 1,5-dicarbonyl **142** (40 mg, 0.20 mmol) and 4-bromoanisole were subjected to General Procedure 7. The crude material was filtered through a cartridge of SiO_2 (petrol-EtOAc 1:0 to 4:1) and then subjected to General Procedure 5. In a modification to the General Procedure $ZnCl_2$ (0.20 mL, 1.0 M in Et_2O, 0.20 mmol) was added Purification by flash column chromatography (petrol-EtOAc 1:0 to 19:1) afforded *arylamine* **198** (20 mg, 32%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.36 (m, 6 H, Ar*H*), 7.26 (m, 2 H, ArH), 7.01 (s, 1 H, *H*C(2)), 6.87 (m, 2 H, Ar*H*), 3.77 (m, 3 H, OCH_3), 2.83 (br. s., 4 H, 2 x NCH_2), 2.12 (m, 3 H, CCH_3), 1.66 (br. s., 4 H, 2 x NCH_2CH_2); *the product proved to be unstable and a satisfactory 13C spectra could not be obtained;* **FTIR**: 2959, 1607, 1483, 1461, 1395, 1244, 1176, 1033, 909, 833, 773, 730, 703, 666 cm^{-1}; **HRMS** m/z $[C_{24}H_{25}NO+H]^+$ cal. 344.2009, found 344.2009 (Δ − 0.1).

Ethyl 5'-methyl-2'-(pyrrolidin-1-yl)-[1,1':4',1''-terphenyl]-4-carboxylate, 200

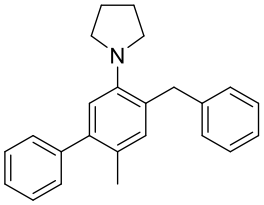


Unsaturated 1,5-dicarbonyl **200** (70 mg, 0.37 mmol) and 4-ethylbromobenzoate were subjected to General Procedure 7. The crude material was filtered through a cartridge of SiO_2 (petrol-EtOAc 9:1) and then subjected to General Procedure 5. In a modification to the General Procedure $ZnCl_2$ (0.37 mL, 1.0 M in Et_2O, 0.37 mmol) was added Purification by

flash column chromatography (petrol-EtOAc 1:0 to 19:1) afforded *arylamine* **200** (34 mg, 52%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.98 (2 H, d, *J*=8.6 Hz, Ar*H*), 7.51 (2 H, d, *J*=8.6 Hz, Ar*H*), 7.31 (m, 5 H, Ar*H*), 7.01 (1 H, m, Ar*H*), 6.72 (1 H, s, *H*C(2)), 4.32 (2 H, q, *J*=7.1 Hz, C*H*$_2$CH$_3$), 2.81 (4 H, m, NC*H*$_2$), 2.14 (s, 3 H, CC*H*$_3$), 1.66 (m, 4 H, NCH$_2$C*H*$_2$), 1.34 (3 H, t, *J*=7.1 Hz, CH$_2$C*H*$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 166.8, 147.7, 145.9, 142.2, 141.9, 133.9, 129.4, 129.2, 129.0, 128.3, 128.2, 128.1, 126.8, 125.2, 116.6, 60.9, 51.3, 25.4, 19.4, 14.4; **FTIR**: 1740, 1677, 1632, 1369, 1230, 1015, 975, 748 cm^{-1}; **HRMS** m/z [C$_{26}$H$_{27}$NO$_2$+H]$^+$ cal. 386.2115, found 386.2115 (Δ + 0.1).

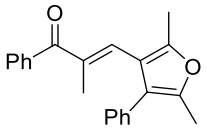
1-(4-Benzyl-6-methyl-[1,1'-biphenyl]-3-yl)pyrrolidine, 201



To a solution of unsaturated 1,5-dicarbonyl **142** (40 mg, 0.20 mmol), and benzyl bromide (101mg, 0.84 mmol, 70 μL) in THF (2 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (40 μL, 0.27 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc and extracted with saturated aq. NH$_4$Cl (2×). The aqueous layers were combined and extracted with EtOAc (2×). The organic extracts were combined and extracted with brine (20 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. The crude material was filtered through a cartridge of SiO$_2$ (petrol-EtOAc 1:0 to 4:1) and subjected to General Procedure 5. In a modification to the General Procedure ZnCl$_2$ (0.20 mL, 1.0 M in Et$_2$O, 0.20 mmol) was added. Purification by flash column chromatography (petrol-EtOAc 1:0 to 19:1) afforded *arylamine* **201** (42 mg, 68%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.23 (m, 10 H, Ar*H*), 6.89 (m, 2 H, *H*C(2) and Ar*H*), 4.06 (m, 2 H, CCH_2), 3.05 (br. s., 4 H, 2 x NCH_2), 2.07 (s, 3 H, CH_3), 1.82 (m, 4 H, 2 x NCH_2CH_2); *the product proved to be unstable and a satisfactory 13C spectra could not be obtained*; **FTIR**: 2964, 1601, 1542, 1487, 1452, 1395, 1074, 908, 770, 729, 702 cm^{-1}; **HRMS** m/z $[C_{24}H_{25}N+H]^+$ cal. 328.2060, found 328.2064 (Δ − 2.1).

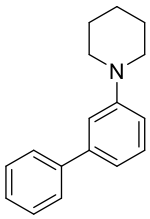
(*E*)-3-(2,5-Dimethyl-4-phenylfuran-3-yl)-2-methyl-1-phenylprop-2-en-1-one, 203



To a solution of 1,5-dicarbonyl **142** (40 mg, 0.20 mmol) and *trans*-β-methyl-β-nitrostyrene (**202**) (97 mg, 0.60 mmol) in THF (2 mL) was added 1,8-diazabicycloundec-7-ene (DBU) (33 mg, 0.22 mmol). The reaction was stirred for 1 hour then diluted with ethyl acetate and a saturated solution of NH_4Cl. The aqueous layer was washed with ethyl acetate (3x) and the organic layers combined, dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (petrol-CH_2Cl_2, 3:2) afforded *furan* **203** (30 mg, 51%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.50 - 7.61 (2 H, m, Ar*H*), 7.12 - 7.42 (8 H, m, Ar*H*), 6.75 (1 H, s, C=C*H*), 2.25 (3 H, s, CH_3), 2.17 (3 H, s, CH_3), 1.84 (3 H, s, CH_3); **^{13}C NMR** (*CHLOROFORM-d*) δ ppm 199.0, 147.3, 146.9, 138.4, 137.7, 135.4, 133.5, 131.6, 129.4, 129.0, 128.4, 128.1, 126.7, 121.7, 117.0, 14.9, 13.5, 12.3; **FTIR**: 2919, 1647, 1599, 1496, 1445, 1352, 1268, 1190, 1074, 1012, 938, 761, 700, 636 cm^{-1}; **HRMS** m/z $[C_{22}H_{20}O_2+Na]^+$ cal. 339.1356, found 339.1361 (Δ − 1.6).

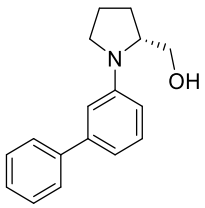
1-([1,1'-Biphenyl]-3-yl)piperidine, 208



Unsaturated 1,5-dicarbonyl **133 (**40 mg, 0.21 mmol) and piperidine were subjected to General Procedure 4. In a modification to the General Procedure $ZnCl_2$ (0.21 mL, 1.0 M in Et_2O, 0.21 mmol) was added. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **208** (36 mg, 72%) as a colourless oil.

^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.60 (2 H, d, *J*=7.3 Hz, Ar*H*), 7.39 - 7.47 (2 H, m, Ar*H*), 7.28 - 7.39 (2 H, m, Ar*H* & *H*C(5)), 7.18 (1 H, s, *H*C(2)), 7.07 (1 H, d, *J*=7.6 Hz, *H*C(6)), 6.97 (1 H, d, *J*=6.9 Hz, *H*C(4)), 3.17 - 3.31 (4 H, m, NCH_2), 1.67 – 1.87 (4 H, m, NCH_2CH_2), 1.54 - 1.65 (2 H, m, $NCH_2CH_2CH_2CH_2$); **^{13}C NMR** (125 MHz, *CHLOROFORM-d*) δ ppm 152.7, 142.2, 141.9, 129.4, 128.6, 127.3, 127.1, 118.4, 115.7, 115.6, 50.9, 25.8, 24.3. Data were consistent with those previously reported.[168]

(1-([1,1'-Biphenyl]-3-yl)pyrrolidin-2-yl)methanol, 209

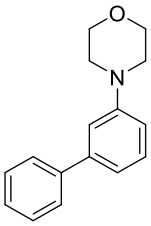


Unsaturated 1,5-dicarbonyl **133 (**50 mg, 0.27 mmol) and D-prolinol were subjected to General Procedure 4. In a modification to the General Procedure $ZnCl_2$ (0.27 mL, 1.0 M in Et_2O, 0.27 mmol) was added. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **209** (43 mg, 66%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.58 - 7.69 (2 H, m, Ar*H*), 7.46 (2 H, t, *J*=7.6 Hz, Ar*H*), 7.29 - 7.41 (2 H, m, Ar*H* & *H*C(5)), 6.98 (1 H, d, *J*=7.6 Hz, *H*C(6)), 6.92

(1 H, s, *H*C(2)), 6.74 (1 H, d, *J*=8.1 Hz, *H*C(4)), 3.96 (1 H, d, *J*=4.0 Hz, NC*H*), 3.66 - 3.79 (2 H, m, CH_2O), 3.59 (1 H, t, *J*=7.6 Hz, NCH_aH$_b$), 3.18 - 3.35 (1 H, m, NCH$_a$$H_b$), 1.97 - 2.21 (4 H, m, CHCH_2CH_2), 1.84 (1 H, br. s, O*H*); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 148.4, 142.5, 142.1, 129.6, 128.7, 127.4, 127.2, 115.7, 111.4, 111.3, 63.8, 60.2, 49.6, 28.8, 23.8; **FTIR** 3373, 2952, 1597, 1569, 1487, 1427, 1365, 1261, 1174, 1037, 1174, 1037, 993, 908, 756, 732, 699 cm^{-1}; **HRMS** m/z [$C_{17}H_{19}NO$+H]$^+$ cal. 254.1539, found 254.1539 (Δ + 0.3); **specific rotation** $[\alpha]_D^{20}$ – 18.5 (CH_2Cl_2, c = 0.2). **Chiral HPLC conditions:** Chiral AD column; flow rate = 1.0 mL/min; rt, 9:1 hept/*i*PrOH; retention time: 25.69 min. Racemic material was also synthesised.

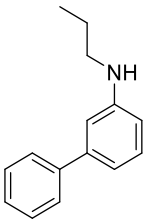
4-([1,1'-Biphenyl]-3-yl)morpholine, 215



Unsaturated 1,5-dicarbonyl **133 (**30 mg, 0.16 mmol) and morpholine were subjected to General Procedure 5. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **215** (30 mg, 78%) as a colourless oil.

^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.60 (2 H, d, J=6.9 Hz, Ar*H*), 7.45 (2 H, t, J=7.3Hz, Ar*H*), 7.34 – 7.40 (2 H, m, Ar*H* & *H*C(5)), 7.11 - 7.18 (2 H, m, *H*C(2) & *H*C(6)), 6.94 (1 H, d, *J*=7.3 Hz, *H*C(4)), 3.91 (4 H, t, *J*=4.5 Hz, CH_2), 3.25 (4 H, t, *J*=4.5 Hz, CH_2); **^{13}C NMR** (125 MHz, *CHLOROFORM-d*) δ ppm 152.1, 142.9, 142.1, 130.0, 129.1, 127.7 (2C), 119.7, 115.3, 115.2, 67.4, 50.0. Data were consistent with those previously reported.[169]

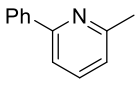
***N*-Propyl-[1,1'-biphenyl]-3-amine, 221**



Unsaturated 1,5-dicarbonyl **133 (**30 mg, 0.16 mmol) and propylamine were subjected to General Procedure 5. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **221** (24 mg, 71%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.61 (2 H, d, *J*=7.6 Hz, Ar*H*), 7.45 (2 H, t, *J*=7.6 Hz, Ar*H*), 7.32 - 7.40 (1 H, m, Ar*H*), 7.27 (1 H, t, *J*=7.8 Hz, *H*C(5)), 6.95 (1 H, d, *J*=7.6 Hz, *H*C(6)), 6.84 (1 H, s, *H*C(2)), 6.64 (1 H, d, *J*=8.1 Hz, *H*C(4)), 3.75 (1 H, br. s, N*H*), 3.17 (2 H, t, *J*=7.5 Hz, NCH_2), 1.70 (2 H, sxt, *J*=7.5 Hz, CH_3CH_2), 1.05 (3 H, t, *J*=7.5 Hz, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 148.9, 142.4, 141.9, 129.6, 128.6, 127.2, 127.1, 116.3, 111.8, 111.5, 45.9, 22.8, 11.7; **FTIR** 2961, 1601, 1573, 1488, 1330, 1229, 908, 756, 731, 698, 649 cm^{-1}; **HRMS** m/z $[C_{15}H_{17}N]^+$ cal. 212.143, found 212.1434 (Δ – 0.1).

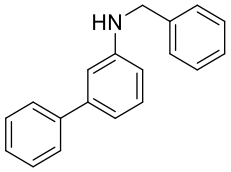
2-Methyl-6-phenylpyridine, 228



$NH_{3(g)}$ (0.5 mL) was condensed into a microwave vial cooled to − 78°C. Unsaturated 1,5-dicarbonyl **133** (20 mg, 0.11 mmol) in CH_2Cl_2 (2.0 mL) was then added and the solution allowed to warm to room temperature, then heated to 55 °C for 12 hours. The reaction mixture was then concentrated and purified by flash column chromatography (petrol-EtOAc, 19:1 to 9:1) to give *pyridine* **228** (8 mg, 42%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.00 (2 H, d, *J*=7.6 Hz, Ar*H*), 7.61 - 7.68 (1 H, m, Ar*H*), 7.45 - 7.55 (3 H, m, Ar*H*), 7.38 - 7.45 (1 H, m, Ar*H*), 7.11 (1 H, d, *J*=7.6 Hz, Ar*H*), 2.65 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 158.4, 157.0, 139.8, 136.9, 128.7 (2C), 127.0, 121.6, 117.7, 24.8. Data were consistent with those previously reported.[170]

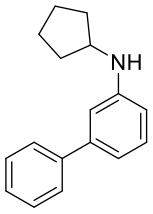
***N*-Benzyl-[1,1'-biphenyl]-3-amine, 239**



Unsaturated 1,5-dicarbonyl **133 (**40 mg, 0.21 mmol) and benzylamine were subjected to General Procedure 5. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **239** (42 mg, 78%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.59 (2 H, d=7.6,Ar*H*), 7.23 – 7.48 (9 H, m, Ar*H*), 6.99 (1 H, d, *J*=7.8 Hz, *H*C(6)), 6.89 (1 H, t, *J*=2.0 Hz, *H*C(2)), 6.66 (1 H, d, *J*=8.0 Hz, *H*C(4)), 4.42 (2 H, s, CH_2), 4.15 (1 H, br. s, N*H*); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 148.5, 142.4, 141.7, 139.4, 129.7, 128.7, 128.6, 127.6, 127.3, 127.2 (2C), 116.8, 111.9, 111.7, 48.4; **FTIR** 2965, 1601, 182, 1394, 1355, 1322, 1183, 1134, 908, 821, 731, 703 cm^{-1}; **HRMS** m/z $[C_{19}H_{17}N+H]^+$ cal. 260.1434, found 260.1431 (Δ + 1.2).

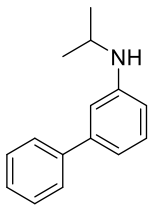
***N*-Cyclopentyl-[1,1'-biphenyl]-3-amine, 240**



Unsaturated 1,5-dicarbonyl **133 (**35 mg, 0.19 mmol) and cyclopentanamine were subjected to General Procedure 5. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **240** (29 mg, 67%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.61 (2 H, d, *J*=6.3, Ar*H*), 7.45 (2 H, t, *J*=7.3 Hz, Ar*H*), 7.35 (1 H, t, *J*=7.3, Ar*H*), 7.22 – 7.30 (1 H, m, *H*C(5)), 6.94 (1 H, d, *J*=8.8, *H*C(2)), 6.84 (1 H, s, *H*C(2)), 6.63 (1 H, d, *J*=9.3, *H*C(4)), 3.88 (1 H, quin, *J*=6.2 Hz, NC*H*), 3.77 (1 H, br. s, N*H*), 2.03 – 2.16 (2 H, m, NCH_aH$_b$), 1.60 – 1.85 (4 H, m, NCH$_2$CH_2), 1.48 – 1.59 (2 H, m, NCH$_a$$H_b$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 148.4, 142.4, 141.9, 129.6, 128.6, 127.2, 127.1, 116.1, 112.2, 112.0, 54.7, 33.7, 24.1; **FTIR** 2954, 1600, 1573, 1484, 1445, 1417, 1332, 1231, 991, 908, 855, 784, 755, 698, 615 cm^{-1}; **HRMS** m/z [C$_{17}$H$_{19}$N+H]$^{+}$ cal. 238.1590, found 238.1584 (Δ + 2.6).

***N*-Isopropyl-[1,1'-biphenyl]-3-amine, 241**

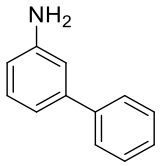


Unsaturated 1,5-dicarbonyl **133 (**30 mg, 0.16 mmol) and isopropylamine were subjected to General Procedure 5. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **241** (18 mg, 55%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.59 (2 H, d, *J*=7.3 Hz, Ar*H*), 7.43 (2 H, t, *J*=7.1 Hz, Ar*H*), 7.26-7.41 (1 H, m, Ar*H*), 7.25 (1 H, t, *J*=8.1 Hz, *H*C(5)), 6.92 (1 H, d, *J*=7.1 Hz, *H*C(6)), 6.81 (1 H, s, *H*C(2)), 6.60 (1 H, d, *J*=8.1 Hz, *H*C(4)), 3.72 (1 H, quin, *J*=6.2 Hz, NC*H*), 1.26 (6 H, d, *J*=6.3 Hz, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 147.8, 142.4, 141.9, 129.6, 128.6, 127.2, 127.1, 116.2, 112.3, 112.1, 44.3, 23.1; **FTIR**

2961, 1601, 1573, 1488, 1330, 1229, 908, 756, 731, 698, 649 cm^{-1}; **HRMS** m/z [$C_{15}H_{17}N$+H] cal.212.1434, found 212.1434 (Δ + 4.3).

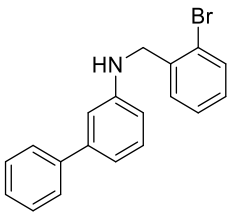
[1,1'-Biphenyl]-3-amine, 242



To a solution of arylamine **239** (15 mg, 0.07 mmol) in MeOH (1 mL) was added Pd/C (10 wt.%, 15 mg, 0.014 mmol). The reaction flask was then evacuated and refilled with H_2 three times. The reaction mixture was then stirred at room temperature for 2 hours and filtered through celite. The filtrate was then concentrated and purified by flash column chromatography (petrol-EtOAc,4:1) to give *aniline* **242** (11 mg, 92 %) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) d ppm 7.58 (2 H, d, *J*=7.3 Hz, Ar*H*), 7.43 (2 H, t, *J*=7.6 Hz, Ar*H*), 7.30 - 7.39 (1 H, m, Ar*H*), 7.25 (1 H, t, *J*=8.3 Hz, *H*C(5)), 7.01 (1 H, d, *J*=7.8 Hz, *H*C(6)), 6.93 (1 H, s, *H*C(2)), 6.70 (1 H, d, *J*=7.9 Hz, *H*C(4)); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) d ppm 146.7, 142.5, 141.4, 129.7, 128.7, 127.3, 127.1, 117.7, 114.1, 114.0. Data were consistent with those previously reported.[171]

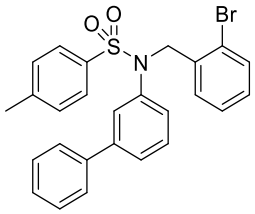
***N*-(2-Bromobenzyl)-[1,1'-biphenyl]-3-amine, 244**



Unsaturated 1,5-dicarbonyl **133 (**35 mg, 0.19 mmol) and (2-bromophenyl)methanamine were subjected to General Procedure 5. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **244** (44 mg, 72%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.43 - 7.63 (3 H, m, Ar*H*), 7.31 - 7.43 (3 H, m, Ar*H*), 7.23 - 7.31 (1 H, m, Ar*H*), 7.12 - 7.23 (2 H, m, Ar*H*), 7.07 (1 H, t, *J*=8.6 Hz, Ar*H*), 6.92 (1 H, d, *J*=7.8 Hz, *H*C(6)), 6.79 (1 H, t, *J*=1.9 Hz, *H*C(2)), 6.54 (1 H, d, *J*=8.1 Hz, *H*C(4)), 4.40 (2 H, s, CH_2), 4.17 (1 H, br. s, N*H*); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 148.0, 142.4, 141.6, 138.1, 132.9, 129.7, 129.3, 128.8, 128.6, 127.6, 127.2, 127.2, 123.3, 117.0, 111.9, 111.9, 48.5; **FTIR** 3423, 3058, 1601, 1573, 1516, 1486, 1441, 1328, 1231, 1025, 908, 755, 732, 699 cm^{-1}; **HRMS** m/z $[C_{19}H_{16}BrN+H]^+$ cal.338.0539, found 338.0538 (Δ + 0.4).

_N_-([1,1'-Biphenyl]-3-yl)-_N_-(2-bromobenzyl)-4-methylbenzenesulfonamide, 245

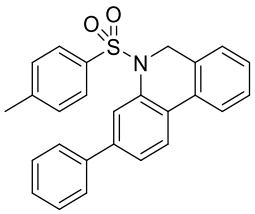


4-Toluenesulfonyl chloride (166 mg, 0.874 mmol) was added in one portion to *N*-(2-bromobenzyl)-[1,1'-biphenyl]-3-amine **244** (98 mg, 0.29 mmol) in pyridine (3.0 mL) at room temperature. The resulting solution was stirred at 80 °C for 12 hours. The reaction mixture was concentrated and the crude product purified by flash column chromatography (petrol-EtOAc, 1:0 to 8:2) to afford *arylamine* **245** (143 mg, 90 %) as a tan foam.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.63 (2 H, d, *J*=7.6 Hz, Ar*H*), 7.58 (2 H, d, *J*=8.1 Hz, Ar*H*), 7.34 - 7.44 (5 H, m, Ar*H*), 7.21 - 7.34 (6 H, m, Ar*H*), 6.95 - 7.10 (2 H, m, Ar*H*), 4.92 (2 H, s, CH_2), 2.42 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 143.7, 142.0, 140.1, 139.7, 135.4, 135.4, 132.6, 130.4, 129.6, 129.2, 129.0, 128.8, 127.9, 127.6, 127.6, 127.4, 127.4, 127.0, 126.6, 123.2, 54.2, 21.5; **FTIR** 3035, 1597, 1478, 1349, 1164, 1091, 1024, 880, 811, 756, 701, 658, 638 cm^{-1}; **HRMS** m/z

$[C_{26}H_{22}BrNO_2S+Na]^+$ cal. 514.0433, found 514.0447 (Δ + 2.7); **m.p.** 117-119 (CH_2Cl_2:petrol).

3-Phenyl-5-tosyl-5,6-dihydrophenanthridine, 246

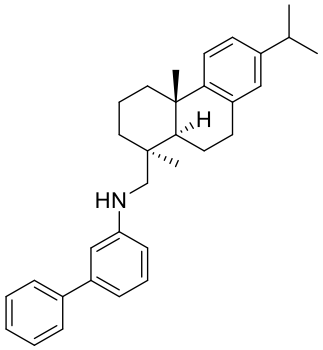


Crushed potassium carbonate (56 mg, 0.41 mmol), 1-phenyl-5-tosyl-5,6-dihydrophenanthridine **245** (80 mg, 0.16 mmol), palladium acetate (2.0 mg, 0.01 mmol)and tricyclohexylphosphonium tetrafluoroborate (7.0 mg, 0.02 mmol) were placed in a microwave vial equipped with a magnetic follower. The vial was purged with argon and degassed *N*,*N*-dimethylacetamide (1.0 mL) was added. The reaction was heated to 130 ºC for 18 hours. The reaction mixture was then loaded directly onto silica and purified by flash column chromatography (petrol-EtOAc, 0:1 to 4:6) to give the desired product gave *tricycle* **246** (80 mg, 96 %) as a white dry film.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.08 (1 H, d, *J*=1.8 Hz, Ar*H*), 7.71 (2 H, d, *J*=7.1 Hz, Ar*H*), 7.63 (1 H, d, *J*=8.1 Hz, Ar*H*), 7.57 (1 H, dd, *J*=8.1, 1.8 Hz, Ar*H*), 7.47 (2 H, t, *J*=7.6 Hz, Ar*H*), 7.38 (1 H, t, *J*=7.6 Hz, Ar*H*), 7.23 - 7.28 (1 H, m, Ar*H*), 7.05 - 7.18 (3 H, m, Ar*H*), 7.00 (2 H, d, *J*=8.1 Hz, Ar*H*), 6.69 (2 H, d, *J*=8.1 Hz, Ar*H*), 4.88 (2 H, s, CH_2), 2.14 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 142.9, 141.2, 139.8, 136.5, 134.8, 131.3, 130.8, 129.4, 128.9, 128.4, 127.8, 127.8, 127.6, 127.1, 127.1, 126.5, 126.1, 125.9, 124.1, 122.8, 50.0, 21.2; **FTIR** 1598, 1479, 1455, 1406, 1345, 1161, 1088, 1071, 1027, 899, 834, 812, 777, 760, 739, 689, 665, 629 cm^{-1}; **HRMS** m/z $[C_{26}H_{21}NO_2S+Na]^+$ cal. 434.1179, found 434.1185 (Δ + 2.2); **m.p.** 158-160 °C

(CH_2Cl_2:petrol); single crystal X-ray diffraction data also collected for this compound, see appendix 2.

***N*-(((1*S*,4a*S*,10a*R*)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)-[1,1'-biphenyl]-3-amine, 249**



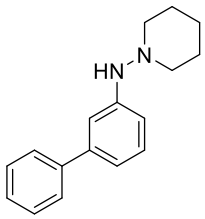
Method A Unsaturated 1,5-dicarbonyl **133 (**40 mg, 0.21 mmol) and (+)-dehydroabietylamine were subjected to General Procedure 5. In a modification to the General Procedure $ZnCl_2$ (1.0 M in Et_2O, 0.216 mmol) was added. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **249** (62 mg, 64%) as a colourless oil.

Method B (+)-Dehydroabietylamine (120 mg, 0.421 mmol) and $ZnCl_2$ (1.0 M in Et_2O, 0.053 mmol) were dissolved in DCE (1.0 mL) and heated to 55 °C. To this solution, unsaturated 1,5-dicarbonyl **133** (50 mg, 0.28 mmol) was added dropwise over 12 hours. The reaction mixture was stirred for a further 6 hours, cooled and then concentrated. The crude product was purified by flash column chromatography (petrol - EtOAc, 98:2) to yield *arylamine* **249** (52 mg, 54%).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.49 (2 H, d, *J*=7.3 Hz, Ar*H*), 7.33 (2 H, t, *J*=7.5 Hz, Ar*H*), 7.20 - 7.27 (1 H, m, Ar*H*), 7.09 - 7.17 (2 H, m, Ar*H*), 6.93 (1 H, d, *J*=7.1 Hz, *H*C(6)), 6.78 - 6.84 (2 H, m, Ar*H*), 6.72 (1 H, s, *H*C(2)), 6.51 (1 H, dd, *J*=8.1, 1.7 Hz, *H*C(4)), 3.63 (1 H, br. s, N*H*), 3.03 (1 H, d, *J*=12.2 Hz, NCH_aH_b), 2.88 (1 H, d, *J*=12.2 Hz,

NCH_aH_b), 2.69 - 2.84 (3 H, m, CH_3CH and $ArCH_2$), 2.23 (1 H, d, *J*=13.0 Hz, CC*H*), 1.53 - 1.82 (5 H, m, CH_2), 1.30 - 1.47 (3 H, m, CH_2), 1.16 (6 H, d, *J*=4.6 Hz, $C(CH_3)$), 1.14 (3 H, s, CH_3), 0.95 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 149.3, 147.4, 145.7, 142.5, 141.9, 134.7, 129.6, 128.6, 127.2, 127.1, 126.9, 124.3, 124.0, 116.1, 111.8, 111.4, 54.9, 53.4, 45.4, 38.4, 37.6, 37.6, 36.4, 33.5, 30.1, 25.4, 24.0, 19.4, 19.0, 18.8; **FTIR** 2928, 1600, 1573, 1489, 1383, 1228, 908, 823, 755, 732, 698 cm^{-1}; **HRMS** m/z $[C_{32}H_{39}N+H]^+$ cal.438.3155, found 438.3146 (Δ − 2.2); **specific rotation** $[\alpha]_D^{20}$ – 18.5 (CH_2Cl_2, c = 0.2).

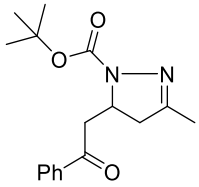
***N*-([1,1'-Biphenyl]-3-yl)piperidin-1-amine, 250**



Unsaturated 1,5-dicarbonyl **133 (**30 mg, 0.17 mmol) and piperidin-1-amine were subjected to General Procedure 5. In a modification to the General Procedure the reaction was heated to 85 °C. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **250** (35 mg, 81%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.59 - 7.65 (2 H, m, Ar*H*), 7.45 (2 H, t, *J*=7.6 Hz, Ar*H*), 7.32 - 7.38 (1 H, m, Ar*H*), 7.25 - 7.31 (1 H, m, Ar*H*), 7.16 (1 H, t, *J*=1.8 Hz, *H*C(2)), 7.03 (1 H, d, *J*=7.6 Hz, *H*C(6)), 6.88 - 6.94 (1 H, m, *H*C(4)), 4.49 (1 H, br. s, N*H*), 2.71 (4 H, s, NCH_2), 1.72 (4 H, quin, *J*=5.6 Hz, NCH_2CH_2), 1.46 (2 H, s, $NCH_2CH_2CH_2$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 148.2, 142.2, 141.8, 129.5, 128.6, 127.2, 127.1, 118.3, 112.7, 112.3, 57.4, 26.1, 23.7; **FTIR** 2935, 2853, 2728, 1602, 1573, 1479, 1443, 1265, 1216, 1153, 1036, 872, 790, 757, 699 cm^{-1}; **HRMS** m/z $[C_{17}H_{20}N_2+H]^+$ cal. 253.1691, found 253.1699 (Δ + 3.4).

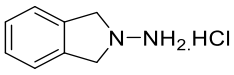
***tert*-Butyl 3-methyl-5-(2-oxo-2-phenylethyl)-4,5-dihydro-1*H*-pyrazole-1-carboxylate, 255**



Unsaturated 1,5-dicarbonyl **133 (**10 mg, 0.058 mmol) and *tert*-butyl carbazate were subjected to General Procedure 5. Purification by flash column chromatography (petrol-EtOAc, 9:1 to 3:1) afforded *dihydropyrazole* **255** (4 mg, 24%) as a colourless oil.

^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.98 (1 H, dd, *J*=8.4, 1.1 Hz, Ar*H*), 7.59 (1 H, t, *J*=7.3 Hz, Ar*H*), 7.48 (1 H, t, *J*=7.9 Hz, Ar*H*), 4.67 - 4.80 (1 H, m, NC*H*), 3.86 (1 H, br. s., C(O)CH_aH$_b$), 3.19 (1 H, dd, *J*=18.3, 11.3 Hz, C(NR)CH_aH$_b$), 3.04 (1 H, dd, *J*=16.4, 10.1 Hz, C(O)CH$_a$$H_b$), 2.54 (1 H, dd, *J*=18.3, 5.4 Hz, C(NR)CH$_a$$H_b$), 2.03 (3 H, s, C(NR)C$H_3$), 1.63 (3 H, br. s., CHC$H_{3(rot\ a)}$), 1.55 (6 H, s, CHC$H_{3(rot\ b)}$). **^{13}C NMR** (125 MHz, *CHLOROFORM-d*) δ ppm 198.1, 155.6, 151.9, 136.5, 133.5, 128.7, 128.1, 81.3, 54.4, 43.0, 28.4, 16.2; **m/z** (ESI$^+$) 325.1 [100, (M + Na)$^+$].

Isoindolin-2-amine hydrochloride, 257

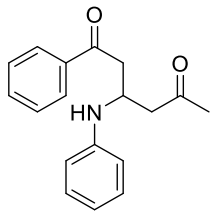


Triethylamine (5.28 mL, 37.8 mmol) was added dropwise to a stirred solution of 1,2-bis(bromomethyl)benzene (5.00 g, 18.9 mmol), and tert-butyl hydrazinecarboxylate (2.50 g, 18.9 mmol) in DMF (10 mL) and the solution warmed to 50°C, over 7 minutes under air. The resulting solution was left at room temperature for 18 hours. Water (40 mL) was added to form a green/white precipitate. This was left for 1 hour and then filtered. This solid was left to dry under air for 30 minutes to yield *tert-butyl isoindolin-2 ylcarbamate* **255**[172] as a

white/green solid which was used without further purification. **^{1}H NMR** (200 MHz, *CHLOROFORM-d*) δ ppm 7.25 - 7.08 (4H, m, Ar*H*), 4.04 (4H, s, CH_2), 3.40 (2H s, NH_2). To a concentrated solution of aqueous HCl was added hydrazine (3.32 g, 14.2 mmol). The reaction was left to stand for 12 h. The resulting suspension was concentrated to yield crude product as its HCl salt **258** (240 mg, 13 %) which was used without further purification.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.20 (4H, s, Ar*H*), 4.36 (4H, s, CH_2), 3.47 (9H s, C(CH_3)$_3$). Data were consistent with those previously reported.[172]

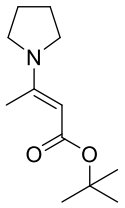
1-Phenyl-3-(phenylamino)hexane-1,5-dione, 262



Unsaturated 1,5-dicarbonyl **133 (**60 mg, 0.35 mmol) and aniline were subjected to General Procedure 5. Purification by flash column chromatography (petrol-EtOAc, 9:1 to 3:1) afforded *aniline adduct* **262** (32 mg, 33%) as a colourless oil.

