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The 1,5-Hydride Shift as a Route into Nitro-Mannich Cyclisations

A thesis by

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Declaration

I, Oliver Ware, confirm that the work presented in this thesis is my own. Where information has been derived from other sources I confirm this has been indicated in the thesis.

Signed……..

Dated……

Abstract

Carbon-hydrogen bonds are typically not viewed as a reactive site, rather they are commonly the backbone of the molecule to which functional groups are attached. We believed that we could find a method of reacting directly at C-H bonds via a hydride transfer to provide a simple, atom efficient method of constructing carbon-carbon bonds, providing a new target site for small molecule synthesis. Our initial targets for C-H activation were benzylic ethers. This was to be achieved with the use of Lewis acid catalysts to promote hydride transfer. It was initially thought that this transformation could be achieved through a modification of the Oppenauer oxidation, which had previously shown a small degree of conversion (8%) within the group.

The yield was improved to 24%, but no further progress was made despite inquiry into a wide range of conditions and substrates. These results led us to consider a method of intramolecular C-H activation which would be achieved via a 1,5-hydride shift. This reaction has seen use previously with electron withdrawn alkenes, but only a very limited number of nitroalkenes had been observed performing this transformation, using a protic solvent. We have developed a method of Lewis acid catalysis to convert nitrostyrene substrates.

The nitrostyrene acts as a hydride acceptor to form a nitronate anion, which then attacks the newly generated cation to form a six-membered ring. A novel route into the synthesis of substituted tetrahydroquinolines has been achieved via a nitro-Mannich cyclisation, something only previously performed with n-BuLi mediated deprotonation of nitroalkanes or the use of an external hydride source to generate the required nitronate. Our reaction has the potential to be incredibly atom efficient, with no gain or loss of mass from the starting material to product, requiring only the use of a catalyst.

Acknowledgements

I would first like to thank Prof. Jim Anderson for his help and support during my PhD and for giving me the opportunity to study under him. Furthermore for the running of our weekly group meetings which have been of great interest and where I have frequently furthered my knowledge of chemistry.

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I would like to thank the Anderson group, especially Helen for her guidance both with the practical aspects of my research and with teaching commitments. Steve was essential during my research as he was always willing to go for a drink on a Monday night after a hard day in the lab.

I want to extend my thanks to other members of lab 457, to Kealan for showing me the ropes when I took over as CPS secretary, to Dave because I'm obliged to and to Tom and James for reminding me that it could always be worse. Further afield, Martin and Dougal deserve thanks for keeping me grounded. I'd also like to thank Rachel for giving me a perspective outside of chemistry and Shivan for putting up with me since we were eight.

Finally I would like to thank my family for their love and support, not only during the last three years but for many before that. I should also thank my girlfriend Hannah for engaging in what must have been excruciatingly dull conversations about chemistry, though I think that the amount I now know about chick embryos and foot ulcers makes up for it!

Abbreviations

Abbreviation	Meaning
Ac	Acetyl
acac	Acetylacetone
AIBN	Azobisisobutyronitrile
aq	Aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
Bpin	Bis(pinacolato)diboron
bpy	2,2'-Bipyridine
Bu	Butyl
CDC	Cross-Dehydrogenative Coupling
CN	Cyano
cod	1,5-Cyclooctadiene
coe	Cyclooctene
Cp	Cyclopentadiene
d	Days
dr	Diastereomeric ratio
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCE	Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminium hydride
DIPEA	N,N-Diisopropylethylamine
DMA	Dimethylacetamide
2,2-DMB	2,2-Dimethylbutane
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethylsulfoxide
dtbbpy	4,4′-Di-tert-butyl-2,2′-dipyridyl
E	Entgegen
ee	Enantiomeric excess
EPR	Electron paramagnetic resonance

Eq	Equivalents
Et	Ethyl
EWG	Electron withdrawing group
h	Hour
Hex	Hexyl
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HPLC	High-performance liquid chromatography
hv	Light
IBX	2-Iodoxybenzoic acid
OiPr	Isopropoxide
IPA	Isopropyl alcohol
iPr	Isopropyl
LCMS	Liquid chromatography–mass spectrometry
m	Minutes
mbar	Millibar
Me	Methyl
MeCN	Acetonitrile
MS	Molecular Sieve
NaBARF	Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
OTf	Triflate
Ph	Phenyl
PhMe	Toluene
PIDA	(Diacetoxyiodo)benzene
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
PLE	Pig Liver Esterase
PMB	Para-methoxybenzene
ppy	2-phenylpyridine
Pr	Propyl
PTAD	(1-adamantyl)-(N-phthalimido)acetato
PyBOX	Pyridine-linked bis(oxazoline)
rac	Racemic
rt	Room Temperature

S-DOSP	*S*-N-(*p*-Dodecylphenyl)sulfonylprolinate
S-PTTL	N-phthaloyl-(*S*)-*tert*-leucinate
SET	Single electron transfer
TBHP	*t*-butyl hydrogen peroxide
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THIQ	Tetrahydroisoquinoline
THQ	Tetrahydroquinoline
TLC	Thin Layer Chromatography
TMB	Trimethoxybenzene
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
tol-BINAP	2,2′-bis(di-p-tolylphosphino)-1,1′-binaphthyl
TRIP	3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
UV-CFL	Ultraviolet Compact Fluorescent Light
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
Z	Zusammen

Contents

1. Introduction

The field of drug discovery requires constant innovation, both in terms of moieties investigated and the processes by which they are made. The most important reactions are those which form carbon-carbon bonds, thereby allowing major structural changes to the molecule in question. An important class of carbon-carbon bond forming reactions is those which occur through C-H activation.

Traditionally, the C-H bond has been viewed as reasonably chemically inert, with transformation reactions preferentially being achieved through functional group interconversions. This is despite the long history of C-H activation, the very first example of this reaction, although it was not known at the time, was published in 1894, when Fenton published a method of achieving the oxidation of tartaric acid in the presence of iron.[1]

Certain processes are now used extensively in academia, namely cross-coupling reactions which have revolutionised areas such as natural product synthesis where it allows major late stage functionalisation.[2,3] Although C-H functionalisation occurs across a truly vast range of substrates, by far the most investigated type of C-H functionalisation is the transition metal catalysed cross-coupling of aryl substrates, with palladium catalysts being all but ubiquitous.[4–11] Indeed, direct C-H bond activation and functionalisation is one of the most active research fields in organic chemistry.[12] This recent interest is perhaps unsurprising considering the current drive towards providing synthetic methodology of greater atom efficiency and sustainability.[13]

The functionalisation of non-aryl C-H bonds is comparatively less well investigated. In the sections that follow, current methods for the functionalisation of C-H bonds adjacent to amines and ethers will be discussed in general terms. This will be followed by further discussions of cross-dehydrogenative couplings adjacent to both amines and ethers and finally, the state of the art in the field of the 1,5-hydride shift.

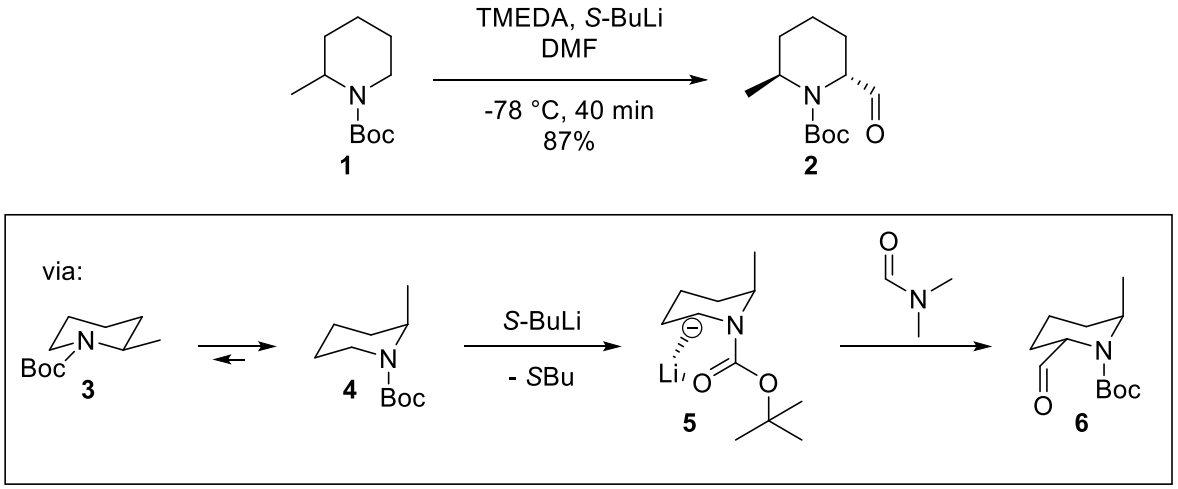
1.1 C-H Functionalisation Adjacent to Amines

The main methods of C-H functionalisation adjacent to amines can be divided into several categories which have been investigated in depth, the deprotonative cross-coupling, radical formation, metal insertion and carbenoid insertion based

approaches.[14] Other key transformations are the cross-dehydrogenative cross coupling and the 1,5-hydride shift, which will be covered in detail in sections 1.3.1 and 1.4.1 respectively.

1.1.1 Deprotonative Cross-Coupling Adjacent to Amines

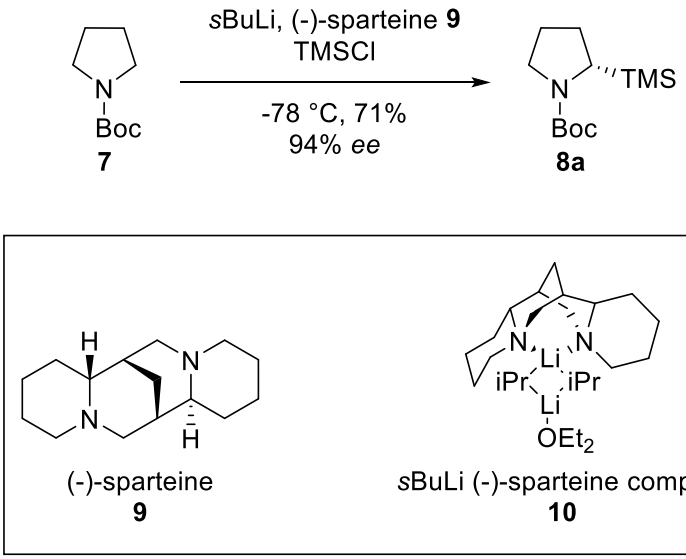
The first reported approach to α-amine C-H functionalisation was deprotonative cross-coupling or α-lithiation.[15,16] This was the first of many publications which functionalised the α-position of N-protected heterocycles such as **1**.[16] The most common activating/directing group in these reactions was the Boc group and a range of electrophiles were successfully inserted (**Scheme 1**). The authors observed that these reactions lead to the *trans*- product when the 2-position is alkylated.[17] However when 2-methylpyrollidines were used in place of 2-methylpiperidines, the *trans*/*cis* selectivity was reduced significantly, with a ratio of 2:1 observed.[17] The authors proposed that the selectivity observed with 6-membered rings such as **1** was through ring interconversion. Equatorially substituted piperidines are less stable than the axially substituted analogues.[17] The 2-methyl piperidine analogue **1** would therefore sit in conformation **4** and undergo the substitution to form **2** (**Scheme 1**). This steric bias is not present to the same extent in 2-methyl pyrrolidines and as a result the diastereoselectivity was decreased.



Scheme 1: Example of deprotonative cross coupling to form 2[17]

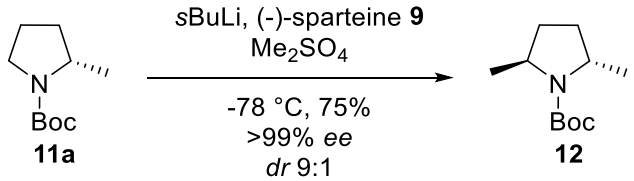
More remarkably, Beak *et al.* discovered that the presence of (-)-sparteine **9** to chelate to the lithium cation in place of TMEDA led to the formation of a chiral organolithium complex **10**. This complex **10** selectively removes the pro-*S* hydrogen from **7**, leading to the formation of a single anionic enantiomer which

retains its chirality upon reaction with an electrophile to give *ee*s which were generally >90% (**Scheme 2**).[18]



Scheme 2: Enantioselective α-lithiation and electrophilic substution[18]

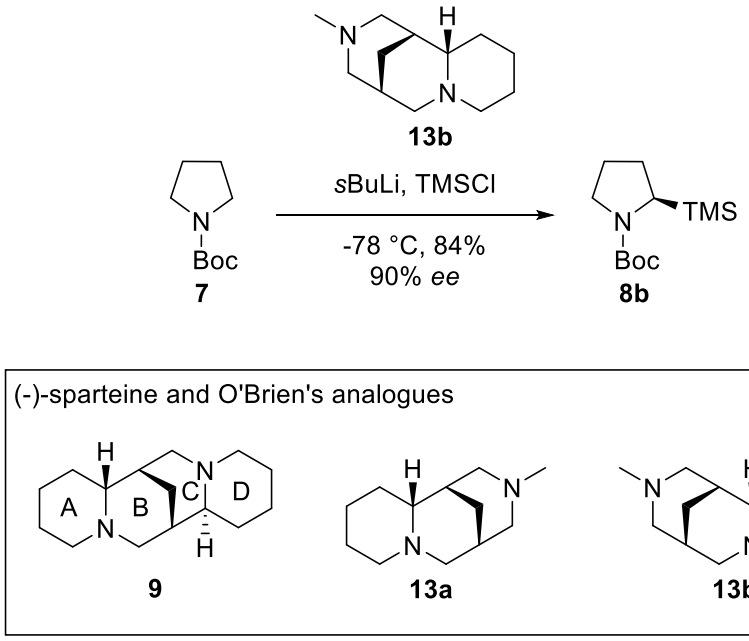
Subsequent studies suggested that the abstraction of the pro-*S* proton is determined kinetically with the resulting intermediate being stable through dipole stabilisation to -50 °C with stereochemistry being retained during electrophilic attack.[19] This enantioselective deprotonation was repeated with 2-methyl pyrrolidines such as **11a** and these yielded *trans*- 2,5-substituted compounds **12** with excellent *dr*s and *ee*s in contrast to the use of TMEDA (discussed above) (**Scheme 3**).[18,19] The scope of protected amine has since been increased.[20–23] However, (+)-sparteine is not readily available and success in preparing other ligands which promote these reactions in a similar manner was generally limited.[24,25]



Scheme 3: Enantioselective alkylation of 11[19]

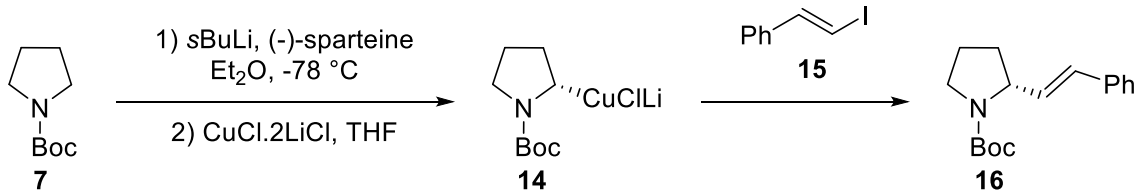
There is, however, one notable success in this area which is ligand **13b**, developed by O'Brien *et al.* in 2004.[26] Through the use of computational modelling, a range of target (±)-sparteine analogues which would form a similar cage upon chelation to lithium were identified. A pair of these ligands, **13a** and

13b were found to provide chelation as per (±)-sparteine without a major decrease in reactivity as had previously been observed with other (±)-sparteine analogues. These new compounds had the advantage of both (-) and (+) analogues being relatively straightforward to synthesise. Crucially, their new ligand **13**, which replaces ring D with a simple methyl group, acts analogously to (+)-sparteine, allowing chemists for the first time to access enantiomers which were inaccessible through the use of (-)-sparteine **9**. An example of this was **8b**, which was prepared in a 90% *ee* and an 84% yield (**Scheme 4**).[26]



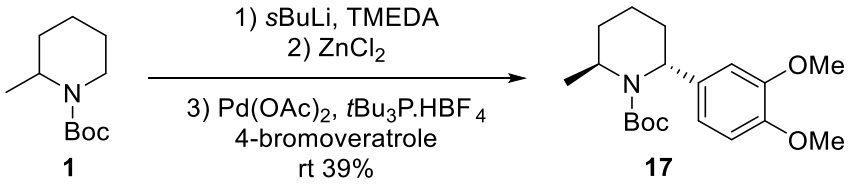
Scheme 4: The first successful synthesis of 11b with a (+)-sparteine analogue[26]

Another breakthrough in the utility of these reactions came in 2004, when Dieter *et al.* discovered that it was possible to transmetallate the generated organolithium with copper salts.[27] The copper salts (e.g. **14**) were able to successfully react with a much wider range of electrophiles, including iodoalkenes and iodoalkynes.[27] This was, however, at a cost to the enantioselectivity, which was reduced, compared to the direct use of simple electrophiles such as the alkyl halides and TMSCl used in the reactions discussed above. A possible explanation for this could be the cuprate being inherently less configurationally stable.[27] An example of this broadened scope is the styrene functionalised pyrrolidine **16** (**Scheme 5**). Transmetalation with zinc species has since been performed, allowing aryl cross-coupling to occur in the presence of a palladium catalyst.[28]



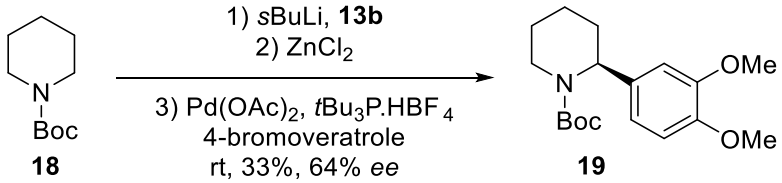
Scheme 5: Example of broadened scope from transmetallation[27]

A further example of transmetallation came in 2008, when the Coldham group reported the arylation of piperidinyl species.[29] Here again a zinc species was used for transmetallation, which was followed with a Negishi-type coupling. Whilst enantioselectivity could not be achieved for the majority of substrates, in contrast to pyrrolidinyl substrates, **17** was obtained as a single diastereomer (**Scheme 6**).[29]



Scheme 6: α-Lithiation and subsequent transmetallation/arylation[29]

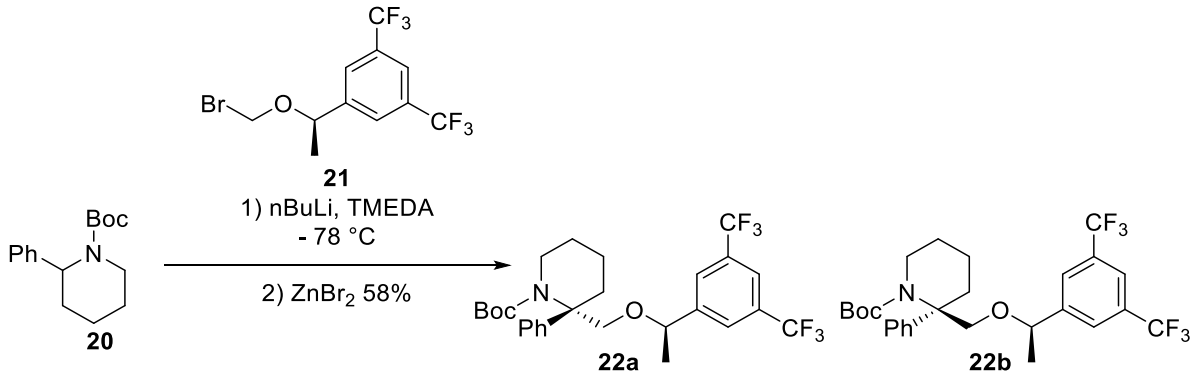
This was followed by work to develop an enantioselective process of functionalising N-Boc piperidines.[30] The best enantioselectivity was found to be attained with the (+)-sparteine derivative **13b** developed by O'Brien (**Scheme 7**).[26,30] Here *ee*s were not achieved to the same extent as with pyrrolidines, instead ranging between 14-74%. Yields were likewise slightly reduced compared to when TMEDA was used (**Schemes 1** and **6**, above).



Scheme 7: Enantioselective synthesis of 9[30]

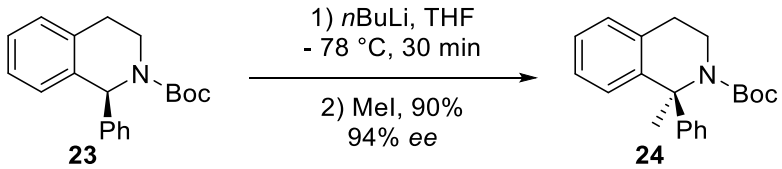
In 2005, Xiao *et al.* published an alternate method of α-lithiation which selectively alkylated the 2-position of nitrogen heterocycles.[31] This difference was due to the presence of a phenyl group in the 2- position rather than an alkyl group, which effectively converts the 2-position into a benzylic C-H. This selectivity was used to synthesise the NK_1 agonist **22** (**Scheme 8**). This reaction failed to proceed in

the presence of (-)sparteine in place of TMEDA and as a result both diastereomers **22a** and **22b** were formed.



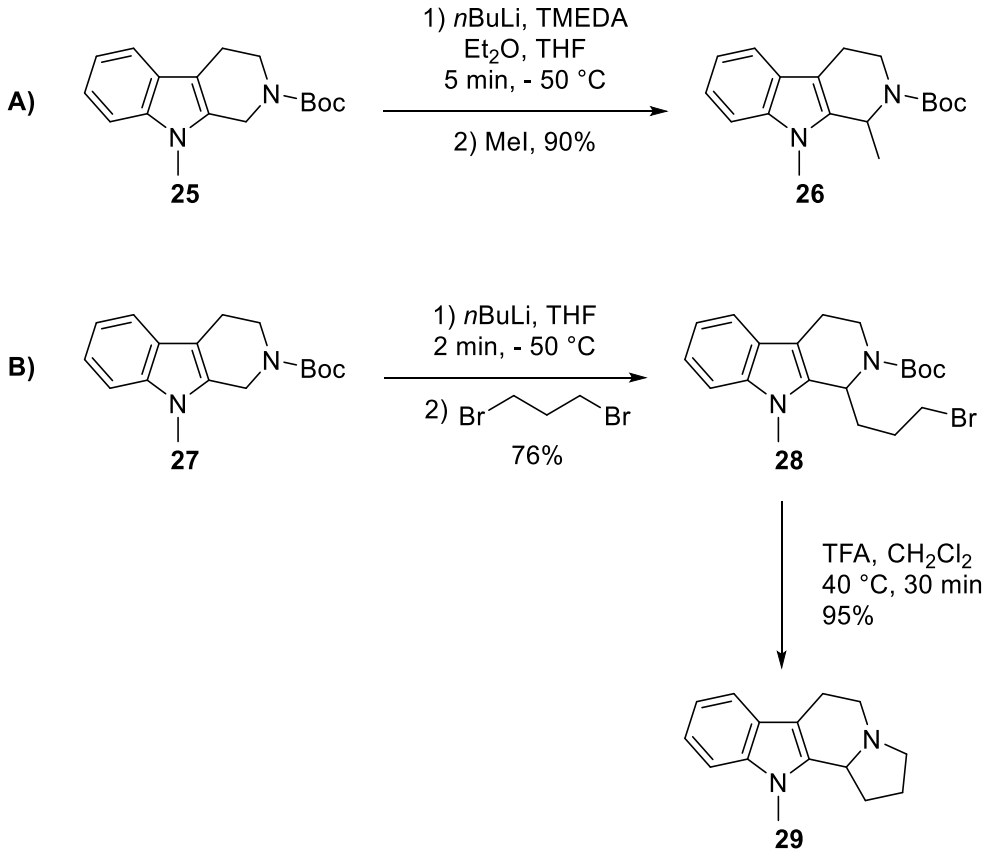
Scheme 8: Synthesis of NK_1 agonists through deprotonative cross coupling

Coldham *et al.* went on to develop a method of preparing 1,1-disubstituted tetrahydroisoquinolines in 2014 (**Scheme 9**).[32] This method was used to prepare, amongst other compounds, a precursor **24** to (+)-FR115427, a noncompetitive antagonist of the NDMA receptor (**Scheme 9**).[32] Once **24** was prepared it was subjected to a simple Boc deprotection to give the desired compound in a 91% yield.[32]



Scheme 9: Preparation of a key intermediate to (+)-FR115427[32]

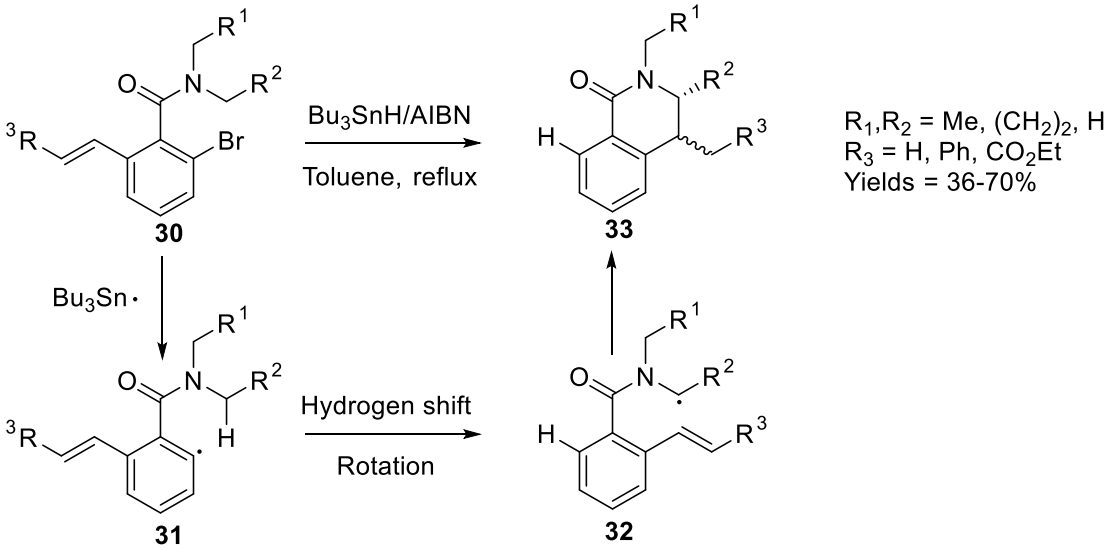
Finally, the Coldham group have also turned the α-lithiation reactions upon which they have worked towards total synthesis.[33] Using this methodology they have successfully prepared two natural products, **26** and **29** (**Scheme 10**).[33] The authors made use of the selectivity seen with N-Boc tetrahydroisoquinolines towards the deprotonation of the benzyl position to prepare **26** in a 90% yield (**Scheme 10, A**). The use of dibromoalkane led to the subsequent successful synthesis of (±)-11-methylharmicine **29** (**Scheme 10, B)**



Scheme 10: Total syntheses of 26 and 29 via α-lithiation[33]

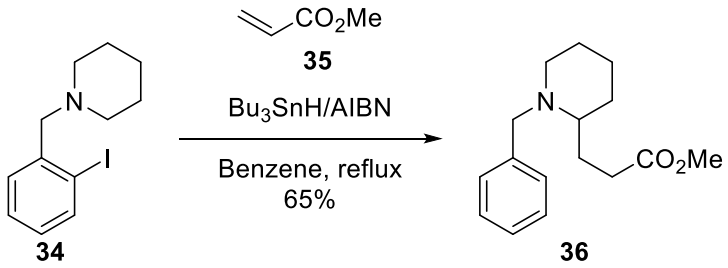
1.1.2 Radical Mediated C-H Functionalisation Adjacent to Amines

The first series of conditions to perform radical mediated C-H functionalisation adjacent to amines were developed through the 1990s. These early methods overcame the difficulties of generating the desired radical intermediate for α-C-H functionalisation through the use of 1,5-hydrogen transfers in a manner analogous to the 1,5-hydride shift, which will be discussed in greater detail in section 1.4.1, below.[34–37] Here, functional groups which more readily form radical species, for example, halides which will homolytically cleave, are the initial site for radical formation. The first example of this came in 1990, when Snieckus *et al.* reported that compounds such as **33** could access α-amino radicals to form new 5- and 6-membered rings in the presence of tethered radical acceptors (**Scheme 11**).[34] The authors also reported that the methodology could be applied to non-tethered radical acceptors.



Scheme 11: The first radical mediated C-H functionalisation adjacent to an amine[34]

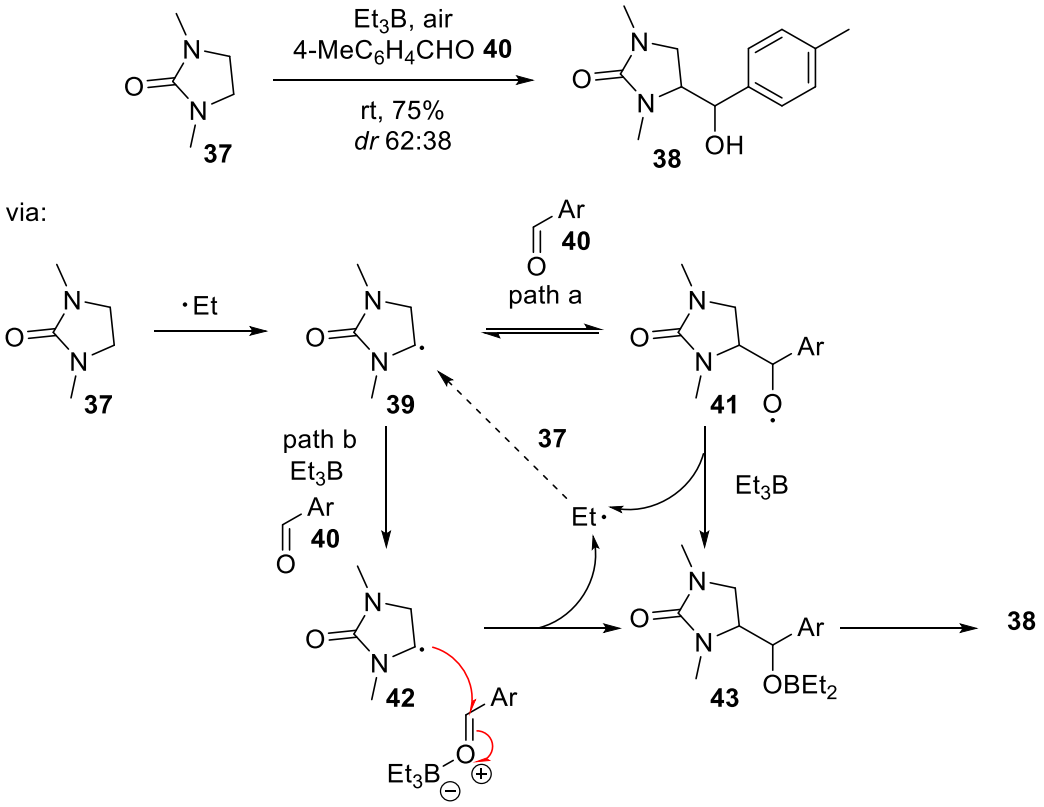
Undheim *et al.* applied this methodology to 2-iodobenzyl protected heterocycles.[35] The radical cleavage of the iodine which led to radical formation also results in a readily cleavable benzyl protecting group on the amine following functionalisation (**Scheme 12**). This methodology was found to work with both diethylamine and a range of heterocycles including morpholine and azepane.[35]



Scheme 12: Example radical mediated functionalisation to leave Bn protecting group[35]

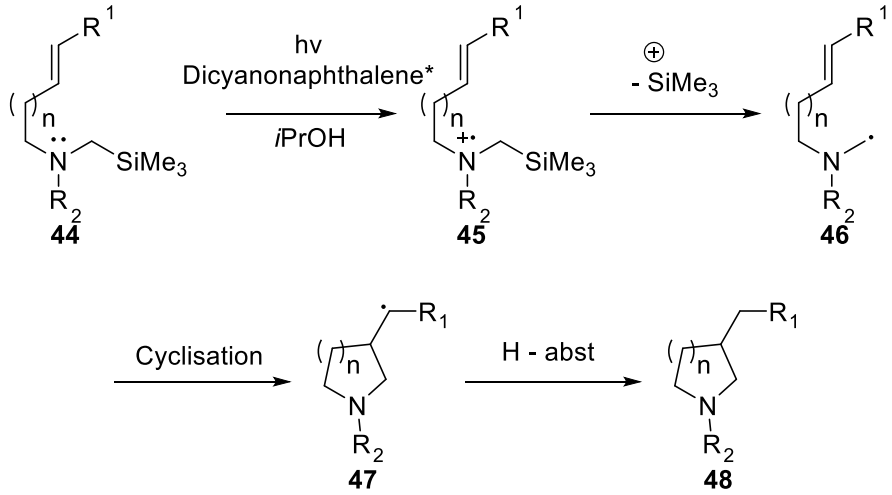
The scope of electrophile was extended over the next decade with the fundamental method of radical formation essentially unchanged until, in 2005, Yoshimitsu published a route to direct α-C-H formation (**Scheme 13**).[38] Here the authors proposed that Et_3B and oxygen react to form an ethyl radical, which serves to abstract a hydrogen from **37**. The subsequent radical **39** has two plausible methods of reacting with the electrophile to form **38** and regenerate the ethyl radical.[38] In path a, the radical **39** reacts with aldehyde **40** to form the oxy radical **41**. This radical then reacts with Et_3B to release an ethyl radical and

generate **43** which forms **38** upon workup. In path b, Et_3B coordinates to aldehyde **40** before reacting with the initially formed radical **39**. This forms intermediate **43** directly which gives the desired product **38** upon workup.



Scheme 13: First direct α-C-H radical formation/functionalisation and proposed mechanism[38]

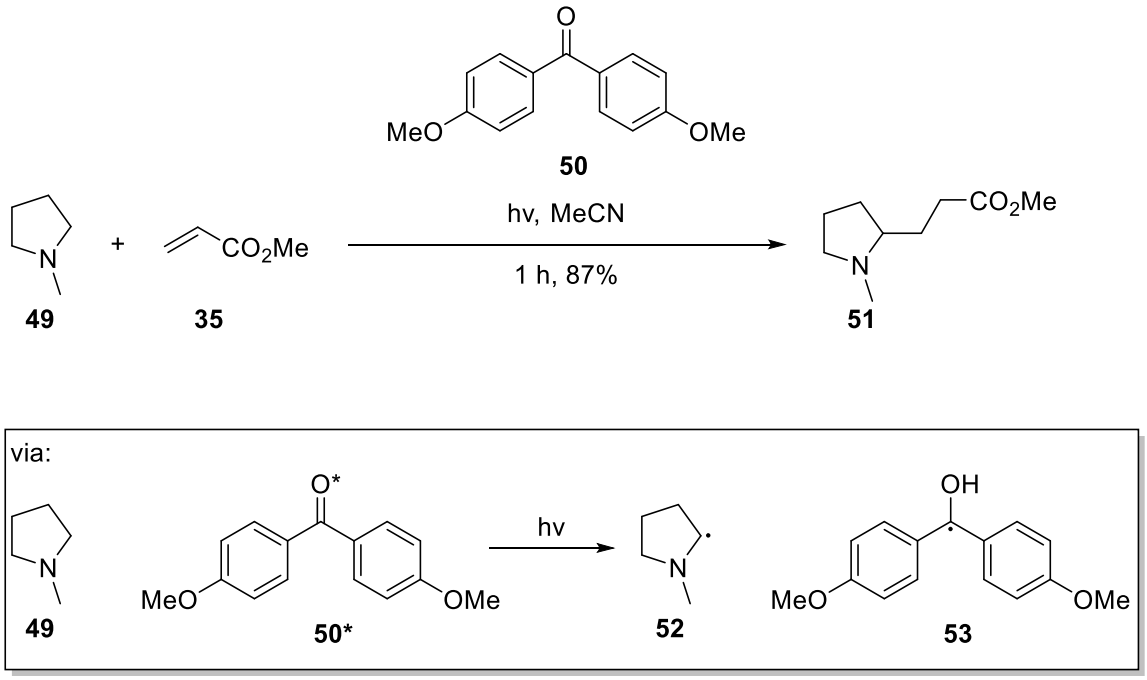
However, the real breakthrough in this area has been with photoinduced radical formation and subsequently photoredox catalyst SET-based methodology. An early example of photoinduced radical formation was seen in 1989 where homolytic cleavage of TMS groups led to a novel method of pyrrolidine synthesis (**Scheme 14**).[39] This was achieved in the presence of dicyanonaphthalene which acts as an electron acceptor from the starting material **44** (**Scheme 14**). Notably, this reaction proceeded with an alkynyl radical acceptor to form an alkenyl-substituted heterocycle which would not form if the reaction proceeded via an iminium pathway.[40]



Scheme 14: An early dicyanonaphthalene[a] mediated radical coupling adjacent to an amine[39]

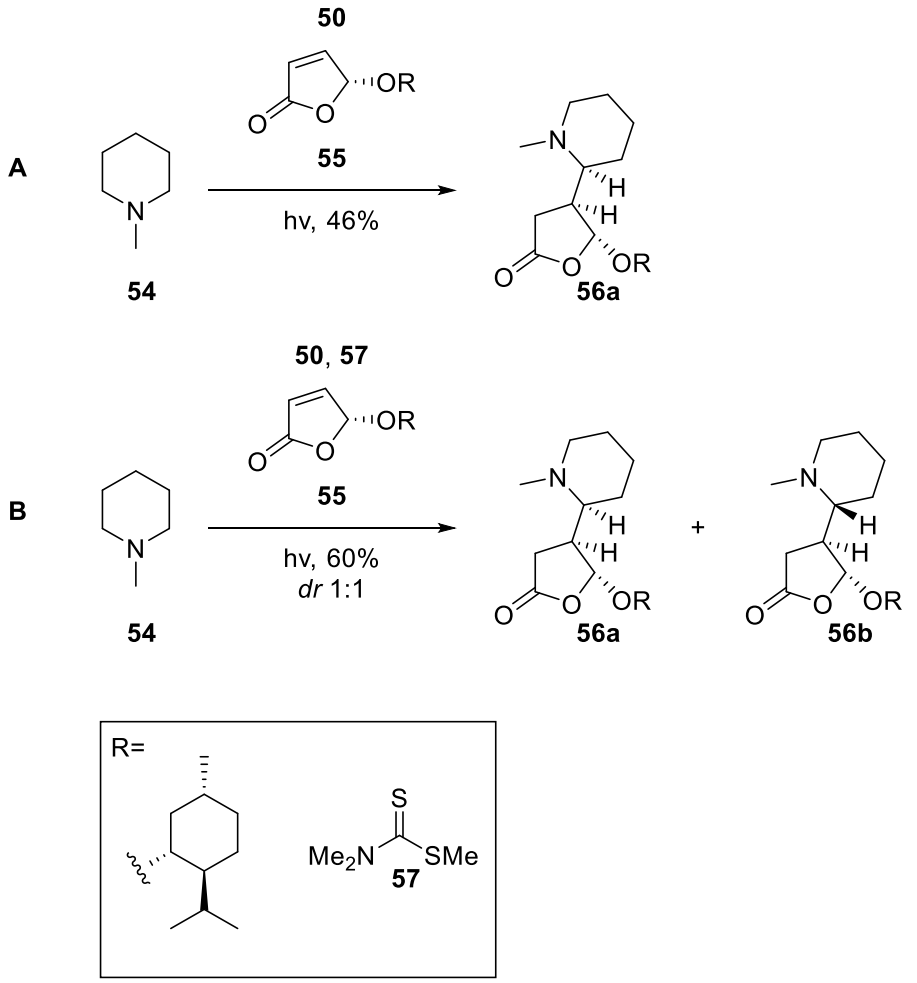
Through the development of alternate sensitisers/electron acceptors, the scope of products which could be formed from radical formation adjacent to an amine was extended. A good example of the importance of the sensitiser is a study published in 1999 by Bertrand *et al.* whereby through sensitiser choice the authors were able to more than double their yield.[41] Using 4,4'-dimethoxybenzophenone **50**, nine analogues were prepared in good yields, though electron deficient alkenes were required as the coupling partner (**Scheme 15**). Unlike earlier reactions, the α-amino radical is generated directly by the sensitizer (**Scheme 15**), this radical then reacting as above, albeit with an external radical acceptor. The Bertrand group subsequently applied this methodology to the synthesis of Necine bases.[42]

[a] Authors do not state the substitution pattern of dicyanonaphthalene



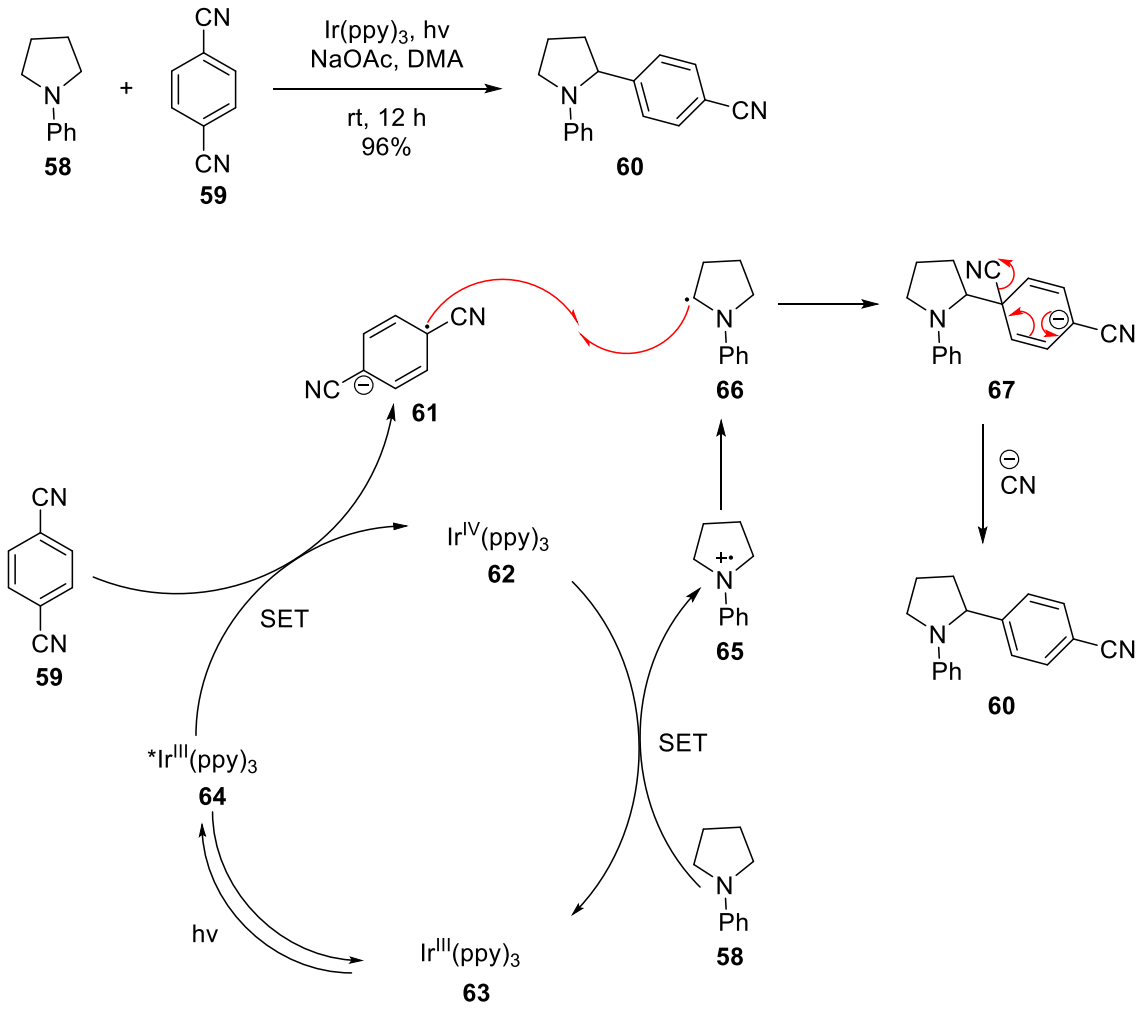
Scheme 15: Radical coupling with 4,4'-dimethoxybenzophenone 50[41]

Harakat reported, in 2006, that the addition of thiocarbonyl compounds leads to decreased reaction times and allows the reaction of less active species of amine.[43] It was proposed that this is achieved through the thiocarbonyl reversibly trapping radical intermediates following their initial generation to form “persistent radicals”.[43] However, the addition of a thiocarbonyl species in many cases led to a loss of diastereoselectivity (**A** vs **B**, **Scheme 16**).



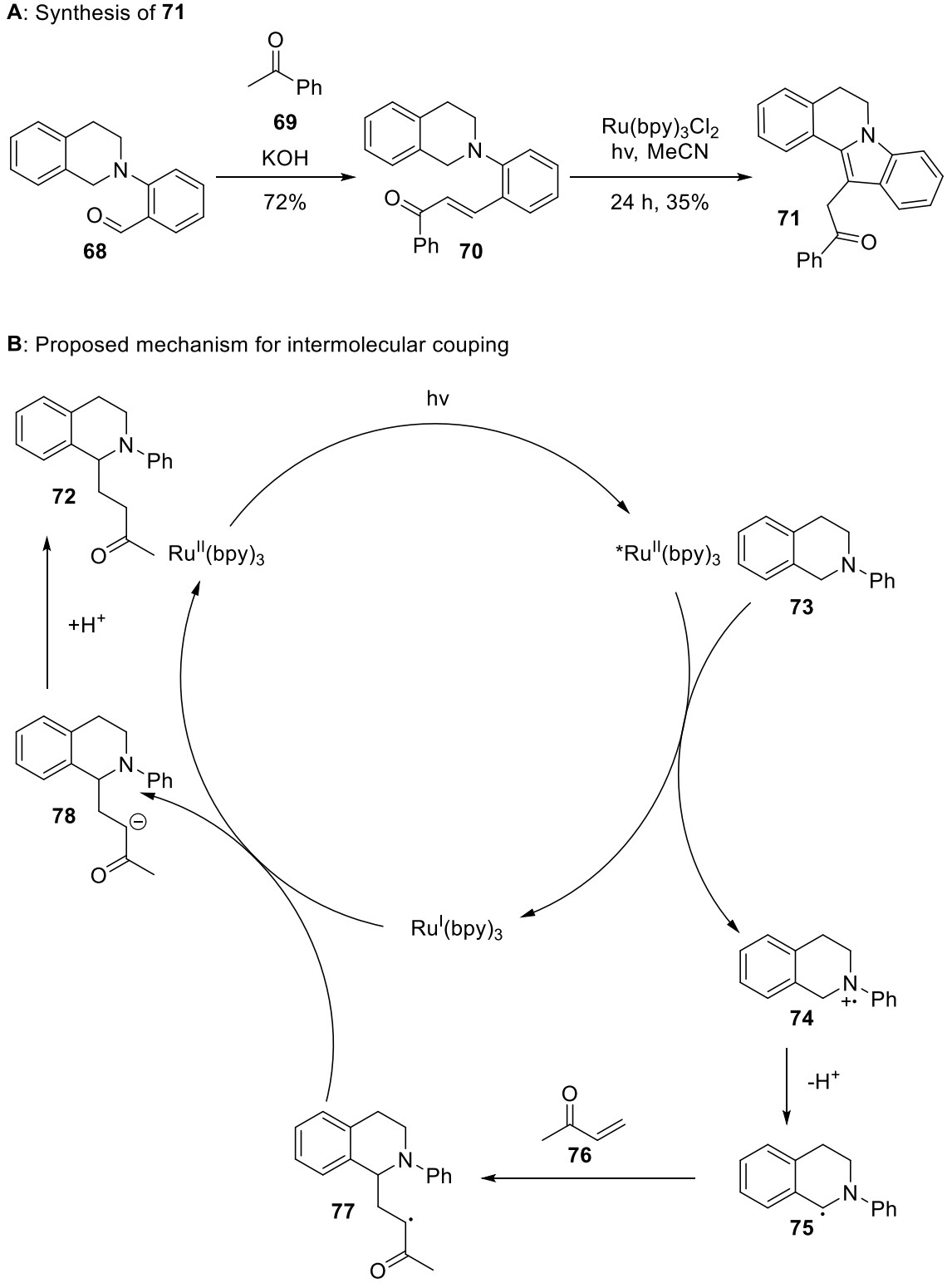
Scheme 16: Effect of thiocarbonyl 57 on radical coupling[43]

A key development in this field was the use of iridium and ruthenium-based photocatalysts, the first clear example of which was the MacMillan group's "accelerated serendipity strategy" which led to the discovery of a method of generating a radical adjacent to an amine.[40] When a tertiary amine was subjected to an iridium catalyst in the presence of 1,4-DCB **59**, a novel coupling was seen (**Scheme 17**). The authors proposed that the excited iridium catalyst undergoes a SET to form a 1,4-DCB radical anion and then abstracts an electron from the amine species, in this case **58**, to form a radical cation. The radical cation and anion subsequently undergo a radical-radical coupling to form **60** following the loss of –CN.[40]



Scheme 17: Photochemically induced radical coupling adjacent to an amine[40]

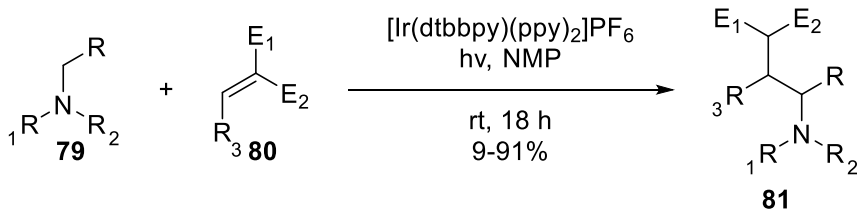
This methodology was developed further by the Reiser group who performed conjugate addition between N-aryltetrahydroisoquinoline **70** and Michael acceptors with both $Ru(bpy)_3Cl_2$ and $[Ir(ppy)_2(dtb\text{-}bpy)]PF_6$ in the presence of blue light.[44] This methodology allowed the synthesis of 5,6-dihydroindolo[2,1-a]tetrahydroisoquinoline **71** in a 25% overall yield across two steps (**Scheme 18**, **A**). However, the authors report that the intramolecular reaction pathway is unclear, with the proposed mechanism for the intermolecular reaction (**Scheme 18**, **B**) not being compatible with the aromatisation of the indole portion of **71**.[44]



Scheme 18: Two step synthesis of 71 via α-amino radical coupling and proposed mechanism for 72[44]

Concurrently, Miyake *et al.* developed a similar method of α-amino radical coupling, though with a wider range of amines than tetrahydroisoquinolines.[45] Here Michael acceptors such as diethyl ethylidenemalonate were reacted in the

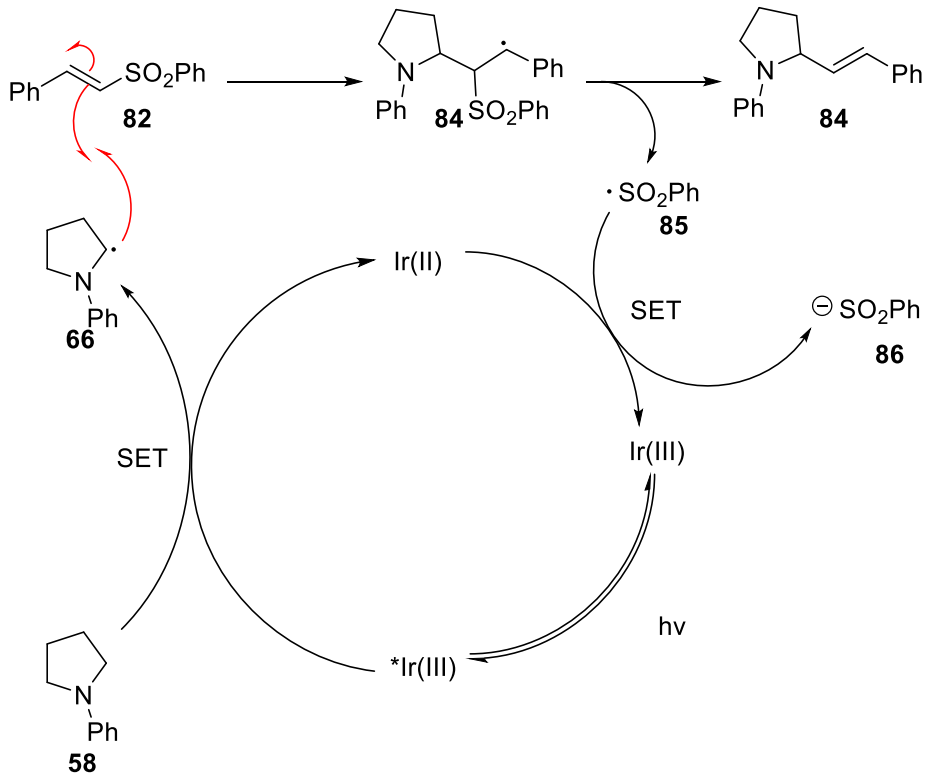
presence of an iridium catalyst (**Scheme 19**). Over 25 analogues were prepared under general conditions, showing the wide applicability of these photoinduced α-amino radical couplings.[45]



R, R_1, R_2 = H, Me, Ph, 4-MePh, 4-MeOPh, 4-FPh, 4-ClPh, 4-MeO(CO)Ph, *t*Bu, *i*Pr, or **79** = N-phenylindoline
R_3 = Me, *n*Pr, *i*Bu, Cy, Ph, 4-MePh, 3-MePh, 4-ClPh, 4-PhPh, 2-naphthyl, EtO, CO_2Me
E_1, E_2 = CO_2Me, CO_2Et, H

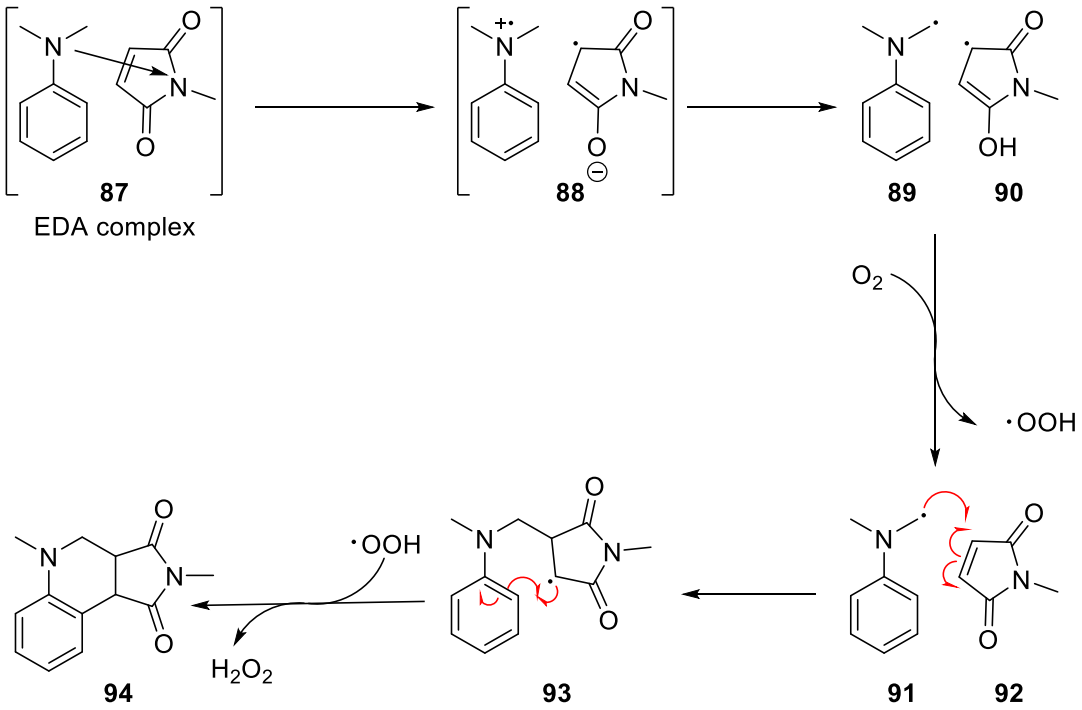
Scheme 19: The scope of Ir catalysed α-amino radical coupling[45]

Noble *et al.* published a photoredox α-vinylation of N-arylamines and α-amino acids.[46] Here a SET occurs between the N-arylamine **58** and the iridium photocatalyst to generate a radical cation which is deprotonated to give the neutral radical **66**. This α-amino radical attacks vinyl sulfone **82** which desulfonates to form the desired allylic amine **84** (**Scheme 20**). Finally, the sulfonyl radical **85** is reduced to the anion via a second SET and regenerates the Ir(iii) species.



Scheme 20: Photoredox catalytic cycle to form 84[46]

Finally, the Sunden group have recently published a new method of α-aminoalkyl radical addition to maleimides, which was achieved through the generation of an electron donor/acceptor (EDA) complex (**Scheme 21**).[47] Using UV-CFL in dioxane at rt, 25 analogues were prepared. The authors submit that the reaction is driven by the photochemical activity of the EDA complex **87**. Once excited, this EDA complex undergoes an SET and subsequent proton transfer to generate species **89** and **90**. Once **90** has undergone oxidation to regenerate maleimide **92**, a radical coupling **93** occurs which, upon a further SET-oxidation, gives the product **94** (**Scheme 21**).

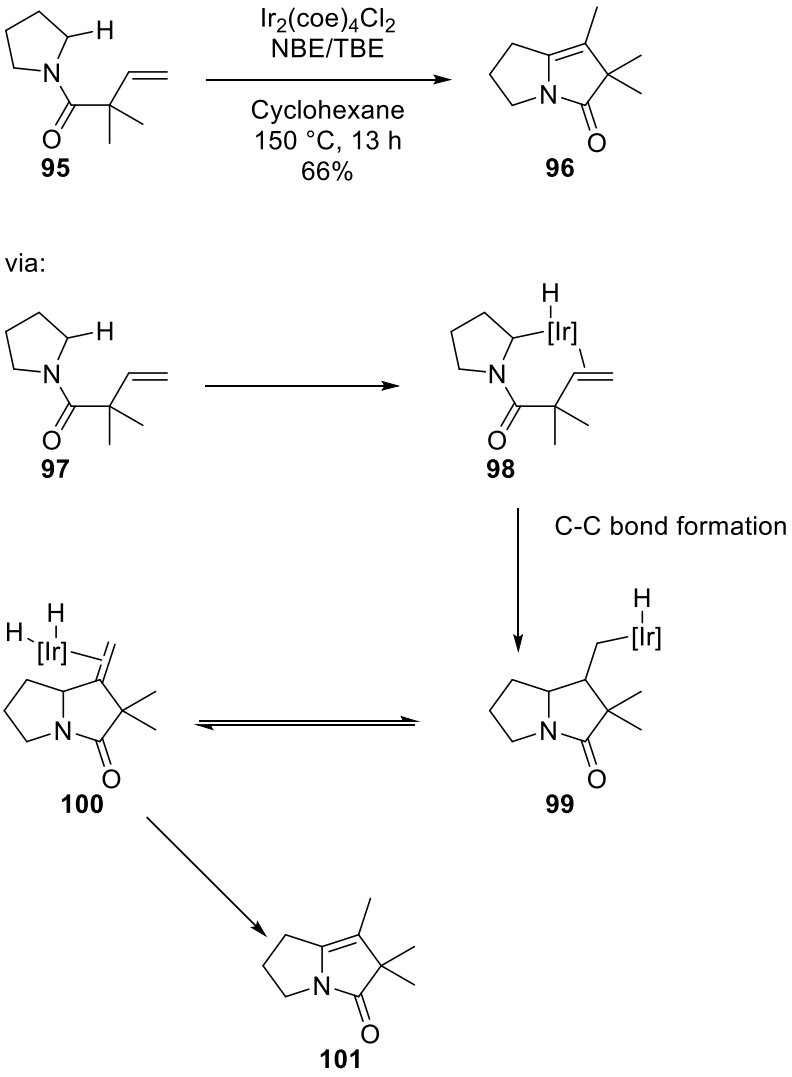


Scheme 21: Mechanism for α-aminoalkyl radical addition to maleimides[47]

Whilst there are examples of photoredox chemistry being used to generate α-amino radicals to react directly, as discussed above, in the majority of reactions in which these α-amino radicals are generated they are oxidised a second time to form an iminium ion which is then reacted with a nucleophile in a manner akin to the CDC reactions explored in detail below. A vast array of reactions have been accessed through this photoredox mediated iminium formation, particularly by the MacMillan and Rueping groups, which will not be discussed in depth.[48–54]

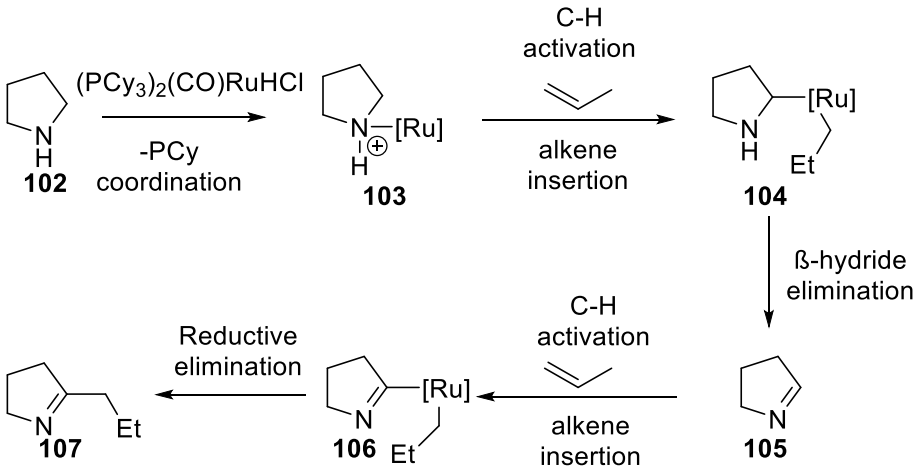
1.1.3 C-H functionalisation through α-C-H metal insertion

Whilst the insertion of transition metals into sp^3 C-H bonds is inherently difficult, there are several examples of this having been performed successfully. An early example was published by the Sames group whereby an iridium catalyst inserts into the α-amino C-H bond of the pyrrolidine derivative **95** and coordinates to the tethered alkene.[55] This tethering leads to C-C bond formation and eventual alkene reformation to give the bicyclic compound **96** (**Scheme 22**).[55]



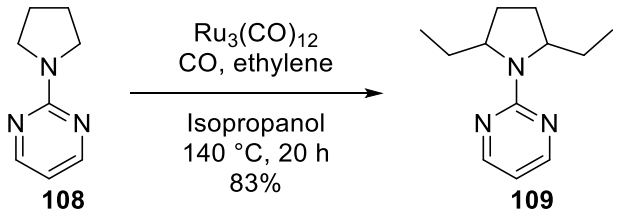
Scheme 22: Early α-amino C-H insertion/functionalisation[55]

An alternate, ruthenium-based, method of metal catalysed C-H insertion was developed by the Yi group.[56] Both the N-H and α-C-H were activated, converting a secondary amine **102** into the corresponding alkylated imine **107** (**Scheme 23**). The proposed mechanism involves C-H activation, β-hydride elimination and secondary C-H activation into the resulting imine **105** before the final reductive elimination to form **107** (**Scheme 23**).[56] The authors reported that these conditions, with a THF solvent, were suitable for a range of amines and alkenes with yields between 29-84%.



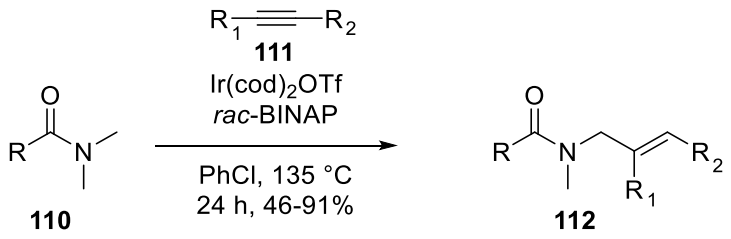
Scheme 23: Ruthenium catalysed α-amine C-H functionalisation[56]

Several other methods of converting secondary and tertiary amines into functionalised imines and enamines have since been developed along similar lines.[57,58] When moving from a rhodium to ruthenium catalyst, Murai *et al.* discovered that the conditions which had previously led to functionalised imines instead formed a di-α-alkylated product (**Scheme 24**).[59] Scope was limited to 2-aminopyridines and other nitrogen containing heterocycles. Accordingly, the authors proposed that the aryl nitrogen was acting to coordinate to the ruthenium to enable α-C-H metal insertion and the subsequent reaction steps.[59] Curiously, other known directing groups were not found to enable the reaction in an analogous manner.



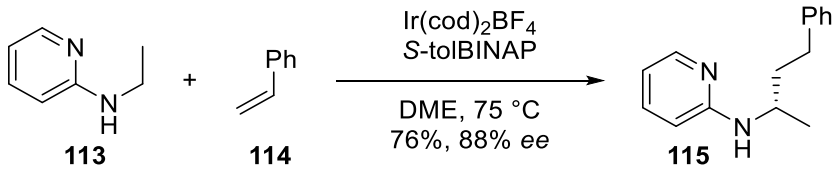
Scheme 24: Example of the Murai group's α-amino alkylation of arylamines[59]

Shibata *et al.* published a selective method of C-H functionalisation using iridium to alkenylate in the α-amine position.[60] The authors report that biaryl scaffolds were essential to see conversion and that *rac*-BINAP performed best of the biaryl scaffolds surveyed. Compounds such as **112** were prepared in moderate to good yields, with diphenylacetylene as the highest yielding alkyne scaffold **111** (**Scheme 25**).[60]



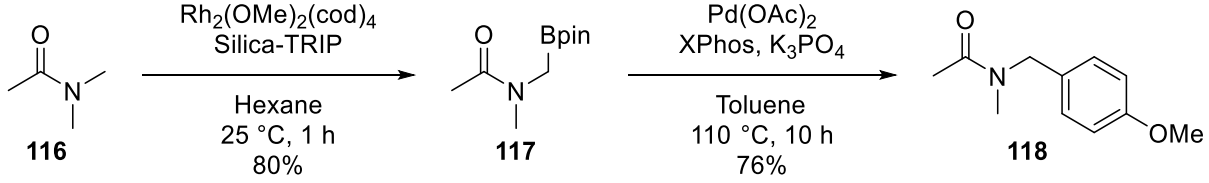
Scheme 25: Alkenylation through C-H insertion of iridium[60]

The Shibata group extended their methodology to provide a method of enantioselective functionalisation through the use of *S*-BINAP.[61] Whilst ruthenium had previously been used to alkylate the α-amino position, it was only with iridium and *S*-tolBINAP (**Scheme 26**) that enantioselectivity was observed.[59,61,62]



Scheme 26: Enantioselective alkylation to form 115[61]

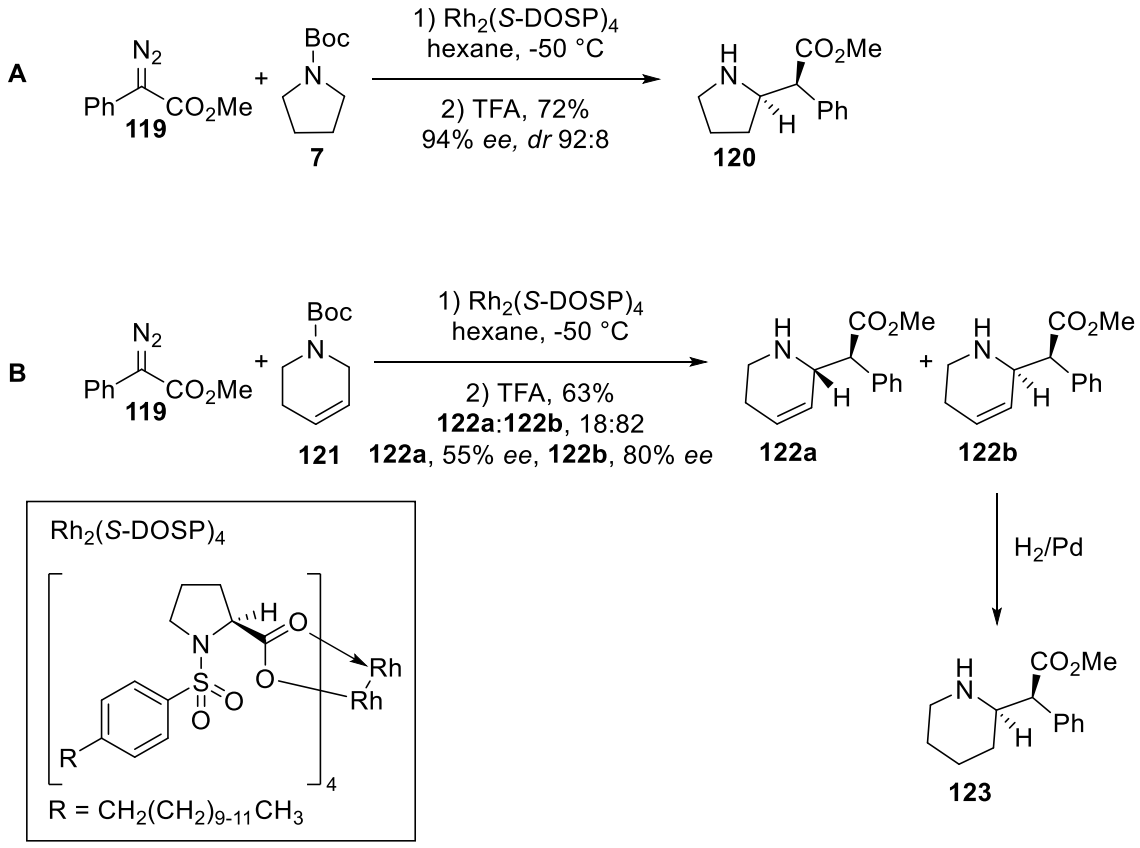
Notably, these insertions are no longer limited to the formation of C-C bonds. In 2012, the Sawamura group reported a novel method of borylation adjacent to amines (**Scheme 27**).[63] This functionalisation was achieved with the immobilised silica-TRIP ligand and $Rh_2(OMe)_2(cod)_4$ and a Bpin dimer. The reaction was found to perform well with amides and N-arylamines with a preference shown for cyclic over aliphatic amines and $–CH_3$ over $-CH_2$ carbons as a site for attack.[63] An example of the general procedure with aliphatic amide **116** is shown, though 16 analogues were prepared and several successfully underwent a subsequent Suzuki coupling, allowing access to a large number of previously inaccessible coupled products.[63]



Scheme 27: α-Amino borylation and subsequent Suzuki coupling[63]

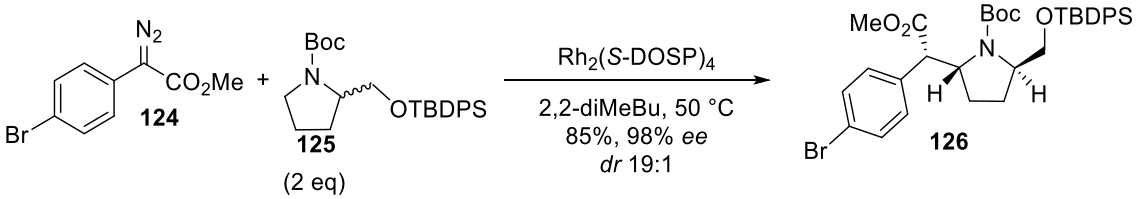
1.1.4 Metal Mediated Carbenoid Insertion to an Amino α-C-H

The research into carbenoid insertion adjacent to amines has been a relatively under-investigated area in C-H functionalisation compared with the corresponding carbenoid insertions in ethereal and alkyl substrates. In 1999 the Davies group developed a new method of α-amino C-H activation, carbenoid insertion.[64] This carbenoid insertion was found to be highly regio- and diastereoselective when Boc-protected cyclic amines were used with a Rh_2(*S*-DOSP)$_4$ catalyst. Unsubstituted substrates such as N-Boc pyrrolidine **7** saw substitution in the 2- position with high diastereo- and enantioselectivity (**Scheme 28**, reaction **A**). However, when moving to N-Boc piperidine, monosubstitution was again observed, albeit with much lower diastereo- and enantioselectivity, however, no explanation in the difference of reactivity was suggested by the authors.[64] In order to access similar enantioselectivity, the unsaturated analogue **121** was used and subsequently hydrogenated to deliver **123** (**Scheme 28**, reaction **B**).



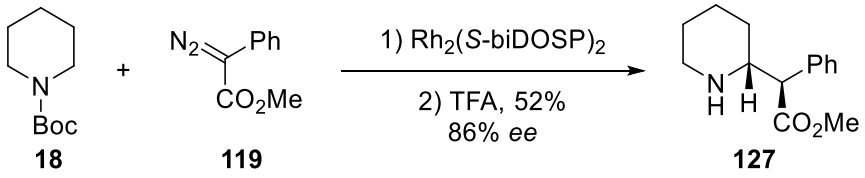
Scheme 28: Alternate reactivity of pyrrolidines and piperidines[64]

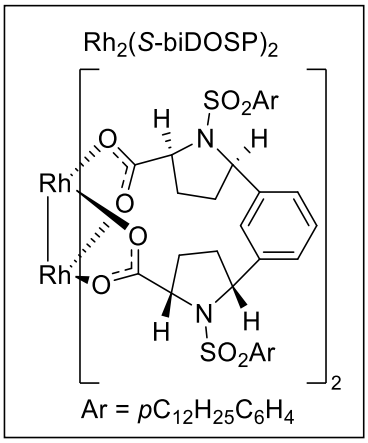
This work was followed by a study into the reactivity of 2-substituted cyclic amines.[65] This study also expanded on the effect of temperature and ring size on diastereoselectivity, with *dr*s of >95:5 seen in 5-, 7- and 8- membered rings, and *ee*s of 88-94%. By contrast, despite a similarly high *ee* (89%), the *dr* in the 6-membered ring was 64:36.[65] The presence of a group in the 2-position was found to lead to the *anti*- product being formed (**Scheme 29**).