^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.93 - 7.98 (2 H, m, Ar*H*), 7.53 - 7.61 (1 H, m, Ar*H*), 7.43 - 7.49 (2 H, m, Ar*H*), 7.14 - 7.21 (2 H, m, Ar*H*), 6.68 - 6.77 (1 H, m, Ar*H*), 6.63 - 6.67 (2 H, m, Ar*H*), 4.40 (1 H, quin, *J*=5.7 Hz, NC*H*), 3.38 (2 H, dd, *J*=5.7, 1.9 Hz, CHCH_2), 2.92 (2 H, d, *J*=5.7 Hz, CHCH_2), 2.12 - 2.16 (3 H, m, CH_3); **^{13}C NMR** (125 MHz, *CHLOROFORM-d*) δ ppm 208.5, 199.4, 146.4, 136.7, 133.4, 129.4, 128.7, 128.1, 118.1, 113.9, 46.6, 46.4, 41.3, 30.6; **FTIR**: 3370, 3056, 1709, 1680, 1600, 1499, 1448, 1357, 1313, 1180, 1002, 752, 693 cm^{-1}; **HRMS** m/z [$C_{18}H_{19}NO_2$+Na] cal.304.1308, found 304.1303 (Δ − 1.0).

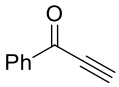
***(E)-tert*-Butyl 3-(pyrrolidin-1-yl)but-2-enoate, 279**



Pyrrolidine (6.74 g, 94.9 mmol) was added to a solution of *tert*-butylacetoacetate (5.00 g, 31.6 mmol), *p*-toluenesulfonic acid (25 mg) in toluene (60 mL) in a flask fitted with a Dean-Stark trap. The reaction was then heated to 140 °C for 18 hours. The reaction was allowed to cool and washed with H_2O (60 mL) and concentrated to give *enamine* **279** (5.72 g, 87 %) which was used without further purification.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 4.40 (1 H, s, C*H*), 3.27 (4 H, br. s, NCH_2), 2.42 (3 H, s. NCCH_3), 1.90 (4 H, t, *J*=6.4 Hz, NCH$_2$CH_2), 1.46 (9 H, s, OCCH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 169.2, 158.8, 85.1, 77.2, 47.8, 28.7, 25.2, 16.5. Data were consistent with those previously reported.[173]

1-Phenylprop-2-yn-1-one, 281

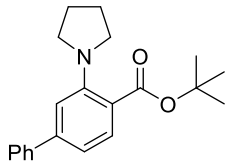


To a solution of DMP (3.80 g, 9.10 mmol) in CH_2Cl_2 (75 mL) cooled to 0 °C, was added 1-phenylprop-2-yn-1-ol (1.00 g, 7.58 mmol) and the reaction stirred for 1 h. A saturated solution of $NaHCO_3$ (75 mL) was added and the mixture extracted with Et_2O. The combined organic layers were filtered through celite, dried ($MgSO_4$), filtered and concentrated to give crude product which was purified by flash column chromatography (petrol-EtOAc,9:1) to give *ketone* **281** (726 mg, 74 %) as a white solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.12 - 8.22 (2 H, m, Ar*H*), 7.65 (1 H, tt, *J*=7.4, 1.4 Hz, Ar*H*), 7.47 - 7.55 (2 H, m, Ar*H*), 3.45 (1 H, s, C*H*); **^{13}C NMR** (100 MHz,

CHLOROFORM-d) δ ppm 177.4, 136.2, 134.6, 129.7, 128.7, 80.8, 80.3. Data were consistent with those previously reported.[174]

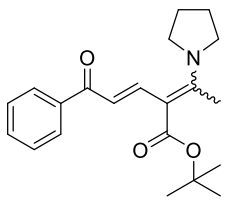
***tert*-Butyl 3-(pyrrolidin-1-yl)-[1,1'-biphenyl]-4-carboxylate, 283**



Enamine **279** (32 mg, 0.15 mmol) and ketone **281** (20 mg, 0.154 mmol) were dissolved in MeOH (1 mL). The reaction was heated to 50 °C for 18 hours and the concentrated. The crude reaction mixture was purified by flash column chromatography (petrol-EtOAc,19:1) to give *arylamine* **283** (32 mg, 90%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.62 (3 H, m, Ar*H*), 7.45 (2 H, t, *J*=7.5 Hz, Ar*H*), 7.37 (1 H, s, Ar*H*), 6.97 (1 H, s, *H*C(2)), 6.93 (1 H, d, *J*=8.1 Hz, *H*C(4)), 3.34 (4 H, m, NC*H*$_2$), 1.98 (4 H, m, NCH$_2$C*H*$_2$), 1.63 (9 H, s, C(C*H*$_3$)$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 168.1, 147.8, 144.3, 141.5, 131.4, 128.7, 127.6, 127.3, 118.2, 114.7, 112.8, 80.4, 50.9, 28.2, 26.0; **FTIR**: 2974, 1703, 1601, 1549, 1479, 1420, 1392, 1367, 1306, 1241, 1173, 1132, 1088, 978, 849, 758, 699 cm^{-1}; **HRMS** m/z [$C_{21}H_{25}NO_2$+H]$^+$ cal. 324.1958, found 324.1952 (Δ + 1.8).

2-(2-Acetylphenyl)cycloheptan-1-one, 282

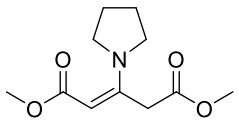


Enamine **279** (30 mg, 0.23 mmol) and ketone **281** (48 mg, 0.23 mmol) were dissolved in MeOH (2 mL). The reaction was stirred at room temperature for 2 hours and then

concentrated. The crude reaction mixture was purified by flash column chromatography (petrol-MeOH, 9:1) to give *enamine* **282** (70 mg, 90 %) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.93 (1 H, d, *J*=14.7 Hz, CH=C*H*CCN), 7.83 - 7.88 (2 H, m, Ar*H*), 7.31 - 7.44 (3 H, m, Ar*H*), 6.74 (1 H, d, *J*=14.7 Hz, C(O)C*H*), 3.40 - 3.53 (4 H, m, NCH_2), 2.34 (3 H, s, CH_3), 1.83 - 1.92 (4 H, m, NCH_2CH_2), 1.51 (9 H, s, $C(CH_3)_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 190.0, 167.4, 165.3, 144.1, 140.4, 131.2, 128.2, 127.9, 111.4, 101.9, 79.8, 52.8, 28.6, 25.3, 21.7; **FTIR** 2974, 1666, 1633, 1549, 1497, 1429, 1365, 1255, 1216, 1158, 1131, 1049, 1010, 923, 853, 790, 731, 704,659 cm^{-1}; **HRMS** m/z [$C_{21}H_{27}NO_3$+H] cal. 342.2064, found 342.2064 (Δ - 0.1).

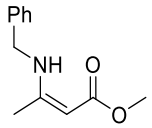
(*Z*)-Dimethyl 3-(pyrrolidin-1-yl)pent-2-enedioate, 286



To a solution of dimethyl-1,3-acetonedicarboxylate (6.05g, 34.7 mmol, 5.00 mL) in EtOH (30 mL) was added pyrrolidine (2.06 g, 34.7 mmol, 2.90 mL) and the reaction stirred for 12 h. The reaction mixture was concentrated and was purified by flash column chromatography (petrol-EtOAc,5:1 to 1:1) to give *enamine* **286** (6.80 g, 86 %) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 4.59 (1 H, s, C*H*), 4.14 (2 H, s, CH_2), 3.72 (3 H, s, OCH_3), 3.61 (3 H, s, OCH_3), 3.29 (4 H, br. s, NCH_2), 1.93 (4 H, br. s, NCH_2CH_2); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 170.1, 169.2, 154.5, 84.9, 52.2, 50.1, 47.9, 35.5, 25.1. Data were consistent with those previously reported.[175]

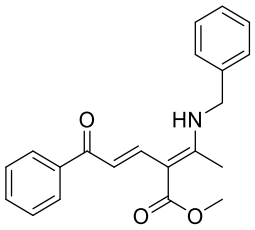
(*Z*)-Methyl 3-(benzylamino)but-2-enoate, 289



To a mixture of methylacetoacetate (1.00 g, 8.62 mmol) and benzylamine (1.38 g, 12.9 mmol, 1.35 mL) was added iodine (432 mg, 1.70 mmol). The reaction was stirred for 30 min and then diluted with CH_2Cl_2 and washed with water. The organic layer was dried (Na_2SO_4), filtered and concentrated to give *enamine* **289** (1.77 g, 100%)

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.98 (1 H, br. s, N*H*), 7.33 - 7.41 (2 H, m, Ar*H*), 7.25 - 7.33 (3 H, m, Ar*H*), 4.57 (1 H, s, C*H*), 4.45 (2 H, d, *J*=6.4 Hz, CH_2), 3.60 - 3.72 (3 H, m, OCH_3), 1.94 (3 H, s, CCH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 170.9, 162.0, 138.7, 128.8, 127.4, 126.7, 82.8, 50.0, 46.8, 19.4. Data were consistent with those previously reported.[176]

Methyl (2*E*,3*E*)-2-(1-(benzylamino)ethylidene)-5-oxo-5-phenylpent-3-enoate, 291

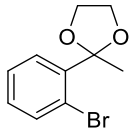


Enamine ***289*** (34 mg, 0.15 mmol) and ketone **281** (20 mg, 0.165 mmol) were dissolved in MeOH (1.5 mL). The reaction was stirred at room temperature for 2 hours and then concentrated. The crude reaction mixture was purified by flash column chromatography (petrol-MeOH, 9:1) to give *enamine* **291** (48 mg, quant.) as a red oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 11.05 (1 H, br. s., N*H*), 7.97 (1 H, d, *J*=14.9 Hz, NCCC*H*), 7.90 (2 H, d, *J*=7.6 Hz, Ar*H*), 7.34 - 7.47 (3 H, m, Ar*H*), 7.21 - 7.34 (4 H, m, Ar*H* and C(O)C*H*), 7.19 (2 H, d, *J*=7.1 Hz, Ar*H*), 4.52 (2 H, d, *J*=5.9 Hz, NCH_2), 3.75 (3 H, s, OCH_3), 2.24 (3 H, m, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm

190.9, 171.0, 168.2, 141.4, 139.9, 136.7, 131.6, 129.1, 128.3, 128.1, 128.0, 126.9, 115.4, 95.2, 51.1, 48.1, 16.3; **FTIR** 1646, 1531, 1447, 1289, 1214, 1095, 1018, 798, 699, 617 cm^{-1}; **HRMS** m/z $[C_{21}H_{21}NO_3+Na]^+$ cal. 358.1414, found 358.1412 (Δ + 0.4).

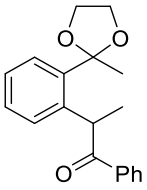
2-(2-Bromophenyl)-2-methyl-1,3-dioxolane, 306



2'-Bromoacetophenone **(**2.00 g, 10.1 mmol) was subjected to General Procedure 8. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *acetal* **306** (2.19 g, 90%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.59 (1 H, dd, *J*=7.8, 1.7 Hz, Ar*H*), 7.47 - 7.55 (1 H, m, Ar*H*), 7.15 - 7.26 (1 H, m, Ar*H*), 7.06 (1 H, td, *J*=7.6, 1.7 Hz, Ar*H*), 3.92 - 4.05 (2 H, m, OCH_2), 3.62 - 3.76 (2 H, m, OCH_2), 1.74 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 141.1, 135.0, 129.5, 127.9, 127.2, 120.6, 108.8, 64.3, 25.3. Data were consistent with those previously reported.[177]

2-(2-(2-Methyl-1,3-dioxolan-2-yl)phenyl)-1-phenylpropan-1-one, 308

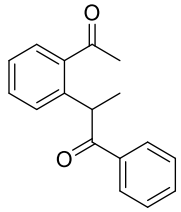


Acetal **306** (250 mg, 1.04 mmol) and propiophenone were subjected to General Procedure 9. Purification by flash column chromatography (petrol-EtOAc, 9:1) afforded *acetal* **308** (234 mg, 76%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.01 - 8.08 (2 H, m, Ar*H*), 7.63 (1 H, dd, *J*=7.8, 1.5 Hz, Ar*H*), 7.52 (1 H, tt, *J*=7.4, 1.7 Hz, Ar*H*), 7.39 - 7.46 (3 H, m, Ar*H*), 7.32 (1

H, t, *J*=7.6 Hz, Ar*H*), 7.24 (1 H, t, *J*=7.8 Hz, Ar*H*), 5.51 (1 H, q, *J*=7.1 Hz, C*H*), 3.97 - 4.05 (1 H, m, CH_aH$_b$), 3.71 - 3.87 (2 H, m, CH_2), 3.46 - 3.54 (1 H, m, CH$_a$$H_b$), 1.78 (3 H, s, CC$H_3$), 1.57 (3 H, d, *J*=7.1 Hz, CHCH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 202.2, 140.0, 138.3, 137.2, 132.4, 129.5, 128.8, 128.7, 128.5, 128.4, 126.7, 126.4, 109.3, 64.4, 64.1, 43.4, 28.1, 19.8. **FTIR** 2986, 2890, 1681, 1597, 1447, 1407, 1374, 1346, 1193, 1106, 1040, 968, 950, 868, 764, 703 cm^{-1}; **HRMS** m/z [$C_{19}H_{20}O_3S$+H]$^+$ cal. 297.1491, found 297.1481 (Δ − 3.2).

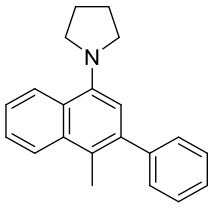
2-(2-Acetylphenyl)-1-phenylpropan-1-one, 309



Acetal **308** (200 mg, 1.04 mmol) was subjected to General Procedure 10. Purification by flash column chromatography (petrol-EtOAc, 9:1) afforded *1,5-dicarbonyl* **309** (137 mg, 81%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.86 - 7.94 (2 H, m, Ar*H*), 7.66 (1 H, d, *J*=7.6 Hz, Ar*H*), 7.36 (1 H, d, *J*=7.3 Hz, Ar*H*), 7.25 - 7.33 (3 H, m, Ar*H*), 7.15 - 7.24 (2 H, m, Ar*H*), 5.60 (1 H, q, *J*=6.8 Hz, C*H*), 2.55 (3 H, s, CCH_3), 1.40 (3 H, d, *J*=6.8 Hz, CHCH_3); **^{13}C NMR** (100 MHz *CHLOROFORM-d*) δ ppm 202.3, 201.3, 141.3, 136.5, 136.2, 132.7, 132.3, 130.0, 129.0, 128.8, 128.5, 126.7, 43.2, 29.8, 18.9; **FTIR** 2977, 1679, 1597, 1572, 1485, 1448, 1356, 1293, 1236, 1180, 1001, 951, 759, 727, 691; **HRMS** m/z [$C_{17}H_{16}O_2$+Na]+ cal. 275.1043, found 275.1043 (Δ + 0.0).

1-(4-Methyl-3-phenylnaphthalen-1-yl)pyrrolidine, 310

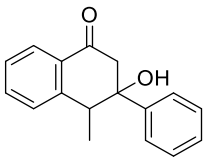


Method A 1,5-dicarbonyl **309** (25 mg, 0.11 mmol) and pyrrolidine was subjected to General Procedure 11. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *naphthylamine* **310** (17 mg, 55%) as a colourless oil.

Method B 1,5-dicarbonyl **309** (40 mg, 0.16 mmol) and pyrrolidine were subjected to General Procedure 12. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *naphthylamine* **310** (34 mg, 76%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.32 (1 H, d, *J*=8.3 Hz, Ar*H*), 8.10 (1 H, d, *J*=8.3 Hz, Ar*H*), 7.49 (7 H, m, Ar*H*), 6.98 (1 H, s, *H*C(2)), 3.37 (4 H, br. s., NC*H*$_2$), 2.56 (3 H,s, C*H*$_3$), 2.05 (4 H, br. s., NCH$_2$C*H*$_2$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 145.4, 143.4, 139.0, 134.2, 129.8, 128.1, 127.9, 126.7, 126.0, 125.0, 124.9, 124.2, 114.7, 53.0, 24.6, 16.0. Missing 1C; **FTIR** 2963, 1587, 1495, 1456, 1389, 1352, 1263, 1158, 1091, 1033, 985, 907, 759, 731, 703, 645 cm^{-1}; **HRMS** m/z [C$_{21}$H$_{21}$N+H]$^{+}$ cal. 288.1747, found 288.1740 (Δ – 2.4).

3-Hydroxy-4-methyl-3-phenyl-3,4-dihydronaphthalen-1(2H)-one, 311

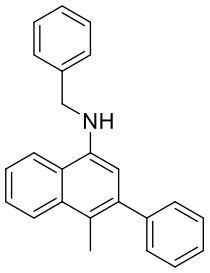


Cyclohexanone **311** was isolated a side product in the synthesis of *naphthylamine* **310**.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.08 (1 H, d, *J*=7.8 Hz, Ar*H*), 7.55 - 7.63 (1 H, m, Ar*H*), 7.51 (2 H, d, *J*=7.6 Hz, Ar*H*), 7.34 - 7.47 (4 H, m, Ar*H*), 7.24 - 7.34 (1 H, m, Ar*H*), 3.68 (1 H, q, *J*=7.1 Hz, CH$_3$C*H*), 3.27 (1 H, d, *J*=16.9 Hz, C*H*$_a$H$_b$), 3.05 (1 H, d,

J=17.1 Hz, CH_aH_b), 2.21 (1 H, m, O*H*), 1.34 (3 H, d, *J*=7.1 Hz, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 196.5, 145.3, 145.2, 134.4, 131.6, 128.6, 127.9, 127.4, 126.9, 126.8, 125.1, 77.8, 51.8, 43.1, 14.6; **FTIR** 3303, 2948, 1641, 1451, 1018 cm^{-1}; **m/z** (ESI^+) 275.1 [100, $(M + Na)^+$]; single crystal X-ray diffraction data also collected for this compound, see appendix 2.

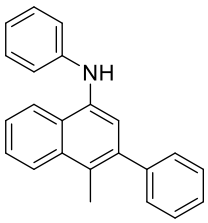
***N*-Benzyl-4-methyl-3-phenylnaphthalen-1-amine, 313**



1,5-Dicarbonyl **309** (50 mg, 0.198 mmol) and benzylamine were subjected to General Procedure 12. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *naphthylamine* **313** (45 mg, 70%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.94 (1 H, d, *J*=8.2 Hz, Ar*H*), 7.74 (1 H, d, *J*=8.2 Hz, Ar*H*), 7.42 (1 H, t, *J*=7.5 Hz, Ar*H*), 7.13 - 7.36 (11 H, m, Ar*H*), 6.48 (1 H, s, *H*C(2)), 4.42 (1 H, br. s., N*H*), 4.30 (2 H, s, CH_2), 2.35 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 143.6, 141.2, 139.5, 139.2, 133.7, 129.8, 128.8, 128.1, 128.0, 127.5, 126.6, 126.2, 125.5, 124.5, 123.3, 120.4, 120.1, 107.7, 48.9, 15.8; **FTIR:** 1592, 1525, 1480, 1443, 1395, 1250, 1113, 1073, 1029, 907, 841, 753, 729, 701, 648; **HRMS** m/z $[C_{24}H_{21}N+H]^+$ cal. 324.1747, found 324.1734 (Δ − 3.8); **m.p.** 123-126 °C (CH_2Cl_2/petrol).

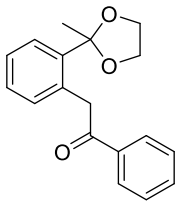
4-Methyl-*N*,3-diphenylnaphthalen-1-amine, 314



1,5-Dicarbonyl **309** (50 mg, 0.20 mmol) and aniline were subjected to General Procedure 12. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *naphthylamine* **314** (33 mg, 54%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.03 (1 H, d, *J*=8.3 Hz, Ar*H*), 8.00 (1 H, d, *J*=8.6 Hz, Ar*H*), 7.50 (1 H, t, *J*=7.2 Hz, Ar*H*), 7.40 (1 H, t, *J*=7.1 Hz, Ar*H*), 7.30 - 7.36 (2 H, m, Ar*H*), 7.22 - 7.29 (3 H, m, Ar*H*), 7.04 - 7.17 (2 H, m, Ar*H*), 6.84 (2 H, d, *J*=7.8 Hz, Ar*H*), 6.76 (1 H, t, *J*=7.2 Hz, Ar*H*), 5.76 (1 H, br. s, N*H*.), 2.49 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 145.5, 142.6, 139.3, 136.4, 134.1, 129.8, 129.4, 128.1, 127.9, 126.9, 126.5, 125.4, 125.3, 122.7, 120.0, 119.8, 116.7, 16.2. Missing 1C; **FTIR:** 3054, 1592, 1492, 1496, 1441, 1391, 1371, 1301, 1250, 1177, 1073, 1030, 907, 749, 731, 700, 649, 617 cm^{-1}; **HRMS** m/z $[C_{23}H_{19}N+Na]^+$ cal. 332.1410, found 332.1398 (Δ + 2.2).

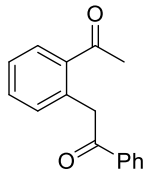
2-(2-(2-Methyl-1,3-dioxolan-2-yl)phenyl)-1-phenylethan-1-one, 316



Acetal **306** (100 mg, 0.413 mmol) and acetophenone were subjected to General Procedure 9. Purification by flash column chromatography (petrol-EtOAc, 9:1) afforded *ketone* **316** (96 mg, 83%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.09 (2 H, d, *J*=8.3 Hz, Ar*H*), 7.57 - 7.68 (2 H, m, Ar*H*), 7.52 (2 H, t, *J*=7.6 Hz, Ar*H*), 7.30 - 7.34 (2 H, m, Ar*H*), 7.15 - 7.20 (1 H, m, Ar*H*), 4.56 (s, 2 H, C(O)CH_2), 3.81 - 3.92 (m, 2 H, CH_aH$_b$$H_aH_b$), 3.60 - 3.68 (m, 2 H, CH$_a$$H_bH_a$$H_b$), 1.70 (3 H, s, C$H_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 197.8, 141.2, 137.4, 133.1, 132.8, 132.3, 128.6, 128.2, 128.1, 127.1, 126.4, 109.1, 64.2, 43.9, 27.7. Data were consistent with those previously reported.[178]

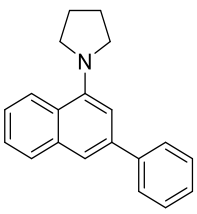
2-(2-Acetylphenyl)-1-phenylethan-1-one, 317



Acetal **316** (90 mg, 0.319 mmol) was subjected to General Procedure 10. Purification by flash column chromatography (petrol-EtOAc, 9:1) afforded *1,5-dicarbonyl* **317** (61 mg, 80%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.07 (2 H, d, *J*=7.6 Hz, Ar*H*), 7.88 (1 H, d, *J*=7.8 Hz, Ar*H*), 7.55 - 7.63 (1 H, m, Ar*H*), 7.47 - 7.54 (3 H, m, Ar*H*), 7.39 - 7.46 (1 H, m, Ar*H*), 7.27 (1 H, d, *J*=7.3 Hz, Ar*H*), 4.68 (2 H, s, CH_2), 2.59 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 201.2, 197.4, 137.3, 137.0, 135.3, 133.1, 133.0, 132.1, 130.2, 128.6, 128.2, 127.3, 44.7, 28.7. Data were consistent with those previously reported.[179]

1-(3-Phenylnaphthalen-1-yl)pyrrolidine, 319

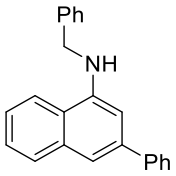


Method A 1,5-dicarbonyl **317** (22 mg, 0.092 mmol) was subjected to General Procedure 11. Purification by flash column chromatography (petrol-EtOAc, 49:1 to 19:1) afforded *naphthylamine* **319** (16 mg, 67%) as a colourless oil.

Method B 1,5-dicarbonyl **317** (50 mg, 0.210 mmol) and pyrrolidine were subjected to General Procedure 12. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *naphthylamine* **319** (39 mg, 69%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.27 (1 H, d, *J*=8.1 Hz, Ar*H*), 7.84 - 7.94 (1 H, m, Ar*H*), 7.75 - 7.80 (2 H, m, Ar*H*), 7.68 (1 H, s, Ar*H*), 7.38 - 7.56 (5 H, m, Ar*H*), 7.24 - 7.28 (1 H, m, *H*C(2)), 3.49 (4 H, t, *J*=5.7 Hz, NCH_2), 2.01 - 2.17 (4 H, m, NCH$_2$CH_2); **^{13}C NMR** (126 MHz, *CHLOROFORM-d*) δ ppm 147.9, 141.7, 138.6, 135.2, 128.7, 128.6, 127.4, 127.2, 127.1, 126.0, 124.5, 119.6, 119.4, 111.4, 52.9, 24.9. Data were consistent with those previously reported.[180]

***N*-Benzyl-3-phenylnaphthalen-1-amine, 320**



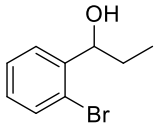
Method A 1,5-dicarbonyl **317** (22 mg, 0.092 mmol) was subjected to General Procedure 11. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *naphthylamine* **320** (16 mg, 58%) as a colourless oil.

Method B 1,5-dicarbonyl **317** (50 mg, 0.21 mmol) and benzylamine were subjected to General Procedure 12. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *naphthylamine* **320** (40 mg, 63%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.83 (1 H, d, *J*=8.1 Hz, Ar*H*), 7.78 (1 H, d, *J*=8.3 Hz, Ar*H*), 7.64 (2 H, d, *J*=7.8 Hz, Ar*H*), 7.27 - 7.49 (11 H, m, Ar*H*), 6.87 (1 H, s,

*H*C(2)), 4.70 (1 H, br. s., N*H*), 4.53 (2 H, s, CH_2); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 143.6, 142.1, 139.4, 139.0, 134.6, 129.0, 128.8, 128.7, 127.9, 127.5, 127.4, 127.2, 126.2, 124.8, 122.8, 119.8, 116.0, 104.6, 48.8; **FTIR** 3063, 1680, 1597, 1579, 1490, 1448, 1338, 1259, 1215, 1096, 1052, 999, 759, 690, 665 cm^{-1}; **HRMS** m/z $[C_{23}H_{19}N+H]^+$ cal. 310.1590, found 310.1581 (Δ + 2.9).

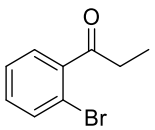
1-(2-Bromophenyl)propan-1-ol, 322



2'-Bromoacetophenone **(**1.00 g, 4.65 mmol) in THF (50 mL) was cooled to −78 °C and ethyl magnesium bromide (5.12 mL, 5.12 mmol, 1.0 M in Et_2O) added dropwise. The reaction was then monitored until full consumption of the aldehyde was observed by TLC. The reaction mixture was allowed to warm to room temperature and then quenched by the addition a saturated aqueous solution of NH_4Cl (3x). The mixture was extracted with EtOAc (3x). The organic layers were combined, dried ($MgSO_4$) and concentrated to give crude reaction mixture. Purification by flash column chromatography (petrol-EtOAc, 9:1 to 7:3) afforded *alcohol* **322** (754 mg, 65%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.46 - 7.59 (2 H, m, Ar*H*), 7.33 (1 H, t, *J*=7.5 Hz, Ar*H*), 7.13 (1 H, t, *J*=7.7 Hz, Ar*H*), 4.96 - 5.06 (1 H, m, C*H*), 2.06 - 2.32 (1 H, m, O*H*), 1.77 - 1.89 (1 H, m, CH_aH_b), 1.60 - 1.76 (1 H, m, CH_aH_b), 1.00 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 143.6, 132.7, 128.7, 127.7, 127.4, 122.2, 74.2, 30.6, 10.1. Data were consistent with those previously reported.[181]

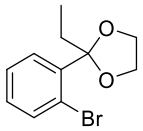
1-(2-Bromophenyl)propan-1-one, 323



Concentrated aqueous H_2SO_4 (0.4 mL) was added to CrO_3 (346 mg, 3.49 mmol) at 0 °C and the solution diluted with cautious addition of H_2O (1.2 mL). This solution was then added to a solution of alcohol **322** (250 mg, 1.16 mmol) in acetone (10 mL) at 0 °C. The reaction was monitored and upon completion poured onto cold water (50 mL). The aqueous layer was then extracted with Et_2O (3 x 15 mL). The combined organic layer was washed with water, dried ($MgSO_4$), and concentred. The crude product was purified by flash column chromatography (petrol-EtOAc, 9:1) to afford *ketone* **323** (330 mg, 83%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.59 (1 H, d, *J*=7.8 Hz, Ar*H*), 7.32 - 7.38 (2 H, m, Ar*H*), 7.23 - 7.31 (1 H, m, Ar*H*), 2.92 (2 H, q, *J*=7.3 Hz, C*H*$_2$), 1.20 (3 H, t, *J*=7.2 Hz, C*H*$_3$); **^{13}C NMR** (101 MHz, *CHLOROFORM-d*) δ ppm 205.1, 142.0, 133.6, 131.3, 128.2, 127.4, 118.5, 36.1, 8.1; **FTIR** 2978, 1701, 1587, 1460, 1428, 1346, 1265, 1215, 1087, 1049, 1026, 943, 748, 673, 638 cm^{-1}; **HRMS** m/z $[C_9H_9BrO+Na]^+$ cal. 234.9729, found 234.9736 (Δ – 2.9). Data were consistent with those previously reported.[182]

2-(2-Bromophenyl)-2-ethyl-1,3-dioxolane, 324

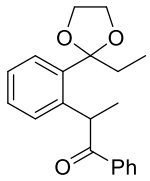


Ketone **323 (**250 mg, 1.18 mmol) was subjected to General Procedure 8. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *acetal* **324** (190 mg, 63%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.60 (1 H, dd, *J*=7.8, 1.0 Hz, Ar*H*), 7.63 (1 H, dd, *J*=7.8, 1.7 Hz, Ar*H*), 7.28 (1 H, td, *J*=7.6, 1.0 Hz, Ar*H*), 7.14 (1 H, td, *J*=7.6, 1.7 Hz, Ar*H*), 3.96 - 4.11 (2 H, m, C*H*$_a$H$_b$*H*$_a$H$_b$), 3.69 - 3.86 (2 H, m, CH$_a$*H*$_b$H$_a$*H*$_b$), 2.18 (2 H, q, *J*=7.3 Hz, C*H*$_2$CH$_3$), 0.89 (3 H, t, *J*=7.5 Hz, CH$_2$C*H*$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 140.4, 135.0, 129.4, 128.8, 126.9, 120.6, 110.8, 64.5, 30.6, 7.7;

FTIR: 2976, 2881, 1461, 1427, 1285, 1177, 1096, 1055, 1040, 944, 756, 689, 640 cm^{-1}; **HRMS** m/z $[C_{11}H_{13}BrO_2+Na]^+$ cal. 278.9991, found 278.9995 (Δ − 1.4).

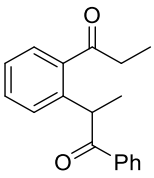
2-(2-(2-Ethyl-1,3-dioxolan-2-yl)phenyl)-1-phenylpropan-1-one, 325



Acetal **324** (150 mg, 0.584 mmol) and propiophenone were subjected to General Procedure 9. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *ketone* **325** (110 mg, 61%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.93 (2 H, d, *J*=7.6 Hz, Ar*H*), 7.48 (1 H, d, *J*=7.8 Hz, Ar*H*), 7.38 - 7.45 (1 H, m, Ar*H*), 7.26 - 7.37 (3 H, m, Ar*H*), 7.21 (1 H, t, *J*=7.5 Hz, Ar*H*), 7.13 (1 H, t, *J*=7.6 Hz, Ar*H*), 5.38 (1 H, q, *J*=7.1 Hz, C*H*), 3.86 - 3.93 (1 H, m, $CH_aH_bH_a\mathit{H}_b$), 3.64 - 3.77 (2 H, m, $CH_a\mathit{H}_b\mathit{H}_aH_b$), 3.40 - 3.48 (1 H, m, $C\mathit{H}_aH_bH_aH_b$), 1.88 - 2.01 (2 H, m, $C\mathit{H}_2CH_3$), 1.45 (3 H, d, *J*=7.1 Hz, $C\mathit{H}CH_3$), 0.84 (3 H, t, *J*=7.5 Hz, $CH_2C\mathit{H}_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 202.3, 139.3, 138.5, 137.3, 132.4, 129.4, 128.7, 128.3, 128.3, 127.2, 126.4, 111.2, 64.7, 64.3, 43.4, 33.6, 19.7, 8.0; FT**IR** 2976, 2882, 1681, 1597, 1448, 1289, 1205, 1178, 1196, 1045, 967, 942, 923, 758, 702 cm^{-1}; **HRMS** m/z $[C_{20}H_{22}O_3+Na]$ cal. 333.1461, found 333.1469. (-2.4).

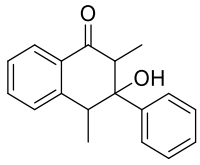
1-Phenyl-2-(2-propionylphenyl)propan-1-one, 336



Acetal **325** (50 mg, 0.161 mmol) was subjected to General Procedure 10. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *1,5-dicarbonyl* **336** (26 mg, 59%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.90 (2 H, d, *J*=7.6 Hz, Ar*H*), 7.59 (1 H, d, *J*=7.6 Hz, Ar*H*), 7.38 (1 H, m, Ar*H*), 7.29 (3 H, t, *J*=7.7 Hz, Ar*H*), 7.18 (2 H, m, Ar*H*), 5.48 (1 H, q, *J*=6.8 Hz, C*H*CH$_3$), 2.90 (2 H, m, C*H*$_2$), 1.40 (3 H, d, J=6.8 Hz, CHC*H*$_3$), 1.16 (3 H, t, J=7.2 Hz, CH$_2$C*H*$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 205.8, 201.2, 140.8, 136.9, 136.5 (2C), 132.7, 131.8, 128.8 (2C), 128.5, 126.7, 43.1, 35.2, 19.2, 8.6; **FTIR** 2970, 1679, 1596, 1483, 1449, 1346, 1214, 1177, 1002, 948, 765, 753, 736, 693, 656 cm^{-1}; **HRMS** m/z [C$_{18}$H$_{18}$O$_2$+Na]$^+$ cal. 289.119, found 289.1203 (Δ − 1.5).

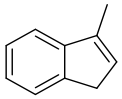
3-Hydroxy-2,4-dimethyl-3-phenyl-3,4-dihydronaphthalen-1(2*H*)-one, 327



1,5-Dicarbonyl **336** (28 mg, 0.11 mmol) was subjected to General Procedure 11. Purification by flash column chromatography (petrol-EtOAc, 9:1) afforded *ketone* **327** (15 mg, 54%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.98 - 8.09 (1 H, m, Ar*H*), 7.46 - 7.58 (1 H, m, Ar*H*), 7.17 - 7.46 (7 H, m, Ar*H*), 3.61 (1 H, q, *J*=6.8 Hz, C(O)C*H*), 3.12 (1 H, q, *J*=6.7 Hz, C$_{Ar}$C*H*), 1.77 (1 H, s, O*H*), 1.05 - 1.17 (3 H, m, C(O)CHC*H*$_3$), 0.89 (3 H, d, *J*=6.8 Hz, C$_{Ar}$CHC*H*$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 198.5, 144.0, 143.6, 134.1, 132.0, 128.5, 127.6, 127.0, 127.0, 126.8, 125.2, 82.0, 52.8, 43.4, 13.5, 9.1; **FTIR** 3499, 2983, 1683, 1600, 1447, 1374, 1325, 1247, 1161, 984, 753, 703, 685 cm^{-1}; **HRMS** m/z [C$_{18}$H$_{18}$O$_2$+Na]$^+$ cal. 289.1199, found 289.1204 (Δ − 1.9).

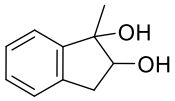
3-Methyl-1H-indene, 330



$CeCl_3$ (4.23 g, 11.4 mmol) was heated at 130 °C under a high vacuum for 2 hours. THF (50 mL) was added and the reaction stirred for 90 min at room temperature. The reaction was cooled for −78 °C and MeLi (7.13 mL, 1.6 M in Et_2O, 11.4 mmol) and stirred for 30 minute. A solution of indanone (1.00 g, 7.58 mmol) in THF (2 mL) was added dropwise and the resulting solution stirred for 1 hour, then allowed to warm to room temperature. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl then the THF removed in vacuo. The mixture was then partitioned between Et_2O and water and the organic layer separated. The aqueous layer was washed with Et2O (2x), the organic layers combined, dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in CH_2Cl_2 (50 mL) and *para*-toluenesulfonic acid monohydrate (72 mg, 0.38 mmol) added. The reaction was stirred for 30 minutes, then concentrated and purified by flash column chromatography (pet-EtOAc, petrol) to give *indene* **330** (845 mg, 86%).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.53 (1 H, d, *J*=7.3 Hz, Ar*H*), 7.35 - 7.46 (2 H, m, Ar*H*), 7.26 - 7.33 (1 H, m, Ar*H*), 6.28 (1 H, s, C*H*), 3.39 (2 H, s, CH_2), 2.26 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 146.2, 144.4, 140.0, 128.8, 126.1, 124.5, 123.7, 118.9, 37.7, 13.1; Data were consistent with those previously reported.[183]

1-Methyl-2,3-dihydro-1H-indene-1,2-diol

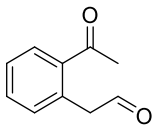


$K_2OsO_2(OH)_4$ (14 mg, 0.051 mmol) was added to a solution of indene (200 mg, 1.54 mmol), *N*-Methylmorpholine *N*-oxide (360 mg, 3.08 mmol) in H_2O/THF/*t*BuOH (1:10:8, 10

mL) and the reaction stirred for 18 hours. The reaction was quenched with a saturated solution of sodium sulphite (10 mL) and extracted with EtOAc (3x). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (petrol-EtOAc, 1:1) afforded *title compound* (170 mg, 69%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.23 - 7.30 (1 H, m, Ar*H*), 7.14 - 7.20 (2 H, m, Ar*H*), 7.08 - 7.14 (1 H, m, Ar*H*), 3.94 (1 H, br. s., O*H*), 3.12 (1 H, br. s., O*H*), 3.03 (1 H, d, *J*=4.9 Hz, C*H*), 2.99 (1 H, d, *J*=5.8 Hz, CH_aH$_b$), 2.73 (1 H, dd, *J*=16.2, 4.6 Hz, CH$_a$$H_b$), 1.37 (3 H, s, C$H_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 145.6, 139.4, 128.8, 127.3, 125.4, 123.4, 80.0, 78.7, 38.2, 24.8; **FTIR** 3231, 2940, 1480, 1368, 1321, 1224, 1170, 1107, 1088, 1061, 1021, 963, 916, 844, 804, 759, 739, 717, 648 cm^{-1}; **HRMS** m/z $[C_{10}H_{12}O_2+Na]^+$ cal. 187.0729, found 187.0729 (Δ − 0.3).

2-(2-Acetylphenyl)acetaldehyde, 329

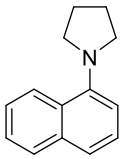


Diol **S1** (170 mg, 1.04 mmol), was dissolved in CH_2Cl_2 (10 mL) and $NaIO_4.SiO_2$ (5.6 g, 3.6 g/mmol, 1.56 mmol) and stirred. After 1 hour the reaction was filtered and washed with CH_2Cl_2. The filtrated was concentrated to yield *keto-aldehyde* **329** (168 mg, 100%) which was used in the next step without further purification.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 9.76 (1 H, s, C(O)*H*), 7.84 - 7.92 (1 H, m, Ar*H*), 7.50 (1 H, td, *J*=7.5, 1.2 Hz, Ar*H*), 7.38 - 7.45 (1 H, m, Ar*H*), 7.23 (1 H, d, *J*=7.6 Hz, Ar*H*), 3.99 (2 H, s, CH_2), 2.60 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 200.8, 199.0, 136.6, 133.5, 133.1, 132.5, 130.5, 127.7, 49.4, 28.7; **FTIR** 1721, 1676,

1600, 1573, 1488, 1357, 1256, 1034, 959, 761 cm^{-1}; **HRMS** m/z [$C_{10}H_{10}O_2$] cal. 162.0681, found 162.0677 (Δ − 2.3).

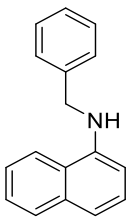
1-(Naphthalen-1-yl)pyrrolidine, 332



1,5-Dicarbonyl **329** (60 mg, 0.37 mmol) and pyrrolidine were subjected to General Procedure 12. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *naphthylamine* **332** (49 mg, 68%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.09 (1 H, s, Ar*H*), 7.67 (1 H, s, Ar*H*), 7.30 (3 H, s, Ar*H*), 7.19 - 7.27 (1 H, m, Ar*H*), 6.84 (1 H, d, *J*=7.3 Hz, *H*C(2)), 3.23 (4 H, br. s, NCH_2), 1.88 (4 H, br. s, NCH_2CH_2); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 147.8, 135.1, 128.4, 128.3, 126.0, 125.6, 124.9, 124.4, 121.4, 111.5, 52.8, 24.9. Data were consistent with those previously reported.[184]

***N*-benzylnaphthalen-1-amine, 333**

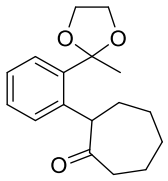


1,5-dicarbonyl **329** (60 mg, 0.368 mmol) and benzylamine were subjected to General Procedure 12. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *naphthylamine* **333** (39 mg, 45%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.68 - 7.79 (2 H, m, Ar*H*), 7.15 - 7.45 (9 H, m, Ar*H*), 6.55 (1 H, d, *J*=7.6 Hz, *H*C(2)), 4.62 (1H, br. s., N*H*), 4.42 (2 H, s, CH_2); **^{13}C NMR (1**01 MHz, *CHLOROFORM-d*) δ ppm 142.2, 138.0, 133.2, 127.7, 127.7, 126.7,

126.4, 125.6, 124.7, 123.7, 122.3, 118.8, 116.6, 103.7, 47.6. Data were consistent with those previously reported.[184]

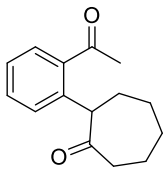
2-(2-(2-Methyl-1,3-dioxolan-2-yl)phenyl)cycloheptan-1-one, 335



Acetal **306** (166 mg, 0.690 mmol) and cycloheptanone were subjected to General Procedure 9. Purification by flash column chromatography (petrol-EtOAc, 19:1 to 9:1) afforded *ketone* **335** (140 mg, 75%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.47 (1 H, dd, *J*=7.7, 1.1 Hz, Ar*H*), 7.04 - 7.30 (3 H, m, Ar*H*), 4.50 - 4.65 (1 H, m, C*H*), 3.85 - 3.98 (1 H, m, OC$H_a$$H_bCH_a$$H_b$), 3.75 - 3.85 (1 H, m, OC$H_a$$H_bCH_a$$H_b$), 3.55 - 3.66 (1 H, m, OC$H_a$$H_bCH_a$$H_b$), 3.33 - 3.43 (1 H, m, OC$H_a$$H_bCH_a$$H_b$), 2.69 (1 H, dt, *J*=16.6, 4.0 Hz, C$H_a$$H_b$(CO)), 2.45 (1 H, ddd, *J*=16.6, 12.1, 4.3 Hz, C$H_a$$H_b$(CO)), 1.73 - 2.03 (6 H, m, CH_2), 1.65 (3 H, s, CH_3), 1.42 - 1.60 (1 H, m, C$H_a$$H_b$), 1.14 - 1.37 (1 H, m, C$H_a$$H_b$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 213.4, 139.5, 139.4, 129.8, 128.1, 126.3, 125.8, 109.1, 64.2, 63.8, 52.9, 43.8, 33.4, 30.5, 29.4, 28.0, 23.9. Data were consistent with those previously reported.[90]

2-(2-Acetylphenyl)cycloheptan-1-one, 336

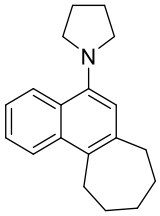


Acetal **335** (90 mg, 0.328 mmol) was subjected to General Procedure 10. In a modification of the General Procedure pyridinium *p*-toluenesulfonate was used instead of *p*-

toluenesulfonic acid. Purification by flash column chromatography (petrol-EtOAc, 9:1 to 3:17) afforded *1,5-dicarbonyl* **336** (70 mg, 93%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.75 (1 H, d, *J*=7.6 Hz, Ar*H*), 7.52 (1 H, t, *J*=7.5 Hz, Ar*H*), 7.31 - 7.41 (2 H, m, Ar*H*), 4.51 (1 H, d, *J*=10.8 Hz, C*H*), 2.89 - 3.03 (1 H, m, CHCH_aH_b), 2.51 - 2.64 (4 H, m CHCH_aH_b and CH_3), 1.91 - 2.15 (4 H, m, CH_2), 1.75 - 1.91 (2 H, m, CH_2), 1.50 - 1.65 (1 H, m, CH_aCH_b), 1.29 - 1.42 (1 H, m, CH_aCH_b); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 213.4, 201.7, 141.7, 136.3, 132.0, 129.9, 129.5, 126.4, 54.1, 44.0, 32.2, 30.3, 29.4, 29.3, 23.7; **FTIR** 2926, 2856, 1678, 1600, 1572, 1486, 1445, 1365, 1253, 1157, 957, 933, 803, 758 cm^{-1}; **HRMS** m/z $[C_{15}H_{18}O_2+Na]^+$ cal. 253.1199, found 253.1202 (Δ − 1.3).

1-(8,9,10,11-Tetrahydro-7*H*-cyclohepta[*a*]naphthalen-5-yl)pyrrolidine, 337



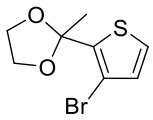
Method A 1,5-dicarbonyl **336** (30 mg, 0.13 mmol) was subjected to General Procedure 11. Purification by flash column chromatography (petrol-EtOAc, 9:1) afforded *naphthylamine* **337** (10 mg, 29%) as a colourless oil.

Method B 1,5-dicarbonyl **336** (39 mg, 0.17 mmol) and pyrrolidine were subjected to General Procedure 12. Purification by flash column chromatography (petrol-EtOAc, 98:2 to19:1) afforded *naphthylamine* **337** (21 mg, 47%) as a colourless oil.

^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 8.24 (1 H, d, *J*=8.5 Hz, Ar*H*), 8.11 (1 H, d, *J*=8.5 Hz, Ar*H*), 7.47 (1 H, t, *J*=7.3 Hz, Ar*H*), 7.38 (1 H, t, *J*=7.4 Hz, Ar*H*), 6.88 (1 H, s, *H*C(2)), 3.31 (4 H, br. s., NCH_2), 3.16 - 3.25 (2 H, m, ArCH_2), 2.91 - 3.03 (2 H, m, ArCH_2), 1.97 - 2.08 (4 H, m, CH_2), 1.91 (2 H, quin, *J*=5.8 Hz, CH_2), 1.65 - 1.76 (4 H, m, NCH_2CH_2);

^{13}C NMR (125 MHz, *CHLOROFORM-d*) δ ppm 144.4, 139.7, 131.8, 130.9, 126.3, 124.4, 123.9, 122.5, 121.9, 114.0, 51.8, 36.1, 31.4, 26.8, 26.1, 23.5; **FTIR** 2919, 2849, 1590, 1512, 1458, 1394, 1354, 1316, 1192, 1113, 961, 909, 830, 759 cm^{-1}; **HRMS** m/z $[C_{19}H_{23}N+H]^+$ cal. 266.1903, found 266.1908 (Δ − 1.8).

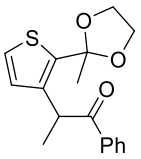
2-(3-Bromothiophen-2-yl)-2-methyl-1,3-dioxolane, 339



Ketone **338 (**2.00 g, 9.76 mmol) was subjected to General Procedure 8. Purification by flash column chromatography (petrol-EtOAc, 9:1) afforded *acetal* **339** (2.25 g, 93%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.16 (1 H, d, *J*=5.1 Hz, Ar*H*), 6.95 (1 H, d, *J*=5.1 Hz, Ar*H*), 4.03 - 4.13 (2 H, m, $CH_aH_bH_aH_b$), 3.89 - 4.00 (2 H, m, $CH_aH_bH_aH_b$), 1.84 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 141.1, 132.3, 124.5, 107.2, 106.3, 65.1, 25.6. **FTIR**: 2890, 1658, 1406, 1373, 1346, 1191, 1044, 1019, 865, 714 cm^{-1}; **HRMS** m/z $[C_8H_9O_2Br^{79}S+H]^+$ cal. 248.9585, found 248.9578 (Δ − 2.7).

2-(2-(2-Methyl-1,3-dioxolan-2-yl)thiophen-3-yl)-1-phenylpropan-1-one, 340

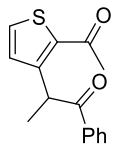


Acetal **339** (200 mg, 0.803 mmol) and propiophenone were subjected to General Procedure 9. Purification by flash column chromatography (petrol-EtOAc, 19:1 to 9:1) afforded *ketone* **340** (90 mg, 37%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 8.00 (2 H, d, *J*=7.3 Hz, Ar*H*), 7.39 - 7.60 (1 H, m, Ar*H*), 7.31 - 7.38 (2 H, m, Ar*H*), 7.03 (1 H, d, *J*=5.4 Hz, Ar*H*), 6.91 (1 H, d, *J*=5.1

Hz, Ar*H*), 5.21 (1 H, q, *J*=6.9 Hz, C*H*), 3.85 - 4.04 (2 H, m, $CH_aH_bH_aH_b$), 3.60 - 3.75 (2 H, m, $CH_aH_bH_aH_b$), 1.73 (3 H, s, CCH_3), 1.43 (3 H, d, *J*=6.8 Hz, $CHCH_3$); ^{13}C NMR (100 MHz, *CHLOROFORM-d*) δ ppm 201.6, 141.2, 136.8, 136.6, 132.8, 128.8, 128.7, 128.5, 123.7, 107.8, 65.0, 64.9, 40.5, 28.0, 19.4; **FTIR**: 2977, 1682, 1597, 1448, 1375, 1221, 1191, 1026, 966, 868, 723, 690 cm^{-1}; **HRMS** m/z $[C_{17}H_{18}O_3S+Na]^+$ cal. 325.0869, found 325.0876 (Δ − 2.1).

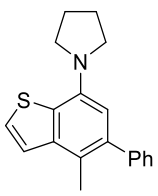
2-(2-Acetylthiophen-3-yl)-1-phenylpropan-1-one, 341



Acetal **340** (47 mg, 0.30 mmol) was subjected to General Procedure 10. Purification by flash column chromatography (petrol-EtOAc, 9:1 to 3:17) afforded *1,5-dicarbonyl* **341** (47 mg, 60%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.97 - 8.11 (2 H, m, Ar*H*), 7.36 - 7.61 (4 H, m, Ar*H*), 7.10 (1 H, d, *J*=5.1 Hz, Ar*H*), 6.01 (1 H, q, *J*=6.9 Hz, C*H*), 2.60 (3 H, s, CCH_3), 1.50 (3 H, d, *J*=6.8 Hz, $CHCH_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 200.8, 191.5, 148.3, 136.4, 133.0, 130.4, 130.0, 128.7, 128.6, 128.1, 41.2, 30.0, 18.3; **FTIR:** 2976, 1683, 1661, 1597, 1516, 1448, 1409, 1381, 1277, 1225, 1205, 953, 905, 843, 726, 690, 621 cm^{-1}; **HRMS** m/z $[C_{15}H_{14}O_2S+Na]^+$ cal. 281.0607, found 281.0609 (Δ − 1.3).

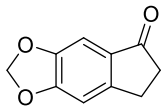
1-(7-Methyl-6-phenylbenzo[*b*]thiophen-4-yl)pyrrolidine, 342



1,5-Dicarbonyl **341** (40 mg, 0.15 mmol) and pyrrolidine were subjected to General Procedure 12. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *naphthylamine* **342** (29 mg, 65%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.33 - 7.52 (7 H, m, Ar*H*), 6.54 (1 H, s, *H*C(2)), 3.61 (4 H, br. s., NC*H*$_2$), 2.45 (3 H, s, C*H*$_3$), 1.98 - 2.11 (4 H, m, NCH$_2$C*H*$_2$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 142.9, 142.7, 141.6, 138.7, 129.8, 128.0, 127.3, 126.6, 125.6, 123.2, 119.5, 110.5, 50.0, 25.4, 16.6; **FTIR**: 2965, 2865, 1575, 1516, 1494, 1448, 1433, 1389, 1286, 1176, 1085, 1004, 903, 824, 763, 702; **HRMS** m/z [$C_{19}H_{19}NS$+Na]+ cal. 316.1130, found 316.1137 (Δ − 2.0).

6,7-Dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-one, 411

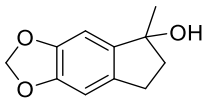


To a solution of 3-(3,4-methylenedioxyphenyl)propionic acid (4.00g, 20.6 mmol) in toluene (40 mL) was added thionyl chloride (8.48 g, 72.0 mmol, 5.20 mL) in one portion and the reaction heated to reflux. After 3 h the reaction mixture was cooled and concentrated *in vacuo*. The residue was then dissolved in CH_2Cl_2 and cooled to 0 °C. $SnCl_4$ (24.0 mL, 1.0 M in pentane) was added over 10 min and the reaction warmed to rt. After 30 min the reaction mixture was poured over crushed ice and separated. The organic phase was washed with 3 M aqueous HCl (2 x 20 mL) and water (20 mL), dried, filtered through a plug of silica and concentrated *in vacuo.* The crude product was purified by recrystallisation (toluene/hexane) to give *ketone* **411** (3.15 g, 92%)

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.08 (1 H, s, Ar*H*), 6.81 (1 H, s, Ar*H*), 6.05 (2 H, s, OC*H*$_2$O), 3.00 (2 H, m, C(O)C*H*$_2$), 2.66 (2 H, m, C$_{Ar}$C*H*$_2$); **^{13}C NMR** (100 MHz,

CHLOROFORM-d) δ ppm 204.9, 154.2, 152.7, 148.3, 131.8, 105.7, 102.3, 102.2, 36.8, 25.8. Data were consistent with those previously reported.[185]

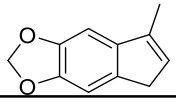
5-Methyl-6,7-dihydro-5H-indeno[5,6-*d*][1,3]dioxol-5-ol, 414



A suspension of $CeCl_3$ (2.80 g, 11.4 mmol) in THF (50 mL) was stirred for 30 minutes at room temperature and then cooled to −78 °C. MeLi (7.13 mL, 1.6 M in Et_2O, 11.4 mmol) was added drop wise over 5 minutes. A solution of ketone **411** (1.00 g, 5.68 mmol) was then added and the reaction stirred for 1 hour then warmed to room temperature. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl and the THF removed *in vacuo*. The aqueous layer was extracted with diethyl ether (3x) and the organic layers combined, dried ($MgSO_4$) and concentrated to give *alcohol* **414** which was used without further purification.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.71 (1 H, s, Ar*H*), 6.57 (1 H, s, Ar*H*), 5.85 (2 H, d, *J*=2.2 Hz, OCH_2), 2.83 (1 H, m, ArCH_aH$_b$), 2.64 (1 H, m, ArCH$_a$$H_b$), 2.11 (2 H, m, COHC$H_2$), 1.80 (1 H, br. s, O*H*), 1.44 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 147.9, 146.9, 141.4, 135.7, 105.1, 102.8, 101.1, 81.1, 42.8, 29.2, 27.4; **FTIR** 2885, 1469, 1381, 1344, 1272, 1246, 1216, 1156, 1098, 1038, 940, 851, 748 cm^{-1}.

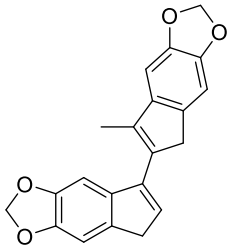
7-Methyl-5*H*-indeno[5,6-d][1,3]dioxole, 410



Alcohol **414** was dissolved in CH_2Cl_2 and pyridinium *p*-toluenesulfonate (71 mg, 0.28 mmol) added. The reaction was stirred for 30 minutes at room temperature and concentrated *in vacuo*. The crude residue was purified by flash column chromatography (petrol-EtOAc,19:1) to give *indene* **410** (761 mg, 77%) as a tan solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.99 (1 H, s, Ar*H*), 6.86 (1 H, s, Ar*H*), 6.15 (1 H, s, C=C*H*), 5.99 (2 H, s, OCH_2), 3.26 (2 H, br. s., CHCH_2), 2.15 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 146.5, 145.6, 140.2, 139.6, 138.0, 127.6, 105.2, 100.9, 100.1, 37.6, 13.2; **FTIR** 2890, 1594, 1500, 1467, 1331, 1270, 1246, 1100, 1034, 936, 863, 812, 746 cm^{-1}; **HRMS** m/z $[C_{11}H_{10}O_2+H]^+$ cal. 175.0754, found 175.0753 (Δ + 2.0).

7'-Methyl-6,7-dihydro-5*H*,5'*H*-[5,6'-biindeno[5,6-*d*][1,3]dioxol]-5-ol, 418

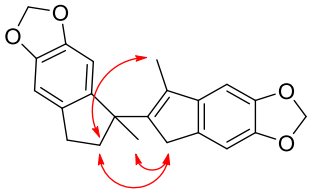


To a suspension of ketone **411** (500 mg, 2.84 mmol) in THF (20 mL) cooled to −78 °C was added methyl magnesium bromide (3.0 M in Et_2O, 1.40 mL) dropwise and the reaction stirred to 2 hours. The reaction was quenched by the addition of 1 M HCl and extracted into EtOAc. The organic layers were combined, dried ($MgSO_4$) and concentrated. The crude residue was purified by flash column chromatography (petrol-EtOAc, 9:1) to give *alkene* **410** (198 mg, 40 %) as a tan solid and *dimer* **418** (195 mg, 41%) as a red solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.91 (1 H, s, Ar*H*), 6.89 (1 H, s, Ar*H*), 6.80 (1 H, s, Ar*H*), 6.78 (1 H, s, Ar*H*), 6.24 (1 H, t, *J*=2.0 Hz, C=C*H*), 5.89 (2 H, s, OCH_2), 5.87 (2 H, s, OCH_2), 3.51 (2 H, m, CH_2C=CCH$_3$), 3.33 (2 H, m, CH_2CH), 2.04 (3 H, m, CH_3);

^{13}C NMR (100 MHz, *CHLOROFORM-d*) δ ppm 146.7, 146.6, 145.8, 145.7, 141.1, 140.9, 138.8, 138.1, 136.4, 135.9, 134.7, 130.6, 105.3, 105.0, 102.0, 101.0, 100.9, 100.3, 41.4, 38.3, 12.6; **FTIR** 1700, 1470, 1378, 1238, 1125, 1034, 933, 839, 749 cm^{-1}; **HRMS** m/z $[C_{21}H_{15}O_4+H]^+$ cal 332.1049, found 332.1057 (Δ − 2.5); **m.p.** 155-157 °C (petrol/CH_2Cl_2); single crystal X-ray diffraction data also collected for this comound, see appendix 2.

5,7'-Dimethyl-6,7-dihydro-5*H*,5'*H*-5,6'-biindeno[5,6-*d*][1,3]dioxole, 416

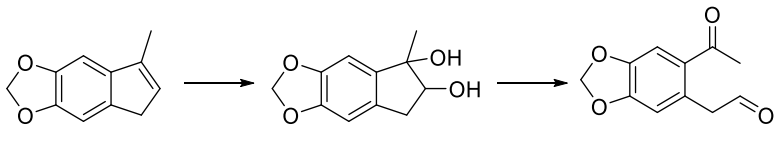


A suspension of $CeCl_3$ (5.88 g, 23.9 mmol) in THF (140 mL) was stirred for 30 minutes at room temperature and then cooled to −78 °C. Methyl lithium (34.0 mL, 1.6 M in Et_2O, 21.3 mmol) was added drop wise over 5 minutes. A solution of ketone **411** (2.5 g, 14.2 mmol) was then added and the reaction stirred for 1 hr then warmed to room temperature. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl and the THF removed *in vacuo*. The aqueous layer was extracted with diethyl ether and the organic layers combined washed with 1 M HCl, dried ($MgSO_4$) and concentrated. The crude product was purified by flash column chromatography (petrol-EtOAc,19:1) to give *dimer* **416** (1.70 g, 69 %) as an olive oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.91 (1 H, s, Ar*H*), 6.76 (1 H, s, Ar*H*), 6.73 (1 H, s, Ar*H*), 6.59 (1 H, s, Ar*H*), 5.95 (4 H, m, OCH_2), 3.29 (2 H, dd, *J*=8.1, 1.7 Hz, C=CCH_2), 2.86 (2 H, m, $C_{Ar}CH_2CH_2$), 2.43 (1 H, dt, *J*=12.3, 7.5 Hz, $C_{Ar}CH_2CH_aH_b$), 2.14 (1 H, ddd, *J*=12.5, 7.5, 6.0 Hz, $C_{Ar}CH_2CH_aH_b$), 1.74 (3 H, t, *J*=2.0 Hz, C=CCH_3), 1.54 (3 H, s, CH_2CCH_3) *Key NOE enhancements associated with dimer **416** are represented by red arrows on the compound structure*; **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 147.3, 146.7, 146.6, 146.5, 145.0, 144.8, 142.2, 135.4, 135.3, 132.3, 104.9, 104.7, 104.5, 101.0,

100.7, 99.5, 49.7, 43.0, 40.7, 30.5, 27.7, 11.9; **FTIR** 2885, 1499, 1470, 1352, 1330, 1297, 1261, 1237, 1205, 1159, 1127, 1036, 939, 848, 822, 736 cm^{-1}; **HRMS** m/z (EI/FI^+) $[C_{22}H_{20}O_4]^+$ cal. 348.1362, found 348.1366 (Δ + 1.3).

5-Methyl-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxole-5,6-diol, 419 and 2-(6-Acetylbenzo[*d*][1,3]dioxol-5-yl)acetaldehyde, 408



419 **408**

Method A To a solution of indene **410** (320 mg, 1.84 mmol) and *N*-methylmorpholine *N*-oxide (430 mg, 3.68 mmol) in THF/*t*BuOH 10:8 (10 mL) was added a solution of $K_2OsO_2(OH)_4$ (17 mg, 0.046 mmol) in water (1 mL). The reaction was stirred for 18 hours and then quenched by the addition of a saturated solution of N_2SO_3 and extracted into EtOAc. The organic layers were combined, dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash column chromatography (petrol-EtOAc, 1:1) to give *diol* **419**. Diol **419** was then dissolved in CH_2Cl_2 (10 mL) and $NaIO_4.SiO_2$ (9.94 g, 3.6 g/mmol, 2.76 mmol) and stirred. After 1 hour the reaction was filtered and washed with CH_2Cl_2. The filtrate was concentrated to give *dicarbonyl* **408** (280 mg, 74%) which was used in the next step without further purification.

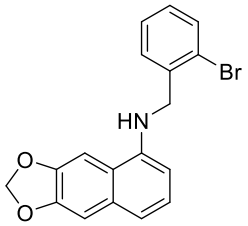
Method B To a solution of indene **410** (50 mg, 0.29 mmol), 2,6-lutidine (77 mg, 0.72 mmol) and $(nBu_4N)_2IO_4$ (547 mg, 1.26 mmol) in acetone/water 3:1 (4 mL) was added OsO_4 (7 mg, 0.029 mmol, 2.5% in *t*BuOH). The reaction was stirred for 1 hour and then diluted with CH_2Cl_2 and washed with a saturated solution of $NaHCO_3$, then a saturated solution of N_2SO_3 and finally H_2O. The organic layer was dried (Na_2SO_4), filtered and concentrated.

The crude material was purified by flash column chromatography on pH 7 buffered silica (petrol-EtOAc, 4:1 to 1:1) to give *dicarbonyl* **408** (28 mg, 48%).

Compound 419 ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.77 (1 H, s, Ar*H*), 6.59 (1 H, s, Ar*H*), 5.86 (2 H, s, OCH_2), 4.05 (1 H, t, *J*=5.5 Hz, C*H*OH), 3.00 (1 H, dd, *J*=15.9, 6.1 Hz, CH_aH$_b$), 2.70 (1 H, dd, *J*=15.9, 4.6 Hz, CH$_a$$H_b$), 2.24 (1 H, br. s, O*H*), 1.61 (1 H, br. s, O*H*), 1.41 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 148.4, 147.2, 138.4, 132.4, 105.7, 103.9, 101.1, 79.6, 78.8, 38.2, 24.7; **FTIR** 3257, 1499, 1472, 1346, 1286, 1244, 1219, 1165, 1109, 1075, 1035, 933, 914, 883, 864, 795, 723, 616 cm^{-1}; **HRMS** m/z [$C_{11}H_{12}O_4$+Na]$^+$ cal 231.0628, found 231.0627 (Δ − 0.5).

Compound 408 ^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 9.64 (1 H, s, C(O)*H*), 7.27 (1 H, s, Ar*H*), 6.60 (1 H, s, Ar*H*), 5.98 (2 H, s, OCH_2), 3.82 (2 H, s, CH_2), 2.45 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 199.0, 198.4, 150.8, 147.0, 130.1, 130.0, 113.0, 110.5, 102.2, 49.5, 28.7; **FTIR** 720, 1671, 1608, 1506, 1489, 1371, 1240, 1113, 1036, 951, 915, 869, 728, 620 cm^{-1}; **HRMS** m/z [$C_{11}H_{10}NaO_4$] cal. 229.0471, found 229.0474 (Δ − 1.2).

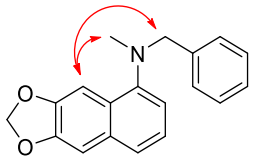
***N*-(2-Bromobenzyl)naphtho[2,3-d][1,3]dioxol-5-amine, 421**



To a solution of aldehyde **408** (50 mg, 0.24 mmol) in CH_2Cl_2 was added benzylamine **423** (226 mg, 1.21 mmol, 0.152 mL). The reaction stirred at 55 °C for 18 hour. The reaction mixture was then concentrated and purified by flash column chromatography (petrol-EtOAc, 99:1 to 9:1) to give *arylamine* **422** (25 mg, 29%) as a white dry film.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.59 (1 H, d, *J*=8.1 Hz), 7.42 (0 H, d, *J*=7.6 Hz), 7.25 (1 H, t, *J*=7.6 Hz), 7.04 - 7.21 (5 H, m), 6.49 (1 H, d, *J*=6.6 Hz), 6.01 (2 H, s), 4.54 (2 H, s), 4.42 - 4.50 (1 H, br.s); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 147.4, 147.3, 142.4, 138.0, 132.9, 131.4, 129.4, 128.8, 127.6, 125.0, 123.5, 119.8, 117.8, 105.1, 104.9, 101.1, 97.2, 48.8; **FTIR:** 3411, 1538, 1499, 1465, 1442, 1406, 1348, 1287, 1252, 1241, 1170, 1137, 1037, 934, 861, 828, 777, 749, 732, 673; **HRMS** m/z $[C_{18}H_{14}O_2NBr^{79}+H]^+$ cal. 356.0281, found. 356.0273 (Δ − 2.1); **m.p.** 129-131 °C (petrol/CH_2Cl_2); single crystal X-ray diffraction data also collected for this comound, see appendix 2.