Scheme 29: Kinetic resolution of 125 through asymmetric carbenoid insertion[65]

This methodology was used to develop a new synthesis of Ritalin.[64,66] A mixture of N-Boc piperidine and carbenoid precursor **119** were reacted with Rh_2(*S*-biDOSP)$_2$ with a TFA to remove the Boc group to give Ritalin in a 52% yield with an *ee* of 86% (**Scheme 30**).

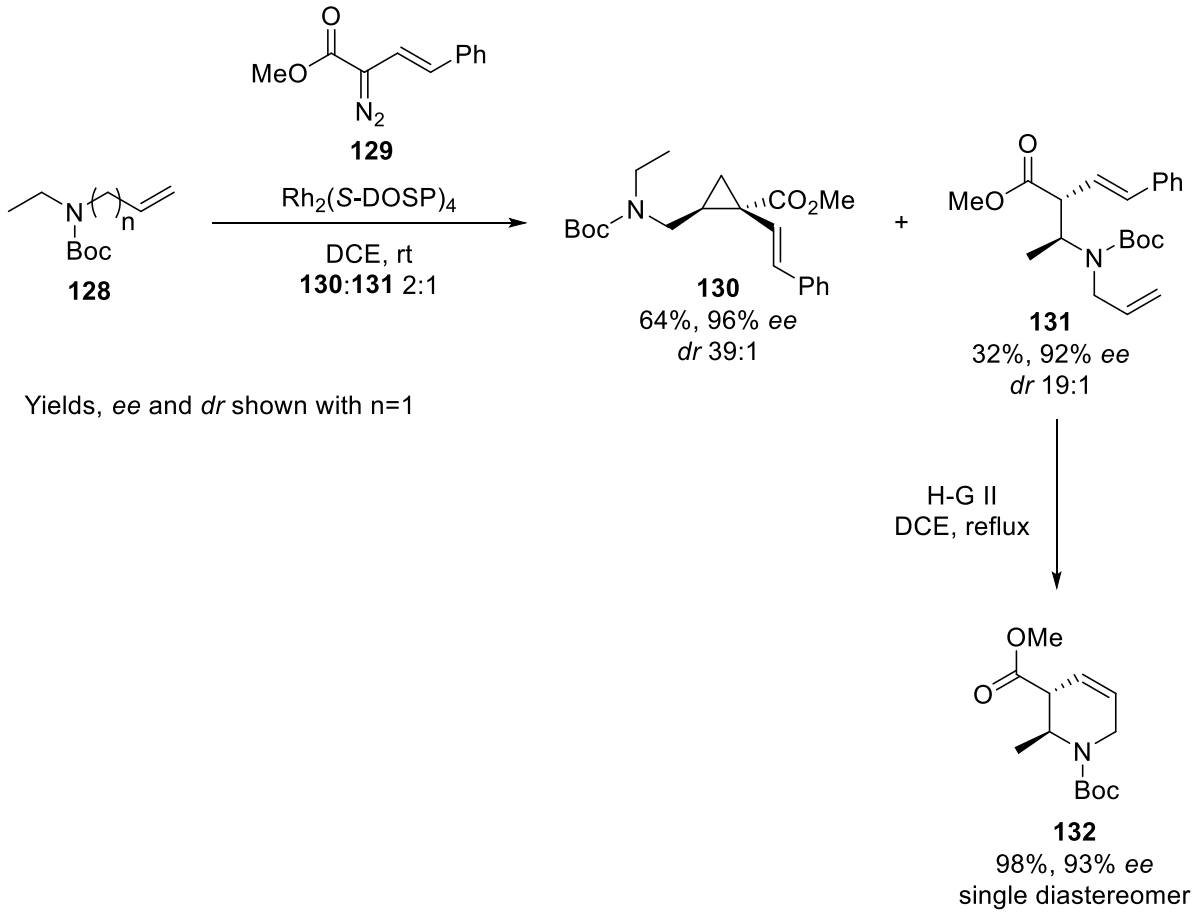




Scheme 30: Synthesis of Ritalin via carbenoid insertion

Whilst this earlier work required the presence of a cyclic amine, aliphatic α-amino carbenoid insertion methods have now been developed. In 2012, McMills *et al.* published a rhodium catalysed carbenoid insertion which led to two products **130** and **131** being formed, only the lower yielding of which was desired (**Scheme**

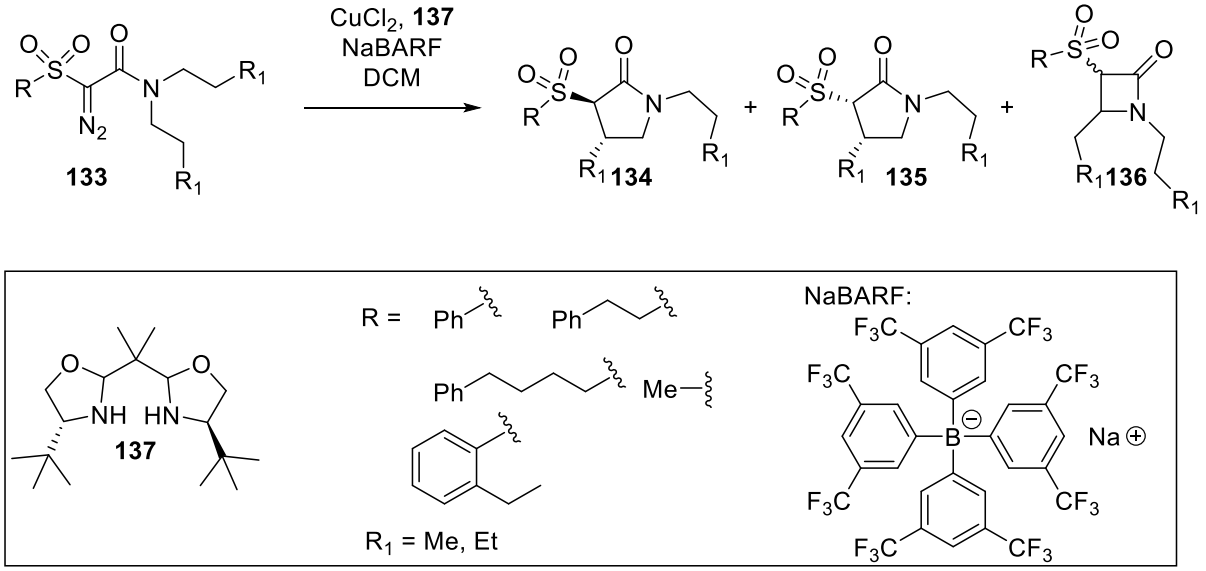
31).[67] The major product was instead formed through the cyclopropanation reaction of the double bond present in the starting material **128**. The minor product **131** resulted from the desired regioselective carbenoid insertion. This minor product was subsequently cyclised through cross-metathesis with a Grubbs (II) catalyst to provide a new route to nitrogen containing heterocycles.[67] This methodology was found to form 6-8 membered rings successfully with n = 1-3; n=4 saw successful carbenoid insertion but failed to cyclise. In all analogues the equivalents to **130** and **131** maintained their 2:1 ratio.[67]



Scheme 31: Carbenoid insertion as a route to new N-heterocycles[67]

The Maguire group have since developed a technique for carbenoid insertion which does not rely on the use of expensive rhodium catalysts. Instead, the cheaper, more environmentally benign copper was used to insert a sulfonyl carbenoid.[68] The authors had previously used their catalyst system to perform carbenoid insertions in a range of non-nitrogen containing substrates and were able to apply the same methodology successfully (**Scheme 32**).[68–73] The predominant product for these cyclisations was the *anti*-sulfonyl substituted pyrrolidine (>75% of yield), with the *syn*- product (<15% of yield) and

corresponding β-lactam (2-16% of yield) also formed. However, the tertiary amine was limited to substitution with alkyl chains and the sulfonyl R- group was limited to alkyl, aryl and alkylaryl substituents, though within this group yields for **134** were between 40-70% with *ees* between 51-70%.[68] Less bulky ligands than **137** increased overall yields but at the expense of reduced enantioselectivity.

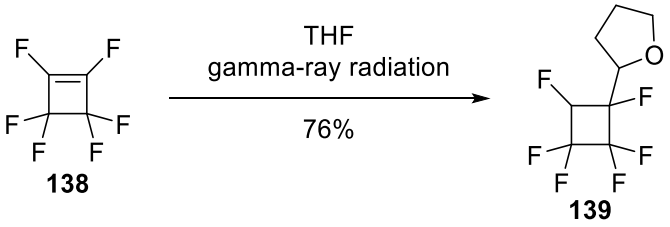


Scheme 32: Copper catalysed carbenoid insertion[68]

1.2 C-H Functionalisation Adjacent to Oxygen

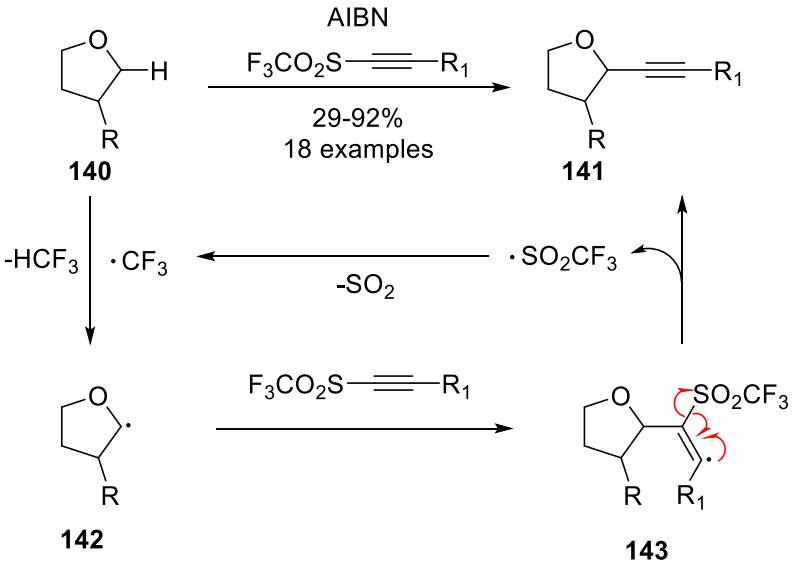
1.2.1 Radical Mediated C-H Functionalisation Adjacent to Ethers

In comparison to C-H functionalisation adjacent to amines, as described in section 1.1, C-H activation adjacent to ethers has received very little attention. This is despite the first C-H activations adjacent to ethers being published by LaZerte *et al.* in 1955, achieved through a radical reaction.[74] Polyfluoroalkenes such as perfluorocyclobut-1-ene were converted to radicals with gamma-ray radiation which then reacted with THF in situ to form products such as **139** in yields between 95-22% (**Scheme 33**).[74]



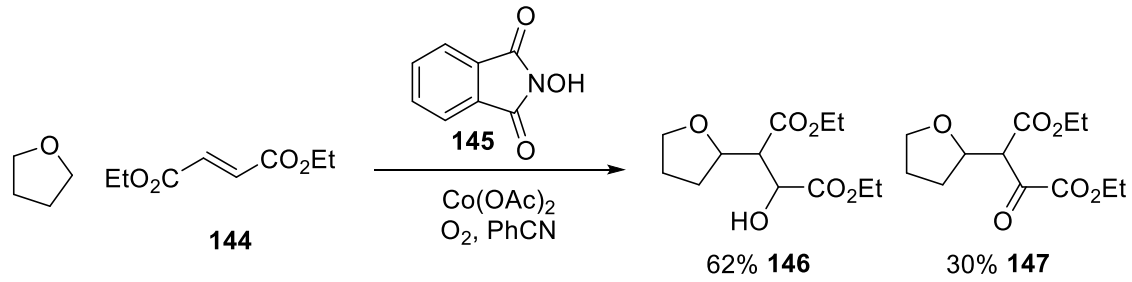
Scheme 33: First reported functionalisation of C-H adjacent to ethers[74]

Muramatsu *et al.* continued the work of LaZerte *et al.* with two papers furthering their methodology in the mid-1960s.[75,76] However, until the 1990s when Fuchs *et al*. reported radical addition/elimination of ethers with alkynyl triflones (**Scheme 34**) there was little else published.[12,77] Fuchs *et al*. followed this alkynylation with alkenylation which proceeded in an analogous manner, albeit with a mix of E/Z isomers formed.[78] These reactions generated a range of functionalised ethers in moderate to excellent yields following the reaction of cyclic ethers with alkynyl or alkenyl triflones in the presence of AIBN or *hv* with the proposed mechanism of **Scheme 34**.



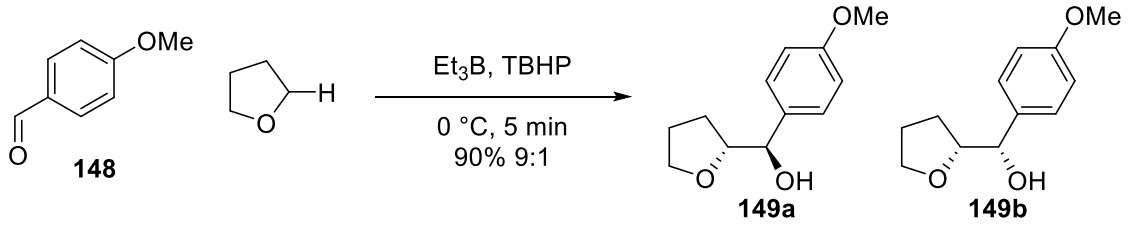
Scheme 34: Radical alkynylation of ethers[77]

This was followed by Hirano *et al.* again functionalising THF with electrophilic alkenes in the presence of *N*-hydroxyphthalimide **145**, $Co(OAc)_2$ and molecular oxygen (**Scheme 35**). Unlike with polyfluoroalkenes, above, the THF did not functionally add across the alkene. Instead, oxygen was added on the opposite end of the alkene to the ether to form both secondary alcohols **146** and ketones **147**. The proposed mechanism involved an *N*-hydroxyphthalimide **145** O radical and $Co(OAc)_2$ combining to abstract an H· radical from THF which reacts with alkene **144** to provide a second alkyl radical. This radical reacts with the oxygen and the resulting peroxide collapses to either form the alcohol **146** or ketone **147**.



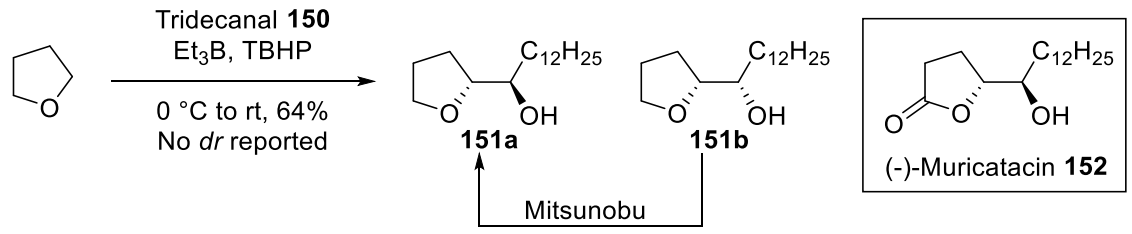
Scheme 35: THF functionalisation with electrophilic alkenes[79]

Further functionalisation of THF was achieved by Yoshimitsu *et al*, who first performed the α-hydroxyalkylation of THF with aldehydes via radical C−H abstraction (**Scheme 36**). This was achieved through the use of triethylborane and *t*-butyl hydroperoxide which caused rapid conversion to the desired product .



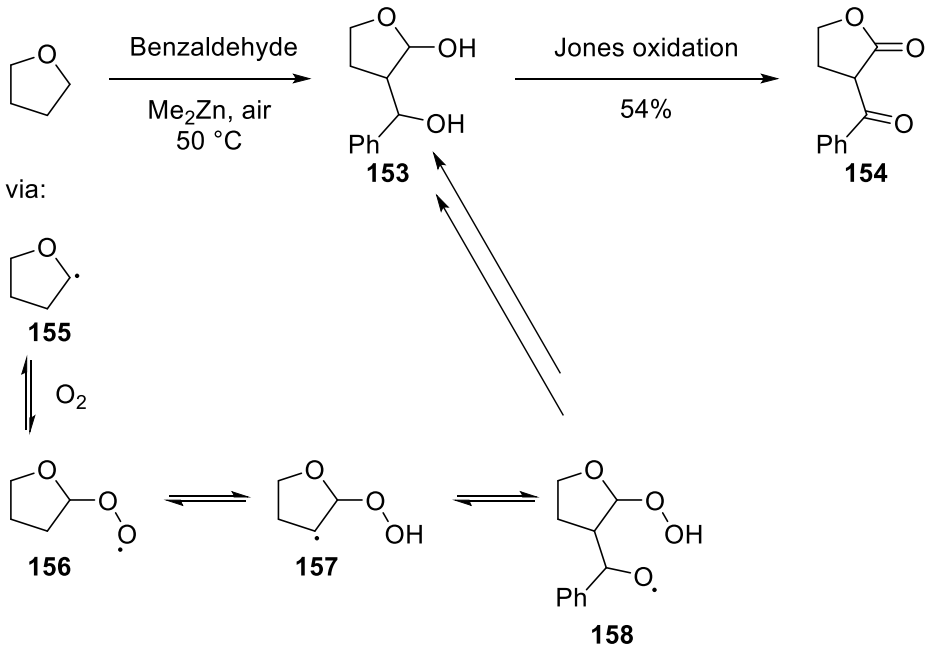
Scheme 36: Radical mediated α-hydroxyalkylation of THF[80]

Crucially, this reaction was applied to the synthesis of (−)-Muricatacin, which was achieved through the functionalisation of THF.[81] This marked the first time that C-H functionalisation adjacent to ethers was used in the total synthesis of a natural product, albeit a simple one. The key transformation used the same conditions as in **Scheme 36** with tridecanal as the aldehyde (**Scheme 37**).[81] The undesired diastereomer was converted through Mitsunobu reaction. The *anti* diastereomer was taken and resolved using PLE before undergoing oxidation and deprotection to give the desired product **152**.



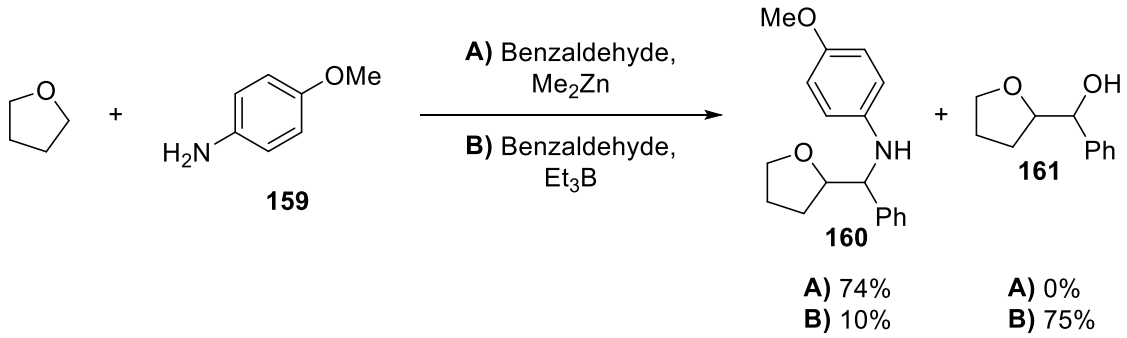
Scheme 37: Radical mediated α-hydroxyalkylation of THF applied to total synthesis[81]

This was followed in 2004 with the discovery by Tomioka *et al.* of an alternate product **153** which was attainable through the use of Me_2Zn in lieu of triethylborane.[82] It was proposed that following radical formation, when Me_2Zn was used, molecular oxygen reacted with THF first rather than the aldehyde **153** leading to the observed reactivity (**Scheme 38**).[83]



Scheme 38: Formation of product 154 and proposed mechanism[83]

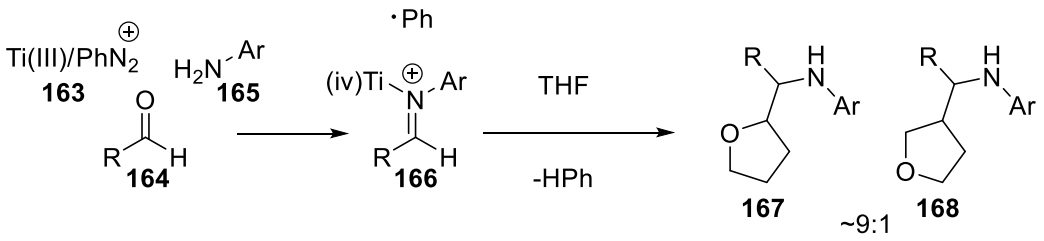
The decreased reaction speed when using Me_2Zn was applied as a method of chemoselectivity.[82] Tomioka *et al.* found that, if THF, *p*-methoxyaniline **159** and benzaldehyde were mixed together, the previously described alcohol **161** was formed as the major product in the presence of triethylborane. However, if Me_2Zn was used, amine **160** was instead isolated (**Scheme 39**).



Scheme 39: Product differentiation through choice of Lewis acid[82]

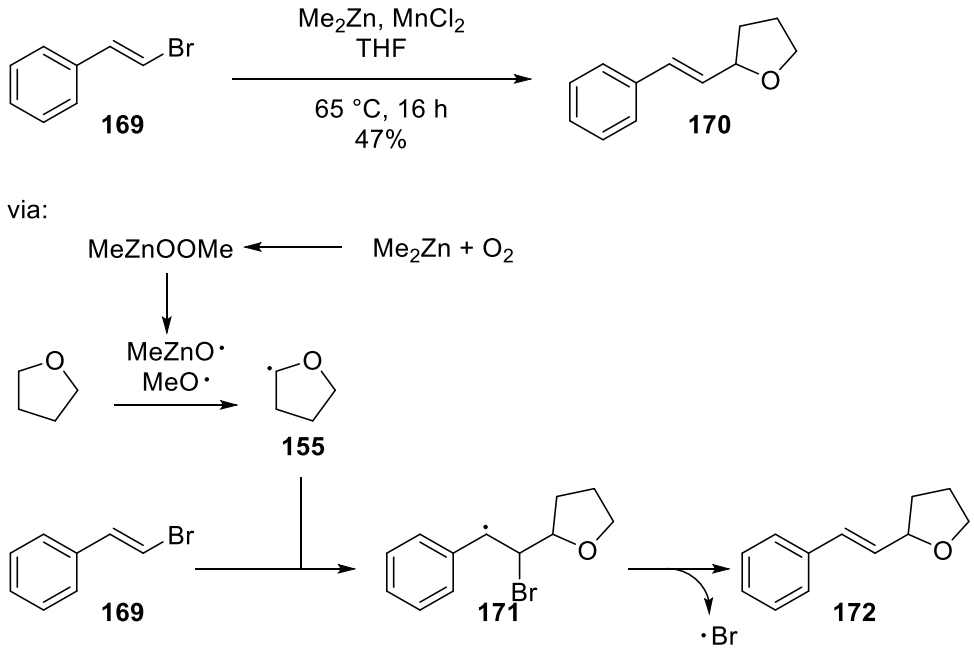
Around the same time, Porta *et al.* developed a novel three component coupling using Ti and TBHP (**Scheme 40**).[84] Here a phenyl radical is generated from

phenyldiazonium cation. The phenyl radical then abstracts a hydrogen from THF to form a nucleophilic radical which reacts with the C-atom of the methylene iminium salt, forming functionalised tetrahydrofurans **167** or **168** following a final SET reduction.



Scheme 40: Formation of functionalised tetrahydrofurans[84]

Finally, in 2012, Sølvhøj *et al.* developed a method of radical coupling between THF and bromostyrenes such as **169** with dimethyl zinc acting as an initiator (**Scheme 41**).[85] The substrate scope was extended to cover a range of ethers and tertiary amines and could tolerate substitution on the styrene aromatic ring.[85]

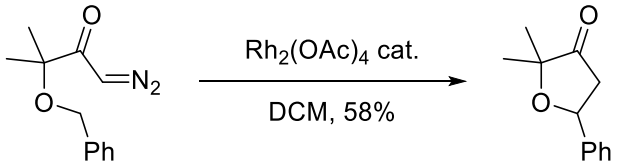


Scheme 41: Dimethylzinc catalysed radical coupling adjacent to an ether[85]

1.2.2 Metal Mediated Carbenoid Insertion to an Ethereal α-C-H

Carbenoid insertion into C-H bonds adjacent to ethers has developed into a powerful method of C-H activation, used both in the formation of new aliphatic and 5-membered cyclic compounds.

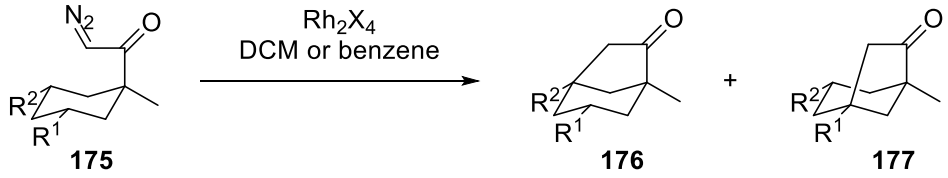
This use of carbenoid insertion to form a 5-membered ring was first developed as a useful reaction in 1989, whereby Adams *et al.* used rhodium acetate to form cyclic esters such as **174** (**Scheme 42**).[86] Once the diazo-ketone **173** was prepared from the corresponding acid, it was cyclised with the rhodium diacetate catalyst to form the cyclised product **174** in a 58% yield.



173 **174**

Scheme 42: An early example of carbenoid insertion adjacent to an ether[86]

This initial study by Adams *et al.* was followed with a model study into the stereoelectronic effects of the above-mentioned reaction (**Scheme 42**).[86,87] This study was performed exclusively with cyclic substrates in order to avoid steric and conformational effects which the authors believed could predominate with acyclic structures.[87] Cyclohexane based scaffolds were prepared then the further cyclisation was catalysed with $Rh_2(OAc)_4$ or $Rh_2(Cap)_4$ (**Scheme 43**). Unsurprisingly, it was found that electron-donating groups adjacent to the reaction site led to increased reactivity, with conversion to **177** preferred to **176** when R_1 is a better electron donating group than R_2. This is a result of the δ+ charge generated at the R_1/R_2 C-H position during carbene insertion, which is more effectively stabilised by electron donating groups and as such reacts more readily.



175 **176** **177**

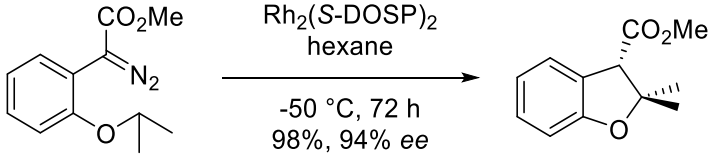
R_1 = OAc, OH, TBDMSO, TIPSO, N_3, $TMSCH_2$, MeO
R_2 = MeO, H
X = OAc or Cap

Scheme 43: General reaction conditions for investigations into stereoelectronic effects in carbenoid insertion adjacent to ethers[87]

Since these initial results, the scope of catalysts and asymmetric conditions has increased massively, with several groups working to develop new protocols over the past 20 years, rhodium does, however, remain the catalytic metal of choice.

A key ligand in the enantioselective insertion of carbenoids is *S*-DOSP, which was first prepared by the Davies group in 1997.[88] This ligand was found, in subsequent publications, to enable enantioselective C-H activation in cyclohexadienes, cycloheptatrienes, Boc-protected amines and allyl silyl-ethers.[64,89–91]

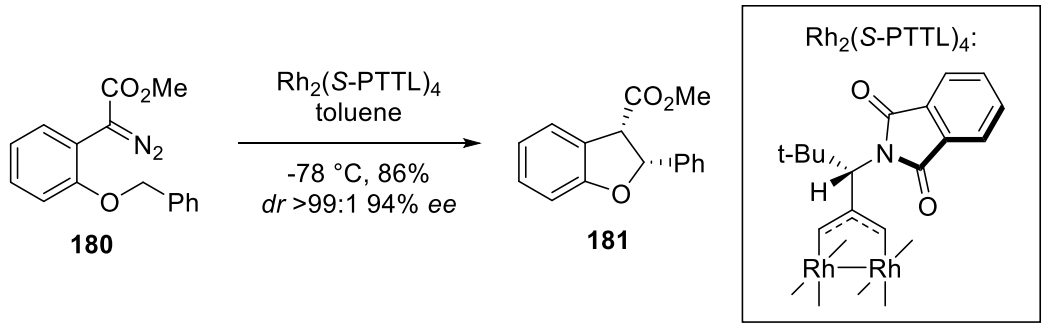
This scope was extended at the turn of the millennium when Davies *et al.* published a method of enantioselectively preparing substituted dihydrobenzofurans such as **179** (**Scheme 44**).[92] This was achieved through the use of Rh_2(*S*-DOSP)$_4$ to catalyse the intramolecular insertion of the aryl diazoacetate derived carbenoid into the methine C-H bond adjacent to the phenyl oxygen. However, whilst the example shown (**Scheme 44**) had an excellent yield and *ee*, overall the extent of asymmetric induction was highly dependent on the site of C-H activation and the catalyst, with little scope for general conditions.[92]



178 **179**

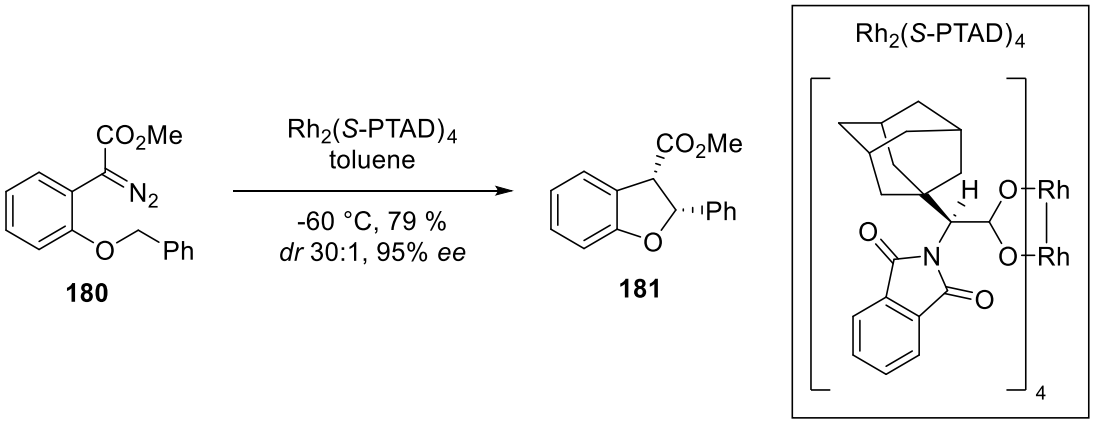
Scheme 44: dihydrobenzofuran formation via carbenoid insertion[92]

In 2002, this work was followed by a publication from Hashimoto *et al*, which improved upon the results of Davies through the use of an Rh_2(*S*-PTTL) catalyst (**Scheme 45**).[93] Whilst yields were similar to those of Davies *et al.* (**Scheme 44**, above), crucially, these high yields and *ee*s were maintained with a monosubstituted α-C-H adjacent to the ether (**Scheme 45**).[93]



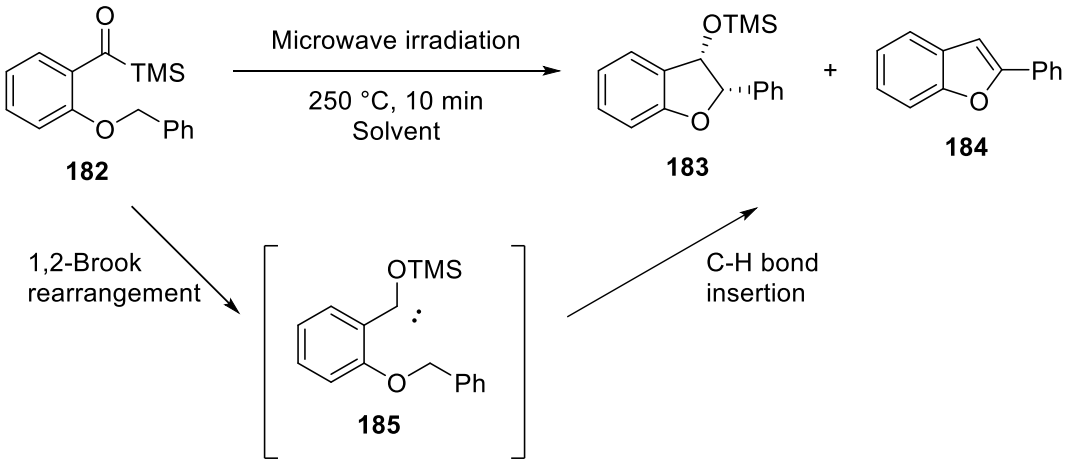
Scheme 45: Alternate catalyst in the formation of dihydrobenzofurans[93]

The Davies group had likewise been developing new chiral rhodium catalysts for carbenoid insertion, which culminated in Rh_2(*S*-PTAD)$_4$, a catalyst which, in addition to providing decent yields and high *dr*/*ee*s, could be recycled and reused with a limited loss of stereoselectivity (**Scheme 46**).[94] This ability to reuse the catalyst is of increasing importance with the current focus on decreasing the environmental impact of more traditional organic syntheses.



Scheme 46: A third method of preparing dihydrobenzofurans[94]

Whilst all of the carbenoid insertions discussed above have relied on the use of rhodium catalysts and the presence of a diazo group, in 2009 a novel method of cyclisation via carbene insertion was reported which was free of both rhodium and diazo compuounds[95] This was achieved via a MW assisted high temperature Brook rearrangement to form a siloxycarbene which subsequently inserted into the neighbouring C-H bond adjacent to an oxygen (**Scheme 47**). Shen *et al.* discovered that the choice of solvent was essential, with *o*-dichlorobenzene leading to the formation of the dihydrobenzofuran product **183**, whereas when DMSO was used, the dihydrobenzofuran **183** underwent a subsequent loss of silanol to give **184** (**Scheme 47**).



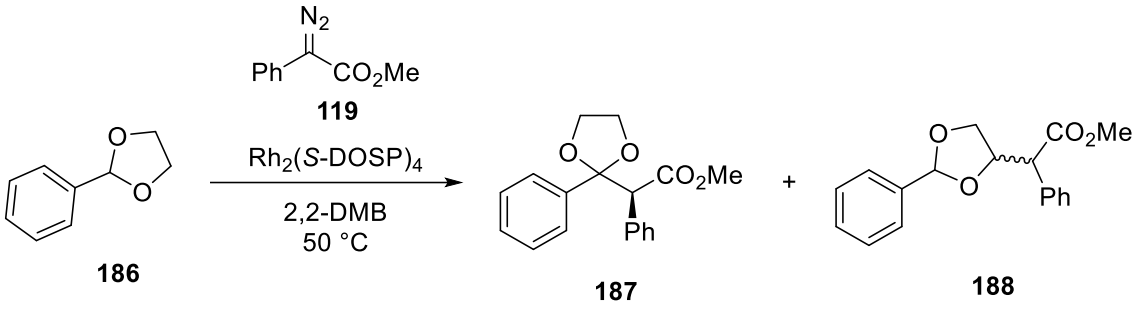
Scheme 47: MW assisted formation of 183 and 184[95]

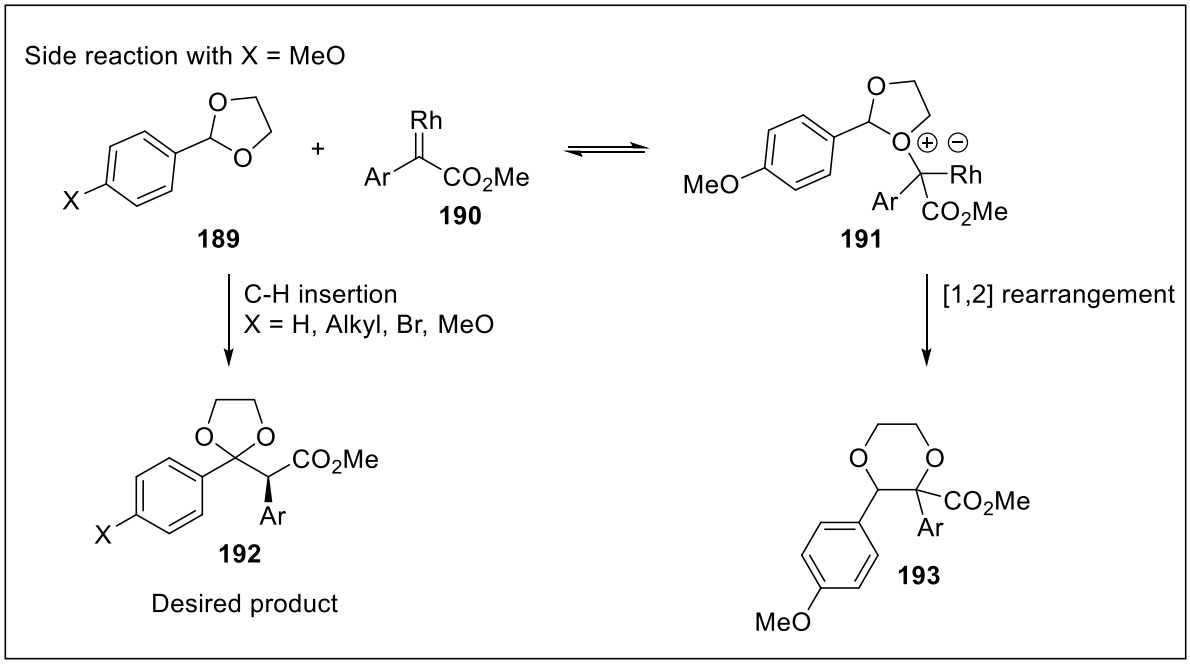
Table 1: Solvent dependent change in product

Solvent	Product	Yield (%)
o-dichlorobenzene	**183**	92 (72:28 cis:trans)
DMSO	**184**	80

With robust protocols in place for the intramolecular reaction of carbenoids with tethered C-H bonds adjacent to ethers, many groups turned their attention to the corresponding intermolecular reaction. Whilst the reaction was known, the development of enantioselective protocols had lagged behind the advances seen with intramolecular insertion.

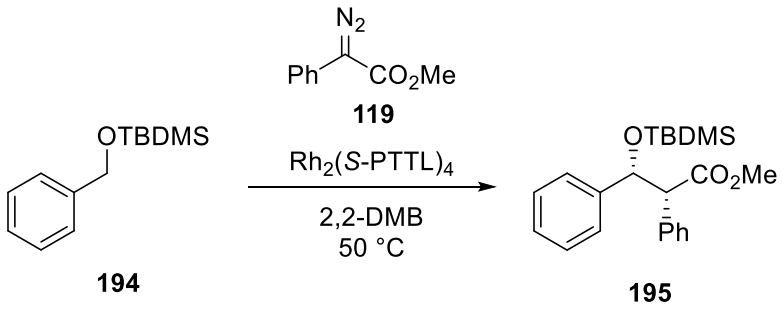
The Davies group published an early example of an enantioselective carbenoid insertion into an acetal C-H.[96] Here Rh_2(*S*-DOSP)$_4$ was used to catalyse the insertion of **119** into **186** to give the products **187** and **188** in a 76% yield with a ratio of 71:29 **187** to **188** (as determined by ^{1}H NMR) (**Scheme 49**). However, these conditions had issues with regioselectivity for the C-H insertion on the acetal with any substituents on the acetal aryl group (**Scheme 49**) limiting the utility of the reaction. When the acetal aryl group had a MeO group, a ring expansion was also seen. Reducing the temperature led to greater selectivity towards **192** at the cost of significantly poorer yields.





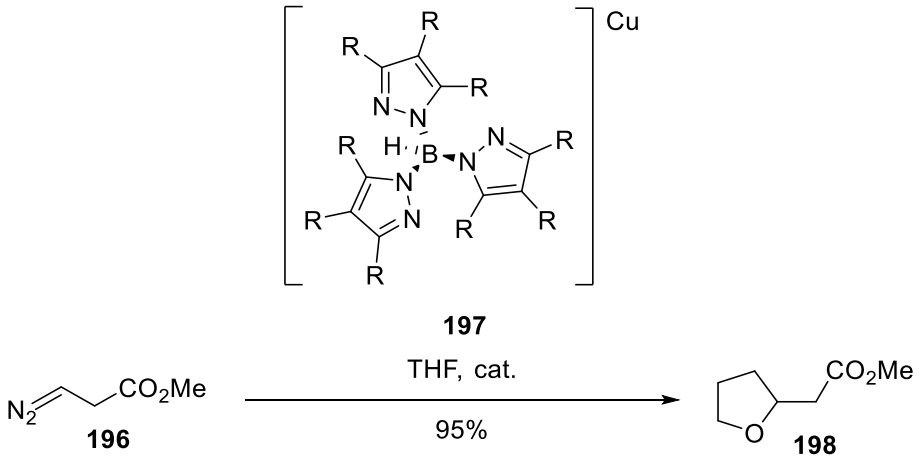
Scheme 48: Carbenoid insertion into acetal C-H[96]

When a TBDMS ether was used as the site of C-H insertion, improved *dr*s and yields were observed when using the same *S*-DOSP ligands.[97] These *dr*s and yields increased further when *S*-PTTL ligands were applied (**Scheme 49**), reaching a 95% yield with a *dr* of 19:1 and a 98% *ee*. Unsurprisingly, the overall yield of **195** was improved versus **187** as there were no competing insertion sites.



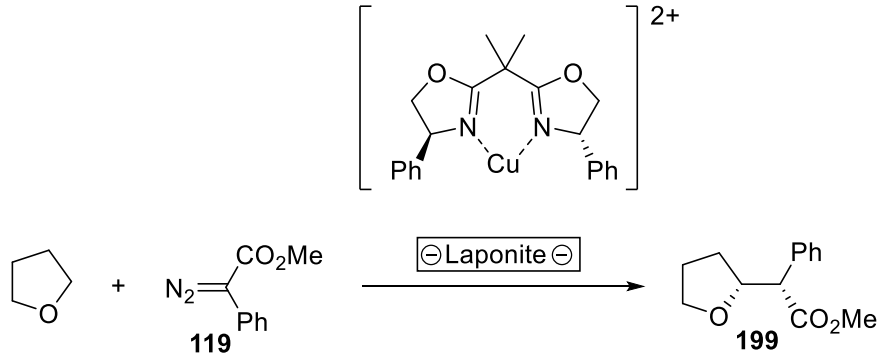
Scheme 49: Carbenoid insertion to functionalise TBDMS ethers[97]

Compared to intramolecular carbenoid insertion, there is a wider choice of metal catalysts available when pursuing an intermolecular insertion. Pérez *et al.* published, in 2002, a method of inserting ethyl diazoacetate **196** into, amongst other non-ethereal substrates, THF (**Scheme 50**).[98] This was achieved in a 95% yield through the use of Tp^{x}Cu **197** as catalyst. Through tuning the R groups of the Tp^x ligand the authors were able to observe yields approaching those reported with the much more expensive rhodium catalysts used elsewhere.[98]



Scheme 50: Tp^{x}Cu 197 catalysed carbenoid insertion into THF[98]

Heterogenous copper catalysis has also been developed for carbenoid insertion into ethereal C-H bonds. Fraile *et al.* reported the use of immobilised box-Cu complexes supported on laponite in 2007.[99] The use of the laponite support led to both increased *ee*s and allowed washing and reuse of the catalyst. Here yields were less impressive, ranging from 20 to 85% with up to 88% *ee* and *dr*s of 56:44 to 78:22 syn:anti dependent on the box ligand used (**Scheme 51**).[99]



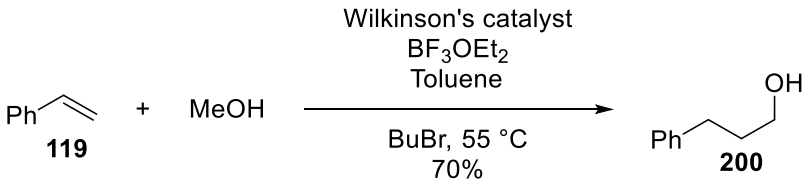
Scheme 51: Heterogeneously catalysed C-H functionalisation to form 199[99]

1.2.3 C-H Activation Adjacent to Alcohols

In addition to the above, there have been limited examples of C-H activation adjacent to alcohols which, depending on the mechanism, may likewise provide insight towards novel methods of C-H activation adjacent to ethers. The most common method of performing this transformation is via transfer hydrogenative coupling, which is analogous to cross-dehydrogenative coupling as will be discussed in greater detail in Section 1.3.2, page 53 whereby the alcohol is oxidised to form an aldehyde which subsequently reacts.

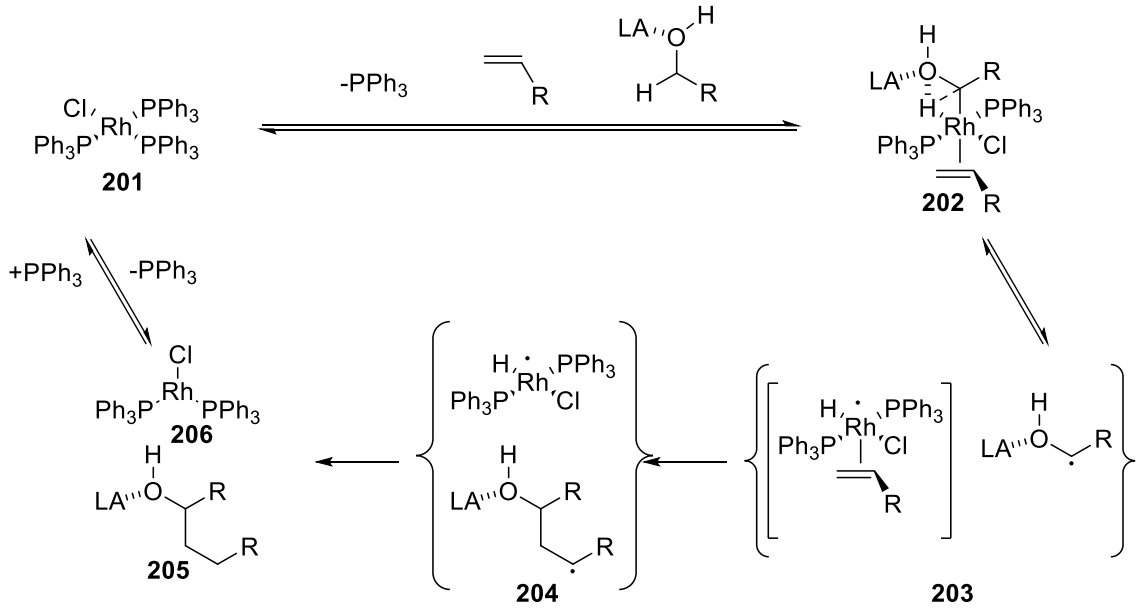
1.2.4 α-Oxygen C-H Activation Through Transition Metal Insertion

Alternatively, cross-coupling conditions have been developed whereby alcohols and alkenes are reacted via C-H insertion. The first example of this reaction was observed as a side product by Shi *et al.* in 2005.[100] Here the use of Wilkinson's catalyst and $BF_3.OEt_2$ as co-promoter in tandem led to the formation of secondary and tertiary alcohols such as **200** from alkenes and primary or secondary alcohols respectively (**Scheme 52**).



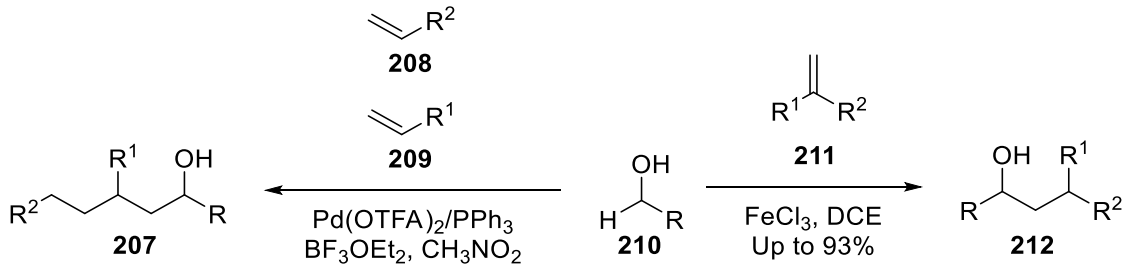
Scheme 52: The first reported TM catalysed insertion of an alkene into an alcohol C-H bond[100]

A series of deuterium labelling experiments and experiments with radical scavengers were performed by the authors. A statistical distribution of deuterium was observed and the reaction was completely inhibited in the presence of these radical scavengers. Shi *et al.* therefore proposed a radical mechanism to explain the formation of **205** (**Scheme 53**).[100]



Scheme 53: Proposed mechanism for the formation of 205[100]

Further experimentation by the authors led to improved rhodium-catalysed reaction conditions as well as the development of two new protocols, which were based on the use of palladium with BF_3OEt_2 and $FeCl_3$ (**Scheme 54**). The palladium catalysed reaction suffered from the same limitations as with rhodium, that the use of non-aryl alkenes and non-aliphatic alcohols led to sharply decreasing yields.[101] When $FeCl_3$ was used, Shi *et al.* reported that the reactions proceed with high efficiency and without the need of an additive or co-promoter as with rhodium and palladium.[102]

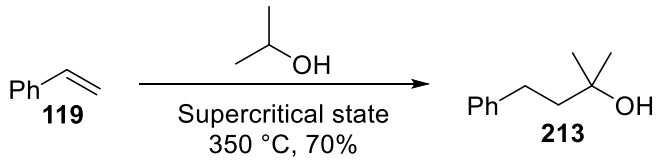


Scheme 54: Alcohol-alkene cross-coupling with palladium (L) and iron (R) catalysts[101,102]

1.2.5 Catalyst Free C-H Activation Adjacent to Alcohols

Finally, Harada *et al.* have developed a method of performing a catalyst-free coupling between an alkene and alcohol as a method of direct C-H

functionalisation.[103] However, due to the extreme conditions required (**Scheme 55**), whilst interesting, there is little practical application to this reaction.

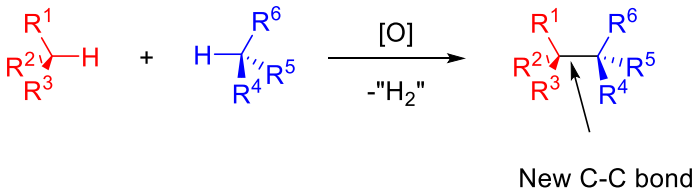


Scheme 55: Catalyst free synthesis of 213[103]

Two key areas of C-H functionalisation adjacent to oxygen which have not been discussed in this section are the cross-dehydrogenative coupling reaction and the 1,5-hydride shift. Due to the importance of these reactions to the research presented herein, cross-dehydrogenative coupling and the 1,5-hydride shift are discussed in greater detail in separate sections 1.3.2 and 1.4.2 respectively, below.

1.3 Cross-Dehydrogenative Coupling

Following from the general introduction of C-H functionalisation adjacent to two important heteroatoms, oxygen and nitrogen, attention will now be turned to two specific examples of C-H functionalisation. The first to be covered is the Cross-Dehydrogenative Coupling (CDC) reaction, which has found use adjacent to both ethers and amines. The basic process for the reaction features the removal of hydrogen across two molecules to form a carbon-carbon bond. In practice molecular hydrogen itself is rarely formed, with the hydrogen sequestered elsewhere in the reaction mixture (**Scheme 56**). There is the possibility of this reaction occurring catalytically, which would be particularly useful in the modern green conscious world.



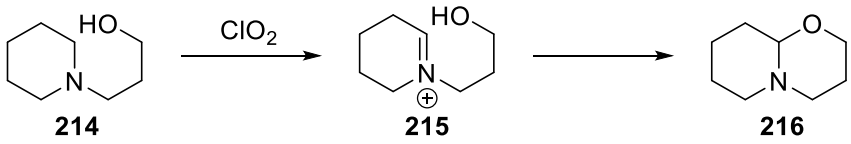
Scheme 56: CDC reaction

1.3.1 Cross-Dehydrogenative Coupling Adjacent to Amines

In general terms, in order to effect a cross-dehydrogenative coupling adjacent to an amine, the amine must first be oxidised to form an iminium ion which subsequently undergoes nucleophilic attack. An early example of this came in

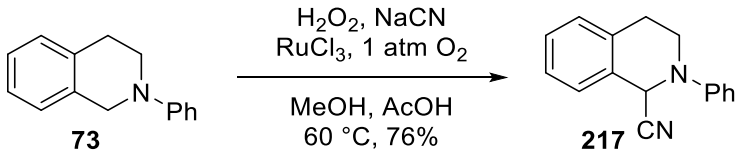
1999 when low-temperature electrolysis was used to generate iminium ions as a "cation pool" to subsequently react.[104] As noted by the authors, a key requirement for successful cross-dehydrogenative coupling was the ability of the nucleophile and iminium ion to react before degradation occured.[104] Despite this, the functionalisation of an amine α-C-H with cyano groups was first described in 1969.[105] This reaction was achieved through the use of electrochemistry and was followed in 1977 with an improved method.[106]

A key early example of chemical oxidation to form an imine for cross-dehydrogenative coupling was published in 1988.[107] Chen *et al.* had developed a method of generating bicycle **216** from 1-piperidine-propanol **214** using ClO_2 as a stoichiometric oxidant (**Scheme 57**).



Scheme 57: A key early chemically induced α-amino cross-dehydrogenative coupling[107]

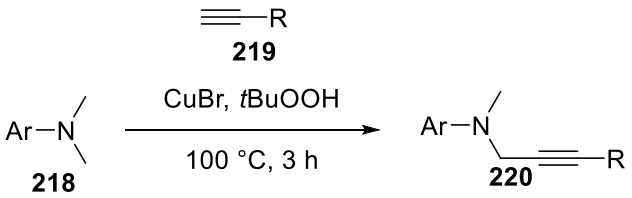
It wasn't until 2003 that an intermolecular cross-dehydrogenative coupling adjacent to an amine was achieved, when Murahashi *et al.* developed a method of coupling a cyano group to compounds such as **73** (**Scheme 58**).[108] Here the oxygen and peroxide both act as oxidants in competing mechanisms to form α-cyanoamine adducts, which are useful precursors to both 1,2-diamines and amino acids.[108,109]



Scheme 58: Synthesis of a functionalised tetrahydroisoquinoline through a CDC reaction[108]

This was followed, in 2004, by Li *et al.* who developed a method of alkynylating N,N-dimethyanilines **218** under neat conditions (**Scheme 59**).[110] This reaction was found to proceed with both Cu(I) and Cu(II) species, with CuBr providing the highest yields. The same conditions were applied to N,N,dimethylbenzylamine and the alkynylation preferentially occurred on the methyl groups, with none of

the product which would result from addition to the benzyl C-H being isolated.[110] However, when tetrahydroquinolines were used, cross coupling occurred at the benzylic position rather than the homobenzylic position.

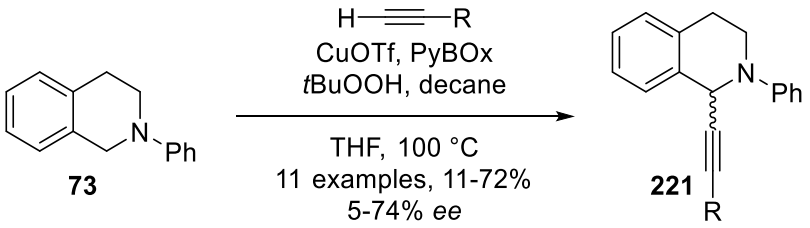


Scheme 59: Alkynylation of N,N-dimethylanilines 218[110]

Table 2: Range of substituents for alkynylation of N,N-dimethylanilines

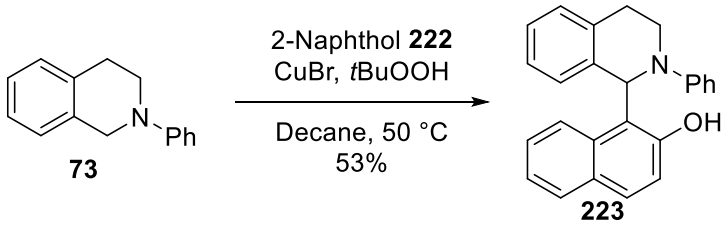
Ar	R	Yield (%)
Ph	Ph	74
Ph	4-MeOPh	82
Ph	4-MePh	74
Ph	4-BrPh	74
Ph	4-PhPh	60
Ph	2-Py	36
Ph	CH_2OH	40
Ph	CH_2O_2CEt	58
Ph	CO_2CH_3	25
Ph	Bu	12
4-MePh	Ph	73
2-MePh	Ph	53
4-BrPh	Ph	69

A development of the reaction saw the addition of PyBOx as a chiral ligand.[111] Its use led to modest to good *ee*s (**Scheme 60**), which the authors viewed as supporting a mechanism whereby the copper binds to the iminium ion prior to attack by the alkyne.[110,111] In 2008, Li (C-J) *et al.* extended the scope of the alkynylation reaction published by Li (Z) *et al.* to cover glycine derivatives, although again the nucleophile scope was restricted to aryl alkynes.[112]



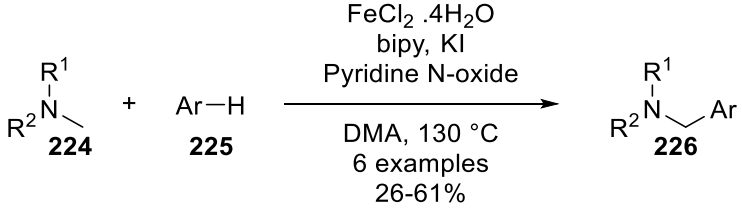
Scheme 60: Synthesis of enantioenriched substituted tetrahydroquinolines[111]

Elsewhere, progress had been made with nucleophile scope. The reaction of tetrahydroquinolines with electron rich aromatic rings such as indoline was first published in 2005, whereby the coupling occurred via a Friedel-Crafts style mechanism.[113] With indole substrates C3 alkylation predominates and with naphthols, Betti bases such as **223** were prepared (**Scheme 61**).[113] However, when naphthols are used, a degree of homocoupling to form BINOL derivatives was observed.[113]



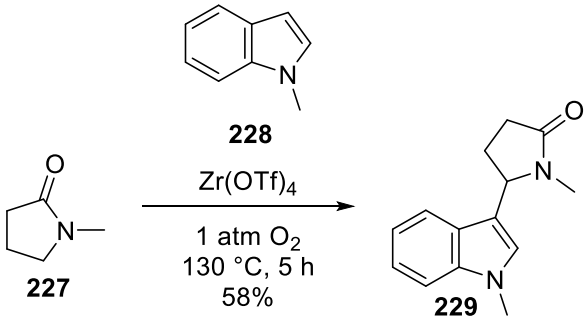
Scheme 61: Synthesis of Betti base derivative 223[113]

These same indole and naphthol nucleophiles can be cross-dehydrogenatively coupled with dimethylanilines such as **224** in a manner analogous to alkynyl aryls as shown above (**Scheme 59**).[114] Around the same time, Itami *et al.* developed an iron catalysed cross-dehydrogenative coupling with a scope which extended beyond indoles to cover monocycles such as thiophene and furan.[115] Unlike the examples above, the CDC did not proceed with CuBr as the catalyst. Instead, $FeCl_3$/bipy provided the best conversion, with pyridine N-oxide acting as a stoichiometric oxidant (**Scheme 62**).[115]



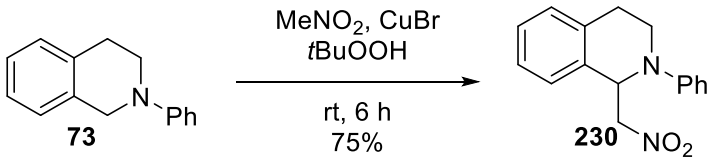
Scheme 62: Iron catalysed arylation adjacent to an amine[115]

It is also possible to cross-dehydrogenatively couple N-methyl amides and heteroaromatics.[116] Tsuchimoto *et al.* developed a zirconium triflate method in the presence of oxygen (**Scheme 63**). The authors surveyed a range of Lewis acids including scandium and indium triflate which showed catalytic activity, albeit to a lesser extent than zirconium.[116] In the proposed mechanism, the amide **227** is oxidised by the oxygen via radical cation intermediates. The heteroaromatic nucleophile then undergoes electrophilic aromatic substitution to couple to the N-acyliminium cation. The authors report that the presence of TEMPO as a radical scavenger inhibits the reaction, which supports their proposed mechanism.



Scheme 63: Zirconium triflate catalysed coupling of amide 227 with electron rich heteroaromatic 228[116]

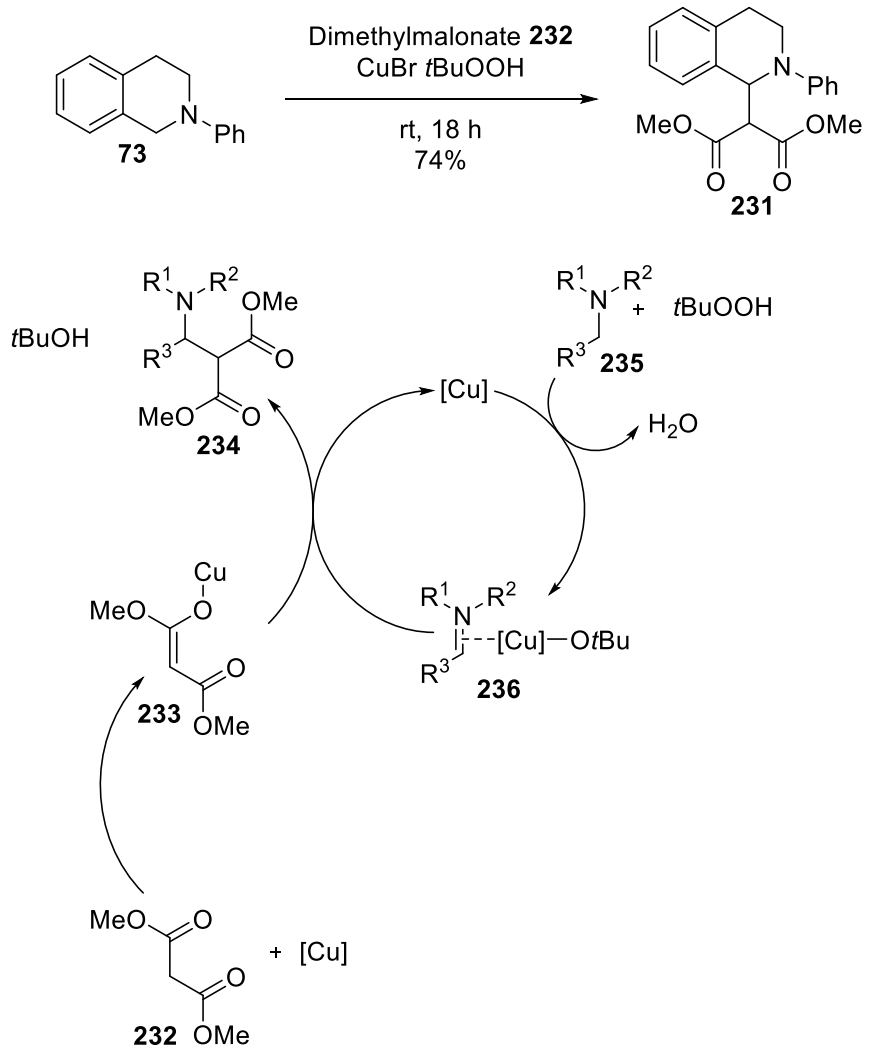
Cross-dehydrogenative coupling adjacent to amines has also been observed with nitronate and enolate nucleophiles. An early example of a nitronate nucleophile was published by the ever-present Li group.[117] Here a range of tetrahydroisoquinolines such as **73** were functionalised via a nitro-Mannich type reaction (**Scheme 64**). Here nitromethane was used both as reagent and solvent with *t*BuOOH and CuBr present.



Scheme 64: Nitro-Mannich type CDC[117]

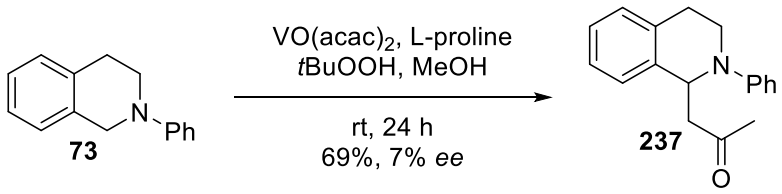
Li *et al.* extended their nucleophile scope to include malonates first under neat and then aqueous conditions with an analogous mechanism to nitroalkenes, shown below with dimethylmalonate **232** (**Scheme 65**).[117–119] This reaction was also found to work with malonitrile, albeit poorly.[118] The authors proposed that the

copper catalyst is involved in the generation of both reactive species **233** and **236**.



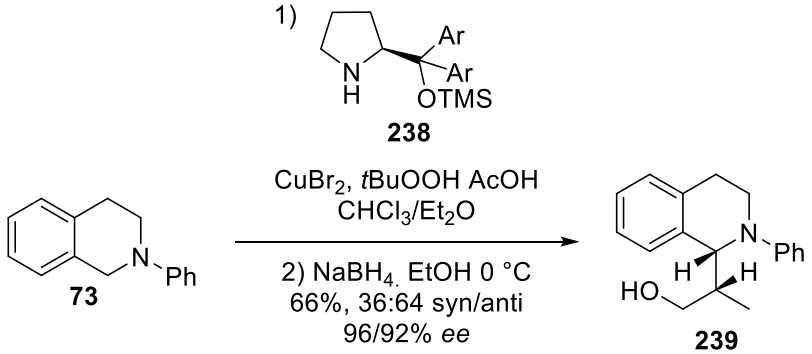
Scheme 65: Extended nucleophile scope for Li *et al*'s CuBr based CDC conditions and proposed mechanism[118]

Some progress has been made regarding asymmetric CDC reactions adjacent to amines, which started with a study published by Klussmann *et al.* combining L-proline and $VO(acac)_2$ to obtain modest enantioselectivity (**Scheme 66**).[120] The authors note that enantiopure **237** obtained by prep TLC was observed to slowly racemise, which the authors propose may explain the poor *ee*s they obtained. Despite this, the conditions developed by Klussmann still provided the first route into using ketone nucleophiles in CDC reactions.



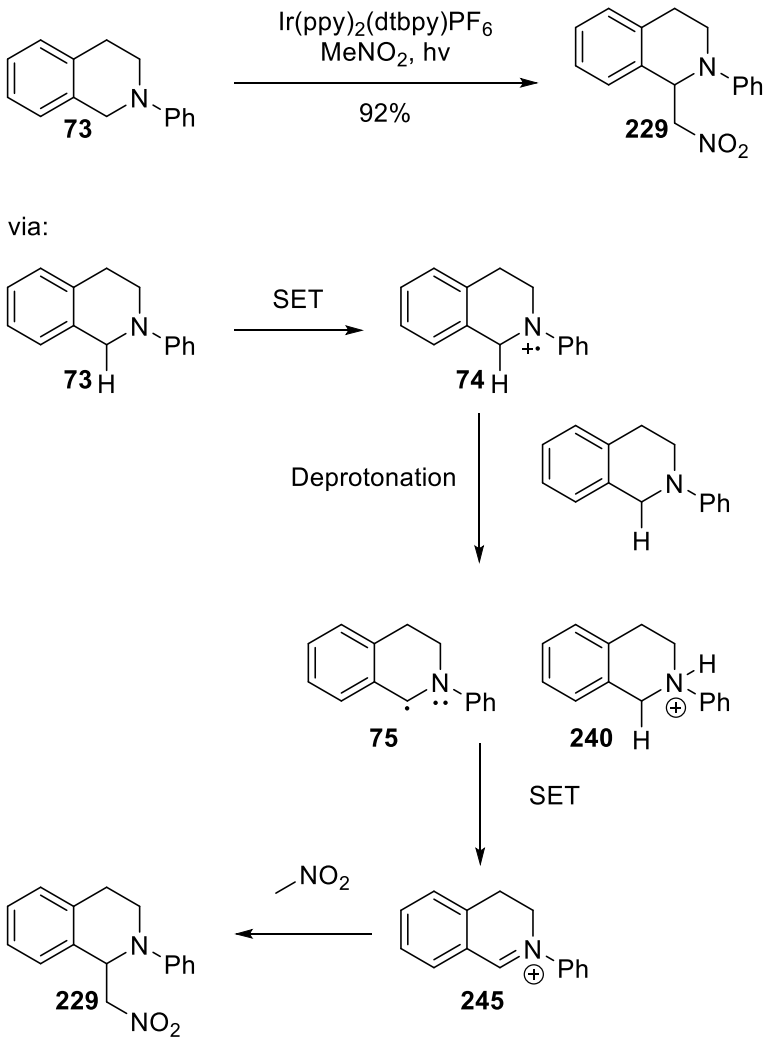
Scheme 66: Cross-dehydrogenative coupling with moderate selectivity[120]

Enantioselective control in a CDC reaction was achieved by Chi *et al.* in 2012 through the use of $CuBr_2$ and a Jørgenson-Hayashi diphenyl prolinol catalyst **238** (**Scheme 67**).[121] This reaction was found to proceed well with aldehydes, however, moving to ketones led to low enantioselectivity and the use of N,N-dimethylaniline or N-aryl pyrrolidine gave low enantioselectivities or yields.[121]



Scheme 67: Enantioselective synthesis of 239[121]

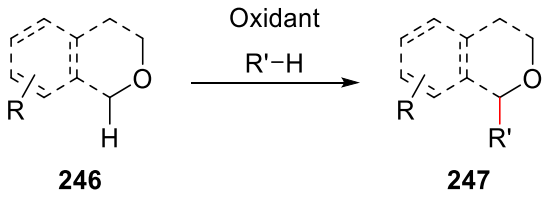
Finally, the Stephenson group have also developed a method of coupling nitroalkanes and tetrahydroisoquinolines through the use of photocatalysis to perform a SET initiated process (**Scheme 68**).[48] Notably, this reaction proceeds in the absence of oxygen, suggesting that the nitroalkane can act as an electron acceptor and light acts to initiate the SET process leading to coupling.[48]



Scheme 68: Visible light/Ir catalysed nitro-Mannich type CDC[48]

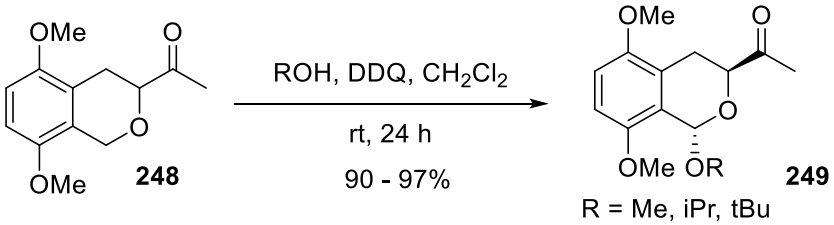
1.3.2 Cross-Dehydrogenative Coupling Adjacent to Ethers

As discussed above in section 1.3.1, in the past decade cross-dehydrogenative coupling (CDC) reactions on the amine α-carbon have been widely explored as a method of C-C bond formation. The application of this methodology to oxygen in the ether functional group is an attractive prospect as at present the vast majority of carbon-carbon bond forming reactions proceed via functional group manipulation. In comparison, C-H functionalisation can be far more atom efficient.[109] A CDC reaction adjacent to an ether would proceed similarly to **Scheme 68**, with the aim of functionalising at the benzylic position, again with the loss of H_2 and an oxidant required (**Scheme 69**).



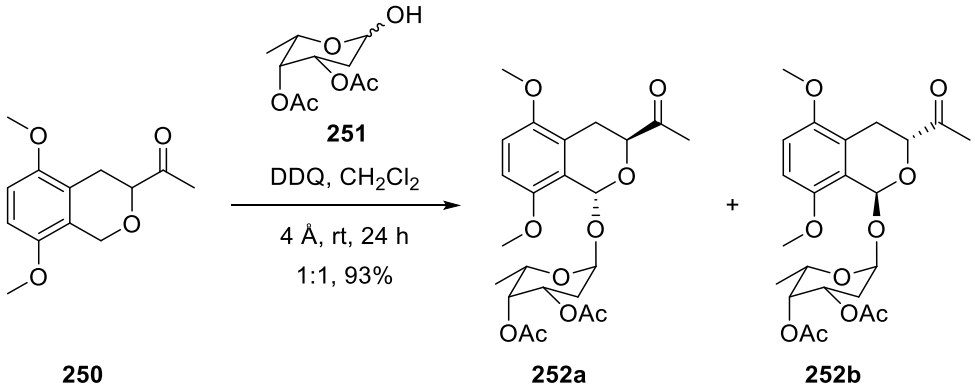
Scheme 69: CDC reaction adjacent to an either

Far less work has been published on the functionalisation of ethers compared to equivalent amines. The first published benzylic C-H activation adjacent to an ether was published in 1993 by Xu *et al*.[122] Here DDQ was used to generate an oxocarbenium cation from a range of isochroman derivatives which were then attacked by the alcohol present (**Scheme 70**).