***N*-((5-Bromobenzo[*d*][1,3]dioxol-4-yl)methyl)-*N*-methylnaphtho[2,3-*d*][1,3]dioxol-5-amine, 422**

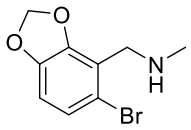


To a solution of aldehyde **408** (44 mg, 0.21 mmol) and $ZnCl_2$ (1.0 M in Et_2O, 0.21 mL, 0.21 mmol) in CH_2Cl_2 was added *N*-methylbenzylamine (129 mg, 1.06 mmol, 0.135 mL). The reaction stirred at 55 °C for 18 hour. The reaction mixture was then concentrated and purified by flash column chromatography (petrol-EtOAc, 19:1) to give *arylamine* **422** (25 mg, 40 %) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.64 (1 H, s, Ar*H*), 7.29 (5 H, m, Ar*H*), 7.19 (2 H, m, Ar*H*), 7.04 (1 H, s, Ar*H*), 6.97 (1 H, dd, *J*=7.5, 1.1 Hz, Ar*H*), 5.95 (2 H, s, OCH_2), 4.13 (2 H, s, NCH_2), 2.64 (3 H, s, CH_3); *NOE enhancements associated with naphthylamine **422** are represented by red arrows on the compound structure*; **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 149.8, 147.6, 147.5, 138.9, 131.9, 128.4 (2C), 127.1, 126.4, 124.4, 122.8, 115.2, 104.4, 101.0, 100.6, 61.3, 42.0; **FTIR** 2896, 1601, 1519, 1497,

1458, 1364, 1240, 1160, 1093, 1039, 951, 917, 851, 745, 698 cm^{-1}; **HRMS** m/z $[C_{19}H_{17}NO_2+H]^+$ cal. 292.1332, found 292.1329 (Δ + 1.2).

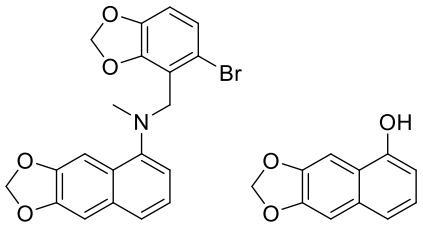
1-(5-Bromobenzo[*d*][1,3]dioxol-4-yl)-*N*-methylmethanamine, 409



To a solution of 5-bromo-1,3-benzodioxole-4-carboxaldehyde (1.00 g, 4.39 mmol) in MeOH (20 mL) was added methylamine (40% in MeOH, 6.7 mL, 74.0 mmol) and the reaction stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the crude residue dissolved in MeOH (20 mL) and cooled to 0 °C. $NaBH_4$ (334 mg, 8.78 mmol) was added portionwise and the reaction allowed to warm to room temperature. After stirring for 1 hour the reaction was quenched with 1 M NaOH and extracted into EtOAc (3x). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash column chromatography (CH_2Cl_2 - MeOH, 19:1) to yield *amine* **409** (1.07 g, 100%).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.94 (1 H, d, *J*=8.3 Hz, Ar*H*), 6.54 (1 H, d, *J*=8.1 Hz, Ar*H*), 5.91 (2 H, s, OCH_2), 3.76 (1 H, s, CH_2), 2.35 (3 H, s, CH_3), 1.65 (1 H, br. s., N*H*); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 147.4, 146.7, 125.2, 121.2, 115.7, 108.5, 101.6, 49.3, 35.6; **FTIR** 2896, 1451, 1240, 1046, 927, 849, 796, 733, 644 cm^{-1}; **HRMS** m/z $[C_9H_{10}BrNO_2+H]^+$ cal. 243.9968, found 243.9971 (Δ − 1.5).

***N*-((5-Bromobenzo[*d*][1,3]dioxol-4-yl)methyl)-*N*-methylnaphtho[2,3-*d*][1,3]dioxol-5-amine, 407 and naphtho[2,3-*d*][1,3]dioxol-5-ol, 423**



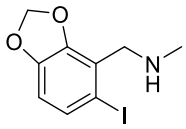
Method A Aldehyde **408 (**70 mg, 0.33 mmol) and amine **409** were subjected to General Procedure 11. In a modification to the General Procedure $ZnCl_2$ (1.0 M in Et_2O, 0.33 mmol, 0.33 mL) was added. Purification by flash column chromatography (petrol-EtOAc, 19:1) afforded *arylamine* **407** (84 mg, 61%) as a white solid.

Method B Amine **409** (50 mg, 0.206 mmol) and $ZnCl_2$ (1.0 M in Et_2O, 0.035 mmol) were dissolved in DCE (1 mL) and heated to 55 °C. To this solution, unsaturated 1,5-dicarbonyl **408** (23 mg, 0.112 mmol) was added dropwise over 12 hours . The reaction mixture was stirred for 24 hours, cooled and then concentrated. The crude product was purified by flash column chromatography (petrol - EtOAc, 19:1) to yield *arylamine* **407** (20 mg, 54%) and *phenol* **423** (5 mg, 24%).

Compound 407: ^{1}**H NMR** (400 MHz, *CHLOROFORM-d*) δ ppm 7.70 (1 H, s, Ar*H*), 7.31 (1 H, d, *J*=8.1 Hz, Ar*H*), 7.17 (1 H, m, Ar*H*), 7.05 (1 H, d, *J*=7.3 Hz, Ar*H*), 7.00 (1 H, s, Ar*H*), 6.94 (1 H, d, *J*=8.3 Hz, *H*C(2)), 6.52 (1 H, d, *J*=8.3 Hz, *H*C(4)), 5.92 (2 H, s, OCH_2), 5.80 (2 H, s, OCH_2), 4.22 (2 H s, NCH_2), 2.67 (3 H, s, CH_3); ^{13}**C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 149.6, 147.9, 147.5, 147.5, 146.7, 131.8, 127.2, 125.5, 124.3, 123.2, 119.9, 117.1, 115.9, 108.6, 104.1, 101.5, 101.2, 100.9, 54.2, 42.8; **FTIR** 2894, 1499, 1453, 1237, 1160, 1103, 1041, 935, 904, 850, 797, 733 cm^{-1}; **HRMS** m/z $[C_{20}H_{16}Br^{79}NO_4+H]^+$ cal. 414.0335, found 414.0326 (Δ + 2.9); **m.p.** 122-124 °C (petrol/CH_2Cl_2); single crystal X-ray diffraction data also collected for this compound, see appendix 2.

Compound 423: **^{1}H NMR** (400 MHz, *CHLOROFORM-d*) δ ppm 7.50 (1 H, s, Ar*H*), 7.27 (1 H, m, Ar*H*), 7.16 (1 H, m, Ar*H*), 7.10 (1 H, s, Ar*H*), 6.70 (1 H, d, *J*=7.6 Hz, Ar*H*), 6.04 (2 H, m, CH_2), 5.28 (1 H, s, O*H*); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 151.0, 148.1, 147.2, 132.1, 124.4, 120.8, 119.9, 107.8, 103.8, 101.1, 98.6. Data were consistent with those previously reported.[186]

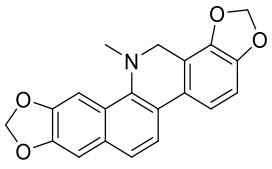
1-(5-Iodobenzo[*d*][1,3]dioxol-4-yl)-*N*-methylmethanamine, 457



A microwave vial was charged with CuI (8 mg, 0.04 mmol), NaI (123mg, 0.823 mmol) and dioxane (4 mL). 1,3-Diaminopropane (6 mg, 0.08 mmol) and aryl bromide **409** (100 mg, 0.412 mmol) were added by syringe and the reaction vessel back filled with Ar. The reaction was then stirred at 130 °C for 24 hour then cooled and diluted with 30% aqueous ammonia. The reaction mixture was poured onto water and extracted with CH_2Cl_2. The organic layers were combined, dried ($NaSO_4$) and concentrated to give crude product which was purified by flash column chromatography (CH_2Cl_2 - MeOH, 19:1) to yield *amine* **457** (75 mg, 63%).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.27 (1 H, d, *J*=8.3 Hz, Ar*H*), 6.50 (1 H, d, *J*=8.3 Hz, Ar*H*), 5.98 (2 H, s, OCH_2), 3.80 (2 H, br. s., CH_2), 2.44 (3 H, br. s., CH_3), 1.89 (1 H, m, N*H*); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 147.8, 146.6, 132.1, 123.7, 109.5, 101.5, 89.4, 53.3, 35.5; **FTIR** 2889, 1449, 1239, 1047, 931, 846, 795 cm^{-1}; **HRMS** m/z $[C_9H_{10}INO_2+H]^+$ cal. 291.9829, found 291.9827 (Δ − 0.7).

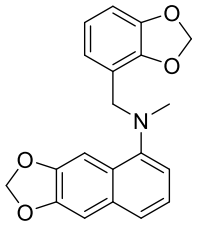
Dihydrosanguanine, 2



A Schlenk tube was charged with bromide **407** (50 mg, 0.12 mmol), neocuprine (25 mg, 0.12 mmol), freshly sublimed KO^{t}Bu (81 mg, 0.72 mmol) and mesitylene (1 mL). The Schlenk tube was then back filled with argon, and heated to 100 °C for 5 h. The reaction mixture was loaded directly onto SiO_2 and eluted with petrol:EtOAc (9:1). Fractions containing the desired product were combined and concentrated *in vacuo* to give *dihydrosanguanine* **2** (23 mg, 58%) as a tan solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.67 - 7.72 (2 H, m, Ar*H*), 7.49 (1 H, d, *J*=8.6 Hz, Ar*H*), 7.31 (1 H, d, *J*=8.1 Hz, Ar*H*), 7.12 (1 H, s, Ar*H*), 6.86 (1 H, d, *J*=8.1 Hz, Ar*H*), 6.06 (2 H, s, OCH_2), 6.05 (2 H, s, OCH_2), 4.21 (2 H, s, NCH_2), 2.63 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 148.2, 147.5, 147.1, 144.7, 142.5, 130.8, 127.3, 126.5, 124.4, 124.0, 120.4, 116.2, 113.6, 107.2, 104.4, 101.4, 101.1, 100.8, 48.5, 41.6; **m.p.** 268-270 °C.

***N*-(Benzo[*d*][1,3]dioxol-4-ylmethyl)-*N*-methylnaphtho[2,3-*d*][1,3]dioxol-5-amine, 428**

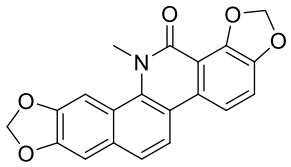


A Schlenk tube was charged with iodide **457** (30 mg, 0.065 mmol), neocuprine (31 mg, 0.13 mmol) and freshly sublimed KO^{t}Bu (102 mg, 0.78 mmol) and benzene (1 mL). The Schlenk tube was then back filled with argon, then heated to 100 °C for 5 hours. The reaction mixture was loaded directly onto SiO_2 and eluted with petrol:EtOAc (9:1). Fractions

containing the desired product were combined and concentrated *in vacuo* to give *dihydrosanguianine* **2** (9 mg, 43%) and *amine* **428** (4 mg, 19%).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.79 (1 H, s, Ar*H*), 7.41 (1 H, d, *J*=8.1 Hz, Ar*H*), 7.26 (1 H, t, *J*=7.8 Hz, Ar*H*), 7.12 (1 H, s, Ar*H*), 7.06 (1 H, d, *J*=7.3 Hz, Ar*H*), 6.91 (1 H, d, *J*=7.3 Hz, Ar*H*), 6.81 (1 H, t, *J*=7.6 Hz, Ar*H*), 6.76 (1 H, dd, *J*=7.6, 1.2 Hz, Ar*H*), 6.05 (2 H, s, OCH_2), 5.95 (2 H, s, OCH_2), 4.18 (2 H, s, NCH_2), 2.77 (3 H, s, CH_3); ^{13}C NMR (100 MHz, *CHLOROFORM-d*) δ ppm 149.5, 147.6, 147.4, 147.2, 145.9, 131.8, 126.6, 124.3, 123.0, 122.6, 121.4, 120.1, 115.3, 107.4, 104.3, 100.9, 100.8 (2C), 55.2, 41.9; **FTIR** 2895, 1458, 1245, 1039, 932, 851, 748 cm^{-1}; **HRMS** m/z $[C_{20}H_{17}NO_4+H]^+$ cal. 336.1230, found 336.1232 (Δ − 0.5).

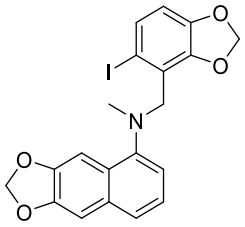
Oxysanguanine, 348



Activated MnO_2 (65 mg, 0.750 mmol) was added to a stirred solution of dihydrosanguanine **(2)** (10 mg, 0.030 mmol) in chloroform (0.7 mL) under nitrogen at room temperature. After stirring for 36 hours, the mixture was filtered and the filtrate was evaporated *in vacuo* to give a brown oil which was purified by flash column chromatography (CH_2Cl_2-MeOH, 99.5:0.5) to give *oxysanguanine* **(348)** (4 mg, 42%).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.99 (1 H, d, *J*=8.6 Hz, Ar*H*), 7.77 (1 H, d, *J*=8.6 Hz, Ar*H*), 7.59 (1H, s, Ar*H*), 7.54 (1 H, d, *J*=8.8 Hz, Ar*H*), 7.25 (1H, d, *J* =8.4 Hz, Ar*H*), 7.17 (1 H, s, Ar*H*), 6.28 (2 H, s, OCH_2), 6.11 (2 H, s, OCH_2), 3.92 (3 H, s, CH_3). Solvent containments could not be removed even under prolonged exposure to heat and high vacuum. Data were consistent with those previously reported.[187]

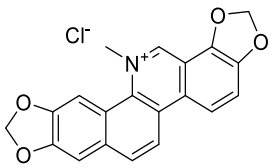
***N*-((5-Iodobenzo[*d*][1,3]dioxol-4-yl)methyl)-*N*-methylnaphtho[2,3-*d*][1,3]dioxol-5-amine, 458**



Amine **457** (70 mg, 0.206 mmol) and $ZnCl_2$ (1.0 M in Et_2O, 0.04 mL) were dissolved in DCE (1.5 mL) and heated to 55 °C. To this solution, aldehyde **408** (33 mg, 0.16 mmol) was added dropwise over 12 hours. The reaction mixture was stirred for 24 hours, cooled and then concentrated. The crude product was purified by flash column chromatography (petrol - EtOAc, 19:1 to 9:1) to yield *arylamine* **458** (40 mg, 55%).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.78 (1 H, s, Ar*H*), 7.38 (1 H, d, *J*=8.1 Hz, Ar*H*), 7.27 (2 H, m, Ar*H*), 7.16 (1 H, d, *J*=7.1 Hz, Ar*H*), 7.07 (1 H, s, Ar*H*), 6.48 (1 H, d, *J*=8.1 Hz, Ar*H*), 6.00 (2 H, s, OCH_2), 5.90 (2 H, s, OCH_2), 4.25 (2 H, s, NCH_2), 2.74 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 149.6, 147.7, 147.5 (2C), 147.0, 132.5, 131.8, 127.1, 124.3, 123.2, 122.5, 115.9, 109.5, 104.1, 101.5, 101.3, 100.9, 90.8, 57.4, 43.3; **FTIR** 2893, 1458, 1240, 1160, 1200, 1047, 934, 848, 797, 748 cm^{-1}; **HRMS** m/z $[C_{20}H_{16}INO_4+H]^+$ cal. 462.0197, found 462.0186 (Δ − 2.6).

Sanguanine, 344

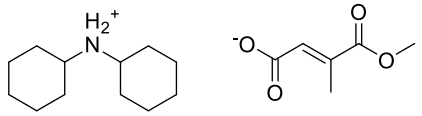


To a vigorously stirred solution of dihydrosanguanine **(2)** (10 mg, 0.030 mmol) in PhMe (10 mL) was added, 5% NaOH (1 mL) then DDQ (17 mg, 0.075 mmol). The reaction was stirred for 2 hours at room temperature. Water (5 mL) was added and the mixture was

extracted with EtOAc (3 x 10 mL), the organic layers combined, dried ($MgSO_4$) and concentrated. Concentrated HCl was then added to the resulting residue and the precipitate collected by filtration to yield *sanguanine* **(344)** (10 mg, 90%).

^{1}H NMR (200 MHz, *METHANOL-d_4*) δ ppm 9.93 (1 H, s, Ar*H*), 8.59 (1 H, d, *J*=9.2 Hz, Ar*H*), 8.50 (1 H, d, *J*=8.9 Hz, Ar*H*), 8.19 (1 H, d, *J*=8.9 Hz, Ar*H*), 8.13 (1 H, s, Ar*H*), 7.94 (1 H, d, *J*=8.5 Hz, Ar*H*), 7.54 (1 H, s, Ar*H*), 6.53 (2 H, s, OCH_2), 6.28 (2 H, s, OCH_2), 4.94 (3 H, s, CH_3); **^{13}C NMR** (500 MHz, *DMSO-d_6*) δ ppm 149.9, 148.7 (2C), 147.5, 146.3, 132.2, 131.5, 131.3, 127.2, 125.7, 120.3, 119.9, 118.9, 117.3, 109.5, 105.7, 104.9, 104.2, 102.8, 52.1. Data were consistent with those previously reported.[188]

Dicyclohexylammonium (*E*)-4-methoxy-3-methyl-4-oxobut-2-enoate, 465



To a solution of citraconic anhydride (20.0 g, 0.179 mmol) cooled to −10 °C was added dicyclohexylamine (35.6 g, 0.196 mmol, 39.1 mL) dropwise. The reaction was stirred at room temperature for 30 minutes then concentrated. EtOAc was added to the residue and stirred. After 1 hour the solid was isolated by filtration and washed with EtOAc to give *salt* 465 (28.2g, 49%) as a white solid.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.04 (1 H, d, *J*=1.5 Hz, C=C*H*), 3.70 (3 H, s, OCH_3), 2.95 (2 H, tt, *J*=11.5, 3.5 Hz, NCH_2), 1.97 - 2.07 (5 H, m, CH_2), 1.94 (3 H, s, CCH_3), 1.72 - 1.84 (5 H, m, CH_2), 1.57 - 1.68 (2 H, m, CH_2), 1.40 - 1.56 (5 H, m, CH_2), 1.14 - 1.30 (6 H, m, CH_2); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 171.2, 170.0, 132.9, 52.5, 51.4, 29.1, 25.1, 24.9, 19.7. Data were consistent with those previously reported.[189]

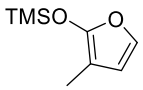
3-Methylfuran-2(5*H*)-one, 467



A suspension of salt **465** (28.0 g, 0.862 mmol) in CH_2Cl_2 was cooled to −10 °C and isobutyl chloroformate (13.0 g, 0.948 mmol) added carefully. The reaction was stored for 12 hours at 0 °C. The reaction mixture was cooled to −10 °C and THF (75 mL) added. The solid was isolated by filtration and washed with THF (75 mL). A cooled solution of $NaBH_4$ (65.5 g, 1.72 mmol) in water (15 mL) was added over 1 hour to the isolated solid and the reaction stirred for a further 2 hours whilst maintaining the temperature at 0 °C. The reaction mixture was filtered and the solid washed with Et_2O. The filtrate was dried ($MgSO_4$), concentrated and purified by distillation (80 °C, 13 mbar) to give *furanone* **467** (5.19 g, 62%) as a colourless oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.09 (1 H, q, *J*=1.7 Hz, C=C*H*), 4.70 (2 H, t, *J*=2.2 Hz, CH_2), 1.87 (3 H, q, *J*=2.0 Hz, CH_3). **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 174.9, 145.1, 129.8, 70.1, 10.7. Data were consistent with those previously reported.[190]

3-Methylfuran-2(5H)-one, 463

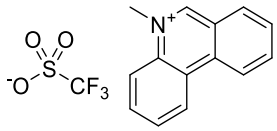


To a solution of furanone **467** (2.00 g, 20.4 mmol) and triethylamine (2.47 g, 24.5 mmol, 3.68 mL) in CH_2Cl_2 (50 mL) cooled to 0 °C was added TMSOTf (4.61 g, 20.4 mmol, 4.13 mL) and the reaction stirred for a further 1 hour at 0 °C, then warmed to room temperature and stirred for a further 30 minutes. The reaction mixture was diluted with CH_2Cl_2 and washed with a 1 M $CuSO_4$ solution. The organic layer was dried, concentrated at 200 mbar

and purified by distillation (80 °C, 80 mbar) to give *furan* **463** (2.12 g, 61 %) as a colourless oil.

^{1}H NMR (200 MHz, *CHLOROFORM-d*) δ ppm 6.77 (1 H, d, *J*=1.7 Hz, Ar*H*), 6.11 (1 H, d, *J*=1.7 Hz, Ar*H*), 1.83 (3 H, s, CCH_3), 0.28 (9 H, s, $SiCH_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 206.5, 131.7, 128.6, 124.8, 66.7, 30.4. Data were consistent with those previously reported.[191]

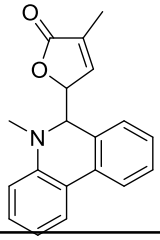
5-Methylphenanthridin-5-ium, 476



To a solution of phenanthridine (1.79 g, 10.0 mmol) in CH_2Cl_2 (20 mL) was added a solution of methyl triflate (1.65 g, 10.0 mmol) in CH_2Cl_2 (10 mL) cautiously. After the exotherm had subsided the reaction was quenched by the addition of Et_2O and filtered. The salt was collected and recrystallised from MeCN:EtOAc to give *pyridinium salt* **476** (2.66 g, 78%).

^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm 10.22 (1 H, d, *J*=8.6 Hz, Ar*H*), 8.95 - 9.18 (2 H, m, Ar*H*), 8.50 (2 H, d, *J*=5.1 Hz, Ar*H*), 8.34 (1 H, d, *J*=8.3 Hz, Ar*H*), 7.97 - 8.16 (3 H, m, Ar*H*), 4.55 - 4.66 (3 H, m, CH_3); **^{13}C NMR** (100 MHz, *DMSO-d*$_6$) δ ppm 156.4, 138.4, 138.3, 134.6, 133.1, 132.4, 130.8, 125.8, 125.1, 124.0, 123.7, 123.6, 120.5, 46.3. Data were consistent with those previously reported.[192]

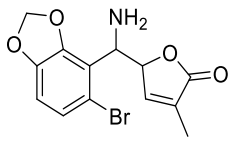
3-Methyl-5-(5-methyl-5,6-dihydrophenanthridin-6-yl)furan-2(5*H*)-one, 477



To a solution of pyridinium salt **476** (50 mg, 0.146 mmol) and triethylamine (90 mg, 0.292 mmol) in dimethyl sulfoxide (5 mL) was added furan **463** (49 mg, 0.292 mmol) and the reaction stirred for 1 hour. The reaction was quenched by the addition of a saturated solution of NH_4Cl and extracted into diethyl ether (x5). The crude product was purified by flash column chromatography (petrol - EtOAc, 9:1) to yield *dihydropyridine* **477** (38 mg, 95%, 1:0.6 dr).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.70 - 7.84 (3.2 H, m, Ar*H*), 7.36 - 7.46 (1.6 H, m, Ar*H*), 7.15 - 7.35 (3.8 H, m, Ar*H*), 7.08 (1 H, d, *J*=7.3 Hz, Ar*H*), 6.87 - 6.95 (1 H, m, Ar*H*), 6.78 - 6.86 (1.6 H, m, Ar*H*), 6.55 - 6.61 (1.6 H, m, Ar*H* and C=C*H*), 6.48 - 6.51 (0.6 H, m, C=C*H*), 4.93 - 4.99 (1.6 H, m, OC*H* and NC*H*), 4.88 - 4.92 (0.6 H, m, OC*H*), 4.32 (1 H, d, *J*=7.6 Hz, NC*H*), 3.24 (3 H, s, NCH_3), 3.13 (1.8 H, s, NCH_3), 1.77 (3 H, t, *J*=1.6 Hz, CCH_3), 1.53 (1.8 H, t, *J*=1.6 Hz, CCH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 173.8, 173.8, 146.0, 145.0, 144.6, 143.5, 131.8, 131.8, 130.5, 130.4, 130.0, 129.9 (2C), 129.6, 128.7, 128.7, 127.3, 127.1, 127.0, 126.7, 123.3, 123.1, 123.0, 122.7, 121.9, 121.2, 118.5, 117.9, 113.4, 112.4, 86.7, 81.2, 67.3, 65.2, 40.3, 39.2, 10.7, 10.3; **FTIR** 1750, 1602, 1494, 1445, 1214, 1090, 1058, 751, 730 cm^{-1}; **HRMS** m/z $[C_{19}H_{17}O_2N+H]^+$ cal. 292.1338, found 292.1329 (Δ − 3.0).

5-(Amino(5-bromobenzo[*d*][1,3]dioxol-4-yl)methyl)-3-methylfuran-2(5*H*)-one, 471

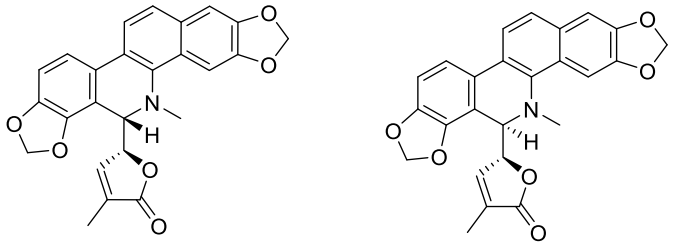


5-Bromo-1,3-benzodioxole-4-carboxaldehyde (200 g, 1.15 mmol) and o-Anisidine (141 mg, 1.15 mmol, 0.129 mL) were stirred in a round bottom flask and stirred for 15 minute. Furan **463** (293 mg, 1.73 mmol) was added and the reaction stirred for a further 30 min. The crude material was filtered through a cartridge of SiO_2 (petrol - EtOAc, 7:3 to 1:1). The fractions

containing the target product were combined and concentrated *in vacuo*. The crude residue was dissolved in MeOH and added over 15 minute to a stirring solution of $PhI(OAc)_2$ (849 mg, 2.64 mmol) in MeOH (5 mL) cooled to 0 °C. The reaction was stirred for 30 minute then 1.0 M aqueous HCl (5 mL) was added and the reaction stirred for 1 hour at room temperature. The reaction was diluted with CH_2Cl_2, the aqueous layer washed with CH_2Cl_2, the organic layers combined and washed with 1.0 M aqueous HCl. The aqueous layers were then combined, neutralised with 1 M aqueous NaOH, extracted with CH_2Cl_2, dried ($NaSO_4$) and concentrated. The crude material was purified by flash column chromatography (CH_2Cl_2- MeOH, 19:1) to yield *amine* **471** (50 mg, 13 %, 1:0.4 dr).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.12 - 7.17 (0.4 H, m, C=C*H*), 7.08 (1.0 H, d, *J*=8.3 Hz, Ar*H*), 7.05 (0.4 H, d, *J*=8.3 Hz, Ar*H*), 6.76 - 6.82 (1.0 H, m, C=C*H*), 6.68 (1.0 H, d, *J*=8.3 Hz, Ar*H*), 6.65 (0.4 H, d, *J*=8.3 Hz, Ar*H*), 6.04 (2.0 H, d, *J*=3.9 Hz, OCH_2), 6.02 (0.8 H, d, *J*=5.7 Hz, OCH_2), 5.15 - 5.23 (1.4 H, m, C*H*NH_2), 4.56 (0.4 H, d, *J*=5.9 Hz, OC*H*), 4.26 (1.0 H, d, *J*=7.8 Hz, OC*H*), 2.00 (2.8 H, br. s, NH_2), 1.89 - 1.95 (4.2 H, s, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm174.0, 147.7, 147.6, 146.7, 146.5, 146.3, 145.9, 131.7, 131.2, 126.2, 126.1, 122.0, 121.5, 114.5, 114.3, 109.5, 109.3, 101.9, 101.8, 83.8, 82.8, 57.9, 56.5, 10.8, 10.7 (1 signal missing); **FTIR:** 1755, 1452, 1240, 1092, 1049, 931, 869, 801; **HRMS** m/z $[C_{13}H_{12}BrNO_4+H]^+$ cal. 326.0022, found 326.0028.(Δ − 1.7).

Maclekarpine B, (459a) and maclekarpine C, (459b)



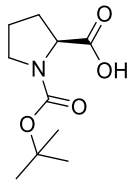
To a solution of diisopropyl amine (6 mg, 0.04 mmol) in THF (0.7 mL) at −78 °C was added *n*BuLi (0.15 mL, 0.43 mmol, 2.5 M in hexanes). The reaction was allowed to warm to

room temperature and stirred for 10 minutes. The solution was then cooled to −78 °C and a suspension of sanguanine (10 mg, 0.03 mmol) **(21)** added dropwise. The solution was allowed to stir for a further 30 minute then warmed to room temperature. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl and extracted into EtOAc (3 x 5 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated. The crude material was purified by flash column chromatography (petrol- EtOAc, 8:2) to give maclekarpine B **(459a)** and maclekarpine C **(459b)** (8 mg, 73 %, 0.85:1 dr) as an inseparable mixture.

Maclekarpine B: ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.67 (2 H, d, *J*=8.5 Hz), 7.53 (1 H, s), 7.46 (1 H, d, *J*=8.5 Hz), 7.38 (1 H, d, *J*=8.2 Hz), 7.09 (1 H, s), 6.93 (1 H, d, *J*=7.9 Hz), 6.51 (1 H, s), 6.14 (1 H, d, *J*=1.6 Hz), 6.07 (2 H, d, *J*=1.3 Hz), 6.06 (1 H, br. s.), 4.79 - 4.84 (1 H, m), 4.62 (1 H, d, *J*=6.0 Hz), 2.72 (3 H, s), 1.34 (3 H, s); ^{13}C NMR (125 MHz, *CHLOROFORM-d*) δ ppm 174.2, 148.4, 147.7, 147.4, 145.8, 145.6, 140.0, 131.1, 129.5, 126.8, 126.0, 124.2, 123.2, 119.7, 116.3, 111.9, 108.5, 104.3, 101.8, 101.1, 100.6, 81.3, 60.2, 43.5, 10.1. Data were consistent with those previously reported.[193]

Maclekarpine C: ^{1}H NMR (500 MHz, *CHLOROFORM-d*) δ ppm 7.76 (1 H, s), 7.67 (3 H, d, *J*=8.5 Hz), 7.50 (1 H, d, *J*=8.5 Hz), 7.35 (1 H, d, *J*=8.2 Hz), 7.12 (1 H, s), 6.91 (1 H, d, *J*=8.2 Hz), 6.45 (1 H, s), 6.10 (1 H, br. s), 6.07 (6 H, br. s), 6.03 (1 H, br. s), 4.75 - 4.83 (1 H, m), 4.48 (1 H, d, *J*=7.6 Hz), 2.74 (3 H, s), 1.72 (3 H, s); ^{13}C NMR (125 MHz, *CHLOROFORM-d*) δ ppm 173.9, 148.4, 147.9, 147.3, 146.0, 145.5, 139.3, 131.0, 130.2, 127.1, 126.6, 124.3, 123.4, 119.7, 116.6, 110.9, 108.6, 104.3, 101.7, 101.2, 101.1, 81.3, 60.9, 43.2, 10.6. Data were consistent with those previously reported.[10]

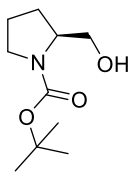
(*S*)-1-(*tert*-Butoxycarbonyl)pyrrolidine-2-carboxylic acid



To a solution of (L)-proline (10.0 g, 115 mmol) dissolved in saturated aqueous solution $NaHCO_3$ (aq.) (125 mL) was added a solution di-*tert*-butyl dicarbonate (20.7 g, 95.0 mmol) in THF (50 mL) and stirred for 12 hours. The THF was removed *in vacuo* and the remaining mixture quenched with 3 M HCl and extracted with EtOAc (x3). The organic layers were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield *title compound* (18.4 g, 75%) which was used without further purification.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 11.06 (1 H, br. s., COO*H*), 4.17 - 4.41 (1 H, m, C*H*COOH), 3.27 - 3.64 (2 H, m, NCH_2), 2.18 - 2.36 (1 H, m, CH_aH$_b$CH), 1.80 – 2.17 (3 H, m, $CH_2CH_2CH_2$ and $CH_2CH_aH_bCH$), 1.37 - 1.53 (9 H, m, 3 x CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 178.9, 156.0, 81.1, 59.0, 46.9, 30.8, 28.4, 24.3; **m.p.** 131 - 133 ^{o}C (petrol/CH_2Cl_2); **specific rotation** $[\alpha]_D^{20}$ −124.3 (CH_2Cl_2, c = 1.0). The (*R*) enantiomer was also synthesised: **specific rotation** $[\alpha]_D^{20}$ +124.1 (CH_2Cl_2, c = 1.0). Data were consistent with those previously reported.[194]

***tert*-Butyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate**

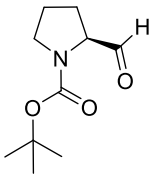


To a stirred solution of 1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxylic acid **S2** (15.0 g, 69.8 mmol) in THF (300 mL) was added dropwise $BH_3.SMe_2$ (6.90 g, 90.7 mmol, 8.60 mL) over 45 minutes. The reaction was then heated to reflux. After a further 2 hours stirring at

reflux the reaction mixture was cooled and concentrated *in vacuo*. The crude mixture was diluted with CH_2Cl_2 and washed sequentially with water and brine. The organic layer was isolated dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield *title compound* (13.2 g, 94%) which was used without further purification.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 4.71 - 4.81 (1 H, m, O*H*), 3.81 - 4.03 (1 H, m, NC*H*), 3.59 (2 H, dd, *J*=7.8, 2.8 Hz, C*H*$_2$OH), 3.39 - 3.51 (1 H, m, NC*H*$_a$H$_b$), 3.32 (1 H, m, NCH$_a$*H*$_b$), 2.00 (1 H, m, CH$_2$CH$_a$*H*$_b$), 1.81 (2 H, m C*H*$_2$CH$_a$H$_b$), 1.51 - 1.65 (1 H, m, CH$_2$C*H*$_a$H$_b$), 1.47 (9 H, s (C*H*$_3$)$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 159.0, 80.2, 67.8, 60.2, 53.4, 47.5, 28.7, 24.1; **specific rotation** $[\alpha]_D^{20}$ + 46.0 (CH_2Cl_2, c = 1.0). The (*R*) enantiomer was also synthesised: **specific rotation** $[\alpha]_D^{20}$ − 38.6 (CH_2Cl_2, c = 1.0). Data was consistent with those previously reported in the literature.[195]

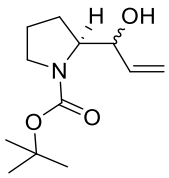
***(S)-tert-B*utyl 2-formylpyrrolidine-1-carboxylate, 505**



A stirred solution of oxalyl chloride (7.80 g, 61.0 mmol, 5.30 mL) dissolved in CH_2Cl_2 (125 mL) was cooled to −78 ºC. A solution of $(CH_3)_2SO$ (8.70 g, 111 mmol, 7.90 mL) in CH_2Cl_2 (25 mL) was then added dropwise. After a further 10 minutes stirring a solution of *tert*-butyl-2-(hydroxymethyl)pyrrolidine-1-carboxylate (10.2 g, 50.5 mmol) in CH_2Cl_2 (50 mL) was added dropwise. After stirring for 30 minutes, Et_3N (20.4 g, 202 mmol, 28.2 mL) was added over 4 minutes and the reaction allowed to warm to room temperature slowly. The reaction mixture was then washed with 1 M HCl (x3), water (x3) and brine and the organic layer dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was then purified by flash column chromatography (petrol-EtOAc, 1:1) to yield *aldehyde* **505** (8.50 g, 84%).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 9.55 (1 H, d, *J*=2.8Hz, C*H*(O)), 4.16 - 4.24 (1 H, m, NC*H*C(O)), 3.38 - 3.62 (2 H, m, NCH_2CH_2), 1.77 - 2.25 (4 H, m, NCH$_2$CH_2 and NCH$_2$CH_2), 1.48 (9H, s, (CH_3)$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 200.7, 153.9, 80.6, 65.0, 46.8, 28.4, 28.0, 24.6; **specific rotation** $[\alpha]_D^{20}$ + 85.9 (CH_2Cl_2, c = 1.0). The (*R*) enantiomer was also synthesised: **specific rotation** $[\alpha]_D^{20}$ − 81.5 (CH_2Cl_2, c = 1.0). Data was consistent with those previously reported in the literature.[195]

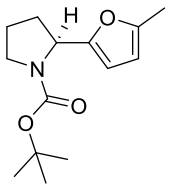
***(S)-tert*-Butyl 2-(1-hydroxyallyl)pyrrolidine-1-carboxylate, 506**



tert-Butyl 2-formylpyrrolidine-1-carboxylate **505** (1.00 g, 5.00 mmol) was subjected to General Procedure 13. The crude product was purified by flash column chromatography (petrol-EtOAc, 1:1) to yield *allylic alcohol* **506** (205 mg, 90%, 1:1 dr) as an oil and mixture of diastereomers which were not separated.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 5.65 - 5.85 (1 H, m, CH$_2$=C*H*), 5.04 - 5.30 (3 H, m, CH_2=CH, O*H*), 3.66 - 4.46 (2 H, m, NC*H*CHOH and NCHC*H*OH), 3.07 - 3.56 (2 H, m, NCH_2,), 1.59 - 1.91 (4 H, m, NCH$_2$CH_2CH_2), 1.40 (9 H, br. s, (CH_3)$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 157.7, 138.3, 116.7, 80.4, 75.7, 62.7, 48.0, 28.3, 28.1, 24.0; **specific rotation** $[\alpha]_D^{20}$ +72.0 (CH_2Cl_2, c = 1.0). The (*R*) enantiomer was also synthesised: **specific rotation** $[\alpha]_D^{20}$ −68.5 (CH_2Cl_2, c = 1.0). Data was consistent with those previously reported in the literature.[196]

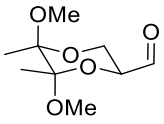
***tert*-Butyl (S)-2-(5-methylfuran-2-yl)pyrrolidine-1-carboxylate, 507**



tert-Butyl-2-(1-hydroxyallyl)pyrrolidine-1-carboxylate **506** (60 mg, 0.26 mmol) and methyl vinyl ketone were subjected to general conditions 14. The reaction was purified by flash column chromatography (petrol-EtOAc, 19:1) to yield *furan* **507** (35 mg, 53%) as an oil.

^{1}H NMR (500 MHz, *DMSO-d*$_6$, 90 °C) δ ppm 5.96 (1 H, d, *J*=2.5 Hz, Furan-*H*), 5.93-5.95 (1 H, m, Furan-*H*), 4.74 - 4.78 (1 H, m, NC*H*), 3.37 (2 H, t, *J*=6.3 Hz, NCH_2), 2.22 (3 H, s, Furan-CH_3), 2.07 - 2.17 (1 H, m, $CH_2CH_aH_b$), 1.89 - 1.97 (2 H, m, $CH_2CH_aH_b$), 1.86 (1 H, d, *J*=6.6 Hz, $CH_2CH_aH_b$), 1.35 (9 H, s, C(CH_3)$_3$); **^{13}C NMR** (125 MHz, *DMSO-d*$_6$, 90 °C) δ ppm 154.9, 154.0, 150.3, 106.5, 106.2, 78.8, 54.8, 46.4, 31.9, 28.6, 23.6, 13.5; **FTIR**: 2976, 1695, 1390, 1365, 1160, 1113, 1019, 875, 780 cm^{-1}; **HRMS** m/z $[C_{14}H_{21}NO_3+Na]^+$ cal. 274.1414, found 274.1413 (Δ + 0.3 ppm); **specific rotation** $[\alpha]_D^{20}$ −37.0. (CH_2Cl_2, c = 1.0, ee >95%); **HPLC conditions**: Chiral AD column; flow rate = 1.0 mL/min; rt, 199:1 hept/*i*-PrOH; retention time: 16.0 min, 18.45 min.

(2*S*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2-carbaldehyde, 509

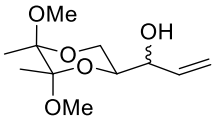


To a stirred solution of D-mannitol (10.0 g, 54.9 mmol), anhydrous trimethyl orthoformate (23.3 g, 220 mmol, 26.2 mL) and butane-2,3-dione (9.90 g, 115 mmol, 10.1 mL) in MeOH (70 mL) was added $BF_3.Et_2O$ (1.90 g, 13.7 mmol, 1.65 mL) dropwise. After stirring for a further 5 hours at room temperature the mixture was neutralised by the addition of Et_3N and concentrated *in vacuo*. The crude product was washed sequentially with water and brine and

the organic layer dried ($MgSO_4$), filtered and concentrated. The crude product was dissolved in CH_2Cl_2 (65 mL) and a saturated aqueous solution of $NaHCO_3$ (40 mL) and $NaIO_4$ (32.0 g, 150 mmol) was added portionwise and the mixture stirred for 12 hours. $MgSO_4$ (80 g) was added and the mixture stirred for 20 minutes after which the mixture was filtered, stirred with $Na_2S_2O_3$ (16 g) for 30 minutes, filtered and concentrated *in vacuo*. The crude product was purified by distillation (21 mbar, 117-119 ^oC) to yield *aldehyde* **509** (6.4 g, 64 %).

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 9.65 (1 H, s, C*H*O), 4.35 (1 H, dd, *J*=10.0, 5.2 Hz, C*H*CH_aH_b), 3.71 (1 H, d, *J*=10.1 Hz, CHC*H*$_a$H$_b$), 3.70 (1 H, d, *J*=5.1 Hz, CHCH$_a$*H*$_b$), 3.32 (3 H, s,OC*H*$_3$), 3.27 (3 H, s, OC*H*$_3$), 1.38 (3 H, s, CC*H*$_3$), 1.30 (3 H, s, CC*H*$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 200.3, 99.8, 98.3, 72.4, 58.3, 48.4, 48.2, 17.6, 17.5; **specific rotation** $[\alpha]_D^{20}$ − 1.165 (CH_2Cl_2, c = 1.0). Data was consistent with those previously reported in the literature.[197]

1-((2*S*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)prop-2-en-1-ol, 510

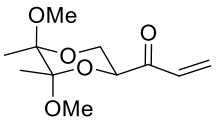


5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2-carbaldehyde **509** (1.70 g, 7.32 mmol) was subjected to General Procedure 13. The crude product was purified by flash column chromatography (petrol-EtOAc, 4:1 to 1:1) to yield *allylic alcohol* **510** (1.61 g, 82%) as an oil and 2:1 mixture of diastereomers which were not separated.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 5.81 (1 H, ddd, *J*=17.4, 10.7, 5.3 Hz, C*H*=CH_2), 5.30 (1 H, dt, *J*=17.2, 1.6 Hz, CH=C*H*$_{trans}$H$_{cis}$), 5.14 (1 H, dt, *J*=10.6, 1.5 Hz, CH=CH$_{trans}$*H*$_{cis}$), 4.04 - 4.17 (1 H, m, C*H*COH), 3.70 (1 H, t, *J*=10.6 Hz, C*H*$_a$H$_b$CH), 3.76 (1 H, ddd, *J*=11.1, 4.8, 2.5 Hz, CH$_a$H$_b$C*H*), 3.45 (1 H, dd, *J*=10.6, 2.5 Hz, CH$_a$*H*$_b$CH), 3.19 (3

H, s, OC*H*$_3$), 3.19 (3 H, s, OC*H*$_3$), 2.76 (1H, br.s., O*H*) 1.22 (3 H, s, CC*H*$_3$), 1.20 (3 H, s, CC*H*$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 136.0, 116.2, 99.2, 97.9, 72.2, 69.8, 59.3, 47.9, 47.9, 17.6, 17.4; **FTIR** 3457, 2929, 1722, 1459, 1383, 1031, 907, 731, 647 cm^{-1}; **HRMS** m/z $C_{11}H_{20}NaO_5$ calculated 255.1203, found 255.1205 (Δ − 0.8 ppm); **specific rotation** $[\alpha]_D^{20}$ + 22.0 (CH_2Cl_2, c = 0.01). Racemic material was also synthesised *via* the same route.

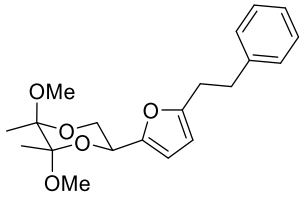
1-((2*S*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)prop-2-en-1-one, 511



To a solution of Dess-Martin periodinone (601 mg, 2.59 mmol) in CH_2Cl_2 (25 mL) cooled to 0 ^oC was added a solution of 1-(5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)prop-2-en-1-ol **(510)** (500 mg, 2.16 mmol) in CH_2Cl_2 (20 mL) and stirred for 2 hours. The reaction mixture was diluted in Et_2O and washed sequentially with 1 M NaOH, water, brine. The organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash column chromatography (petrol-EtOAc, 8:2) to yield *enone* **511** (415 mg, 84 %) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.85 (1 H, dd, *J*=17.4, 10.6 Hz, C*H*=CH$_a$H$_b$), 6.43 (1 H, dd, *J*=17.4, 1.8 Hz, CH=C*H*$_a$H$_b$), 5.81 (1 H, dd, *J*=10.6, 1.5 Hz, CH=CH$_a$*H*$_b$), 4.54 (1 H, t, *J*=7.5 Hz, CH$_2$C*H*O), 3.76 (2 H, d, *J*=7.3 Hz, C*H*$_2$CHO), 3.33 (3 H, s, OC*H*$_3$), 3.26 (3 H, s, OC*H*$_3$), 1.38 (3 H, s, C*H*$_3$), 1.31 (3 H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 196.5, 131.1, 130.0, 99.7, 98.0, 72.0, 59.6, 48.3, 48.1, 17.6, 17.5; **FTIR** 2950, 1699, 1612, 1375, 1141, 1118, 1036, 948, 880 cm^{-1}. **HRMS** m/z [$C_{11}H_{18}NaO_5$] calculated 253.1046, found 369.1668 (Δ − 1.0 ppm); **specific rotation** $[\alpha]_D^{20}$ −1.5 (CH_2Cl_2, c = 1.0).

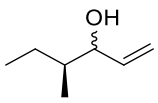
2,3-Dimethoxy-2,3-dimethyl-5-(5-phenethylfuran-2-yl)-1,4-dioxane, 513



Enone **513** (53 mg, 0.25 mmol) and allylic alcohol **512** (15 mg, 0.092 mmol) were subjected to general conditions 14. In a modification to the reaction conditions the reaction was heated at 55 °C for 72 hours. The reaction was purified by flash column chromatography (petrol-EtOAc, 19:1) to yield *furan* **513** (35 mg, 53%) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.12 - 7.37 (5 H, m, 5 x Ar-*H*), 6.25 (1 H, d, *J*=3.1 Hz, Furan-*H*), 5.94 (1 H, d, *J*=3.1 Hz, Furan-*H*), 4.92 (1 H, dd, *J*=11.3, 3.1 Hz, C*H*CH_aCH_b), 4.06 (1 H, t, *J*=11.3 Hz, CHC*H*$_a$$CH_b$), 3.59 (1 H, dd, *J*=11.3, 3.1 Hz, $CHCH_aCH_b$), 3.38 (3 H, s, OC*H*$_3$), 3.34 (3 H, s, OC*H*$_3$), 2.95 (4 H, s, C*H*$_2$C*H*$_2$), 1.36 (3 H, s, CC*H*$_3$), 1.35 (3 H, s, CC*H*$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 155.9, 149.1, 141.1, 128.4, 128.3, 126.0, 109.0, 105.8, 99.5, 97.9, 63.7, 61.4, 48.1, 48.1, 34.2, 29.8, 17.8, 17.6; **FTIR:** 2949, 1455, 1374, 1141, 1120, 1038, 947, 878, 789, 699 cm^{-1}; **HRMS** m/z $[C_{20}H_{26}O_5+Na]^+$ cal. 369.1672, found 369.1668.(Δ + 1.2 ppm); **specific rotation** $[\alpha]_D^{20}$ −73.0 9 (100% ee, CH_2Cl_2, c = 1.0); **Chiral HPLC conditions:** Chiral AD column; flow rate = 1.0 mL/min; rt, 99:1 hept/*i*PrOH; retention time: 5.80 min. Racemic material was also synthesised.

(*S*)-2-Methylbutanal, 516

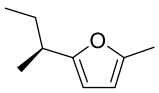


2-Methylbutyraldehyde (500 mg, 5.81 mmol) was subjected to General Procedure 13. The crude product was purified by flash column chromatography (petrol-EtOAc, 4:1 to 1:1) to

yield *allylic alcohol* **516** (1.6 g, 82 %, 1:0.5 dr) as an oil and mixture of diastereomers which were not separated.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 5.76 - 5.93 (1.5 H, m, C*H*=CH_2), 5.22 (1.5 H, d, *J*=17.1 Hz, CH=CH_aH_b), 5.14 (1.5 H, d, *J*=10.5 Hz, CH=CH_aH_b), 4.00 (1 H, t, J=4.9 Hz, C*H*OH), 3.95 (0.5 H, t, J=5.7 Hz, C*H*OH), 1.61 - 1.74 (1.5 H, m, CHO*H*), 1.39 - 1.60 (3 H, m, CH_2), 1.02 - 1.23 (1.5 H, m, CH_3C*H*), 0.79 - 0.97 (9 H, m, CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 140.0, 139.3, 115.7, 115.1, 77.0, 76.6, 40.3, 40.2, 25.3, 25.0, 14.4, 13.9, 11.7, 11.5; **specific rotation** $[\alpha]_D^{20}$ − 11 (CH_2Cl_2, c = 1.0). Data was consistent with those previously reported in the literature.[198]

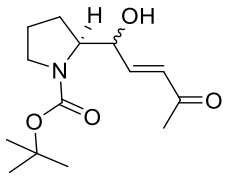
2-(*sec*-Butyl)-5-methylfuran, 517



(*S*)-2-Methylbutanal **516** (60 mg, 0.26 mmol) and methyl vinyl ketone were subjected to general conditions 14. The reaction was purified by flash column chromatography (petrol-EtOAc, 19:1) to yield *furan* **517** (35 mg, 53%) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 5.71 - 5.80 (2 H, m, Furan-*H*), 2.59 (1 H, sxt, *J*=6.8 Hz, C*H*), 2.18 (3 H, s, Furan-CH_3), 1.61 (1 H, dquin, *J*=13.9, 7.2 Hz, CH_aH_b), 1.44 (1 H, dsxt, *J*=13.8, 7.0 Hz, CH_aH_b), 1.12 (3 H, d, *J*=7.1 Hz, CHCH_3), 0.81 (3 H, t, *J*=7.3 Hz, CH_2CH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 159.0, 149.9, 105.5, 104.0, 34.7, 28.6, 18.6, 13.5, 11.6. **FTIR**: 2960, 2364, 2364, 2342, 2199, 2199, 2167, 2083, 2010, 1984, 1261, 1020, 800, 674, 650, 635, 625 cm^{-1}; **HRMS** m/z $[C_9H_{13}+H]^+$ cal. 138.1045, found 138.1045.(Δ + 0.3 ppm). **Specific rotation** $[\alpha]_D^{20}$ +11.4 (CH_2Cl_2, c = 1.0). The two enantiomers could not be separated by chiral HPLC experimentation in our hands.

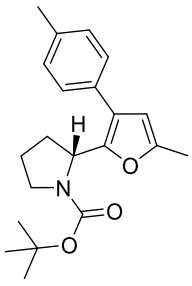
(*R*)-*tert*-Butyl 2-((*E*)-1-hydroxy-4-oxopent-2-en-1-yl)pyrrolidine-1-carboxylate, 521



tert-Butyl-2-(1-hydroxyallyl)pyrrolidine-1-carboxylate **506** (176 mg, 0.654 mmol) and methyl vinyl ketone were subjected to general conditions 15. The reaction was purified by flash column chromatography (petrol-CH_2Cl_2, 4:1 to 2:1) to yield *alkene* **521** (174 mg, 79%, 1:1 dr) as an oil and mixture of diastereomers which were not separated.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 6.59 - 6.81 (2 H, m, C*H*=CHC(O)), 6.32 (1 H, s, CH=C*H*C(O)), 6.36 (1 H, s, CH=C*H*C(O)), 5.28 - 5.49 (2 H, m, C*H*OH), 4.35 (1 H, br. s., NC*H*), 4.21 (1 H, br. s., NC*H*), 4.06 (1 H, br. s., CO*H*), 3.85 (1 H, br. s., CO*H*), 3.43 (2 H, br. s., NCH_2), 3.22 - 3.34 (1 H, m, NCH_aH$_b$), 3.12 – 3.17 (1 H, br. s., NCH$_a$$H_b$), 2.23 (3 H, s, CH_3), 2.22 (3 H, s, CH_3), 1.94 - 2.13 (2 H, m), 1.82 - 1.93 (1 H, m), 1.59 - 1.82 (5 H, m), 1.30 - 1.49 (18 H, m, C(CH_3)$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 198.5, 198.1, 157.8, 156.8, 145.8, 145.0, 130.8, 130.7, 80.8, 80.5, 75.3, 74.1, 62.6, 62.2, 47.9, 47.4, 28.4, 28.3, 27.8, 27.7, 24.0 (2x), missing 2 carbon signals; **FTIR** 3417, 2971, 1739, 1366, 1217, 912, 732 cm^{-1}; **HRMS** m/z [$C_{14}H_{23}NO_4$+Na]$^+$; calculated 292.1519, found 292.1508 .(Δ + 3.8); **specific rotation** $[\alpha]_D^{20}$ +69.5 (CH_2Cl_2, c = 1.0). The (*R*) enantiomer was also synthesised: **specific rotation** $[\alpha]_D^{20}$ -79.8 (CH_2Cl_2, c = 1.0).

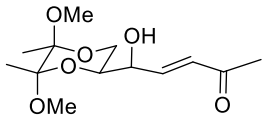
***(R)*-*tert*-Butyl 2-(5-methyl-3-(*p*-tolyl)furan-2-yl)pyrrolidine-1-carboxylate, 522**



(*R*)-*tert*-Butyl 2-((*E*)-1-hydroxy-4-oxopent-2-en-1-yl)pyrrolidine-1-carboxylate **521** (176 mg, 0.654 mmol) and tolyl bromide were subjected to General Procedure 16. The crude product was purified by flash column chromatography (petrol-CH_2Cl_2, 7:3) to yield *furan* **522** (174 mg, 79%) as an oil.

^{1}H NMR (500 MHz, *DMSO-d$_6$*, 90 °C) δ ppm 7.30 (2 H, m, 2 x Ar*H*), 7.20 (2 H, m, 2 x Ar*H*), 6.17 (1 H, d, *J*=0.9 Hz, Furan-*H*), 4.95 (1 H, dd, *J*=7.9, 4.7 Hz, NC*H*), 3.43 (2 H, t, *J*=6.8 Hz, NCH_2), 2.33 (3 H, s, Ar-CH_3), 2.26 (3 H, d, *J*=0.9 Hz, Furan-CH_3), 2.19 - 2.30 (1 H, m, CHCH_aH$_b$), 1.81 - 1.94 (1 H, m, $CH_2CH_aH_b$), 1.48 - 1.63 (2 H, m, $CHCH_aH_b$ and $NCH_2CH_aH_b$), 1.23 (9 H, s, C(CH_3)$_3$); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 154.3, 150.3, 150.2, 136.4, 131.6, 129.9, 128.5, 122.1, 108.3, 79.1, 54.2, 47.5, 33.7, 28.9, 24.2, 21.4, 13.9; **FTIR** 2976, 1694, 1391, 1260, 1161, 1115, 823 cm^{-1}; **HRMS** m/z **[**$C_{21}H_{27}NO_3$+Na]$^+$ calculated 364.1887, found 364.1883 (Δ − 1.0 ppm); **specific rotation** $[\alpha]_D^{20}$ +2.5 (94% ee, CH_2Cl_2, c = 1.0). The (*R*) enantiomer was also synthesised: **specific rotation** $[\alpha]_D^{20}$ −2.5 (92% ee, CH_2Cl_2, c = 1.0). **Chiral HPLC conditions:** Chiral AD column; flow rate = 1.0mL/min; RT, 98:2 hept/*i*-PrOH; retention time: 5.85 min, 7.96 min.

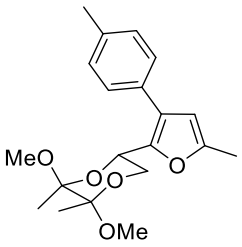
(*E*)-5-((2*S*,5*S*,6*S*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-5-hydroxypent-3-en-2-one 523



1-(5,6-dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)prop-2-en-1-ol **510** (100 mg, 0.364 mmol) and methyl vinyl ketone were subject to General Procedure 15. The crude product was purified by flash column chromotography (petrol:EtOAc, 1:1 - 1:3) to give **523** (96 mg, 88%) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ_H 6.78 (1 H, dd, *J*=15.9, 4.3 Hz, CH=C*H*CHOH), 6.37 (1 H, dd, *J*=16.0, 1.9 Hz, C*H*=CHCHOH), 4.28-4.38 (1 H, m, C*H*OH), 3.82 - 3.93 (1 H, m, CH_2C*H*OCCH3), 3.76 (1 H, dd, *J*=11.1, 4.8 Hz, CHC*H*aHb), 3.47 (1 H, dd, *J*=11.2, 3.2 Hz, CHCHa*H*b), 3.23 (3 H, s, OCH_3), 3.22 (3 H, s, OCH_3), 2.93 (1 H, br. s., O*H*), 2.24 (3 H, s, C(O)CH_3), 1.28 (3 H, s, OCH_3), 1.25 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ_c 198.1, 143.9, 131.1, 99.5, 98.0, 70.8, 69.6, 60.0, 48.1, 48.0, 27.6, 17.7, 17.5; **FTIR** 3447, 2998, 2950, 2898, 1678, 13.74, 1257, 1121, 1036, 878, 736 cm^{-1}; **HRMS** m/z **[**$C_{13}H_{22}O_6$+Na]$^+$ calculated 297.1309, found 297.1308 (Δ − 0.1 ppm); **specific rotation** $[\alpha]_D^{20}$ −130.6 (CH_2Cl_2, c = 1). Racemic material was also synthesised.

(2*S*,3*S*,5*S*)-2,3-Dimethoxy-2,3-dimethyl-5-(5-methyl-3-(*p*-tolyl)furan-2-yl)-1,4-dioxane, 524

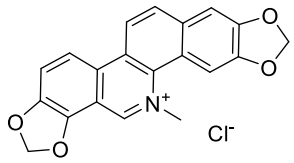


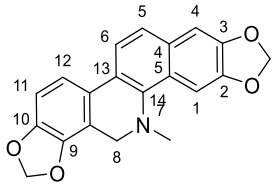
(*E*)-5-(5,6-Dimethoxy-5,6-dimethyl-1,4-dioxan-2-yl)-5-hydroxypent-3-en-2-one **523** (46 mg, 0.18 mmol) was subjected to General Procedure 14. The crude product was purified by flash column chromatography (petrol:EtOAc, 50:1 to 20:1) to give *furan* **524** (45 mg, 73%) as an oil.

^{1}H NMR (400 MHz, *CHLOROFORM-d*) δ ppm 7.29 - 7.34 (2 H, m, Ar*H*), 7.14 - 7.19 (2 H, m, Ar*H*), 6.09 (1 H, s, Furan-*H*), 5.12 (1 H, dd, *J*=11.4, 3.3 Hz, C*H*CH_aH_b), 4.27 (1 H, t, *J*=11.5 Hz CHC*H*$_a$H$_b$), 3.49 (1 H, dd, *J*=11.6, 3.3 Hz, CHCH$_a$*H*$_b$), 3.34 (3 H, s, OCH_3), 3.24 (3 H, s, OCH_3), 2.37 (3 H, s, CH_3), 2.33 (3 H, s, CH_3), 1.36 (3 H, s, OCCH_3), 1.33 (3 H, s, OCCH_3); **^{13}C NMR** (100 MHz, *CHLOROFORM-d*) δ ppm 152.4, 143.8, 136.7, 130.3, 129.1, 128.3, 127.0, 108.1, 99.8, 97.8, 62.5, 61.1, 48.4, 48.1, 21.1, 17.9, 17.7, 13.7; **FTIR**

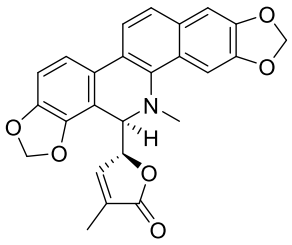
2947, 1738, 1575, 1447, 1373, 1208, 1141, 1119, 1037, 954, 878, 823 cm^{-1}; **HRMS** m/z $C_{20}H_{26}NaO_5$; calculated 369.1672, found 369.1668 (Δ + 1.3 ppm); **specific rotation** $[\alpha]_D^{20}$ − 50.9 (<95% ee, CH_2Cl_2, c = 1.0); **chiral HPLC conditions:** Chiral AD column; flow rate = 1.0 mL/min; rt, 98:2 hept/*i*PrOH; retention time: 5.79 min, 6.78 min. Racemic material was also synthesised.

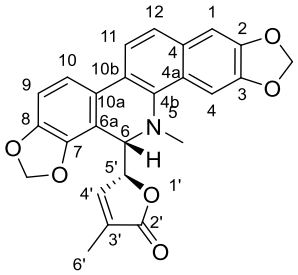
Appendix 1: Natural product ^{1}H & ^{13}C comparison tables





sanguanine, 344					dihydrosanguanine, 2					
δ ^{1}H lit.	δ ^{1}H	δ ^{13}C lit.	δ ^{13}C	Δ	Position	δ ^{1}H lit.	δ ^{1}H	δ ^{13}C lit.	δ^{13}C	Δ
9.95 s	9.93 s	149.8	149.9	0.1	**2**			148.1	148.2	0.1
8.57 d (8.9)	8.59 d (9.2)	148.6	148.7	0.1	**3**			147.5	147.5	0
8.48 d (8.8)	8.50 d (8.9)	148.6	148.7	0.1	**8**			147.1	147.1	0
8.19 d (8.9)	8.19 d (8.9)	147.4	147.5	0.1	**7**			144.6	144.7	0.1
8.13 s	8.13 s	146.1	146.3	0.2	**4b**			142.5	142.5	0
7.95 d (8.8)	7.94 d (8.5)	132.1	132.2	0.1	**12a**			130.8	130.8	0
7.55 s	7.54 s	131.3	131.5	0.2	**10a**			127.3	127.3	0
6.54 s	6.53 s	131.2	131.3	0.1	**4a**			126.5	126.5	0
6.30 s	6.28 s	127	127.2	0.2	**10b**			124.4	124.4	0
4.49 s	4.94 s	125.5	125.7	0.2	**12**	7.49 d (8.5)	7.49 d (8.6)	124.0	124.0	0
		120.2	120.3	0.1	**11**	7.69 d (8.5)	7.70 d (8.6)	120.4	120.4	0
		119.8	119.9	0.1	**10**	7.30 d (8.1)	7.31 d (8.1)	116.2	116.2	0
		118.7	118.9	0.2	**6a**			113.6	113.6	0
		117.2	117.3	0.1	**9**	6.85 d (8.1)	6.86 d (8.1)	107.2	107.2	0
		109.3	109.5	0.2	**1**	7.11 s	7.12 s	104.4	104.4	0
		105.6	105.7	0.1	**OCH$_2$O**	6.05 s	6.06 s	101.3	101.4	0.1
		104.8	104.9	0.1	**OCH$_2$O**	6.03 s	6.05 s	101.0	101.1	0.1
		104.1	104.2	0.1	**4**	7.68 s	7.68 s	100.8	100.8	0
		102.7	102.8	0.1	**6**	4.20 s	4.21 s	48.5	48.5	0
		52.0	52.1	0.1	**NMe**	2.62 s	2.63 s	41.6	41.6	0





	maclekarpine B, 459a					maclekarpine C, 459b				
Position	**δ ^{1}H lit.**	**δ ^{1}H**	**δ^{13}C lit.**	**δ^{13}C**	**Δ**	**δ ^{1}H lit.**	**δ ^{1}H**	**δ^{13}C lit.**	**δ^{13}C**	**Δ**
1	7.08	7.09	104.3	104.3	0.0	7.11	7.12	104.3	104.3	0.0
2			147.7	147.7	0.0			147.8	147.9	0.1
3			148.4	148.4	0.0			148.4	148.4	0.0
4	7.52	7.53	100.6	100.6	0.0	7.75	7.76	101.0	101.1	0.1
4a			126.8	126.8	0.0			127.0	127.1	0.1
4b			140.0	140.0	0.0			139.3	139.3	0.0
6	4.61, d (5.5)	4.62, d (6.0)	60.2	60.2	0.0	4.46, d (7.5)	4.48, d (7.6)	60.8	60.9	0.1
6a			111.9	111.9	0.0			110.9	110.9	0.0
7			145.6	145.6	0.0			145.5	145.5	0.0
8			147.4	147.4	0.0			147.2	147.3	0.1
9	6.92, d (8.5)	6.93, d (8.2)	108.5	108.5	0.0	6.91, d(8.5)	6.92, d (8.2)	108.6	108.6	0.0
10	7.37, d (8.5)	7.38, d (8.2)	116.3	116.3	0.0	7.34, d (8.5)	7.35, d (8.2)	116.6	116.6	0.0
10a			126.0	126.0	0.0			126.6	126.6	0.0
10b			123.2	123.2	0.0			123.4	123.4	0.0
11	7.66, d (8.5)	7.67, d (8.5)	119.7	119.7	0.0	7.66, d (9.0)	7.67, d (8.6)	119.7	119.7	0.0
12	7.45, d (8.5)	7.46, d (8.5)	124.1	124.2	0.1	7.49, d (9.0)	7.50, d (8.6)	124.3	124.3	0.0
12a			131.0	131.1	0.1			131.1	131.1	0.0
1'										
2'			174.2	174.2	0.0			173.9	173.9	0.0
3'			129.5	129.5	0.0			130.2	130.2	0.0
4'	6.50, s	6.51	145.8	145.8	0.0	6.45	6.45	146.0	146.0	0.0
5'	4.80, d (6.0)	4.81, m	81.2	81.3	0.1	4.80, d (8.0)	4.80 m	81.3	81.3	0.0
6'	1.33, s	1.34	10.1	10.1	0.0	1.72, s	1.73	10.5	10.6	0.1

NMe	2.71, s	2.72	43.4	43.5	0.1	2.73, s	2.74	43.2	43.2	0.0
OCH_2O	6.07, br s	6.07, br s	101.2	101.1	0.1	6.06, br s	6.07, br s	101.2	101.2	0.0
OCH_2O	6.06, 6.14, 2 x br s	6.06, 6.14, 2 x br s	101.8	101.8	0.0	6.02, 6.10, 2 x br s	6.03, 6.10, 2 x br. s	101.6	101.7	0.1