Scheme 70: First published isochroman CDC reaction[122]

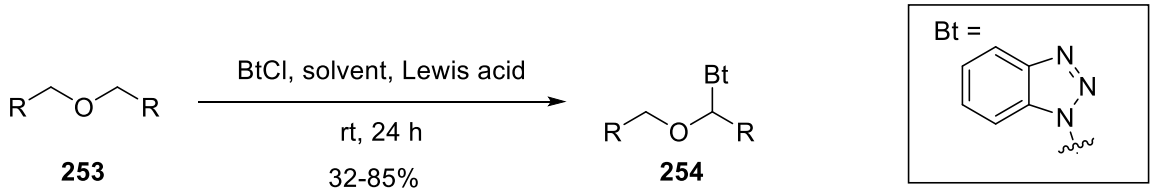
This work was followed up by the same group in 1994, where DDQ was again used to achieve glycosidation at the desired site.[123] Whilst no chiral catalyst or auxiliaries were used, when isochroman had a substituent in the 3-position, only the *anti* products were observed (**Scheme 71**).



Scheme 71: Glycosidation of isochroman derivative 250 with DDQ[123]

Nothing further was published in this field until 1999, when Katritzky *et al*. published a novel method of synthesising α-(Benzotriazol-1-yl)alkyl ethers directly via C-H activation using only boron or titanium Lewis acids.[124] However, the authors state that there was not enough data to suggest a mechanism; there

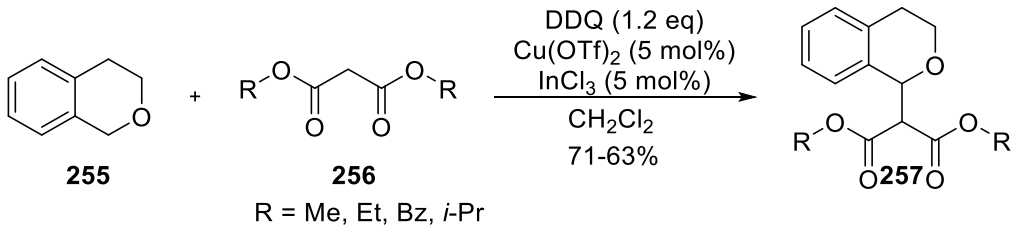
was no clear oxidant and barring isochroman only symmetrical ethers were used (**Scheme 72**).



R = aryl, alkyl

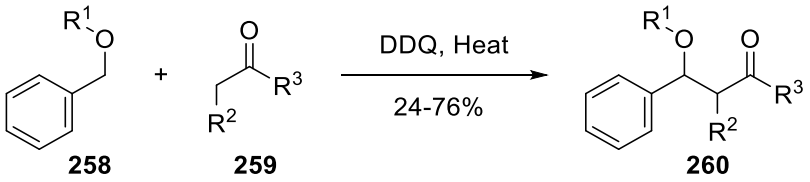
Scheme 72: Synthesis of α-(Benzotriazol-1-yl)alkyl ethers[124]

DDQ was used as a terminal oxidant by Li *et al*. in 2006 with a copper/indium catalyst pair (**Scheme 73**).[125] However, their approach was limited to the use of malonates as nucleophiles and it required indium as a Lewis acid, both of which restrict its utility.



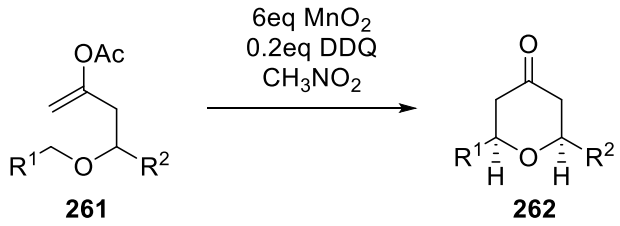
Scheme 73: DDQ mediated CDC on isochroman 255

A second paper was published in 2006 by Li *et al*. showing a metal-free approach to benzylic ether functionalisation.[126] Whilst minor conversion was seen using solely DDQ in solvent, in order to obtain high conversion the reactions were required to be neat (**Scheme 74**).[126]



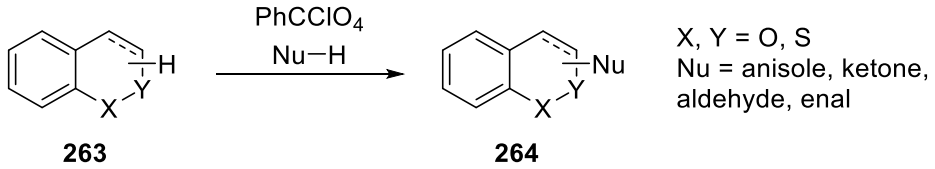
Scheme 74: DDQ mediated CDC without metal catalyst

In 2010, Floreancig *et al*. reported a DDQ mediated C-H functionalisation adjacent to a non-benzylic ether (**Scheme 75**).[127] The procedure used DDQ as an organocatalyst, however, 6 equivalents of MnO_2 were required for the reaction to proceed. Despite the broad scope shown, the high quantity of metal present imposes a limit on the usefulness of the reaction beyond an academic setting.



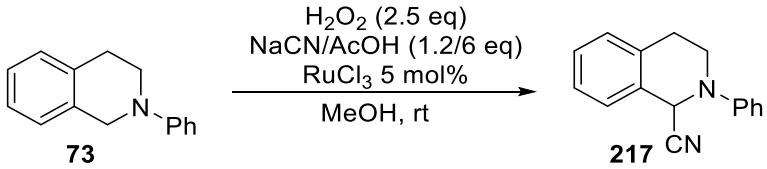
Scheme 75: MnO_2 and DDQ mediated cyclisation via C-H functionalisation

Non-DDQ oxidants have found use in the functionalisation of benzylic ethers. Liu *et al*. published a procedure in 2014 which used a trityl cation as an oxidant.[128] This reaction was notable in its broad substrate scope, something that has traditionally been difficult to achieve within this field (**Scheme 76**).



Scheme 76: Trityl cation mediated C-H functionalisation

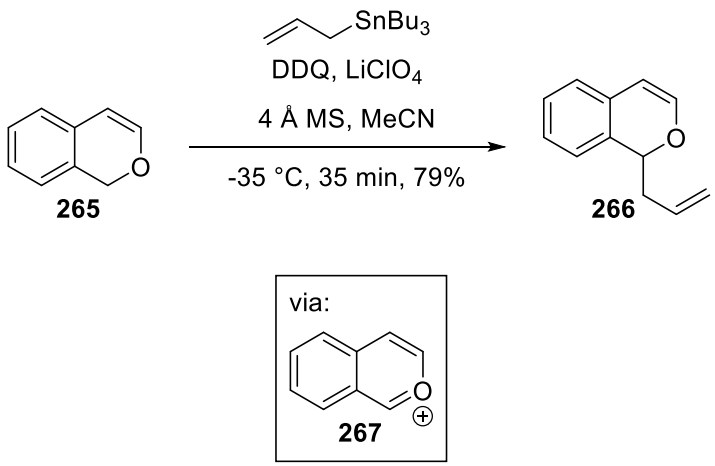
A potential method of ether functionalisation could be via the modification of amine CDC reactions such as those of Murahashi (**Scheme 77**).[129] However, α-oxidation of ethers seems to be harder to achieve than with amines, as the number of reported reactions of the latter far outstrips the former. A possible rationale for the increased difficulty could lie in the difference in electronegativity between oxygen and nitrogen leading to the oxocarbenium ion being less stable and hence harder to form.



Scheme 77: Introduction of CN moiety adjacent to amine using CDC

Another potential target for improved C-H functionalisation could be isochromene **265**, which only one group have investigated as a substrate for C-H activation.[130] In this case DDQ was used as the primary oxidant with lithium perchlorate also present as a means to break up a proposed isochromene-DDQ dimer. The reactions were performed at between -35 and 0 °C in MeCN with the nucleophile component being either allyl silanes/stannanes or aryl potassium trifluoroborates giving yields between 46-92% (**Scheme 78**). Crucially these reactions proceeded

much faster than corresponding ones with isochroman, potentially due to the more stable aromatic oxocarbenium ion **267** formed.[130]



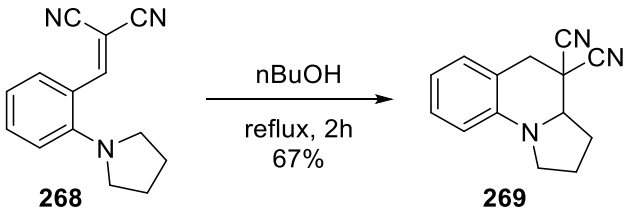
Scheme 78: Functionalisation of isochromene[130]

1.4 The 1,5-Hydride Shift

1.4.1 The 1,5-Hydride Shift in Amino Substrates

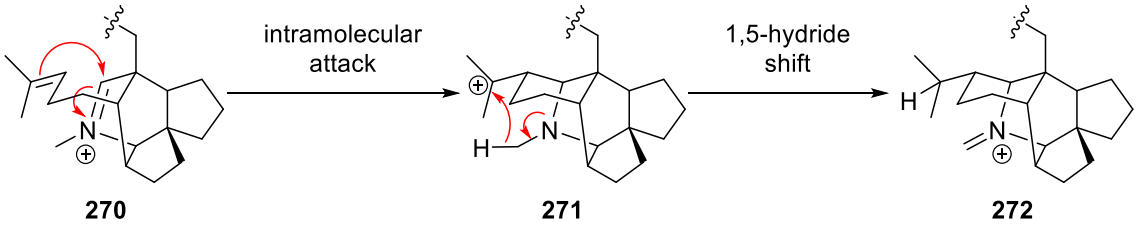
Despite first being reported by Pinnow in 1885, the 1,5-hydride shift languished in relative obscurity for most of the following century, with the main body of work in this area coming from Meth-Cohn, who published two major reviews in 1972 and 1996.[131–133] These reviews are mainly notable for coining the term *tert*-amino effect as a way of describing these hydride shifts when they occur adjacent to an amine, though they have since been reported adjacent to other heteroatoms, and, in some cases, without the presence of a heteroatom at all.[132–135] Interest in these reactions has steadily increased in the past 15-20 years, especially in the last 10, thanks, in part to the same driving forces that have moved research towards all types of C-H activation, the desire for atom-efficient “green” chemistry.[13,136]

A key example of the 1,5-hydride shift occurring with amine substrates came in 1984 when Reinhoudt *et al.* published a novel method of preparing substituted tetrahydroquinolines such as **269** (**Scheme 79**).[137] Here the aniline derivative **268** was heated in nBuOH for 2 h to form tetrahydroquinoline **269** in a 67% yield.[137] Reinhoudt observed that the 1,5-hydride shift benefits from the presence of a 6-membered ring in the backbone of the molecule, as this provides a closer framework to the required spatial orientation for the shift to occur.[137]



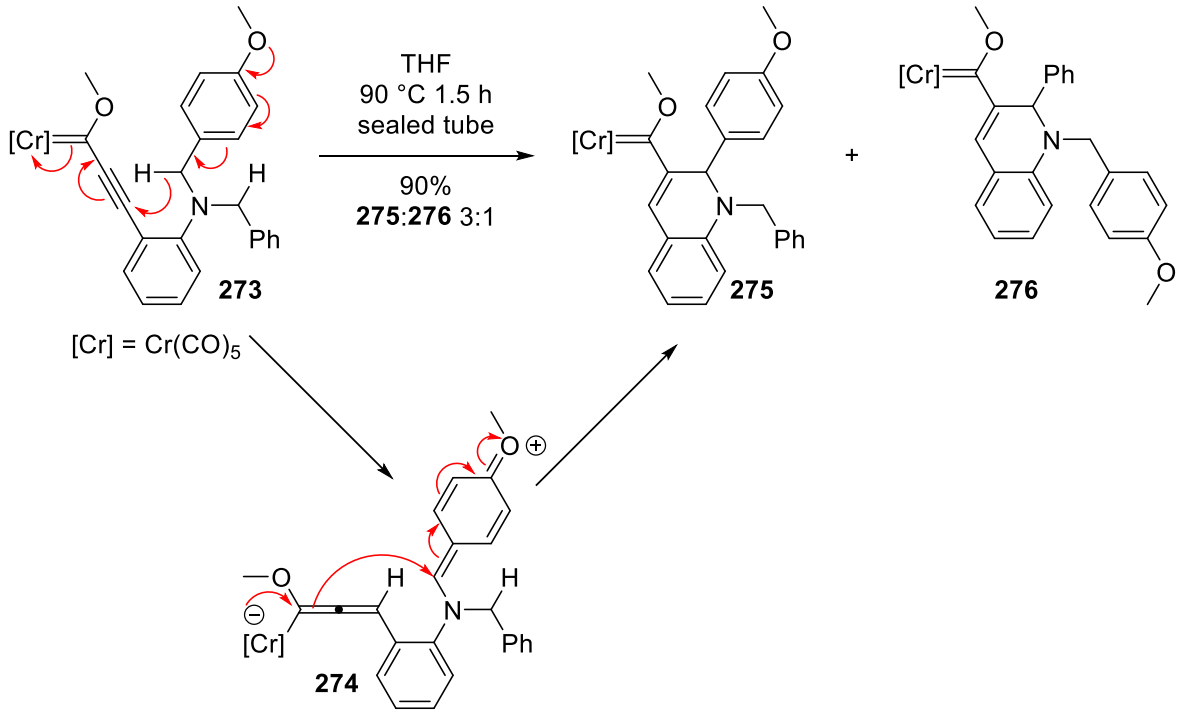
Scheme 79: Novel method of tetrahydroquinoline formation through a 1,5-hydride shift[137]

In the 1990s interest in 1,5-hydride shifts started to increase, with Heathcock *et al.* discovering, during their work on daphniphylline alkaloids, a new transformation (**Scheme 80**).[138,139] Iminium ion **270** underwent an attack by the pendent alkene to form the carbocation **271**. This cation acted as the hydride acceptor for a 1,5-hydride shift to form a second iminium ion **272** that subsequently hydrolysed.



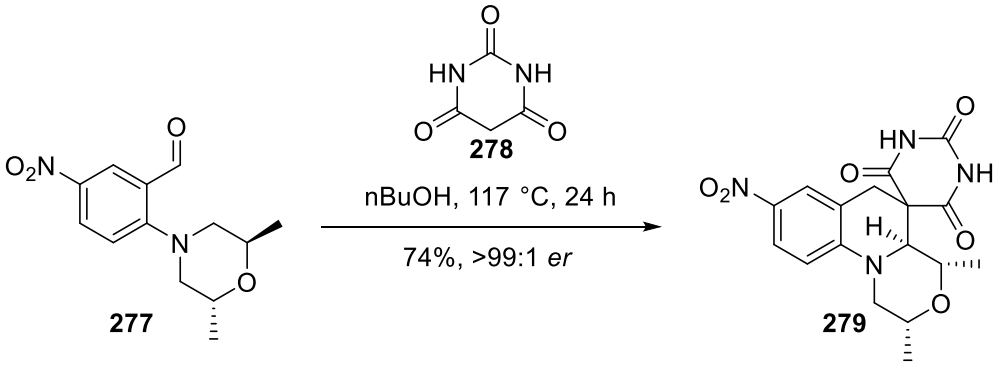
Scheme 80: Unexpected 1,5-hydride shift[139]

A good early example of the modern 1,5-hydride shift, using Bronsted acids, came in 2008 from Barluenga *et al.* using alkynyl Fischer carbene complexes.[140] Here an iminium ion was generated via a 1,5-hydride shift to the alkyne **273** to form an allene **274** which subsequently underwent cyclisation (**Scheme 81**).[140] Whilst a 91% yield was obtained in 1.5 h at 90 °C there were issues with selectivity, the reaction giving **275** and **276** in a ratio of 3:1 respectively.[140]



Scheme 81: Competition between hydride shift sites[140]

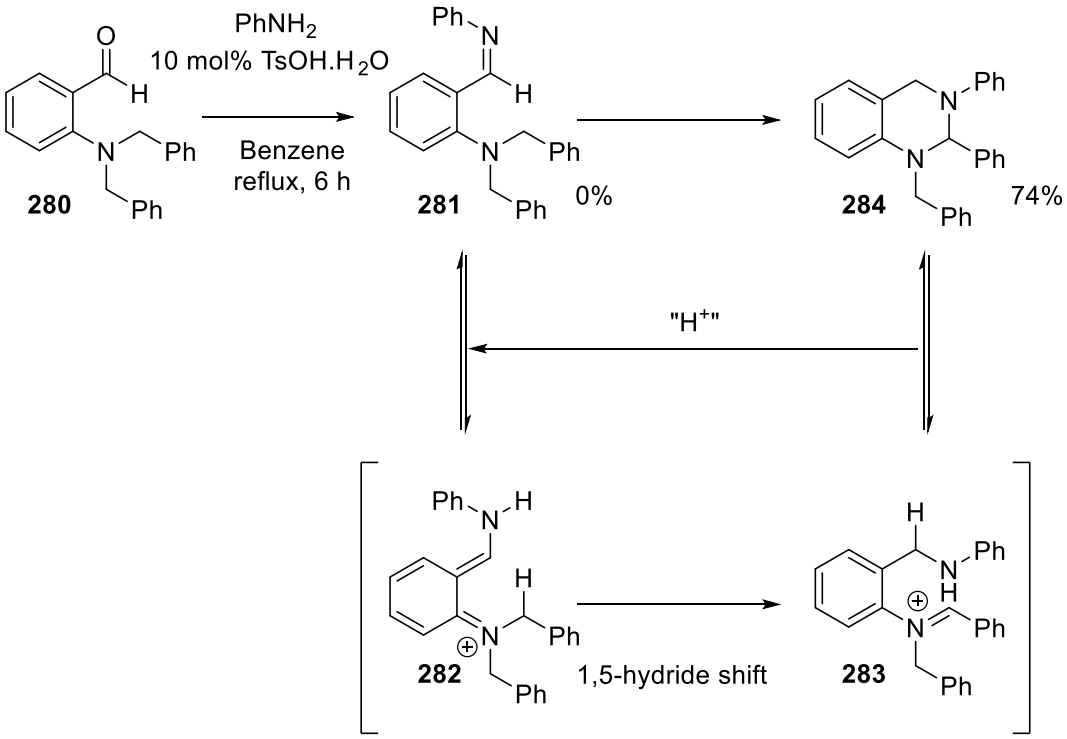
This catalyst free hydride shift has also been used in the synthesis of potential antibiotic targets such as (-)-PNU-286607 **279**, with it forming the final step in the route published by Ruble *et al*.[141] This offers a clear example of the advantages these generally high yielding reactions can provide, though here it is referred to as the *tert*-amino effect rather than a 1,5-hydride shift.[141] The reaction is performed in tandem with the incorporation of barbituric acid **278** which the authors believe to be the limiting step. Regardless, this incorporation/cyclisation reaction has given yields of 74% (**Scheme 82**).[141]



Scheme 82: Synthesis of 279 via a 1,5-hydride shift terminal step[141]

In 2009 both the Seidel[142] and Akiyama[143] groups published methods of producing tetrahydroquinazolines with the use of heat and an acid catalyst (**Scheme 83**). In both cases the reaction proceeded via the formation of an imine

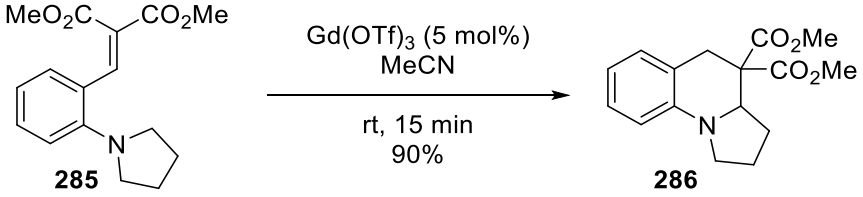
from a 2-aminobenzaldehyde derivative **280** which subsequently underwent a 1,5-hydride shift and cyclisation following imine protonation[142,143]



Scheme 83: 1,5-hydride shift mediated quinazoline synthesis[143]

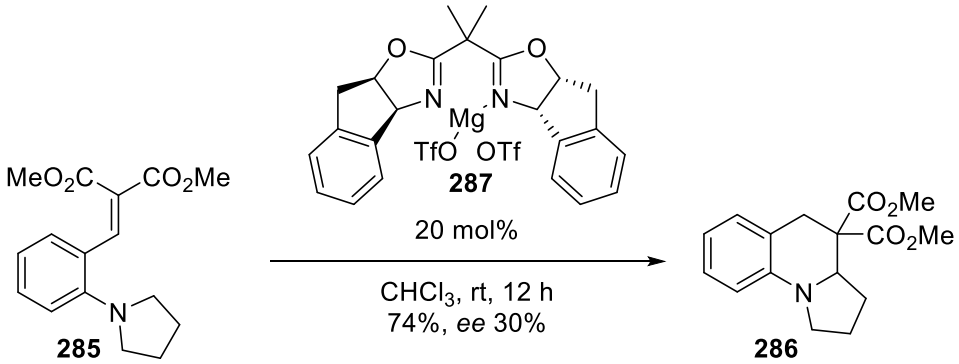
As shown by the reactions above, and as is clear by Meth-Cohn's reviews, 1,5-hydride shift conditions tended to be performed with Bronsted acids or under thermal conditions.[132,133,144]

Seidel *et al.* investigated, in 2009, the use of Lewis acids to effect these transformations.[145] The authors screened a wide range of Lewis acids and discovered that $Sc(OTf)_3$ and $Gd(OTf)_3$ could lead to the formation of tetrahydroquinolines similar to those prepared by Reinhoudt. No reaction was observed with the dicyano- substrate Reinhoudt themselves cyclised (**Schemes 79** and **84**).[137,145] Instead, dicarbonyl substrates were required, though both ketones and esters were tolerated, suggesting chelation. Similar yields were seen with $Sc(OTf)_3$ and $Gd(OTf)_3$ but the latter catalyst led to reduced reaction times.



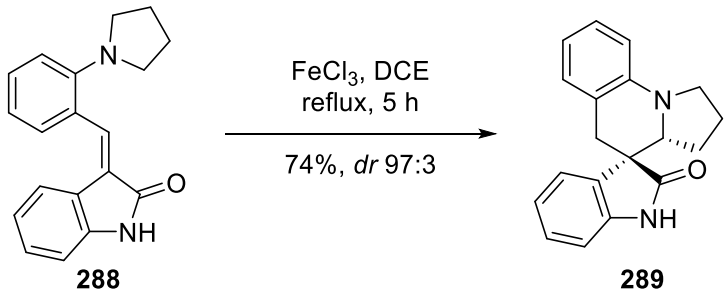
Scheme 84: Formation of 286 through Lewis acid catalysis[145]

Seidel *et al.* also investigated the possibility of performing these reactions enantioselectively, the only research in this direction to date.[145] The best result obtained was with the magnesium (II) complex **287**, which gave the desired compound in a 74% yield with an *ee* of 30% (**Scheme 85**). The enantioenriched material **286** was found to racemise in the presence of $Gd(OTf)_3$.



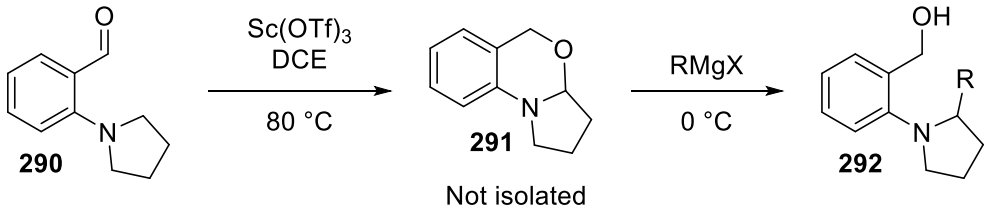
Scheme 85: The first enantioselective 1,5-hydride shift in amino substrates[145]

The use of more common metals as catalysts was described in 2012. Yuan *et al.* used iron (III) chloride to form spirooxindole **289** in a high yield and excellent *dr* (**Scheme 86**).



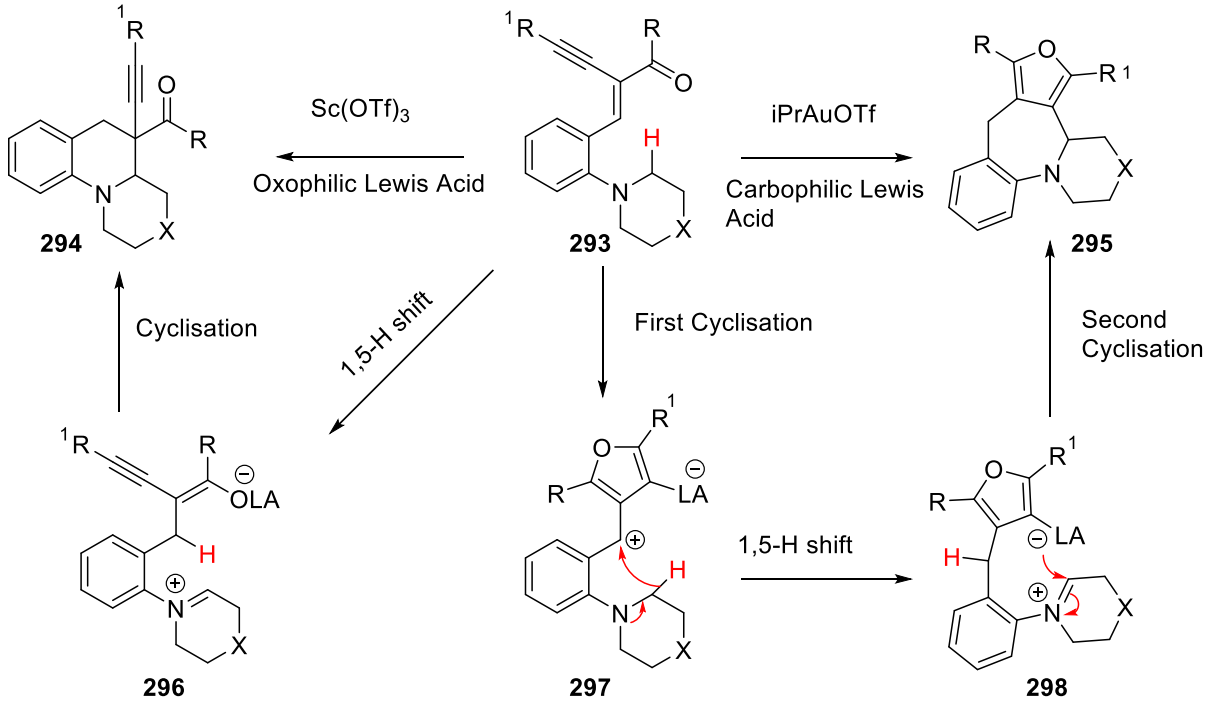
Scheme 86: Yuan *et al*'s synthesis of spirooxindolines[146]

An interesting use of the 1,5-hydride shift was described in 2012 by Jurberg *et al*.[147] The authors found that 2-carbonylanilines such as **290**, when in the presence of $Sc(OTf)_3$ in DCE, were found to form N,O-acetals such as **291**. These acetals were not isolated and were instead reacted with Grignard reagents to functionalise adjacent to the amine with the carbonyl reduced to an alcohol (**Scheme 87**).[147]



Scheme 87: The use of a 1,5-hydride shift to functionalise amines with a Grignard reagent[147]

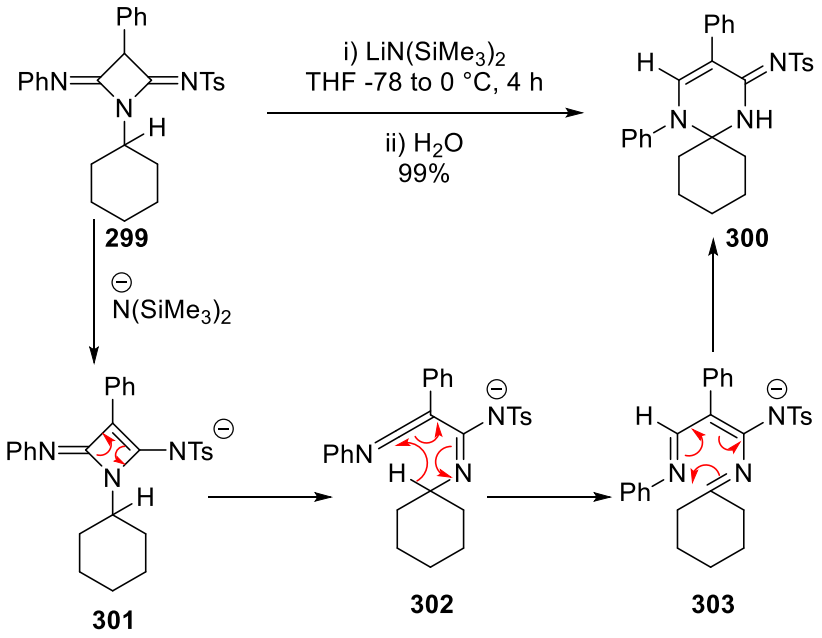
Zhang *et al.* described, in 2012, another interesting method of applying the 1,5-hydride shift (**Scheme 88**) through the use of a carbophilic Lewis acid to first enact a cyclisation to form a furanyl derivative **297** which then induced a 1,5-hydride shift by virtue of an incipent C^+ to give **295**. However, in the presence of an oxophilic Lewis acid, the 1,5-hydride shift and cyclisation proceeded before any furanyl derivative could form.[145,148] This route gives the highly functionalised tetrahydrofuran **294** via intermediate **296**.



Scheme 88: Alternate heterocycles through choice of Lewis acid[148]

A method of using a 1,5-hydride shift for ring expansion was discovered by Zhang *et al*, again in 2012.[149] According to the mechanism as proposed, the 1,4-diiminoazetidine **299** was treated with $LiN(SiMe_3)_2$ to provide the dihydropyrimidinesulfonamide **300** in a 99% yield, with 28 further substrates prepared (**Scheme 89**). After an initial sigmatropic rearrangement of **301** to form

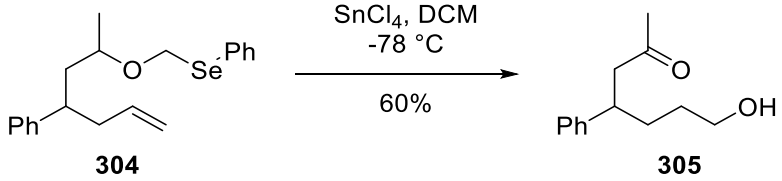
302, a 1,5-hydride shift occurs to give **303** which subsequently rearranges in a ring-closure reaction to give **300**.



Scheme 89: 1,5-hydride shift catalysed ring opening[149]

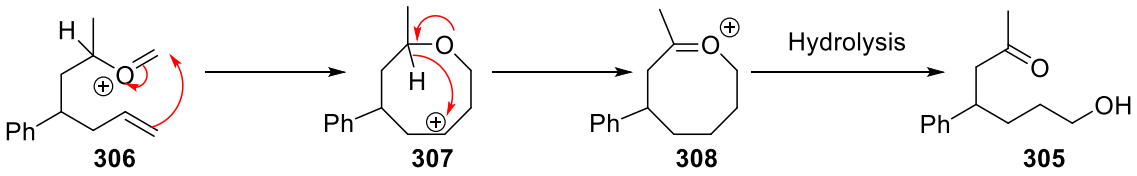
1.4.2 The 1,5-Hydride Shift in Ethereal Substrates

Non-amine 1,5-hydride shifts are, by comparison, a much less studied area. An early example of a 1,5-hydride shift adjacent to an oxygen came in 1993 when Kataoka *et al.* discovered that it was possible to functionalise alkenes such as **308** tethered to an O,Se acetal in the presence of $SnCl_4$ to form a hydroxyketone such as **309** (**Scheme 92**).[153]



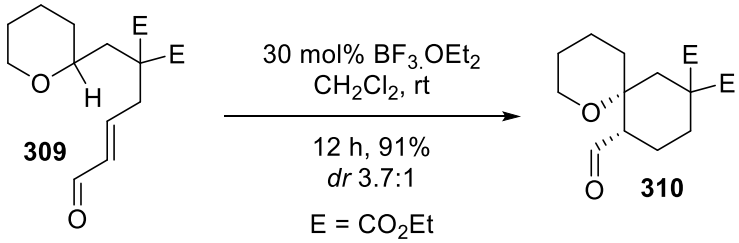
Scheme 90: Hydroxyketone formation via a 1,5-hydride shift[153]

The mechanism, as proposed by Kataoka, first proceeds by the formation of **306** following the $SnCl_4$-mediated cleavage of the acetal (**Scheme 91**).[153] This is followed by a Prins cyclisation and subsequent hydride shift before hydrolysis occurs on workup to give **305**.



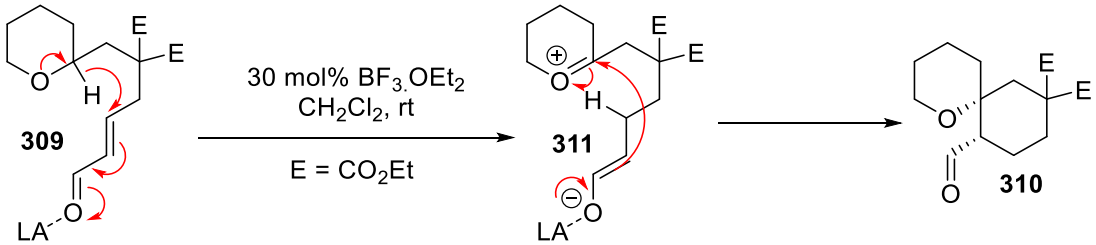
Scheme 91: Mechanism for hydroxyketone formation[153]

The first major papers in this area in the modern era came from Sames *et al*. in 2005 when the authors reported a novel method of forming bicyclic ether spirocycles, which was followed with a second more complete publication of increasing scope (**Scheme 92**).[135,154] This is further notable as the 1,5-hydride shift was performed with an ether moiety rather than with amines as had predominantly been published previously. As with Atkinson (see above) the hydride shift was found only to occur with a 1,5- arrangement, attempts at 1,4- and 1,6-hydride shifts with analogous substrates failed.[135] This highlights the importance of the relative arrangements of the reacting portions of the molecule in space.[135]



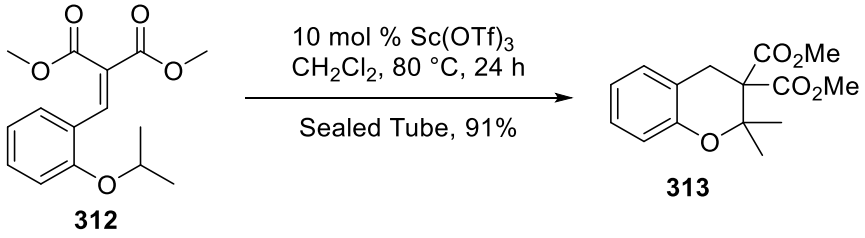
Scheme 92: Sames *et al*. first 1,5-hydride shift mediated cyclisation[135]

This reaction was performed via a 1,5-hydride shift to form an intermediate which contained both an enolate and an oxocarbenium ion **311** (**Scheme 93**). The oxocarbenium ion then underwent rapid nucleophilic attack from the tethered enolate to give the spirocycle **310** at room temperature with a Lewis acid catalyst.



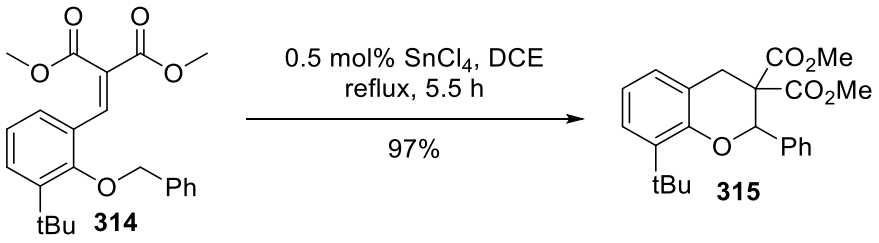
Scheme 93: Mechanism for 1,5-hydride shift mediated cyclisation[135]

Further studies by both Sames and Akiyama suggested some general reactivity rules for ethereal substrates.[155,156] Sames *et al*. did so by developing a novel method of preparing dihydrobenzopyrans from salicylaldehyde derived ethers.[155] By generating an oxonium ion adjacent to an aromatic ring the authors were able to achieve 91% yield with full consumption of starting material within 24 h at 80 °C (**Scheme 94**).[155] Here $Sc(OTf)_3$ proved to be uniquely effective as a catalyst, with many lanthanide triflates showing no or low yields. The authors found that esters perform better than ketones as whilst diketones cyclised, a significant amount of side product was formed that wasn't seen with esters. The authors also observed that ring substitution is preferred in the *para*- position relative to the ethereal oxygen and that electron donating groups in the aromatic ring increase the reaction rate.[155]



Scheme 94: Dihydrobenzopyran synthesis via 1,5-hydride transfer[155]

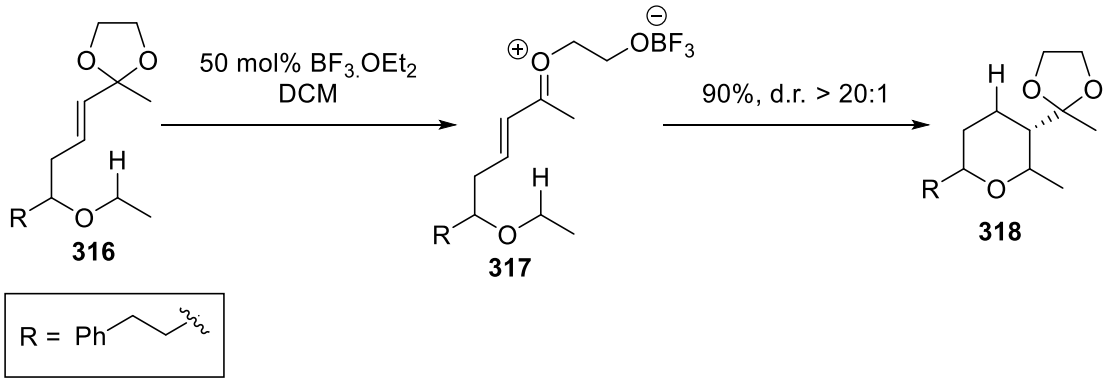
Concurrently, Akiyama *et al.* found that the presence of a bulky group *ortho*- to the hydride source greatly improved the reaction rate.[156] This improvement occurred to the extent that it was possible to form substituted chroman **315** in a 97% yield with a 0.5 mol% catalyst loading (**Scheme 95**). It was proposed that the presence of the bulky *ortho*- group forced **314** to sit in the desired conformation for the 1,5-hydride shift.[156]



Scheme 95: Effect of an *ortho*- substituent on 1,5-hydride shifts[156]

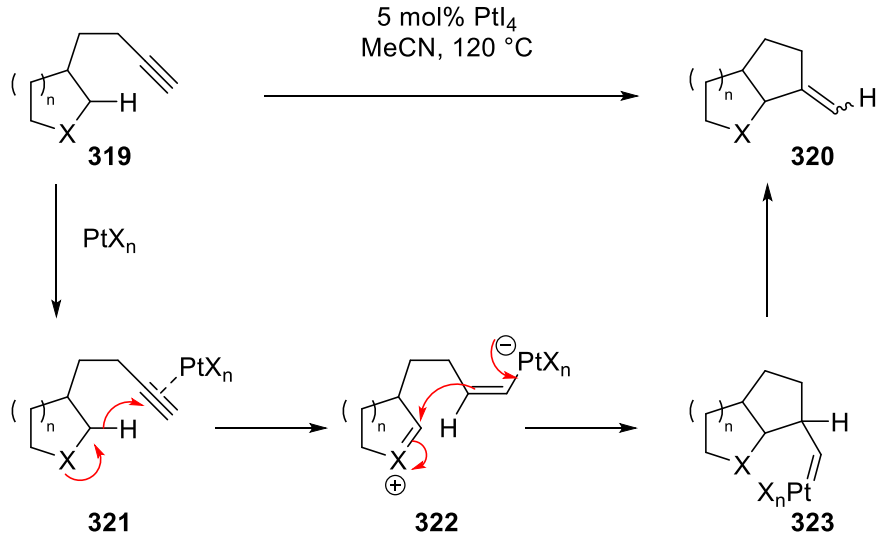
The carbonyl-substituted alkene hydride acceptors shown above have been found to perform better when the carbonyl is an ester or aldehyde.[157] McQuaid *et al.* published a new method of performing 1,5-hydride shifts with ketones which

proceeded much more swiftly and without the formation of side products due to the protection of the ketones as acetals, leading to the formation of an oxocarbenium ion (**Scheme 96**).[157]



Scheme 96: Improved 1,5-hydride shift with acetals[157]

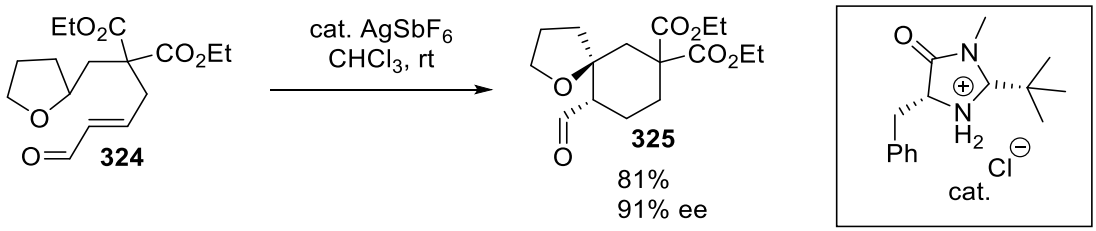
Later in 2009 Sames *et al*. published a method of forming 5-membered rings with a platinum catalysed hydride shift to an alkyne. This generated a reactive cation that then underwent nucleophilic attack from the platinated alkene to form a ring (**Scheme 97**).[158] This reaction was found to successfully convert both amino and ethereal substrates.



Scheme 97: Sames *et al*. platinum catalysed cyclisation[158]

Since then, several papers have been published using the formation of α,β-unsaturated iminium ions as a means to promote the hydride shift. These reactions proceed similarly to that shown above (**Scheme 93**), with the iminium ion replacing the enone as a hydride acceptor. In 2012 Tu *et al*. first demonstrated iminium ion activation to form spiroethers similar to those in Sames' 2005 paper

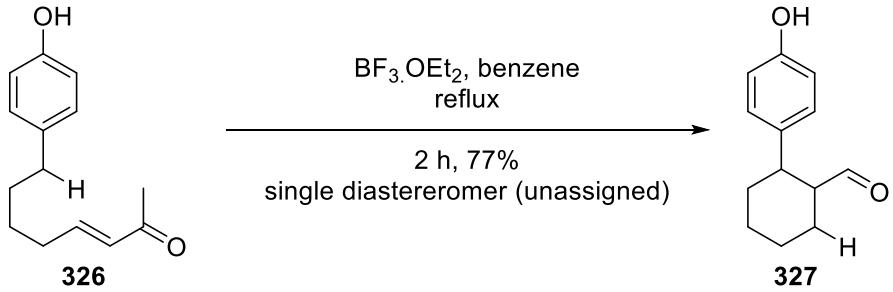
but leading to a product that was enantioenriched.[159] Here the weakly coordinating Cl^- counterion increases the electrophilicity of the generated iminium ion, promoting the hydride shift (**Scheme 98**).



Scheme 98: Enantioenriched cyclisation via hydride shift[154]

1.4.3 The 1,5-Hydride Shift in Substrates Without an Adjacent Heteroatom

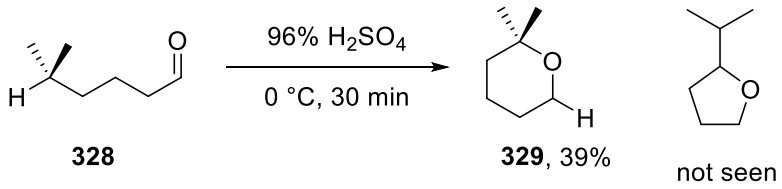
The first non-heteroatom adjacent example of a 1,5-hydride shift was published in 1969 by Atkinson.[150] Atkinson discovered that if enone **326** was heated in in $BF_3.OEt_2$, cyclised product **327** was formed in a 77% yield as a single diastereomer (**Scheme 99**).



Scheme 99: First example of a non-amine based 1,5-hydride shift[150]

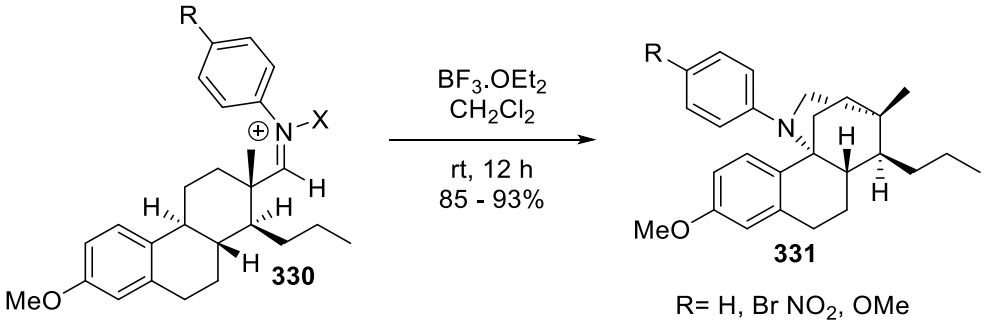
This initial result was shown to be an intramolecular process through a deuterium labelling experiment where a mixture of D labelled and standard starting materials were reacted as per **Scheme 99**, and no mono-deuterated products were obtained.[150] Also notable was a further study by Atkinson which both broadened the range of catalysts which could be used to effect this transformation and showed that a 1,4-hydride shift would not occur under the same conditions.[151]

However, despite this early result, the work of Atkinson suffered, as did *tert*-amino effect induced cyclisations, from forcing reaction conditions. Atkinson's reactions required either a 1:1 mix of $BF_3.OEt_2$ and benzene as solvent/catalyst or 96% H_2SO_4 as solvent for products to be obverved.[150,152] The aforementioned H_2SO_4 reaction saw substituted aldehydes such as **328** converted into tetrahydropyrans such as **329**.



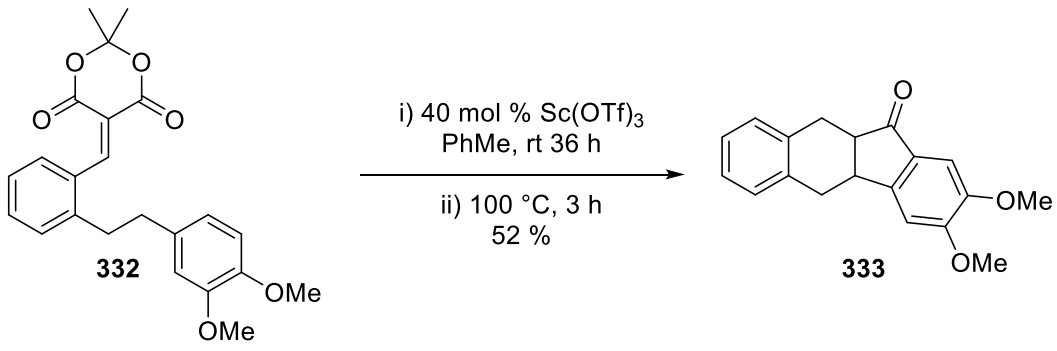
Scheme 100: Formation of tetrahydropyran 307[152]

Another early example of a 1,5-hydride shift occurring without the presence of an adjacent heteroatom came in 1999, when Wölfling *et al.* described the synthesis of aliphatic rings with $BF_3.OEt_2$ as a catalyst before its adoption by Sames *et al.* for 1,5-hydride shifts adjacent to ethers (**Scheme 101**).[160]



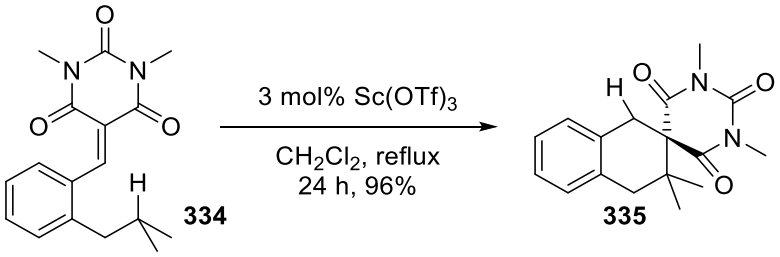
Scheme 101: Synthesis of bridged steroid alkaloids via 1,5-hydride shift[160]

Following Sames *et al.* publication of $Sc(OTf)_3$ catalysed 1,5-hydride shifts in 2005, this same methodology was applied to substrates without an adjacent heteroatom.[135,161] In 2009 Fillion *et al.* used $Sc(OTf)_3$ methodology as a means of preparing complex tetracycles with Meldrum's acid.[161] Here 40 mol% was used to effect the initial 1,5-hydride shift at room temperature in 36 h, followed by 3 h at 100 °C for the subsequent decarboxylation and Friedel-Crafts acylation with a 52% yield of **333**.[161] This publication was notable as with Meldrum's acid and $Sc(OTf)_3$ the authors managed to functionalise a benzylic carbon at rt (**Scheme 102**).[161]



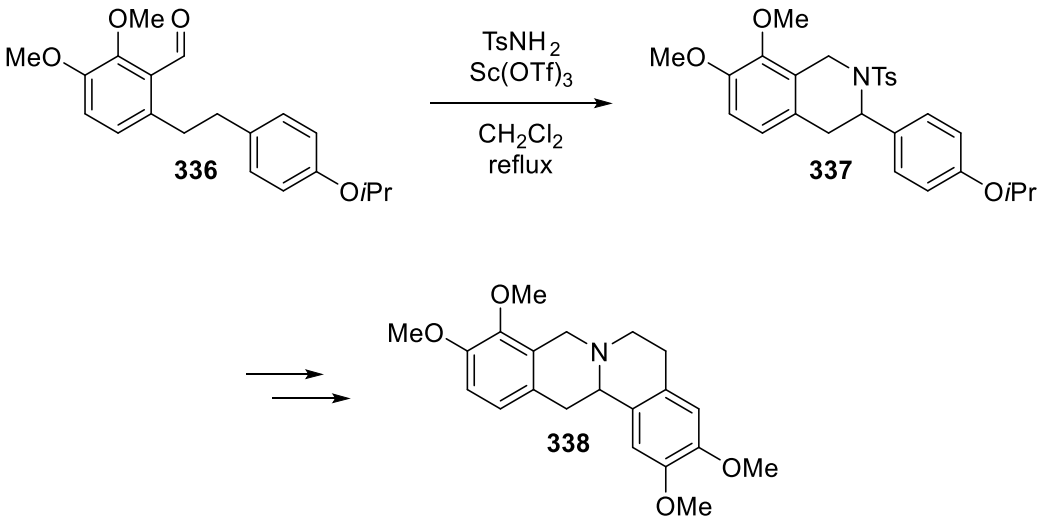
Scheme 102: Tetracycle synthesis via 1,5-hydride shift[161]

This was followed in 2011 by Akiyama *et al*, who published a method of forming 6 membered aliphatic rings with $Sc(OTf)_3$ via a 1,5-hydride transfer and cyclisation via a tertiary carbocation (**Scheme 103**).[162] This was performed in dichloromethane at reflux for 24 h, giving yields of 93-97%.[162] This was achieved without a heteroatom adjacent to the hydride donor or electron donating substituents on the aromatic ring.



Scheme 103: 1,5-hydride shift to form aliphatic ring

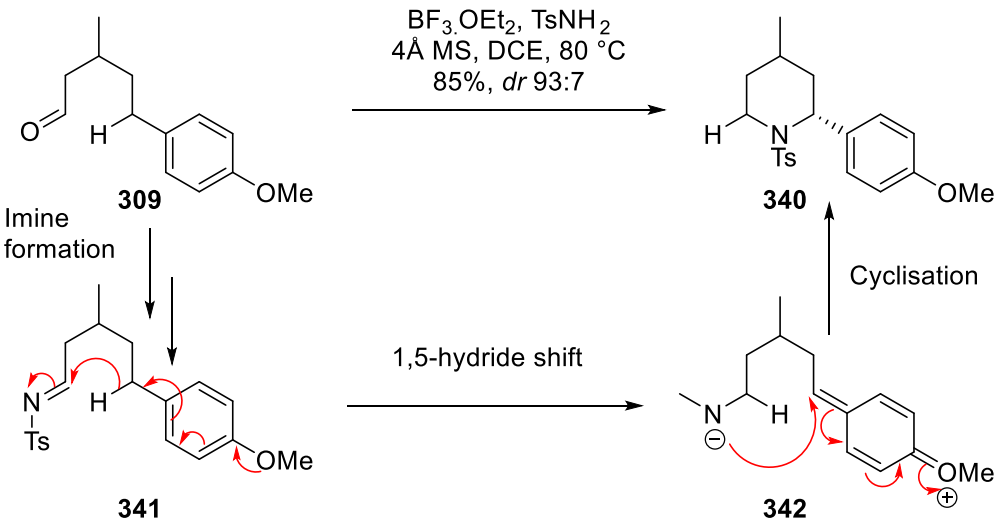
In 2012 the authors applied this methodology to the formal synthesis of (±)-tetrahydropalmatine **338**, forming **337** via imine formation and a subsequent 1,5-hydride shift (**Scheme 104**).[163] This compound is a key intermediate in the synthetic route to (±)-tetrahydropalmatine **338** published by Enders *et al*. in 2005.[163,164]



Scheme 104: Formal synthesis of (±)-tetrahydropalmatine via a 1,5-hydride shift[163,164]

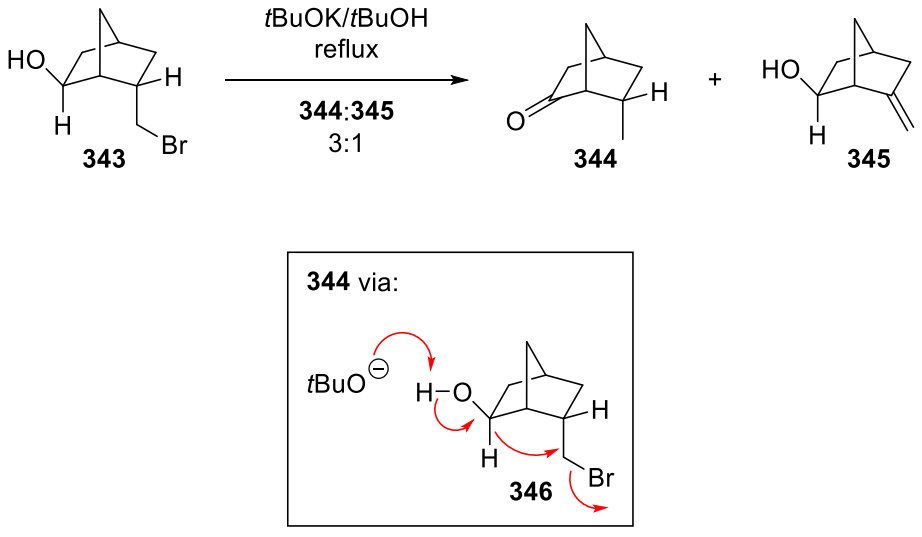
In 2012 the Sames and Akiyama groups both published separate methods of forming new nitrogen containing heterocycles via a 1,5-hydride shift with the formation of an imine in situ.[163,165] The amine formed by the hydride shift then attacks the new cation **342** to form a 6 membered ring (**Scheme 105**).

Impressively, in the case of Sames, this transformation involved a hydride donor without an adjacent heteroatom.



Scheme 105: Sames' nitrogen heterocycle formation[165]

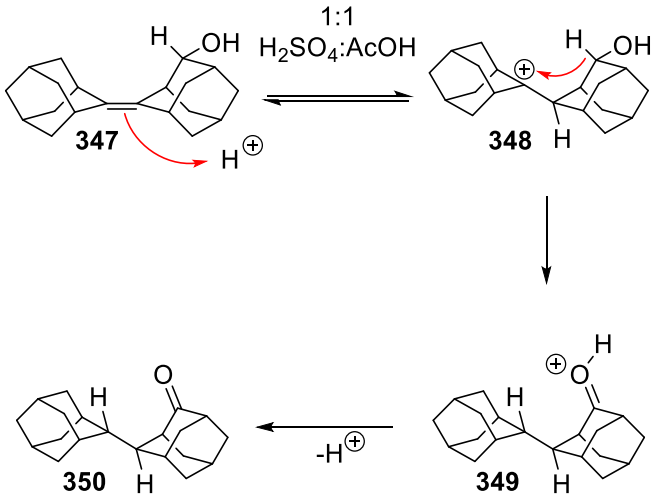
In addition to the varied 1,5-hydride shifts discussed above, there have been a small number of successful 1,4-hydride shifts. An early example of a 1,4-hydride shift came in 1968, when Gwynn *et al*. published a novel oxidation of *endo*-6-bromomethyl-*exo*-2-norbornanol **343**.[166] In addition to the desired elimination product **345**, the ketone **344** was formed in a 3:1 ratio (**Scheme 106**). The authors proposed that this was the result of an unexpected 1,4-hydride shift leading to elimination of Br^- and the oxidation of the alcohol group to a ketone.[166]



Scheme 106: An unexpected 1,4-hydride shift[166]

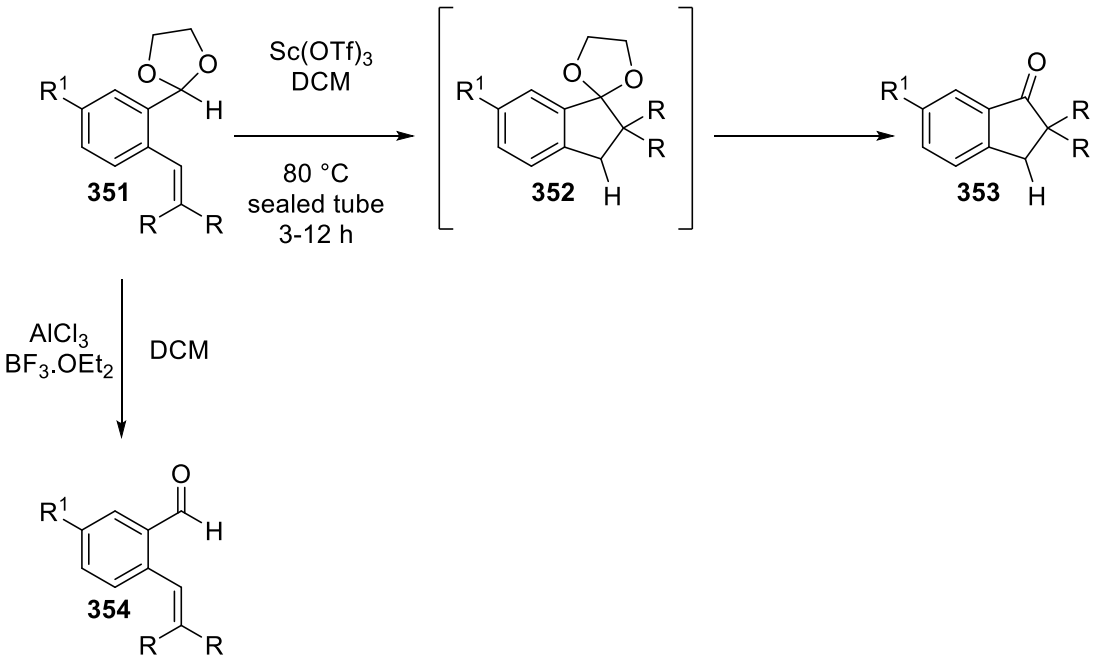
A similar process involving a 1,4-hydride shift has also been observed in the rearrangement of sterically congested homoallyl alcohol **347** to the corresponding

alkyl ketone **350** in a 1:1 mixture of AcOH/H_2SO_4.[167] Rather than relying on the elimination of a bromide, instead the authors propose a mechanism wherein the alkene is protonated and the generated cation acts as the hydride acceptor (**Scheme 107**). The authors also report that, due to steric hindrance, no corresponding 1,3-hydride shift can occur.[167]



Scheme 107: 2-step rearrangement involving a 1,4-hydride shift[167]

Alajarin *et al.* developed, in 2011, a method of C-H functionalisation via a 1,4-hydride shift which used the hydride acceptors used elsewhere in 1,5-hydride shifts.[145,168] The authors discovered that 1,3-dioxolanes, 1,3-dithiolanes or 1,3-dithianes were required as a hydride source, rather than the wider range of donors seen in 1,5-hydride shifts.[168] A wide range of Lewis acids were screened, with $Sc(OTf)_3$ providing the desired products in yields between 30-58%, with the acetal cleaving *in situ* following cyclisation (**Scheme 108**).[168] The authors discovered that when $BF_3.OEt_2$ and $AlCl_3$ were used as the catalyst, **354** was formed instead, the acetal having cleaved to provide the aryl aldehyde.



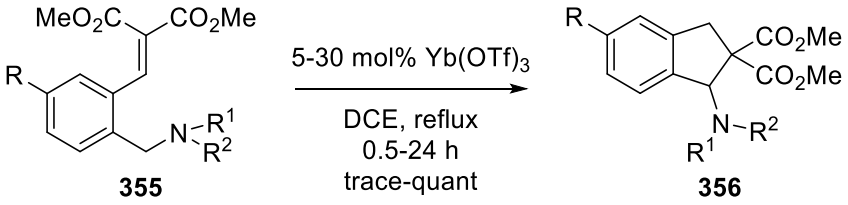
Scheme 108: 1,4-hydride shift to form 353[168]

Table 3: Results of condition screen to form 353

351	R	R^1	Catalyst (eq)	Temp (°C)	**353** Yield (%)
351a	CO_2Et	H	$AlCl_3$	25	
351a	CO_2Et	H	$BF_3.OEt_2$	80	
351a	CO_2Et	H	$Sc(OTf)_3$	25	
351a	CO_2Et	H	$Sc(OTf)_3$	50	
351a	CO_2Et	H	$Sc(OTf)_3$	60	
351a	CO_2Et	H	$Sc(OTf)_3$	80	**353a** (30)
351a	CO_2Et	H	$Sc(OTf)_3$	80	**353a** (58)
351a	CO_2Et	H	$Sc(OTf)_3$	80	**353a** (55)
351b	CO_2Me	H	$Sc(OTf)_3$	80	**353b** (54)
351c	CO_2Et	OMe	$Sc(OTf)_3$	80	**353c** (41)
351d	CO_2Me	OMe	$Sc(OTf)_3$	80	**353d** (35)

Finally, Mori, whose work with Akiyama on the 1,5-hydride shift work has been discussed in detail in section 1.4, page 59 onwards, has also published one successful 1,4-hydride shift reaction (**Scheme 109**).[169] The authors discovered that, contrary to their 1,5-hydride shift reactions, the presence of bulky groups on the amine adjacent to the hydride donor saw a decrease in reaction time and increase in yield.[169] This difference was rationalised as the steric clash between the bulky amine substituents and the hydride acceptor preventing the nucleophile

attack of the hydride acceptor by the amine, ensuring the desired 1,4-hydride shift occurred.[169]

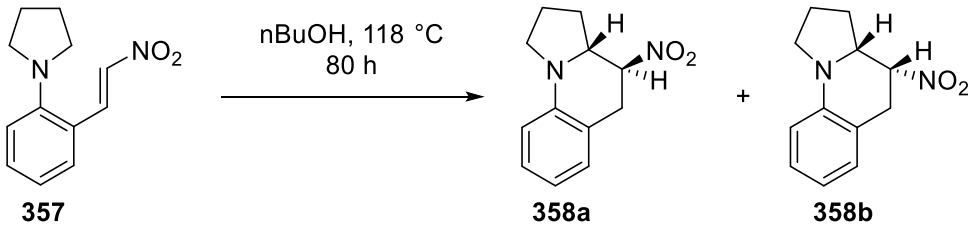


R = H, F, Me, OMe
R_1, R_2 = Et, *i*Pr, Ph, Bn, piperidine, 1,2,3,4-tetrahydroquinoline

Scheme 109: General reaction Scheme for formation of 356[169]

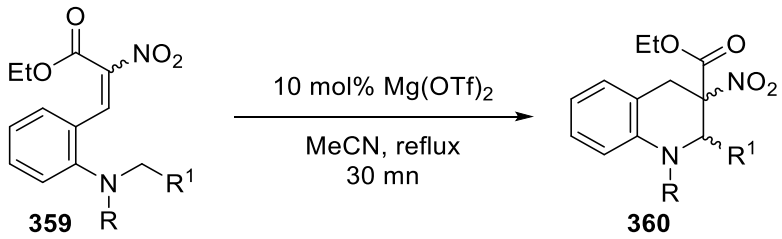
As is apparent from the above discussion, the hydride acceptor in a 1,5-hydride shift needs to be suitably electron withdrawn for reactions to proceed. Generally, where a vinyl aldehyde will readily act as a hydride acceptor, a less electrophilic vinyl ester would require a second electron withdrawing group in order to react, such as a second ester or a nitro group.[154,170] This also goes some way to explaining the decreased reactivity seen with vinyl ketones compared to the corresponding aldehyde, with the highest yielding reactions requiring the generation of an oxocarbenium or iminium ion.[157] These reactive iminium anions have also found use in asymmetric syntheses, with the iminium formed through reaction with the chiral auxiliary being more reactive than the starting aldehyde, for example (**Scheme 100**).[159]

Despite the wide range of synthetic methods as described in the sections above, when we commenced our investigations a 1,5-hydride shift had been used to form a nitronate to allow a nitro-Mannich cyclisation to occur on just one occasion.[171] This reaction was published in 2007 by Jordis *et al*, where the cyclisation occurred in refluxing nBuOH for 80 hours with a combined yield of **358a** and **358b** of 25% with a ratio of 12:1 (**Scheme 110**).[171]



Scheme 110: Literature cyclisation via 1,5-hydride shift then nitro-Mannich[171]

A second 1,5-hydride shift with a nitro- group present was published in 2016 by Briones *et al*.[170] The authors observed that $Mg(OTf)_2$ catalysed the formation of bicycle **360** (**Scheme 111**) as a key intermediate in a route towards tetrahydroquinoline-3-spirohydantoin derivatives via the synthesis of spirocycles.



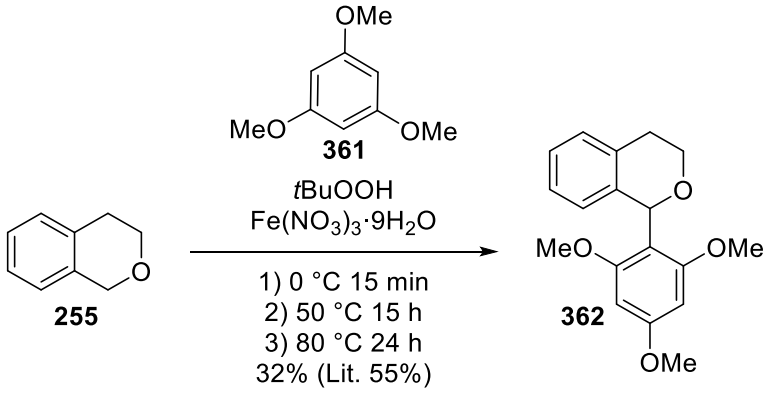
Scheme 111: Literature route featuring Lewis acid catalysis[170]

The use of the nitro-Mannich reaction to perform a cyclisation following the internal generation of a nitronate was therefore an area ripe for further exploration.

2. Results and Discussion

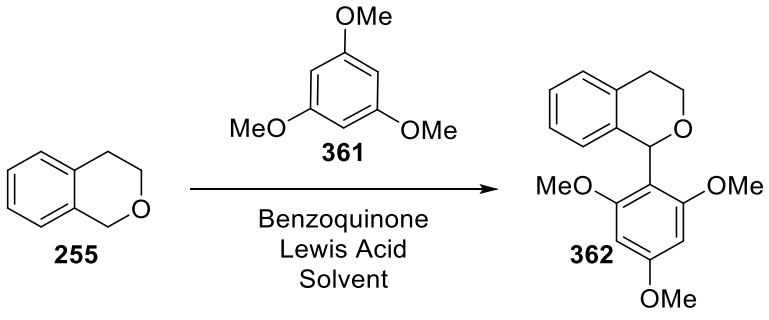
2.1 Previous Work in the Group

The cross-dehydrogenative coupling of ethers as a method of C-H activation adjacent to ethers had previously been investigated by an exchange student within the group who had focused on choices of Lewis acids when working with benzoquinone as an oxidant. He had first prepared 1-(2,4,6-trimethoxyphenyl)isochroman **362** in order to obtain clean NMR data with which to compare conversion during methodological investigation (**Scheme 112**).[172]



Scheme 112: Literature synthesis of 362 to give ^{1}H NMR data[172]

Once ^{1}H NMR data was obtained for **362** attention was turned to screening of reaction conditions to effect the formation of **362** via an Oppenauer oxidation. Both solvent and Lewis acid were investigated with benzoquinone in use as an oxidising agent (**Scheme 113, table 4**). The conversion was measured by the relative intensities of the ^{1}H NMR peaks of isochroman **255** and the desired product **362**.



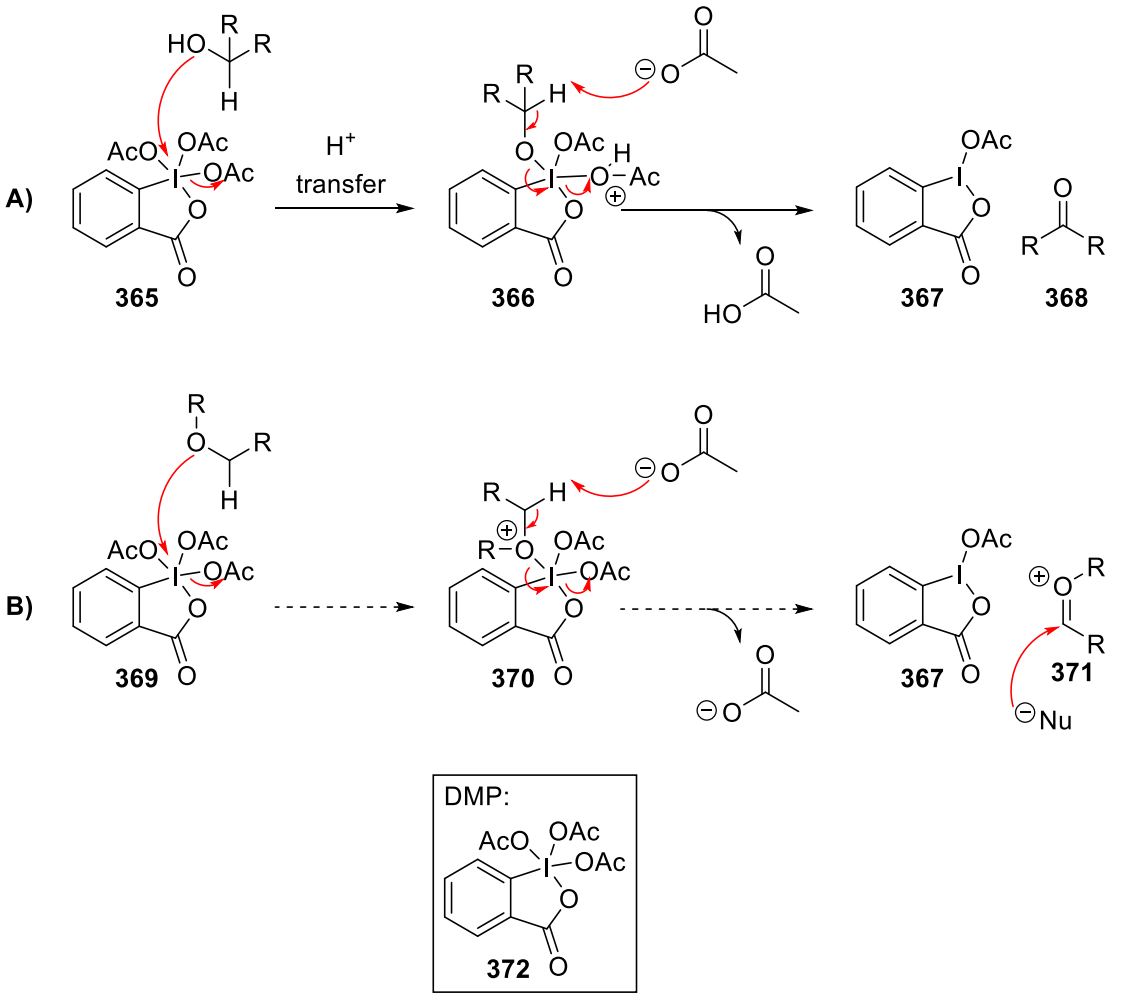
Scheme 113: General Scheme for reaction screening

Table 4: Conditions screened previously within the group

Solvent	Lewis Acid(s)	Catalyst Load (mol%)	Temperature (°C)	Conversion (%)
Toluene	$InCl_3$	10	110	0
Toluene	$ZrCl_4$	20	110	6
Toluene	$CuBr_2$	25	110	8
Toluene	$ZrCp_2Cl_2$	25	110	2
Toluene	$CeCl_3.7H_2O$	25	110	6
Toluene	$IrCl_3.H_2O$	5	110	6
Toluene	$CuBr_2$	10	50	6
Toluene	CuCl	10	50	5
Toluene	$BF_3.OEt_2$	30	50	0
Toluene	$FeBr_3$	20	50	2
Toluene	None	n/a	50	0
Toluene	$Ti(iOPr)_4$	10	80	0
Toluene	$NiCl_2.6H_2O$	10	80	0
Toluene	$AgNO_3$	20	80	0
Toluene	$RuCl_3.H_2O$	10	80	6
Toluene	$ZnBr_2$	10	80	1
MeCN	$CuBr_2/ZnBr_2$	10	60	8

2.2 Proposed Research

It was clear from the results achieved previously within the group that a great deal of improvement would be required in order to develop a synthetically useful reaction. Due to this lack of success two routes into C-H activation were pursued. We proposed the use of hypervalent iodine compounds, both iodine (III) species such as (diacetoxyiodo)benzene (PIDA) **363** and iodosobenzene **364** based on their ability to oxidise alcohols to carbonyls.[173] Our scope also included iodine (V) species such as Dess-Martin periodinane (DMP) which has also found much use in alcohol oxidation **365** (**A)**, **Scheme 114**).[174] By analogy, we proposed that should DMP oxidise an ether **369**, the generated oxonium ion **371** would then be susceptible to nucleophilic attack (**B) Scheme 114**)



Scheme 114: DMP oxidation of alcohol and potential application to ethers

Alongside this work with hypervalent iodine oxidants, we planned to continue the investigation into the oxidation of ethers via the proposed Oppenauer oxidation. It was thought that the choice of oxidant could be key and would be a good starting point for improving reactivity. We proposed to find an initial method of oxidation adjacent to ethers which could then be extended to cover a wide range of substrates and nucleophiles (**Figure 1**).