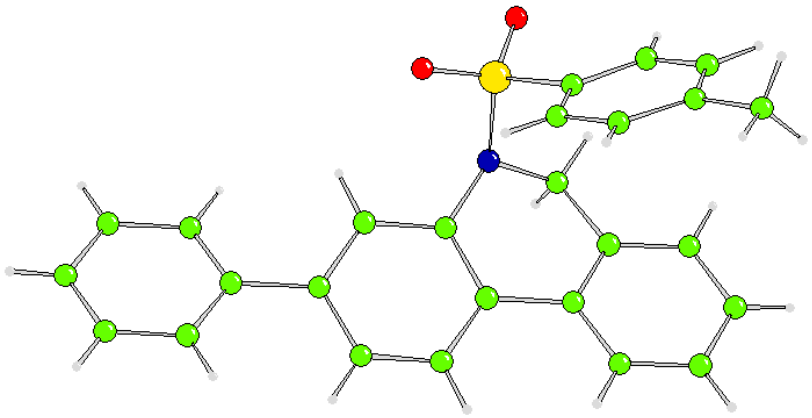
Appendix 2: X-ray Crystallography Data

Single crystal X-ray diffraction report for tricycle 246

Computing details

Data collection: SuperNova, (Oxford Diffraction, 2010); cell refinement: *CrysAlis PRO*, (Agilent, 2011); data reduction:*CrysAlis PRO*, (Agilent, 2011); program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Structure



Crystal data

$C_{26}H_{21}NO_2S$	$F(000) = 864$
$M_r = 411.52$	$D_x = 1.307$ Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, $\lambda = 0.71070$ Å
$a = 13.4387$ (10) Å	Cell parameters from 7619 reflections
$b = 11.3409$ (8) Å	$\theta = 2$–$27°$
$c = 13.8597$ (10) Å	$\mu = 0.18$ mm^{-1}
$\beta = 97.9540$ (7)°	$T = 300$ K
$V = 2091.99$ (15) Å^3	Block, colourless
$Z = 4$	0.14 × 0.12 × 0.11 mm

Data collection

Oxford Diffraction SuperNova diffractometer	3640 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.026$
ω scans	$\theta_{max} = 29.9°$, $\theta_{min} = 2.0°$
Absorption correction: multi-scan *CrysAlis PRO*, (Agilent, 2011)	$h = -18\rightarrow17$
$T_{min} = 0.86$, $T_{max} = 0.98$	$k = -15\rightarrow14$
23192 measured reflections	$l = -12\rightarrow19$
7627 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Other
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.054$	H-atom parameters constrained
$wR(F^2) = 0.149$	Method, part 1, Chebychev polynomial, (Watkin, 1994,*P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 0.110E + 04 0.178E + 04 0.106E + 04 405. 76.3
$S = 0.98$	$(\Delta/\sigma)_{max} = 0.0004$
5462 reflections	$\Delta\rho_{max} = 0.59$ e Å^{-3}
271 parameters	$\Delta\rho_{min} = -0.46$ e Å^{-3}

Bond Lengths

Bond	Length (Å)	Bond	Length (Å)
N1—C2	1.473 (10)	C17—C25	1.385 (4)
N1—C3	1.436 (9)	C18—C19	1.369 (4)
N1—C16	1.409 (8)	C18—Br26	1.929 (4)
C3—C4	1.372 (11)	C19—C20	1.322 (5)
C3—C15	1.411 (11)	C20—C21	1.333 (5)
C4—C5	1.401 (12)	C21—O22	1.417 (4)
C5—C6	1.369 (13)	C21—C25	1.363 (4)
C6—C7	1.413 (11)	O22—C23	1.295 (5)
C7—C8	1.430 (12)	C23—O24	1.220 (5)
C7—C15	1.420 (10)	O24—C25	1.455 (4)
C8—C9	1.352 (12)	C27—C28	1.388 (5)
C9—O10	1.371 (10)	C27—C35	1.389 (6)
C9—C13	1.399 (11)	C28—C29	1.372 (5)
O10—C11	1.437 (12)	C28—Br36	1.933 (7)
C11—O12	1.423 (11)	C29—C30	1.325 (6)
O12—C13	1.371 (9)	C30—C31	1.329 (5)
C13—C14	1.361 (11)	C31—O32	1.432 (6)
C14—C15	1.435 (10)	C31—C35	1.368 (4)
C16—C17	1.498 (6)	O32—C33	1.262 (5)
C16—C27	1.516 (7)	C33—O34	1.263 (5)
C17—C18	1.392 (4)	O34—C35	1.432 (6)

Bond Angles

Bond	Angle (°)	Bond	Angle (°)
C2—N1—C3	113.2 (6)	C17—C18—C19	123.07 (4)

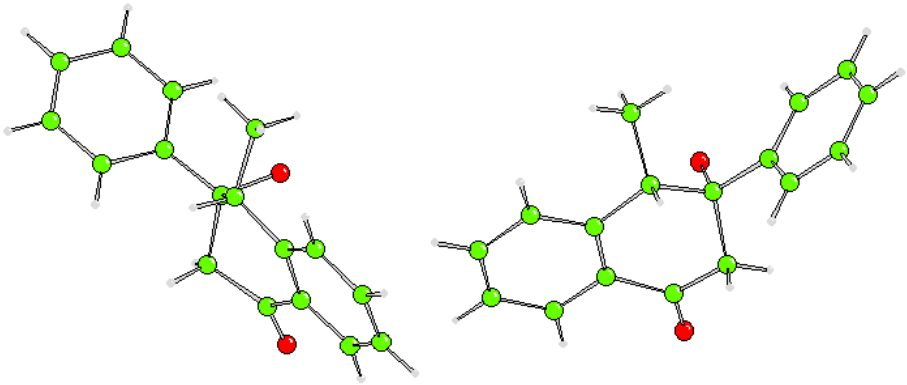
C2—N1—C16	114.4 (6)	C17—C18—Br26	118.51 (6)
C3—N1—C16	115.4 (6)	C19—C18—Br26	118.41 (6)
N1—C3—C4	122.2 (7)	C18—C19—C20	120.15 (6)
N1—C3—C15	116.7 (6)	C19—C20—C21	120.22 (7)
C4—C3—C15	121.0 (7)	C20—C21—O22	132.87 (9)
C3—C4—C5	119.5 (8)	C20—C21—C25	120.25 (7)
C4—C5—C6	121.2 (7)	O22—C21—C25	106.88 (7)
C5—C6—C7	120.3 (8)	C21—O22—C23	101.67 (7)
C6—C7—C8	120.9 (7)	O22—C23—O24	121.92 (7)
C6—C7—C15	118.7 (7)	C23—O24—C25	101.72 (7)
C8—C7—C15	120.3 (7)	O24—C25—C17	129.89 (9)
C7—C8—C9	117.9 (7)	O24—C25—C21	106.92 (7)
C8—C9—O10	129.2 (8)	C17—C25—C21	123.18 (6)
C8—C9—C13	122.1 (8)	C16—C27—C28	123.46 (6)
O10—C9—C13	108.7 (7)	C16—C27—C35	123.44 (6)
C9—O10—C11	106.4 (7)	C28—C27—C35	113.10 (6)
O10—C11—O12	108.5 (7)	C27—C28—C29	123.10 (4)
C11—O12—C13	105.6 (7)	C27—C28—Br36	118.47 (6)
C9—C13—O12	110.6 (7)	C29—C28—Br36	118.44 (6)
C9—C13—C14	122.5 (7)	C28—C29—C30	120.20 (7)
O12—C13—C14	126.9 (7)	C29—C30—C31	120.25 (7)
C13—C14—C15	117.6 (7)	C30—C31—O32	132.68 (9)
C14—C15—C7	119.5 (7)	C30—C31—C35	120.22 (7)
C14—C15—C3	121.2 (7)	O32—C31—C35	107.10 (7)
C7—C15—C3	119.1 (7)	C31—O32—C33	101.85 (7)
N1—C16—C17	114.7 (5)	O32—C33—O34	122.09 (7)
N1—C16—C27	114.3 (6)	C33—O34—C35	101.85 (7)
C16—C17—C18	123.49 (6)	O34—C35—C27	129.77 (9)
C16—C17—C25	123.40 (6)	O34—C35—C31	107.10 (7)
C18—C17—C25	113.09 (5)	C27—C35—C31	123.14 (7)

Single crystal X-ray diffraction report for intermediate 311

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction:*DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Stucture



Crystal data

$C_{28}H_{21.33}O_{5.33}$	$F(000) = 696$
$M_r = 443.14$	$D_x = 1.440$ Mg m^{-3}
Monoclinic, $C2$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 25.7376$ (7) Å	Cell parameters from 1910 reflections
$b = 4.0255$ (1) Å	$\theta = 5–27°$
$c = 18.4130$ (7) Å	$\mu = 0.10$ mm^{-1}
$\beta = 126.5529$ (14)°	$T = 150$ K
$V = 1532.48$ (6) Å^3	Plate, colourless
$Z = 4$	0.30 × 0.20 × 0.10 mm

Data collection

Nonius KappaCCD diffractometer	1639 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.030$
ω scans	$\theta_{max} = 27.5°$, $\theta_{min} = 5.2°$
Absorption correction: multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	$h = -31 \rightarrow 32$
$T_{min} = 0.98$, $T_{max} = 0.99$	$k = -5 \rightarrow 4$
3273 measured reflections	$l = -23 \rightarrow 23$
1984 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Other
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.058$	H-atom parameters constrained
$wR(F^2) = 0.164$	Method, part 1, Chebychev polynomial, (Watkin, 1994,*P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)]

	where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 28.9 44.1 22.0 5.69
S = 0.91	$(\Delta/\sigma)_{max}$ = 0.0001
1984 reflections	$\Delta\rho_{max}$ = 0.64 e Å^{-3}
226 parameters	$\Delta\rho_{min}$ = −0.32 e Å^{-3}
1 restraint	

Bond Lengths

Bond	Length (Å)	Bond	Length (Å)
O1—C2	1.432 (4)	C13—C17	1.349 (5)
O1—C5	1.389 (4)	C14—C15	1.512 (4)
C2—O3	1.433 (5)	C14—H141	0.967
C2—H22	0.973	C14—H142	0.982
C2—H21	0.968	C15—C16	1.397 (5)
O3—C4	1.388 (4)	C15—C25	1.394 (5)
C4—C5	1.385 (5)	C16—C17	1.457 (5)
C4—C9	1.371 (5)	C16—C19	1.411 (5)
C5—C6	1.369 (5)	C17—C18	1.499 (5)
C6—C7	1.407 (5)	C18—H182	0.969
C6—H61	0.947	C18—H183	0.968
C7—C8	1.401 (5)	C18—H181	0.976
C7—C12	1.475 (4)	C19—C20	1.376 (5)
C8—C9	1.398 (5)	C19—H191	0.947
C8—C10	1.501 (5)	C20—O21	1.388 (4)
C9—H91	0.935	C20—C24	1.387 (5)
C10—C11	1.502 (5)	O21—C22	1.420 (5)
C10—H102	0.976	C22—O23	1.409 (5)
C10—H101	0.984	C22—H221	0.970
C11—C12	1.351 (5)	C22—H222	0.968
C11—H111	0.934	O23—C24	1.385 (4)
C12—C13	1.472 (5)	C24—C25	1.375 (5)
C13—C14	1.526 (5)	C25—H251	0.947

Bond Angles

Bond	Angle (°)	Bond	Angle (°)
C2—O1—C5	105.0 (3)	C13—C14—C15	102.8 (3)
O1—C2—O3	107.8 (3)	C13—C14—H141	111.1
O1—C2—H22	109.5	C15—C14—H141	110.7
O3—C2—H22	109.4	C13—C14—H142	110.8
O1—C2—H21	109.8	C15—C14—H142	111.9
O3—C2—H21	109.9	H141—C14—H142	109.5
H22—C2—H21	110.4	C14—C15—C16	108.2 (3)
C2—O3—C4	105.0 (3)	C14—C15—C25	129.4 (3)
O3—C4—C5	109.6 (3)	C16—C15—C25	122.4 (3)

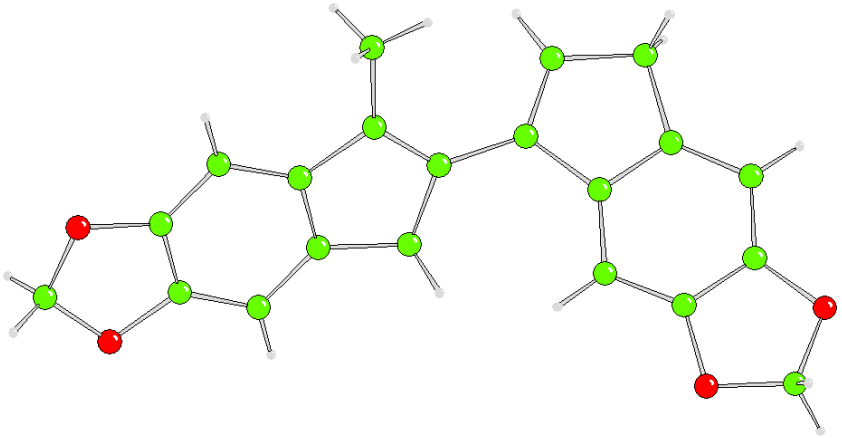
O3—C4—C9	128.1 (3)	C15—C16—C17	109.5 (3)
C5—C4—C9	122.2 (3)	C15—C16—C19	121.6 (3)
O1—C5—C4	109.6 (3)	C17—C16—C19	128.9 (3)
O1—C5—C6	127.1 (3)	C16—C17—C13	109.5 (3)
C4—C5—C6	123.3 (3)	C16—C17—C18	121.1 (3)
C5—C6—C7	115.5 (3)	C13—C17—C18	129.4 (3)
C5—C6—H61	121.7	C17—C18—H182	109.8
C7—C6—H61	122.8	C17—C18—H183	111.9
C6—C7—C8	121.2 (3)	H182—C18—H183	107.9
C6—C7—C12	130.0 (3)	C17—C18—H181	110.7
C8—C7—C12	108.8 (3)	H182—C18—H181	107.0
C7—C8—C9	121.9 (3)	H183—C18—H181	109.4
C7—C8—C10	108.7 (3)	C16—C19—C20	115.0 (3)
C9—C8—C10	129.3 (3)	C16—C19—H191	123.1
C8—C9—C4	115.9 (3)	C20—C19—H191	121.9
C8—C9—H91	123.1	C19—C20—O21	127.7 (3)
C4—C9—H91	121.0	C19—C20—C24	122.9 (3)
C8—C10—C11	102.9 (3)	O21—C20—C24	109.4 (3)
C8—C10—H102	112.1	C20—O21—C22	105.2 (3)
C11—C10—H102	112.7	O21—C22—O23	109.7 (3)
C8—C10—H101	110.9	O21—C22—H221	107.2
C11—C10—H101	110.0	O23—C22—H221	107.5
H102—C10—H101	108.2	O21—C22—H222	111.0
C10—C11—C12	111.3 (3)	O23—C22—H222	112.3
C10—C11—H111	125.2	H221—C22—H222	108.9
C12—C11—H111	123.4	C22—O23—C24	105.6 (3)
C7—C12—C11	108.2 (3)	C20—C24—O23	109.6 (3)
C7—C12—C13	124.8 (3)	C20—C24—C25	123.0 (3)
C11—C12—C13	127.0 (3)	O23—C24—C25	127.4 (3)
C12—C13—C14	121.8 (3)	C15—C25—C24	115.1 (3)
C12—C13—C17	128.2 (3)	C15—C25—H251	122.1
C14—C13—C17	109.9 (3)	C24—C25—H251	122.8

Single crystal X-ray diffraction report for side product 418

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO*/*SCALEPACK*(Otwinowski & Minor, 1997); program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007); program(s) used to refine structure:*CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication:*CRYSTALS* (Betteridge *et al.*, 2003).

Structure



Crystal data

$C_{28}H_{21}O_5$	$F(000) = 696$
$M_r = 443.14$	$D_x = 1.440$ Mg m^{-3}
Monoclinic, $C2$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 25.7376$ (7) Å	Cell parameters from 1910 reflections
$b = 4.0255$ (1) Å	$\theta = 5–27°$
$c = 18.4130$ (7) Å	$\mu = 0.10$ mm^{-1}
$\beta = 126.5529$ (14)°	$T = 150$ K
$V = 1532.48$ (6) Å^3	Plate, colourless
$Z = 4$	0.30 × 0.20 × 0.10 mm

Data collection

Refinement on F^2	Primary atom site location: Other
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.058$	H-atom parameters constrained
$wR(F^2) = 0.164$	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 28.9 44.1 22.0 5.69
$S = 0.91$	$(\Delta/\sigma)_{max} = 0.0001$
1984 reflections	$\Delta\rho_{max} = 0.64$ e Å^{-3}
226 parameters	$\Delta\rho_{min} = -0.32$ e Å^{-3}
1 restraint	

Bond length

Bond	Length (Å)	Bond	Length (Å)

O1—C2	1.432 (4)	C13—C14	1.526 (5)
O1—C5	1.389 (4)	C13—C17	1.349 (5)
C2—O3	1.433 (5)	C14—C15	1.512 (4)
O3—C4	1.388 (4)	C15—C16	1.397 (5)
C4—C5	1.385 (5)	C15—C25	1.394 (5)
C4—C9	1.371 (5)	C16—C17	1.457 (5)
C5—C6	1.369 (5)	C16—C19	1.411 (5)
C6—C7	1.407 (5)	C17—C18	1.499 (5)
C7—C8	1.401 (5)	C19—C20	1.376 (5)
C7—C12	1.475 (4)	C20—O21	1.388 (4)
C8—C9	1.398 (5)	C20—C24	1.387 (5)
C8—C10	1.501 (5)	O21—C22	1.420 (5)
C10—C11	1.502 (5)	C22—O23	1.409 (5)
C11—C12	1.351 (5)	O23—C24	1.385 (4)
C12—C13	1.472 (5)	C24—C25	1.375 (5)

Bond Angles

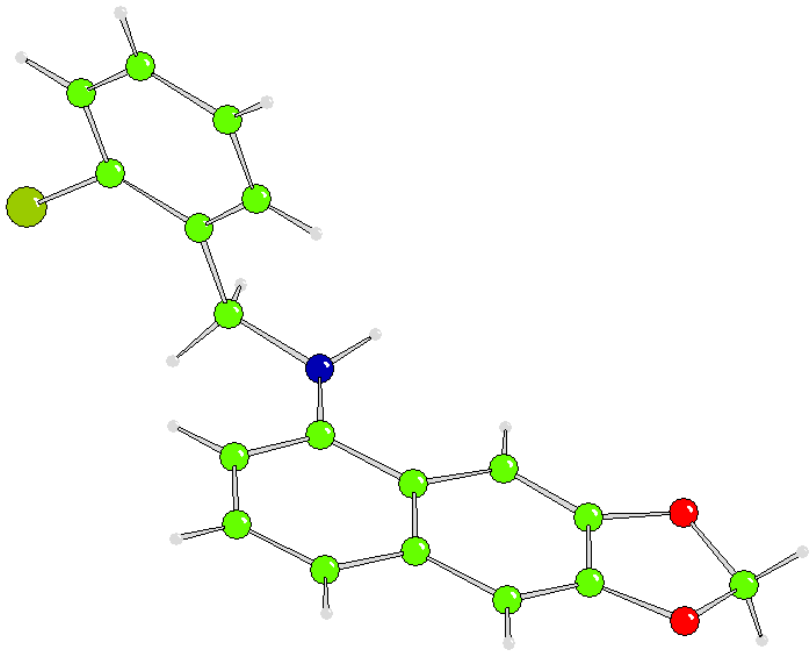
Bond	Angle (°)	Bond	Angle (°)
C2—O1—C5	105.0 (3)	C12—C13—C17	128.2 (3)
O1—C2—O3	107.8 (3)	C14—C13—C17	109.9 (3)
C2—O3—C4	105.0 (3)	C13—C14—C15	102.8 (3)
O3—C4—C5	109.6 (3)	C14—C15—C16	108.2 (3)
O3—C4—C9	128.1 (3)	C14—C15—C25	129.4 (3)
C5—C4—C9	122.2 (3)	C16—C15—C25	122.4 (3)
O1—C5—C4	109.6 (3)	C15—C16—C17	109.5 (3)
O1—C5—C6	127.1 (3)	C15—C16—C19	121.6 (3)
C4—C5—C6	123.3 (3)	C17—C16—C19	128.9 (3)
C5—C6—C7	115.5 (3)	C16—C17—C13	109.5 (3)
C6—C7—C8	121.2 (3)	C16—C17—C18	121.1 (3)
C6—C7—C12	130.0 (3)	C13—C17—C18	129.4 (3)
C8—C7—C12	108.8 (3)	C16—C19—C20	115.0 (3)
C7—C8—C9	121.9 (3)	C19—C20—O21	127.7 (3)
C7—C8—C10	108.7 (3)	C19—C20—C24	122.9 (3)
C9—C8—C10	129.3 (3)	O21—C20—C24	109.4 (3)
C8—C9—C4	115.9 (3)	C20—O21—C22	105.2 (3)
C8—C10—C11	102.9 (3)	O21—C22—O23	109.7 (3)
C10—C11—C12	111.3 (3)	C22—O23—C24	105.6 (3)
C7—C12—C11	108.2 (3)	C20—C24—O23	109.6 (3)
C7—C12—C13	124.8 (3)	C20—C24—C25	123.0 (3)
C11—C12—C13	127.0 (3)	O23—C24—C25	127.4 (3)
C12—C13—C14	121.8 (3)	C15—C25—C24	115.1 (3)

Single crystal X-ray diffraction report for naphthylamine 421

Computing details

Data collection: COLLECT (Nonius, 2001).; cell refinement: DENZO/SCALEPACK (Otwinowski & Minor, 1997); data reduction: DENZO/SCALEPACK (Otwinowski & Minor, 1997); program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007); program(s) used to refine structure: CRYSTALS (Betteridge et al., 2003); molecular graphics: CAMERON (Watkin et al., 1996); software used to prepare material for publication: CRYSTALS (Betteridge et al., 2003).

Stucture



Crystal data

Chemical formula	$C_{18}H_{14}BrNO_2$
M_r	356.22
Crystal system, space group	Triclinic, *P*1
Temperature (K)	150
a, *b*, *c* (Å)	7.6005 (3), 8.5581 (3), 11.6015 (5)
α, β, γ (°)	89.7159 (17), 74.2904 (16), 89.7993 (15)
V (Å^3)	726.43 (3)
Z	2
Radiation type	Mo *K*α
μ (mm^{-1})	2.84
Crystal size (mm)	0.10 × 0.10 × 0.10

Data collection

Diffractometer	Nonius KappaCCD diffractometer
Absorption correction	Multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)

T_{min}, T_{max}	0.75, 0.75
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	5558, 3301, 3002
R_{int}	0.020
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.650
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.032, 0.078, 0.86
No. of reflections	3301
No. of parameters	199
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.59, −0.52

Bond lengths

Bond	Length (Å)	Bond	Length (Å)
Br1—C2	1.901 (2)	C11—C19	1.432 (3)
C2—C3	1.389 (3)	C12—C13	1.357 (3)
C2—C7	1.397 (3)	C13—O14	1.378 (3)
C3—C4	1.385 (3)	C13—C17	1.405 (3)
C4—C5	1.384 (4)	O14—C15	1.446 (3)
C5—C6	1.387 (3)	C15—O16	1.422 (3)
C6—C7	1.396 (3)	O16—C17	1.373 (3)
C7—C8	1.521 (3)	C17—C18	1.347 (3)
C8—N9	1.451 (3)	C18—C19	1.428 (3)
N9—C10	1.398 (3)	C19—C20	1.416 (3)
C10—C11	1.436 (3)	C20—C21	1.367 (3)
C10—C22	1.382 (3)	C21—C22	1.404 (3)
C11—C12	1.429 (3)		

Bond Angles

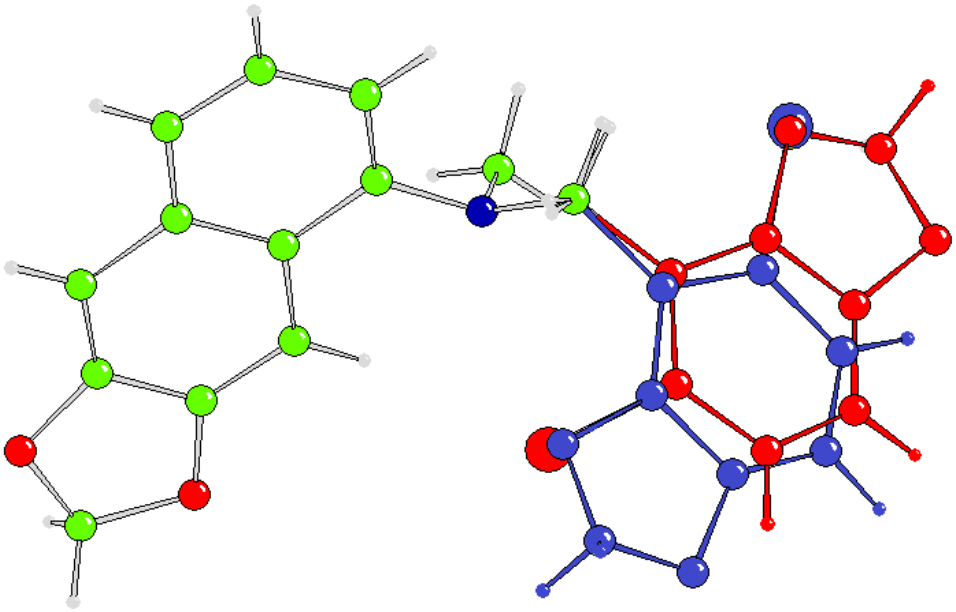
Bond	Angle (°)	Bond	Angle (°)
Br1—C2—C3	117.82 (16)	C11—C12—C13	117.58 (19)
Br1—C2—C7	119.41 (16)	C12—C13—O14	128.3 (2)
C3—C2—C7	122.8 (2)	C12—C13—C17	122.3 (2)
C2—C3—C4	119.0 (2)	O14—C13—C17	109.42 (18)
C3—C4—C5	119.8 (2)	C13—O14—C15	105.88 (17)
C4—C5—C6	120.4 (2)	O14—C15—O16	107.95 (17)
C5—C6—C7	121.5 (2)	C15—O16—C17	106.85 (17)
C2—C7—C6	116.58 (19)	C13—C17—O16	109.41 (19)
C2—C7—C8	120.62 (19)	C13—C17—C18	122.5 (2)
C6—C7—C8	122.80 (19)	O16—C17—C18	128.1 (2)
C7—C8—N9	116.56 (18)	C17—C18—C19	117.9 (2)
C8—N9—C10	120.97 (18)	C11—C19—C18	119.7 (2)
N9—C10—C11	118.46 (19)	C11—C19—C20	119.8 (2)
N9—C10—C22	121.9 (2)	C18—C19—C20	120.5 (2)
C11—C10—C22	119.6 (2)	C19—C20—C21	120.3 (2)
C10—C11—C12	121.67 (19)	C20—C21—C22	120.7 (2)
C10—C11—C19	118.38 (19)	C21—C22—C10	121.1 (2)
C12—C11—C19	119.94 (19)		

Single crystal X-ray diffraction report for arylamine 407

Computing details

Data collection: SuperNova, (Oxford Diffraction, 2010); cell refinement: *CrysAlis PRO*, (Agilent, 2011); data reduction: *CrysAlis PRO*, (Agilent, 2011); program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Structure (modelled disorder shown of aryl bromide ring shown in red and light blue)



Crystal data

$C_{26}H_{21}NO_2S$	$F(000)$ = 864
M_r = 411.52	D_x = 1.307 Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, λ = 0.71070 Å
a = 13.4387 (10) Å	Cell parameters from 7619 reflections
b = 11.3409 (8) Å	θ = 2–27°
c = 13.8597 (10) Å	μ = 0.18 mm^{-1}
β = 97.9540 (7)°	T = 300 K

V = 2091.99 (15) Å^3	Block, colourless
Z = 4	0.14 × 0.12 × 0.11 mm

Data collection

Oxford Diffraction SuperNova diffractometer	3640 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	R_{int} = 0.026
ω scans	θ_{max} = 29.9°, θ_{min} = 2.0°
Absorption correction: multi-scan *CrysAlis PRO*, (Agilent, 2011)	h = −18→17
T_{min} = 0.86, T_{max} = 0.98	k = −15→14
23192 measured reflections	l = −12→19
7627 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Other
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)]$ = 0.054	H-atom parameters constrained
$wR(F^2)$ = 0.149	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 0.110E + 04 0.178E + 04 0.106E + 04 405. 76.3
S = 0.98	$(\Delta/\sigma)_{max}$ = 0.0004
5462 reflections	$\Delta\rho_{max}$ = 0.59 e Å^{-3}
271 parameters	$\Delta\rho_{min}$ = −0.46 e Å^{-3}

Bond lengths

Bond	Length (Å)	Bond	Length (Å)
N1—C2	1.473 (10)	C17—C25	1.385 (4)
N1—C3	1.436 (9)	C18—C19	1.369 (4)
N1—C16	1.409 (8)	C18—Br26	1.929 (4)
C3—C4	1.372 (11)	C19—C20	1.322 (5)
C3—C15	1.411 (11)	C20—C21	1.333 (5)
C4—C5	1.401 (12)	C21—O22	1.417 (4)
C5—C6	1.369 (13)	C21—C25	1.363 (4)
C6—C7	1.413 (11)	O22—C23	1.295 (5)
C7—C8	1.430 (12)	C23—O24	1.220 (5)
C7—C15	1.420 (10)	O24—C25	1.455 (4)
C8—C9	1.352 (12)	C27—C28	1.388 (5)
C9—O10	1.371 (10)	C27—C35	1.389 (6)
C9—C13	1.399 (11)	C28—C29	1.372 (5)

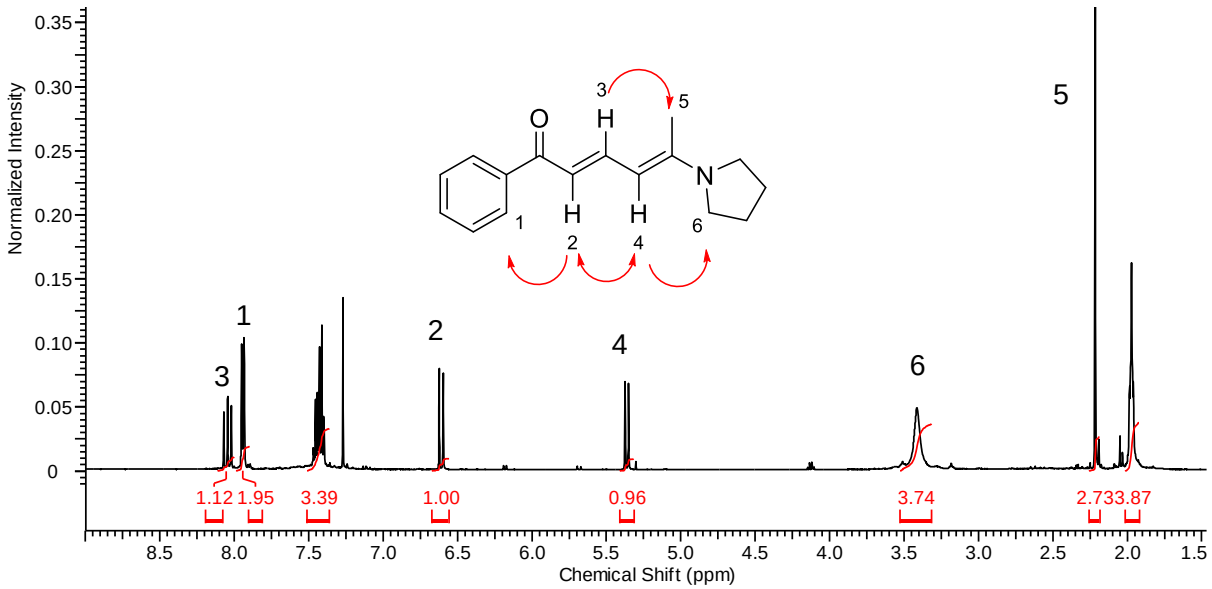
O10—C11	1.437 (12)	C28—Br36	1.933 (7)
C11—O12	1.423 (11)	C29—C30	1.325 (6)
O12—C13	1.371 (9)	C30—C31	1.329 (5)
C13—C14	1.361 (11)	C31—O32	1.432 (6)
C14—C15	1.435 (10)	C31—C35	1.368 (4)
C16—C17	1.498 (6)	O32—C33	1.262 (5)
C16—C27	1.516 (7)	C33—O34	1.263 (5)
C17—C18	1.392 (4)	O34—C35	1.432 (6)