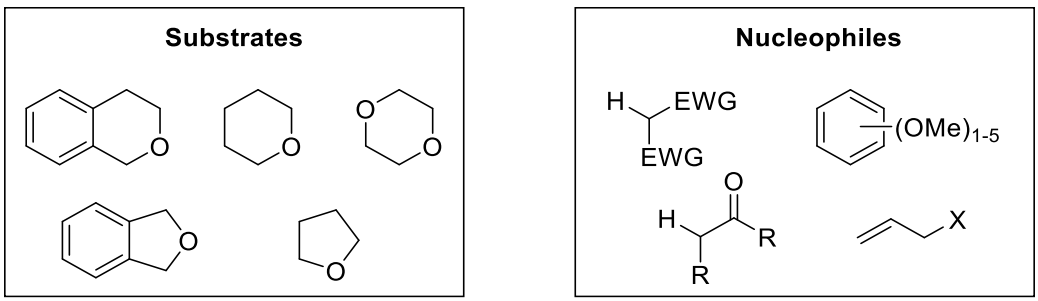
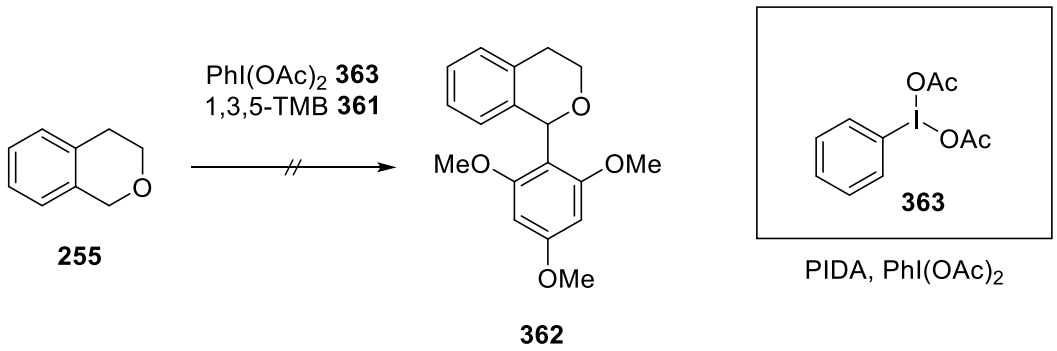


Figure 1: A selection of substrates and nucleophiles

2.3 The Functionalisation of C-H Bonds Adjacent to Ethers

2.3.1 Hypervalent Iodine

The first conditions attempted used PIDA and was based on the reaction conditions from a Liu *et al.* paper which used a trityl cation as an oxidant to functionalise via a CDC (**Scheme 115**).[128] This showed no conversion as was reported by the Liu group for their substrates.[128]



Scheme 115: Attempted functionalisation with PIDA oxidant

The reaction was then repeated, using DMP **372** in lieu of PIDA **363**. The reactions were performed under an inert atmosphere, but with standard dichloromethane.[175] The initial attempt was a modification of the PIDA conditions used by Liu *et al*. (**Scheme 115**) with the use of DMP and a slight increase in the ratio of 1,3,5-TMB to isochroman **255**. This saw a conversion to product **362** of 1%, due to the appearance of a signal at δ 6.69 (d, *J* = 7.7 Hz, 1H) in $CDCl_3$ of the product **362** compared to δ 4.79 (s, 2H) of isochroman **255**. Both peaks appeared as single resonances in their respective regions of the spectrum. Whilst conversion was poor, this result implied that DMP **372** could be used to functionalise isochroman **255**.

Reaction optimisation was attempted with DMP **372** as the oxidant for oxonium ion formation (**Table 5**). However, as conversion couldn't be increased above 2%, the use of DMP **272** as an oxidant with 1,3,5-TMB **361** as the nucleophile was abandoned.

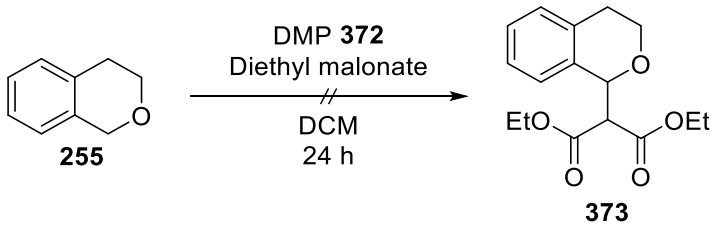
Both triethylamine and pyridine were trialled as a basic additive as the desired oxidation with DMP produces two equivalents of acetic acid (**Scheme 114**). It was proposed that the use of basic conditions could quench this acetic acid produced by DMP **372** reduction. However, in both cases no conversion was seen.

Table 5: DMP and 1,3,5-trimethoxybenzene screening conditions

Solvent	Additive	Temperature	Time (h)	% Conversion
Dichloromethane	None	Room Temp	24	1
Dichloromethane	None	Room Temp	72	2
Dichloromethane	NEt_3	Room Temp	24	0
Dichloromethane	Pyridine	Room Temp	24	0
MeCN	None	Room Temp	24	1
MeCN	None	75 °C	24	2
Dichloromethane	None	40 °C	72	1*

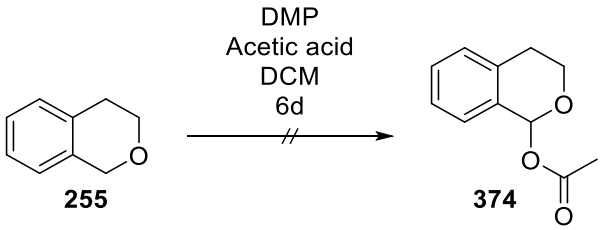
**This reaction saw another unknown product forming in a slightly larger, but still minor, quantity.*

Despite the limited success of DMP **372** when using 1,3,5-TMB as a nucleophile, several other nucleophiles were trialled in an attempt to improve functionalisation. If increased conversion was observed it would have suggested that the lack of conversion with 1,3,5-TMB was due to the nucleophile itself rather than DMP **372**. Initially diethyl malonate was used without a base to increase the nucleophilicity of diethyl malonate. This was due to the previous reactions with a basic additive seeing a complete lack of conversion (**table 5**, entries 3 and 4). No conversion was seen here either (**Scheme 116**).



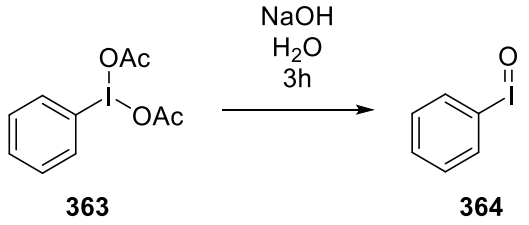
Scheme 116: Attempted DMP oxidation with diethyl malonate nucleophile

The DMP **372** mediated reaction was attempted again using acetic acid as a possible nucleophile, in this case with 5 equivalents. Whilst a stoichiometric amount of DMP **372** was used only trace amounts of **255** were present in crude ^{1}H NMRs despite poor conversion. However, no conversion to **374** was seen after 6 days (**Scheme 117**).



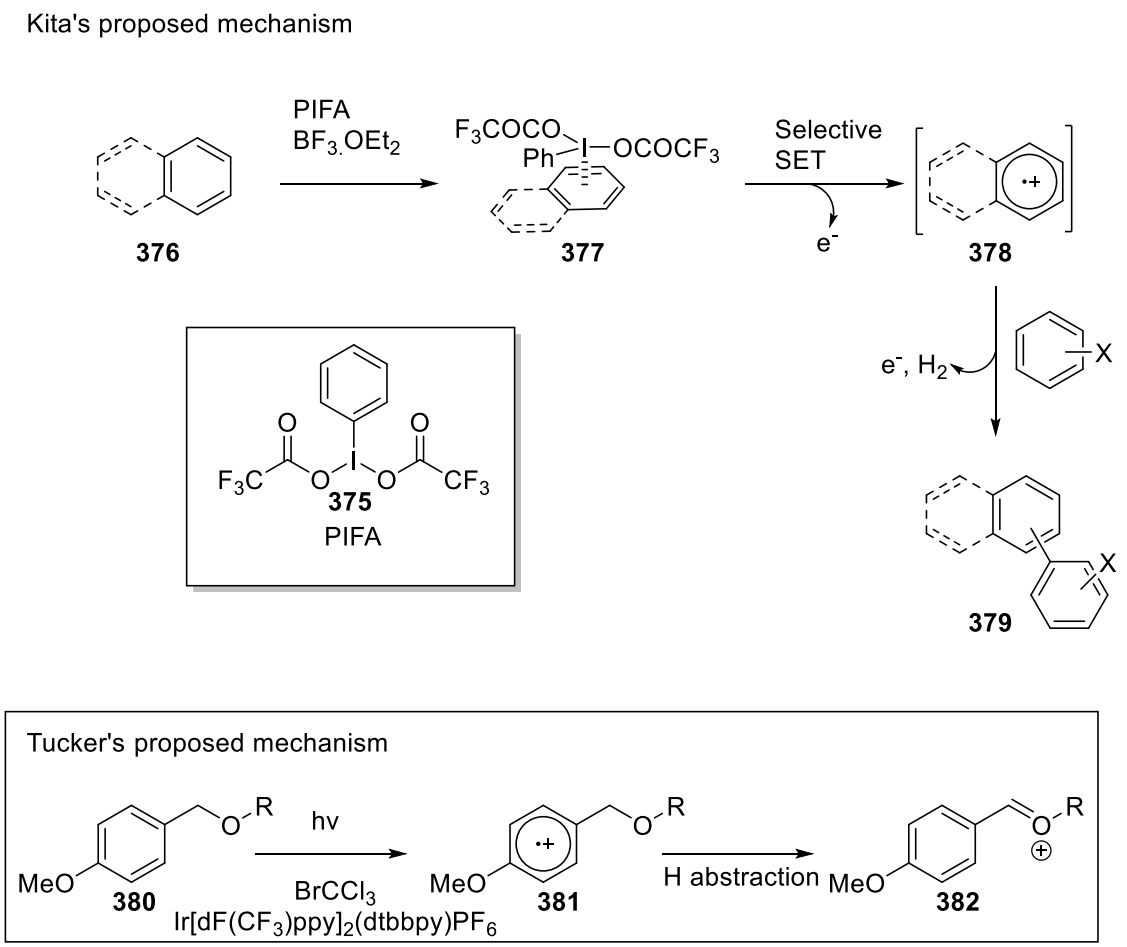
Scheme 117: Attempted DMP oxidation with acetic acid nucleophile

At this point, the use of DMP **372** as a reagent for C-H functionalisation was abandoned due to the inability to improve conversion beyond 2%. A harsher reagent, iodosobenzene **364**, was synthesised from (diacetoxyiodo)benzene **363** with the use of a strong base. The resulting product is a highly insoluble heat and shock sensitive material when fully dry and as such was kept slightly wet. As it is insoluble, it was not possible to obtain a ^{1}H NMR spectrum. The IR obtained matches that of Woggon *et al*., but this is not a sensible method of determining purity.[176] Plattner *et al*., from whom the synthetic route was obtained, stated that their product was determined to be 99.5% purity by iodometric titration, however, as both the product and starting material are $I^{(III)}$ species, a method of differentiating via iodometric titration was not apparent to us.[177] The synthesised material was not used in screening reactions as we could not be certain of its identity and it proved to be insoluble in every solvent in which dissolution was attempted.



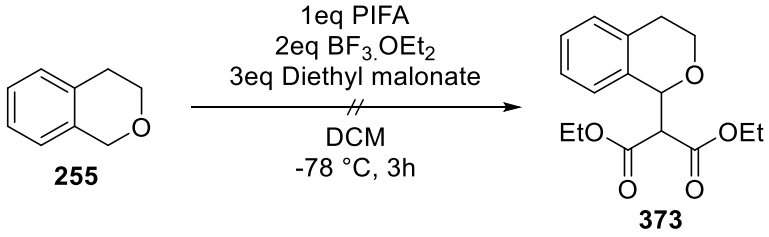
Scheme 118: Synthesis of iodosobenzene 364[177]

It was at this point that a paper by Kita *et al*. was found utilising [bis(trifluoroacetoxy)iodo]benzene (PIFA) **375** to mediate a radical based cross coupling reaction (**Scheme 119**).[178] The initial reaction intermediate after single electron transfer resembles that of the iridium mediated PMB deprotection as postulated by Tucker *et al*. (**Scheme 119**)[179] Though Kita *et al*. believe their reaction to be a cross coupling via radical cation, they provide no clear mechanism for this actual process, instead providing a basic Scheme (**Scheme 119**).[178]



Scheme 119: PIFA mediated radical cross coupling[178]

By analogy, a possible functionalisation of isochroman **255** with PIFA **375** was considered as the radical cation **378** generated appears to be similar to that **381** formed prior to oxocarbenium ion **382** generation in iridium catalysed PMB deprotection (**Scheme 120**).[179] No conversion to the desired product or any other was observed. The PIFA **375** used was later seen to be partially degraded by ^{1}H NMR and the $BF_3.OEt_2$ discoloured, a usual sign of degradation.

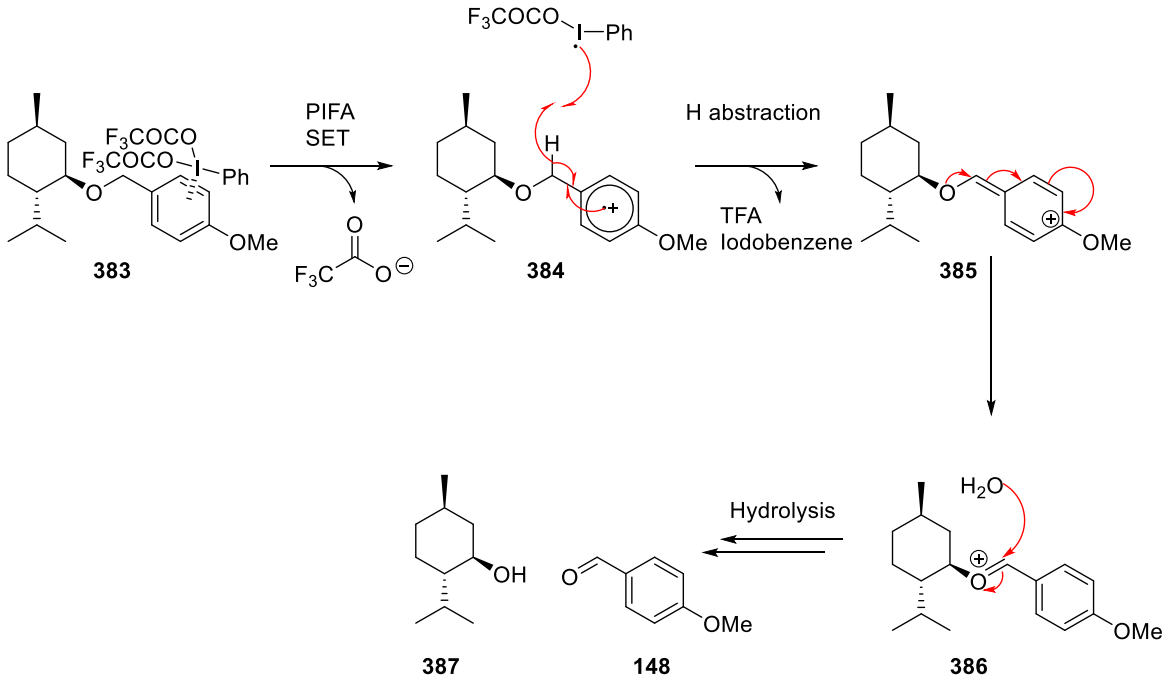


Scheme 120: Attempted PIFA mediated functionalisation

As this reaction failed to form the desired product, a control experiment was planned to ensure PIFA **375** could perform the desired oxidation. Using a substrate from the original PMB deprotection paper (**Scheme 121**) PIFA was

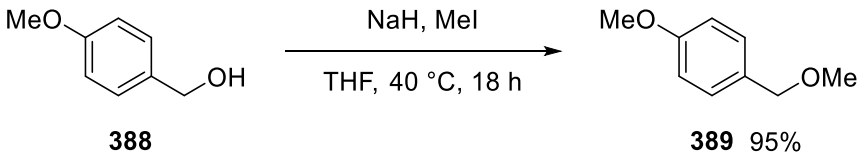
used, instead of an iridium photocatalyst, as the oxidant. This attempted deprotection was successful, seeing almost complete conversion to *p*-anisaldehyde **148** and L-menthol **387** as predicted after 3 hours.

A plausible mechanism for this (**Scheme 121**) could be via the same radical cation reactive intermediate **384** as proposed in the Tucker and Kita papers.[178,179] This intermediate could then undergo a hydrogen abstraction conceivably involving PIFA's initial degradation product to form iodobenzene and trifluoroacetic acid to give the desired oxonium ion **385**. This could be hydrolysed into *p*-anisaldehyde **148** and L-menthol **387**.



Scheme 121: Potential mechanism for PMB cleavage with PIFA

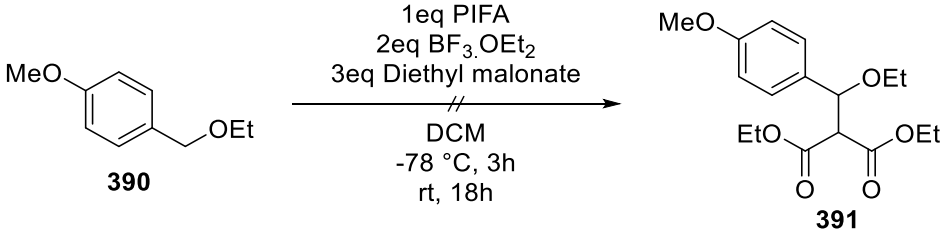
This successful use of PIFA **375** as a method of PMB removal suggested that it might form the oxocarbenium ion intermediate **386**. Potentially this could be intercepted by a nucleophile other than water. Therefore simple PMB ethers were prepared with which to attempt functionalisation. Methylation of *p*-methoxybenzyl alcohol **388** by deprotonation and treatment with iodomethane in THF was performed. The analogous ethyl ether, *p*-methoxy(ethoxymethyl)benzene **390**, was prepared from *p*-methoxybenzyl bromide and ethanol in THF, albeit with a much lower yield of 23% due to the ethanol being used as supplied with no additional precautions against likely adventitious water.



388 **389** 95%

Scheme 122: Synthesis of *p*-methoxy(methoxymethyl)benzene 389

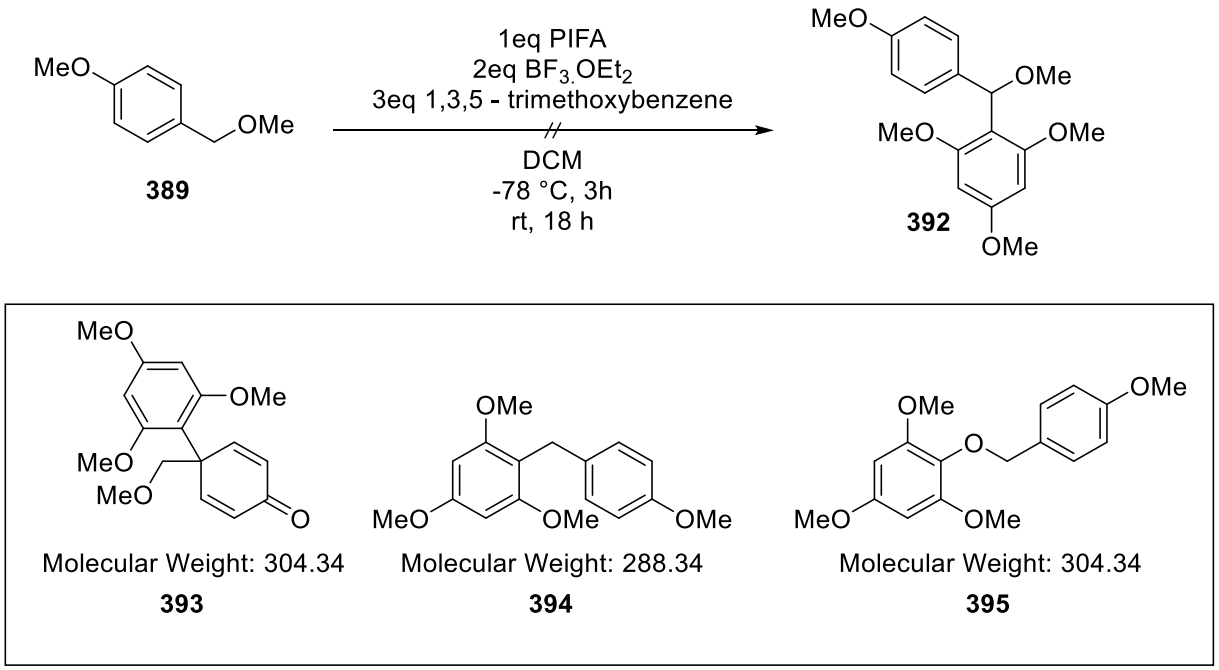
The first reaction attempted was with **390** and diethyl malonate, and was monitored via TLC. Diethyl malonate was chosen as a nucleophile, as the Kita *et al*. paper showed coupling between aromatics and for an initial reaction we wanted to avoid this further complication by using a non-aromatic nucleophile.[178] From TLC it was apparent that within three hours of the reaction commencing *p*-anisaldehyde **148** was present, but there was no evidence of any functionalised product (**Scheme 123**). The simplest explanation was that the oxonium ion was formed but was not reacting with the desired nucleophile and was instead hydrolysed either during workup or reaction.



390 **391**

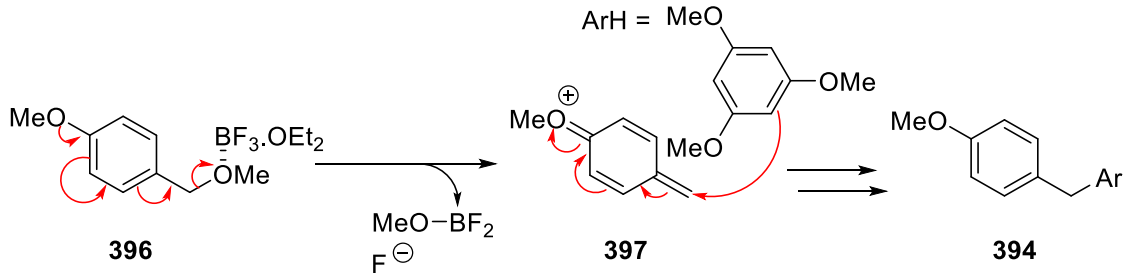
Scheme 123: Attempted functionalisation of *p*-methoxy(ethoxymethyl)benzene 390 with PIFA

In a second attempt, 1,3,5-TMB was used as a nucleophile because it had previously given conversion when diethyl malonate had not (**Table 5, Scheme 116**). As before, *p*-anisaldehyde **148** appeared within three hours and ceased to appear after 24 h. However, the desired product was not formed, instead the ^{1}H NMR suggested one of three plausible structures (**Scheme 124**).



Scheme 124: Attempted functionalisation of *p*-methoxy(methoxymethyl)benzene 389 with PIFA

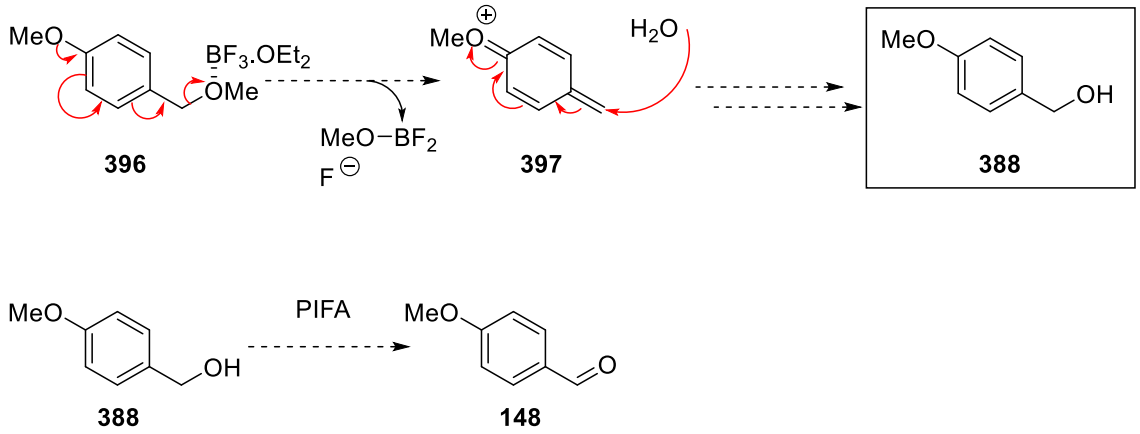
The structure was determined by a combination of ^{1}H NMR and LCMS which gave a mass peak of 289.20, corresponding to structure **394**+H^{+} (**Scheme 124**). The formation of this product was not compatible with our initial mechanism (**Scheme 121**). A plausible mechanism to account for the formation of **394** would most probably involve $BF_3.OEt_2$ acting as a Lewis acid to eliminate the methoxy group at the benzyl position. The resultant quinone-methine like intermediate **397** could then undergo nucleophilic attack from 1,3,5-TMB (**Scheme 125**).



Scheme 125: Alternate mechanism to account for 394

This reaction pathway can also be used to account for the formation of *p*-anisaldehyde if water were to act as the nucleophile to form PMB alcohol **388** which would then be oxidised by PIFA **375** in an analogous method to PIDA oxidation of alcohols (**Scheme 114**). Therefore the L-menthol deprotection observed previously was not proof of the radical mechanism.

In order to probe the mechanism of this reaction a range of conditions were attempted. Firstly, in order to test if the reaction was in fact $BF_3.OEt_2$ mediated, with PIFA **375** acting only to oxidise the resulting PMB alcohol **388** (**Scheme 126**), *p*-methoxy(methoxymethyl)benzene **389** was reacted with $BF_3.OEt_2$ only. This was considered as other hypervalent iodine compounds such as IBX, DMP **363** and PIDA **372** have all found use as oxidants.[173,175,180–182] If this hypothesis was correct, the resulting products would be methanol, which would evaporate, and PMB alcohol **388**, which would be observed. However, the *p*-methoxy(methoxymethyl)benzene **389** degraded into a complex mixture by TLC both pre- and post-aqueous workup. This complex mixture could not be separated, giving no conclusive answer.

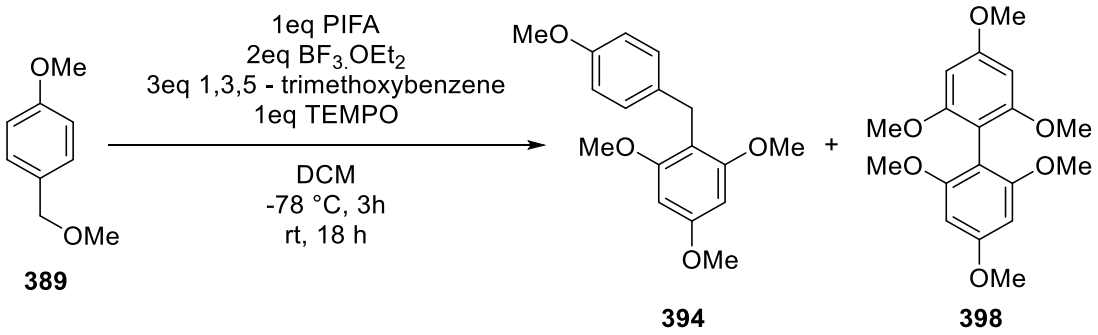


Scheme 126: Alternate mechanism for *p*-anisaldehyde formation

In order to see if PIFA **375** could act as an oxidant for any PMB alcohol formed during reaction, the two were reacted together under the standard conditions for the PIFA/$BF_3.OEt_2$ reaction, but without the $BF_3.OEt_2$ present. This gave a complex mixture of products that could not be separated via column chromatography but which crucially lacked a diagnostic aldehyde peak.

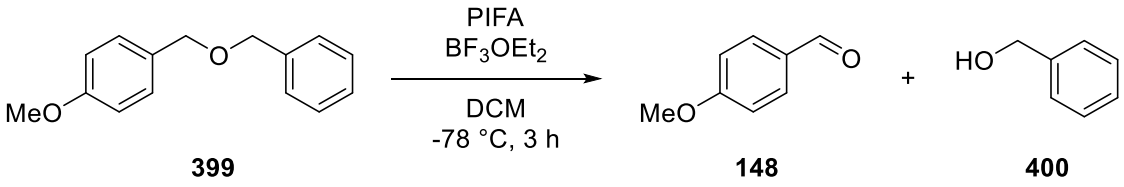
When PMB alcohol **394** was reacted with both PIFA **375** and $BF_3.OEt_2$ under the standard conditions as discussed above, full conversion was seen to *p*-anisaldehyde **148** by NMR, with no starting material remaining. This showed that a benzyl alcohol, if formed, could be oxidised to the aldehyde that had been observed in previous reactions. However, this formation could be accounted for by both proposed reaction pathways (**Schemes 121 and 125**), with the latter seeming more likely.

TEMPO is generally known to act both as a radical inhibitor and initiator dependent on reaction. TEMPO was therefore added as an additive to the reaction mixture in order to see if it affected the reaction or trapped some form of radical intermediate (**Scheme 127**). This gave the same product **394** as before, along with a trace of 1,3,5-trimethoxybenzene dimer **398**. This could be formed via a PIFA **375** mediated radical cross coupling as shown by Kita *et al*. (**Scheme 127**).[178] The mechanism shown in **Scheme 125** seemed more likely due to the same product being obtained despite the presence of TEMPO.



Scheme 127: PIFA mediated reaction with TEMPO

In order to probe whether the selection of which alcohol to oxidise was purely steric or had an electronic bias, it was decided to prepare 1-((benzyloxy)methyl)-4-methoxybenzene **399**. Benzyl alcohol **400** and PMB chloride were reacted with NaH in THF to give **399** in a 79% yield. Treatment of **399** with the conditions used as standard previously (**Scheme 128**) gave a mixture of only the benzyl alcohol **400** and *p*-anisaldehyde **148**, suggesting an electronic bias for PIFA oxidation. This would help explain why menthol wasn't oxidised (**Scheme 121**).



Scheme 128: PIFA deprotection of 1-((benzyloxy)methyl)-4-methoxybenzene 399

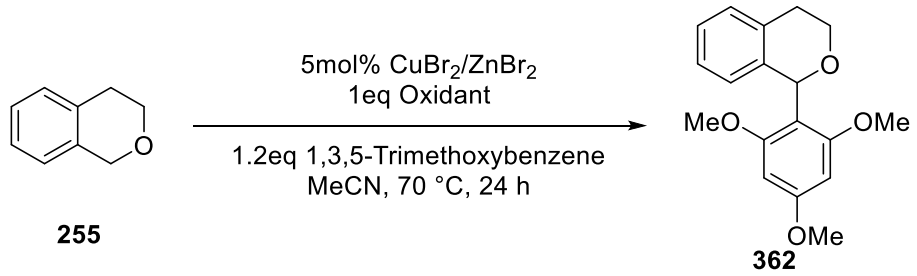
The evidence obtained mostly suggested that the Lewis acid mediated route was the mechanism of deprotection and not that of the desired radical based route. This is due to the failure to synthesise the desired product **392** and instead seeing the formation of **394**, which could not be explained satisfactorily with a radical

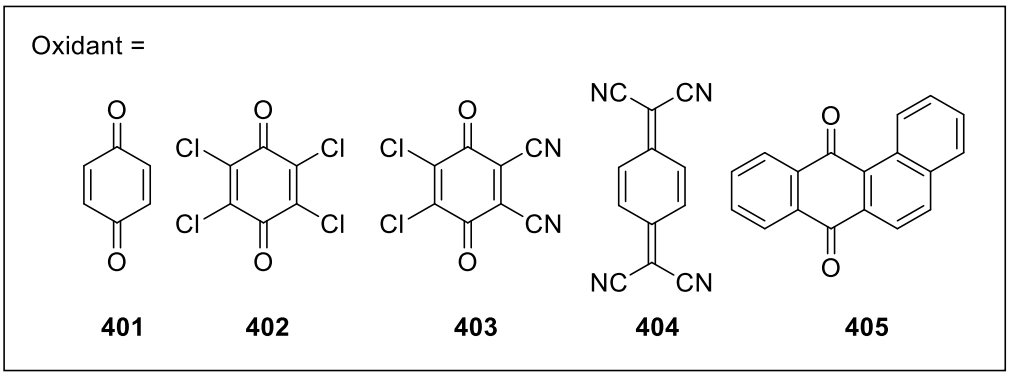
mechanism. With this in mind, attention was turned away from hypervalent iodine as an oxidant and back to more traditional hydride acceptors such as quinones.

2.3.2 Isochroman and Isochromene

2.3.2.1 Isochroman

Previous work within the group found that the best conversion of isochroman **255** to **362** used benzoquinone as an oxidant with a 5 mol% loading of each of $CuBr_2$ and $ZnBr_2$ with 8% conversion seen after 24 h. In an attempt to improve this, other oxidants were screened under identical conditions to those used previously within the group (**Schemes 113 and 129**). These were heated in sealed tubes under nitrogen, aliquots were taken at 24 h. The acetonitrile was then removed via rotary evaporation and the metal salts removed via filtration with $CDCl_3$. Conversion was again obtained comparing δ 6.69 (1H, d, *J* = 7.7 Hz, ArC*H*(Ar)O) in $CDCl_3$ of the product **362** to δ 4.79 (s, 2H) of isochroman **255** due to both peaks appearing as single resonances in their respective regions of the spectrum.



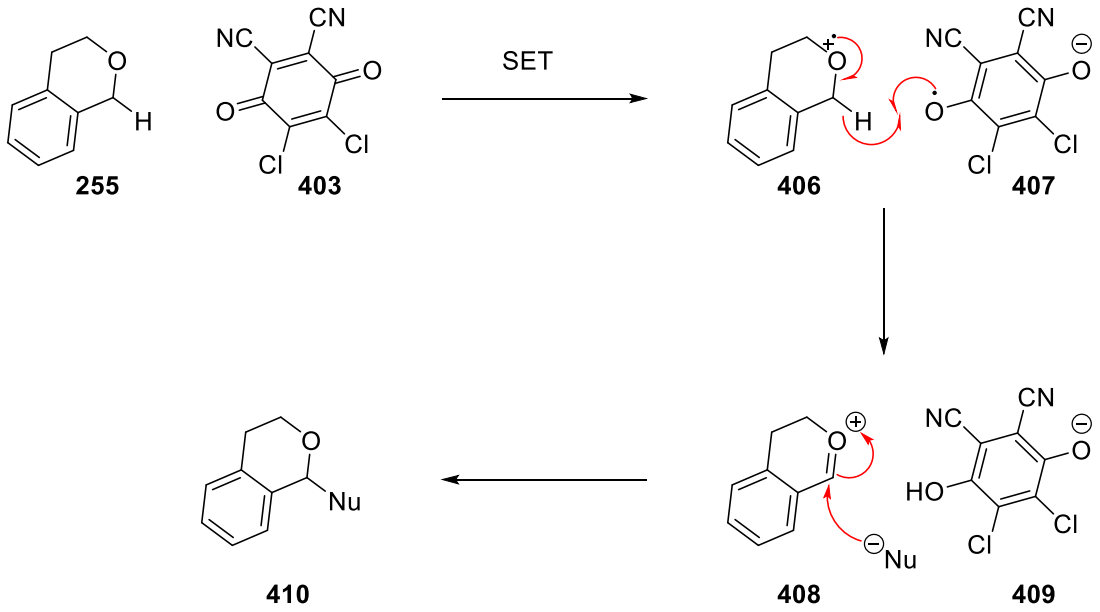


Scheme 129: General functionalisation procedure and trialled oxidants

Table 6: Comparison of various hydride acceptors

Oxidant	Temperature (°C)	% Conversion after 24 h
401	70	8
402	70	<5
403	60	12
404	70	Trace
405	70	Trace

From the initial experiments DDQ **403** seemed to be the best choice of oxidant for further trials, outperforming all others, albeit with a low 12% conversion. Whilst we had initially proposed the oxidation occurring via an Oppenauer oxidation-like mechanism, the improvement shown by DDQ could potentially have been achieved via a SET mechanism (**Scheme 130**).



Scheme 130: Potential SET mechanism for the oxidation of isochroman

A very similar mechanism was proposed by Zhang *et al*. in 2009 in their functionalisation of isochroman with simple ketones.[126] However, as both mechanisms would generate the same oxonium ion **408** it was not considered important to investigate further the mechanism at this point in time. If the distinction between routes were to be viewed as relevant to the reaction, monitoring via EPR could be performed. There was no change in performance

when the reaction with DDQ as oxidant was repeated with the addition of TEMPO as a radical scavenger. With DDQ as the best performing oxidant under the initial reaction conditions, a range of modifications were trialled in an attempt to increase conversion via screening of Lewis acids, solvents, and temperature, with conversion measured by ^{1}H NMR after 24 h.

Table 7: Brief reaction optimisation with MeCN and solvent screen

Solvent	Temperature (°C)	Lewis Acid	% Conversion
MeCN	80	$CuBr_2$	9
MeCN	80	$ZnBr_2$	7
MeCN	80	CuCl	9
MeCN	150*	$CuBr_2$, $ZnBr_2$	5
MeCN	80	$CuBr_2$, $ZnBr_2$	10
Toluene	90	$CuBr_2$, $ZnBr_2$	24
Toluene	110	$CuBr_2$, $ZnBr_2$	12
DMSO	110	$CuBr_2$, $ZnBr_2$	0
Benzonitrile	110	$CuBr_2$, $ZnBr_2$	Trace
DMF	110	$CuBr_2$, $ZnBr_2$	6
Xylenes	110	$CuBr_2$, $ZnBr_2$	Trace
Chlorobenzene	110	$CuBr_2$, $ZnBr_2$	0
Neat	80	$CuBr_2$, $ZnBr_2$	0

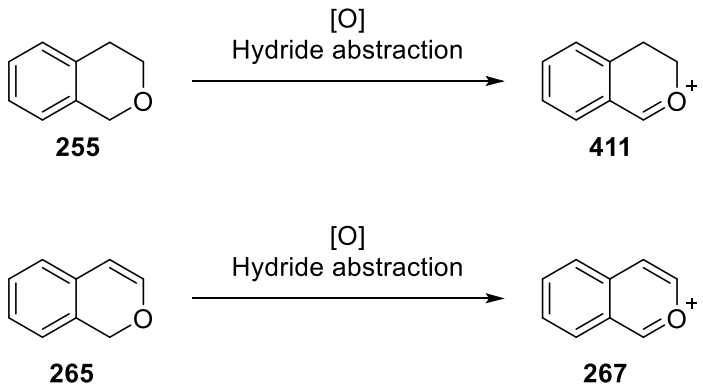
**Reaction performed via microwave irradiation for 2 h*

Toluene with a mixture of 5 mol% $CuBr_2$ and 5 mol% $ZnBr_2$ at 90 °C (entry 6) was found to give the best conversion at 24%. However, this was still far lower than desired and the reaction was capricious. As such, the decision was made to turn to the synthesis of isochromene to prepare a more active hydride donor.

2.3.2.2 Isochromene Synthesis

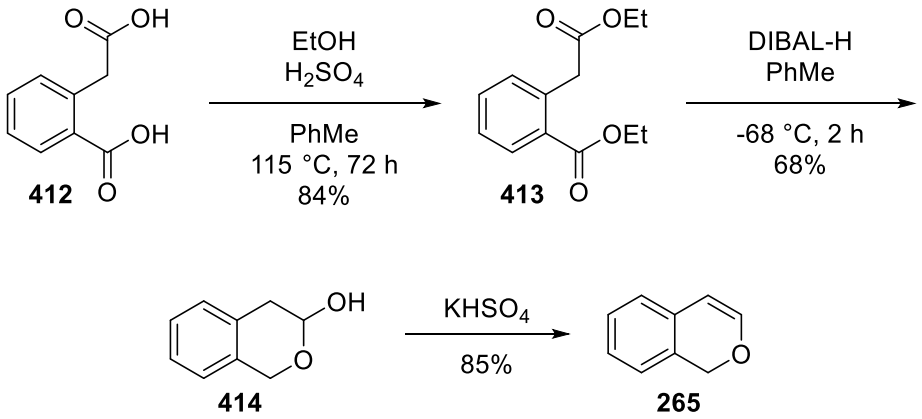
As limited progress had been made with isochroman **255**, attention was turned instead to isochromene **265**. The generation of the oxonium ion **267** should be more favourable compared to that of isochroman **411** due to hydride abstraction leading to an aromatic intermediate for isochromene **267**, (**Scheme 131**).[130] It was thought that the low conversion previously seen in **Scheme 129** could be due to difficulty in hydride abstraction rather than the nucleophile failing to react with a generated oxonium ion, assuming lower activation energy to reach the

more stable intermediate. Related work has similarly shown an increase in reactivity for isochromene relative to isochroman (**Scheme 78**).[130]



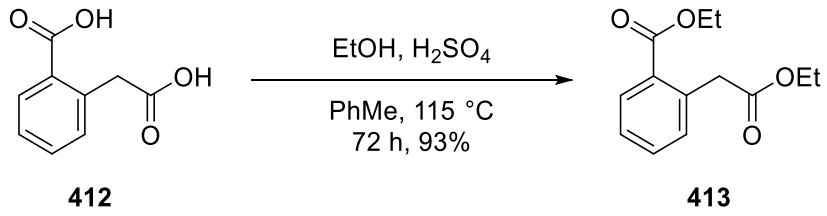
Scheme 131: Reactive intermediates for isochroman 255 and isochromene 265

A synthetic route to isochromene is known in the literature (**Scheme 132**) and was followed directly.[183]



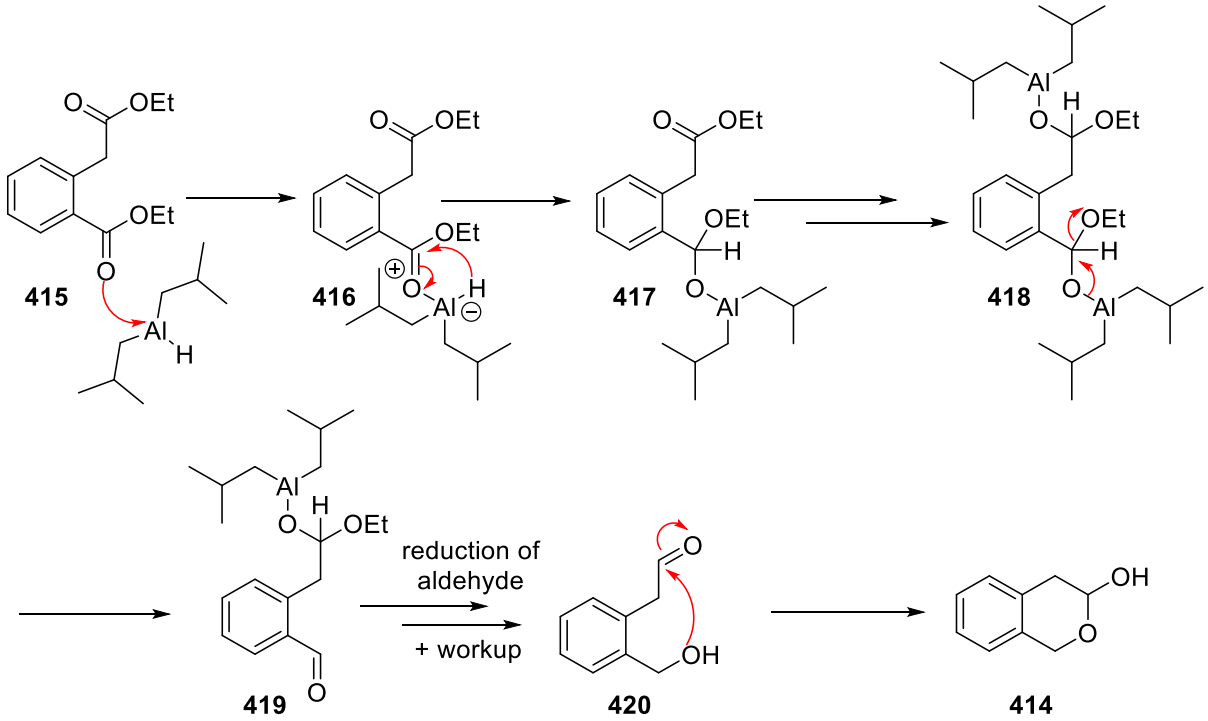
Scheme 132: Literature route to isochromene[183]

The first step for this route was a simple Fischer esterification of homophthalic acid **412** and ethanol to give diethyl homophthalate **413** as a yellow oil.[183] Toluene was required as a solvent as homophthalic acid is insoluble in ethanol. This proceeded in generally good yields of up to 93% (lit 84%, **Scheme 133**).[183]



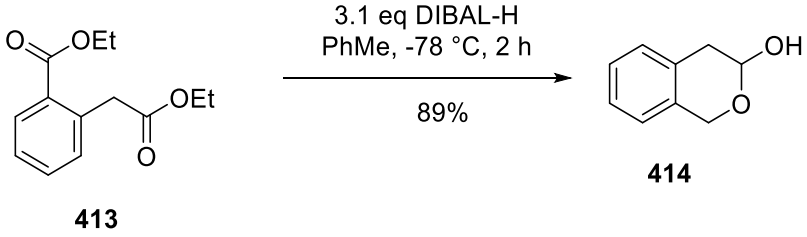
Scheme 133: Synthesis of diethyl homophthalate 413

Following this, a cyclisation was attempted using DIBAL-H, with the proposed mechanism in **Scheme 134**. The unusual selectivity is believed to come from the relative ease of collapse of the benzylic aluminium hemiacetal compared to that further from the aromatic ring, as a more stable aldehyde is formed which is then reduced in the presence of the tetrahedral intermediate.



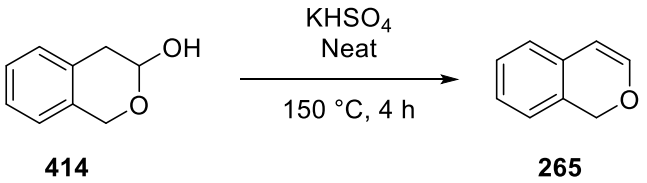
Scheme 134: Proposed mechanism for 3-hydroxyisochroman formation

This procedure was low yielding with yields of 40-45% (lit 68%)[183,184] and tended to proceed with difficulty with large amounts of over-reduction leading to the diol product being observed. The over-reduction was generally mitigated through the use of a cannula rather than syringe to add the DIBAL-H slowly, keeping the temperature at -78 °C for the duration of the reaction. The yield was vastly improved when the reaction scale was increased to 5 g (**Scheme 135**).



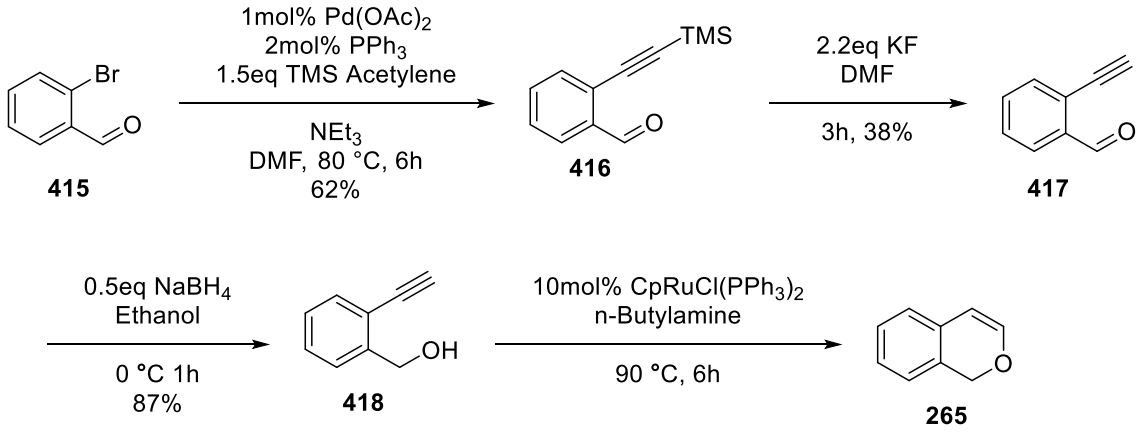
Scheme 135: DIBAL-H mediated cyclisation to form 3-hydroxyisochroman 414[184]

The dehydration reaction conditions reported were very brief.[183] The neat mixture of **414** and $KHSO_4$ was heated at 1 atm for 4 h (**Scheme 136**). The desired product **265** was visible in the crude ^1H NMR as the major product, with no starting material remaining, however, when purification via Kugelrohr vacuum distillation was attempted, only degradation products were obtained. Likewise, purification via column chromatography could not separate isochromene from another unknown impurity, rendering it too impure to be used as a methodological starting material.



Scheme 136: Dehydration to form isochromene

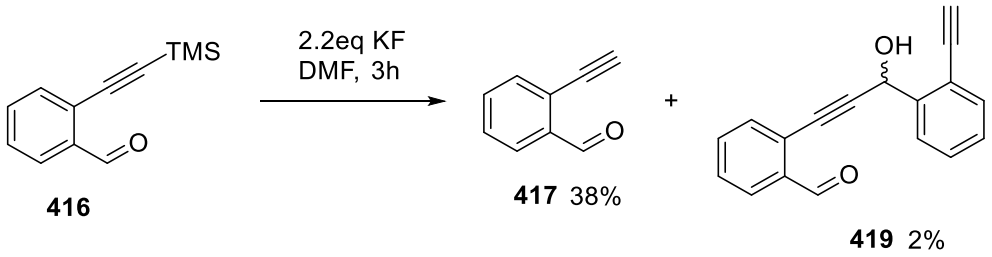
At this point an alternate method of isochromene synthesis was discovered following a literature search.[185] Here isochromene was formed via a cyclisation of 2-ethynyl benzyl alcohol **418** (**Scheme 137**) [185] A synthetic route to **418** was then planned from 2-bromobenzaldehyde **415**. A paper following this route to **418** was then found and followed directly (**Scheme 137**).[186]



Scheme 137: Synthetic route to isochromene via 2-ethynyl benzyl alcohol 418[185,186]

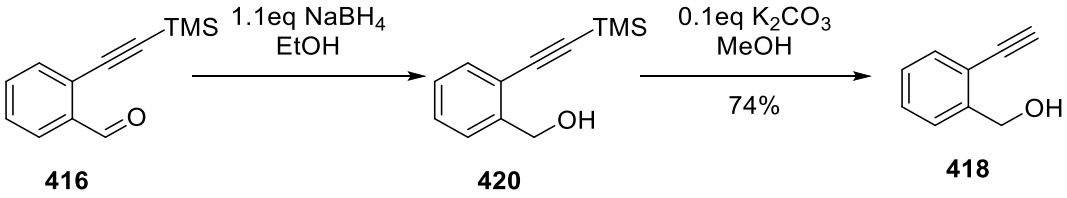
The Sonogashira reaction of 2-bromobenzaldehyde **415** and TMS acetylene gave 2-[(trimethylsilyl)ethynyl]benzaldehyde **416** in a 62% yield (lit. 90%) as a yellow liquid.[186] Removal of the TMS group with KF gave a poor yield of **417** (38%) with a mixture of byproducts, including a dimer byproduct **419**, which was isolated in a 2% yield. This dimer byproduct **419** could be formed by the

intermolecular addition of the alkynyl anion to the aldehyde to form a propargyl alcohol.



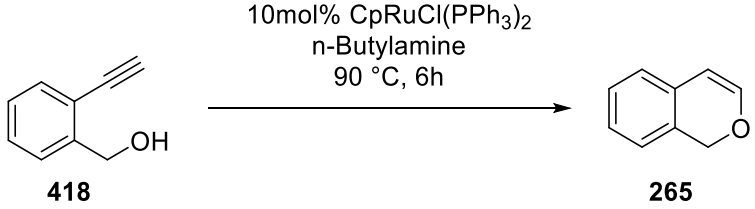
Scheme 138: TMS deprotection and side product formation

Due to the formation of the dimer product **419** and generally low yields, the order of the TMS deprotection and aldehyde reduction were reversed. The reduction of 2-[(trimethylsilyl)ethynyl]benzaldehyde **416** to the alcohol **420** was achieved with $NaBH_4$ in ethanol. Following workup the crude ^1H NMR contained only the desired product and 2-ethynylbenzyl alcohol in a 2:1 ratio and so was carried directly to the TMS deprotection. Treatment with K_2CO_3 in MeOH (**Scheme 139**) gave the desired product **418** in 74% over two steps.



Scheme 139: Alternate route to 2-ethynylbenzyl alcohol 418

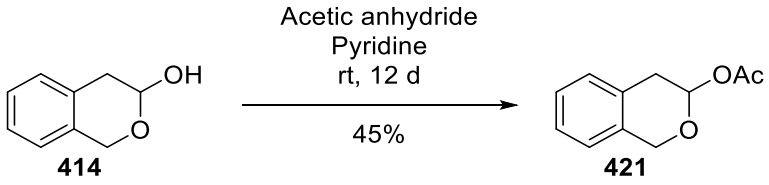
The prepared 2-ethynylbenzyl alcohol **418** was reacted with 10 mol% $CpRuCl(PPh_3)_2$ in *n*butylamine at 90 °C for 6 h. Within this time the starting material was consumed and the crude ^1H NMR showed the peaks indicative of isochromene **265**. However, there were many impurities present and due to the small scale of the reaction (13 mg) no purification was attempted.



Scheme 140: Ruthenium catalysed cyclisation[185]

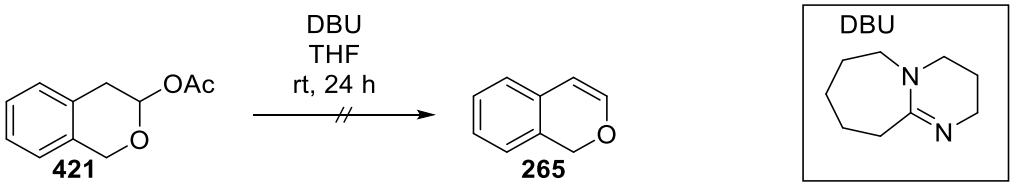
As this route requires a greater number of reactions than that using homophthalic acid, using materials of greater expense, with no clear advantage in terms of

yield, it was abandoned as a method of preparing isochromene **265**. Attention was therefore returned to the dehydration based isochromene preparation. An acetylation of 3-hydroxyisochroman was performed with acetic anhydride and pyridine with a 45% yield in order to provide a better leaving group.



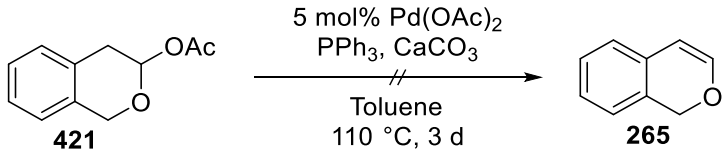
Scheme 141: Acetylation of 3-hydroxyisochroman 414

Dehydration was first attempted using DBU in THF at room temperature. This saw no conversion after 24 h so the reaction was repeated at 50 °C but this saw no improvement in conversion.



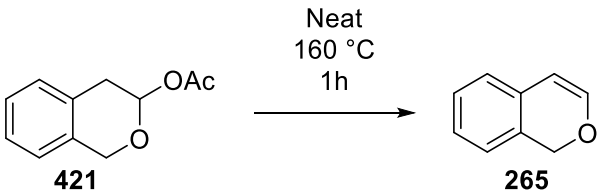
Scheme 142: Dehydration of 3-acetoxyisochroman with DBU

Following a search of the literature, a palladium catalysed elimination to form an alkene was found using palladium acetate and calcium carbonate in toluene.[187] This failed to provide any conversion even after 3 days of reflux despite the literature seeing full conversion after 2 h.



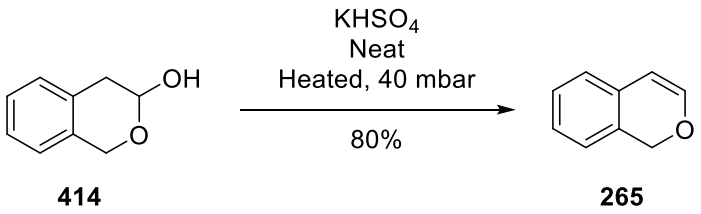
Scheme 143: Palladium catalysed isochromene formation

There had been difficulties obtaining a mass spec for 3-acetoxyisochromene **421** as it appeared to be degrading during the mass spec process. However, the major mass peak matched that of isochromene, suggesting that a decarboxylation was occurring at some point prior to data collection. With this in mind the controlled decarboxylation of **421** was attempted at 160 °C on a 2 mmol scale in an inert atmosphere. This did give isochromene as desired, but with an isolated yield of 3%, limiting its utility.



Scheme 144: Pyrolysis of 3-acetoxyisochroman 421

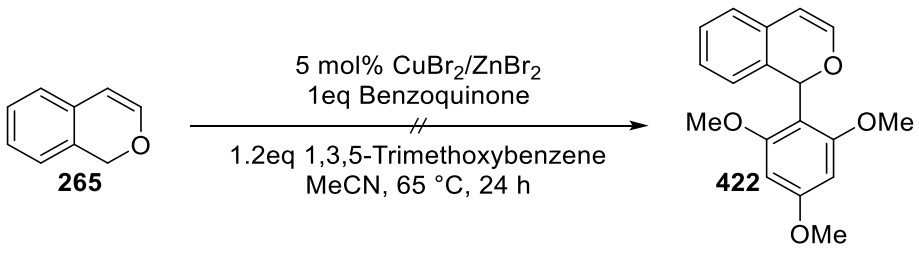
At this point we returned to the original route as this seemed to be the most promising of making isochromene, providing a method of purification could be found. This was discovered via the quick distillation of the starting material **414** through a short air column (Vigreux) under vacuum.[188] It was important to use a Bunsen burner rather than an oil bath in order to ensure the air column was hot enough for distillation. This gave the desired product as a yellow oil in 80% yield (**Scheme 145**). With pure isochromene obtained, cross-dehydrogenative couplings could be investigated.



Scheme 145: Synthesis of isochromene from 3-hydroxyisochroman

2.3.2.3 Oxidant Screening

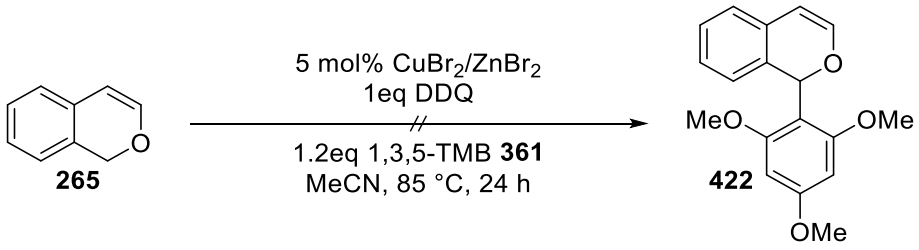
As isochromene **265** could be more amenable to oxidation than isochroman **255**, the initial conditions for CDC with benzoquinone were attempted (**Schemes 113 and 146**). No conversion to **422** was observed under these reaction conditions. It was thought this could be due to isochromene **265** less readily undergoing hydride abstraction than isochroman **255**.



Scheme 146: Initial attempted isochromene functionalisation

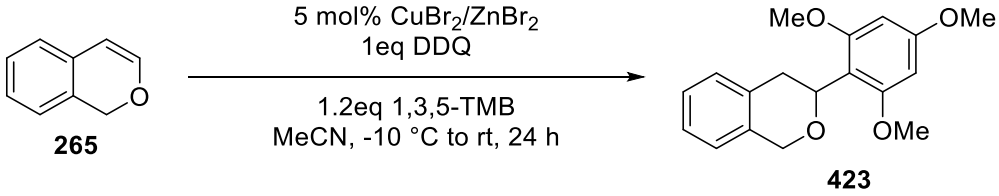
A range of nucleophiles (diethyl malonate, furan, phenol, allyl-TMS) were then screened with benzoquinone. However, no conversion was seen with any of the

screened nucleophiles, the reactions returning only starting material. The stronger oxidant DDQ was trialled as oxidant in place of benzoquinone with 1,3,5-TMB **361** as the nucleophile and conditions otherwise remaining the same. This showed full consumption of isochromene **265** within 5 minutes by TLC, degrading to a complex mixture over 24 h (**Scheme 147**).



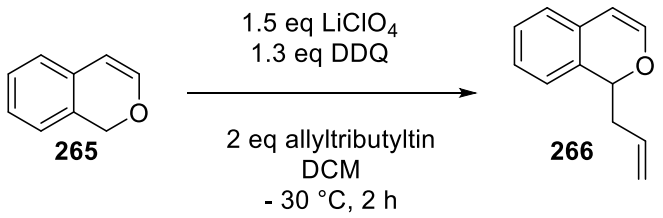
Scheme 147: Attempted isochromene functionalisation with DDQ

This degradation continued to be observed with decreasing temperatures until -10 °C at which point a product was formed after 24 h. Isolation by column chromatography gave **423** in a 16% yield (**Scheme 148**). Presumably, this could be formed by protonation then electrophilic substitution into the enol ether double bond. There was also a large amount of degradation and some trimethoxybenzene dimer was also isolated in trace amounts.



Scheme 148: Unexpected product 423 from DDQ oxidation at -10 °C

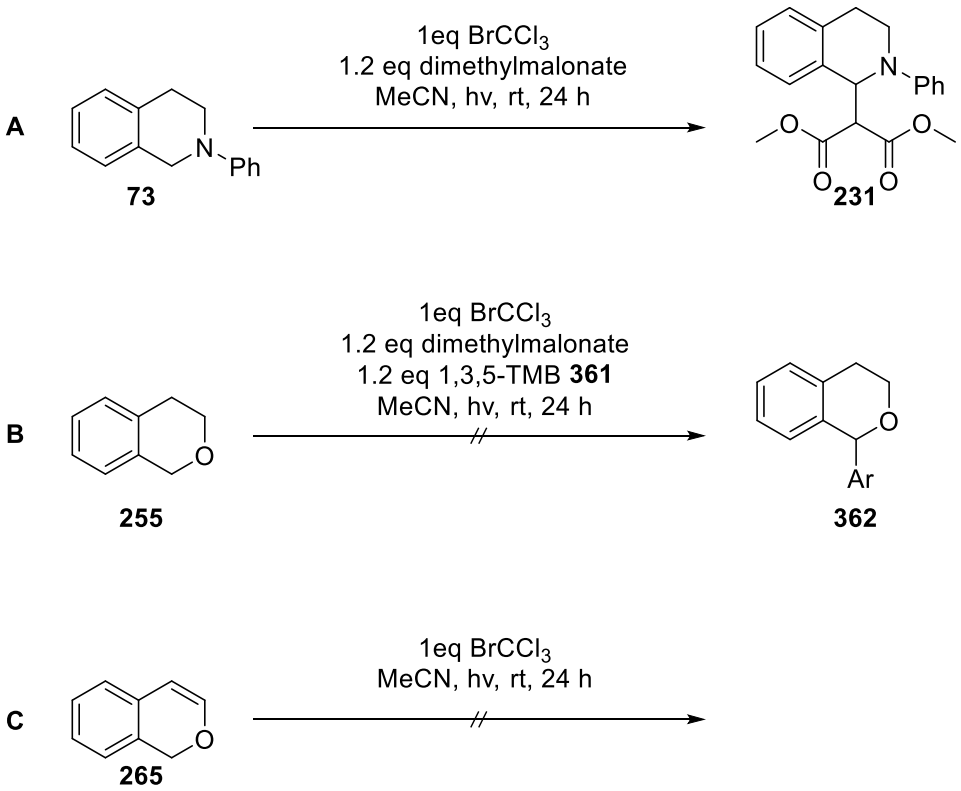
Finally, in order to examine 1,3,5-TMB as a nucleophile, a literature procedure was attempted both with the allyl-tin nucleophile used in the literature procedure and 1,3,5-TMB.[130] The desired product, 1-allyl isochromene **266** was isolated as per the literature in a 17% yield (lit. 79%), with large amounts of degradation observed by ^{1}H NMR.[130] When the reaction was repeated with 1,3,5-TMB as the nucleophile only degradation products were observed. At this point it was decided to move away from isochromene **265** functionalisation with DDQ **403** as our conditions did not see conversion to the desired product. Attention was turned to other methods of oxidation that do not rely on DDQ.



Scheme 149: Formation of 1-allyl isochromene

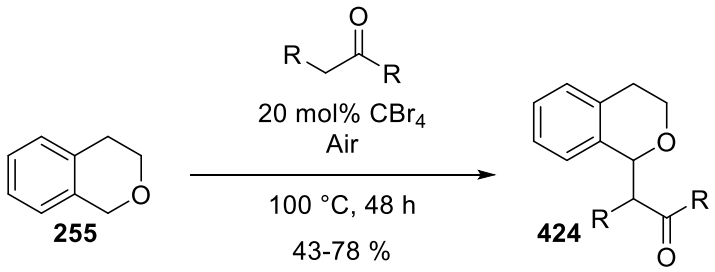
The functionalisation of the amine α-CH has been achieved using LED-sourced blue light to form polyhalogenated carbocations as the oxidant (**Scheme 150, reaction A**).[53] We speculated whether the generated CCl_3 radical could act in a similar manner with isochromene **165** or isochroman **255** to form the analogous oxonium cation. Isochroman **255** was used as a substrate rather than 2-phenyl-1,2,3,4-tetrahydroisoquinoline **73** with either dimethylmalonate or 1,3,5-TMB, the conditions otherwise remaining constant (**Scheme 150, reaction B**). Isochromene **265** was also used as a substrate for oxidation without a nucleophile, with the reaction monitored by ^{1}H NMR for the formation of chloroform (**Scheme 150, reaction C**).

In reaction **B** no conversion was seen, with only starting material observed by ^{1}H NMR and TLC. Isochromene **265** failed to show degradation when subjected to blue light in the reaction mixture, which would have shown its oxidation as discussed previously (**Scheme 147**). The literature procedure showed full conversion to the desired product after 24 h with aniline. This suggested that the desired CCl_3 radical was forming as required by the proposed mechanism for hydrogen abstraction. However, the absence of chloroform in the monitoring ^{1}H NMRs of the isochroman reactions suggest that the CCl_3 radical was not abstracting hydrogen from isochroman or isochromene.



Scheme 150: Attempted polyhalogenated carbocation mediated functionalisation

Several months after these light-mediated reactions were attempted Huo *et al.* published a paper using CBr_4 as a catalytic oxidant to functionalise isochroman in air at 100 °C as shown (**Scheme 151**).[189] This suggests that polyhalogenated carbons can find use as a method of generating an oxonium ion. However, there does not seem to be any particular use for this as a method of isochromene oxidation due to the high temperature required and the observed instability of the oxidised isochromene at even room temperature, as discussed above (**Schemes 147 and 150**).



Scheme 151: Literature CDC with CBr_4 and oxygen

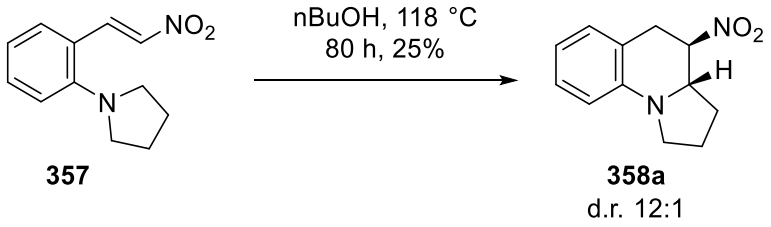
2.3.3 Conclusions

This chapter has focussed on attempts to functionalise the C-H bond adjacent to an ethereal oxygen. Ultimately, although the functionalisation of isochroman saw an improved conversion rate of 24%, up from the 8% previously reported within the group, no further progress was achieved. Due to a lack of success and the saturated nature of the field, the decision was made to investigate the functionalisation of C-H bonds intramolecularly via a 1,5-hydride shift. It was decided that this would give a greater chance of success and could use some more mature chemistry from within the group, namely the nitro-Mannich reaction.

2.4 The Functionalisation of C-H Bonds via a 1,5-Hydride Shift

2.4.1 Proposed Research

Since the 1,5-hydride shift is a fairly well studied method of forming carbon-carbon bonds via the *in situ* generation of a tethered cation and anion we proposed the use of a tethered nitroalkene as the hydride acceptor to generate a nitronate and an iminium ion that could then rapidly ring close via a 6-endo-trig cyclisation.[190,191] One example of this occurring was reported in the literature by Rabong *et al*., albeit in a very low yield with long reaction times, with stereochemistry assigned by NMR (**Scheme 152**).[171]

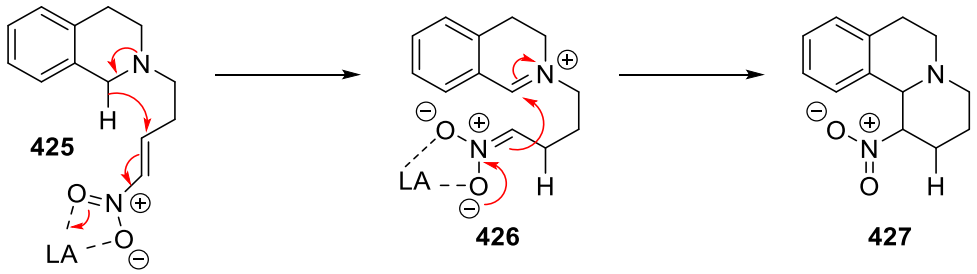


Scheme 152: Literature precedent for 1,5-hydride shift/nitro-Mannich cyclisation

We proposed to improve upon these conditions through a screening of Lewis and Brønsted acids as well as solvents. In addition, as Rabong *et al*. only report this transformation for **357** and for the piperidinyl derivative, in the latter case only by TLC, we were further seeking to improve the scope of this reaction beyond a single substrate. During the course of our studies into the scope of the 1,5-hydride shift mediated cyclisation we developed, Kim *et al.* published an analogous $Sc(OTf)_3$ catalysed cyclisation.[192] The authors reported yields between 62-99% albeit with a more limited substrate scope than was eventually achieved.

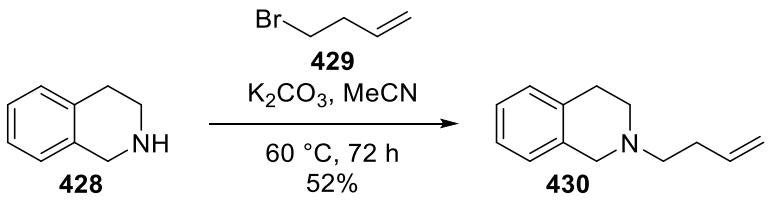
2.4.2 Synthesis of Starting Materials for Synthetic Development

The first nitroalkene **425** that we planned was expected to provide a simple example of an intramolecular nitro-Mannich reaction as shown in **Scheme 153**. It was proposed that **425** could be prepared from tetrahydroisoquinoline (THIQ) **428** in two steps. First the secondary amine of THIQ **428** could be reacted with homoallyl bromide **429**, with the resulting compound being nitrated directly as had previously been achieved with non-amine containing substrates.[193]



Scheme 153: Ring formation via a 1,5-hydride shift followed by nitro-Mannich cyclisation

As a result, the first synthetic target was **430**, (**Scheme 154**). The first reaction attempted towards this was an amination of **429** to give **430** with K_2CO_3 to act as a proton scavenger following S_N2 attack of homoallyl bromide to form an ammonium ion. This gave full conversion by ^1H NMR after 72 h (**Scheme 154**) in a reaction based upon the analogous procedure with allyl bromide to form 2-allyl-1,2,3,4-tetrahydroisoquinoline **430**.[194]

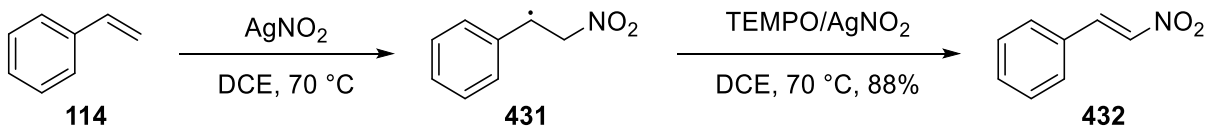


Scheme 154: Initial synthesis of 2-(but-3-en-1-yl)-1,2,3,4-THIQ

A modification of this reaction with catalytic quantities of KI was used to shorten the reaction time to 18 h through a Finkelstein reaction.[195] This modified reaction proceeded well, giving an 81% yield of **430** as a brown oil that was judged >95% pure by ^1H NMR following removal of baseline impurities with a silica plug.