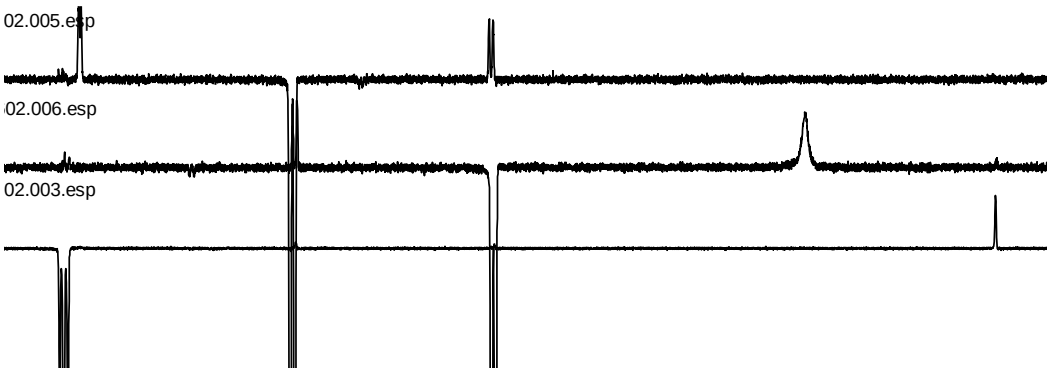
Bond Angles

Bond	Angle (°)	Bond	Angle (°)
C2—N1—C3	113.2 (6)	C17—C18—C19	123.07 (4)
C2—N1—C16	114.4 (6)	C17—C18—Br26	118.51 (6)
C3—N1—C16	115.4 (6)	C19—C18—Br26	118.41 (6)
N1—C3—C4	122.2 (7)	C18—C19—C20	120.15 (6)
N1—C3—C15	116.7 (6)	C19—C20—C21	120.22 (7)
C4—C3—C15	121.0 (7)	C20—C21—O22	132.87 (9)
C3—C4—C5	119.5 (8)	C20—C21—C25	120.25 (7)
C4—C5—C6	121.2 (7)	O22—C21—C25	106.88 (7)
C5—C6—C7	120.3 (8)	C21—O22—C23	101.67 (7)
C6—C7—C8	120.9 (7)	O22—C23—O24	121.92 (7)
C6—C7—C15	118.7 (7)	C23—O24—C25	101.72 (7)
C8—C7—C15	120.3 (7)	O24—C25—C17	129.89 (9)
C7—C8—C9	117.9 (7)	O24—C25—C21	106.92 (7)
C8—C9—O10	129.2 (8)	C17—C25—C21	123.18 (6)
C8—C9—C13	122.1 (8)	C16—C27—C28	123.46 (6)
O10—C9—C13	108.7 (7)	C16—C27—C35	123.44 (6)
C9—O10—C11	106.4 (7)	C28—C27—C35	113.10 (6)
O10—C11—O12	108.5 (7)	C27—C28—C29	123.10 (4)
C11—O12—C13	105.6 (7)	C27—C28—Br36	118.47 (6)
C9—C13—O12	110.6 (7)	C29—C28—Br36	118.44 (6)
C9—C13—C14	122.5 (7)	C28—C29—C30	120.20 (7)
O12—C13—C14	126.9 (7)	C29—C30—C31	120.25 (7)
C13—C14—C15	117.6 (7)	C30—C31—O32	132.68 (9)
C14—C15—C7	119.5 (7)	C30—C31—C35	120.22 (7)
C14—C15—C3	121.2 (7)	O32—C31—C35	107.10 (7)
C7—C15—C3	119.1 (7)	C31—O32—C33	101.85 (7)
N1—C16—C17	114.7 (5)	O32—C33—O34	122.09 (7)
N1—C16—C27	114.3 (6)	C33—O34—C35	101.85 (7)
C16—C17—C18	123.49 (6)	O34—C35—C27	129.77 (9)
C16—C17—C25	123.40 (6)	O34—C35—C31	107.10 (7)
C18—C17—C25	113.09 (5)	C27—C35—C31	123.14 (7)

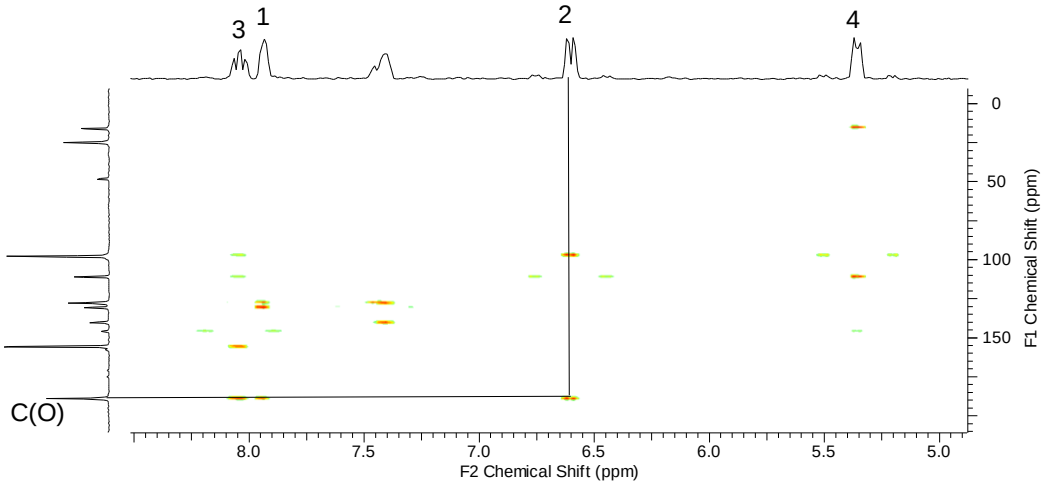
Appendix 3: NOE data

NOE experiments for compound 135

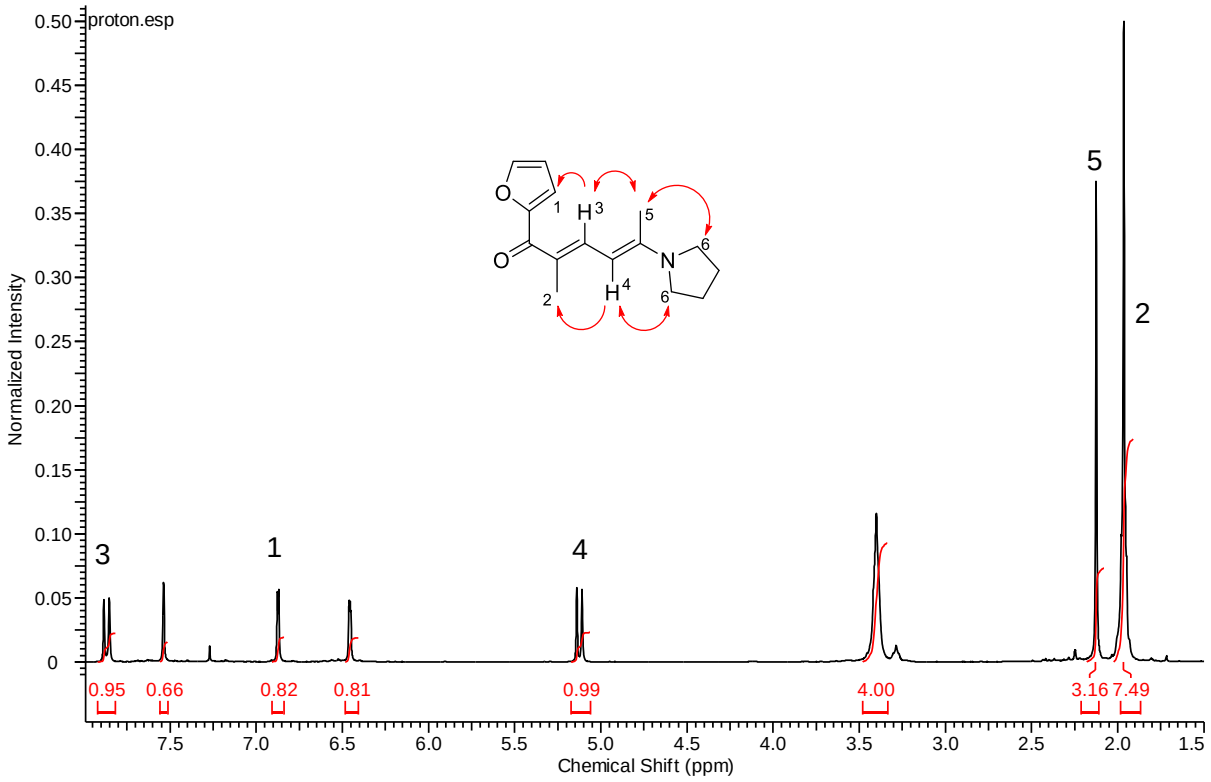


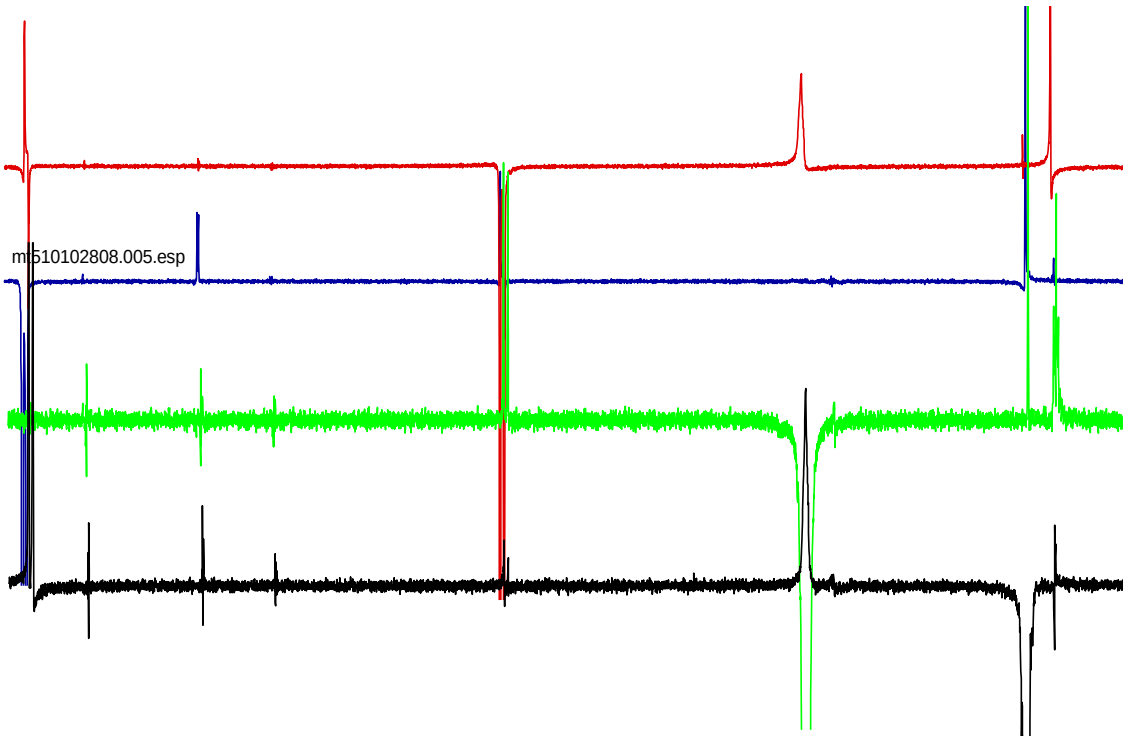


Key HMBC experiment

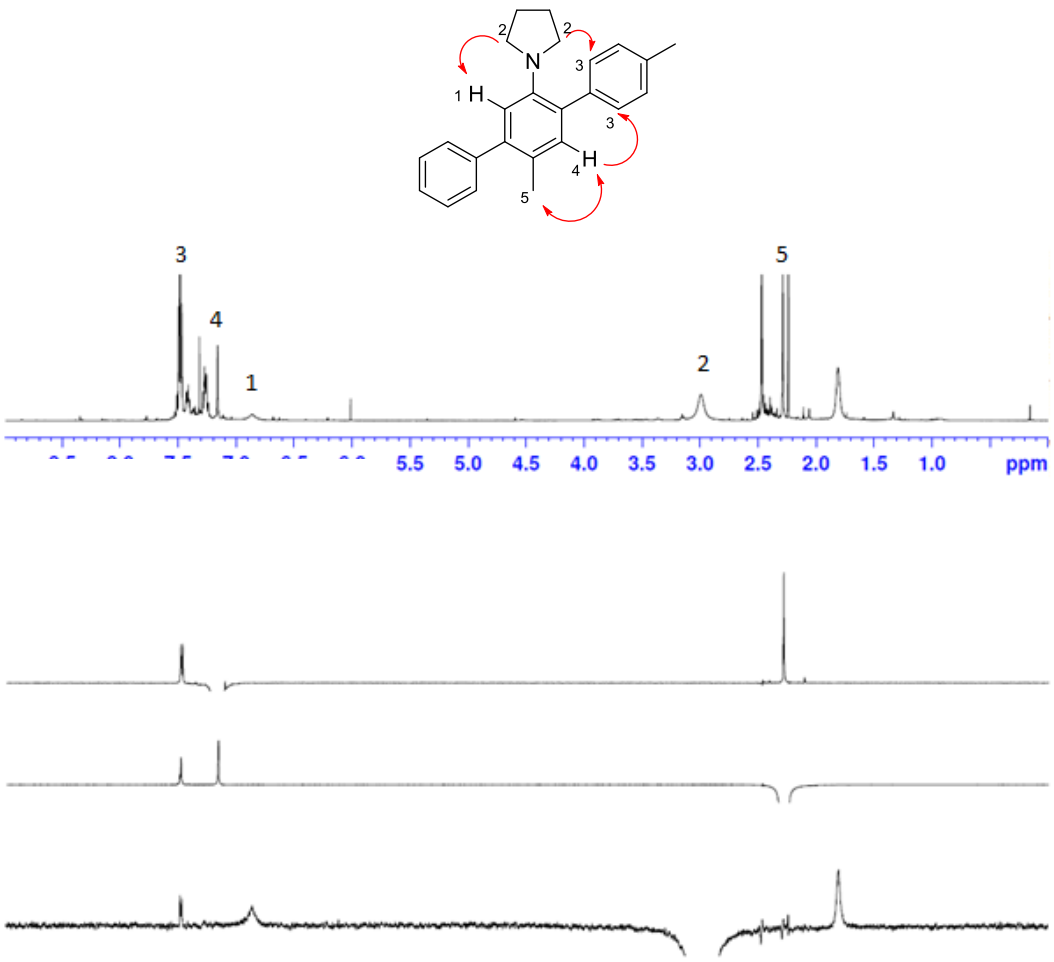


NOE experiments for compound 171

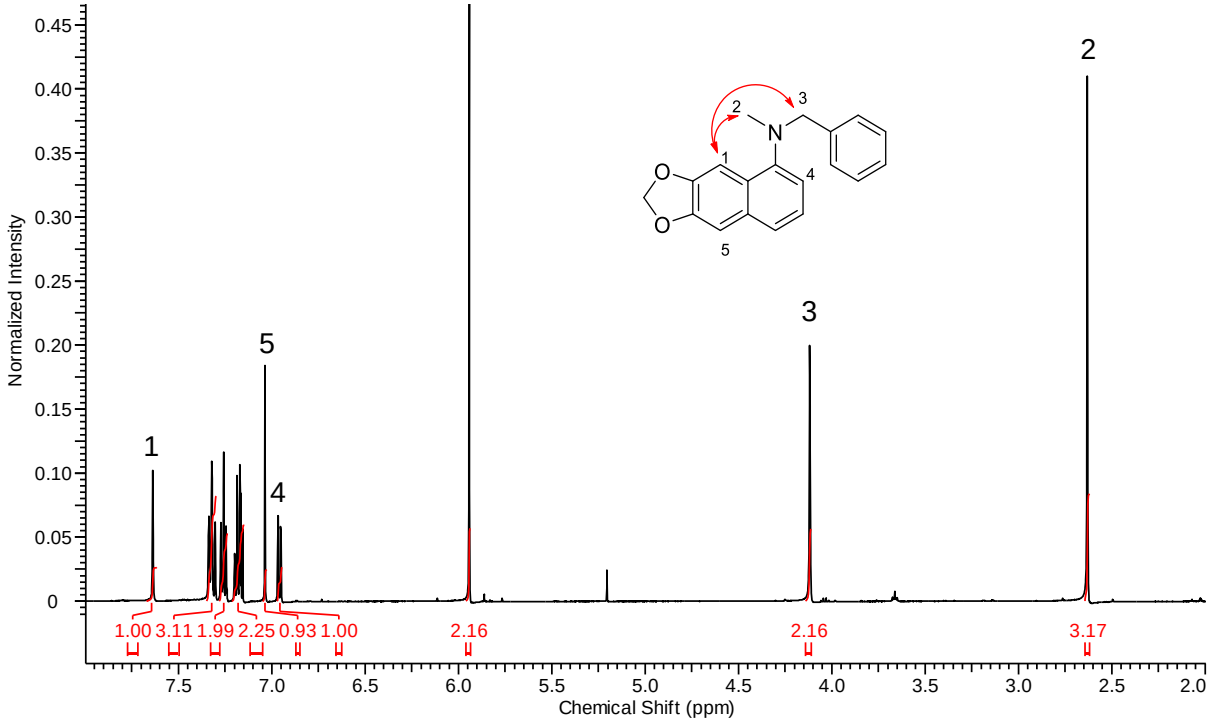


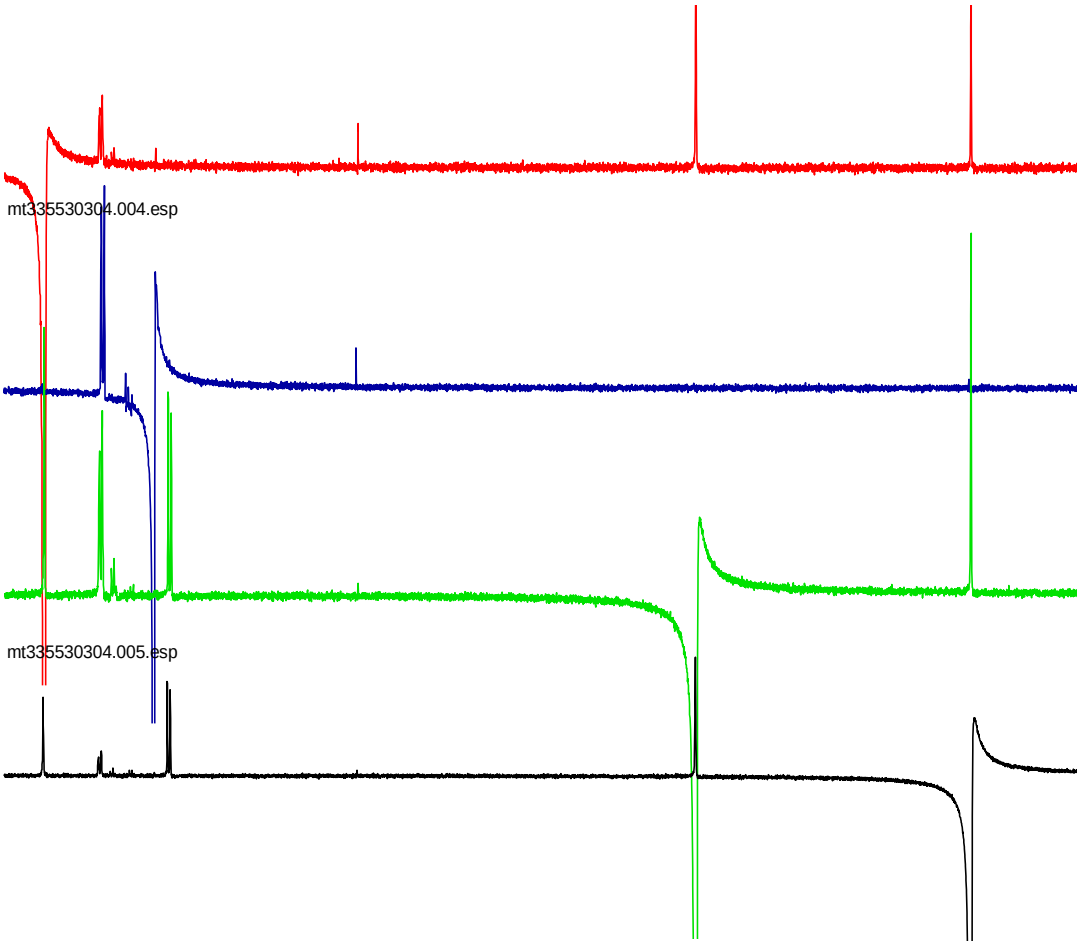


NOE experiments for compound 196



NOE experiments for compound 422

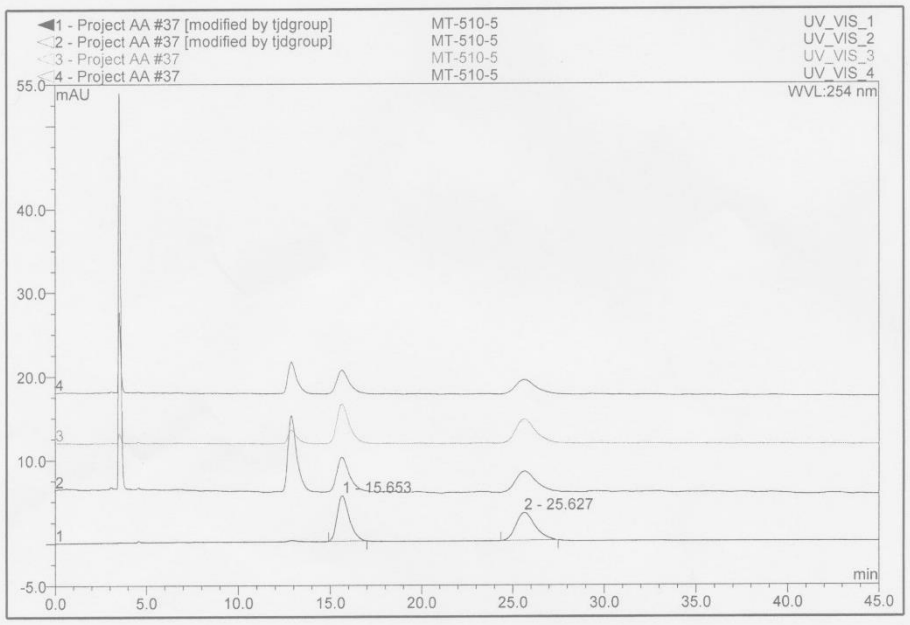




Appendix 4: HPLC Traces

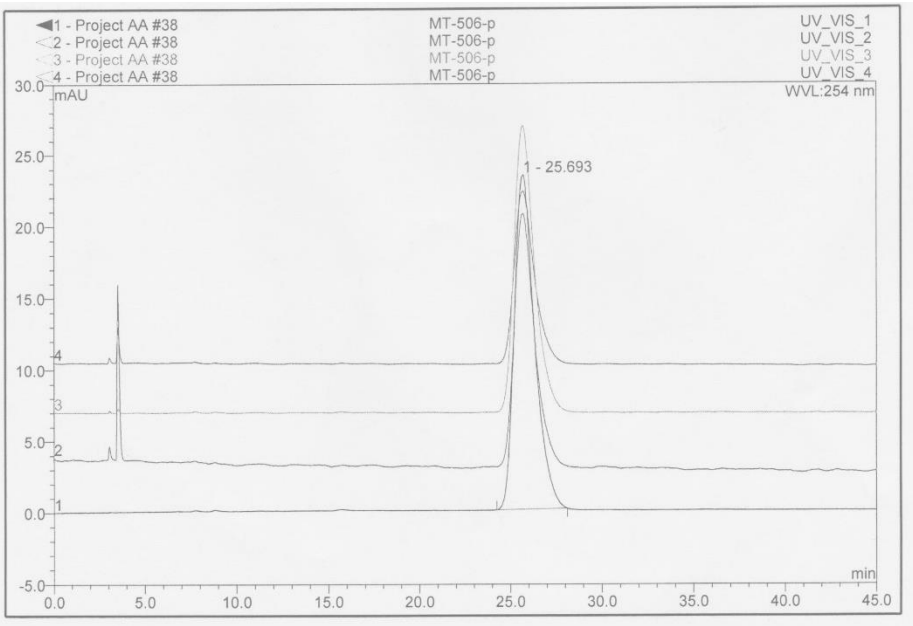
HPLC traces for compound 209

209-rac



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15.65	n.a.	5.400	4.120	50.37	n.a.	BMB*
2	25.63	n.a.	3.297	4.059	49.63	n.a.	BMB*
Total:			8.697	8.179	100.00	0.000	

209

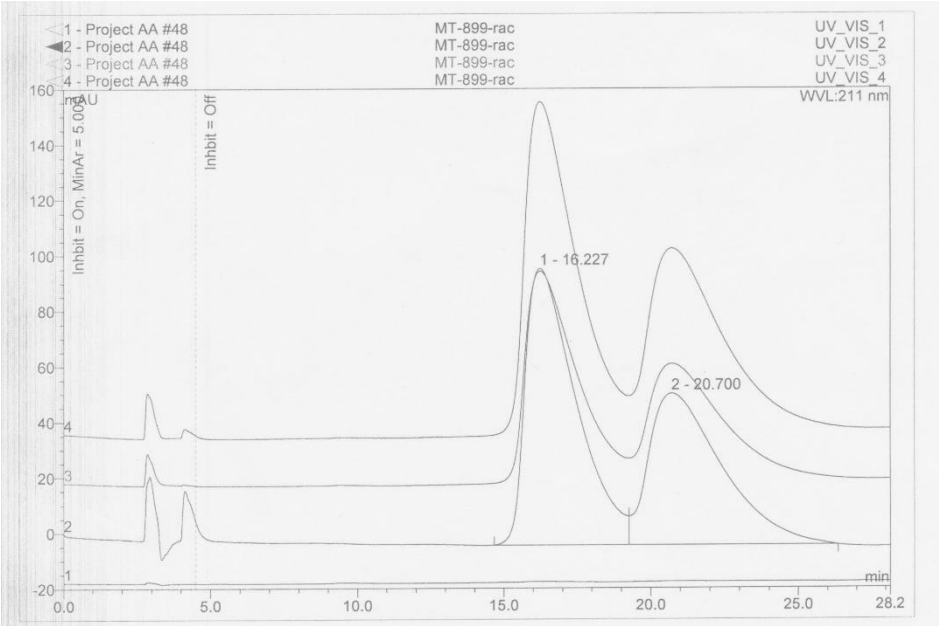


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25.69	n.a.	23.311	30.074	100.00	n.a.	BMB
Total:			23.311	30.074	100.00	0.000	

ee of **arylamine 209** is >95%

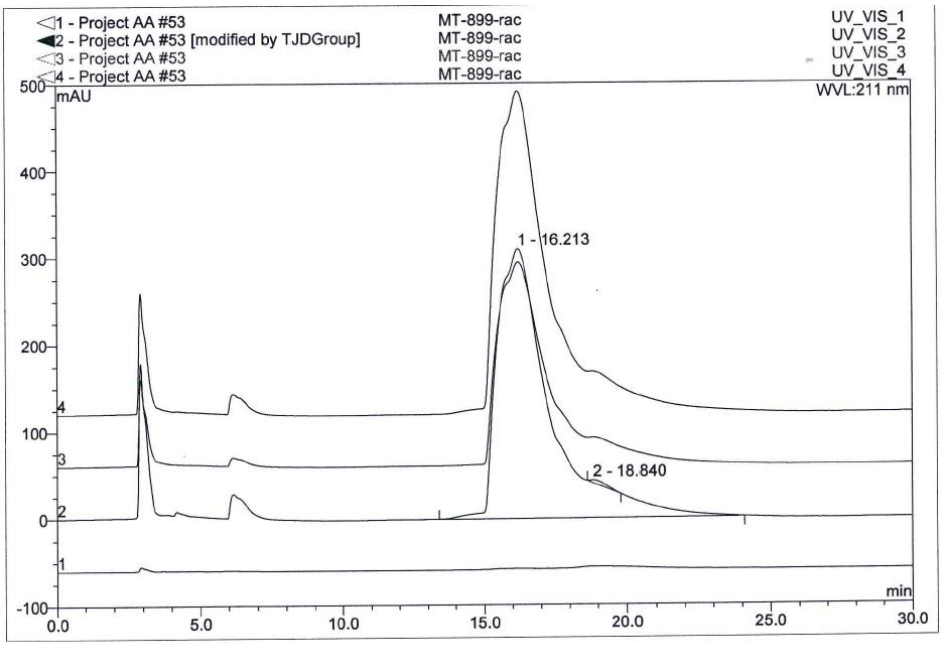
HPLC traces for compound 507

507-rac



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16.23	n.a.	99.624	199.501	55.97	n.a.	BM
2	20.70	n.a.	54.498	156.968	44.03	n.a.	MB
Total:			154.122	356.468	100.00	0.000	

507

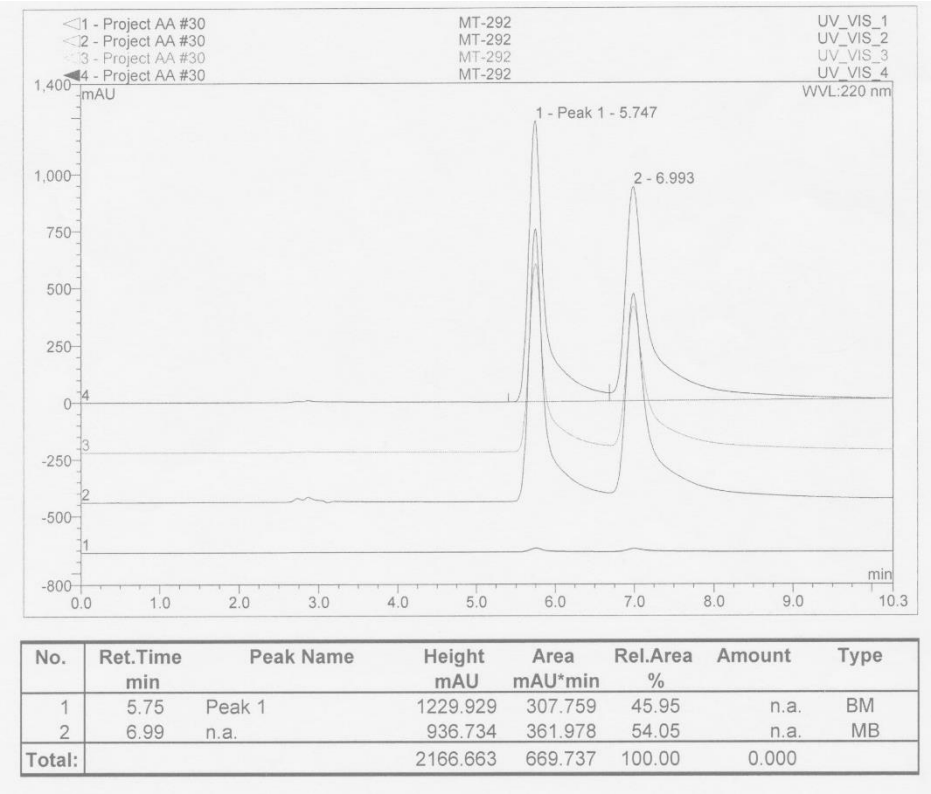


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16.21	n.a.	310.210	667.446	99.60	n.a.	BMB
2	18.84	n.a.	3.188	2.678	0.40	n.a.	Rd
Total:			313.398	670.124	100.00	0.000	

ee of **arylamine 507** is >95%.

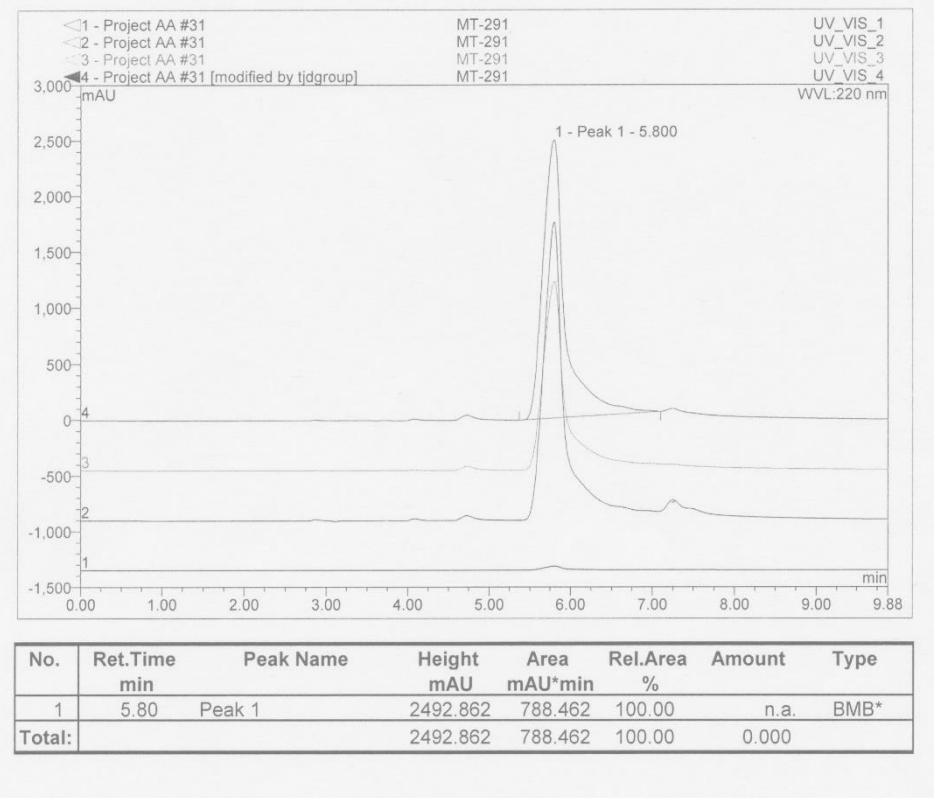
HPLC traces for compound 513

513-rac



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.75	Peak 1	1229.929	307.759	45.95	n.a.	BM
2	6.99	n.a.	936.734	361.978	54.05	n.a.	MB
Total:			2166.663	669.737	100.00	0.000	

513

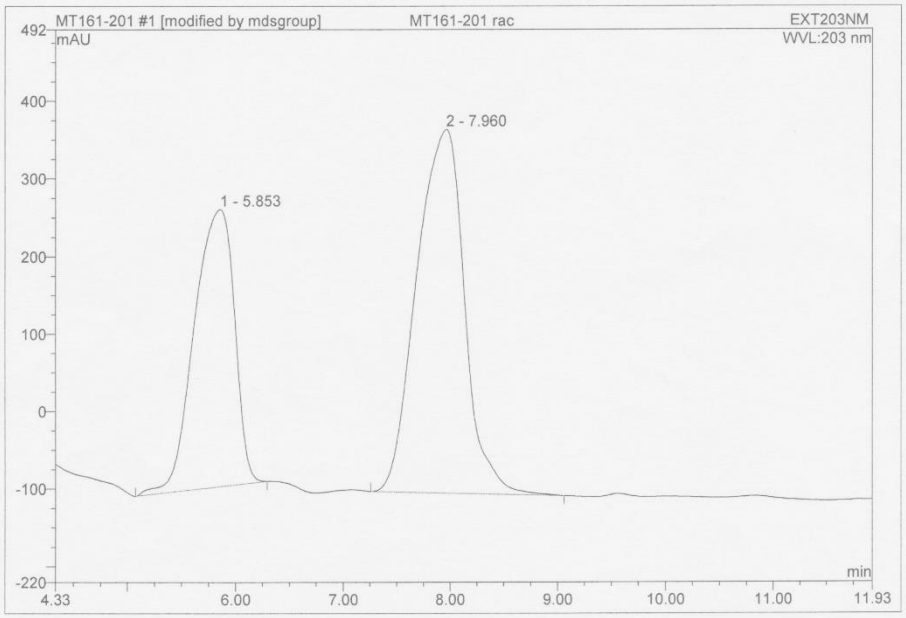


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.80	Peak 1	2492.862	788.462	100.00	n.a.	BMB*
Total:			2492.862	788.462	100.00	0.000	

ee of **arylamine 513** is >95%.

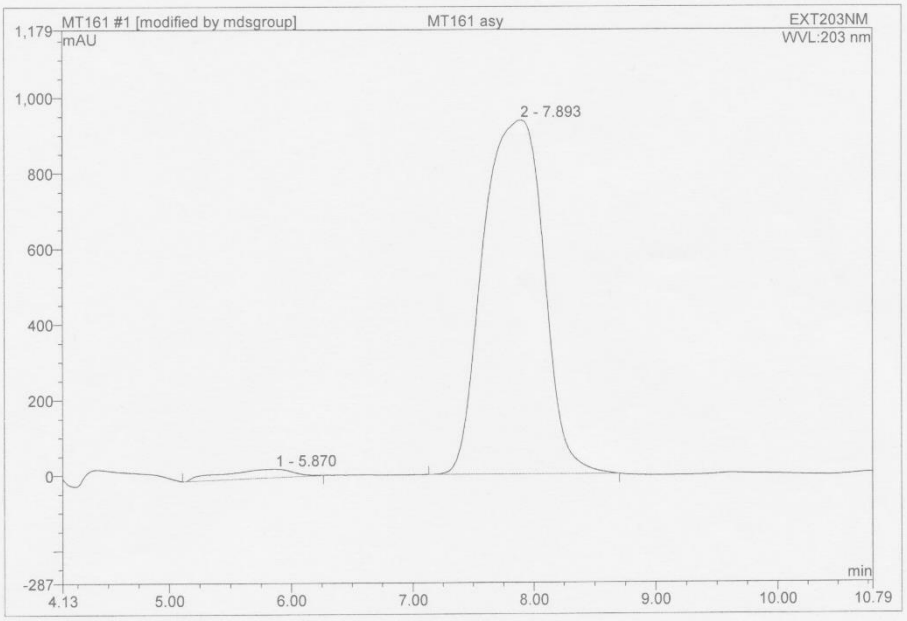
HPLC traces for compound 522

522-rac



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.85	n.a.	357.552	154.699	38.94	n.a.	BMB*
2	7.96	n.a.	468.734	242.610	61.06	n.a.	BMB
Total:			826.286	397.309	100.00	0.000	

522

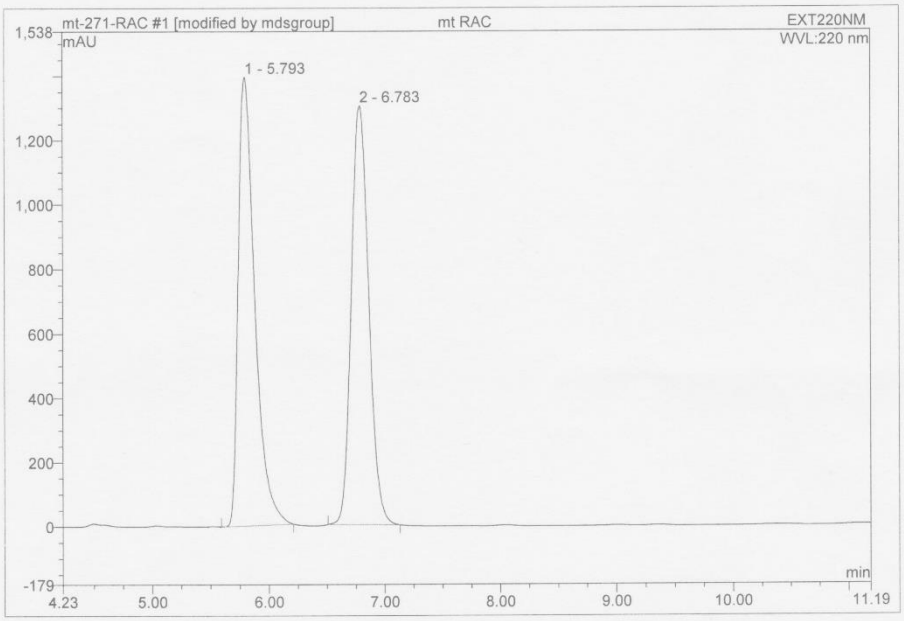


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.87	n.a.	22.151	15.813	2.83	n.a.	BMB*
2	7.89	n.a.	937.812	543.569	97.17	n.a.	BMB*
Total:			959.963	559.381	100.00	0.000	

ee of **arylamine 522** is >95%.

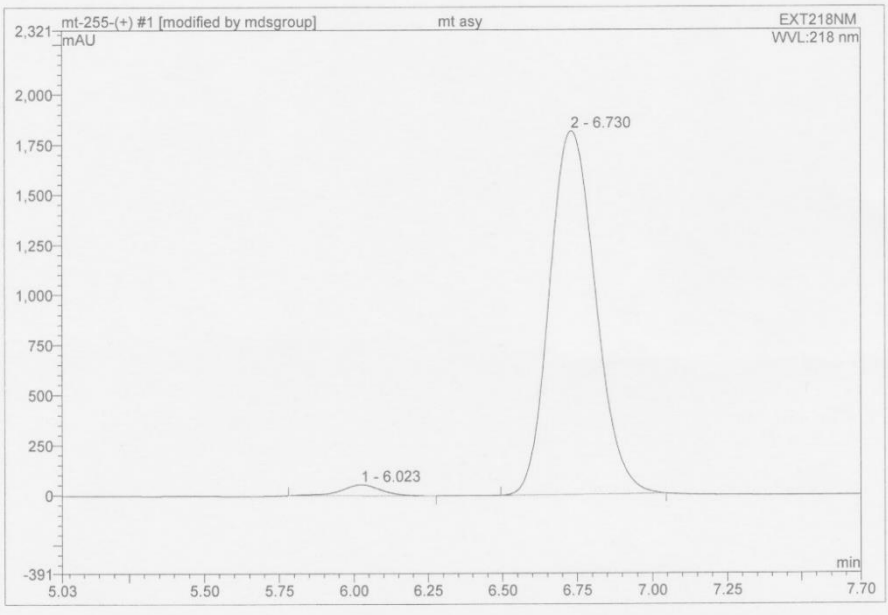
HPLC traces for compound 524

524-rac



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	5.79	n.a.	1395.135	229.261	50.05	n.a.	BMB*
2	6.78	n.a.	1301.219	228.810	49.95	n.a.	BMB*
Total:			2696.353	458.072	100.00	0.000	

524



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6.02	n.a.	54.322	8.511	2.57	n.a.	BMB*
2	6.73	n.a.	1812.526	323.066	97.43	n.a.	BMB*
Total:			1866.847	331.578	100.00	0.000	

ee of **arylamine 524** is >95%.

Appendix 5: References

[1] Balitz, D. M.; Bush, J. A.; Bradner, W. T.; Doyle, T. W.; O'Herron, F. A.; Nettleton, D. E. *J. Antibiot.* **1982**, *35*, 259.

[2] Fang, Y.; Linardic, C. M.; Richardson, A. D.; Cai, W.; Behforouz, M.; Abraham, R. T. *Mol. Cancer Ther.* **2003**, 517.

[3] Schellhammer, P. F.; *Expert Opin. Pharmacother*, **2002**, *3*, 1313.

[4] Mack, D. J.; Brichacek, M.; Plichta, A.; Njarðarson, J. T. *J. Chem. Ed.* **2010**, *87*, 1348.

[5] Watkinsa, D. L. Fujiwara, T. L. *J. Mater. Chem. C*, **2013**, *1*, 506.

[6] Paul, F.; Patt, J.; Hartwig, J.F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.

[7] Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901.

[8] Muci, A. R.; Buchwald, S. L. *Topics in Curr. Chem.* **2002**, 219, 131.

[9] Shekhar, S.; Ryberg, P.; Hartwig, J.; Mathew, J. R.; Blackmond, D.; Strieter, E. R.; Buchwald, S. *J. Am. Chem. Soc.* **2006**, *128*, 3584.

[10] Kosugi, M.; Kameyama, M.; Migita, T. *Chem. Lett.* **1983**, *12*, 927.

[11] Wolfe, J. P.; Wagaw, S.; Buchwald S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

[12] Driver M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

[13] Guari, Y.; Reek, J. H.; Kamer P. C.; Leeuwen, P. V. *Tetrahedron Lett.* **1999**, *40*, 3789.

[14] Haider, J.; Kunz, K.; Scholz, *Adv. Synth. Catal.* **2004**, *346*, 717.

[15] Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586.

[16] Old, D. W.; Wolfe, J. P.; Buchwald, S. L.; *J. Am. Chem. Soc.* **1998**, *120*, 9722.

[17] Marion, N.; Navarro, O.; Mei, J. G.; Stevens, E. D.; Scott N. M.; Nolan, S. P. *J. Am. Chem. Soc.*, **2006**, *128*, 4101.

[18] Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617.

[19] Ullmann F. *Ber*. **1903**, *36*, 2382.

[20] Goldberg, I. *Ber*. **1906**, *39*, 1691.

[21] For a recent review see: (a) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (b) Thomas, A. W.; Ley, S. V. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400

[22] (a) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39,* 2933. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39,* 2941 (c) Monnier, F.; Tailefer, M. *Angew. Chem., Int. Ed.* **2009**, *48,* 6954. For a recent review see:

(d) Qiao, J., X.; Lam, P., Y., S. *Recent Advances in Chan–Lam Coupling Reaction: Copper-Promoted C–Heteroatom Bond Cross-Coupling Reactions with Boronic Acids and Derivatives, in Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials* , 2nd ed.; Hall, D., G., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011; Vol. 1 & 2, Chapter 6.

[23] Quach, T. D.; Batey, R. A. *Org. Lett.*, **2003**, *5*, 4397.

[24] Moskalev, N.; Makosza, M. *Chem. Commun.* **2001**, *24*, 1248.

[25] Srinivas, G.; Periasamy, M. *Tetrahedron Lett.* **2002**, *43*, 2785.

[26] Ishikaura, T.; Uedo, E.; Tani, R.; Saito, S. *J. Org. Chem.* **2001**, 66, 186.

[27] Cossy, J.; Belotti, D. *Org. Lett.* **2002**, *4*, 2557.

[28] Hajra, A.; Wei, Y.; Yoshikai, N.; *Org. Lett.*, **2012**, *14*, 5488.

[29]Girard, S. A.; Hu, X.; Knauber, T.; Zhou, F.; Simon, M.; Deng, G.; Li, C. *Org. Lett.*, **2012**, *14***,** 5606.

[30] Hong, W. P.; Iosub, A. V.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 13664.

[31] For recent reviews on *de novo* arene synthesis see: (a) Serra, S.; Fuganti, C.; Brenna, E. *Chem. Eur. J.* **2007**, *13*, 6783; (b) Wessig, P.; Muller, G. *Chem. Rev.* **2008**, *108*, 2051; (c) Saito, S.; Yamamoto, Y.; *Chem. Rev.* **2000**, *100*, 2901.

[32] (a) Lam, T. Y.; Wang, Y.; Danheiser, R. L. *J. Org. Chem.*, **2013**, *78*, 9396; (b) Willumstad, T. P.; Haze, O.; Mak, X. Y.; Lam, T. Y.; Wang, Y.; Danheiser, R. L. *J. Org. Chem.*, **2013**, *78*, 11450; (c) Mak, X. Y.; Crombie, A. L.; Danheiser, R. L. *J. Org. Chem.*, **2011**, *76*, 1852.

[33] Li, L.; Zhao, M.; Ren, Z.; Li, J.; Guan, Z. *Org. Lett.* **2012**, *14*, 3506.

[34] Neumann, H.; Wangelin, A. J.; Klaus, S.; Strobing, D.; Grdes, D.; Beller M.; *Angew. Chem. Int. Ed.* **2003**, *42*, 4503.

[35] Kiren S.; Padwa A. *J. Org. Chem.* **2009**, *74*, 778.

[36] Saito, S.; Uchiyama, N.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **2000**, *65*, 4338.

[37] (a) Calderon, N.; Ofstead, E. A.; Judy, W. A. *J. Poly. Sci.* **1967**, *5*, 2209; (b) Calderon, N.; Chen, H. Y.; Scott, W. K. *Tetrahedron Lett.* **1967**, *34*, 3327.

[38] Hérisson, J.; Chauvin, Y. *Macromol Chem.* **1971**, *141*, 161.

[39] Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J; Dimare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, 112, 3875.

[40] Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974.

[41] M., Ulman, R. H. Grubbs *J. Org. Chem.* **1999**, *64*, 7202.

[42] Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.

[43] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

[44] A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs *J. Am. Chem. Soc.* **2003**, *125*, 11360.

[45] Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus Jr., P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

[46] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda *J. Am. Chem. Soc.* **2000**, *122*, 8168.

[47] Vorfalt, T.; Wannowius, K.; Plenio, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 5533.

[48] Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038.

[49] Zhan, Z.-Y. J. WO Patent 2007003135, **2007**.

[50] Rix, D.; Caijo, F.; Laurent, I.; Boeda, F.; Clavier, H.; Nolan, S. P.; Mauduit, M. *J. Org. Chem.* **2008**, *73*, 4225.

[51] Fu, G. C.; Grubbs, R. H.; *J. Am. Chem. Soc.* **1992**, *114*, 5426.

[52] Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.

[53] Donohoe, T. J.; Orr, A. J.; Gosby, K.; Bingham, M. *Eur. J. Org. Chem.* **2005**, 1969.

[54] Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

[55] Donohoe, T. J.; Fishlock, L. P.; Lacy, A. R.; Procopiou, P. A. *Org. Lett.* **2007**, *9*, 953.

[56] Donohoe, T. J.; Bower, J. F.; Basutto, J. A.; Fishlock, L. P.; Procopiou P. A.; Callens, C. K. A. *Tetrahedron*, **2009**, *65*, 8969.

[57] Donohoe, T. J.; Jones, C. R.; Barbosa, L. C. A. *J. Am. Chem. Soc.* **2011**, *133*, 16418.

[58] Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

[59] Donohoe, T.; Bower J., *Proc. Natl. Acad. Sci. U.S.A.* **2010**, 3373.

[60] Shafi, S.; Kędziorek, M.; Grela, *Synlett*, **2011**, 124.

[61] Donohoe, T.; Race N.; Bower J., *Org. Lett.* **2010**, *12*, 4094.

[62] Hoveyda, A. H.; Lombardi, P. J.; O'Brien R. V.; Zhugralin, A.R. *J. Am. Chem. Soc.* **2009,** 131, 8378.

[63] Donohoe, T. J.; Basutto, J. A.; Rathi, A. H.; Bower, J. F. *Org. Lett.* **2011**, *13*, 1036.

[64] Davies, I. W.; Marcoux, J.; Taylor, J. D.; Dormer, P. G.; Deeth, R. J.; Marcotte, F.; Hughes, D. L.; Reider P. J. *Org. Lett.* **2002**, *4*, 439.

[65] Guner, V. A.; Houk, K. N.; Davies I. W. *J. Org. Chem.* **2004**, *69*, 8024.

[66] Yu, T.; Fu, Y.; Liu, L.; Guo, Q. *J. Org. Chem.* **2006**, *71*, 6157.

[67] Tan, K. T.; Chang, S. S.; Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 2958.

[68] Sezgin, K.; *J. Org. Chem.* **2009**, *74*, 7781.

[69] Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484.

[70] Littke, A.; Fu, G., *J. Am. Chem. Soc.* **2001**, 6989.

[71] Ballini, R.; Bosica, G.; Fiorini, D.; Petrini, M. *Tetrahedron Lett.*, **2002**, *43*, 5233.

[72] Wagaw, S.; Rennels, R.; Buchwald , S. *J. Am. Chem. Soc.* **1997**, *119*, 8451

[73] Zincke, T.; Heuser, G.; Möller, W. *Justus Liebigs Annalen der Chemie* **1904**, 333, 296; (b) Kunugi, S.; Okubo, T.; Ise, N. *J. Am. Chem. Soc.* **1976**, *98*, 2282.

[74] Campeau, L.; Parisien, M.; Jean, J.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 681.

[75] Gohil, V. M.; Agrawal, S. K.; Saxena, A. K.; Garg, D.; Gopimonhan,; Bhuntani, K. K., *Indian J. Exp. Biol.*, **2010**, *48*, 265.

[76] Robinson, B.; *Chem. Rev.*, **1963**, *63*, 373.

[77] Heindel, N. D.; Kennewell, P. D.; Pfau M. A. *J. Org. Chem.*, **1970**, *35*, 80.

[78] Wagaw, S.; Yang, B. H.; Buchwald, S. *J. Am. Chem. Soc.* **1998**, *120*, 6621.

[79] *J. Chem. Ed.* **2010**, 87, 1348.

[80] Bohlmann, F.; Rahtz, D. Chem. Ber. **1957**, *90*, 2265.

[81] Moody, C. J.; Bagley, M. C. *Synlett* **1998**, 361.

[82] Bashford, K. E.; Burton, M. B.; Cameron, S.; Cooper, A. L.; Hogg, R. D.; Kane, P. D.; MacManus, D. A.; Matrunola, C. A.; Moody, C. J.; Robertson, A. A.B.; Warneb, M. R. *Tetrahedron Lett.* **2003**, *44*, 1627.

[83] Bagley, M. C.; Brace. C.; Dale, J. W.; Ohnesorge, M.; Phillips. N. G.; Xiong, X.; Bower, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, *14*, 1663.

[84] Bagley, M. C.; Dale, J. W.; Bower J. *Synlett* **2001**, *7*, 1149.

[85] Bagley, M. C.; Lunn, R.; Xiong, X. *Tetrahedron Lett.* **2002**, *43*, 8331.

[86] Bagley, M. C.; Jenkins, R. L.; Lubinu, M. C.; Mason, C.; Wood, R. *J. Org. Chem.* **2005**, *70*, 7003.

[87] Williams, R. D; Ellis, B. E. *Phytochemistry*, **1993**, *32*, 719.

[88] Lima, L. M.; Silva, V. A.; Palmieria, L. C.; Oliveira, M. C.; Foguelc, D.; Polikarpovd, I. *Bioorg. Med. Chem.* **2010**, *18*, 100.

[89] Riaz, U.; Ashraf, S. M. *Separation and Purification Technology*, **2012**, *95*, 97.

[90] Donohoe, T. J.; Pilgrim, B. S.; Jones, G. R.; Bassuto, J. A. P*roc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 11605.

[91] Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

[92] Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

[93] Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 1740.

[94] Colacot, T. J.; Johansson, C. C. C. *Angew. Chem. Int. Ed.*, **2010**, *49*, 676.

[95] (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369; (b) Kawatsura, M.; Hartwig J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

[96] Grasa, G. A.; Colacot, T. J. *Org. Lett.* **2007**, *9*, 5489.

[97] Arambasic, M.; Hooper, J. F.; Willis, M. C. *Org. Lett.* **2013**, *15*, 5162.

[98] Chen, X.; Jin, J.; Wang, N.; Lu, P.; Wang, Y. *Eur. J. Org. Chem.*, **2012**, *4*, 824.

[99] Hesp, K. D.; Lundgren, R. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2011**, *133*, 5194.

[100] VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

[101] Cui, X.; Dai, X.; Deng, Y.; Shi, F. *Chem. Eur. J.* **2013**, *19*, 3665.

[102] Chen, X.; Jin, J.; Wang, N.; Lu, P.; Wang, Y. *Eur. J. Org. Chem.*, **2012**, *4*, 824.

[103] Wang, S. Q.; Wang G. Q.; Wamg, B. K.; Huanag, B. K.; Zhang, Q. Y.; Qin, L. P. *Chem. Mat. Compd.* **2007**, *43*, 100.

[104] Hu, J.; Zhang, R. H.; Liu, R. H.; Zhang, C.; Shen, Y. H.; Li, H. L. Liang, M. J.; Xu, X. K.; *Chem. Biodiversity* **2006**, *3*, 990.

[105] (a) Vavreckova, C.; Gawlik, I.; Muller, K. *Planta Med.* **1996**, *62*, 397; (b) Schemeller, T.; Latz-Bruning, B.; Wink, M. *Phytochemistry* **1997**, *44*, 257; (c) Huang, F.C.; Kutchan, T. M. *Phytochemistry*, **2000**, *53*, 555.

[106] (a) Taira, Z.; Matsumoto, M.; Ishida, S.; Ichikawa, T.; Sakiya, Y. *Chem. Pharm. Bull.*, **1994**, *42*, 1556; (b) Herbert, J. M.; Augereau, J. M.; Gleye J.; Maffrand, J. P. *Biochem. Biophys. Res. Commun.*, **1990**, *172*, 993; (c) Fang, S. D.; Wang, L. K.; Hecht, S. M. *J. Org. Chem.***1993**, *58*, 5025; (d) Nakanishi, T.; Suzuki, M. *J. Nat. Prod.* **1998**, *61*, 1263.

[107] Leete, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 473.

[108] Dewick, P. (2009). *Medicinal Natural Products: A Biosynthetic Approach*, 3rd ed.; West Sussex, England: Wiley. p. 358.

[109] A.R. Battersby, J. Staunton, H.R. Wiltshirs, R.J. Francis & R. Southgate, *J. Chem. Soc., Perkin I*, **1975**, 12, 1147.

[110] (a) Richardson, T.; Robinson, R.; Seigo, E. *J. Chem. Soc.*, **1937**, 835; (b) Robinson, R.; Bailey, A. S. *J. Chem. Soc.*, **1950**, 1375. (c) Bailey, A. S.; Robinson, R.; Staunton, R. S. *J. Chem. Soc.*, **1950**, 2277.

[111] A. S. Bailey and C. R. Worthing, *J. Chem. Soc.*, **1956**, 4535.

[112] I. Ninomiya, T. Naito, H. Ishii, T. Ishida, M. Ueda and K. Harada, *J. Chem. Soc.*, Perkin I, **1975**, 762.

[113] Perez, D.; Guitian, E.; Castedo, L. *J. Org. Chem.*, **1992**, *57*, 5911

[114] Clark, R. D.; Jahangir, *J Org. Chem.*, **1988**, *53*, 2378

[115] Le, T. N.; Gang, S. G.; Cho, W. J. *J. Org. Chem.*, **2004**, *69*, 2768.

[116] Cheng C.; Korivi, R. P. *Chem. Eur. J.* **2010**, *16*, 282.

[117] Lv, P.; Huang, K.; Xie, L.; Xu, X. *Org. Biomol. Chem.*, **2011**, *9*, 3133.

[118] Ishihara, Y.; Azuma, S.; Choshi, T.; Kohno, K.; Ono, K.; Tsutsumi, H.; Ishizu, T.; Hibino, S. *Tetrahedron*, **2011**, *67*, 1320.

[119] Imamoto, T.; Suguira, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25* 4233.

[120] Mu, Y. Q.; Gibbs, R. A. *Bioorg. Med. Chem.* **1997**, *5*, 1327.

[121] Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, 21, 478.

[122] Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **1995**, *34*, 1059.

[123] Ryan D. A.; Gin D. Y. *J. Am. Chem. Soc.*, **2008**, *130*, 15228.

[124] Howell, C.R.; Stipanovic, R.D.; Bell, A. A. *Pesticide Biochemistry and Physiology*, **1972**, *2*, 364.

[125] Bowman, W. B.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, *36*, 1803.

[126] Studer, A; Curran, D. *Angew. Chem. Int. Ed.* **2011**, *50*, 5018.

[127] Nakanishi, T.; Masanobu, S.; Mashiba, A.; Ishikawa, K.; Yokotsuka, T. *J. Org. Chem.* **1998**, *63*, 4235.

[128] Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673.

[129] Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737.

[130] Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044.

[131] Shirakawa, E.; Itoh, K.-I.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537.

[132] (a) Liu, W.; Cao, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737; (b) Sun, C.-L.; Li, H.; Da-Gang, Y.; Miao, Y.; Xiao, Z.; Xing, L.; Huang, K, Zheng, S, Li, B.; Shi, Z. –J. *Nature Chemistry*, **2010** *2*, 1044; (c) Shirakawa, E.; Itoh, K.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.*, **2010**, *132*, 15537.

[133] Sun, C. -L.; Gu, Y.; Huang, W.; Shi, Z.-J *Chem. Commun.*, **2011**, *47*, 9813.

[134] Roman, D. S.; Takahashi, Y.; Charette, A. B. *Org. Lett.* **2011**, **13**, 3242.

[135] De, S.; Ghosh, S.; Bhunia, S.; Sheikh, J. A.; Bisai, A. *Org. Lett.* **2012**, *14*, 4466.

[136] Zhou, S.; Anderson, G. M.; Mondal, B.; Doni, E.; Ironmonger, V.; Kranz, M.; Tuttle, T.; Murphy, *J. Chem. Sci*. **2014**, *5*, 476.

[137] Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844.

[138] Deng A.; Qin, H. *Phytochemistry*, **2010**, *71*, 816.

[139] Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 570.

[140] Nefkens, G. H. L.; Thuring, J. W. J. F.; Zwanenburg, B. *Synthesis* **1997**, *3*, 290.

[141] Landelle, G.; Claraz, A.; Oudeyer S.; Levacher, V. *Tetrahedron Lett.* **2012**, *53*, 2414.

[142] Cheng, P; Zhou, J; Qing, Z; Kang, W; Liu, S; Liu, W; Xie, H; Zeng, J. *Bioorg. Med. Chem. Lett.* **2014**, 24, 2712.

[143] SandMartin, R.; Marigorta, E. M.; Moreno, I.; Dominguez, E. *Heterocycles*, **1997**, *45*, 757.

[144] Rodriguez, A. D.; Shi, J.-G. *J. Org. Chem.* **1998**, *63*, 420.

[145] Marion, F.; Williams, D. E.; Patrick, B. O.; Hollander, I.; Mallon, R.; Kim, S. C.; Roll, D. M.; Feldberg, L.; Soest, R. V.; Andersen, R. J. *Org. Lett.* **2006**, *8*, 322.

[146] Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475.

[147] For a recent review see: Poulsen, T.; Jørgensen, K.; *Chem. Rev.* **2008**, 2903.

[148] Bigi, F.; Casiraghi, G.; Casnati, G.; Sartori, G.; Fava, G. G.; Belicchi, M. F. *J. Org. Chem.* **1985**, *50*, 5018.

[149] Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

[150] Gao F.; Lee Y.; Mandai K.; Hoveyda A., *Angew. Chemie. Int. Ed*. **2010**, 8370.

[151] Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal. V. *Nature Chem.*, **2014**, *6*, 584.

[152] Albrecht L.; Ransborg L.; Gschwend B.; Jørgensen K., *J. Am. Chem. Soc*. **2010**, 17886.

[153] Michel P.; Ley S., *Angew. Chem. Int. Ed.* **2002**, 3898.

[154] Russo, V.; Herron, J. R.; Ball Z. T. *Org. Lett.* **2010**, 12, 220.

[155] Donohoe, T. J.; Basutto, J. A.; Rathi, A. H.; Bower, J. F. *Org. Lett.* **2011**, *13*, 1036.

[156] Sezen, B.; Sames, D.; *J. Am. Chem. Soc.* **2006**, *128*, 3102.

[157] Tan, K. T.; Chang, S. S.; Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 2958.

[158] Tan, X.; Hou, Y.; Huang, C.; Liu, L.; Guo, Q. *Tetrahedron* **2004** 60 6129

[159] Donohoe, T. J.; Fishlock, L. P.; Lacy, A. R.; Procopiou, P. A. *Org. Lett.* **2007**, *9*, 953.

[160] Doucet, H.; Santelli, M. *Tetrahedron: Asymmetry* **2000**, 11, 4163.

[161] Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Tetrahedron*, **2001**, 57, 835.

[162] Jang, D. O.; Lee, B. S. *Euro. J. Org. Chem.* **2013**, *15*, 3123.

[163] Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc*. **2004**, *126*, 6776.

[164] Warner, M. C.; Shevchenko, G. A.; Jouda, S.; Bogar, K.; Baeckvall, *Chem. Eur. J.* **2013**, 19, 13859.

[165] Sumida, S.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, 122, 1310.

[166] Felpin, F. X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192.

[167] Ogasawara, M.; Ge, Y.; Uetake, K.; Takahashi, T. *Org. Lett,* **2005**, 7, 5697.

[168] Girard, S. A.; Hu, X.; Knauber, T.; Zhou, F.; Simon, M.; Deng, G.; Li, C. *Org. Lett.* **2012**, *14*, 5606.

[169] Zhang, L.; Wu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12250.

[170] Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Chem. Eur. J*. **2005**, *11*, 3294.

[171] Sarkar, S. M.; Uozumi, Y.; Yamada, Y. M.; *J. Am. Chem. Soc.* **2012**, 134, 3190.

[172] Carpino, L.; *J. Am. Chem. Soc.* **1957**, 79, 4427.

[173] Hebbachea, H.; Hanka, Z.; Bruneau, C.; Renaud, J. *Synthesis* **2009**, *15*, 2627.

[174] Aulakh, V. S.; Ciufolini, M. A. *J. Org. Chem.*, **2009**, *74*, 5750.

[175] Toum, V.; Kadouri-Puchot, C.; Hamon, L.; Lhommet, G.; Mouriès-Mansuy, V., Vanucci-Bacqué, C., Dechoux, L.; *Synthesis*, **2011**, 2781.

[176] Reddy, D. S.; Rajale, T. V.; Shivakumar K.; Iqbal, J. *Tetrahedron Lett.* **2005**, 46, 979.

[177] Novodomskà, A.; Dudičovà, M.; Leroux, F. R.; Colobert, F. *Tetrahedron: Asymmetry* **2007**, *18*, 1628-1634.

[178] Pilgrim, B. S.; Gatland, A. E.; McTernan, C. T.; Procopiou, P. A.; Donohoe, T. J. *Org. Lett.*, **2013** , 15, 6190.

[179] Hooper, J. F.; Chaplin, A. B.; Gonzalez-Rodriguez, C.; Thompson, A. L.; Weller, A. S.; Willis, M. C. *J. Am. Chem. Soc.*, **2012** , 134, 2906.

[180] Chen, X.; Jin, J.; Wang, N.; Lu, P.; Wang, Y. *Eur. J. Org. Chem.*, **2012** , 4, 824.

[181] García, J. L.; Aranda, M. T.; Puente, M. *Tetrahedron* **2005**, 61, 10099.

[182] Matsuda, T.; Shigeno, K.; Makino, M.; Murakami, M.; *Org. Lett.* **2006**, *8*, 3379.

[183] Adamczyk, M.; Watt, D.S.; Netzel, D.A. *J. Org. Chem.* **1984**, 49, 4226.

[184] Cui, X.; Dai, X.; Deng, Y.; Shi, F. *Chem. Eur. J.* **2013**, 19, 3665.

[185] Nichols, D. E.; Brewster, W. K.; Johnson, M. P.; Oberlender, R.; Riggs, R. M. *J. Med. Chem.*, **1990**, 33, 703.

[186] Suarez-Meneses, J. V.; Bonilla-Reyes, E.; Ble-Gonzalez, E. A.; Ortega-Alfaro, M. C.; Toscano, R. A.; Cordero-Vargas, A.; Lopez-Cortes, J. G. *Tetrahedron*, **2014** , *70*, 1422.

[187] Lv, P.; Huang, K.; Xie, L.; Xu, X; *Org. Biomol. Chem.*, **2011**, 9, 3133.

[188] (a) Miao, F.; Yangab, X.; Zhouab L.; Hub, H.; Feng, Z.; Ding, X.; Zhou, C.; Sun, W. *Natural Product Research*, **2011**, *25*, 863; (b) Joshi, B. S.; Puar, M. S.; Moore, K. M.; Pelletier, S. W. *Heterocycle*, **1991**, *32*, 1365.

[189] Nefkens, G. H. L.; Thuring, J. W. J. F.; Zwaneburg, B *Synthesis* **1997**, *3*, 290.

[190] Boukouvalas, J.; Loach, R. P. *J. Org. Chem.* **2008**, *73*, 8109.

[191] Zheng, X.; Dai, X.; Yuan, H.; Ye, C.; Ma, J.; Huang, P. *Angew. Chem. Int. Ed.* **2013**, *125*, 3578.

[192] Cheng, P; Zhou, J; Qing, Z; Kang, W; Liu, S; Liu, W; Xie, H; Zeng, J. *Bioorg. Med. Chem. Lett.* **2014**, 24, 2712.

[193] Deng, A.; Qin, H. *Phytochemistry*, **2010**, *71*, 816.

[194] Huy P.; Neudörfl J.; Schmalz H., *Org. Lett.* **2001**, 216.

[195] Reed P.; Katzenellenbogen J., *J. Org. Chem*. **1991**, 2629.

[196]Caline C.; Khalid I.; Alain A.; Ali Al M.; Christiane P.; Pierre P., *Tetrahedron* **2000**, 1837.

[197] Michael, P.; Ley, S. *Angew. Chem., Int. Ed*. **2002**, 3898.

[198] Kaga, H.; Goto, K.; Takahashi, T.; Hino, M.; Tokuhashi, T.; Oritol, K. *Tetrahedron*, **1996**, *52*, 8451.