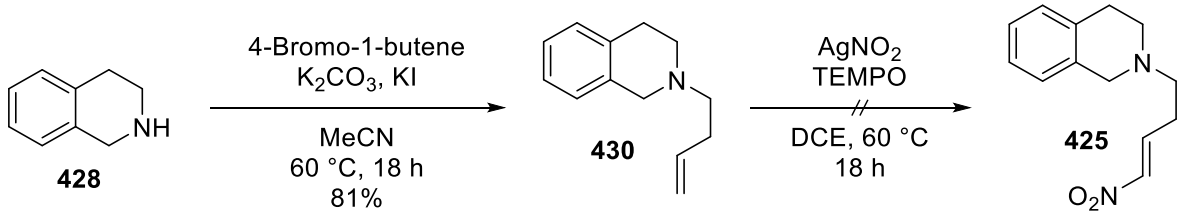
A method of directly preparing nitroalkenes from alkenes was developed by Maity *et al*.[193] Here an NO_2 radical adds to an alkene to generate a carbon centred

radical **431**.[193] TEMPO is then reduced via hydrogen abstraction to regenerate the alkene, exclusively giving the *E* isomer (**Scheme 155**).



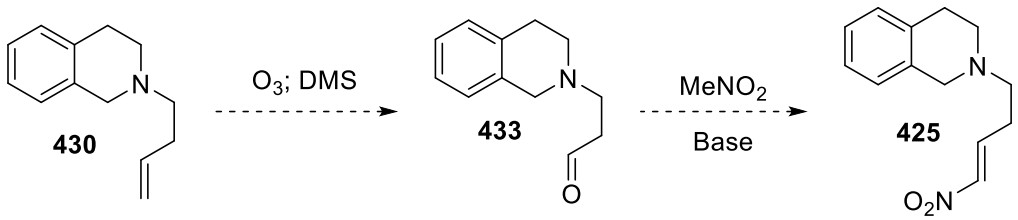
Scheme 155: Literature nitration of alkene with $AgNO_2$/TEMPO[193]

The nitration conditions developed by Maity were applied to **430** (**Scheme 156**). However, this nitration did not proceed as desired, causing degradation into a mixture of products with no clear formation of the desired nitroalkene. This could be due to the amine in **430** chelating to the $AgNO_2$ or TEMPO oxidising **430**. There are no literature examples of this reaction being performed successfully on amine containing substrates.[193]



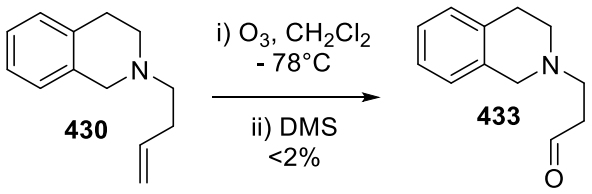
Scheme 156: Synthetic route to nitro-Mannich precursor

A new route for nitroalkene synthesis using a modified Henry reaction with nitromethane was considered. One possible route to the aldehyde required could be from **430** via ozonolysis (**Scheme 157**).



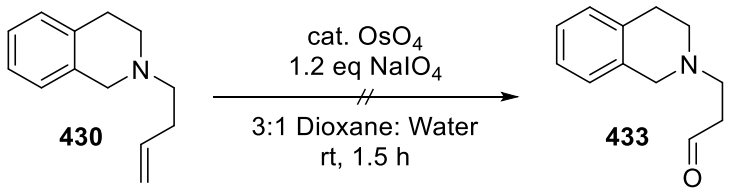
Scheme 157: Alternate route to desired nitroalkene 425[196]

Ozonolysis of **430** was attempted, giving **433** in trace quantities (10 mg, 2%) with impurities present and all starting materials consumed. The product was not successfully isolated, instead coeluting with a mixture of complex degradation products when purification was attempted via column chromatography (EtOAc) (**Scheme 158**).



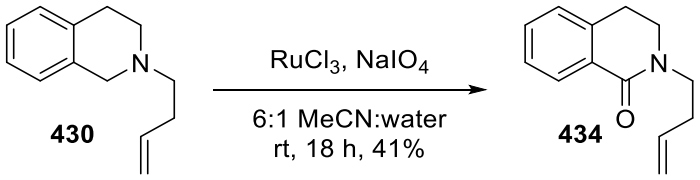
Scheme 158: Ozonolysis of 430

As traditional ozonolysis failed, a Lemieux-Johnson oxidation, an alternate "chemical ozonolysis", was attempted with osmium tetroxide and sodium periodate (**Scheme 159**). This was performed with a mixtutre of dioxane and water as the solvent but ^{1}H NMR showed mostly starting material and degradation products after 1.5 h, with no aldehyde peaks present, the starting material being recovered in an 84% yield.



Scheme 159: Lemieux-Johnson oxidation of 430

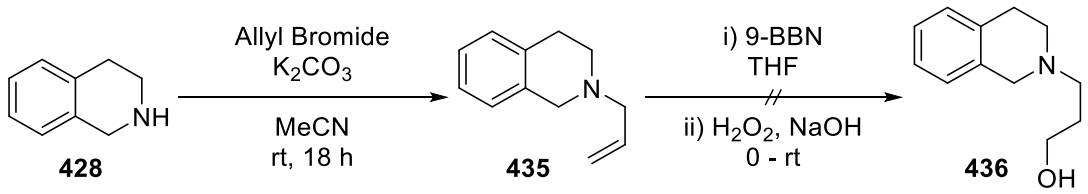
A second "chemical ozonolysis" with ruthenium chloride and sodium periodate was attempted.[197] This gave amide **434** as a brown oil (41%) rather than the desired aldehyde (**Scheme 160**). A subsequent search of the literature showed ruthenium oxide has been used as a method of oxidising amines to amides.[198] The ruthenium oxide generated in situ from the reaction of ruthenium chloride and sodium periodate (**Scheme 160**) selectively oxidised the benzylic amine of **434** over cleaving the alkene.



Scheme 160: Formation of 434 with $RuCl_3$ catalysis

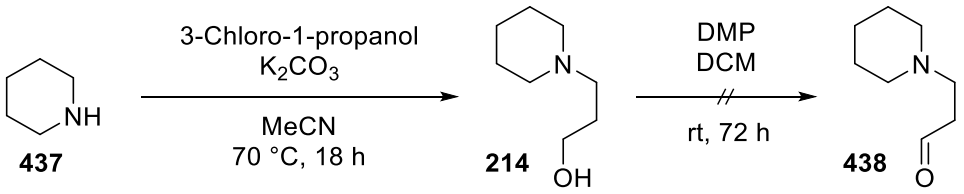
Oxidation of a precursor alcohol **436** was considered as a route to the aldehyde **433**. We thought the alcohol **436** could come from the hydroboration of **435**. Alkene **435** was prepared by reaction of allyl bromide and **428** in a 43% yield (lit. 53%) (**Scheme 161**).[194] Hydroboration with 9-BBN was attempted with **435**,

though, after base peroxide workup the crude ^{1}H NMR showed <5% conversion with 95% of **435** remaining.



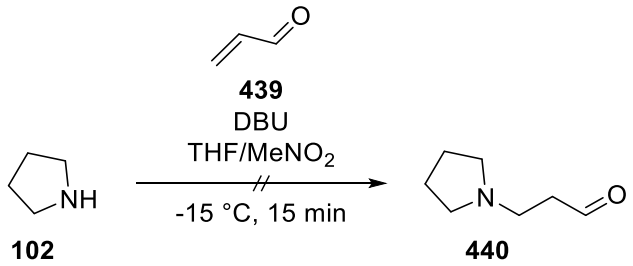
Scheme 161: Initial route to 436

At this point a search through the chemical literature found a procedure to prepare **214** directly from cyclic secondary amines and 3-chloro-1-propanol. This was performed on piperidine **437**. It was not possible to move **214** from the baseline on silica so the product was used impure for an oxidation with Dess-Martin Periodinane. This crude material did not oxidise to give an aldehyde but it was not clear from the crude ^{1}H NMR what had happened, with a complex mixture of products observed (**Scheme 162**).



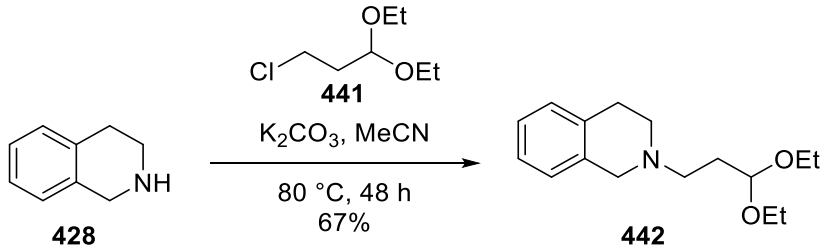
Scheme 162: Synthesis of 214 and attempted Dess-Martin oxidation

Conjugate addition of amines to acrolein **439** to generate species such as **440** has literature precedent, however β-amino aldehydes generated in this manner are unstable and prone to polymerisation when isolation is attempted.[199] The use of benzylic amines causes the reaction to fail.[199] Nevertheless the reaction of pyrrolidine **102** and acrolein **439** was attempted with catalytic quantities of DBU with both THF, the literature solvent for the reaction of pyrrolidine **102** and acrolein, and $MeNO_2$ as a solvent (**Scheme 163**). After 15 min at -15 °C an aliquot was taken and submitted for ^{1}H NMR. With THF as a solvent multiple aldehyde peaks were present in the crude ^{1}H NMR but the ^{13}C NMR showed a range of products and did not match the literature peaks for **440**.[199] However, it is possible that the product polymerised in the NMR tube prior to ^{13}C NMR collection and no ^{1}H NMR data are reported.[199] The use of $MeNO_2$ as solvent led to degradation immediately upon the addition of acrolein; as such this did not seem to provide a promising route towards the synthesis of nitroalkenes in situ.



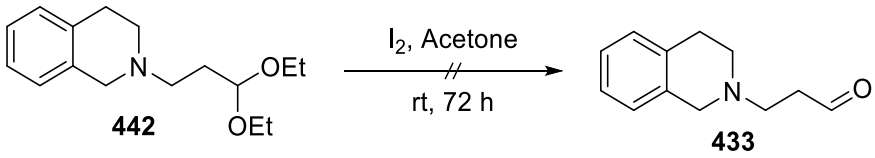
Scheme 163: Attempted conjugate addition of acrolein 439 to pyrrolidine 102[199]

As the desired aldehyde **440** could not be prepared successfully via conjugate addition or from alkene **430**, attention was turned to the protected aldehyde **442**. This was prepared from **428** and **441** in a 67% yield after 48 h (**Scheme 164**).



Scheme 164: Preparation of protected aldehyde 442

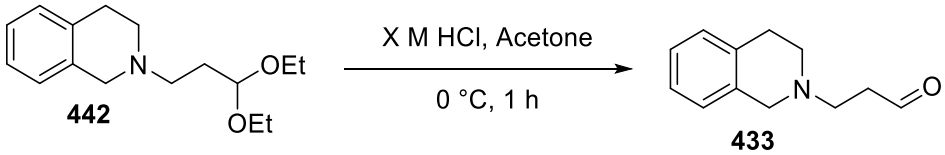
With **442** prepared, a range of deprotections were screened. First a procedure using 0.2 eq iodine in acetone was attempted (**Scheme 165**).[200] This returned starting material only even after 72 h (lit. 45 min).[200] The tertiary amine present in **442** may be the cause of the lack of reaction as there are no amine containing compounds deprotected in this manner in the published literature.[200]



Scheme 165: Iodine mediated deprotection

A deprotection with HCl was then attempted at a range of molarities (**table 8**). At 12 M full consumption of the starting material was observed, however the crude ^{1}H NMR showed a ratio of 1:20 for the aldehyde:aromatic peaks, rather than the 1:4 expected. The 6 M HCl solution again showed full consumption but the ^{1}H NMR showed degradation to a complex mixture. This reaction was performed separately to the others with a pre-prepared solution of 6 M HCl rather than one prepared from dilution of 12 M HCl immediately prior to reaction so it is possible

that this reaction was cross-contaminated. This could be the reason for the difference in results but this reaction was left as an anomaly as the obtained ratios were not useful. The ratio of aldehyde to aromatics for the 3 M solution was 1:46 suggesting poor conversion and at 1.5 M the ratio was 1:55. These results suggest that HCl will deprotect the acetal as desired but at too strong a molarity a mixture of unwanted side products were also formed.

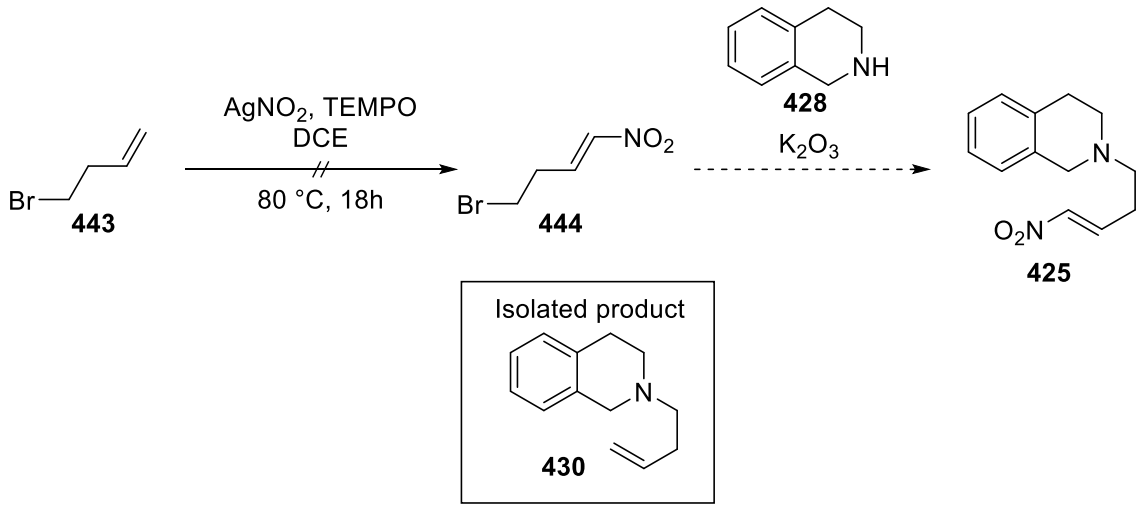


Scheme 166: HCl mediated deprotection

Table 8: Conversion to aldehyde at a range of HCl concentrations

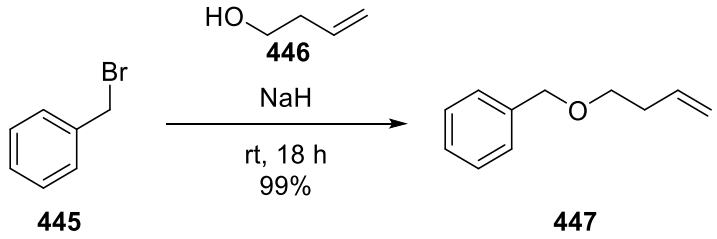
HCl Molarity	Quantity of **442** (mmol)	Time (h)	Ratio aldehyde:aromatic peaks
1.5	0.25	1	1:55
3	0.25	1	1:46
6	1	1	n/a
12	0.25	1	1:20

The direct nitration of alkenes by Maiti *et al*. has been shown to work with alkenyl bromides.[193] We therefore proposed to prepare nitroalkene **444** directly and then react this with tetrahydroisoquinoline **428** directly to form **425**. However, the desired nitroalkene **444** may be volatile so a two-step reaction was attempted. Homoallyl bromide **443** was subjected to the nitration conditions as discussed above for 18 h then **428** was added with K_2CO_3 and the reaction stirred at 80 °C for a further 18 h (**Scheme 167**). Rather than forming the desired product **425**, **430** was isolated in a 34% yield. It seems likely that the nitration did not proceed as desired.



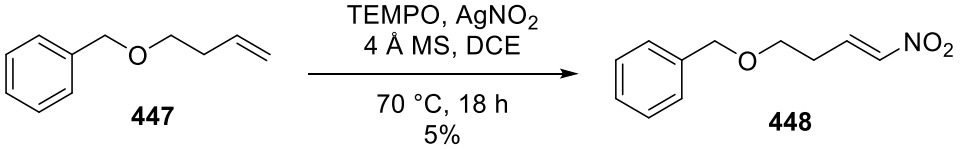
Scheme 167: Attempted synthetic route to 425 and isolated product 430

As the synthesis of amine containing nitroalkene substrates was proving challenging, attention was turned to materials which did not contain an amine moiety. First **447** was prepared from benzyl bromide **445** and homoallyl alcohol **446** in a 99% yield (**Scheme 168**).



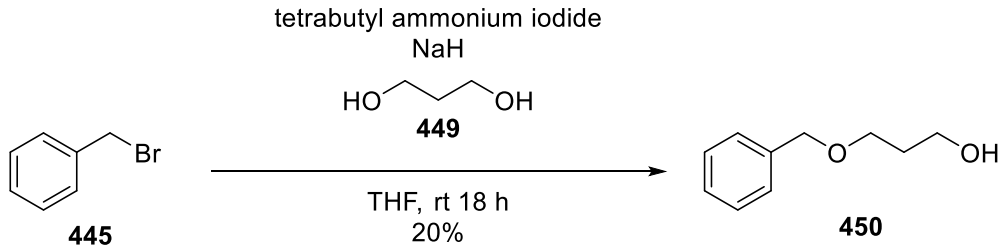
Scheme 168: Preparation of alkene 447

This alkene was then subjected to the nitration conditions of Maiti *et al*. that caused the degradation of the corresponding amino alkene **430**.[193] This gave the desired product in a 5% yield with large amounts of degradation, including the formation of benzaldehyde (**Scheme 169**). This suggested that the reaction conditions were oxidising the benzylic ether, leading to the formation of a hemiacetal which then cleaved to form benzaldehyde either during the reaction or workup.



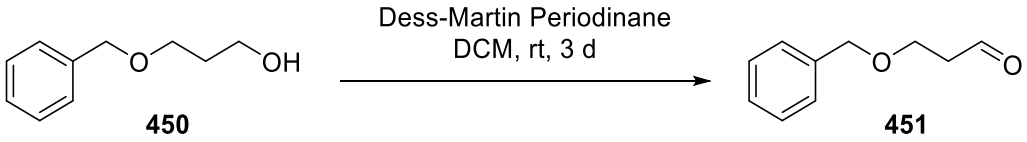
Scheme 169: nitration of alkene 447

A further route to **448** via the aldehyde **451** was followed starting from benzyl bromide **445** and 1,3-propane diol **449** (**Scheme 170**).[201] The desired alcohol **450** was isolated in a 20% yield with respect to benzyl bromide after 18 h at rt.



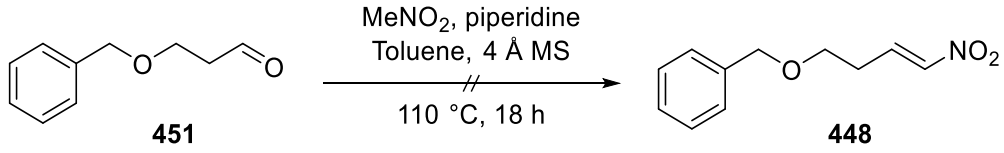
Scheme 170: Preparation of alcohol 450

Oxidation of **450** was performed with DMP in DCM at rt (**Scheme 171**). This gave complete conversion by TLC after 3 d and the crude ^{1}H NMR showed mostly product with minor impurities. However, the crude product polymerised in air during workup before purification was attempted.



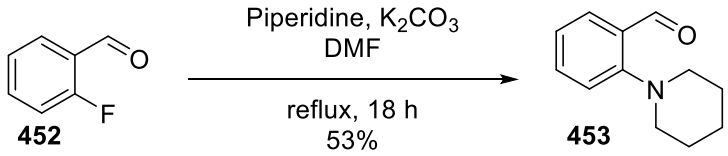
Scheme 171: DMP oxidation of 450 to give 451

The oxidation of **450** was then repeated with the crude material telescoped into a Henry reaction.[196] This gave trace conversion by ^{1}H NMR following 18 h of reflux and **448** could not be isolated (**Scheme 172**).



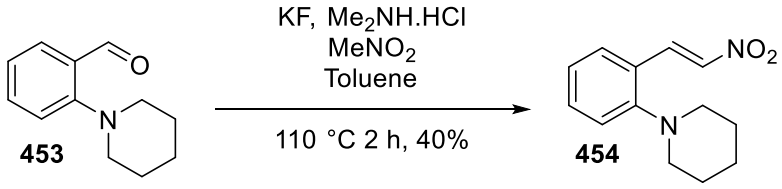
Scheme 172: Attempted reaction of 451 to give 448

In tandem the synthesis of other amine substrates was attempted, first looking to prepare **454**. This was reported in the only literature example, published by Rabong *et al*, of a 1,5-hydride shift with a nitroalkene moiety.[171] Piperidine was reacted with 2-fluorobenzaldehyde in DMF to give **453** in a 53% yield (lit 95%)[202] as a yellow oil following purification by column chromatography (**Scheme 174**).



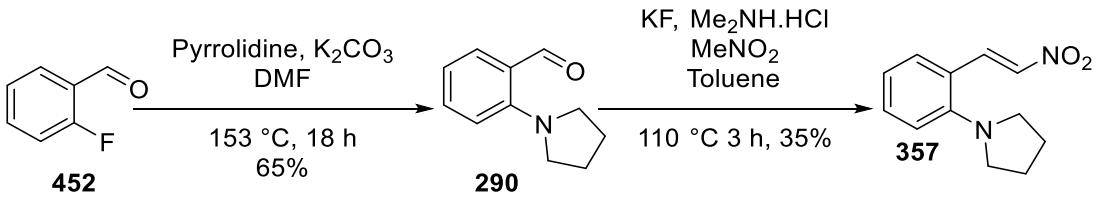
Scheme 174: Preparation of 453

The prepared aldehyde **453** converted to a nitroalkene via a Henry reaction to give nitroalkene **454** in a 40% yield as a red oil (lit. 65%) (**Scheme 175**).[171] This gave enough material for an investigation into the 1,5-hydride shift as a route into nitro-Mannich cyclisation to proceed.



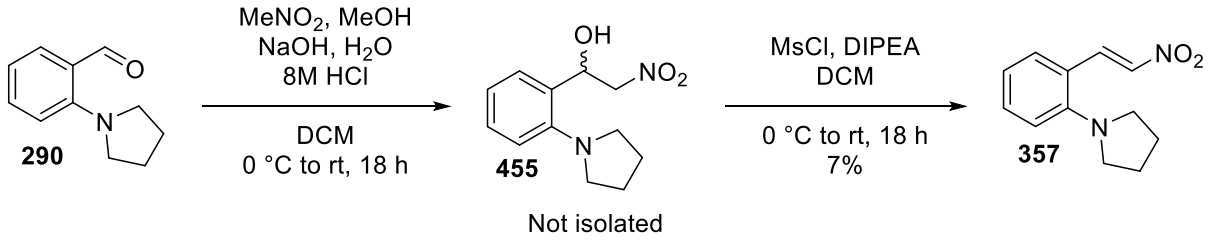
Scheme 175: Henry reaction of 453 to form 454

Similarly moderate yields were seen when forming the pyrrolidinyl derivative **357**. This analogue **357** was prepared in a 35% yield after 3 h, with the initial aldehyde **290** being formed in a 65% yield (**Scheme 176**).



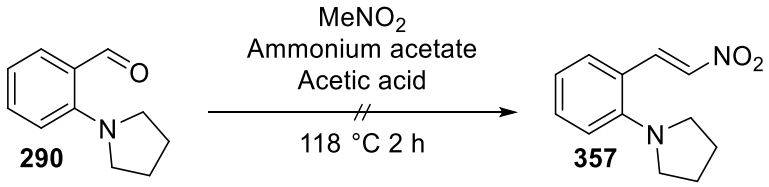
Scheme 176: Preparation of 357

As a result, a range of other reaction conditions were trialled. A two-step Henry reaction used within the group previously was followed.[203] First the aldehyde **290** was reacted with an excess of nitromethane in methanol with NaOH (aq) and HCl (aq) to give a mixture of the desired nitroalkene and alcohol **455**. This was then converted to the alkene with mesyl chloride and DIPEA to give **357** in a 7% yield following purification via column chromatography (**Scheme 177**).



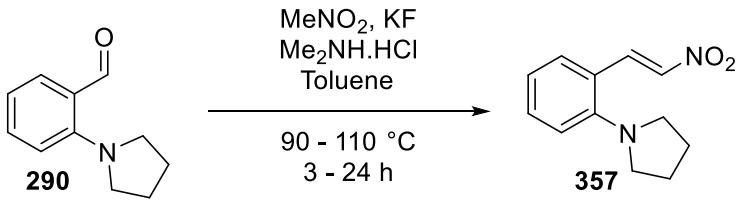
Scheme 177: Alternate route to 357[203]

Secondly a published method for a similar compound was followed using ammonium acetate in acetic acid.[204] Though this was claimed to form similar species in high yield only degradation was observed when the procedure was followed using **290** (**Scheme 178**).



Scheme 178: Attempted alternate formation of 357

No other conditions attempted gave an improved yield compared to the conditions modified from Rabong *et al.*[171] As a result a systematic optimisation of this reaction (**Scheme 179**) was performed (**Table 9**). A range of temperatures were trialled, with 90 °C giving the best conversion by HPLC. The addition of molecular sieves reduced the conversion observed and a tweak of the equivalents of KF and $Me_2NH.HCl$ raised conversion to 72% This saw an increase in isolated yield from the 35% originally seen to 60% (**Table 9 reaction E**).



Scheme 179: General conditions for the formation of 357

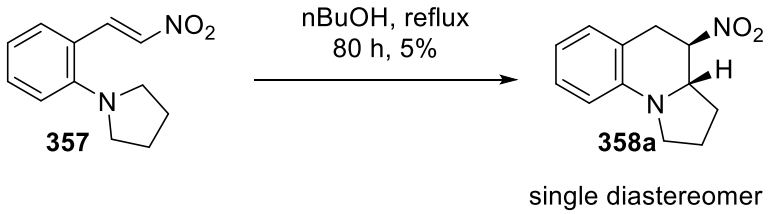
Table 9: Reaction screening for the formation of 357

Reaction	Temperature (°C)	Eq KF	Eq $Me_2NH.HCl$	Additive	Yield*
A	110	0.25	2	n/a	45%
B	100	0.25	2	n/a	66%
C	90	0.25	2	n/a	68%
D	110	0.25	2	4 Å MS	52%
E	90	0.19	1.5	n/a	72%†

**Yield determined by HPLC. †Yield determined to be 70% by crude ^1H NMR with an internal standard, isolated yield of 60% following column chromatography*

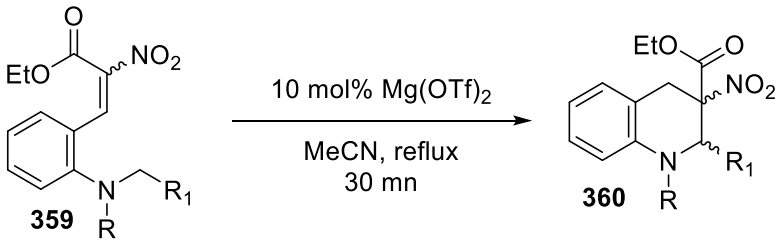
2.4.3 Reaction Screening Towards a Suitable Lewis/Brønsted Acid

With the route to **357** optimised, a screen of methods to promote a 1,5-hydride shift reaction was performed. Initially the sole literature example of a 1,5-hydride shift mediated cyclisation with a nitroalkene was repeated (**Scheme 180**).[171] Here **357** was heated in nBuOH at 118 °C for 90 h, giving **358a** in a 5% isolated yield (lit. 25%).



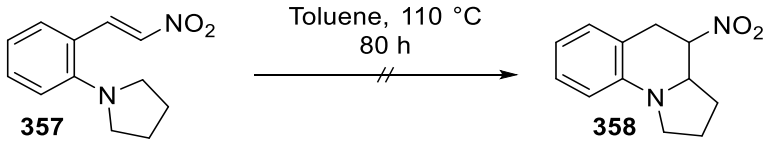
Scheme 180: Repeat of the literature cyclisation to form 358a[171]

Briones *et al.* reported, in 2016, a Lewis acid mediated 1,5-hydride shift with a nitro-acrylate hydride acceptor.[170] This is the only example of a 1,5-hydride shift featuring a nitro group following the work by Rabong *et al*., discussed above. Here $Mg(OTf)_2$ was used to catalyse the formation of bicycle **360** as a key intermediate in the synthesis of spirocycles as a route towards tetrahydroquinoline-3-spirohydantoin derivatives (**Scheme 181**). The presence of the acrylate was essential for the reaction to proceed, with no conversion observed in the nitrostyrenyl analogue of **360**, as discussed below.



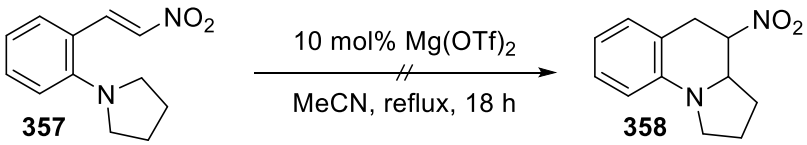
Scheme 181: Literature route featuring Lewis acid catalysis[170]

The reaction conditions published by Rabong *et al*. were repeated with toluene in place of nBuOH in order to investigate whether the alcohol was acting as a Brønsted acid mediating the cyclisation or if it occurred without the need for an external reagent (**Scheme 182**). No reaction was seen, with only degradation observed over the course of 80 h.



Scheme 182: Attempted cyclisation with toluene

The conditions of Briones *et al*. were applied to **357** (**Scheme 183**). Here no conversion was seen, even when extending the length of reaction from 30 min to 18 h.

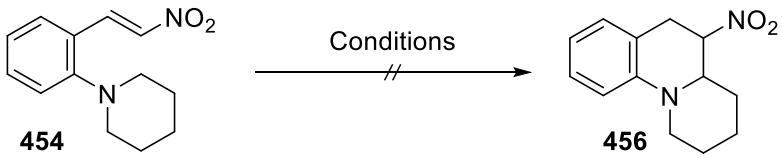


Scheme 183: Attempted $Mg(OTf)_3$ catalysed cyclisation

This result was notable for its lack of conversion. This suggests that, rather than the nitro group of the nitro-acrylate being crucial to the cyclisation, it is the vinyl ester-Lewis acid interaction which allows the cyclisation to proceed. This is perhaps unsurprising as the use of vinyl esters in 1,5-hydride shift cyclisations is well documented.[135,145,161]

As neither literature procedure provided a useful cyclisation, a screen was performed with common Lewis acid catalysts used for 1,5-hydride shifts. These reactions were performed with either (E)-1-(2-(2-nitrovinyl)phenyl)pyrrolidine **357** or (E)-1-(2-(2-nitrovinyl)phenyl)piperidine) **454**. First $BF_3.OEt_2$, one of the most widely used Lewis acids, was added to a solution of **454** in DCM at room

temperature (**Scheme 184**).[135,154,157,160,165,205,206] Upon the addition of $BF_3.OEt_2$ an orange precipitate was formed and the starting material **454** appeared fully consumed by TLC. However, following aqueous workup, only starting material was recovered, suggesting the $BF_3.OEt_2$ was coordinating strongly to **454** to form a material insoluble in DCM. As no hydride shift was observed it is likely that coordination was to the tertiary amine rather than the nitro group as hoped.

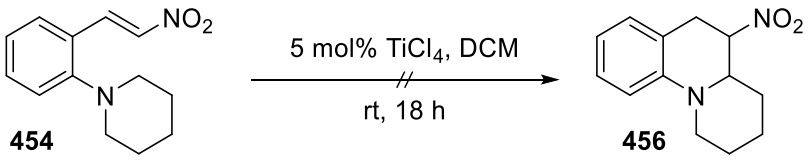


Scheme 184: General Scheme for attempted cyclisation

Another common Lewis acid catalyst for 1,5-hydride shifts is $Sc(OTf)_3$.[148,154,157,161–163] (E)-1-(2-(2-nitrovinyl)phenyl)piperidine) **454** was dissolved in DCM at room temperature and 5 mol% $Sc(OTf)_3$ was added. Here no reaction was observed after 18 h at room temperature, with only starting material recovered. No reaction was seen upon heating to reflux or the addition of 1 eq of $Sc(OTf)_3$.

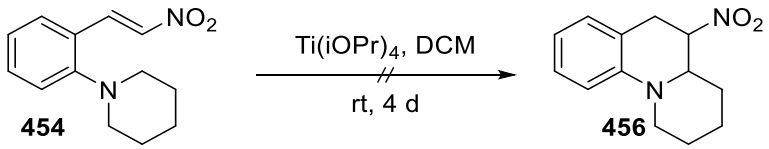
As no degradation was observed, cyclisation of **454** was attempted again with 1 equivalent of $Sc(OTf)_3$, in a higher boiling solvent DCE, which allowed the reaction to be performed at 80 °C, albeit as a heterogenous mixture. This initially showed a new material forming by TLC after 18 h, with starting material still present. After 36 h the crude ^1H NMR was unclear and the majority of the recovered material was insoluble, which suggested that polymerisation may have occurred. This could be due to the $Sc(OTf)_3$ either not dissolving in DCE or only partially dissolving. However, DCM has previously been successfully used as a reaction solvent with $Sc(OTf)_3$.[135]

Titanium Lewis acids were also trialled. Titanium tetrachloride (5 mol%) was used with DCM and stirred at rt. The reaction turned cloudy and a new spot appeared on the baseline in addition to the spot corresponding to the starting material when the reaction was visualised by TLC but this disappeared if a workup was performed prior to running the TLC as with $BF_3.OEt_2$ (**Scheme 185**). It seemed likely that $TiCl_4$ was chelating preferentially with the amine in **454** rather than the nitro group.



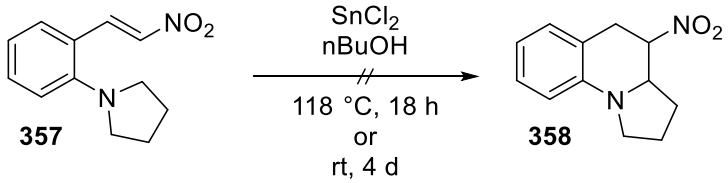
Scheme 185: $TiCl_4$ as the Lewis acid catalyst

Titanium isopropoxide (5 mol%) was used as a Lewis acid to generate a comparison to $TiCl_4$ (**Scheme 186**). After 18 h there was no sign of conversion, but after 4 d there was potential conversion by TLC, with a new spot appearing that matched that from the cyclisation in nBuOH (**Scheme 180**). This new product was not visible in the crude ^{1}H NMR, suggesting conversion was very poor.



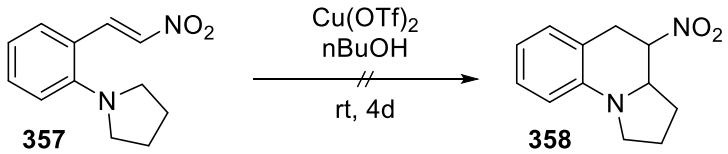
Scheme 186: $Ti(iOPr)_4$ as the Lewis acid catalyst

$SnCl_2$ was used as a Lewis acid (**Scheme 187**) as tin species have previously been used as Lewis acids for conjugate addition to nitroalkenes.[207] This was used in 0.5 eq in two experiments for 4 d at rt and 18 h at reflux in nBuOH. In the former case starting material was recovered with a minor quantity of degradation and in the latter case the starting material polymerised to give an insoluble black material.



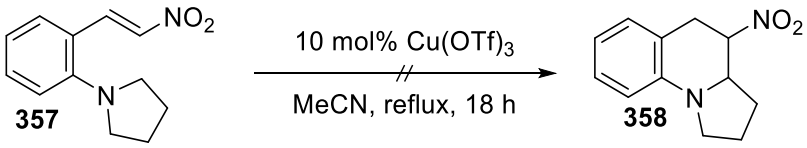
Scheme 187: Attempted cyclisations with $SnCl_2$ as Lewis acid

Following a literature search, copper triflate was identified as a promising Lewis acid, having previously been used to catalyse conjugate addition to aliphatic and aromatic nitroalkenes.[208,209] Furthermore, these reactions proceeded in the presence of chiral ligands, leading to good to excellent enantioselectivities. Copper triflate was therefore used as a Lewis acid, again with 0.5 eq at rt for 4 d. As with $SnCl_2$ this gave mostly starting material with a small amount of degradation (**Scheme 188**).



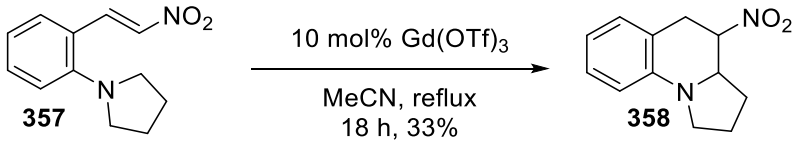
Scheme 188: Attempted cyclisation with $Cu(OTf)_2$ as Lewis acid

We considered it possible that the nBuOH solvent was ligating to the copper species present to the extent that it was preventing the copper triflate from effectively catalysing the desired cyclisation. As a result, copper triflate (10 mol%) was then screened with (E)-1-(2-(2-nitrovinyl)phenyl)pyrrolidine **357** in MeCN at reflux. After 18 h there was apparent conversion by TLC, with a faint product spot appearing, but this product could not be isolated due to the small amount of material present (**Scheme 189**).



Scheme 189: $Cu(OTf)_3$ as the Lewis acid catalyst

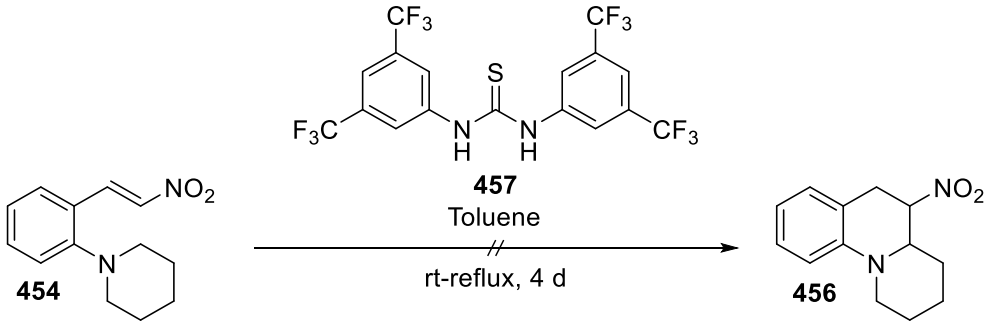
As discussed above, gadolinium triflate has been reported as successfully catalysing the cyclisation of **360** by Briones *et al*, though the presence of the vinyl ester there proved key.[170] Accordingly, gadolinium triflate (10 mol%) was used as a Lewis acid in MeCN at reflux (**Scheme 190**). An isolated yield of 33% was obtained as a single diastereomer. This was notable as being the best yield we had observed for a Lewis acid catalysed cyclisation of a nitroalkene via a 1,5-hydride shift and took the isolated yield of **358** above that reported of the thermal reaction in the literature.[171]



Scheme 190: $Gd(OTf)_3$ as Lewis acid catalyst

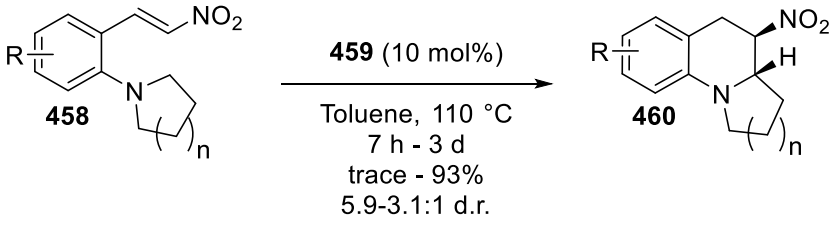
With the yields of Lewis acid catalysed cyclisations disappointing, attention was turned to the use of Brønsted acid catalysts for 1,5-hydride shift cyclisations. Thiourea catalysts have previously seen use in mediating conjugate additions to nitroalkenes, including the intermolecular addition of a hydride from a Hantzsch ester to form a nitronate.[210–212] A non-chiral thiourea catalyst **457** was chosen as

the organocatalyst for an attempted cyclisation. The nitroalkene **454** was stirred with 5 mol% **457** for 18 h at rt in toluene, with no conversion by TLC (**Scheme 191**). The reaction was then heated to reflux for 42 h, several new spots then appeared by TLC but the starting material was still the major substrate visible. The desired product was not visible by TLC, in line with the lack of conversion observed at reflux in toluene without the presence of a catalyst.

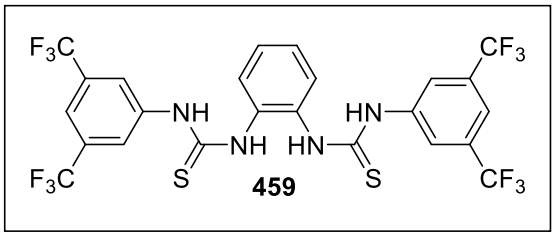


Scheme 191: Thiourea catalysed cyclisation attempt

Subsequent to our studies, Kim *et al*. published a thiourea catalysed cyclisation of nitrostyrenes analogous to our work.[213] The authors discovered that thiourea **459** in toluene effectively catalyses the 1,5-hydride shift with compounds **460**, giving yields between 35-93% other than the piperidinyl substrate **456**, where only trace conversion was observed, in line with our own findings (**Scheme 192**).

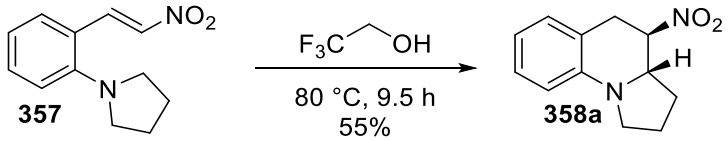


R = H, OMe, CF_3, F, Cl, Br
n = 1-5



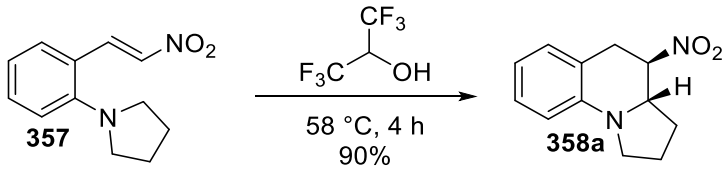
Scheme 192: Literature thiourea catalysed cyclisation[213]

With no conversion seen by TLC with a catalytic amount of an H-bonding catalyst, fluoroalcohol solvents were considered as a potential H-bonding solvent. These compounds show greater acidity than the equivalent alcohols which we proposed would allow a stronger H-bonding interaction with the oxygens of the nitro group, promoting the desired cyclisation. Trifluoroethanol was chosen as solvent (**Scheme 193**). After 9.5 h nitroalkene **357** was fully consumed by TLC, with some degradation apparent. Upon workup and purification via column chromatography the desired cyclised product **358a** was obtained in a 55% isolated yield as a single diastereomer.



Scheme 193: Cyclisation of 357 with trifluoroethanol

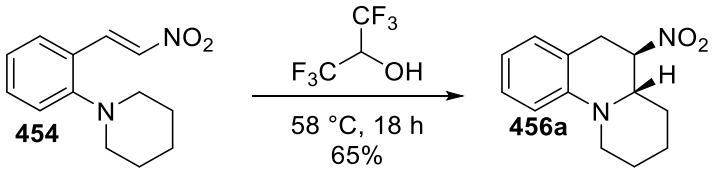
Following the increased yield from moving to trifluoroethanol from nBuOH, this reaction was repeated with HFIP as solvent. HFIP is also widely used as a solvent for polymers based upon its increased ability to solvate through H-bonding.[214] This reaction saw the isolated yield of **358a** increase to 90% whilst still generating a single diastereomer within 4 hours at 58 °C (**Scheme 194**). However, the use of HFIP in stoichiometric amounts with toluene or DCM as solvent saw no conversion, with only starting material recovered.



Scheme 194: HFIP as solvent and Brønsted acid

2.4.4 Scope of the HFIP Catalysed 1,5-Hydride Shift

With the success of cyclisation of **357** with HFIP, attention was turned to the scope of the reaction. First the reaction was performed with the piperidinyl analogue **454** (**Scheme 195**). The larger 6-membered ring inhibited the reaction, leading to a reduced yield of 65% and an increased reaction time for full consumption of nitroalkene **454**, going from 4 h to 18 h.



Scheme 195: The cyclisation of 454 with HFIP

In addition to amines, an ethereal substrate **465** was prepared from salicyl aldehyde **463**. It was thought that the adjacent benzyl group could promote hydride transfer via the stabilisation of the generated carbocation (**Figure 2**).

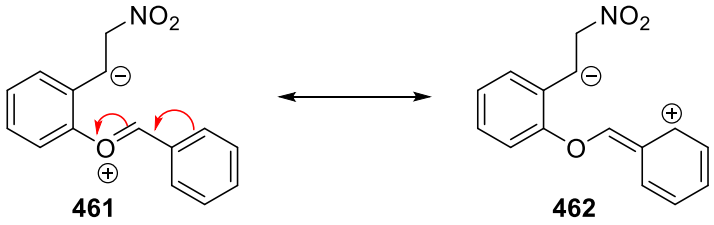
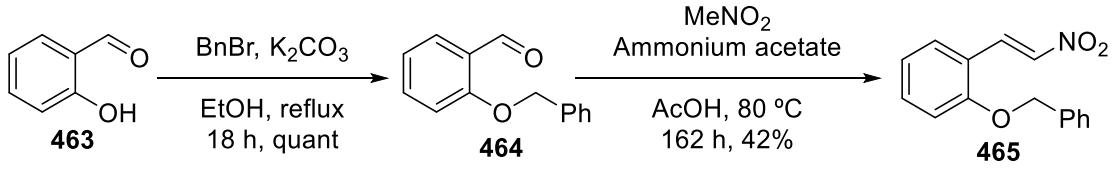


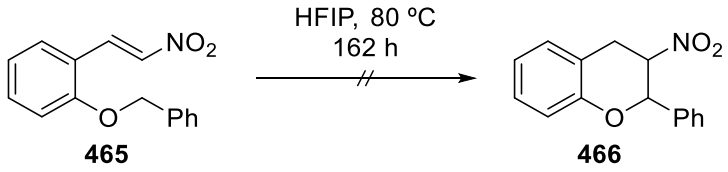
Figure 2: stabilisation of generated positive charge in 465

This was prepared via using conditions published by Waters *et al*. to prepare *tert*-butyl-dimethyl-[1,4,5,7,8-pentamethoxy-3-(2-nitro-vinyl)-naphthalen-2-yl methoxy]-silane as an intermediate towards the synthesis of purpuromycin.[215] First salicyl aldehyde **463** was benzylated in ethanol with K_2CO_3 to act as a proton scrubber (**Scheme 196**). Following purification, aldehyde **464** was used directly in a Henry reaction to give the nitroalkene **465**. This was formed in acetic acid with nitromethane and ammonium acetate (**Scheme 196**).



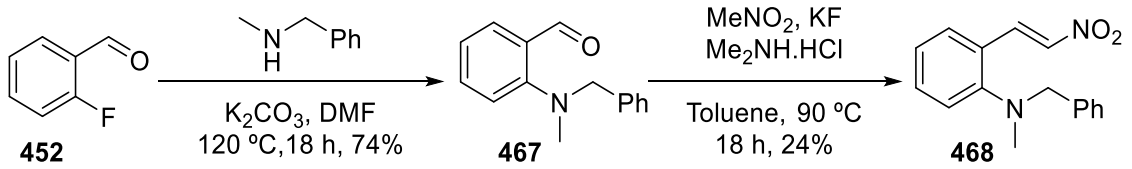
Scheme 196: Henry reaction to form 465

The nitroalkene **465** was heated in HFIP as with **357** and **454** (**Schemes 194 and 195**). Here no reaction was observed, with only starting material recovered after 18 h (**Scheme 197**). We believe that the increased electronegativity of the oxygen in **465** inhibited the reaction. Crucially, no reduction of the nitroalkene or debenzylation was observed, suggesting that no hydride shift was occurring.



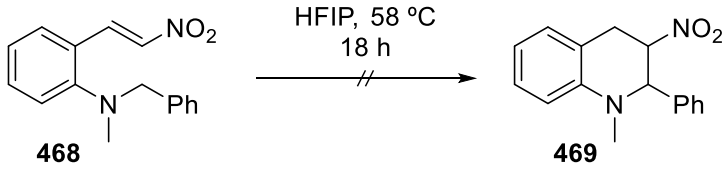
Scheme 197: Attempted cyclisation with 465 and HFIP

An amino analogue of **465** was prepared, (*E*)-*N*-benzyl-*N*-methyl-2-(2-nitrovinyl)aniline **468** to investigate benzyl N-CH in the hydride shift. The amino aldehyde **467** was prepared from 2-fluorobenzaldehyde **452** via an S_NAr reaction as with amino aldehydes **290** and **453**. This aldehyde **467** was then transformed to the corresponding nitroalkene **468** using the optimised Henry reaction as described above (**Scheme 198**). This gave the nitroalkene **468** in a 28% yield.



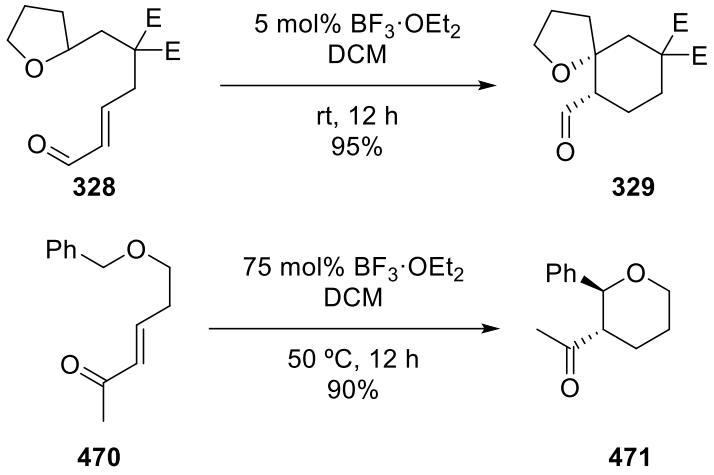
Scheme 198: Formation of 468 via Henry reaction

Once nitroalkene **468** was prepared it was heated in HFIP (**Scheme 199**). Here, as with **464**, no conversion was observed.



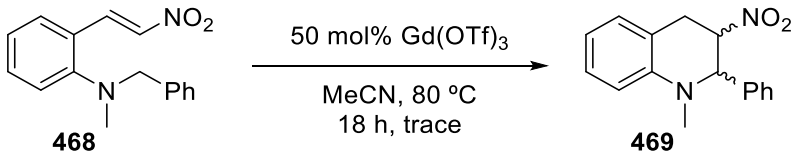
Scheme 199: Attempted cyclisation of 468 with HFIP

The increased difficulty of a 1,5-hydride shift from a benzyl group was observed by Pastine *et al*, where an increased quantity of the $BF_3.OEt_2$ catalyst (5 to 75 mol%), time (12 to 45 h) and temperature (rt to 50 °C) was required to achieve cyclisation of **470** compared to the equivalent tetrahydrofuran **328** (**Scheme 200**).[135]



Scheme 200: Cyclisation with a cycloalkyl ethereal substrate vs a benzyl ethereal substrate[135]

Following the lack of success of HFIP with benzylic substrates, (*E*)-*N*-benzyl-*N*-methyl-2-(2-nitrovinyl)aniline **468** was reacted with $Gd(OTf)_3$ as the best performing Lewis acid catalyst (**Scheme 201**). Conversion was seen to give **469** as a mixture of diasteromers in a <5% isolated yield. Further investigations into the use of gadolinium triflate to catalyse 1,5-hydride shift reactions were therefore performed to optimise the yields and extend the scope of substrates beyond those with which HFIP allowed successful cyclisation.

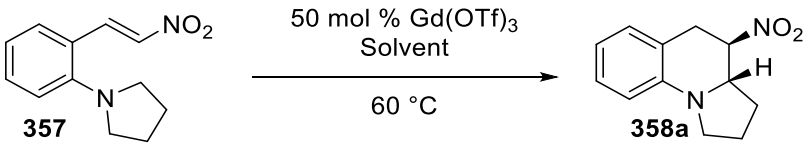


Scheme 201: Initial $Gd(OTf)_3$ catalysed cyclisation of 468

2.4.5 Improvement of Reaction Conditions

The $Gd(OTf)_3$ catalysed cyclisation conditions had shown minor success with **357** and **468** (**Schemes 190 and 201**). As the higher yields obtained when using fluorinated alcohols had been discovered shortly after $Gd(OTf)_3$ was first screened, no work had been done towards the optimisation of the reaction conditions. Attention was first turned towards the choice of solvent for this catalyst. A mixture of **357** and 50 mol% $Gd(OTf)_3$ were added to a range of solvents (**Scheme 202**). TIBCO Spotfire® was used to visualise principal component analysis (PCA), whereby solvent data from an internal AstraZeneca database was arranged by orthogonal “properties”. The axes used to portray the solvents in 3D space were not linked to specific properties (e.g. boiling point or

dielectric constant) but instead were functions generated from these properties. From this 3D visualisation it was possible to divide solvents which should behave similarly into octants of “chemical space” and one solvent was picked from each octant to screen.



Scheme 202: General conditions for solvent screen

Each reaction was heated to 60 °C for 12 h with aliquots taken at t = 0, 0.33, 0.67, 1, 2, 3, 4, 6, 8 and 12 h and monitored by HPLC (**table 10**). As degradation was observed under some conditions the time chosen for comparison was when the percentage area of the product peak was at its greatest for each set of conditions. Whilst MeCN was used in the initial catalyst screen, it was observed to perform poorly as a solvent in these conditions with the product peak accounting for 47% of the total peak area. Perhaps surprisingly toluene appeared to perform best, with a 94% conversion after 12 h and very little side product formation or degradation occurring despite the reaction proceeding more slowly than with MeCN and 2MeTHF, for example.

Table 10: Solvent screen with $Gd(OTf)_3$

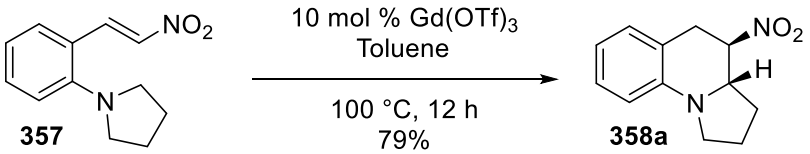
Solvent	Time (h)	Area of HPLC Product Peak	Observations
DMF	12	0%	-
Toluene	12	94%	Clean conversion
MeCN	4	47%	Major degradation peak
2MeTHF	3	65%	Several degradation peaks
IPA	4	41%	Large range of products
p-Xylene	12	75%	20% starting material
1-hexanol	6	46%	Large range of products
NBu_3	12	0%	-

The percentage area for the desired product **358** steadily increased over the course of the 12 h of monitoring with toluene as solvent and so a series of experiments was performed in order to find the optimal conditions for cyclisation with $Gd(OTf)_3$ and toluene (**table 11**). The concentration of the reaction mixture, the temperature of reaction and the catalyst loading were each compared and modified to create a reaction map.

Table 11: Reaction map for condition optimisation

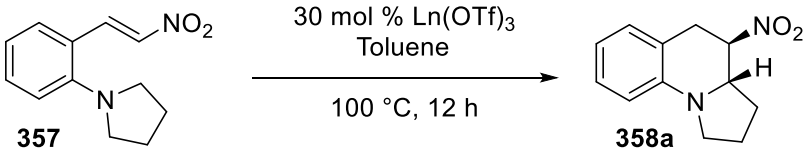
Entry	Concentration (g/mL)	$Gd(OTf)_3$ (mol%)	Temp (°C)	Time (h)	Area of HPLC Peak (% of total area)
A	0.01	10	50	24	0
B	0.01	10	100	4	90
C	0.01	60	50	24	7
D	0.01	60	100	2	94
E	0.1	10	50	24	27
F	0.1	10	100	12	94
G	0.1	60	50	24	44
H	0.1	60	100	1	94
I	0.055	35	75	16	97

Unsurprisingly it was found that a higher catalyst loading, higher reaction temperature and a more concentrated reaction mixture led to a faster reaction time. It was found that the reaction was greatly temperature dependent, with no conversion observed at 50 °C with low catalyst loading. Even at high catalyst loading and concentration the product area peak did not get above 44% (**table 11**, entry G). It was decided to use the conditions in entry F (**table 11**) with **357** in order to obtain an isolated yield of the cyclised product **358a** and determine the relationship between HPLC area and directly quantifiable yields (**Scheme 203**). Entry F was selected as providing the best compromise between catalyst loading, reaction time, and yield. This gave the product **358a** as the *anti* diastereomer in a 79% yield.



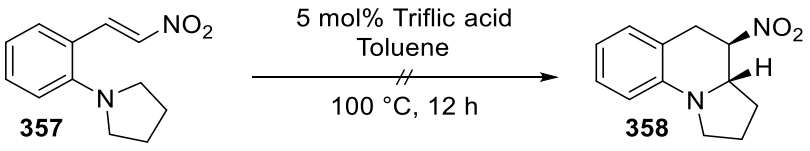
Scheme 203: Optimised conditions to form 358a

Two further lanthanide triflates were then trialled as Lewis acid catalysts with **357**, using the reaction conditions optimised for $Gd(OTf)_3$ (**Scheme 204**). A conversion of 14% was observed by HPLC with ytterbium triflate and no conversion was apparent after 12 h with cerium triflate.



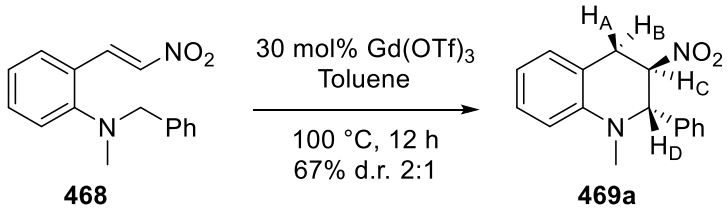
Scheme 204: Cyclisation to form 358a with other Lanthanide triflates

Lanthanide triflates are known to exist in an equilibrium between the $Ln(OTf)_3$ and $Ln(OTf)_2^+ + {}^-OTf$ species.[216] As a result, trace amounts of triflic acid are present. Cyclisation with triflic acid in toluene was attempted to determine whether triflic acid was capable of catalysing the cyclisation rather than $Gd(OTf)_3$ as we believed (**Scheme 205**). No conversion was observed over the course of 12 hours, reaffirming that $Gd(OTf)_3$ was indeed responsible for the formation of **358a**. This result was in line with our experience with other Brønsted acid catalysts, none of which provided detectable levels of conversion when present in catalytic or stoichiometric amounts (see **Schemes 191** and **194**, above).



Scheme 205: Attempted cyclisation of 357 with triflic acid

The optimised $Gd(OTf)_3$ conditions were then applied to (*E*)-*N*-benzyl-*N*-methyl-2-(2-nitrovinyl) aniline **468** (**Scheme 206**). Here conversion proceeded slowly, with very limited conversion observed until the addition of 30 mol% $Gd(OTf)_3$, at which point full conversion was reached within 12 h. Upon repetition of this reaction with 30 mol% $Gd(OTf)_3$ at the outset, conversion was obtained within 12 h, giving the desired product in a 67% yield as a mixture of diastereomers (2:1 *anti*:*syn*) (**Scheme 206**).



468 469a

Scheme 206: Cyclisation to form 469a

The ^{1}H NMR of the major diastereomer **469a** showed a loss of nitroalkene proton shifts compared to the starting material **468**, with the corresponding peaks shifted greatly downfield, in line with the shifts seen with **358**, above. The previous benzyl CH_2 singlet (δ 4.13) was replaced with a pair of multiplets (δ 3.42, 3.01), which were assigned as being H_A and H_B. The multiplet observed at δ 4.84 was seen to couple to both benzyl protons and was shown to be attached to the *C*NO_2 carbon by ^{13}C-^{1}H correlation, the *C*NO_2 carbon being assigned by analogy to the *C*NO_2 carbon shift in **358a**, this multiplet was therefore assigned as H_c. The final non-aromatic proton peak present in the ^{1}H NMR was an apparent singlet at δ 5.19 which was assigned as H_D. Unlike the pyrrolidinyl analogue **358a** the NC*H* proton in **469a** was further shifted than the C*H*NO_2 proton. This was apparent from the HSQC spectrum (**Figure 3**).

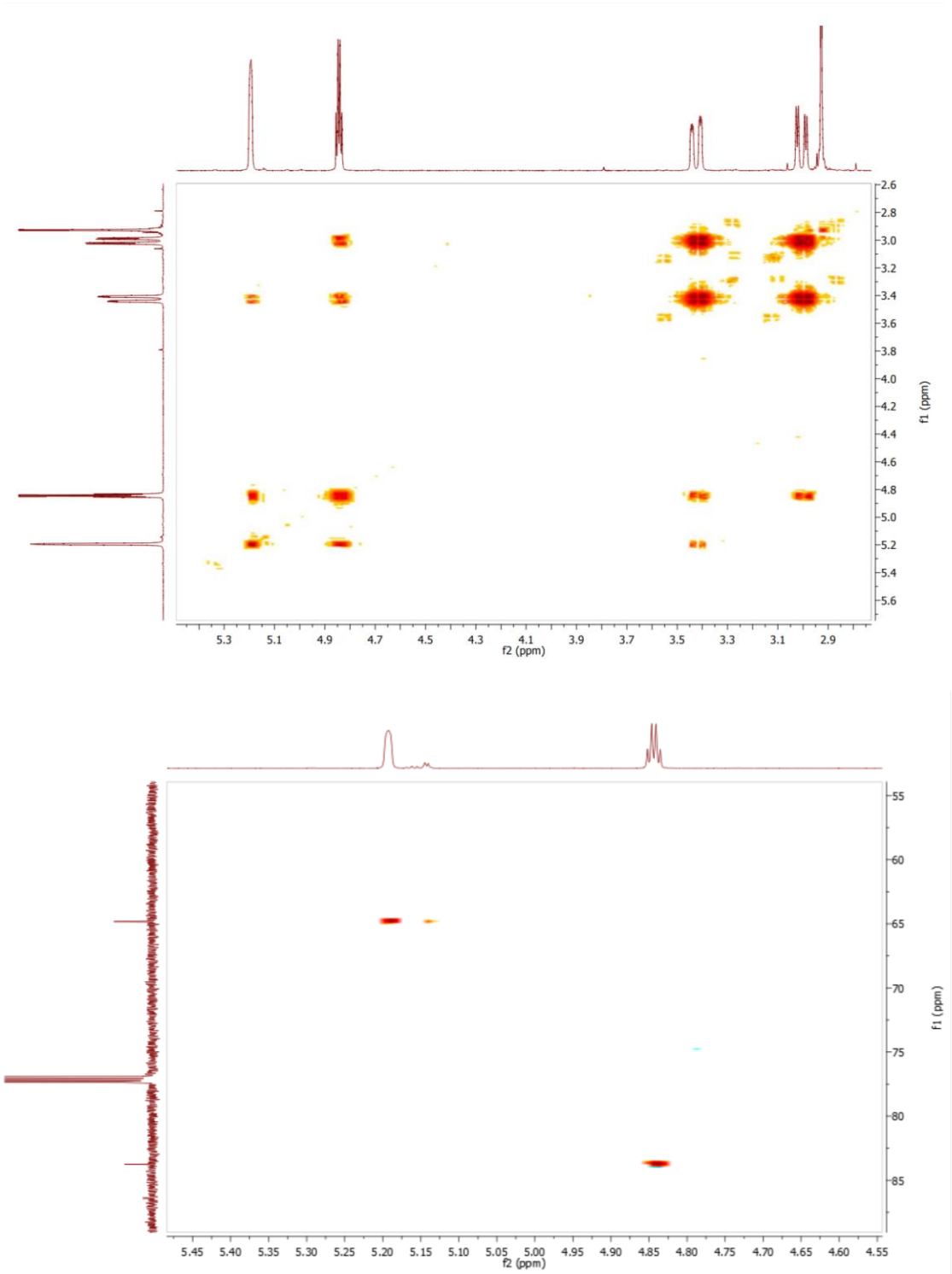


Figure 3: Coupling between ring protons and C-H coupling for NCH and $CHNO_2$

Despite appearing as a singlet, H_D, δ 5.19, (1H, s) showed a small coupling to H_A δ 3.42 (1H, ddd, *J* = 16.8, 3.7, 1.4 Hz) as well as to H_C δ 4.84 (1H, apparent dd, *J* = 7.8, 3.9 Hz), whereas H_C coupled to both H_A δ 3.42 (1H, ddd, *J* = 16.8, 3.7, 1.4 Hz), and H_B δ 3.01 (1H, dd, *J* = 16.8, 4.4 Hz). The small values of the coupling constants suggests that the dihedral angle between H_C and H_D is around 90°.

The NOESY spectrum showed faint coupling between H_A and H_D which suggests that they both sit on the same face, whereas no coupling was seen between H_B and H_D. H_D did show strong coupling to the adjacent NC*H*$_3$ group, reaffirming the assignment of this peak. H_A and H_B have a coupling constant between them of 16.8 H_Z, as would be expected for geminal ring protons.

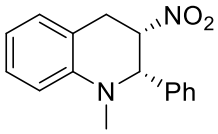
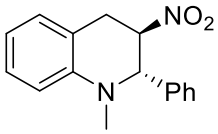
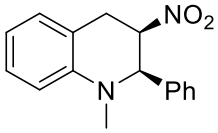
H_C appears to be a double doublet, however, there are merged peaks and comparison to the splitting patterns of H_A and H_B suggest couplings of 3.7 and 4.4 H_Z respectively. This is in line with a flattened ring system with an unsaturated C-C bond, where $^3J_{ax\text{-}eq}$ and $^3J_{eq\text{-}eq}$ would be expected to fall between 2-4 H_Z (**Figure 4**). In a partially unsaturated 6-membered ring, $^3J_{ax\text{-}ax}$ would be expected to be in the range of 10-12 H_Z. This level of splitting is not observed between C*H*NO_2 and the adjacent CH_2, we can therefore determine that the C*H*NO_2 proton sits equatorially and at an angle that leads to an undetectable level of splitting with the adjacent NC*H* (**Figure 4**, Quinoline1).

If we consider these splittings together, the conclusion is that both the nitro- and phenyl- groups sit in a more axial position, which can be rationalised as minimising the steric interaction between these more bulky groups. This assignment was corroborated by computational modelling (**table 12, Figure 4**), which compared the energy of the proposed diaxial *anti*- product (Quinoline2) to that of two *cis*- conformers (Quinoline1 and Quinoline3). These calculations gave the diaxial *anti*- product suggested by NMR as lower energy than either *cis*- conformer, with the highest energy arrangement calculated to be that of Quinoline3, where the Ph group is in an equatorial position. Energies were calculated using B3LYP/6-31G* with the relative energies listed in **table 12**.[b] These values are relative to the lowest energy isomer (Quinoline2).

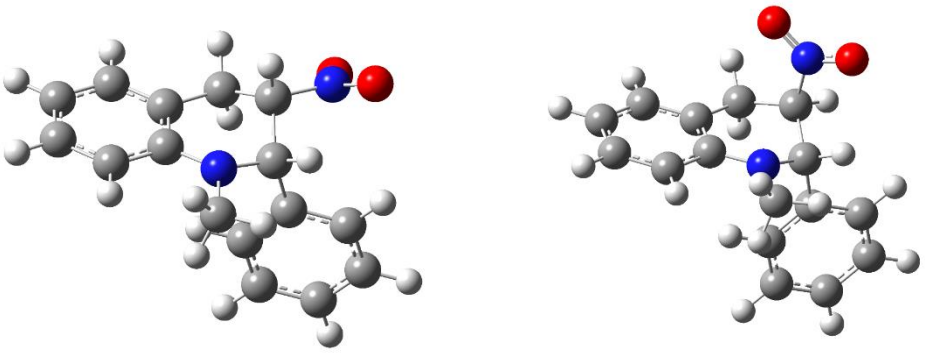
Energies are in Hartrees, 1 Hartree = 27.2114 eV.

[b] Energies calculated by David Freeman

Table 12: Calculated energies of possible conformers

Isomer	Designation	Calc Energy	Relative Energy (Hartree)	Relative Energy (kJ mol^{-1}
	Quinoline1	-879.19455451	0.00017632	0.46
	Quinoline2	-879.19473083	0	0
	Quinoline3	-879.18771543	0.00701540	18.42

Quinoline1 Quinoline2



Quinoline3

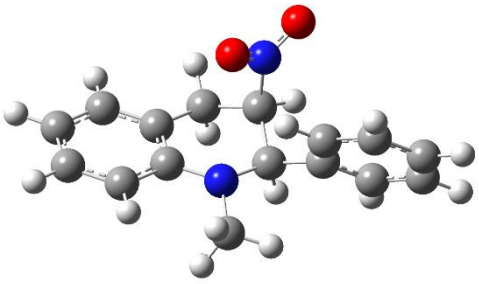


Figure 4: Calculated spatial arrangements of 469

A method of cyclisation which worked with both **357** and **468** had therefore been developed that was considerably more efficient than the single literature report.[171] A compound library with which to investigate the scope of the 1,5-hydride shift as a route into nitro-Mannich cyclisations was therefore required.

2.4.6 Preparation of Nitroalkene library

The preparation of nitroalkenes suitable for cyclisation via the conditions were prepared by the route optimised for the synthesis of **357**. The decision was made to prepare separate groups of nitroalkenes to cover a broad range of potential reactivities. Our initial groups fell into 5 categories. Group **A** (**Figure 5**) was designed to investigate the effect of ring size and the presence of heteroatoms within the ring on the reaction.

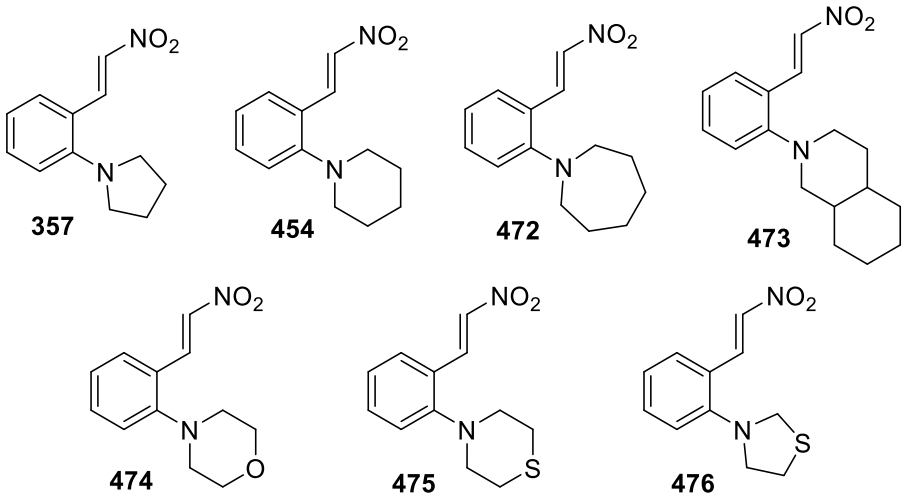
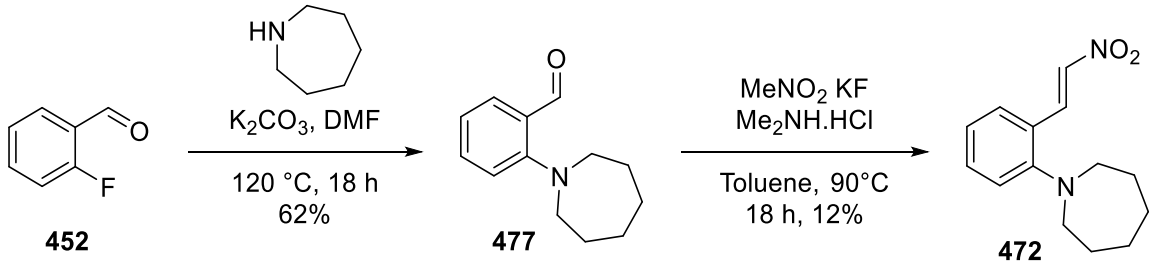


Figure 5: Group A target compounds

Compounds **357** and **454** had previously been prepared via an S_NAr reaction followed by a Henry reaction when preparing substrates with which to screen for cyclisation reaction conditions. This route was therefore applied to compounds **472**, **473** and **474**.

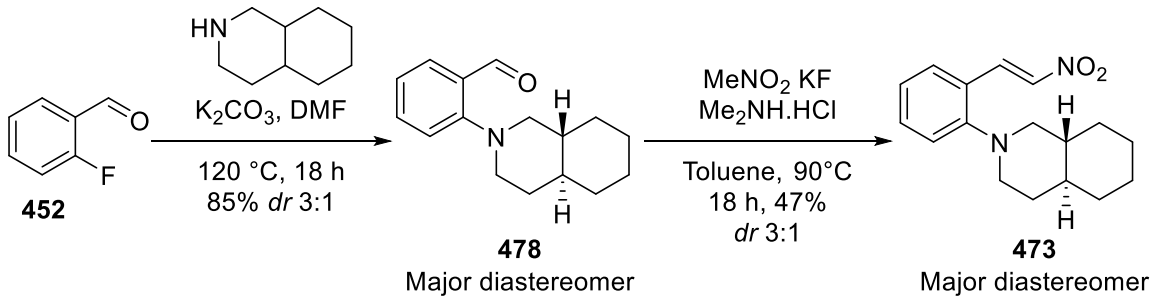
The synthesis of 2-(azepan-1-yl)benzaldehyde **477** proceeded smoothly with the product isolated in a 62% yield. The optimised Henry reaction conditions were applied to **477** to form the desired nitroalkene **472** in a low 12% yield (**Scheme 207**).



Scheme 207: Synthesis of 472

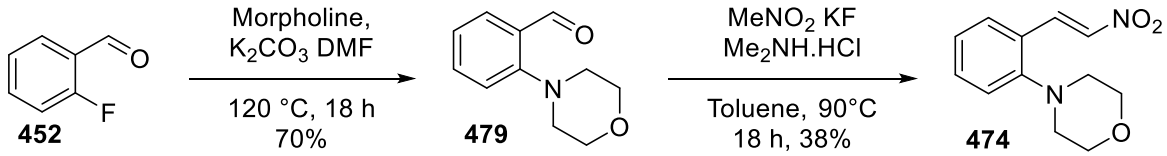
However, when preparing 2-(perhydroisoquinolin-2-yl)benzaldehyde **478**, a *dr* of 3:1 trans:cis was observed by HPLC owing to perhydroisoquinoline solely being available in this ratio of diastereomers. The desired product **478** was formed in an 86% yield after 18 h under the same S_NAr conditions as used previously (**Scheme 208**) but it was not possible to separate the diastereomers obtained.

The mixture of diasteromers **478** were reacted under standard conditions to give the nitroalkene **473** (**Scheme 208**). Here again the same ratio of diastereomers was observed in a 47% yield.



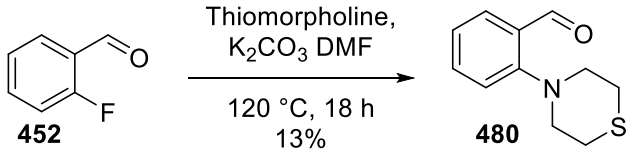
Scheme 208: Synthesis of 473

In order to also investigate the effect of additional heterocycles within the cyclic amine, the synthesis of three additional compounds was attempted. First morpholine was reacted with 2-fluorobenzaldehyde **452** via an S_NAr reaction in DMF with K_2CO_3 (**Scheme 209**). The desired aldehyde **479** was obtained in a 70% yield. This aldehyde was converted to the corresponding nitroalkene **474** (**Scheme 209**). The product was isolated in a 28% yield after 18 h.



Scheme 209: Synthesis of 474

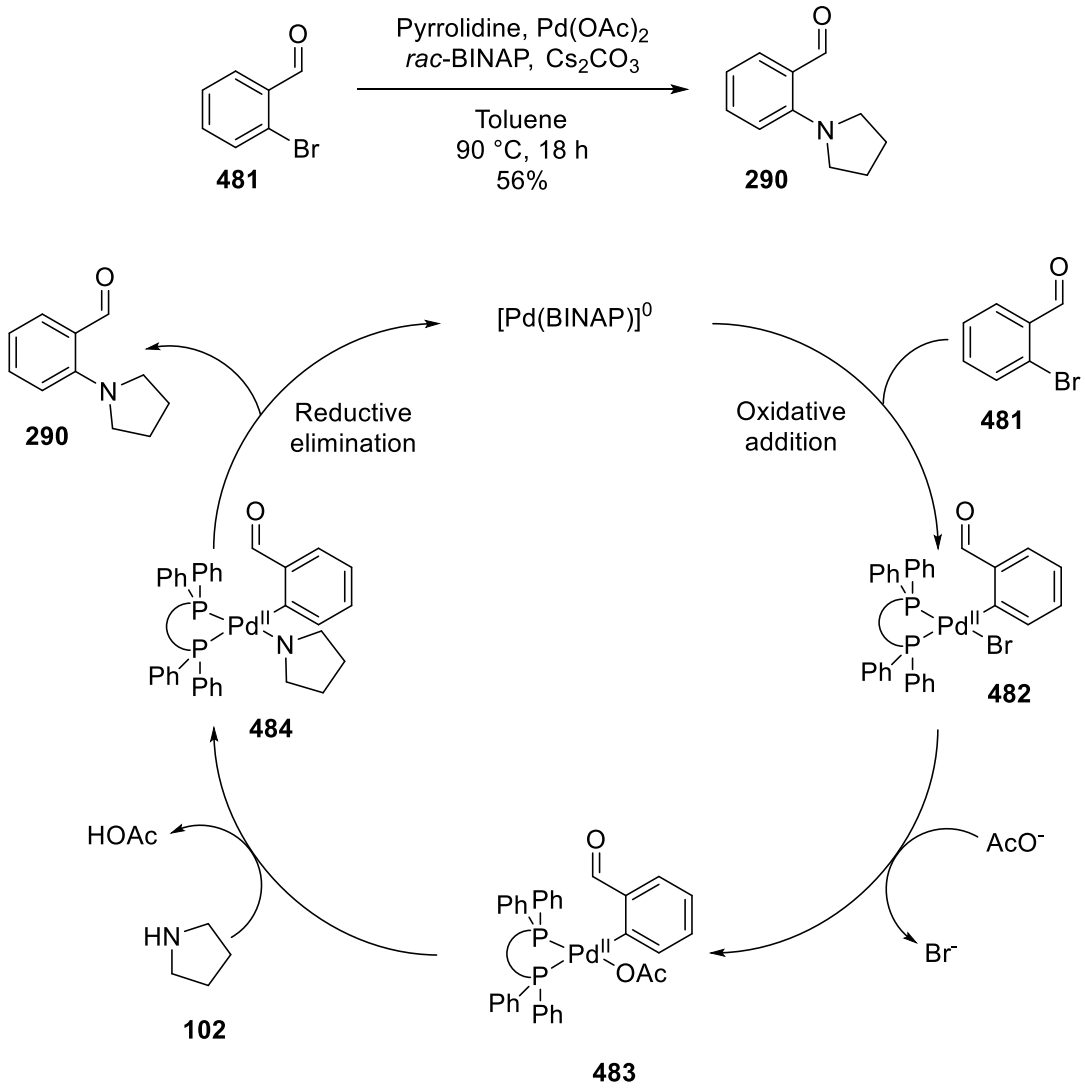
Secondly the thio- equivalent **480** of **479** was prepared, again via the S_NAr reaction with thiomorpholine (**Scheme 210**). A lot of degradation was observed with 2-thiomorpholinobenzaldehyde **480** obtained in a 13% yield.



Scheme 210: Synthesis of 480

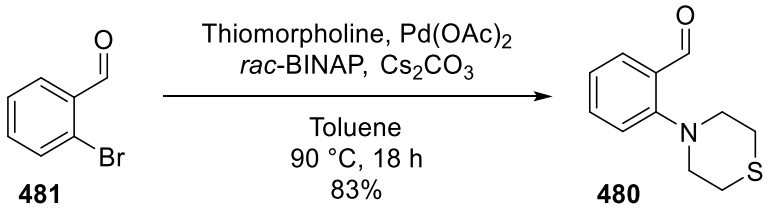
Due to this low yield, the use of a Buchwald-Hartwig cross-coupling reaction was considered.

The Buchwald-Hartwig reaction was used as an alternate route into preparing amino-substituted aryl aldehydes. This reaction was first attempted with 2-bromobenzaldehyde **481** with pyrrolidine which formed **290** in a 56% yield in 18 h, substantially lower than the 87% observed via the S_NAr reaction due to incomplete conversion via the mechanism shown (**Scheme 211**).



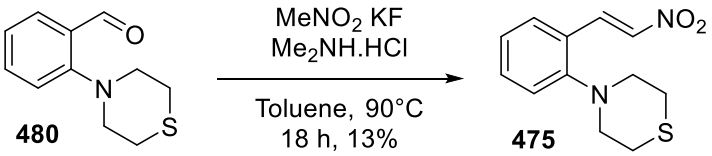
Scheme 211: Buchwald-Hartwig reaction to form 290 and mechanism

These conditions were applied to 2-bromobenzaldehyde **481** with thiomorpholine to form 2-thiomorpholinobenzaldehyde **480** in a much improved 83% yield (**Scheme 212**).



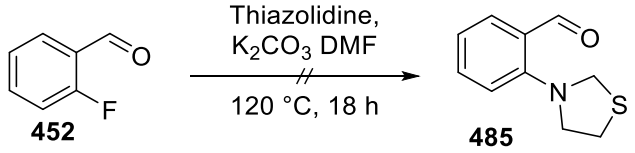
Scheme 212: Alternate route to 480

The corresponding nitroalkene **475** was prepared via a Henry reaction (**Scheme 213**). This formed the desired product in a 13% yield with large amounts of degradation observed.



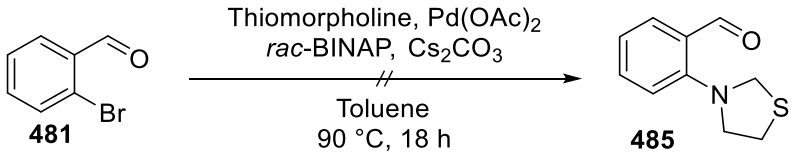
Scheme 213: Synthesis of nitroalkene 475

Additionally, to compare the effect of having a sulfur in the α- or β-position relative to the C-H bond broken during cyclisation, **476** was targeted as a substrate to compare to the thiomorpholino analogue. Thiazolidine was stirred with 2-fluorobenzaldehyde **452** in DMF with K_2CO_3 in attempt to form **485** via an S_NAr reaction without success (**Scheme 214**). Here no conversion was seen, instead the thiazolidine degraded over time.



Scheme 214: Attempt to form 485 via S_NAr

Another attempt was made to prepare **485** via a Buchwald-Hartwig reaction (**Scheme 215**). Here again no conversion was seen, with a mixture of degradation products observed.



Scheme 215: Attempted Buchwald-Hartwig to form 485

Group **B** (**Figure 6**) compounds were chosen to probe the reactivity around benzylamines and other non-cyclic amines. In addition to the previously prepared aldehyde **468**, the electron rich *p*-methoxy substituted aldehyde **486** and the electron poor *p*-chloro substituted aldehyde **487** were targeted, along with the diethylamine derivative.

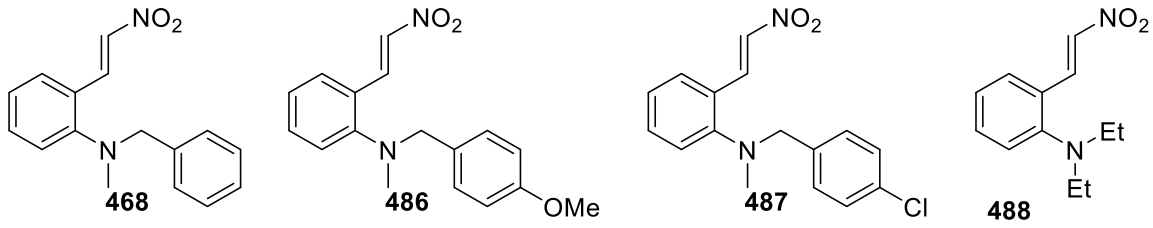
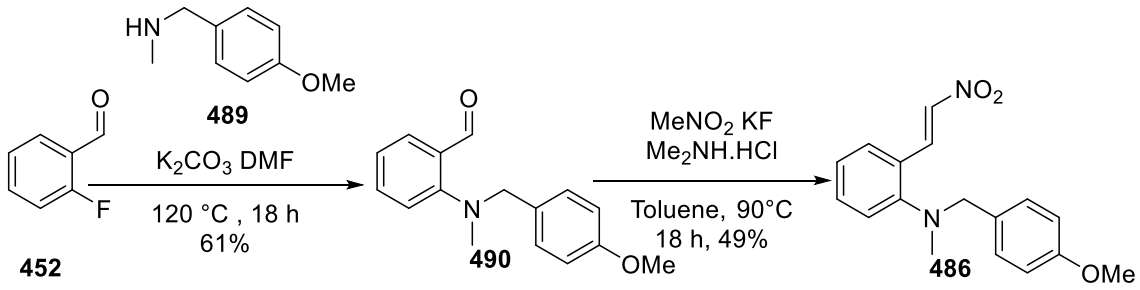


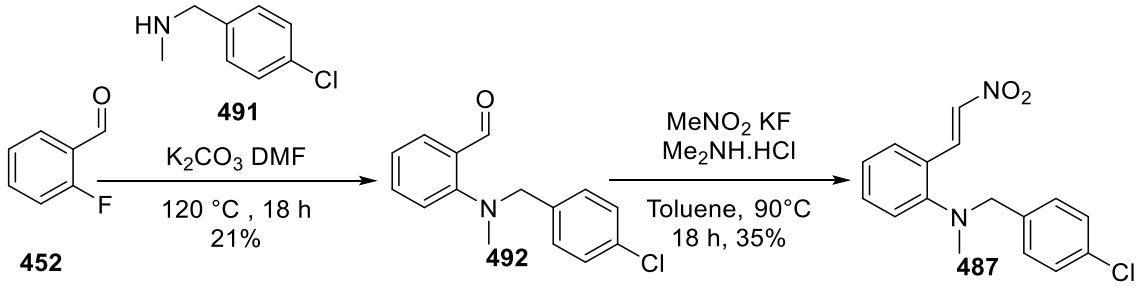
Figure 6: Group B target compounds

Aldehyde **490** was prepared under standard conditions, seeing a good yield of 61% after 18 h. This aldehyde was then subjected to a Henry reaction (**Scheme 216**). This gave the desired nitroalkene in a 49% yield.



Scheme 216: Synthesis of 486 via Henry reaction

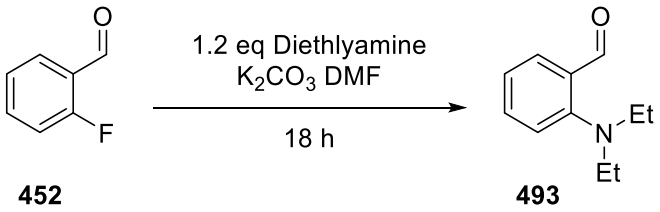
The reaction of 2-fluorobenzaldehyde **452** with 1-(4-chlorobenzyl)-N-methylamine **491**, again under standard conditions, gave a poor isolated yield of **492** of 21% with a large amount of degradation observed (**Scheme 217**). This aldehyde **492** was then reacted with $MeNO_2$ in a Henry reaction (**Scheme 217**). The desired nitroalkene **487** was formed in a 35% yield after 18 h.



Scheme 217: Preparation of 487

Diethylamine was reacted with 2-fluorobenzaldehyde **452** in DMF with K_2CO_3 for 18 h under a range of conditions (**Scheme 218**, **table 13**). First (entry **A**) the standard conditions were used, with only partial conversion to **493** observed, this was likely through the loss of diethylamine to the atmosphere due to its low boiling point. The reaction was repeated with the temperature lowered to 80 °C with no

great increase in conversion (entry **B**). Doubling the equivalents of diethylamine (entry **C**) likewise saw an increase in conversion to **493** but the reaction did still not reach completion.



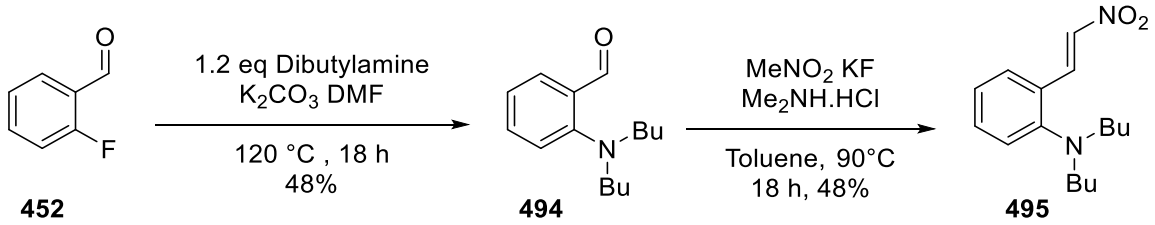
452 **493**

Scheme 218: General Scheme for the synthesis of 493

Table 13: Reaction conditions for attempted synthesis of 493

Entry	Temperature (°C)	Diethylamine eq.	Conversion (%)
A	120	1.2	15
B	80	1.2	23
C	120	2.4	37

At this point dibutylamine was used as a higher boiling replacement for diethylamine. This reaction proceeded generally well under standard conditions, giving the desired product **494** in a 48% yield after 18 h (**Scheme 219**). This aldehyde **494** was transformed into the corresponding nitroalkene **495**. The desired compound was formed in a 48% yield.



452 **494** **495**

Scheme 219: Synthesis of 495

Group **C** was designed to investigate the effect of electron density on the cyclisation reaction. To this end compounds with a range of modified aromatic rings were selected to undergo a 1,5-hydride shift (**Figure 7**).

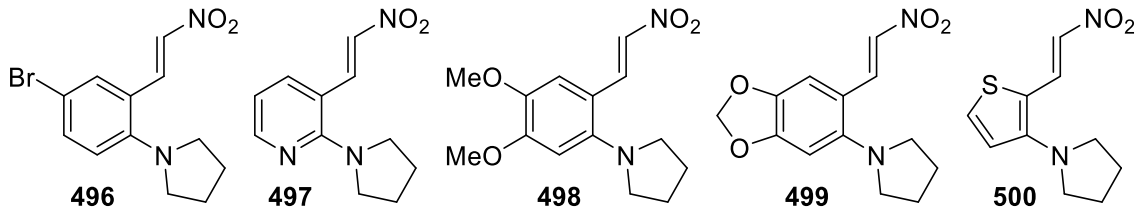
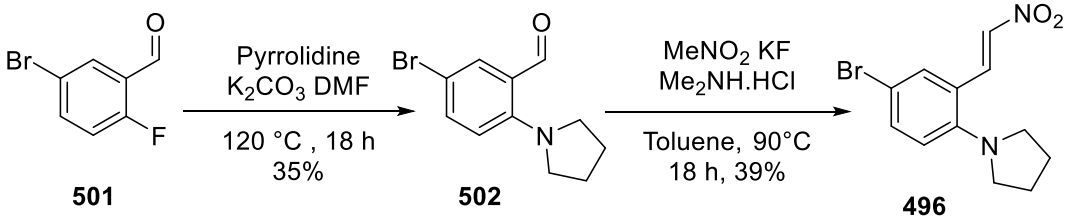


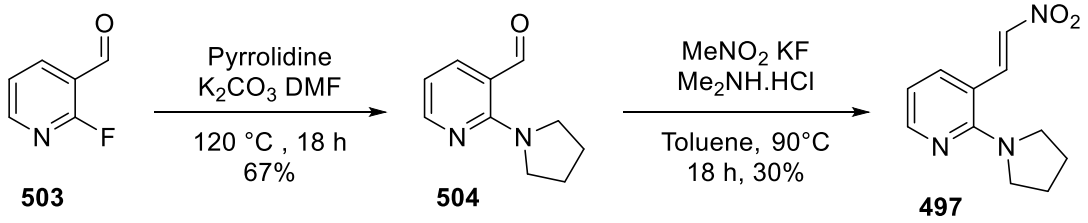
Figure 7: Group C target compounds

First the bromo- substituted aldehyde **501** was prepared under standard conditions in a 35% yield (**Scheme 220**). Pyrrolidine was used as the amine for the S_NAr reaction with 5-bromo-2-fluorobenzaldehyde **501**. This aryl aldehyde **502** was subjected to a Henry reaction (**Scheme 220**) with the modification of the reaction being performed in darkness to prevent debromination. The desired product was formed in a 39% yield.



Scheme 220: Synthesis of 496

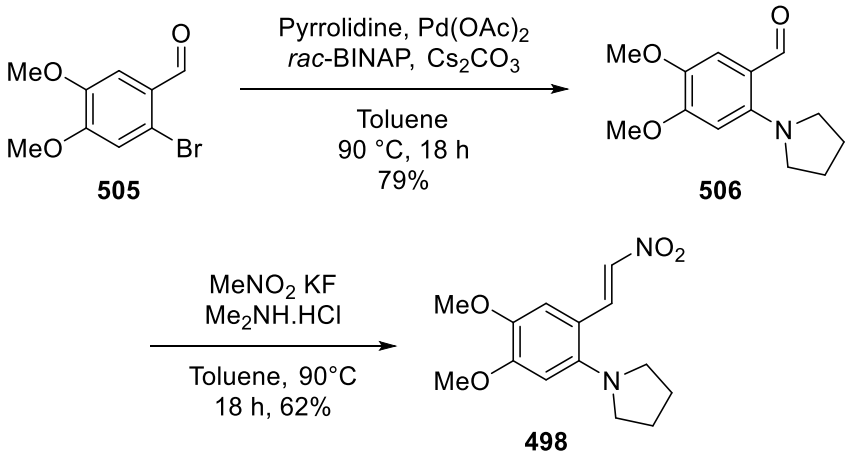
Attention was then turned to 2-fluoronicotinaldehyde **503**, which was reacted with pyrrolidine in DMF with K_2CO_3 (**Scheme 221**). The desired product **504** was obtained in a 67% yield. The isolated 2-(pyrrolidin-1-yl)nicotinaldehyde **504** was transformed into the nitroalkene **497**. This product was formed in a 30% yield after 18 h.



Scheme 221: Preparation of 497

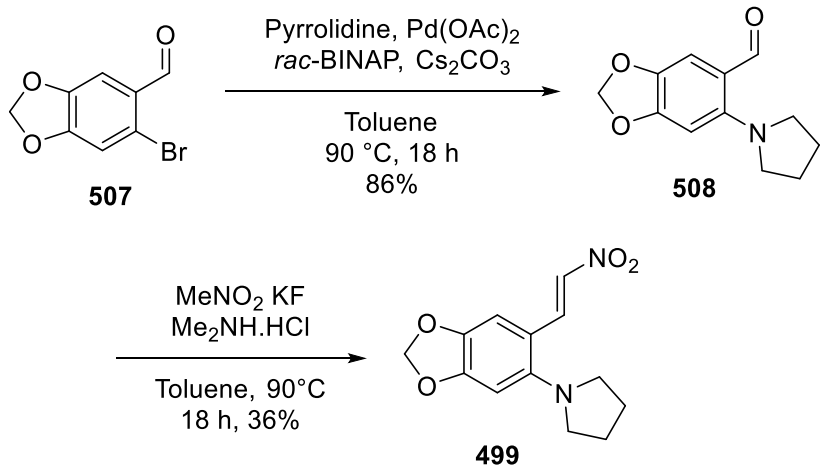
All the above amino-aldehydes were prepared via S_NAr reactions, which requires an electron withdrawn aromatic ring to proceed. The desired electron rich substrates therefore required an alternate method of preparation. The S_NAr reactions were replaced with a Buchwald-Hartwig coupling, as discussed above. These conditions were applied to 6-bromoveratraldehyde **505** with pyrrolidine

again used as the secondary amine (**Scheme 222**). This gave the desired product **506** in a 79% yield. Under the standard Henry reaction conditions nitroalkene **498** was prepared (**Scheme 222**). This gave the desired compound **498** in a 62% yield after 18 h.



Scheme 222: Synthesis of nitroalkene 498

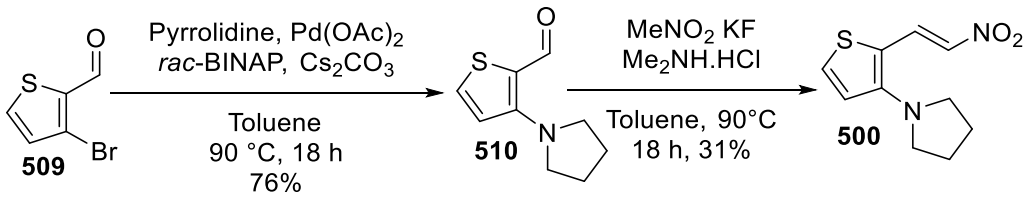
The Buchwald-Hartwig reaction conditions were repeated with 6-bromopiperonal **507** as the aryl bromide with pyrrolidine. The desired product **508** was formed in an 86% yield after 18 h. The prepared 6-(pyrrolidin-1-yl)piperonal **508** was reacted with $MeNO_2$ in a Henry reaction (**Scheme 223**). This gave the desired compound **499** in an isolated yield of 36% after 18 h.



Scheme 223: Preparation of nitroalkene 499

The final compound of this group, 3-(pyrrolidin-1-yl)thiophene-2-carbaldehyde **510**, was prepared via a Buchwald-Hartwig cross-coupling between 3-bromothiophene-2-carbaldehyde **509** and pyrrolidine. The thiophene **510** was

converted into the corresponding nitroalkene **500** (**Scheme 224**). The desired product **500** was isolated in a 31% yield after 18 h.



Scheme 224: Synthesis of 500

Proposed group **D** combined features of both groups **A** and **B** so as to look into the effects of a benzylic vs non-benzylic position on cyclisation when using a 5- or 6-membered ring amine (**Figure 8**).

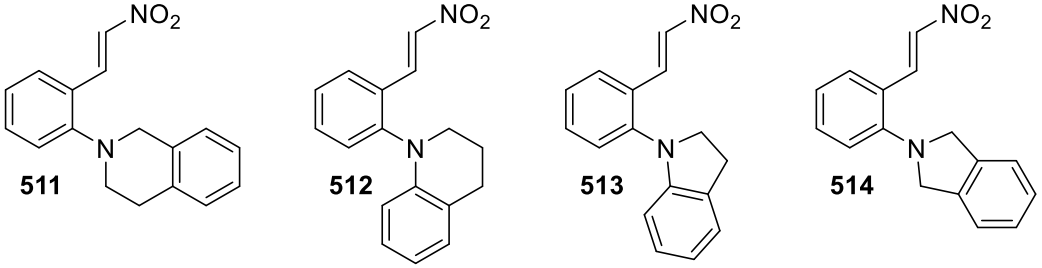
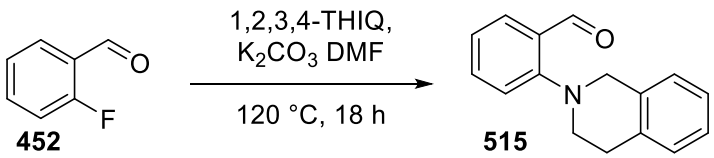


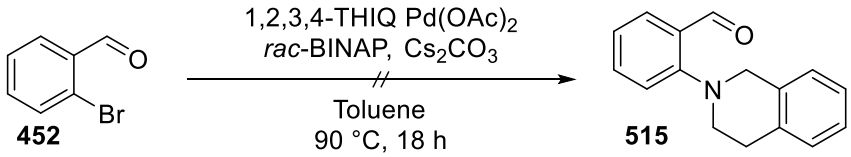
Figure 8: Proposed group D target compounds

First, 1,2,3,4-tetrahydroisoquinoline (THIQ) was reacted with 2-fluorobenzaldehyde **452** under the standard S_NAr conditions used for preparing 2-amino aryl aldehydes (**Scheme 225**). The product **515** was observed by HPLC and ^{1}H NMR but it was not possible to isolate **515** via column chromatography or automatic column chromatography.



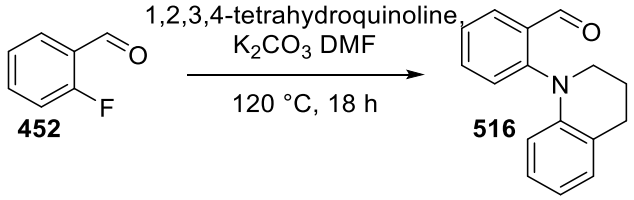
Scheme 225: Attempted synthesis of 515

It was hoped that synthesis via a Buchwald-Hartwig reaction would solve the purification issues, as the side products observed could be different and separable. However, when this reaction (**Scheme 226**) was attempted, the desired product **515** was again observed by ^{1}H NMR but could not be isolated cleanly.



Scheme 226: Attempted Buchwald-Hartwig cross coupling to form 515

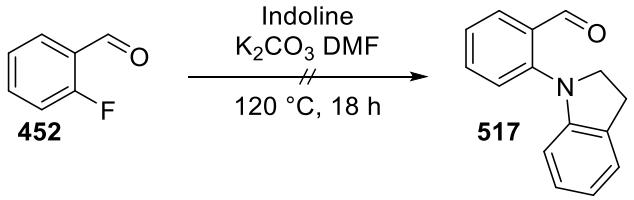
Tetrahydroquinoline was the next amine to be used as a basis for forming a 2-amino aryl aldehyde (**Scheme 227**). Here no conversion was seen when reacting via an S_NAr reaction in DMF. This is likely due to the amine of tetrahydroquinoline being deactivated relative to 1,2,3,4-THIQ as the nitrogen lone pair is in in partial conjugation with the adjacent aromatic ring.



Scheme 227: Attempted synthesis of 516

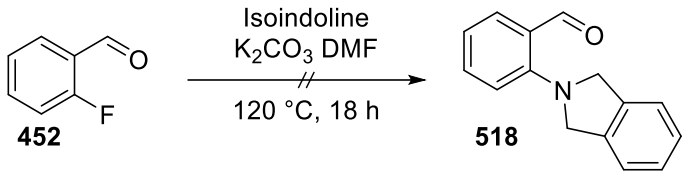
Due to the purification issues present with 1,2,3,4-THIQ, the decision was made not to attempt the synthesis of **516** via a Buchwald-Hartwig reaction as it would not be possible to compare the two nitroalkenes **511** and **512**. Attention was instead turned to the synthesis of the indoline and isoindoline analogues **513** and **514**.

First the reaction between indoline and 2-fluorobenzaldehyde was trialled under the standard S_NAr conditions (**Scheme 228**). Here no conversion was seen and only a mixture of starting materials and degradation was observed.



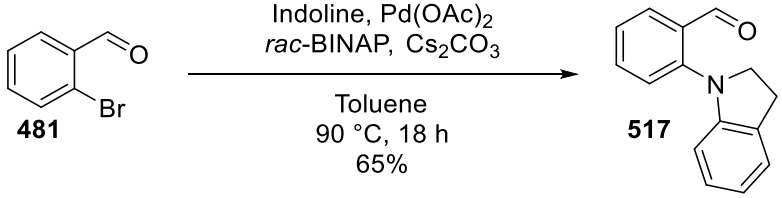
Scheme 228: Attempted reaction to form 517

When the S_NAr reaction was attempted with isoindoline (**Scheme 229**) again no formation of the desired product **518** was observed. Isoindoline instead degraded under the reaction conditions required by the S_NAr.



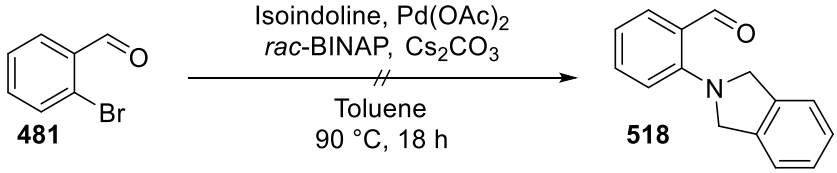
Scheme 229: Attempted formation of 518

The preparation of both substrates was subsequently attempted via a Buchwald-Hartwig cross coupling. When using 2-bromobenzaldehyde **481** and indoline (**Scheme 230**), the desired product **517** was formed in a 65% yield.



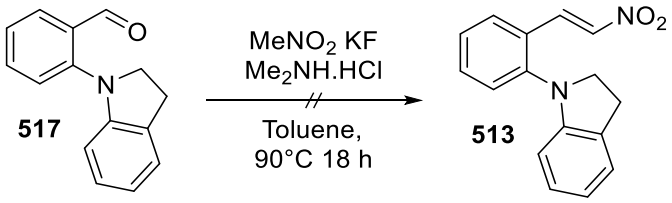
Scheme 230: Synthesis of 517 via Buchwald-Hartwig cross-coupling

The equivalent cross-coupling conditions used with 2-bromobenzaldehyde **481** and isoindoline did not lead to the desired product **518**. Instead, as with the S_NAr reaction, degradation of the isoindoline was observed and no product was isolated (**Scheme 231**).



Scheme 231: Attempted synthesis of 518

The isolated 2-(indolin-1-yl)benzaldehyde **517** was reacted with $MeNO_2$ under the optimised conditions developed above (**Scheme 232**). The desired product was not formed, instead an alternate product was observed. Based upon the ^1H NMR it was apparent that a substitution had occurred on an aromatic ring but the identity of the substitution was not apparent.



Scheme 232: Attempted synthesis of 513

No further investigation of these substrates was performed. The final group of compounds prepared were group **E** (**Figure 9**), which did not fit clearly into groups **A** to **D**.

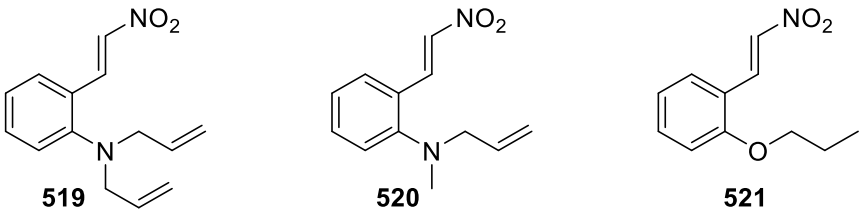
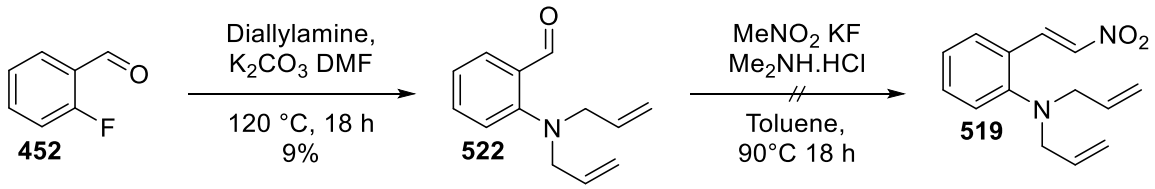


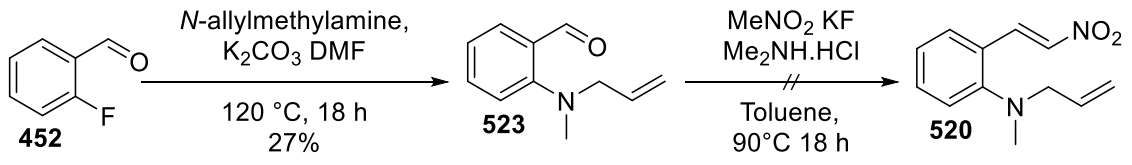
Figure 9: Proposed group E target compounds

First 2-fluorobenzaldehyde **452** and diallylamine were reacted in DMF with K_2CO_3 (**Scheme 233**). This led to the desired product **522** being formed in only a 9% yield with large amounts of degradation of the diallylamine observed. The diallyl substrate **522** was subjected to the Henry conditions that had been optimised previously. It was not possible to isolate the desired product **519**. Instead, only degradation was observed.



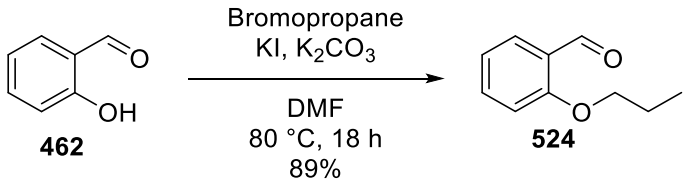
Scheme 233: Synthesis of N,N-diallyl-2-(2-nitrovinyl)aniline 519

An allyl,methyl-amino analogue **523** to **522** was prepared in an equivalent S_NAr reaction (**Scheme 234**). Here an improved yield of 27% was obtained. However, when the conversion of **523** to the corresponding nitroalkene **520** was attempted, the desired product was not obtained (**Scheme 234**). Instead, only degradation was observed with no nitroalkene isolable.



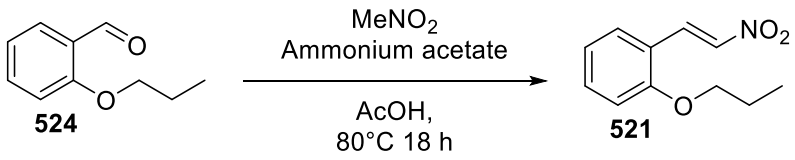
Scheme 234: Attempted synthesis of 520

Finally, 2-propoxybenzaldehyde was prepared (**Scheme 235**). Salicyl aldehyde **463** was alkylated with bromopropane with KI and K_2CO_3 under Finkelstein conditions. This gave the desired compound **524** in an 89% yield.



Scheme 235: Synthesis of 2-propoxybenzaldehyde 524

The isolated 2-propoxybenzaldehyde **524** was reacted with $MeNO_2$ in acetic acid with ammonium acetate (**Scheme 236**).[217] This gave the desired product in an isolated yield of 77%.



Scheme 236: Literature synthesis of 521[217]

This then gave us a library of nitroalkenes (**Figure 10**) with which to probe the extent of the reactivity of the $Gd(OTf)_3$ catalysed cyclisation reaction.

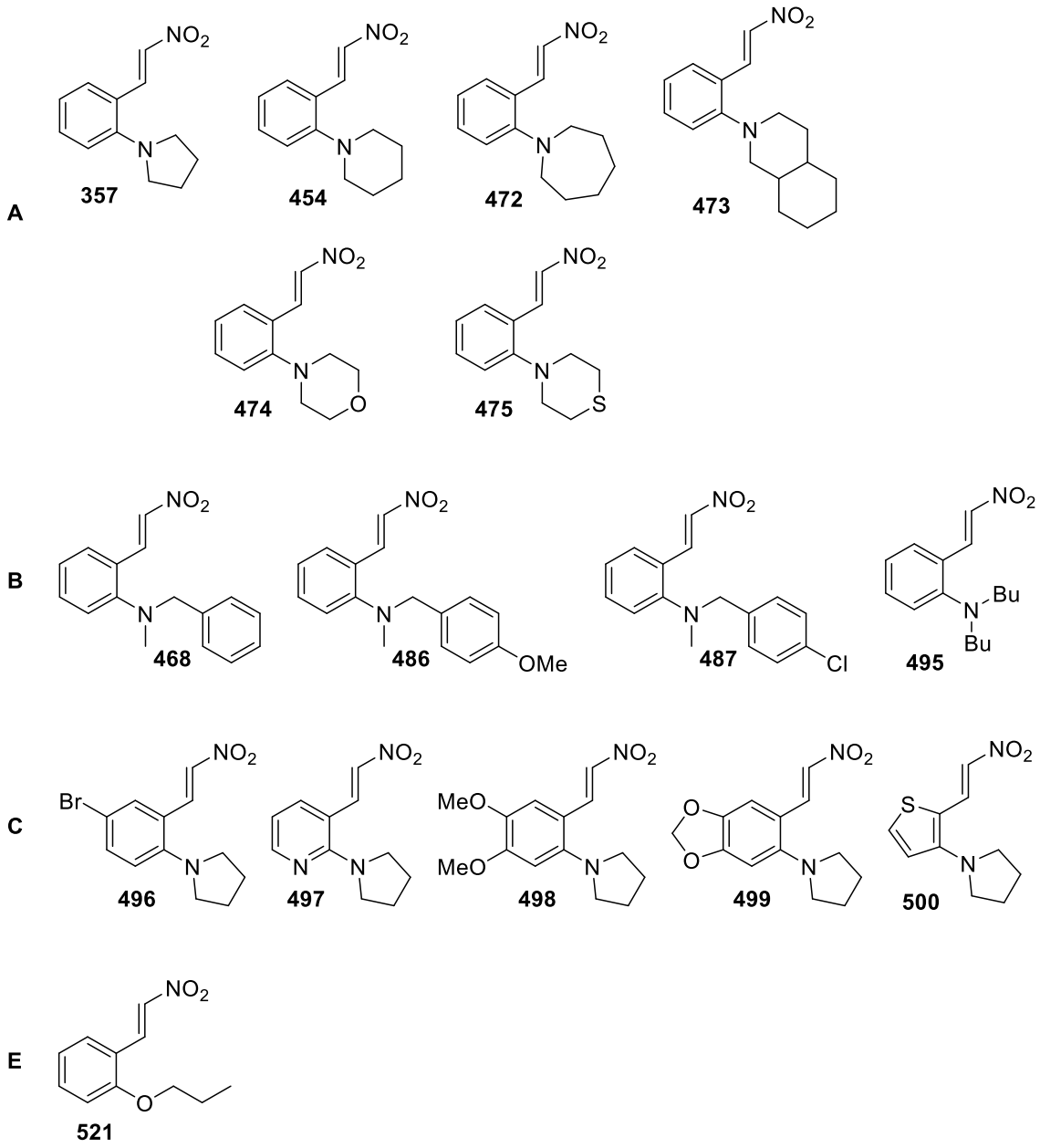
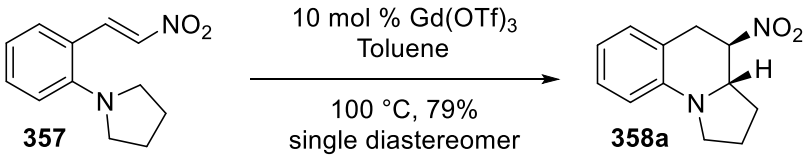


Figure 10: Nitroalkene library

2.4.7 Scope of the Gd(OTf)$_3$ Catalysed 1,5-Hydride Shift

With the alkene library prepared we investigated the scope of the 1,5-hydride shift reaction. The standard conditions, developed with nitroalkenes **357** and **468**, with 30 mol% Gd(OTf)$_3$ catalyst in toluene, were used with each of the nitroalkenes prepared for the investigation into scope.

First group **A** were tested, initially looking at the yield as the ring size changed from a 5 to 6 to 7 membered ring. The 5-membered ring **358a** (**Scheme 237**) gave the previously recorded yield of 79% as a single diastereomer that matched the literature data for the *anti* diastereomer.[171]

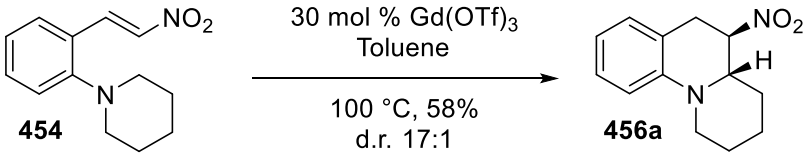


Scheme 237: Synthesis of 358a

Solely isolating the *anti* diastereomer **358a** was expected. This would allow both the nitro and cycloalkyl groups to sit in the equatorial position of the newly formed 6 membered ring and minimise steric interaction (**Figure 11**). By contrast, the *syn* diastereomer **525b** forces the nitro group into the axial position.

Figure 11: *anti*- 525a and *syn* 525b diastereomers of 358

The piperidinyl, or 6-membered ring nitroalkene **454** was slower, with 10 mol% catalyst loading leading to trace conversion by HPLC after 72 h. Increasing to a 30 mol% catalyst loading saw full consumption of the starting material to form **456** within 18 h (**Scheme 238**) in a 57% yield with a 17:1 *dr anti*:*syn*.



Scheme 238: Synthesis of 456

The key peaks for identifying the major diastereomer of **456** were assigned by ^{1}H and ^{13}C NMR. There was a loss of nitroalkene peaks compared to the starting material **454** and the piperidinyl ring lost symmetry. The key ^{1}H NMR peaks for assigning the major diastereomer were H_A δ 3.44 (1H, dd, *J* = 15.5, 7.8 Hz), and H_B δ 3.16 (1H, dd, *J* = 15.5, 5.0 Hz), the two benzyl protons, with a coupling between them of 15.5 Hz. The C*H*NO_2 peak coupled to each with couplings of 7.8 and 5.0 Hz respectively and was therefore assigned as H_C δ 4.70 (1H, ddd, *J* = 7.7, 6.2, 5.1 Hz). The coupling of 6.2 Hz was therefore between H_C and NC*H* (H_D) δ 3.54 (1H, ddd, *J* = 10.8, 6.2, 2.5 Hz). H_D's remaining two couplings are to H_E and H_F, the adjacent protons on the adjacent ring CH_2 (**Figure 12**).

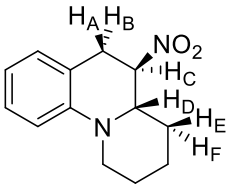


Figure 12: Compound 456a with relevant protons labelled

The coupling between H_C and H_D is 6.2 Hz, which corresponds to an angle of either around 30° or 130°, suggesting a partially eclipsed ring system. The saturated ring does not have the same flattening and the coupling between H_D and H_E is 2.5 Hz, which correlated to an $_{eq\text{-}ax}$ coupling in a 6-membered ring. The coupling of H_D and H_F is 10.8 Hz, which is typical of an $_{ax\text{-}ax}$ interaction, requiring H_D to sit axial and suggesting that the angle between H_D and H_C is more likely to be around 130° than 30°. The coupling between H_C and H_A and H_B are again suggestive of an $_{ax\text{-}eq}$ relationship (5.0 Hz) and an $_{ax\text{-}ax}$ relationship (7.8 Hz), which would put H_C in an axial position. We propose that both H_C and H_D therefore sit in an $_{ax\text{-}ax}$ relationship with both functional groups equatorial, with the major diastereomer therefore the *anti*- diastereomer (**Figure 13**).

We proposed that the difference in reactivity between **357** and **454** was due to the differing sterics of the 5- versus 6- membered ring system. We suggest that the reactive conformer of (E)-1-(2-(2-nitrovinyl)phenyl)pyrrolidine **357** sits closer to the idealised angle of hydride attack into the tethered nitroalkene than is the case with (E)-1-(2-(2-nitrovinyl)phenyl)piperidine **454**, where the piperidinyl protons sit out of plane with the aromatic ring.[218] This seems likely especially as the α-amino carbon that undergoes hydride abstraction in **357** and **454** has similar electronic character.

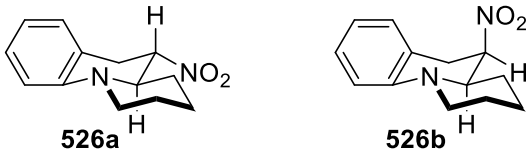
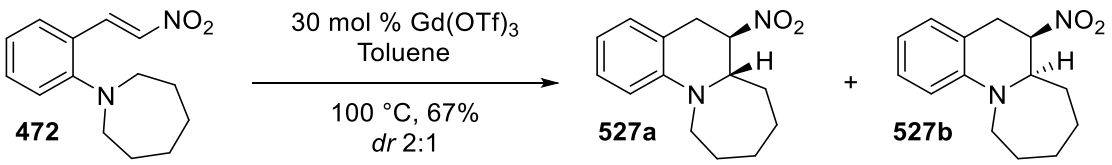


Figure 13: *anti*- 526a and *syn*- 526b diasteromers

The corresponding azepanyl ring nitroalkene **472**, gave an increased yield of 67%, albeit with a lower *dr* of 2:1, compared to the piperidinyl nitroalkene **454** (**Scheme 239**). We proposed that this was due to the less rigid nature of the 7-membered ring compared to the 6, which would lead to less difference in energy

of the two diastereomeric transition states. This increases the likelihood of the conformation required for the hydride transfer being reached.



Scheme 239: Synthesis of 527

The key peaks for identifying the major diastereomer **527a** were assigned by ^{1}H and ^{13}C NMR. There was a loss of nitroalkene peaks compared to the starting material **472** and the azepanyl ring lost symmetry. The key ^{1}H NMR peaks were H_A δ 3.21 (1H, dd, *J* = 17.8, 5.4 Hz) and H_B δ 3.54 (1H, d, *J* = 17.8 Hz), the two benzyl protons with a geminal coupling between them of *J* = 17.8 Hz (**Figure 14**). It was not possible to identify *J* values for H_C δ 4.69 – 4.67 (1H, m), though from the benzyl peaks it was apparent that H_A and H_C had a coupling (5.4 Hz) which suggested an $_{eq\text{-}ax}$ relationship. The lack of coupling between H_B and H_C suggested an $_{eq\text{-}eq}$ relationship in a flattened ring system. H_D δ 4.12 (1H, ddd, *J* = 7.6, 6.4, 3.1 Hz), the NC*H* proton, had *J* values corresponding to both $_{ax\text{-}eq}$ and $_{eq\text{-}eq}$ arrangements. The adjacent ring CH_2 protons did not have identifiable coupling values, so it was not possible to positively identify the spatial arrangement of H_D for **527a** directly.

The minor diastereomer **527b** had analogous benzyl proton peaks $H_{A'}$ δ 3.53 (1H, dd, *J* = 16.2, 12.4 Hz) and $H_{B'}$ δ 3.27 – 3.16 (2H, m, also NCH_2). The coupling of *J* = 16.2 Hz was assigned as the geminal coupling between $H_{A'}$ and $H_{B'}$. $H_{C'}$ δ 4.90 (1H, ddd, *J* = 12.4, 5.7, 4.3 Hz) therefore had a coupling of *J* = 12.4 Hz to $H_{A'}$, suggesting an $_{ax\text{-}ax}$ relationship between them. The NC*H* proton $H_{D'}$ δ 4.08 (1H, dt, *J* = 8.5, 4.3 Hz) had a coupling to $H_{C'}$ of *J* = 4.3 Hz, suggesting an $_{ax\text{-}eq}$ relationship. The final coupling for $H_{C'}$, *J* = 5.7 Hz, was therefore to $H_{B'}$, another $_{ax\text{-}eq}$ spatial relationship, consistent with the other assignments. $H_{C'}$ therefore sits axially and $H_{D'}$ is equatorial, identifying the minor diastereomer **527b** as the *syn* diastereomer. As a result, the major diastereomer **527a** is the *anti* diastereomer.

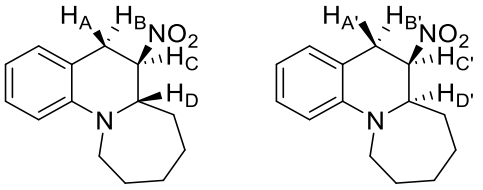
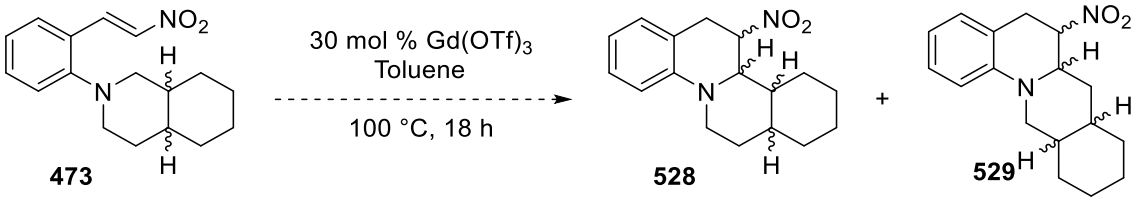


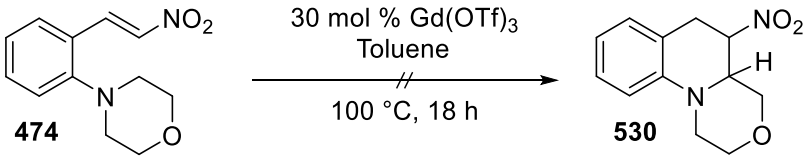
Figure 14: Diastereomers of 527

The next compound of Group **A** to be subjected to cyclisation conditions was the perhydroisoquinolinyl nitroalkene **473**, which was present as a 3:1 mixture of diastereomers (**Scheme 240**). Here a wide range of structural isomers and diastereomers were observed by HPLC/LCMS. However, it was not possible to isolate any of these isomers in pure enough form to characterise.



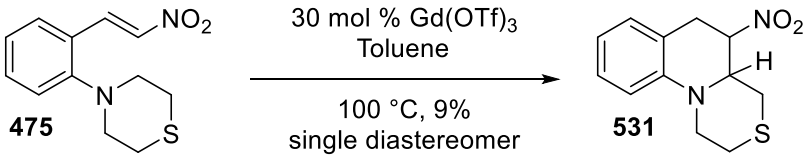
Scheme 240: Proposed products from attempted cyclisation of 473

The attempted rearrangement of (E)-4-(2-(2-nitrovinyl)phenyl)morpholine **474**, gave no conversion by UHPLC/LCMS (**Scheme 241**). It was rationalised that this was due to decreased reactivity of the 6-membered ring coupled with the electron withdrawing oxygen disfavouring any hydride migration β- to it.



Scheme 241: Attempted formation of 530

Finally in group **A**, switching to the thiomorpholine analogue **530**, conversion was observed, albeit in a 9% yield (**Scheme 242**). We rationalised that this was due to the decreased electronegativity of sulfur compared to oxygen. The product **531** was obtained as a single diastereomer.



Scheme 242: Formation of 531

Group **B** were subsequently subjected to the developed cyclisation conditions. The benzyl- substituted amine **468** had previously been reacted to give the desired compound **469** in a 67% yield with a 2:1 *dr* (**Scheme 206**, above).

We proposed that the corresponding *p*-methoxybenzyl- nitroalkene **486** would react more readily under the same conditions than the unsubstituted benzyl equivalent, because the *p*-methoxy group would stabilise the generated positive charge (**Figure 15**).

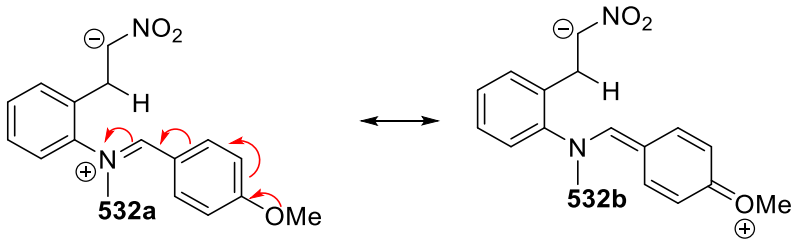
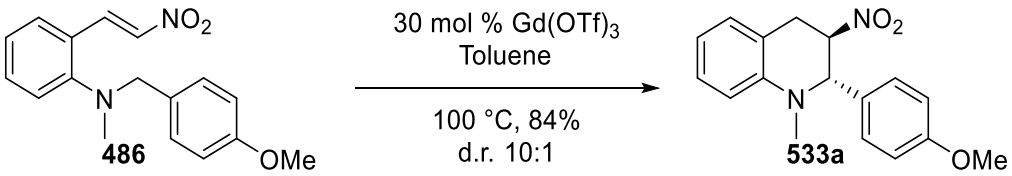


Figure 15: Resonance of generated positive charge following hydride transfer

The cyclisation of **486** with a $Gd(OTf)_3$ catalyst proceeded as predicted, to give the desired product **533** in an 84% yield with a *dr* of 10:1 (**Scheme 243**). The major product was determined to be the *anti*-diastereomer.



Scheme 243: Cyclisation to form 533

The key peaks for identifying the major diastereomer of **533** were assigned though the use of ^{1}H and ^{13}C NMR. There was a loss of nitroalkene peaks compared to the starting material, in line with the shifts seen elsewhere. The key ^{1}H peaks for assignment are the two benzyl protons H_A and H_B, δ 3.77 (1H, ddd, J = 11.9, 6.7, 1.1 Hz), and 3.58 (1H, dd, J = 12.0, 3.4 Hz), with a coupling between them of 12.0 Hz. The H_A coupling of 1.1 Hz is a long range coupling to an aromatic

ring proton and the couplings of 6.7 and 3.4 Hz are to H_C, the C*H*NO_2 proton δ 4.90 (1H, td, *J* = 6.6, 3.4 Hz). Finally, H_D δ 4.80 (1H, d, *J* = 6.6 Hz) was assigned, the apparent triplet of H_C masking two separate 6.6 Hz couplings to adjacent protons (**Figure 16**).

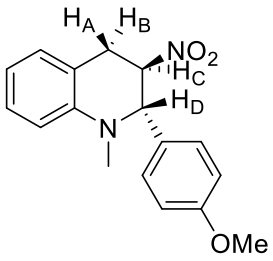


Figure 16: Key protons for diastereomer assignment of 533a

The coupling of 6.6 Hz between H_A and H_C and H_C and H_D suggests an almost eclipsed arrangement for these three protons. The coupling of 3.4 Hz between H_B and H_C would be expected for an angle between the two protons of about 60°. We can therefore propose a structure similar to **469**, above, with the NO_2 and aryl groups in a *trans*- diaxial arrangement, with protons H_A, H_C and H_D sitting equatorially. This assignment was supported by the lowest energy conformer as predicted using the GAMESS interface, using the HF method and the 3-21G Basis Set, which has both bulky groups in the axial position (**Figure 17**).

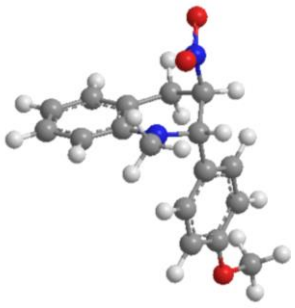
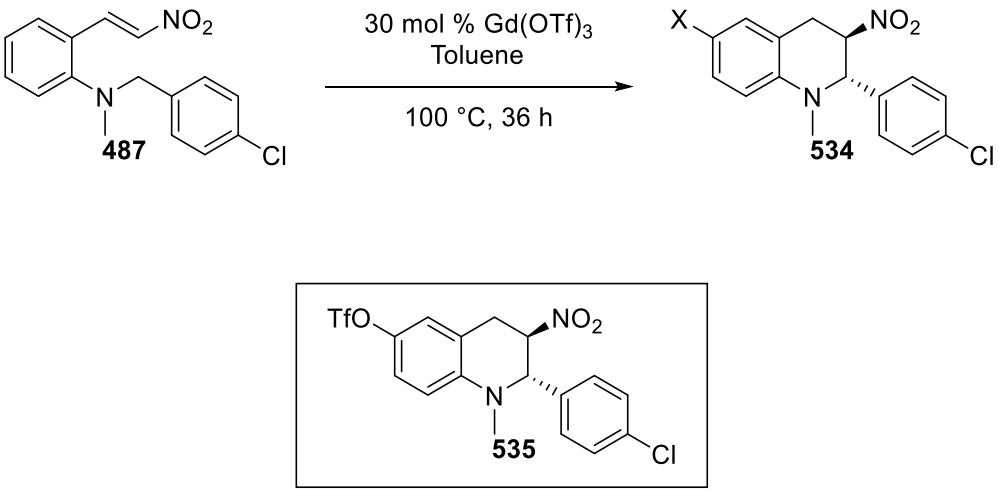


Figure 17: Lowest energy conformation of 533a

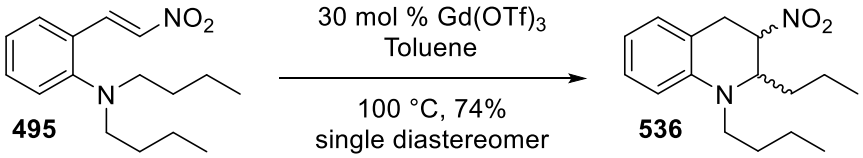
We proposed that the *p*-chloro- analogue **487** would react less readily than the non-substituted corresponding nitroalkene **468** as chloro- groups have an electron withdrawing effect on an aromatic ring, especially in the *o* and *p* positions, making said aromatic ring less able to stabilise the generated positive charge. Here the starting nitroalkene **486** was consumed in 36 hours (**Scheme 245**). However the ^{1}H NMR of the isolated material did not match that of the desired compound. A splitting consistent with an additional substitution on the

first aromatic ring as well as the desired cyclisation was observed. This new substitution did not appear to consist of a group featuring ^{1}H atoms as no additional ^{1}H peaks were present. A new ^{13}C NMR peak at δ 115.9 suggested that the new product contained a single additional carbon atom and the shift was indicative of an ^{-}OTf group, however, the corresponding LCMS peak (451.8 m/z) was not observed. The identity of the isolated product **534** is therefore unknown but could cautiously be assigned as **535**.



Scheme 245: Cyclisation of 487

Finally, dibutyl analogue **495**, which has no conformational restriction from a ring or bias from separate amine groups, gave the desired compound **536** in a high yield of 74% as a single diastereomer (**Scheme 246**).



Scheme 246: Synthesis of 536

The two benzyl protons δ 3.52 (1H, d, *J* = 18.1 Hz), 3.12 (1H, dd, *J* = 18.1, 5.6 Hz) have a coupling of 18.1 Hz to each other. One benzyl proton does not appear to have a coupling to the C*H*NO_2 proton δ 4.75 (1H, m). This is consistent with a 90° angle between the protons, suggesting an $_{eq\text{-}eq}$ relationship in a flattened ring system. The other coupling, 5.6 Hz, is indicative of an angle of about 30°, which is consistent with a flattened ring system and an $_{ax\text{-}eq}$ relationship. It therefore seems likely that the nitro group in **536** sits axially as with **469**, above. Unfortunately, whilst COSY NMR shows coupling between the C*H*NO_2 and NC*H*

δ 4.04 (1H, m) proton, it was not possible to ascertain *J* values for their coupling. Computational modelling using the GAMESS interface, with the HF method and the 3-21G Basis Set, suggested that the *anti* diastereomer is lower energy (**Figure 18**). The *anti* diastereomer, when modelled, sits with the NO_2 group axial in the lowest energy conformation, whereas the *syn* diastereomer sits with the NO_2 group equatorial. It may therefore be possible to cautiously assign the single diastereomer **536** as the *anti* diastereomer, though this cannot be claimed with any great certainty.

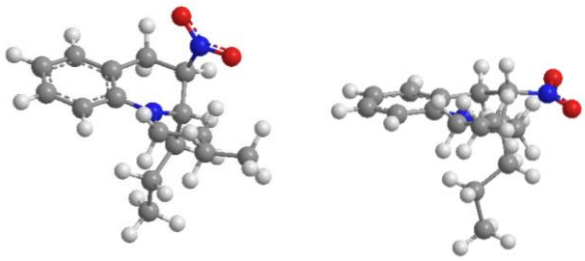
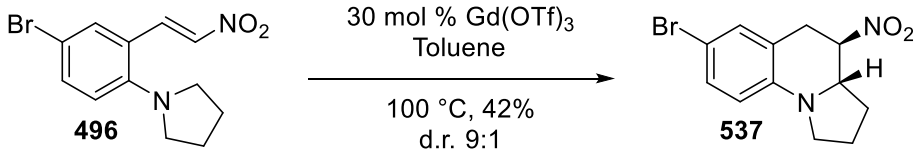


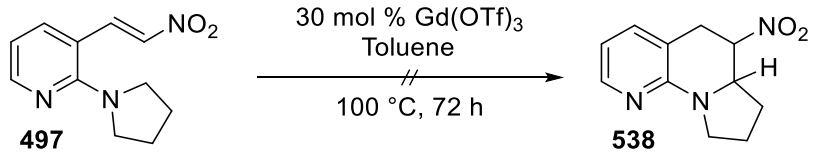
Figure 18: *anti*- and *syn*- diastereomers of 536

The next group of compounds to be screened was Group **C**. Analogue **496**, with a 5-bromo substitution, was cyclised under the standard conditions (**Scheme 247**). The desired compound was obtained in a 9:1 *dr* with a decreased yield of 42% compared to the non-substituted equivalent. Here again the *anti* diasteromer dominated, with the ^{1}H NMR peak for the C*H*NO_2 proton δ 4.42 (1H, ddd, *J* = 12.0, 9.7, 4.7 Hz) matching the peak for the non-substituted analogue **358a** δ 4.46 (1H, ddd, *J* = 11.9, 9.7, 4.8 Hz). The lower yield may possibly be indicative of the deactivating effect of the Br atom.



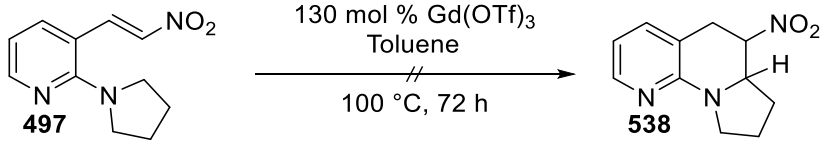
Scheme 247: Synthesis of 537

The more electron withdrawn (E)-3-(2-nitrovinyl)-2-(pyrrolidin-1-yl)pyridine **497** was likewise subjected to cyclisation conditions (**Scheme 248**). Here no conversion was observed, only degradation.



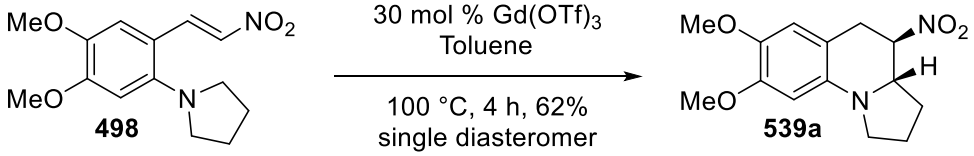
Scheme 248: Attempted cyclisation of 497

The reaction was repeated with 1.3 equivalents of $Gd(OTf)_3$ (**Scheme 249**) in an attempt to drive the cyclisation to occur, the additional equivalent of $Gd(OTf)_3$ added to overcome the potential co-ordination of the $Gd(OTf)_3$ to the pyridine N lone pair. Here again mostly degradation was observed. There was a possible trace amount of the desired product visible in the crude ^{1}H NMR but it was not possible to isolate this material via column chromatography.



Scheme 249: Second attempted cyclisation of 497

Electron rich aryl systems were likewise reacted to form substituted tetrahydroquinolines. First a dimethoxy- substituted nitroalkene **498** was cyclised in a 62% yield after 4 h, giving the product as a single diastereomer (**Scheme 250**).



Scheme 250: Cyclisation to form 539a

This analogue gave the same *anti* diastereomer as the other pyrrolidinyl substituted compounds as determined from comparison of their ^{1}H NMRs, with the C*H*NO_2 peak for **539a**, δ 4.45 (1H, ddd, *J* = 11.8, 9.8, 4.9 Hz) matching that for the unsubstituted analogue **358a**. In order to prove this assignment, a crystal structure of **539a** was obtained (see **Figure 19** and Appendix 2). The compound being present as both enantiomers which make up the *anti* diastereomer was confirmed.

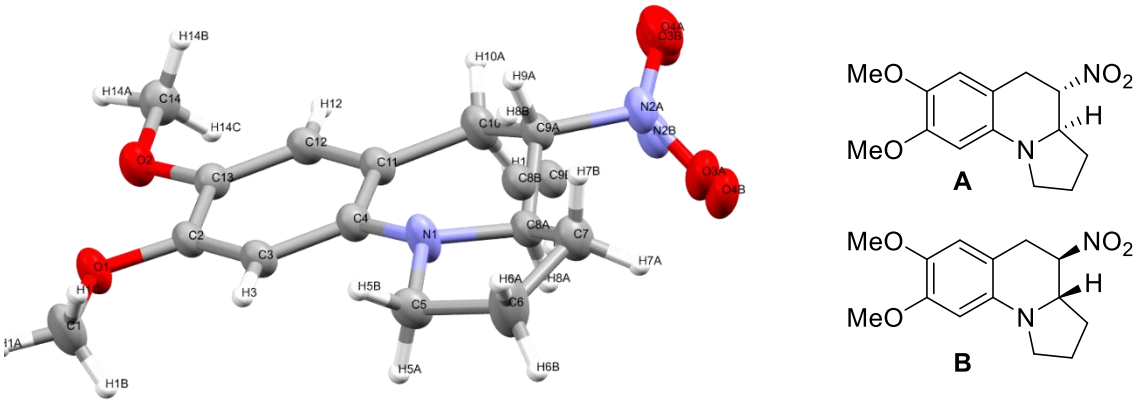
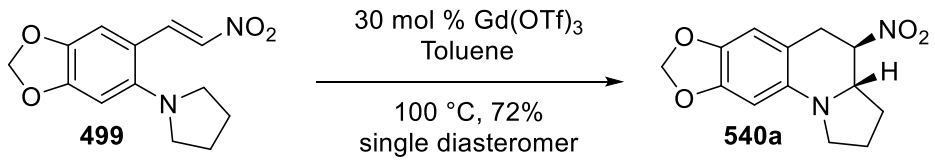


Figure 19: Crystal structure of 539a[c]

The piperonaldehyde derived analogue **499** was also cyclised (**Scheme 251**). Here the analogous product **540a** was isolated in a 72% yield as a single diastereomer after 18 h.



Scheme 251: Cyclisation of 499 to form 540a

We believe the difference in reaction time could be due to the arrangement of the lone pair orbitals of the oxygens attached to each aromatic ring. In the case of the dimethoxy compound, free rotation of each bond is possible, allowing a conformation whereby the lone pair is able to combine with the delocalised π-cloud of the aromatic ring and greatly increase the electron density. In contrast, the two oxygens of the cyclic compound **499** are much more constrained, so the 5-membered ring does not allow idealised sp^2 hybridisation of the oxygen atoms to allow the more favourable p-orbital overlap.

Two further analogues were prepared in order to investigate the relative effects of the decreased reactivity of the morpholino- and thiomorpholino- substrates **541** and **542** and the increased reactivity achieved with the dimethoxy- compound **498** (**Figure 20**).

[c] Crystal structure obtained by Merina Corpinot

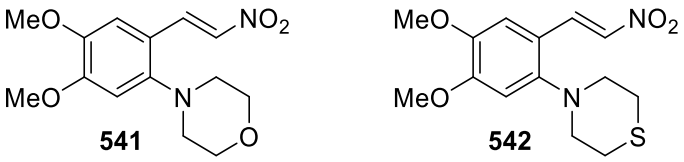
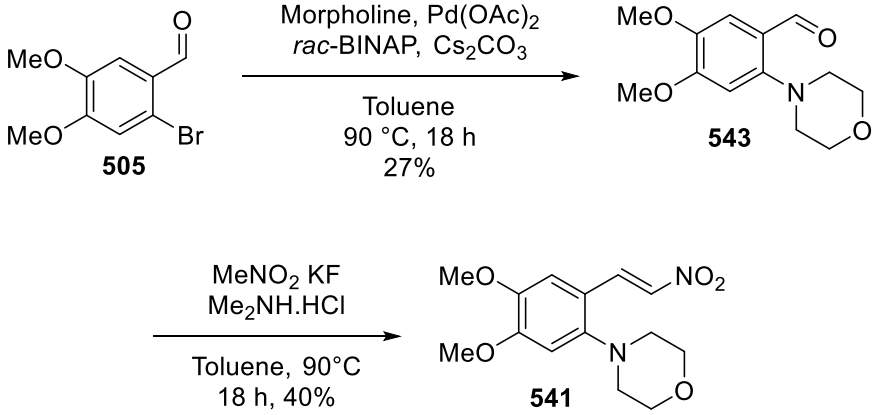


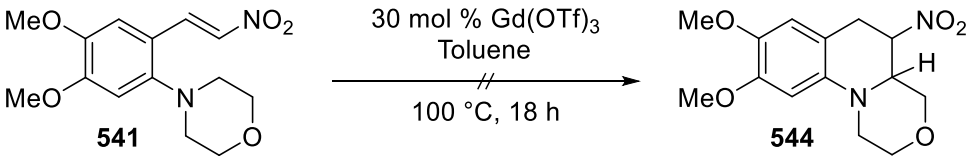
Figure 20: The two new proposed substrates

Attention was first turned towards the morpholino- aldehyde **543** (**Scheme 252**). 6-bromoveratraldehyde **505** was reacted with morpholine under the previously discussed Buchwald-Hartwig conditions. The desired nitroalkene **541** was subsequently formed under standard conditions (**Scheme 252**). This compound **541** was isolated in a 40% yield.



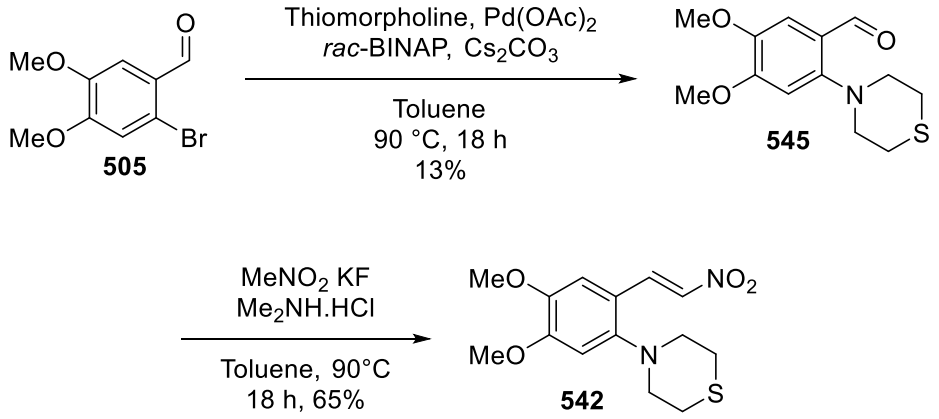
Scheme 252: Synthesis of nitroalkene 541

With nitroalkene **541** prepared, cyclisation was attempted (**Scheme 253**). Here no conversion was observed as with the corresponding non-dimethoxy-morpholino analogue **474**.



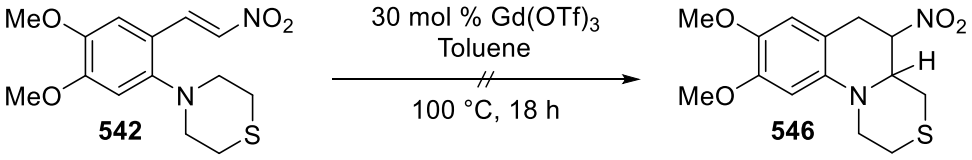
Scheme 253: Failed cyclisation of 541

Attention was therefore turned to the thiomorpholino- analogue in the hope that, as with the non-dimethoxy- substrates, cyclisation would be more successful. First the required aldehyde **545** was prepared in a poor 13% yield (**Scheme 254**). The aldehyde **545** was converted to the corresponding nitroalkene **542**. This conversion was performed under the standard conditions discussed above.



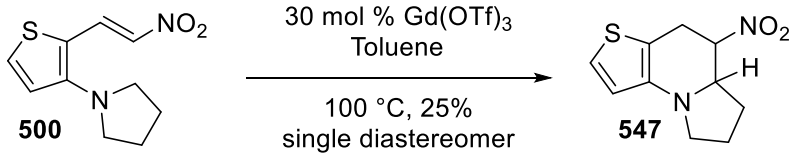
Scheme 254: Synthesis of nitroalkene 542

Cyclisation with $Gd(OTf)_3$ was then attempted (**Scheme 255**). To our surprise no conversion was detected, although it was made more difficult due to the small scale of the reaction. A similar yield to analogue **531** (9%) would have produced under 5 mg of product.



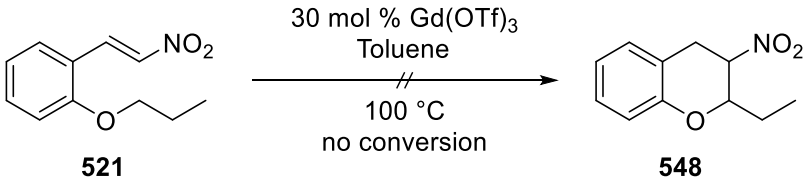
Scheme 255: Attempted cyclisation to form 546

The final compound of group **C**, (E)-1-(2-(2-nitrovinyl)thiophen-3-yl)pyrrolidine **500** was cyclised with $Gd(OTf)_3$ under the optimised conditions discussed above (**Scheme 256**). The desired compound **547** was obtained in a 25% yield as a single diastereomer.



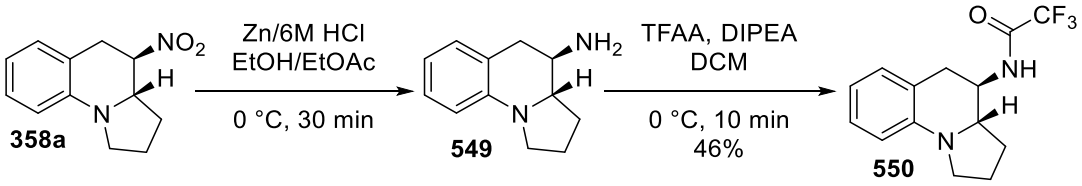
Scheme 256: Cyclisation to form 547

The sole compound **521** of group **E** was then subjected to standard cyclisation conditions with $Gd(OTf)_3$ (**Scheme 257**). Here no conversion was observed. We propose that the increased electronegativity of oxygen versus nitrogen led to a decrease in reactivity.



Scheme 257: Attempted cyclisation of 521 to form 548

Finally, we attempted a Zn/HCl reduction, TFA protection of cyclised product **358a** (**Scheme 258**) as has been used previously within the group.[219–221] This reaction proceeded in a 46% yield in two steps with full retention of diastereoselectivity.



Scheme 258: Reduction and protection of nitro group to form 550

The ^{1}H NMR of **550** showed a shift downfield of the C*H*NO$_2$ proton from δ 4.46 to δ 4.08, consistent with the conversion of a nitro group to a TFA protected amine. A new broad amine proton peak was also present in the ^{1}H NMR δ 6.12 (1H, br). The C*H*NCOCF$_3$ peak δ 4.08 (1H, ddd, *J* = 11.9, 9.7, 5.1 Hz,) of the product **550**, retained the coupling pattern seen in the C*H*NO$_2$ δ 4.46 (1H, ddd, *J* = 11.9, 9.7, 4.8 Hz) proton of **358a**. We therefore assigned the single diastereomer we observed as the *anti*- diastereomer by analogy to the starting material.

2.5 Conclusions and Future Work

A series of aldehydes were synthesised, initially via S_NAr reactions and then via Buchwald-Hartwig cross couplings. These aldehydes were then converted into nitroalkenes and subjected to a 1,5-hydride shift followed by a nitro-Mannich cyclisation. The Henry reaction generally proceeded poorly and further optimisation would improve the overall route to novel tetrahydroquinolines greatly.

Ultimately, we were able to cyclise the following compounds in the corresponding yields (**Figure 21**). This gives a decent range of results and gives some insight into the reactivity of these conditions. It appears that the ability of the compounds to access a reactive conformation is an important factor as to the yield and speed of reaction.

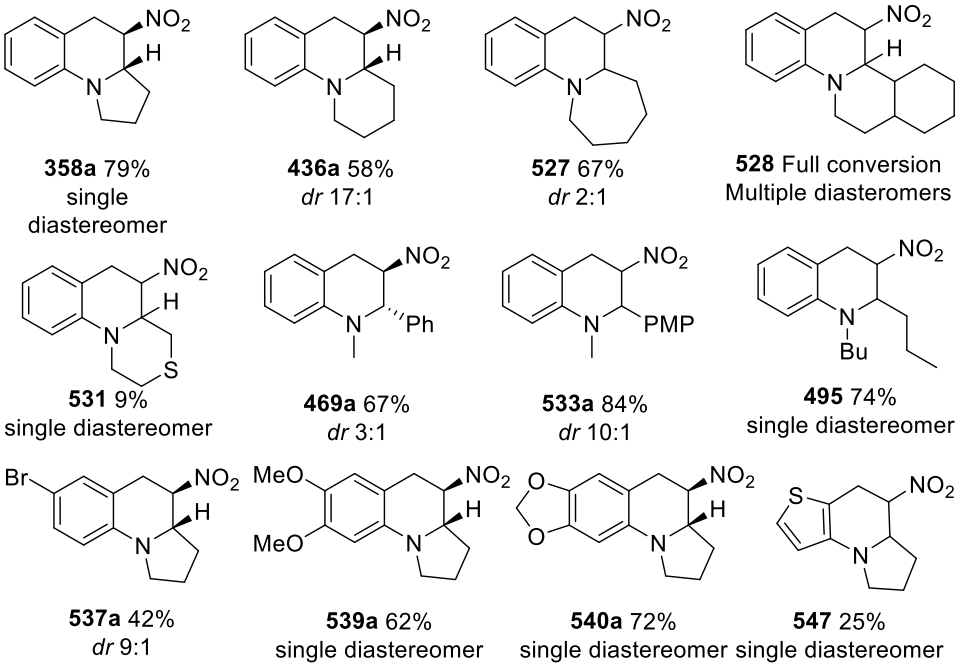


Figure 21: Final determined scope of the Gd(OTf)$_3$ catalysed 1,5-hydride shift and resulting nitro-Mannich reaction

The results show the Gd(OTf)$_3$ catalysed 1,5-hydride shift and subsequent nitro-Mannich cyclisation does have limitations. The reaction proceeds poorly or not at all when using electron deficient substrates; the addition of a bromo- substituent to the aromatic ring, for example, reduced the yield from 79 to 42% between **358a** and **537a**. To the contrary, electron rich substrates formed the corresponding products such as **539a** and **540a** more quickly, though without a clear trend in yield.

Providing an improved synthetic route to relevant nitroalkenes was developed, it would be interesting to continue the synthesis of further substrates that proved difficult. For example, allylamino substrates such as **519** and **520** (**Figure 22**) for comparison with the benzyl substrates **468** and **486** which were successfully prepared. This would give a window into the relevance of adjacent unsaturation in aromatic versus non-aromatic substrates for the 1,5-hydride shift reaction.

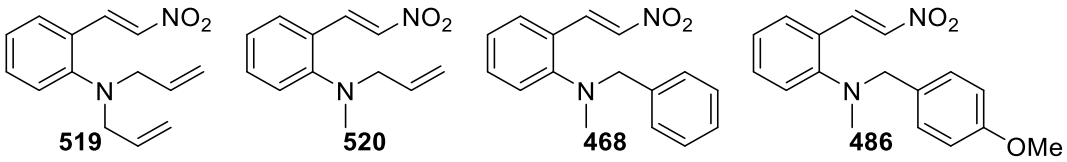
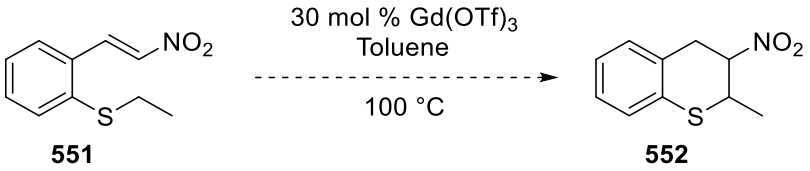


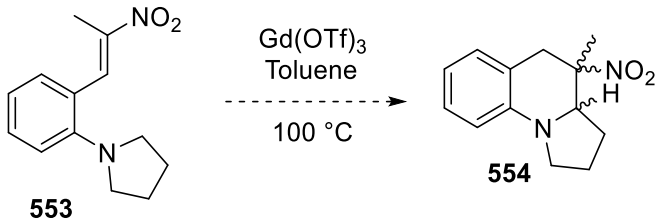
Figure 22: Proposed allyl-nitroalkenes and prepared unsaturated equivalents

Likewise, a thio- analogue of **521** should be prepared and the subsequent cyclisation attempted (**Scheme 259**). This would provide a route to substituted thiochromans such as 2-methyl-3-nitrothiochroman **552**. A route to the required aldehyde to form **551** is known and the Henry reaction used to form the ethereal analogue should then be trialled.[222]



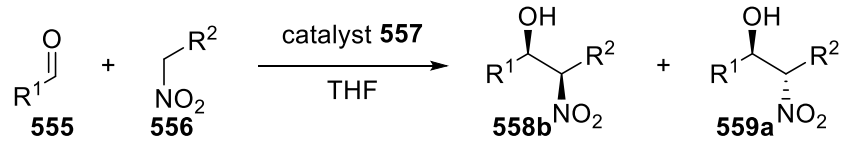
Scheme 259: Proposed cyclisation to form 552

The use of nitroalkanes other than nitromethane is another area worth investigating, though the Henry reactions to form these have traditionally been challenging. The clear first choice to investigate would be nitroethane, adding a methyl group to the final substituted tetrahydroquinoline **554** (**Scheme 260**).

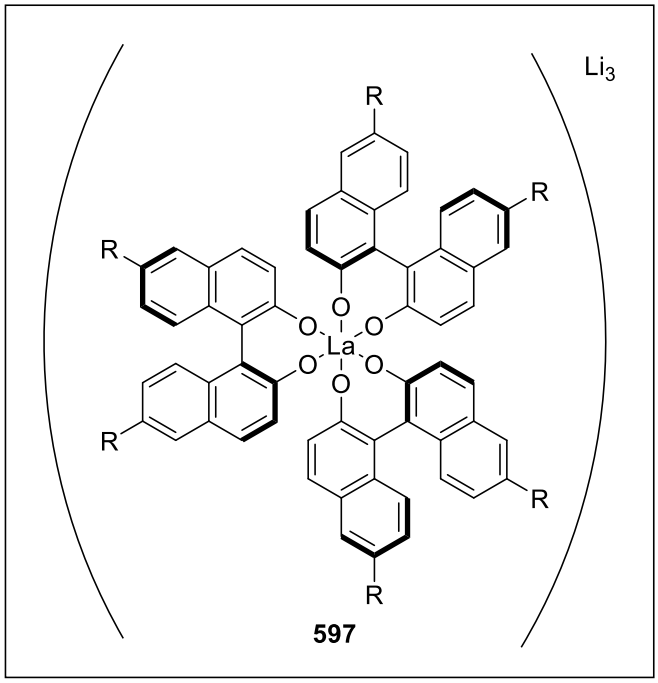


Scheme 260: Proposed cyclisation of 553 to form 554

Selectivity appears to be a clear area to improve on. There are limited examples of gadolinium and other lanthanides being used in asymmetric complexes to form enantioenriched products.[223–225] For example, Shibasaki *et al.* reported several lanthanide-lithium binol complex catalysed reactions.[224] Amongst them was a nitroaldol reaction (**Scheme 261**) with yields of 21-97%, *syn*:*anti dr*s of between 74:26 and 94:6 and ees for the *syn* diastereomer of 66-97%.[224] The authors report that the catalyst complexes were highly tunable through the choice of lanthanide and may be a promising set of catalysts which which to start.



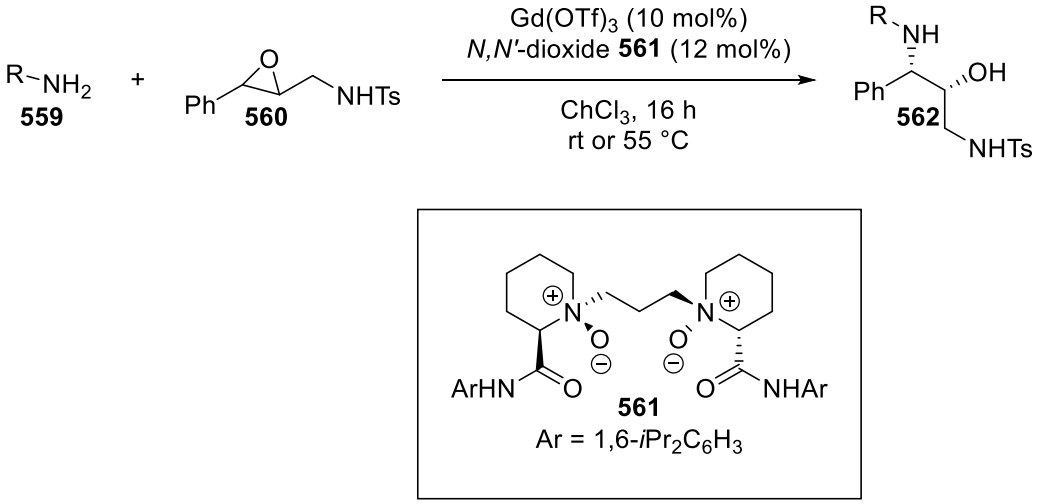
R = H, Me, CCH, $CCSiMe_3$ $CCSiEt_3$
R_1 = CH_2CH_2Ph, $(CH_2)_4CH_3$
R_2 = Me, Et, CH_2OH



597

Scheme 261: Chiral catalysed nitroaldol reaction

More recently, the Yamamoto group published a method of aminolysing aromatic *trans*-2,3-epoxy sulfonamides with a gadolinium-*N,N'*-dioxide (**Scheme 262**).[223] This reaction was found to proceed well with a wide range of amines, seeing yields between 93-98% and ees of 88-98%. However, changes to the epoxide were far less tolerated, with yields reduced to 25% and ees reduced to 7% in some instances.[223]



Scheme 262: Enantioselective epoxide ring opening[223]

Conditions such as these could be adapted to perform nitro-Mannich cyclisations. Alternatively, enantioenriched cyclisations in this manner have previously been performed within the group with the use of an external hydride source.[210]

3. Experimental

3.1 General Experimental Details

All non-aqueous reactions were carried out in oven-dried glassware under an inert atmosphere unless otherwise indicated. All reaction temperatures refer to the values of the external heating element and not that of the reaction mixture. Room temperature implies a temperature range of 20-25 °C. A temperature of 0 °C was achieved using an ice-water bath whereas cryogenic conditions (-78 °C or -68 °C) were achieved using a dry ice and acetone or DCM bath respectively. All additions of reagent occurred as a single portion or fast unless otherwise stated. Column chromatography was carried out using BDH (40-60 µm) silica gel and analytical thin layer chromatography was carried out using Merck Keiselgel aluminium-backed plates coated with silica gel. Automatic column chromatography was carried on a Biotage® Isolera™ Spektra or CombiFlash® EZ Prep fitted with RediSep® or Biotage® SNAP Ultra cartridges. Components were visualised using ultra-violet light (254 nm) and a basic potassium permanganate dip. Removal of solvent *in vacuo* was achieved using Büchi rotary evaporators and either the house vacuum or a Büchi Vac® V-500 pump. Where a compound has been prepared using a specific literature procedure, this is referenced by the compound name.

3.2 Purification of Solvents and Reagents

All commercial chemicals and solvents were used as supplied unless otherwise stated. The dry solvents toluene and THF were obtained from a solvent tower, where degassed solvents were passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure. Other anhydrous solvents were purchased bottled from the Aldrich chemical company and used as provided. Activation of 4 Å molecular sieves was achieved by heating under a high vacuum.

3.3 Characterisation

Melting points are uncorrected and were obtained using a Reichert Melting Point Apparatus. Infrared (IR) spectra were recorded on a Perkin Elmer spectrum 100 FT-IR (ATR mode). ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance 300 spectrometer, at 400 MHz on a Bruker Avance 400 spectrometer, at 500 MHz on a Bruker Avance 500 spectrometer, at 600 MHz on a Bruker Avance 600 spectrometer or at 700 MHz on a Bruker Avance 700 spectrometer in the

stated solvent using the residual protic solvent $CHCl_3$ (δ = 7.26 ppm, s) or DMSO (δ = 2.56 ppm, qn) as the internal standard. Chemical shifts are quoted in ppm using the following abbreviations: s, singlet d, doublet t, triplet q, quartet qn, quintet m, multiplet, br, broad or a combination of these. The coupling constants (*J*) are measured in Hertz. ^{13}C NMR spectra were recorded at 125 MHz on a Bruker Avance 600 Spectrometer or at 175 MHz on a Bruker Avance 700 Spectrometer in the stated solvent using the internal reference of $CHCl_3$ (δ = 77.0 ppm, t) or DMSO (δ = 39.52 ppm, sept) as the internal standard.[226] Chemical shifts are reported to the nearest 0.1 ppm. Mass spectrometry data was collected on Thermo Finnigan Mat900xp (EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments.

3.4 Experimental Procedures

3.4.1 Synthesis of 2-Aminobenzaldehydes

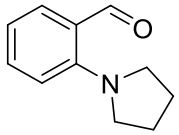
General Procedure A[171]

A secondary amine (1.2 equivalents) was added to a suspension of potassium carbonate (1.2 equivalents) in a solution of a 2-fluoroaryl aldehyde (1 equivalent) and DMF (1 mL per mmol) at rt. The solution was heated to 120 °C for 18 h before cooling to rt. The reaction mixture was diluted with water (30 mL) and the mixture extracted with EtOAc (50 mL). The organic layer was then washed with sat. $NaHCO_3$ solution (4 x 50 mL) and brine (50 mL) before being dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude product was then purified via column chromatography to give the pure product.

General Procedure B

A 2-bromoaryl aldehyde (1 equivalent) was added to a suspension/solution of caesium carbonate (1.4 equivalents), $Pd(OAc)_2$ (0.01 equivalents) and (±)BINAP (0.03 equivalents) in toluene (10 mL per mmol). The reaction mixture was stirred at rt for 5 min before a secondary amine (1.1 equivalents) was added and the resulting mixture was heated to 90 °C for 18 h. Following cooling to rt, the solvent was removed *in vacuo* and the crude product was purified via column chromatography.

2-(Pyrrolidin-1-yl)benzaldehyde 290[171]

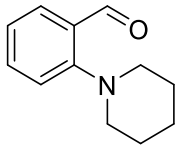


Prepared via general procedure A. Potassium carbonate (1.66 g, 12.0 mmol), DMF (10 mL), 2-fluorobenzaldehyde (1.08 mL, 10.0 mmol), pyrrolidine (1.02 mL, 12.0 mmol). Purified via column chromatography (10% EtOAc in hexane) to give the product as a bright orange oil (1.52 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (1H, s, ArC*H*O), 7.71 (1H, dd, *J* = 7.8, 1.8 Hz, Ar*H*), 7.38 (1H, ddd, *J* = 8.7, 7.0, 1.8 Hz, Ar*H*), 6.86 – 6.75 (2H, m, Ar*H*), 3.36 (4H, ddd, *J* = 6.5, 4.2, 2.6 Hz, NCH_2), 2.05 – 1.92 (4H, m, NCH_2CH_2).

Data in agreement with literature values[171]

2-(Piperidin-1-yl)benzaldehyde 453[171]

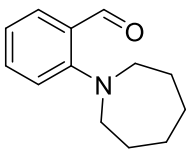


Prepared via general procedure A. Potassium carbonate (835 mg, 6 mmol), DMF (5 mL), 2-fluorobenzaldehyde (0.54 mL, 5.0 mmol) and piperidine (0.60 mL, 6.0 mmol). Purified via column chromatography (5% TBME in hexane) to give the product as a yellow oil (509 mg, 53%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (1H, d, *J* = 0.6 Hz, ArC*H*O), 7.79 (1H, dd, *J* = 7.7, 1.7 Hz, Ar*H*), 7.50 (1H, ddd, *J* = 8.3, 7.3, 1.8 Hz, Ar*H*), 7.12 – 7.03 (2H, m, Ar*H*), 3.08 – 3.00 (4H, m, NCH_2), 1.80 – 1.73 (4H, m, NCH_2CH_2), 1.66 – 1.58 (2H, m, $NCH_2CH_2CH_2$).

Data in agreement with literature values[202]

2-(Azepan-1-yl)benzaldehyde 477

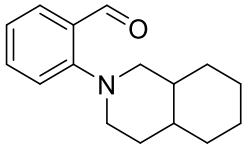


Prepared via general procedure A. Potassium carbonate (1.68 g, 12.2 mmol), DMF (10 mL), 2-fluorobenzaldehyde (1.10 mL, 10.4 mmol) and hexamethyleneimine (1.4 mL, 1.2 mmol). Purified via column chromatography (10% EtOAc in hexane) to give the product as a yellow oil (1.27 g, 62%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (1H, s, C*H*O), 7.74 (1H,dd, *J* = 7.8, 1.8 Hz, Ar*H*), 7.41 (1H, ddd, *J* = 8.6, 7.1, 1.8 Hz, Ar*H*), 7.08 (1H, d, *J* = 8.4 Hz, Ar*H*), 6.93 (1H, t, *J* = 7.4 Hz, Ar*H*), 3.44 – 3.36 (4H, m, NC*H*$_2$), 1.86 – 1.76 (4H, m, NCH$_2$C*H*$_2$), 1.74 – 1.63 (4H, m, NCH$_2$CH$_2$C*H*$_2$).

Data in agreement with literature values[227]

2-(Perhydroisoquinolin-2-yl)benzaldehyde 478

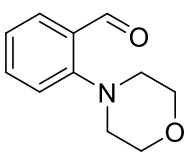


Prepared via general procedure A. Potassium carbonate (1.65 g, 11.9 mmol), DMF (10 mL), 2-fluorobenzaldehyde (1.08 mL, 10.0 mmol) and perhydroisoquinoline (1.79 mL, 12.0 mmol). Purified via automatic column (0-10% EtOAc in heptane) to give the product as a yellow oil as a mixture of diastereomers (2.10 g, 86%, d.r. 3:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (1H, s, C*H*O), 7.79 (1H, dd, *J* = 7.7, 1.6 Hz, Ar*H*), 7.52 – 7.45 (1H, m, Ar*H*), 7.14 – 7.03 (2H, m, Ar*H*), 3.25 – 3.18 (1H, m), 3.15 – 3.08 (1H, m), 2.96 (1H, d, *J* = 10.0 Hz), 2.94 – 2.85 (1H, m), 2.04 (1H, s), 1.94 – 1.82 (2H, m), 1.66 (2H, td, *J* = 10.0, 4.1 Hz), 1.60 – 1.40 (7H, m), 1.29 (4H, dd, *J* = 15.1, 7.6 Hz).

Data in agreement with literature values[228]

2-Morpholinobenzaldehyde 479



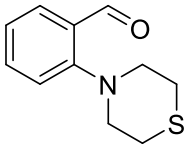
Prepared via general procedure A. Potassium carbonate (1.66 g, 12.0 mmol), DMF (10 mL), 2-fluorobenzaldehyde (1.08 mL, 10.0 mmol) and morpholine

(1.05 mL, 12.0 mmol). Purified via automatic column chromatography (2-20% EtOAc in heptane) to give the product as a yellow oil (1.34 g, 70%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (1H, d, *J* = 0.5 Hz, C*H*O), 7.82 (1H, dd, *J* = 7.7, 1.6 Hz, Ar*H*), 7.55 (1H, ddd, *J* = 8.2, 7.3, 1.7 Hz, Ar*H*), 7.20 – 7.08 (2H, m, Ar*H*), 3.93 – 3.86 (4H, m, OCH_2), 3.09 (4H, dd, *J* = 5.5, 3.8 Hz, NCH_2).

Data in agreement with literature values[227]

2-Thiomorpholinobenzaldehyde 480

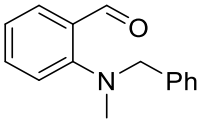


Prepared via general procedure B. Caesium carbonate (915 mg, 2.81 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), (±)BINAP (40 mg, 0.06 mmol), toluene (20 mL), 2-bromobenzaldehyde (0.23 mL, 2.0 mmol), thiomorpholine (0.22 mL, 2.2 mmol). Purified via column chromatography (10% EtOAc in hexane) to give the product as a yellow oil (340 mg, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.33 (1H, d, *J* = 0.5 Hz, C*H*O), 7.82 (1H, dd, *J* = 7.7, 1.7 Hz, Ar*H*), 7.54 (1H, ddd, *J* = 8.1, 7.3, 1.7 Hz, Ar*H*), 7.15 (2H, m, Ar*H*), 3.38 – 3.33 (4H, m, NCH_2), 2.88 – 2.83 (4H, m, SCH_2).

Data in agreement with literature values[229]

2-(Benzyl(methyl)amino)benzaldehyde 468

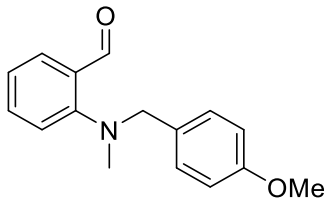


Prepared via general procedure A. Potassium carbonate (1.68 g, 12.2 mmol), DMF (10 mL), 2-fluorobenzaldehyde (1.01 mL, 9.59 mmol) and N-benzylmethylamine (1.51 mL, 11.7 mmol). Purified via automatic column (2-20% EtOAc in heptane) to give the product as a yellow oil (1.67 g, 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (1H, d, *J* = 0.5 Hz, C*H*O), 7.82 (1H, dd, *J* = 7.7, 1.7 Hz, Ar*H*), 7.48 (1H, ddd, *J* = 8.3, 7.2, 1.8 Hz, Ar*H*), 7.35 – 7.30 (2H, m, Ar*H*), 7.28 (3H, apparent triplet, *J* = 3.0 Hz, Ar*H*), 7.12 – 7.04 (2H, m, Ar*H*), 4.34 (2H, s, NCH_2Ar), 2.82 (3H, s, NCH_3).

Data in agreement with literature values[170]

2-((4-Methoxybenzyl)(methyl)amino)benzaldehyde 490

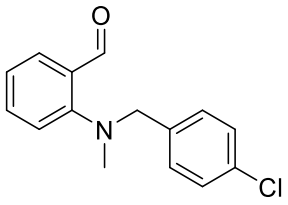


Prepared via general procedure A. Potassium carbonate (832 mg, 6.02 mmol), DMF (5 mL), 2-fluorobenzaldehyde (0.54 mL, 5.0 mmol) and 4-methoxy-N-methylbenzylamine (0.90 mL, 6.0 mmol). Purified via column chromatography (10% EtOAc in hexane) to give the product as a yellow oil (616 mg, 48%)

^{1}H NMR (700 MHz, $CDCl_3$) δ 10.39 (1H, s, C*H*O), 7.82 (1H, dd, *J* = 7.7, 1.7 Hz, Ar*H*), 7.47 (1H, ddd, *J* = 8.8, 7.3, 1.7 Hz, Ar*H*), 7.16 (2H, d, *J* = 8.6 Hz, Ar*H*), 7.07 (2H, m, Ar*H*), 6.85 (2H, d, *J* = 8.6 Hz, Ar*H*), 4.26 (2H, s, NCH_2), 3.80 (3H, s, OCH_3), 2.79 (3H, s, NCH_3).

Data in agreement with literature values[230]

2-((4-Chlorobenzyl)(methyl)amino)benzaldehyde 492

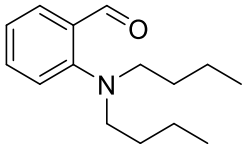


Prepared via general procedure A. Potassium carbonate (835 mg, 6.04 mmol), DMF (5 mL), 2-fluorobenzaldehyde (0.54 mL, 5.0 mmol) and N-(4-chlorobenzyl)-N-methylamine (0.80 mL, 6.0 mmol). Purified via column chromatography (10% EtOAc in hexane) to give the product as a yellow oil (277 mg, 21%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (1H, s, C*H*O), 7.82 (1H,dd, *J* = 7.9, 1.7 Hz, Ar*H*), 7.48 (1H, td, *J* = 8.0, 1.7 Hz, Ar*H*), 7.32 – 7.27 (2H, m, Ar*H*), 7.20 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.09 (2H, t, *J* = 7.8 Hz, Ar*H*), 4.29 (2H, s, NCH_2Ar), 2.80 (3H, s, NCH_3).

Data in agreement with literature values[230]

2-(Dibutylamino)benzaldehyde 494

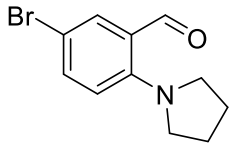


Prepared via general procedure A. Potassium carbonate (1.68 g, 12.2 mmol), DMF (10 mL), 2-fluorobenzaldehdye (1.10 mL, 10.4 mmol), dibutylamine (2.0 mL, 12 mmol). Purified via column chromatography (0-2% EtOAc in hexane) to give the product as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (1H, d, *J* = 0.6 Hz, C*H*O), 7.80 (1H, dd, *J* = 7.7, 1.7 Hz, Ar*H*), 7.48 (1H, ddd, *J* = 8.3, 7.2, 1.8 Hz, Ar*H*), 7.16 (1H, d, *J* = 8.2 Hz, Ar*H*), 7.06 (1H, t, *J* = 7.5 Hz, Ar*H*), 3.18 – 3.07 (4H, t, *J* = 7.4 Hz, NCH_2), 1.52 – 1.41 (4H, m, NCH_2CH_2), 1.26 (4H, apparent sextet, *J* = 14.6, 7.3 Hz, $NCH_2CH_2CH_2$), 0.86 (6H, t, *J* = 7.3 Hz, $NCH_2CH_2CH_2CH_3$).

Data in agreement with literature values[231]

5-Bromo-2-(pyrrolidin-1-yl)benzaldehyde 502

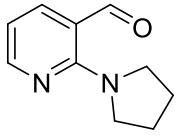


Prepared via general procedure A. Potassium carbonate (1.69 g, 12.3 mmol), DMF (10 mL), 5-bromo-2-fluorobenzaldehyde (1.21 g, 5.96 mmol), pyrrolidine (1.0 mL, 12 mmol). Purified via automatic column chromatography (2 – 20% EtOAc in heptane) to give the product as an orange oil (530 mg, 35%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (1H, s, C*H*O), 7.79 (1H, d, *J* = 2.5 Hz, Ar*H*), 7.42 (1H, dd, *J* = 9.0, 2.6 Hz, Ar*H*), 6.72 (1H, d, *J* = 9.0 Hz, Ar*H*), 3.38 – 3.31 (4H, m, NCH_2), 2.03 – 1.97 (4H, m, NCH_2CH_2).

Data in agreement with literature values[232]

2-(Pyrrolidin-1-yl)nicotinaldehyde 504

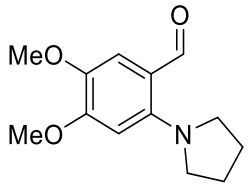


Prepared via general procedure A. Potassium carbonate (1.67 g, 12.1 mmol), DMF (10 mL), 2-fluoro-3-pyridine carboxaldehyde (1.00 mL, 10.4 mmol) and pyrrolidine (1.10 mL, 13.2 mmol). Purified via automatic column chromatography (2 – 20% EtOAc in heptane) to give the product as a yellow oil (1.18 g, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.02 (1H, s, C*H*O), 8.33 (1H, dd, *J* = 4.6, 1.9 Hz, Ar*H*), 7.94 (1H, dd, *J* = 7.6, 2.0 Hz, Ar*H*), 6.71 (1H, dd, *J* = 7.6, 4.6 Hz, Ar*H*), 3.58 – 3.50 (4H, m, NCH_2), 2.01 – 1.95 (4H, m, NCH_2CH_2).

Data in agreement with literature values[134]

4,5-Dimethoxy-2-(pyrrolidin-1-yl)benzaldehyde 506

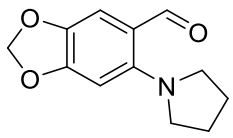


Prepared via general procedure B. Caesium carbonate (911 mg, 2.80 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), (±)BINAP (39 mg, 0.06 mmol). 6-bromoveratraldehyde (493 mg, 2.02 mmol), toluene (20 mL), pyrrolidine (0.19 mL, 2.2 mmol). Purified via column chromatography (40% EtOAc in hexane) to give the product as a yellow crystalline solid (373 mg, 79%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.11 (1H, s, C*H*O), 7.30 (1H, s, Ar*H*), 6.32 (1H, s, Ar*H*), 3.94 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.44 (4H, t, *J* = 6.5 Hz, NCH_2), 2.04 – 1.96 (4H, m, NCH_2CH_2). m.p. 70 – 72 °C Lit. not reported

Data in agreement with literature values[233]

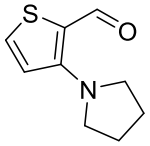
6-(Pyrrolidin-1-yl)piperonal 508



Prepared via general procedure B. Caesium carbonate (915 mg, 2.80 mmol), $Pd(OAc)_2$ (4 mg, 0.02 mmol), (±)BINAP (40 mg, 0.06 mmol), 6-bromopiperonal (460 mg, 2.02 mmol), toluene (20 mL), pyrrolidine (0.19 mL, 2.2 mmol. Purified via column chromatography (20% EtOAc in hexane) to give the product as a yellow crystalline solid (375 mg, 86%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.01 (1H, s, C*H*O), 7.22 (1H, s, Ar*H*), 6.44 (1H, s, Ar*H*), 5.94 (2H, s, OCH_2O), 3.40 – 3.35 (4H, m, NCH_2), 2.02 – 1.96 (4H, m, NCH$_2$CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.1 (*C*HO), 153.7 (Ar*C*), 150.6 (Ar*C*) 140.6 (Ar*C*), 117.4 (Ar*C*), 108.6 (Ar*C*), 101.7 (O*C*H$_2$O), 95.8 (Ar*C*), 54.0 (N*C*H$_2$), 26.0 (NCH$_2$*C*H$_2$). IR (neat) 2969 C-H 2945 C-H 2865 C-H 1627 C=O 1604 C=C 1493 cm^{-1} C=C. LRMS 220.1 (100) 221.1 (22). HRMS Expected: 220.0974 Found: 220.0979 m.p. 71 – 73 °C

3-(Pyrrolidin-1-yl)thiophene-2-carbaldehyde 510

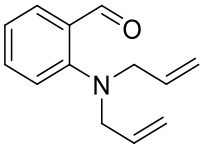


Prepared via general procedure B. Caesium carbonate (910 mg, 2.80 mmol), $Pd(OAc)_2$ (10 mg, 0.02 mmol), (±)BINAP (39 mg, 0.06 mmol), 3-bromothiophene-2-carboxaldehyde (0.22 mL, 2.0 mmol), toluene (20 mL) and pyrrolidine (0.20 mL, 2.2 mmol). The crude mixture was purified via column chromatograpy (40% EtOAc in hexane) to give the product as an off-white solid (275 mg, 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (1H, d, *J* = 1.1 Hz, C*H*O), 7.52 (1H, dd, *J* = 5.5, 1.1 Hz, Ar*H*), 6.55 (1H, d, *J* = 5.5 Hz, Ar*H*), 3.56 – 3.51 (4H, m, NCH_2), 2.14 – 2.01 (4H, m, NCH$_2$CH_2). m.p. 84-85 °C Lit. Not reported

Data in agreement with literature values[234]

2-(Diallylamino)benzaldehyde 519



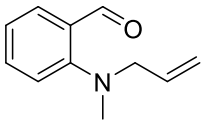
Prepared via general procedure A. Potassium carbonate (1.67 g, 12.1 mmol), DMF (10 mL), 2-fluorobenzaldehyde (1.08 mL, 10.0 mmol) and diallylamine (1.98 mL, 16.0 mmol). Purified via automatic column (2-20% EtOAc in heptane) to give the product as a yellow oil (217 mg, 9%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (1H, d, *J* = 0.4 Hz, C*H*O), 7.92 – 7.85 (1H, m, Ar*H*), 7.80 (1H, dd, *J* = 7.7, 1.7 Hz, Ar*H*), 7.61 (1H, dddd, *J* = 8.4, 7.3, 5.4, 1.9

Hz, Ar*H*), 7.46 (1H, ddd, *J* = 8.3, 7.2, 1.8 Hz, Ar*H*), 5.82 (2H, ddt, *J* = 16.2, 10.3, 6.0 Hz, $NCH_2C\mathit{H}CH_2$), 5.22 (2H, dd, *J* = 16.2, 1.4 Hz, $NCH_2CHC\mathit{H}_2$), 5.18 (2H, dd, *J* = 10.3, 1.4 Hz, $NCH_2CHC\mathit{H}_2$) 3.79 (4H, dt, *J* = 5.9, 1.3 Hz, $NC\mathit{H}_2CHCH_2$).

Data in agreement with literature values[228]

2-(Allyl(methyl)amino)benzaldehyde 520

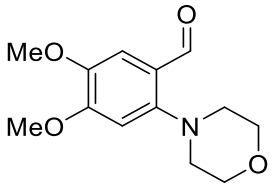


Prepared via general procedure A. Potassium carbonate (830 mg, 6.01 mmol), DMF (5 mL), 2-fluorobenzaldehyde (0.54 mL, 5.0 mmol) and N-allylmethylamine (0.60 mL, 6.0 mmol). Purified via automatic column (2-20% EtOAc in heptane) to give the product as a yellow oil (236 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (1H, s, C*H*O), 7.79 (1H, dd, *J* = 7.7, 1.7 Hz, Ar*H*), 7.47 (1H, ddd, *J* = 8.8, 7.2, 1.8 Hz, Ar*H*), 7.09 (1H, d, *J* = 8.2 Hz, Ar*H*), 7.03 (1H, t, *J* = 7.4 Hz, Ar*H*), 5.91 (1H, ddt, *J* = 16.1, 10.2, 5.9 Hz, $NCH_2C\mathit{H}CH_2$), 5.28 (1H, dd, *J* = 16.1, 1.5 Hz, $NCH_2CHC\mathit{H}_2$), 5.24 (1H, dd, *J* = 10.2, 1.5 Hz, $NCH_2CHC\mathit{H}_2$) 3.74 (2H, d, *J* = 5.9 Hz, $NC\mathit{H}_2CHCH_2$), 2.86 (3H, s, $NC\mathit{H}_2$).

Data in agreement with literature values[228]

4,5-Dimethoxy-2-morpholinobenzaldehyde 543

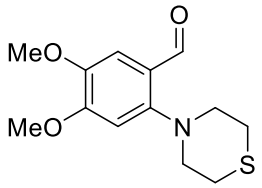


Prepared via general procedure B. Caesium carbonate (1.83 g, 5.62 mmol), $Pd(OAc)_2$ (8 mg, 0.04 mmol), (±)BINAP (78 mg, 0.12 mmol), toluene (40 mL), 6-bromoveratraldehyde (980 mg, 4.02 mmol), morpholine (0.38 mL, 4.4 mmol). Purified via column chromatography (40% EtOAc in hexane) to give the product as a yellow oil (273 mg, 27%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.34 (1H, s, C*H*O), 7.35 (1H, s, Ar*H*), 6.65 (1H, s, Ar*H*), 3.97 (3H, s, $OC\mathit{H}_3$), 3.91 (3H, s, $OC\mathit{H}_3$), 3.90 – 3.89 (4H, m, $OC\mathit{H}_2$), 3.08 –

3.04 (4H, m, NC*H*$_2$). LRMS 252.1 (100) 253.1 (18). HRMS Expected: 252.1236 Found: 252.1242

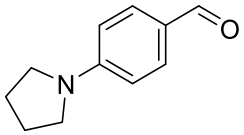
4,5-Dimethoxy-2-thiomorpholinobenzaldehyde 545



Prepared via general procedure B. Caesium carbonate (915 mg, 2.80 mmol), Pd(OAc)$_2$ (5 mg, 0.02 mmol), (±)BINAP (44 mg, 0.07 mmol), toluene (20 mL), 6-bromoveratraldehyde (491 mg, 2.00 mmol), thiomorpholine (0.22 mL, 2.2 mmol). Purified via column chromatography (20% EtOAc in hexane) to give the product as a yellow oil (90 mg, 13%).

^{1}H NMR (700 MHz, CDCl$_3$) δ 10.30 (1H, s, C*H*O), 7.33 (1H, s, Ar*H*), 6.65 (1H, s, Ar*H*), 3.95 (3H, s, OC*H*$_3$), 3.90 (3H, s, OC*H*$_3$), 3.32 – 3.28 (4H, m, NC*H*$_2$), 2.87 – 2.83 (4H, m, SC*H*$_2$). ^{13}C NMR (175 MHz, CDCl$_3$) δ 190.0 (*C*HO), 155.0 (Ar*C*), 153.4 (Ar*C*), 146.0 (Ar*C*), 122.9 (Ar*C*), 109.7 (Ar*C*), 103.5 (Ar*C*), 56.9 (NCH$_2$), 56.3 (OCH$_3$), 56.2 (OCH$_3$), 28.3 (SCH$_2$). IR (neat): 2907 C-H 2828 C-H 1665 C=O 1594 C=C 1503 C=C 1446 1406 cm^{-1}. LRMS: 268.1 (100) 269.1 (15) HRMS Expected: 268.1007 Found: 268.1012

4-(Pyrrolidin-1-yl)benzaldehyde



Potassium carbonate (841 mg, 6 mmol) was suspended in DMF (5.0 mL). To this 4-fluorobenzaldehyde (0.54 mL, 5 mmol) and pyrrolidine (0.51 mL, 6 mmol) were added and the mixture was heated to reflux for 18 h. Following cooling to rt, the reaction was diluted with water (30 mL) and the organics were extracted with EtOAc (50 mL). The organic layer was then washed with sat. NaHCO$_3$ solution (4 x 50 mL) and brine (50 mL) before being dried (MgSO$_4$), filtered and the solvent removed *in vacuo*. The crude product was then purified via column chromatography (33% EtOAc in hexane) to give the product as an orange crystalline solid (713 mg, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (1H, s, C*H*O), 7.78 – 7.67 (2H, m, Ar*H*), 6.57 (2H, d, *J* = 8.9 Hz, Ar*H*), 3.38 (4H, ddd, *J* = 6.6, 4.2, 2.6 Hz, NC*H*$_2$CH$_2$), 2.10 – 1.97 (4H, m, NCH$_2$C*H*$_2$).

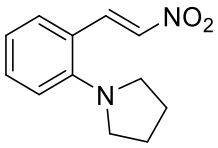
Data in agreement with literature values[235]

3.4.2 Synthesis of Nitroalkenes

General Procedure C

Into toluene (5.0 mL per mmol) an aldehyde (1 equivalent) was added. KF (0.19 equivalents), $Me_2NH.HCl$ (1.5 equivalents) and $MeNO_2$ (3.5 mL per mmol) were added and the solution heated to 90 °C for 18 h. The solvent was then removed *in vacuo* to give the crude product which was then purified directly via column chromatography.

(E)-1-(2-(2-Nitrovinyl)phenyl)pyrrolidine 357

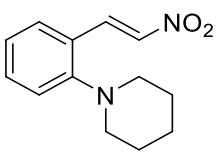


Prepared via general procedure C. Toluene (33 mL), 2-(pyrrolidin-1-yl) benzaldehyde (1.22 g, 6.94 mmol), KF (113 mg, 1.94 mmol), dimethylamine hydrochloride (1.16 g, 14.2 mmol) and $MeNO_2$ (27 mL). Purified via column chromatography (2% EtOAc in hexane) to give the product as a dark red solid (527 mg, 35%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (1H, d, *J* = 13.4 Hz, ArC*H*CHNO$_2$), 7.46 (1H, d, *J* = 13.4 Hz, ArCHC*H*NO$_2$), 7.37 (1H, dd, *J* = 7.8, 1.6 Hz, Ar*H*), 7.32 (1H, ddd, *J* = 8.6, 7.2, 1.6 Hz, Ar*H*), 6.89 (1H, d, *J* = 8.4 Hz, Ar*H*), 6.84 (1H, t, *J* = 7.5 Hz, Ar*H*), 3.39 – 3.32 (4H, m, NC*H*$_2$), 2.01 – 1.93 (4H, m, NCH$_2$C*H*$_2$).

Data in agreement with literature values[171]

(E)-1-(2-(2-Nitrovinyl)phenyl)piperidine 454

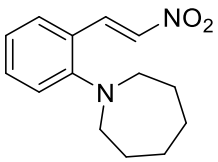


Prepared via general procedure C. Toluene (12 mL), 2-piperidin-1-yl) benzaldehyde (470 mg, 2.50 mmol), KF (37 mg, 0.63 mmol), dimethylamine hydrochloride (407 mg, 5.00 mmol) and $MeNO_2$ (9.0 mL). Purified via column chromatography (1% EtOAc in hexane) to give the product as a dark red oil (232 mg, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (1H, d, *J* = 13.8 Hz, ArC*H*CHNO$_2$), 7.70 (1H, d, *J* = 13.8 Hz, ArCHC*H*NO$_2$), 7.47 (1H, dd, *J* = 7.7, 1.6 Hz, Ar*H*), 7.45 – 7.40 (1H, m, Ar*H*), 7.10 (1H, d, *J* = 8.2 Hz, Ar*H*), 7.06 (1H, t, *J* = 7.5 Hz, Ar*H*), 2.96 – 2.85 (4H, m, NC*H*$_2$), 1.82 – 1.72 (4H, m, NCH$_2$C*H*$_2$), 1.65 – 1.57 (2H, m, NCH$_2$CH$_2$C*H*$_2$).

Data in agreement with literature values[171]

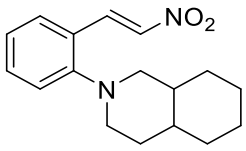
(E)-1-(2-(2-Nitrovinyl)phenyl)azepane 472



Prepared via general procedure C. Toluene (12 mL), 2-(azepan-1-yl) benzaldehyde (690 mg, 3.35 mmol), KF (41 mg, 0.64 mmol), dimethylamine hydrochloride (410 mg, 5.02 mmol) and $MeNO_2$ (10 mL). Purified via column chromatography (2% EtOAc in hexane) to give the product as a dark red oil (477 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (1H, d, *J* = 13.7 Hz, C*H*CHNO$_2$), 7.58 (1H, d, *J* = 13.7 Hz, C*H*NO$_2$), 7.44 (1H, dd, *J* = 7.8, 1.6 Hz, Ar*H*), 7.41 – 7.36 (1H, m, Ar*H*), 7.15 (1H, dd, *J* = 8.3, 0.9 Hz, Ar*H*), 7.00 (1H, m, Ar*H*), 3.23 – 3.17 (4H, m, ring *H*), 1.83-1.73 (8H, m, ring *H*). ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.6 (Ar*C*), 138.2 (*C*HCHNO$_2$), 136.2 (*C*HNO$_2$), 132.6 (Ar*C*), 129.0 (Ar*C*), 123.8 (Ar*C*), 122.0 (Ar*C*), 120.8 (Ar*C*), 56.8 (N*C*H$_2$), 29.3 (NCH$_2$*C*H$_2$), 27.3 (NCH$_2$CH$_2$*C*H$_2$). IR (neat) 3098 C-H 2952 C-H 2912 C-H 2878 C-H 2831 C-H 1624 C=C 1596 C=C 1505 cm^{-1} C=C. LRMS 247.1 (100) 248.1 (20). HRMS: Expected 247.1447 Found: 247.1454

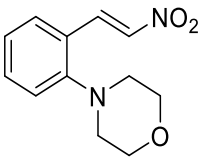
(E)-2-(2-(2-Nitrovinyl)phenyl)perhydroisoquinoline 473



Prepared via general procedure C. Toluene (7.0 mL), 2-(perhydroisoquinolin-2-yl)benzaldehyde (467 mg, 1.80 mmol), KF (23 mg, 0.36 mmol), dimethylamine hydrochloride (236 mg, 2.56 mmol) and $MeNO_2$ (6.0 mL). Purified via automatic column chromatography (0-10% EtOAc in heptane) to give the product as a red oil in a mixture of diastereomers (254 mg, 47%, d.r. 3:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (1H, d, *J* = 13.8 Hz, C*H*CHNO$_2$), 7.63 (1H, d, *J* = 13.8 Hz, C*H*NO$_2$), 7.46 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.42 (1H, ddd, *J* = 9.9, 4.2, 2.1 Hz, Ar*H*), 7.11 (1H, d, *J* = 8.2 Hz, Ar*H*), 7.05 (1H, t, *J* = 7.5 Hz, Ar*H*), 3.12 (1H, dd, *J* = 13.5, 11.3 Hz, NC*H*$_2$), 2.99 (1H, dd, *J* = 11.3, 2.2 Hz, NC*H*$_2$), 2.79 (2H, ddd, *J* = 15.1, 9.6, 2.7 Hz, NC*H*$_2$), 2.04 (2H, m), 1.85 (2H, m), 1.79 – 1.71 (2H, m), 1.70 – 1.62 (2H, m), 1.46 (2H, m), 1.39 – 1.24 (2H, m).

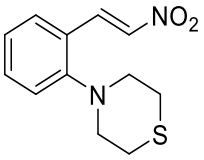
(E)-4-(2-(2-Nitrovinyl)phenyl)morpholine 474



Prepared via general procedure C. Toluene (7.0 mL), 2-morpholino-benzaldehyde (368 mg, 1.88 mmol), KF (23 mg, 0.36 mmol), dimethylamine hydrochloride (237 mg, 2.56 mmol) and $MeNO_2$ (6.0 mL). Purified via automatic column chromatography (0-10% EtOAc in heptane) to give the product as an orange oil (186 mg, 38%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (1H, d, *J* = 13.8 Hz, C*H*CHNO$_2$), 7.67 (1H, d, *J* = 13.8 Hz, C*H*NO$_2$), 7.53 – 7.44 (2H, m, Ar*H*), 7.13 (2H, dd, *J* = 7.7, 6.3 Hz, Ar*H*), 3.94 – 3.88 (4H, m, NCH$_2$C*H*$_2$), 3.00 – 2.96 (4H, m, NC*H*$_2$).

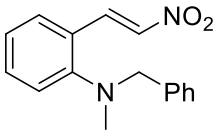
(E)-4-(2-(2-Nitrovinyl)phenyl)thiomorpholine 475



Prepared via general procedure C. Toluene (6.5 mL), 2-thiomorpholino-benzaldehyde (340 mg, 1.64 mmol), KF (18 mg, 0.31 mmol), dimethylamine hydrochloride (202 mg, 2.46 mmol) and $MeNO_2$ (5.7 mL). Purified via column chromatography (10% EtOAc in hexane) to give the product as a light red solid (260 mg, 63%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.39 (1H, d, *J* = 13.8 Hz, C*H*CHNO$_2$), 7.64 (1H, d, *J* = 13.8 Hz, C*H*NO$_2$), 7.51 (1H, d, *J* = 7.8 Hz, Ar*H*), 7.49 – 7.45 (1H, m, Ar*H*), 7.16 – 7.12 (2H, m, Ar*H*), 3.26 – 3.20 (4H, m, NC*H*$_2$), 2.91 – 2.86 (4H, m, NCH$_2$C*H*$_2$) ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.0 (Ar*C*), 137.3 (*C*HCHNO$_2$), 136.3 (*C*HNO$_2$), 133.0 (Ar*C*), 128.9 (Ar*C*), 124.9 (Ar*C*), 124.0 (Ar*C*), 120.8 (Ar*C*), 55.7 (N*C*H$_2$), 28.40 (NCH$_2$*C*H$_2$). LRMS: 250.1 (30) 204.1 (49) 130.1 (100). HRMS: Expected: 250.07705 Found: 250.0771

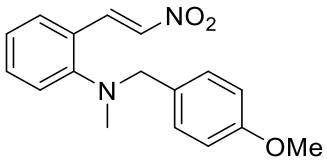
(E)-N-Benzyl-N-methyl-2-(2-nitrovinyl)aniline 468



Prepared via general procedure C. Toluene (40 mL), 2-(benzyl(methyl)amino)benzaldehyde (2.25 g, 10.0 mmol), KF (110 mg, 1.90 mmol), dimethylamine hydrochloride (1.24 g, 15.0 mmol) and $MeNO_2$ (35 mL). Purified via column chromatography (2% EtOAc in hexane) to give the product as a bright red oil (761 mg, 28%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (1H, d, *J* = 13.8 Hz, C*H*CHNO$_2$), 7.64 (1H, d, *J* = 13.8 Hz, C*H*NO$_2$), 7.52 – 7.48 (1H, m, Ar*H*), 7.45 – 7.39 (1H, m, Ar*H*), 7.36 – 7.30 (2H, m, Ar*H*), 7.27 (3H, m, Ar*H*), 7.16 – 7.12 (1H, m, Ar*H*), 7.12 – 7.06 (1H, m, Ar*H*), 4.13 (2H, s, NC*H*$_2$Ar), 2.69 (3H, s, NC*H*$_3$). IR (neat): 3099 C-H 3058 C-H 3025 C-H 2945 C-H 1623 C=C 1593 C=C 1552 NO_2 1507 cm^{-1} C=C. LRMS 269.1 (100) 270.1 (20). HRMS Expected: 269.1290 Found: 269.1298

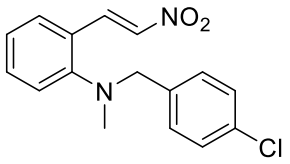
(E)-N-(4-Methoxybenzyl)-N-methyl-2-(2-nitrovinyl)aniline 486



Prepared via general procedure C. Toluene (10 mL), 2-((4-methoxybenzyl)(methyl)amino)benzaldehyde (616 mg, 2.40 mmol), KF (22 mg, 0.46 mmol), dimethylamine hydrochloride (297 mg, 3.62 mmol) and $MeNO_2$ (8.5 mL). Purified via column chromatography (10% EtOAc in hexane) to give the product as a red oil (228 mg, 32%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (1H, d, *J* = 13.8 Hz, C*H*CHNO$_2$), 7.65 (1H, d, *J* = 13.8 Hz, ArC*H*NO$_2$), 7.50 (1H, dd, *J* = 7.7, 1.4 Hz, Ar*H*), 7.46 – 7.39 (1H, m, Ar*H*), 7.19 – 7.15 (2H, m, Ar*H*), 7.13 (1H, d, *J* = 8.2 Hz, Ar*H*), 7.09 (1H, dd, *J* = 11.4, 4.1 Hz, Ar*H*), 6.88 – 6.84 (2H, m, Ar*H*), 4.06 (2H, s, NC*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 2.67 (3H, s, NC*H*$_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1 (Ar*C*), 154.4 (Ar*C*), 137.2 (*C*HCHNO$_2$), 136.9 (*C*HNO$_2$), 132.8 (Ar*C*), 130.0 (Ar*C*), 129.4 (Ar*C*), 129.3 (Ar*C*), 124.8 (Ar*C*), 123.3 (Ar*C*), 121.2 (Ar*C*), 113.9 (Ar*C*), 61.7 (N*C*H$_2$Ar), 55.4 (O*C*H$_3$), 41.6 (N*C*H$_3$). IR (neat): 3097 C-H 3030 C-H 2950 C-H 2832 C-H 2798 C-H 1623 C=C 1609 C=C 1594 C=C 1508 cm^{-1} C=C. LRMS 299.1 (100) 300.1 (18). HRMS Expected: 299.13174 Found: 299.13181

(E)-N-(4-Chlorobenzyl)-N-methyl-2-(2-nitrovinyl)aniline 487

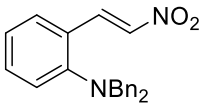


Prepared via general procedure C. Toluene (4.0 mL), 2-((4-chlorobenzyl)(methyl)amino)benzaldehyde (261 mg, 1.00 mmol), KF (13 mg, 0.20 mmol), dimethylamine hydrochloride (126 mg, 1.50 mmol) and $MeNO_2$ (3.6 mL). Purified via column chromatography (10% EtOAc in hexane) to give the product as a red oil (105 mg, 35%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 8.50 (1H, d, *J* = 13.8 Hz, C*H*CHNO$_2$), 7.64 (1H, d, *J* = 13.8 Hz, C*H*NO$_2$), 7.51 (1H, d, *J* = 7.8 Hz, Ar*H*), 7.42 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.30 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.20 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.11 (2H, m, Ar*H*), 4.09 (2H, s, NC*H*$_2$Ar), 2.68 (3H, s, NC*H*$_3$). ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.0 (Ar*C*), 137.1 (Ar*C*HCHNO$_2$), 136.8 (*C*HNO$_2$), 135.8 (Ar*C*), 133.5 (Ar*C*) 132.8 (Ar*C*), 130.0 (Ar*C*), 129.3 (Ar*C*), 128.8 (Ar*C*), 124.8 (Ar*C*), 123.6 (Ar*C*), 121.2 (Ar*C*), 61.4 (N*C*H$_2$Ar), 42.1 (N*C*H$_3$). IR (neat) 3102 C-H 3032 C-H 2879 C-H 2800

C-H 1625 C=C 1596 C=C 1553 NO_2 1509 cm^{-1} C=C. LRMS 303.1 (100) 304.1 (17) 305.1 (37). HRMS Expected: 303.0900 Found: 303.0908

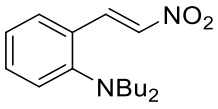
(E)-N,N-Dibenzyl-2-(2-nitrovinyl)aniline



Prepared via general procedure C. Toluene, (5.0 mL), 2-dibenzylamino benzaldehyde (75 mg, 0.25 mmol), KF (3 mg, 0.06 mmol), dimethylamine hydrochloride (46 mg, 0.6 mmol) and $MeNO_2$ (2.0 mL). Purified via column chromatography (0-2% EtOAc in hexane) to give the product as an orange oil (11 mg, 13%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (1H, d, *J* = 13.8 Hz, ArC*H*CHNO$_2$), 7.55 (1H, d, *J* = 13.8 Hz, ArCHC*H*NO$_2$), 7.48 (1H, dd, *J* = 7.7, 1.4 Hz, Ar*H*), 7.40 – 7.33 (2H, m, Ar*H*), 7.32 – 7.21 (6H, m, Ar*H*), 7.21 – 7.15 (3H, m, Ar*H*), 7.09 (2H, t, *J* = 8.1 Hz, Ar*H*), 4.15 (4H, s, ArC*H*$_2$N). ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.4 (Ar*C*), 137.2 (Ar*C*HCHNO$_2$), 136.9 (Ar*C*), 136.7 (*C*HNO$_2$), 132.4 (Ar*C*), 129.0 (Ar*C*), 128.7 (Ar*C*), 128.5 (Ar*C*), 127.6 (Ar*C*), 126.2 (Ar*C*), 124.1 (Ar*C*), 123.6 (Ar*C*), 58.5 ((Ar*C*H$_2$)$_2$N). IR (neat): 2953 C-H 2927 C-H 2858 C-H 1623 C=C 1593 C=C 1509 cm^{-1} C=C. LRMS 345.1 (100), 346.1 (20). HRMS Expected: 345.1063 Found: 345.1605

(E)-N,N-Dibutyl-2-(2-nitrovinyl)aniline 495

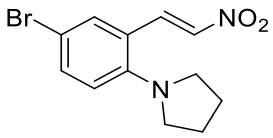


Prepared via general procedure C. Toluene (12 mL), 2-dibutylamino benzaldehyde (700 mg, 3.00 mmol), KF (33 mg, 0.57 mmol), dimethylamine hydrochloride (376 mg, 4.50 mmol) and $MeNO_2$ (11 mL). Purified via column chromatography (0-2% EtOAc in hexane) to give the product as an orange oil (398 mg, 48%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (1H, d, *J* = 13.8 Hz, C*H*CHNO$_2$), 7.65 (1H, d, *J* = 13.8 Hz, C*H*NO$_2$), 7.49 (1H, dd, *J* = 7.8, 1.3 Hz, Ar*H*), 7.43 – 7.40 (1H, m, Ar*H*), 7.17 (1H, d, *J* = 8.2 Hz, Ar*H*), 7.07 (1H, t, *J* = 7.7 Hz, Ar*H*), 3.03 – 2.99 (4H, m, NC*H*$_2$), 1.44 (4H, tt, *J* = 7.7, 6.5 Hz, NCH$_2$C*H*$_2$), 1.30 – 1.22 (4H, m,

$NCH_2CH_2CH_2$), 0.86 (6H, t, *J* = 7.4 Hz, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.4 (Ar*C*), 137.4 (*C*HCHNO$_2$), 136.7 (*C*HNO$_2$), 132.26 (Ar*C*), 129.3 (Ar*C*), 126.1 (Ar*C*), 123.1 (Ar*C*), 122.5 (Ar*C*), 54.5 (NCH_2), 29.6 (NCH_2CH_2), 20.5 ($NCH_2CH_2CH_2$), 14.0 ($NCH_2CH_2CH_2CH_3$). LRMS 277.1 (100), 251.1 (76). HRMS Expected: 277.1916 Found: 277.1921

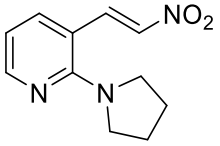
(E)-1-(4-Bromo-2-(2-nitrovinyl)phenyl)pyrrolidine 496



Prepared via general procedure C. Toluene (8.0 mL), 5-Bromo-2-(pyrrolidin-1-yl)benzaldehyde (530 mg, 2.09 mmol), KF (23 mg, 0.40 mmol), dimethylamine hydrochloride (255 mg, 3.13 mmol) and $MeNO_2$ (6.5 mL). Purified via automatic column chromatography to give a red solid (242 mg, 39%).

^1H NMR (600 MHz, $CDCl_3$) δ 8.33 (1H, d, *J* = 13.4 Hz, C*H*CHNO$_2$), 7.46 (1H, d, *J* = 2.4 Hz, Ar*H*), 7.42 (1H, d, *J* = 13.4 Hz, ArC*H*NO$_2$), 7.37 (1H, dd, *J* = 8.9, 2.4 Hz, Ar*H*), 6.75 (1H, d, *J* = 9.0 Hz, Ar*H*), 3.35 (4H, m, NCH_2), 2.01 – 1.96 (4H, m, NCH_2CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.1 (Ar*C*), 138.3 (Ar*C*HCHNO$_2$), 135.4 (Ar*C*), 135.0 (Ar*C*), 131.8 (*C*HNO$_2$), 119.9 (Ar*C*), 117.4 (Ar*C*), 110.9 (Ar*C*), 52.9 (NCH_2), 25.8 (NCH_2CH_2). IR (neat) 3112 C-H 2987 C-H 2950 C-H 2922 C-H 2851 C-H 1607 C=C 1588 C=C 1551 NO_2 1530 cm^{-1}. LRMS: 297.0 (100), 299.0 (97). HRMS Expected: 297.0239 Found: 297.0248 m.p. 88-89 °C

(E)-3-(2-Nitrovinyl)-2-(pyrrolidin-1-yl)pyridine 497

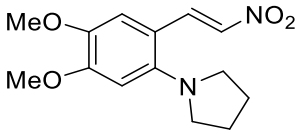


Prepared via general procedure C. Toluene (12 mL), 2-(pyrrolidin-1-yl)-nicotinaldehyde (584mg, 3.35 mmol), KF (41 mg, 0.68 mmol), dimethylamine hydrochloride (412 mg, 5.02 mmol) and $MeNO_2$ (10 mL). Purified via column chromatography (20% EtOAc in hexane) to give the product as a bright red solid (282 mg, 30%).

^1H NMR (600 MHz, $CDCl_3$) δ 8.36 (1H, d, *J* = 13.3 Hz, C*H*CHNO$_2$), 8.25 (1H, dd, *J* = 4.6, 1.8 Hz, Ar*H*), 7.59 (1H, dd, *J* = 7.6, 1.6 Hz, Ar*H*), 7.37 (1H, d, *J* = 13.3

Hz, C*H*NO_2), 6.68 (1H, dd, *J* = 7.6, 4.7 Hz, Ar*H*), 3.65 – 3.60 (4H, m, NCH_2), 1.99 – 1.94 (4H, m, NCH_2CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.4 (Ar*C*), 151.3 (Ar*C*), 138.8 (ArCC*H*CHNO_2), 138.0 (Ar*C*), 135.1 (*C*HNO_2), 113.5 (Ar*C*), 110.6 (Ar*C*), 51.3 (NCH_2CH_2), 25.9 (NCH_2CH_2). IR (neat) 3176 C-H 3104 C-H 2983 C-H 2958 C-H 2876 C-H 2859 C-H 1683 C=C 1607 C=C 1586 C=C 1545 cm^{-1} NO_2. LRMS 279.1 (100). HRMS Expected: 220.1086 Found: 220.1112 m.p. 64-66 °C

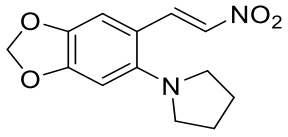
(E)-1-(4,5-Dimethoxy-2-(2-nitrovinyl)phenyl)pyrrolidine 498



Prepared via general procedure C. Toluene (6.0 mL), 4,5-dimethoxy-2-(pyrrolidin-1-yl)benzaldehyde (353 mg, 1.50 mmol), KF (17 mg, 0.29 mmol), dimethylamine hydrochloride (185 mg, 2.27 mmol) and $MeNO_2$ (5.0 mL). Purified via column chromatography (20% EtOAc in hexane) to give the product as a dark purple solid (259 mg, 62%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (1H, d, *J* = 13.3 Hz, C*H*CHNO_2), 7.45 (1H, d, *J* = 13.2 Hz, C*H*NO_2), 6.83 (1H, s, Ar*H*), 6.45 (1H, s, Ar*H*), 3.93 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.36 – 3.33 (4H, m, NCH_2), 2.04 – 1.96 (4H, m, NCH_2CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.9 (Ar*C*), 148.5 (Ar*C*), 143.3 (Ar*C*), 138.8 (*C*H$CHNO_2$), 132.4 (*C*HNO_2), 111.1 (Ar*C*), 110.7 (Ar*C*), 99.9 (Ar*C*), 56.4 (OCH_3), 56.0 (OCH_3), 53.6 (NCH_2), 25.6 (NCH_2CH_2). IR (neat): 3118 C-H 2964 C-H 2918 C-H 2862 C-H 2848 C-H 2826 C-H 1625 C=C 1584 C=C 1569 C=C 1546 NO_2 1517 cm^{-1} C=C. LCMS 279.1 (100) 280.1 (18). HRMS Expected: 279.1345 Found 279.1347 m.p. 136-138 °C

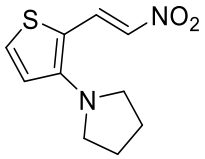
(E)-1-(6-(2-Nitrovinyl)benzo[d][1,3]dioxol-5-yl)pyrrolidine 499



Prepared via general procedure C. Toluene (6.0 mL), 6-(pyrrolidin-1-yl) piperonal (334 mg, 1.53 mmol), KF (19 mg, 0.31 mmol), dimethylamine hydrochloride (186 mg, 2.28 mmol) and $MeNO_2$ (5.0 mL). Purified via column chromatography (10% EtOAc in hexane) to give the produce as a red solid (140 mg, 36%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.41 (1H, d, *J* = 13.3 Hz, C*H*CHNO$_2$), 7.40 (1H, d, *J* = 13.3 Hz, C*H*NO$_2$), 6.84 (1H, s, Ar*H*), 6.55 (1H, s, Ar*H*), 5.96 (2H, s, OC*H*$_2$O), 3.27 (4H, m, NC*H*$_2$), 2.00 – 1.95 (4H, m, NCH$_2$C*H*$_2$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5 (Ar*C*), 150.1 (Ar*C*), 142.1 (Ar*C*), 138.7 (*C*HCHNO$_2$), 132.8 (*C*HNO$_2$), 112.8 (Ar*C*), 106.9 (Ar*C*), 101.8 (O*C*H$_2$O), 98.1 (Ar*C*), 53.9 (N*C*H$_2$), 25.5 (NCH$_2$*C*H$_2$). IR (neat) 3128 C-H 2950 C-H 2917 C-H 2835 C-H 2678 C-H 1596 C=C 1502 cm^{-1} C=C. LCMS 236.1 (50) 264.1 (10) 277.1 (100). HRMS Expected: 263.1032 Found: 263.1040 m.p. 91-93 °C

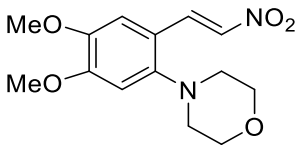
(E)-1-(2-(2-Nitrovinyl)thiophen-3-yl)pyrrolidine 500



Prepared via general procedure C. Toluene (4.0 mL), 3-(pyrrolidin-1-yl)thiophene-2-carbaldehyde (170 mg, 0.94 mmol), KF (12 mg, 0.19 mmol), diemethylamine hydrochloride (122 mg, 1.50 mmol), and MeNO$_2$ (3.5 mL). Purified via column chromatography to give the product as a yellow solid (69 mg, 31%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (1H, dd, *J* = 12.2, 1.0 Hz, C*H*CHNO$_2$), 7.37 (1H, dd, *J* = 5.7, 1.1 Hz, Ar*H*), 7.22 (1H, d, *J* = 12.2 Hz, ArC*H*NO$_2$), 6.56 (1H, d, *J* = 5.7 Hz, Ar*H*), 3.65 – 3.61 (4H, m, NC*H*$_2$), 2.12 – 2.05 (4H, m, NCH$_2$C*H*$_2$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.0 (Ar*C*), 135.0 (Ar*C*HCHNO$_2$), 132.5 (Ar*C*), 127.6 (*C*HNO$_2$), 119.9 (Ar*C*), 105.3 (Ar*C*), 52.2 (N*C*H$_2$), 25.8 (NCH$_2$*C*H$_2$). IR (neat) 3087 C-H 2959 C-H 2922 C-H 2852 C-H 1534 cm^{-1} NO$_2$. LRMS 225 (100). HRMS Expected: 225.0698 Found: 225.0115 m.p. 157-159 °C

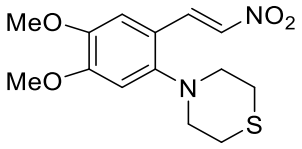
(E)-4-(4,5-Dimethoxy-2-(2-nitrovinyl)phenyl)morpholine 541



Prepared via general procedure C. Toluene (4.0 mL), 4,5-dimethoxy-2-morpholinobenzaldehyde (251 mg, 1.00 mmol), KF (13 mg, 0.2 mmol), dimethylamine hydrochloride (128 mg, 1.57 mmol) and MeNO$_2$ (3.5 mL). Purified via column chromatography to give the product as a dark red solid (118 mg, 40%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (1H, d, *J* = 13.7 Hz, C*H*CHNO$_2$), 7.63 (1H, d, *J* = 13.7 Hz, C*H*NO$_2$), 6.94 (1H, s, Ar*H*), 6.69 (1H, s, Ar*H*), 3.95 (3H, s, OC*H*$_3$), 3.93 – 3.91 (4H, m, NCH$_2$C*H*$_2$), 3.90 (3H, s, OC*H*$_3$), 2.97 – 2.93 (4H, m, NC*H*$_2$). IR (neat) 3106 C-H 2930 C-H 2908 C-H 2829 C-H 1618 C=C 1596 C=C 1564 NO$_2$ 1506 cm^{-1} C=C. LRMS 295.1 (100). HRMS Expected: 295.1294 Found: 295.1282 m.p. 116-118 °C

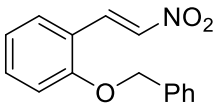
(E)-4-(4,5-Dimethoxy-2-(2-nitrovinyl)phenyl)thiomorpholine 542



Prepared via general procedure C. Toluene (2.0 mL), 4,5-dimethoxy-2-thiomorpholinobenzaldehyde (80 mg, 0.30 mmol), KF (4 mg, 0.08 mmol), diemethylamine hydrochloride (40 mg, 0.45 mmol), and MeNO$_2$ (1.0 mL). Purified via column chromatography to give the product as a red solid (62 mg, 67%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (1H, d, *J* = 13.7 Hz, C*H*CHNO$_2$), 7.60 (1H, d, *J* = 13.7 Hz, C*H*NO$_2$), 6.93 (1H, s, Ar*H*), 6.68 (1H, s, Ar*H*), 3.94 (3H, s, OC*H*$_3$), 3.90 (3H, s, OC*H*$_3$), 3.21 – 3.15 (3H, m, NC*H*$_2$), 2.87 (3H, apparent singlet, NCH$_2$C*H*$_2$) IR (neat) 3109 C-H 2955 C-H 2913 C-H 2890 C-H 2850 C-H 2825 C-H 1618 C=C 1596 C=C 1562 NO$_2$ 1507 cm^{-1} C=C. LRMS 311.1 (100) 312.1 (15). HRMS: Expected: 310.1066 Found: 311.1243 m.p. 103-104 °C

(E)-1-(Benzyloxy)-2-(2-nitrovinyl)benzene 465



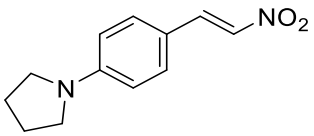
A suspension of K_2CO_3 (303 mg, 2.20 mmol) in EtOH (5.0 mL) was prepared and to this was added salicyl aldehyde (0.24 mL, 2.3 mmol) and benzyl bromide (0.3 mL, 2.5 mg). The resulting mixture was heated to reflux for 18 h before being cooled to rt and the solvent was then removed *in vacuo*. The resulting residue was taken up in EtOAc (25 mL) and washed with water (25 mL), sat. $NaHCO_3$ solution (3 x 25 mL) and brine (25 mL) before drying ($MgSO_4$), filtering and the solvent removed in vacuo to give the benzylated aldehyde as a crude product that was used directly.

To AcOH (5.0 mL) was added 2-(benzyloxy)benzaldehyde (415 mg, 1.96 mmol), ammonium acetate (161 mg, 2.09 mmol) and $MeNO_2$ (1.10 mL, 20 mmol). The resulting mixture was heated to 80 ºC for 162 h before being cooled to rt. The reaction mixture was diluted in EtOAc (50 mL) and washed with sat. NaHCO3 solution (4 x 50 mL) and brine (50 mL) before being dried ($MgSO_4$), filtered and the solvent removed in vacuo. The crude material was purified via column chromatography to give the product as a yellow crystalline solid (187 mg, 42% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (1H, d, *J* = 13.6 Hz, C*H*CHNO$_2$), 7.85 (1H, d, *J* = 13.6 Hz, C*H*NO$_2$), 7.48 (1H, dd, *J* = 7.9, 1.7 Hz, Ar*H*), 7.46 – 7.34 (6H, m, Ar*H*), 7.06 – 7.00 (2H, m, Ar*H*), 5.22 (2H, s, OC*H*$_2$Ph). m.p. 70-72 °C Lit. 71-73 °C[236]

Data in agreement with literature values[215]

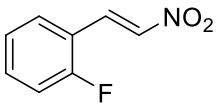
(E)-1-(4-(2-Nitrovinyl)phenyl)pyrrolidine



Prepared via general procedure C. Toluene (14 mL), 4-(pyrrolidin-1-yl)benzaldehyde (502 mg, 2.85 mmol), $Me_2NH.HCl$ (481 mg, 5.90 mmol), KF (47 mg, 0.81 mmol) and $MeNO_2$ (12 mL). Purified via column chromatography (20% EtOAc in hexane) to give the product as a red crystalline solid (315 mg, 51%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (1H, d, *J* = 13.4 Hz, C*H*CHNO$_2$), 7.50 (1H, d, *J* = 13.3 Hz, ArC*H*NO$_2$), 7.44 – 7.39 (2H, m, Ar*H*), 6.58 – 6.53 (2H, m, Ar*H*), 3.41 – 3.35 (4H, m, NC*H*$_2$), 2.10 – 2.02 (4H, m, NCH$_2$C*H*$_2$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.7 (Ar*C*), 140.8 (ArC*C*HCHNO$_2$), 131.8 (Ar*C*), 131.6 (*C*HNO$_2$), 116.9 (Ar*C*), 112.2 (Ar*C*), 47.8 (N*C*H$_2$CH$_2$), 25.5 (NCH$_2$*C*H$_2$). IR (neat): 3103 C-H 2972 C-H 2952 C-H 2853 C-H 1591 C=C 1531 cm^{-1} NO$_2$. LRMS (CI) 219.1 (100). HRMS: Expected: 219.1128 Found: 219.1128 m.p. 136-138 ºC

(E)-1-Fluoro-2-(2-nitrovinyl)benzene

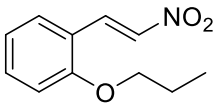


To toluene (1 mL) was added 2-fluorobenzaldehyde (0.11 mL, 1.0 mmol), $MeNO_2$ (0.32 mL, 5.9 mmol), iron (III) chloride (17 mg, 0.10 mmol) and piperidine (9.8 µL, 0.10 mmol) before the mixture was heated to 100 ºC for 18 h. Following cooling to rt the solvent was removed *in vacuo* and the resulting residue was purified via column chromatography (5% EtOAc in hexane) to give the product as an off-white crystalline solid (137 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (1H, d, *J* = 13.8 Hz, C*H*CHNO$_2$), 7.74 (1H, d, *J* = 13.8 Hz, C*H*NO$_2$), 7.57 – 7.44 (2H, m, Ar*H*), 7.29 – 7.13 (2H, m, Ar*H*). m.p. 52-54 °C Lit. 56 °C[217]

Data in agreement with literature[217]

(E)-1-(2-Nitrovinyl)-2-propoxybenzene 521



Ammonium acetate (778 mg, 10.1 mmol) and 2-propoxybenzaldehyde (824 mg, 5.01 mmol) were dissolved in AcOH (12.4 mL). $MeNO_2$ (2.8 mL, 50 mmol) was added and heated to 80 °C for 36 h. The reaction was cooled then neutralised with $NaHCO_3$ (sat. solution). The organics were extracted with EtOAc (3 x 25 mL), combined, washed with sat. $NaHCO_3$ solution (3 x 75 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude residue was purified via column chromatography (10% EtOAc in hexane) to give the product as a yellow crystalline solid (793 mg, 77%).

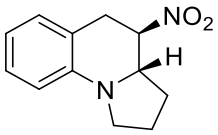
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, d, *J* = 13.6 Hz, C*H*CHNO$_2$), 7.92 (1H, d, *J* = 13.6 Hz, C*H*NO$_2$), 7.44 (2H, t, *J* = 7.7 Hz, Ar*H*), 6.99 (2H, m, Ar*H*), 4.07 (2H, t, *J* = 6.5 Hz, OC*H*$_2$), 1.93 (2H, tq, *J* = 7.4, 6.7 Hz, OCH$_2$C*H*$_2$), 1.10 (3H, t, *J* = 7.4 Hz, OCH$_2$CH$_2$C*H*$_3$)

3.4.3 Synthesis of Cyclised Products

General Procedure D

Nitroalkene (1 equivalent) and $Gd(OTf)_3$ (0.3 equivalents) were heated in toluene (10.0 mL per mmol) to 100 °C until the reaction reached completion (18 h unless otherwise stated). The toluene was then removed *in vacuo* and the resultant residue purified via column chromatography to give the cyclised product.

(3a*S,4*R**)-4-Nitro-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline 358a**

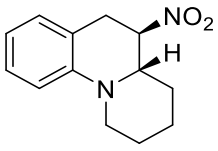


To HFIP (4 mL) was added (E)-1-(2-(2-nitrovinyl)phenyl)pyrrolidine (60 mg, 0.27 mmol). The solution was heated to 58 °C for 4 h then cooled to rt and the solvent removed *in vacuo* to give a crude residue which was purified via column chromatography (2% EtOAc in hexane) to give the product as a yellow crystalline solid (54 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.05 (1H, d, *J* = 7.4 Hz, Ar*H*), 6.66 (1H, td, *J* = 7.4, 1.0 Hz, Ar*H*), 6.50 (1H, d, *J* = 8.1 Hz, Ar*H*), 4.46 (1H, ddd, *J* = 11.9, 9.7, 4.8 Hz, C*H*NO_2), 3.83 – 3.73 (1H, m, (NO_2)CHC*H*N), 3.53 – 3.41 (2H, m, NC*H*$_2$/ArC*H*$_2$), 3.34 – 3.20 (2H, m, NC*H*$_2$/ArC*H*$_2$), 2.24 (1H, ddd, *J* = 12.2, 7.1, 2.0 Hz, (NO_2)CHCHC*H*$_2$), 2.17 – 2.09 (1H, m, (NO_2)CHCHC*H*$_2$), 2.05 – 1.95 (1H, m, NCH_2C*H*$_2$), 1.82 – 1.71 (1H, m, NCH_2C*H*$_2$). m.p. 94-95 °C Lit. not reported

Data in agreement with literature values[171]

(4a*S,5*R**)-5-Nitro-2,3,4,4a,5,6-hexahydro-1H-pyrido[1,2-a]quinoline 456a**

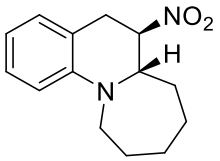


To HFIP (4.0 mL) was added (E)-1-(2-(2-nitrovinyl)phenyl)piperidine (92 mg, 0.40 mmol). The solution was heated to 58 °C for 18 h then cooled to rt and the solvent was removed *in vacuo* to give a crude residue which was purified via column

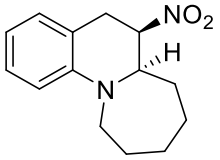
chromatography (2% EtOAc in hexane) to give the product as a waxy yellow solid (53 mg, 58%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 – 7.15 (1H, td, *J* = 8.3, 0.8 Hz, Ar*H*), 7.05 (1H, d, *J* = 7.3 Hz, Ar*H*), 6.84 (1H, d, *J* = 8.3 Hz, Ar*H*), 6.76 (1H, td, *J* = 7.4, 0.8 Hz, Ar*H*), 4.70 (1H, ddd, *J* = 7.7, 6.2, 5.1 Hz, C*H*NO_2), 3.95 – 3.89 (1H, m, NC*H*$_2$), 3.54 (1H, ddd, *J* = 10.8, 6.2, 2.5 Hz, NC*H*CHNO_2), 3.44 (1H, dd, *J* = 15.5, 7.8 Hz, ArC*H*$_2$), 3.16 (1H, dd, *J* = 15.5, 5.0 Hz, ArC*H*$_2$), 2.83 (1H, td, *J* = 12.6, 2.9 Hz, NC*H*$_2$), 1.95 – 1.88 (1H, m, ring H), 1.80 – 1.72 (1H, m, NCH_2C*H*$_2$), 1.69 – 1.44 (4H, m, ring H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.3 (Ar*C*), 129.2 (Ar*C*), 128.3 (Ar*C*), 120.0 (Ar*C*), 118.8 (Ar*C*), 113.1 (Ar*C*), 86.4 (*C*HNO_2), 59.0 (N*C*H), 48.1 (N*C*H_2), 31.5 (Ar*C*H_2), 30.1 (NCH*C*H_2), 24.5 (NCH_2*C*H_2), 24.1 (NCH_2CH_2*C*H_2) IR (neat): 2938 C-H 2850 C-H 1597 C=C 1576 C=C 1540 cm^{-1} NO_2. LRMS: 233.1 (100) 234.1 (15). HRMS: Expected: 233.1290 Found: 233.1305

(6*R,6a*S**)-6-Nitro-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinoline 527a**



(6*R,6a*R**)-6-Nitro-5,6,6a,7,8,9,10,11-octahydroazepino[1,2-a]quinolone 527b**



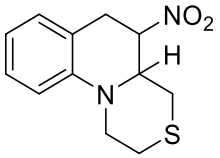
Prepared via general procedure D. Toluene (4.0 mL), (E)-1-(2-(2-nitrovinyl)phenyl)azepane (90 mg, 0.40 mmol), $Gd(OTf)_3$ (74 mg, 0.12 mmol). Purified via column chromatography (5% EtOAc in hexane) to give the product as a yellow oil (60 mg, 67%, *dr* 2:1).

527a ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10 (1H, t, *J* = 7.8 Hz, Ar*H*), 7.06 (1H, d, *J* = 7.4 Hz, Ar*H*), 6.66 (1H, t, *J* = 7.3 Hz, Ar*H*), 6.60 (1H, d, *J* = 8.3 Hz, Ar*H*), 4.69 – 4.67 (1H, m, C*H*NO_2), 4.12 (1H, ddd, *J* = 7.6, 6.4, 3.1 Hz, NC*H*CHNO_2), 3.85 (1H, ddd, *J* = 15.3, 5.9, 2.9 Hz, NC*H*$_2$), 3.54 (1H, d, *J* = 17.8 Hz, ArC*H*$_2$), 3.21 (1H, dd,

J = 17.8, 5.4 Hz, ArC*H*$_2$), 3.11 (1H, ddd, *J* = 15.6, 10.6, 5.3 Hz, NC*H*$_2$), 2.11 – 2.03 (1H, m, NCH$_2$C*H*$_2$), 1.87 – 1.82 (1H, m, NCHC*H*$_2$), 1.72 – 1.59 (4H, m, ring protons), 1.58 – 1.50 (1H, m, NCHC*H*$_2$), 1.48 – 1.40 (1H, m, NCH$_2$CH$_2$C*H*$_2$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 143.0 (Ar*C*), 129.2 (Ar*C*), 128.0 (Ar*C*), 116.5 (Ar*C*), 116.0 (Ar*C*), 111.0 (Ar*C*), 81.9 (*C*HNO$_2$), 60.6 (N*C*HCHNO$_2$), 49.4 (N*C*H$_2$), 33.5 (NCH*C*H$_2$), 27.4 (NCH$_2$*C*H$_2$), 27.2 (Ar*C*H$_2$), 26.1 (NCHCH$_2$*C*H$_2$), 25.9 (NCH$_2$CH$_2$*C*H$_2$). IR (neat): 3025 C-H 2923 C-H 2858 C-H 1602 C=C 1578 C=C 1540 NO_2 1499 cm^{-1} C=C. LRMS (ES+) 247.1 (100) 248.1 (18). HRMS Expected 247.1447 Found 247.1461

527b ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.08 (1H, t, *J* = 6.8 Hz, Ar*H*), 6.67 (1H, td, *J* = 7.4, 0.7 Hz, Ar*H*), 6.62 (1H, d, *J* = 8.3 Hz, Ar*H*), 4.90 (1H, ddd, *J* = 12.4, 5.7, 4.3 Hz, C*H*NO$_2$), 4.08 (1H, dt, *J* = 8.5, 4.3 Hz, NC*H*), 3.92 (1H, ddd, *J* = 15.1, 6.1, 3.1 Hz, NC*H*$_2$), 3.53 (1H, dd, *J* = 16.2, 12.4 Hz, ArC*H*$_2$), 3.27 – 3.16 (2H, m, NC*H*$_2$, ArC*H*$_2$), 2.15 – 2.06 (1H, m, ring H), 1.72 – 1.47 (6H, m, ring H), 1.43 – 1.33 (1H, m, ring H) ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.9 (Ar*C*), 129.9 (Ar*C*), 128.3 (Ar*C*), 116.6 (Ar*C*), 116.1 (Ar*C*), 110.8 (Ar*C*), 81.1 (*C*HNO$_2$), 60.0 (N*C*H), 49.9 (Ar*C*), 28.7 (ring C), 27.0 (ring C), 26.7 (ring C), 26.2 (ring C), 25.6 (ring C) IR (neat): 3021 C-H 2930 C-H 2903 C-H 2855 C-H 1600 C=C 1574 C=C 1530 NO_2 1494 cm^{-1} C=C. LRMS: 247.1 (100) 248.1 (18). HRMS Expected 247.1447 Found 247.1461

5-Nitro-1,2,4,4a,5,6-hexahydro-[1,4]thiazino[4,3-a]quinoline 531

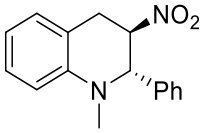


Prepared via general procedure D with a reaction time of 7 d. Toluene (4.0 mL), (E)-4-(2-(2-nitrovinyl)phenyl)thiomorpholine (100 mg, 0.4 mmol), Gd(OTf)$_3$ (72 mg, 0.12 mmol). Purified via column chromatography (10% EtOAc in hexane) to give the product as a yellow waxy solid (9 mg, 9%).

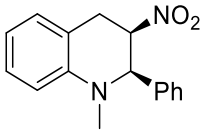
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.17 (1H, td, *J* = 8.3, 1.5 Hz, Ar*H*), 7.09 (1H, d, *J* = 7.2 Hz, Ar*H*), 6.80 (1H, td, *J* = 7.4, 0.8 Hz, Ar*H*), 6.76 (1H, d, *J* = 8.3 Hz, Ar*H*), 4.67 (1H, q, *J* = 5.0 Hz, C*H*NO$_2$), 4.34 (1H, dddd, *J* = 11.0, 4.4, 2.0, 1.1 Hz, NC*H*), 4.29 (1H dt, *J* = 14.5, 2.8 Hz, NC*H*$_2$), 3.48 – 3.42 (2H, m, ArC*H*$_2$, NC*H*$_2$), 3.15

(1H, dd, *J* = 16.6, 5.2 Hz, ArC*H*$_2$), 3.03 (1H, ddd, *J* = 13.5, 12.2, 2.7 Hz, NCH$_2$C*H*$_2$), 2.80 (1H, dd, *J* = 13.0, 11.0 Hz, NCHC*H*$_2$), 2.39 (1H, d, *J* = 13.0 Hz, NCHC*H*$_2$), 2.31 (1H, ddd, *J* = 13.4, 4.0, 2.5 Hz, NCH$_2$C*H*$_2$) ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.9 (Ar*C*), 129.4 (Ar*C*), 128.5 (Ar*C*), 119.6 (Ar*C*), 119.1 (Ar*C*), 113.5 (Ar*C*), 83.9 (*C*HNO$_2$), 60.5 (N*C*H), 50.1 (Ar*C*H$_2$), 28.8 (N*C*H$_2$), 28.2 (NCH*C*H$_2$), 23.4 (NCH$_2$*C*H$_2$). LRMS: 251.1 (100) 252.1 (21) 253.1 (18) 254.1 (10). HRMS: Expected: 251.0854 Found 251.0858

(2*S,3*R**)-1-Methyl-3-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline 469a**



(2*R,3*R**)-1-Methyl-3-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline 469b**



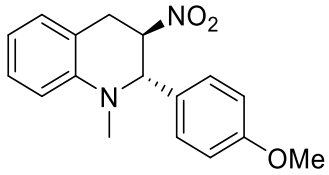
Prepared via general procedure D. Toluene (4.0 mL), (E)-N-benzyl-N-methyl-2-(2-nitrovinyl)aniline (109 mg, 0.41 mmol), Gd(OTf)$_3$ (74 mg, 0.12 mmol). Purified via column chromatography (10% EtOAc in hexane) to give the product as a yellow solid (73 mg, 67%, *dr* 3:1).

469a ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.28 (3H, m, Ar*H*), 7.23 – 7.18 (3H, m, Ar*H*), 7.03 (1H, d, *J* = 7.3 Hz, Ar*H*), 6.72 (2H, m, Ar*H*), 5.19 (1H, apparent singlet, NC*H*Ar), 4.84 (1H, apparent dd, *J* = 7.8, 3.9 Hz, C*H*NO$_2$), 3.42 (1H, ddd, *J* = 16.8, 3.7, 1.4 Hz, ArC*H*$_2$), 3.01 (1H, dd, *J* = 16.8, 4.4 Hz, ArC*H*$_2$) ^{13}C NMR (175 MHz, $CDCl_3$) δ 144.4 (Ar*C*), 139.5 (Ar*C*), 129.3 (Ar*C*), 129.0 (Ar*C*), 128.5 (Ar*C*), 128.4 (Ar*C*), 126.6 (Ar*C*), 117.3 (Ar*C*), 110.6 (Ar*C*), 83.8 (*C*HNO$_2$), 64.8 (*C*HAr), 37.8 (N*C*H$_3$), 27.6 (Ar*C*H$_2$) IR (neat): 3060 C-H 3026 C-H 2895 C-H 2827 C-H 1601 C=C 1576 C=C 1546 NO$_2$ 1497 cm^{-1} C=C. LRMS: 269.1 (100) 270.1 (17). HRMS: Expected: 269.1290 Found: 269.1986 m.p. 93-94 °C

469b ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.20 (5H, m, Ar*H*), 7.08 (1H, d, *J* = 7.4 Hz, Ar*H*), 7.01 (2H, dt, *J* = 3.7, 2.1 Hz, Ar*H*), 6.75 (1H, td, *J* = 7.4, 0.9 Hz, Ar*H*), 6.69 (1H, d, *J* = 8.2 Hz, Ar*H*), 5.16 (1H, dd, *J* = 9.3, 4.6 Hz, C*H*Ar), 5.15 – 5.12 (1H, m, C*H*NO$_2$), 3.33 – 3.25 (1H, m, ArC*H*$_2$), 3.14 – 3.08 (1H, m, ArC*H*$_2$), 1.55

(3H, s, NC*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3 (Ar*C*), 135.7 (Ar*C*), 129.3 (Ar*C*), 128.5 (Ar*C*), 128.5 (Ar*C*), 128.3 (Ar*C*), 127.1 (Ar*C*), 116.8 (Ar*C*), 116.3 (Ar*C*), 109.8 (Ar*C*), 81.5 (*C*HNO_2), 64.5 (N*C*HAr), 37.6 (N*C*H$_3$), 26.4 (ArC*C*H$_2$CHNO_2). IR (neat): 3025 C-H 2895 C-H 2833 C-H 1602 C=C 1577 C=C 1542 NO_2 1499 cm^{-1} C=C. LRMS: 269.1 (100) 270.1 (17). HRMS: Expected: 269.1290 Found 269.1298

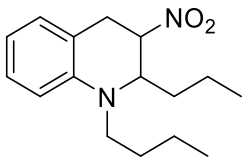
(2*S,3*R**)-2-(4-Methoxyphenyl)-1-methyl-3-nitro-1,2,3,4-tetrahydroquinoline 533a**



Prepared via general procedure D. Toluene (4.0 mL), (E)-N-(4-methoxybenzyl)-N-methyl-2-(2-nitrovinyl)aniline (114 mg, 0.38 mmol), Gd(OTf)$_3$ (72 mg, 0.12 mmol). Purified via column chromatography (10% EtOAc in hexane) to give the product as an orange waxy solid with inseparable diastereomers (96 mg, 84%, d.r. 10:1).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 – 7.16 (1H, m, Ar*H*), 7.07 – 7.03 (2H, m, Ar*H*), 6.87 – 6.84 (2H, m, Ar*H*), 6.82 (1H, d, *J* = 7.6 Hz, Ar*H*), 6.72 (1H, d, *J* = 8.3 Hz, Ar*H*), 6.68 (1H, td, *J* = 7.5, 1.0 Hz, Ar*H*), 4.90 (1H, td, *J* = 6.6, 3.4 Hz, C*H*NO_2), 4.80 (1H, d, *J* = 6.6 Hz, NC*H*Ar), 3.79 (3H, s, OC*H*$_3$), 3.77 (1H, ddd, *J* = 11.9, 6.7, 1.1 Hz, ArC*H*$_2$), 3.58 (1H, dd, *J* = 12.0, 3.4 Hz, ArC*H*$_2$), 2.99 (3H, s, NC*H*$_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0 (Ar*C*), 145.3 (Ar*C*), 133.6 (Ar*C*), 130.4 (Ar*C*), 130.1 (Ar*C*), 128.3 (Ar*C*), 121.7 (Ar*C*), 118.1 (Ar*C*), 114.4 (Ar*C*), 111.7 (Ar*C*), 85.8 (*C*HNO_2), 55.4 (O*C*H$_3$), 51.2 (Ar*C*H$_2$), 46.4 (N*C*HAr), 39.3 (N*C*H$_3$). IR (neat) 2927 C-H 2833 C-H 1603 C=C 1575 C=C 1508 cm^{-1} C=C. LRMS: 269.1 (100) 270.1 (18). HRMS: Expected: 269.1290 Found: 269.1294

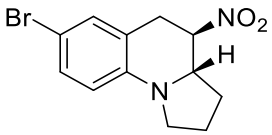
1-Butyl-3-nitro-2-propyl-1,2,3,4-tetrahydroquinoline 536



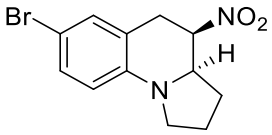
Prepared via general procedure D. Toluene (3.0 mL), (E)-N,N-dibutyl-2-(2-nitrovinyl)aniline (83 mg, 0.3 mmol), $Gd(OTf)_3$ (53 mg, 0.09 mmol). Purified via column chromatography (0-2% EtOAc in hexane) to give the product as a yellow oil (82 mg, 74%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10 (1H, t, *J* = 7.8 Hz, Ar*H*), 7.07 (1H, d, *J* = 7.3 Hz, Ar*H*), 6.68 (1H, td, *J* = 7.4, 0.8 Hz, Ar*H*), 6.58 (1H, d, *J* = 8.3 Hz, Ar*H*), 4.75 (1H, m, C), 4.04 (1H, m, NC*H*), 3.52 (1H, d, *J* = 18.1 Hz, ArCH_2), 3.43 (1H, ddd, *J* = 14.6, 9.7, 5.0 Hz, NCH_2), 3.12 (1H, dd, *J* = 18.1, 5.6 Hz, ArCH_2), 2.99 (1H, ddd, *J* = 14.7, 9.8, 6.4 Hz, NCH_2), 1.60 (2H, ddd, *J* = 10.2, 6.8, 2.7 Hz, NCHCH_2), 1.55 – 1.34 (4H, m, alkyl H), 1.33 – 1.25 (2H, m, alkyl H), 0.97 (3H, td, *J* = 7.2, 2.6 Hz, CH_3), 0.93 (3H, t, *J* = 7.4 Hz, CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.5 (Ar*C*), 129.2 (Ar*C*), 127.7 (Ar*C*), 117.0 (Ar*C*), 116.7 (Ar*C*), 111.9 (Ar*C*), 81.1 (*C*HNO_2), 60.8 (N*C*H), 50.9 (N*C*H_2), 34.4 (*C*H_2), 29.8 (*C*H_2), 26.2 (Ar *C*H_2), 20.2 (*C*H_2), 19.4 (*C*H_2), 14.2 (*C*H_3), 14.1 (*C*H_3). IR (neat) 3036 C-H 2954 C-H 2928 C-H 2868 C-H 1601 C=C 1575 C=C 1544 NO_2 1498 cm^{-1} C=C. LRMS: 277 (100) 278 (20). HRMS Expected: 277.19160 Found: 277.19169

(3a*S,4*R**)-7-Bromo-4-nitro-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolone 537a**



(3a*R,4*R**)-7-Bromo-4-nitro-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolone 537b**



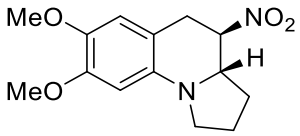
Prepared via general procedure D. Toluene (4.0 mL), (E)-1-(4-bromo-2-(2-nitrovinyl)phenyl)pyrrolidine (118 mg, 0.4 mmol), $Gd(OTf)_3$ (74 mg, 0.12 mmol). Purified via column chromatography (5% EtOAc in hexane) to give the product as an orange crystalline solid (50 mg, 42%, *dr* 9:1).

537a ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (1H, dd, *J* = 8.6, 1.9 Hz, Ar*H*), 7.16 (1H, s, Ar*H*), 6.36 (1H, d, *J* = 8.6 Hz, Ar*H*), 4.42 (1H, ddd, *J* = 12.0, 9.7, 4.7 Hz,

C*H*NO_2), 3.76 (1H, td, *J* = 9.6, 5.5 Hz, NC*H*CHNO_2), 3.47 – 3.41 (2H, m, NCH_2/ArCH_2), 3.27 – 3.21 (m, 2H, NCH_2/ArCH_2), 2.25 (1H, ddd, *J* = 12.3, 6.9, 1.4 Hz, (NO_2)CHCHCH_2), 2.16 (1H, ddd, *J* = 12.8, 9.7, 7.5 Hz, (NO_2)CHCHCH_2), 2.06 – 1.96 (1H, m, NCH_2CH_2), 1.77 (1H, tdd, *J* = 11.9, 9.5, 7.8 Hz, NCH_2CH_2). ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.1 (Ar*C*), 131.4 (Ar*C*), 131.1 (Ar*C*), 119.4 (Ar*C*), 112.7 (Ar*C*), 108.2 (Ar*C*), 83.9 (*C*HNO_2), 60.4 (N*C*H), 47.8 (N*C*H_2), 33.4 (Ar*C*H_2), 30.8 (NCH_2*C*H_2), 23.5 (NCH*C*H_2). IR (neat) 2971 C-H 2946 C-H 2856 C-H 1595 C=C 1532 NO_2 1495 cm^{-1} C=C. LRMS (ES+) 297 (100) 299 (90). HRMS Expected 297.0239 Found 297.0236 m.p. 138 °C (dec.)

537b ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (dt, *J* = 11.1, 5.6 Hz, 1H, Ar*H*), 7.16 – 7.14 (m, 1H, Ar*H*), 6.40 (d, *J* = 8.6 Hz, 1H, Ar*H*), 5.11 (dt, *J* = 5.1, 2.7 Hz, 1H, C*H*NO_2), 3.74 (ddd, *J* = 9.2, 6.3, 2.7 Hz, 1H, NC*H*), 3.39 (td, *J* = 8.8, 3.4 Hz, 1H, NCH_2), 3.33 – 3.26 (m, 3H, NCH_2, ArCH_2), 2.22 (dtd, *J* = 9.5, 6.9, 2.8 Hz, 1H, NCHCH_2), 2.10 – 2.03 (m, 1H, NCH_2CH_2), 2.03 – 1.95 (m, 1H, NCH_2CH_2), 1.86 – 1.78 (m, 1H, NCHCH_2) ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.8 (Ar*C*), 131.1 (Ar*C*), 130.5 (Ar*C*), 118.7 (Ar*C*), 112.9 (Ar*C*), 108.5 (Ar*C*), 78.7 (*C*HNO_2), 58.5 (N*C*H), 47.3 (Ar*C*), 31.6 (NCH_2), 28.4 (NCH*C*H_2), 23.1 (NCH_2*C*H_2). IR (neat) 2970 C-H 2946 C-H 2855 C-H 1594 C=C 1532 NO_2 1495 cm^{-1} C=C. LRMS: 297.0 (85) 298.0 (100). HRMS: Expected: 297.0239 Found: 297.0248 m.p. 137 °C (dec.)

(3a*S,4*R**)-7,8-Dimethoxy-4-nitro-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline 539a**

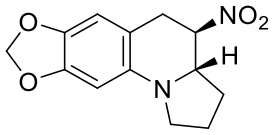


Prepared via general procedure D. Toluene (4.0 mL), (E)-1-(4,5-dimethoxy-2-(2-nitrovinyl)phenyl)pyrrolidine (111 mg, 0.4 mmol), $Gd(OTf)_3$ (73 mg, 0.12 mmol). Purified via column chromatography (20% EtOAc in hexane) to give the product as an orange crystalline solid (69 mg, 62%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.63 (1H, s, Ar*H*), 6.14 (1H, s, Ar*H*), 4.45 (1H, ddd, *J* = 11.8, 9.8, 4.9 Hz, C*H*NO_2), 3.87 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.72 (1H, td, *J* = 9.2, 5.7 Hz, NC*H*), 3.47 (1H, td, *J* = 8.6, 3.0 Hz, NCH_2), 3.42 (1H, ddd, *J* = 14.9, 11.9, 0.7 Hz, ArCH_2), 3.29 (1H, dd, *J* = 16.0, 8.4 Hz, NCH_2), 3.20 (1H, dd, *J* = 15.0, 4.9 Hz, ArCH_2), 2.25 – 2.20 (1H, m, NCHCH_2), 2.16 – 2.09 (1H, m,

NCH_2CH_2), 2.06 – 1.96 (1H, m, NCH_2CH_2), 1.82 – 1.75 (1H, m, $NCHCH_2$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.4 (Ar*C*), 140.9 (Ar*C*), 138.0 (Ar*C*), 113.7 (Ar*C*), 108.5 (Ar*C*), 97.3 (Ar*C*), 84.8 ($CHNO_2$), 60.4 (N*C*H), 57.0 (OCH_3), 56.1 (OCH_3), 48.5 (NCH_2), 33.3 ($ArCH_2$), 30.6 ($NCHCH_2$), 23.5 (NCH_2CH_2). IR (neat): 2989 C-H 2938 C-H 2919 C-H 2878 C-H 1618 C=C 1592 C=C 1535 NO_2 1521 cm^{-1} C=C. LRMS: 279.1 (100) 278.1 (60). HRMS: Expected: 279.1345 Found: 279.1345 m.p. 163-164 °C

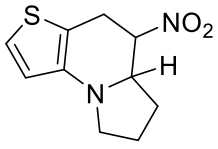
(3a*S,4*R**)-4-Nitro-1,2,3,3a,4,5-hexahydro-[1,3]dioxolo[4,5-g]pyrrolo[1,2-a]quinolone 540b**



Prepared via general procedure D. Toluene (4.0 mL), (E)-1-(6-(2-nitrovinyl)benzo[d][1,3]dioxol-5-yl)pyrrolidine (100 mg, 0.38 mmol), $Gd(OTf)_3$ (72 mg, 0.12 mmol). Purified via column chromatography (10% EtOAc in hexane) to give the product as a yellow crystalline solid (72 mg, 72%).

^1H NMR (600 MHz, $CDCl_3$) δ 6.57 (1H, s, Ar*H*), 6.16 (1H, s, Ar*H*), 5.85 (2H, dd, *J* = 3.3, 1.3 Hz, OCH_2O), 4.43 (1H, ddd, *J* = 11.8, 9.7, 4.9 Hz, $CHNO_2$), 3.70 (1H, td, *J* = 9.3, 5.7 Hz, $NCHCHNO_2$), 3.43-3.38 (2H, m, $ArCH_2CHNO_2$/NCH_2), 3.24 (1H, dd, *J* = 16.1, 8.5 Hz, NCH_2), 3.17 (1H, dd, *J* = 15.1, 4.9 Hz, $ArCH_2$), 2.24 – 2.18 (1H, m, $NCHCH_2$), 2.14 – 2.08 (1H, m, NCH_2CH_2), 2.03 – 1.94 (1H, m, NCH_2CH_2), 1.77 (1H, tt, *J* = 11.1, 8.4 Hz, $NCHCH_2$). ^{13}C NMR (150 MHz,$CDCl_3$) δ 147.7 (Ar*C*), 139.0 (Ar*C*), 138.7 (Ar*C*), 109.0 (Ar*C*), 109.0 (Ar*C*), 100.8 (OCH_2O), 94.4 (Ar*C*), 84.7 ($CHNO_2$), 60.4 ($NCHCHNO_2$), 48.7 (NCH_2), 33.8 ($ArCH_2$), 30.6 ($NCHCH_2$), 23.4 (NCH_2CH_2). IR (neat) 2981 C-H 2942 C-H 2895 C-H 2870 C-H C-H 2836 C-H 2782 C-H 1625 C=C 1614 C=C 1540 NO_2 1502 cm^{-1} C=C. LRMS 263.1 (100). HRMS Expected: 263.1032 Found: 263.1029 m.p. 166-168 °C

5-nitro-4,5,5a,6,7,8-hexahydrothieno[3,2-e]indolizine 547

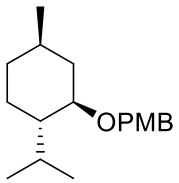


Prepared via general procedure D. Toluene (1.5 mL), (E)-1-(2-(2-nitrovinyl)thiophen-3-yl)pyrrolidine (36 mg, 0.15 mmol), $Gd(OTf)_3$ (27 mg, 0.05 mol). Purified via column chromatography (10% EtOAc in hexane) to give the product as a white waxy solid (9 mg, 25%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.64 (1H, d, *J* = 5.6 Hz, Ar*H*), 6.72 (1H, d, *J* = 5.6 Hz, Ar*H*), 4.52 – 4.48 (ddd, *J* = 10.6, 6.0, 3.2 Hz, C*H*NO_2), 4.46 (1H, dd, *J* = 10.2, 7.0 Hz, NC*H*), 3.96 (1H, d, *J* = 15.7 Hz, ArC*H*$_2$), 3.60 – 3.55 (1H, m, NC*H*$_2$), 3.35 – 3.25 (1H, m, NC*H*$_2$), 3.21 (1H, dd, *J* = 15.7, 3.5 Hz, ArC*H*$_2$), 2.12 (1H, dt, *J* = 12.5, 6.4 Hz, NCHC*H*$_2$), 2.06 (1H, dt, *J* = 9.7, 4.3 Hz, NCH_2C*H*$_2$), 2.03 – 1.98 (1H, m, NCH_2C*H*$_2$), 1.78 (1H, dd, *J* = 12.2, 5.7 Hz, NCHC*H*$_2$) ^{13}C NMR too faint to analyse. IR (neat): 3324 C-H 3295 C-H 2912 C-H 2865 C-H 1715 C=C 1669 C=C 1602 C=C 1547 NO_2 1506 cm^{-1} C=C. LRMS 225.1 (100). HRMS Expected: 225.0692 Found: 225.0701

3.4.4 Synthesis of Other Materials

L-Menthol-PMB ether 383[179]

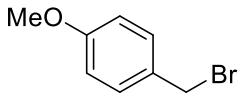


L-Menthol (251 mg, 1.60 mmol) was dissolved in THF (5.0 mL) and cooled to 0 °C. Sodium hydride 60% in mineral oil (131 mg, 3.35) was added portionwise. This suspension was stirred for 10 min, then 4-methoxybenzyl chloride (288 mg, 1.83 mmol) was added and the mixture refluxed overnight. The reaction was quenched with water (10 mL) and the organics were extracted with EtOAc (3 x 10 mL), dried ($MgSO_4$), and the solvent removed *in vacuo*. This crude material was purified via column chromatography (5% EtOAc in hexanes) to give the product as a colourless oil (312 mg, 71%)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.7 Hz, OCH_2CArH), 6.87 (2H, d, *J* = 8.7 Hz, MeOCAr*H*), 4.59 (1H, d, *J* = 11.1 Hz, OCH_2Ar), 4.34 (1H, d, *J* = 11.1 Hz, OCH_2Ar), 3.81 (3H, s, OCH_3), 3.15 (1H, td, *J* = 10.6, 4.1 Hz, $OCHCH_2$), 2.28 (1H, heptd, *J* = 7.0, 2.8 Hz, $CH(CH_3)_2$), 2.19 (1H, ddd, *J* = 12.1, 5.5, 3.8 Hz, $CHCH(CH_3)_2$), 1.69 – 1.59 (2H, m), 1.41 – 1.31 (1H, m), 1.27 (1H, ddt, *J* = 13.3, 10.4, 3.1 Hz), 1.01 – 0.81 (9H, m), 0.70 (3H, d, *J* = 6.9 Hz, $CHCH_3$).

Data in agreement with literature values[179]

***p*-Methoxybenzyl bromide**[237]

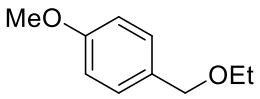


p-Methoxybenzyl alcohol (0.44 mL, 3.6 mmol) was dissolved in Et_2O (10 mL) and was cooled to 0 °C. PBr_3 (4.3 mL, 1.8 mmol) was added and the mixture stirred at 0 °C for 3 h. The reaction was then quenched by the careful dropwise addition to ice water saturated with $NaHCO_3$. The organic layer was separated and washed with sat. $NaHCO_3$ solution (3 x 10 mL). The solvent was then removed *in vacuo* to give the product as a clear oil/white solid (562 mg, 77%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (2H, d, *J* = 8.6 Hz, $ArHCH_2Br$), 6.87 (2H, d, *J* = 8.7 Hz, $ArHCOCH_3$), 4.51 (2H, s, $ArCH_2Br$), 3.81 (3H, s, $ArOCH_3$).

Data in agreement with literature values[238]

_p_-Methoxy(ethoxymethyl)benzene 390

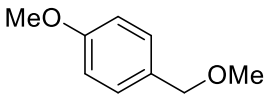


Ethanol (0.38 mL, 6.4 mmol) was mixed with THF (10 mL) and cooled to 0 °C. Sodium hydride 60% in mineral oil (254 mg, 13.0 mmol) was added portionwise at 0 °C and was left to stir for 20 min. To this, 4-methoxybenzyl bromide (465 mg, 2.31 mmol) was added and the mixture stirred at 0 °C for 30 min before being warmed to room temperature and being left overnight. After overnight stirring at room temperature, the reaction was heated to 70 °C and left overnight to ensure conversion. The reaction was then quenched with water (20 mL), then the organics were extracted with DCM (3 x 20 mL). The organic washings were combined and the solvent removed *in vacuo* to give a crude product which was then purified via column chromatography (5% EtOAc in hexanes) to give the product as a yellow oil (120 mg, 23%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (2H, d, *J* = 8.6 Hz, Ar*H*CCH_2OEt), 6.89 (2H, d, *J* = 8.6 Hz, Ar*H*COMe), 4.44 (2H, s, ArC*H*$_2$OEt), 3.81 (3H, s, ArOC*H*$_3$), 3.52 (2H, q, *J* = 7.0 Hz, OC*H*$_2$$CH_3$), 1.24 (3H, t, *J* = 7.0 Hz, OCH_2C*H*$_3$).

Data in agreement with literature values[239]

_p_-Methoxy(methoxymethyl)benzene 389

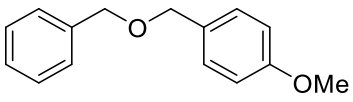


p-Methoxybenzyl alcohol (0.48 mL, 4.0 mmol) was dissolved in THF (20 mL), then sodium hydride 60% in mineral oil (320 mg, 16.0 mmol) was added and the resulting suspension stirred for 30 min. To this, iodomethane (1.0 mL, 16 mmol) was added and the mixture heated to 45 °C and stirred overnight. The reaction was then quenched with water (40 mL), then the organics were extracted with DCM (3 x 20 mL). The combined organic washings were dried ($MgSO_4$) and the solvent removed *in vacuo* to give the pure product as a yellow oil (578 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 10.0 Hz, Ar*H*CCH_2OMe), 6.88 (2H, d, *J*= 10.0, Ar*H*COMe), 4.39 (2H, s, ArC*H*$_2$OMe), 3.81 (3H, s, ArOC*H*$_3$), 3.36 (3H, s, ArCH_2OC*H*$_3$).

Data in agreement with literature values[240]

1-((Benzyloxy)methyl)-4-methoxybenzene 399

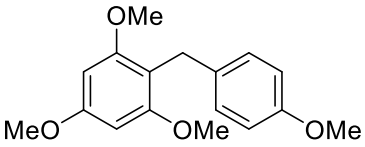


Benzyl alcohol (0.1 mL, 1.0 mmol) was dissolved in THF (2.0 mL), then sodium hydride 60% in mineral oil (156 mg, 3.90 mmol) and tetrabutyl ammonium iodide (cat.) were added and the mixture was stirred for 10 min. To this *p*-methoxybenzyl chloride (0.14 mL, 1.0 mmol) was added and the reaction stirred at rt for 72 h. The reaction was then quenched with water (10 mL) and extracted with dichloroethane (2 x 10 mL). The organic washings were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to give the pure product as a yellow oil (189 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.27 (7H, m, Ar*H*), 6.89 (2H, d, *J* = 8.7 Hz, Ar*H*COMe), 4.53 (2H, s, ArC*H*$_2$OCH_2OPMB), 4.50 (2H, s, ArC*H*$_2$CH_2Ph), 3.81 (3H, s, OC*H*$_3$).

Data in agreement with literature values[241]

1,3,5-Trimethoxy-2-(4-methoxybenzyl)benzene 394



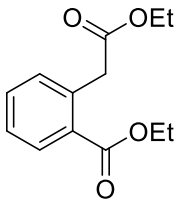
p-Methoxy(methoxymethyl)benzene (308 mg, 2.02 mmol) was added to dihloromethane (6.0 mL) and cooled to -78 °C. To this BF_3.OEt_2 (0.60 mL, 4.8 mmol) was added and the resulting solution was stirred for 10 min. PIFA (870 mg, 2.02 mmol) was added and after 30 min 1,3,5-trimethoxybenzene (1.02 g, 6.06 mmol) was added. The reaction mixture was then allowed to slowly warm to room temperature and was stirred overnight. This solution was quenched with sodium thiosulfate solution (10 mL, sat.), the organics were extracted with DCM (3 x 10 mL) and the solvent was removed *in vacuo* to give the crude product. This

was then purified via column chromatography (20% Et_2O in hexane) to give 1,3,5-trimethoxy-2-(4-methoxybenzyl)benzene as the major product (356 mg, 61%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 – 7.21 (2H, m, CH_2CCHCH), 6.83 – 6.80 (2H, m, MeOCC*H*CH), 6.20 (2H, s, MeOCC*H*COMe), 3.94 (2H, s, ArCH_2Ar), 3.84 (3H, s, ArOCH_3), 3.83 (6H, s, ArOCH_3), 3.79 (3H, s, ArOCH_3).

Data in agreement with literature values[242]

Diethyl homophthalate 413[183]

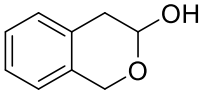


Homophthalic acid (5.03 g, 27.9 mmol) was dissolved in a mixture of ethanol (23 mL) and toluene (12 mL) and stirred in a flask fitted with a Dean-Stark apparatus in air. To this sulphuric acid (1.5ml, conc.) was added and the solution was heated to 115 °C for 72 h. The reaction was cooled to room temperature, quenched with sodium hydrogen carbonate solution (5%, 60 mL) and extracted with toluene (3 x 20 mL). The organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to give the desired product as a yellow oil (6.14 g, 93%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (1H, d, *J* = 7.6 Hz, Ar*H*CCO_2Et), 7.40 (1H, t, *J* = 7.4 Hz, Ar*H*CCH_2), 7.29 (1H, t, *J* = 7.5 Hz, Ar*H*CHCCO_2Et), 7.19 (1H, d, *J* = 7.4 Hz, Ar*H*CHCCH_2), 4.33 (2H, q, J = 7.1 Hz, CH_2OC(O)Ar), 4.16 (2H, q, J = 7.1 Hz, CH_2OC(O)CH_2), 4.01 (2H, s, ArCH_2CO_2Et), 1.37 (3H, t, J = 7.1 Hz, CH_3CH_2OC(O)Ar), 1.25 (3H, t, J = 7.1 Hz, CH_3CH_2OC(O)CH_2).

Data in agreement with literature values[243]

3-Hydroxyisochroman 414[184]



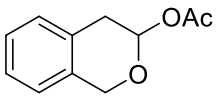
Diethyl homophthalate (4.975g, 21.15 mmol) was dissolved in toluene (250 mL) and cooled to -78 °C. DIBAL-H (1M in hexanes, 65.6 mL, 65.6 mmol) was added dropwise and then the reaction mixture was stirred at -78 °C for 2 h. The reaction mixture was quenched with sodium potassium tartrate solution (100 mL, sat.) and

the organics extracted. The aqueous layer was washed with EtOAc (3 x 150 mL) and the combined organics dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the product as an off-white crystalline solid (2.80 g, 89%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.17 (2H, m, Ar*H*), 7.15 – 7.11 (1H, m, Ar*H*), 7.05 – 7.01 (1H, m, Ar*H*), 5.38 (1H, dd, *J* = 5.2, 3.8 Hz, OC*H*CH_2), 4.98 (1H, d, *J* = 14.8 Hz, ArC*H*$_2$O), 4.80 (1H, d, *J* = 14.8 Hz, ArC*H*$_2$O), 3.09 (1H, dd, *J* = 16.3, 3.7 Hz, ArC*H*$_2$CH), 2.88 (1H, d, *J* = 5.0 Hz, O*H*), 2.84 (1H, dd, *J* = 16.2, 5.2 Hz, ArC*H*$_2$CH). m.p. 70 – 72 °C Lit. 71 – 71.5 °C[184]

Data in agreement with literature values[244]

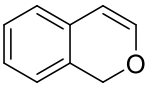
Isochroman-3-yl acetate 421



3-Hydroxyisochroman (160 mg, 1.06 mmol) was dissolved in pyridine (4.0 mL). Acetic anhydride (0.1 mL, 1 mmol) was added, turning the solution from colourless to yellow before being stirred for 12 d. The reaction mixture was then quenched with saturated copper sulfate solution (50 mL) and EtOAc (50 mL) added. The organic layer was washed with saturated copper sulfate solution (3 x 50 mL) then saturated sodium bicarbonate solution (3 x 50 mL). The organic layer was then dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to give a brown oil. The crude product was purified via column chromatography (10% EtOAc in hexanes) to give the product as an orange oil (88 mg, 45%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 – 7.20 (2H, m, Ar*H*), 7.16 – 7.13 (1H, m, Ar*H*), 7.07 – 7.04 (1H, m, Ar*H*), 6.36 (1H, dd, *J* = 4.4, 3.2 Hz, C*H*OAc), 4.93 (1H, d, *J* = 14.6 Hz, ArC*H*$_2$O), 4.82 (1H, d, *J* = 14.6 Hz, ArC*H*$_2$O), 3.20 (1H, dd, *J* = 16.7, 4.4 Hz, ArC*H*$_2$CH), 2.88 (1H, dd, *J* = 16.7, 3.2 Hz, ArC*H*$_2$CH), 2.08 (3H, s, OC(O)C*H*$_3$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2 (O*C*(O)CH_3), 133.4 (Ar*C*), 130.0 (Ar*C*), 128.9 (Ar*C*H), 127.1 (Ar*C*H), 126.6 (Ar*C*H), 124.2 (Ar*C*H), 91.4 (*C*HOAc), 63.4 (Ar*C*H_2O), 32.1 (Ar*C*H_2C), 21.3 (OC(O)*C*H_3). LRMS (CI) 210.1 (67), 150.1 (100), 132.0 (20). HRMS Expected 210.11247 Found 210.11239

Isochromene 265[188]

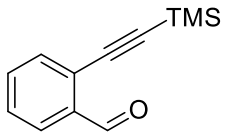


3-Hydroxyisochroman (4.00 g, 26.6 mmol) and $KHSO_4$ (503 mg, 3.69 mmol) were distilled at 100 °C, 40 mbar with a Vigreux condenser. The organic distillate was taken up in ether (40 mL), decanted, then dried ($MgSO_4$). This solution was then filtered and concentrated *in vacuo* to give the product as an orange oil that solidified to orange crystals upon swirling (2.66 g, 74%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.11 (2H, m, Ar*H*), 7.01 – 6.93 (2H, m, Ar*H*), 6.58 (1H, d, *J* = 5.7 Hz, OC*H*CH), 5.81 (1H, d, *J* = 5.7 Hz, OCHC*H*CAr), 5.06 (2H, s, C*H*$_2$OCH). m.p. 20-22 °C Lit. not reported.

Data in agreement with literature values[183]

2-[(Trimethylsilyl)ethynyl]benzaldehyde 416[186]

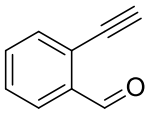


2-Bromobenzaldehyde (500 mg, 2.70 mmol), triphenylphosphine (11 mg, 0.04 mmol), and palladium diacetate (6 mg, 0.03 mmol) were dissolved in triethylamine (25 mL, dried over 4Å MS) and stirred. TMS-acetylene (406 mg, 4.05 mmol) was added, then the reaction mixture was heated to 80 °C and stirred for 6 h. The reaction was allowed to cool to rt and additional triethylamine was added until a suspension formed which was filtered off. The filtrate was collected, combined with water (50 mL) and then washed with DCM (3 x 50 mL). The combined organics dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified via column chromatography (1% EtOAc in hexanes) to give the product as a yellow oil which formed an orange waxy solid upon cooling to -4 °C (340 mg, 52%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.56 (1H, s, ArC*H*O), 7.91 (1H, dd, *J* = 7.9, 0.8 Hz, C*H*CCHO), 7.57 (1H, dd, *J* = 7.7, 1.1 Hz, C*H*CCCTMS), 7.54 (1H, td, *J* = 7.4, 1.3 Hz, C*H*CHCCCTMS), 7.45 – 7.42 (1H, m, C*H*CHCHO), 0.28 (9H, s, Si(C*H*$_3$)$_3$).

Data in agreement with literature values[186]

2-Ethynylbenzaldehyde 417[186]

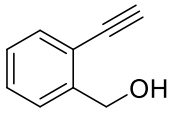


2-[(Trimethylsilyl)ethynyl]benzaldehyde (243 mg, 1.20 mmol) and KF (154 mg, 2.65 mmol) were dissolved in DMF (1.2 mL) and stirred for 3 h. The product was then poured into water (40 mL) and extracted with DCM (3 x 10 mL). The combined organics were dried ($MgSO_4$) and the solvent removed *in vacuo*. This crude product was then purified via column chromatography (20% EtOAc in hexanes) to give the desired product as a white solid (60 mg, 38%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.54 (1H, s, C*H*O), 7.96 – 7.91 (1H, m, C*H*CCHO), 7.65 – 7.60 (1H, m, C*H*CCCH), 7.57 (1H, td, *J* = 7.4, 1.5 Hz, C*H*CHCCCH), 7.52 – 7.45 (1H, m, C*H*CHCCHO), 3.46 (1H, s, CC*H*). m.p. 62 – 64 °C Lit. 62 – 65 °C[245]

Data in agreement with literature values[186]

2-Ethynylbenzyl alcohol 418[186]

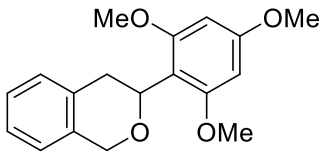


2-[((Trimethylsilyl))phenyl]methanol (204 mg, 1 mmol) was dissolved in methanol (4.0 mL) and K_2CO_3 (17 mg, 0.10 mmol) was added. The resulting mixture was stirred at rt for 3 h. The reaction was then quenched with water and extracted with EtOAc, the organic layers were combined, dried ($MgSO_4$) and the solvent removed *in vacuo* to give the product as a solid (98 mg, 74% over two steps).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (1H, dd, *J* = 7.6, 1.1 Hz, Ar*H*), 7.46 (1H, ddd, *J* = 7.7, 1.3, 0.6 Hz, Ar*H*), 7.38 (1H, td, *J* = 7.7, 1.3 Hz, Ar*H*), 7.29 – 7.25 (4H, m, Ar*H*), 4.85 (2H, s, ArCH_2OH), 3.35 (1H, s, ArCC*H*).

Data in agreement with literature values[186]

3-(2,4,6-Trimethoxyphenyl)isochroman 423

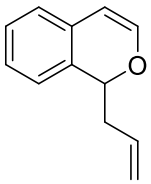


Isochromene (34 mg, 0.25 mmol), 1,3,5-trimethoxybenzene (52 mg, 0.30 mmol), $CuBr_2$ (2 mg, 0.01 mmol), $ZnBr_2$ (3 mg, 0.01 mmol) were dissolved in MeCN (5 mL) and cooled to -10 °C. To this DDQ (58 mg, 0.25 mmol) was added and the

reaction allowed to warm to room temperature overnight. The solvent was then removed in vacuo, then the crude mixture was twice purified via column chromatography (10% EtOAc in hexane) then (30% EtOAc in hexane) to give the product as an off-white solid (12 mg, 16%)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 – 7.15 (2H, m, C*H*Ar), 7.14 – 7.10 (1H, m, C*H*Ar), 7.06 – 7.03 (1H, m, C*H*Ar), 6.17 (2H, s, MeOCC*H*COMe), 5.33 (1H, dd, *J* = 11.6, 3.4 Hz, OC*H*CAr), 4.98 (2H, s, CArC*H*$_2$O), 3.83 (3H, s, CArOC*H*$_3$), 3.82 (1H, dd, *J* = 16.2, 11.6 Hz, ArC*H*$_2$CHAr), 3.80 (6H, s, ArOC*H*$_3$), 2.62 (1H, dd, *J* = 16.2, 3.4 Hz, CArC*H*$_2$CHAr). ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.1 (Ar*C*OMe), 159.9 (Ar*C*OMe), 135.5 (Ar*C*CH$_2$CH), 135.3 (Ar*C*CH$_2$O), 128.9 (Ar*C*), 126.2 (Ar*C*), 125.8 (Ar*C*), 124.5 (Ar*C*), 109.8 (Ar*C*CH), 91.2 (Ar*C*COMe), 69.7 (O*C*HCH$_2$), 69.4 (O*C*H$_2$), 56.0 (CHCCO*C*H$_3$), 55.4 (ArO*C*H$_3$), 31.7 (Ar*C*H$_2$CH). IR (neat): 3004 C-H 2938 C-H 2908 C-H 2836 C-H 1600 C=C 1583 C=C 1494 cm^{-1} C=C. LRMS (EI) 300.12 (32), 195.06 (56), 104.03 (100). HRMS Expected: 300.1356 Found 300.1355 m.p. 112 – 114 °C

1-Allyl-isochromene 266[130]



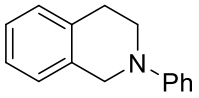
Isochromene (129 mg, 1.0 mmol) was dissolved in DCM (10 mL). 4Å molecular sieves (250 mg) and $LiClO_4$ (162 mg, 1.50 mmol) were added then the solution was cooled to – 40 °C and stirred for 5 min. DDQ (299 mg, 1.32 mmol) was added and the solution stirred for 10 mins. Allyltributylstannane (0.60 mL, 1.9 mmol) was added and the solution allowed to warm to rt over 1.5 h. The reaction was then quenched with sat. $NaHCO_3$ solution (30 mL) and the organics extracted with DCM (3 x 20 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. This crude product was purified via column chromatography (1% EtOAc in hexanes) to give the 1-allyl-isochromene as a clear oil (30 mg, 17%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (1H, td, *J* = 7.4, 1.2 Hz, ArC*H*), 7.14 (1H, td, *J* = 7.5, 1.2 Hz, ArC*H*), 6.98 – 6.94 (2H, m, ArC*H*), 6.49 (1H, d, *J* = 5.7 Hz, OC*H*CH), 5.90 (1H, ddt, *J* = 17.2, 10.3, 7.0 Hz, CH$_2$C*H*CH$_2$), 5.75 (1H, d, *J* = 5.7 Hz,

ArC*H*CHO), 5.15 – 5.10 (2H, m, CH_2CHCH_2), 5.06 (1H, s, ArC*H*O), 2.84 – 2.75 (1H, m, $ArCHCH_2CHCH_2$), 2.55 – 2.48 (1H, m, $ArCHCH_2CHCH_2$).

Data in agreement with literature values[130]

2-Phenyl-1,2,3,4-tetrahydroisoquinoline 73[189]

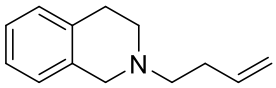


(±)BINAP (32 mg, 5 mol%) was dissolved in toluene (3.0 mL) and stirred. To this bromobenzene (0.12 mL, 1.0 mmol), 1,2,3,4-tetrahydroisoquinoline (0.16 mL, 1.2 mmol), ^tBuOK (170 mg, 1.50 mmol) and $Pd(OAc)_2$ (11 mg, 5 mol%) were added. The reaction mixture was then heated to 100 °C for 18 h, turning dark red. The crude mixture was cooled, concentrated *in vacuo* and purified via column chromatography (10% EtOAc in hexane) to give the product as a brown oil (74 mg, 35%)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (2H, td, *J* = 7.7, 1.3 Hz, C*H*Ar), 7.21 (4H, qd, *J* = 6.4, 3.1 Hz, C*H*Ar), 7.03 (2H, d, *J* = 8.5 Hz, C*H*Ar), 6.87 (1H, td, *J* = 7.3, 0.7 Hz, C*H*Ar), 4.45 (2H, s, $ArCH_2N$), 3.60 (2H, t, *J* = 5.8 Hz, $ArCH_2CH_2N$), 3.03 (2H, t, *J* = 5.8 Hz, $ArCH_2CH_2N$).

Data in agreement with literature values[53]

2-(But-3-en-1-yl)-1,2,3,4-tetrahydroisoquinoline 430

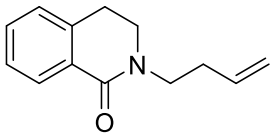


Potassium carbonate (338 mg, 2.45 mmol) and potassium iodide (84 mg, 0.2 mmol) were suspended in MeCN (6.0 mL) and stirred. To this, 1,2,3,4-tetrahydroisoquinoline (0.25 mL, 2.0 mmol) and 4-bromo-1-butene (0.4 mL, 4.0 mmol) were added. The reaction mixture was heated to 80 °C for 18 h, turning brown. The reaction mixture was quenched with sat. $NaHCO_3$ solution (10 mL) and the organics extracted with EtOAc (3 x 10 mL). These organic fractions were combined, dried ($MgSO_4$), filtered then the solvent removed *in vacuo* to give the product as a brown oil (305 mg, 81%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 – 7.08 (3H, m, Ar*H*), 7.02 (1H, dd, *J* = 7.9, 5.7 Hz, Ar*H*), 5.87 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, CH_2CHCH_2), 5.11 (1H, dq, *J* =

17.1, 1.6 Hz, CH_2CHCH_2), 5.03 (1H, ddt, *J* = 10.2, 2.1, 1.2 Hz, CH_2CHCH_2), 3.66 (2H, s, $ArCH_2N$), 2.92 (2H, t, *J* = 5.9 Hz, $ArCH_2CH_2$), 2.76 (2H, t, *J* = 6.0 Hz, $ArCH_2CH_2N$), 2.63 – 2.59 (2H, m, $NCH_2CH_2CHCH_2$), 2.38 (2H, dt, *J* = 7.6, 6.8 Hz, $NCH_2CH_2CHCH_2$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.7 (CH_2CHCH_2), 134.9 (Ar*C*), 134.4 (Ar*C*), 128.8 (Ar*C*H), 126.7 (Ar*C*H), 126.2 (Ar*C*H), 125.7 (Ar*C*H), 115.8 (CH_2CHCH_2), 57.9 ($ArCCH_2N$), 56.2 ($ArCCH_2CH_2N$), 51.0 ($NCH_2CH_2CHCH_2$), 31.9 ($ArCCH_2CH_2N$), 29.2 ($NCH_2CH_2CHCH_2$). IR (neat): 3064 C-H 3020 C-H 2917 C-H 2799 C-H 2762 C-H 1640 C=C 1497 cm^{-1} C=C. LRMS (EI) 189.15 (10), 188.14 (100). HRMS Expected 188.1439 Found 188.1440

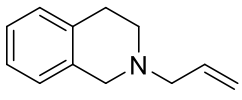
2-(But-3-en-1-yl)-3,4-dihydroisoquinolin-1-one 434



Into a mixture of MeCN (3.5 mL) and water (0.5 mL) 2-(but-3-en-1-yl)-1,2,3,4-tetrahydroisoquinoline (94 mg, 0.50 mmol) was added. $RuCl_3$ hydrate (cat.) was added and the mixture stirred for 5 min. Sodium periodate (214 mg, 1.00 mmol) was added portionwise and stirring was continued at rt for 18 h. The reaction was then quenched with sat. sodium bisulfate solution (5.0 mL), diluted with EtOAc (10 mL). The organics were then washed with sat. sodium bisulfate solution (3 x 15 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude residue was purified via column chromatography (25% EtOAc in hexane) to give the product as a brown oil (41 mg, 41%).

^1H NMR (600 MHz, $CDCl_3$) δ 8.08 (1H, dd, *J* = 7.7, 1.0 Hz, Ar*H*), 7.41 (1H, td, *J* = 7.4, 1.4 Hz, Ar*H*), 7.34 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.17 (1H, d, *J* = 7.5 Hz, Ar*H*), 5.86 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, $NCH_2CH_2CHCH_2$), 5.11 (1H, ddd, *J* = 17.1, 3.2, 1.5 Hz, $NCH_2CH_2CHCH_2$), 5.07 – 5.01 (1H, m, $NCH_2CH_2CHCH_2$), 3.65 (2H, t, *J* = 7.1 Hz, $NCH_2CH_2CHCH_2$), 3.58 – 3.55 (2H, t, *J* = 6.6 Hz, $ArCH_2CH_2N$), 2.98 (2H, t, *J* = 6.6 Hz, $ArCH_2CH_2N$), 2.41 (2H, q, *J* = 7.0 Hz, $NCH_2CH_2CHCH_2$). LRMS (CI) 203.1 (15), 202.1 (100). HRMS Expected: 202.1226 Found 202.1227

2-Allyl-1,2,3,4-tetrahydroisoquinoline 435

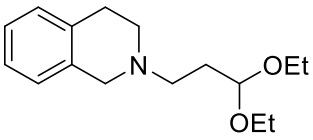


Potassium carbonate (341 mg, 2.47 mmol) was suspended in MeCN (6.0 mL) and stirred. To this 1,2,3,4-tetrahydroisoquinoline (0.25 mL, 2.0 mmol) was added and the mixture stirred for 30 min prior to the addition of allyl bromide (18 mL, 2.0 mmol). This reaction mixture was then stirred at rt for 18 h. The reaction was then quenched with water (10 mL) and the organics extracted with EtOAc (3 x 10 mL). The organic fractions were combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the desired product as a yellow oil (152 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.06 (3H, m, Ar*H*), 7.05 – 6.99 (1H, m, Ar*H*), 5.96 (1H, ddt, *J* = 16.7, 10.1, 6.5 Hz, NCH_2CHCH_2), 5.26 (1H, ddt, *J* = 17.1, 3.3, 1.5 Hz, NCH_2CHCH_2), 5.20 (1H, ddt, *J* = 10.1, 2.1, 1.1 Hz, NCH_2CHCH_2), 3.63 (2H, s, $ArCH_2N$), 3.18 (2H, dt, *J* = 6.5, 1.3 Hz, NCH_2CHCH_2), 2.92 (2H, t, *J* = 5.9 Hz, $ArCH_2CH_2N$), 2.74 (2H, t, *J* = 6.0 Hz, $ArCH_2CH_2N$).

Data in agreement with literature values[246]

2-(3,3-Diethoxypropyl)-1,2,3,4-tetrahydroisoquinoline 442

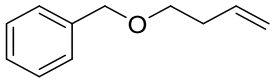


Potassium carbonate (321 mg, 2.32 mmol) was suspended in MeCN (25 mL) and 1,2,3,4-tetrahydroisoquinoline (0.25 mL, 2.0 mmol) was added. 3-chloropropionaldehyde diethyl acetal (0.33 mL, 2.0 mmol) was added and the reaction heated to reflux for 48 h. The reaction mixture was then cooled to rt and filtered through a silica plug (EtOAc) and the solvent removed *in vacuo* to give the product as a yellow oil (355 mg, 67%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (1H, m, Ar*H*), 7.15 – 7.08 (2H, m, Ar*H*), 7.02 (1H, d, *J* = 6.3 Hz, Ar*H*), 4.63 (1H, t, *J* = 5.7 Hz, $NCH_2CH_2CH(OEt)_2$), 3.71 – 3.64 (2H, m, OCH_2CH_3), 3.64 (2H, s, $ArCH_2N$), 3.56 – 3.49 (2H, m, OCH_2CH_3), 2.90 (2H, t, *J* = 5.9 Hz, $ArCH_2CH_2N$), 2.74 (2H, t, *J* = 5.9 Hz, $ArCH_2CH_2N$), 2.62 – 2.57 (2H, m, $NCH_2CH_2CH(OEt)_2$), 1.92 (2H, dt, *J* = 18.2, 9.0 Hz, $NCH_2CH_2CH(OEt)_2$) 1.25 – 1.19 (6H, m, OCH_2CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.0 (Ar*C*), 134.5 (Ar*C*), 128.8 (Ar*C*), 126.7 (Ar*C*), 126.2 (Ar*C*), 125.7 (Ar*C*), 101.7 ($NCH_2CH_2CH_2(OEt)_2$), 61.4 (OCH_2CH_3), 56.3 ($ArCH_2N$), 54.0 ($ArCH_2CH_2N$), 51.2 ($ArCH_2CH_2N$), 31.6 ($NCH_2CH_2CH(OEt)_2$), 29.3 ($NCH_2CH_2CH(OEt)_2$), 15.5

(OCH_2CH_3). IR (neat) 3019 C-H 2969 C-H 2926 C-H 2894 C-H 2804 C-H 1697 1606 C=C 1579 C=C 1495 cm^{-1} C=C. LRMS (ES+) 264.2 (100), 265.2 (20). HRMS Expected: 264.1964 Found: 264.1959

4-Benzyloxybut-1-ene 447

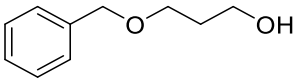


NaH (60% in mineral oil, 107 mg, 2.80 mmol) was suspended in THF and 3-buten-1-ol (0.19 mL, 2.2 mmol) was added dropwise and the mixture stirred for 5 min. Benzyl bromide (0.25 mL, 2.0 mmol) was then added and the reaction was stirred at rt for 18 h. The reaction was then quenched with water (10 mL) and the organics extracted with EtOAc (3 x 10 mL). The organics were combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the pure product as a yellow oil (336 mg, 99%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.24 (5H, m, Ar*H*), 5.85 (1H, ddt, *J* = 16.9, 10.1, 6.7 Hz, $OCH_2CH_2CHCH_2$), 5.16 – 5.01 (2H, m, $OCH_2CH_2CHCH_2$), 4.53 (2H, s, $ArCH_2O$), 3.53 (2H, t, *J* = 6.8 Hz, $OCH_2CH_2CHCH_2$), 2.38 (2H, q, *J* = 6.7 Hz, $OCH_2CH_2CHCH_2$).

Data in agreement with literature values[247]

3-(Benzyloxy)propan-1-ol 450



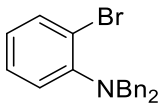
Benzyl bromide (2.10 mL, 17.9 mmol) was dissolved in THF (30 mL) and cooled to 0 °C. TBAI (1.32 g, 3.58 mmol) was added and stirred, followed by 1,3-propane diol (3.87 mL, 53.5 mmol) and NaH (0.76 g, 19 mmol). This mixture was stirred at 0 °C for 15 min then allowed to warm to rt and stirred overnight. The reaction was then quenched with sat. NH_4Cl solution (50 mL) and extracted with EtOAc (4 x 50 mL). The organics were collected, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product which was purified via column chromatography (30% hexane in EtOAc) to give the product as a yellow oil (589 mg, 20%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (5H, m, Ar*H*), 4.53 (2H, s, $ArCH_2O$), 3.88 – 3.74 (2H, m, $OCH_2CH_2CH_2OH$), 3.67 (2H, t, *J* = 5.8 Hz,

ArCH$_2$OC*H*$_2$CH$_2$CH$_2$OH), 2.29 (1H, s, OH), 1.91 – 1.84 (2H, m, OCH$_2$C*H*$_2$CH$_2$OH).

Data in agreement with literature values[248]

N,N-Dibenzyl-2-bromoaniline

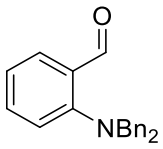


Potassium carbonate (2.77g, 20.0 mmol) and *o*-bromoaniline (678 mg, 3.94 mmol) were added to DMF (8.0 mL). Benzyl bromide (1.9 mL, 16 mmol) was then added and the mixture heated to 120 °C for 48 h. The reaction was then cooled to 0°C and quenched with diethylamine (1.05 mL). The crude product was then extracted with Et$_2$O (4 x 20 mL) and the combined organic extracts washed with brine (4 x 50 mL). The organics were then dried (MgSO$_4$), filtered and the solvent removed *in vacuo* to give the crude product which was purified via column chromatography (3% EtOAc in hexane) to give the product as a pale yellow oil (915 mg, 65%)

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59 (1H, dd, *J* = 7.9, 1.5 Hz, Ar*H*), 7.35 – 7.18 (10H, m, Ar*H*), 7.12 (1H, ddd, *J* = 8.0, 7.3, 1.5 Hz, Ar*H*), 6.92 (1H, dt, *J* = 3.5, 1.7 Hz, Ar*H*), 6.91 – 6.85 (1H, m, Ar*H*), 4.18 (4H, s, ArC*H*$_2$N).

Data in agreement with literature values[249]

2-(Dibenzylamino)benzaldehyde

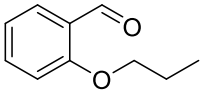


THF (10 mL) was cooled to -78 °C and n-BuLi in hexanes (1.6 mL, 2.25 mmol) was added. To this N,N-dibenzyl-2-bromoaniline (609 mg, 1.73 mmol) in THF (10 mL) was added dropwise and stirred for 5 min at -78 °C. DMF (0.80 mL, 35 mmol) was added dropwise and the reaction stirred 5 min before being quenched with sat. NaHCO$_3$ solution (25 mL) before warming to rt. The organics were then extracted in DCM (3 x 25 mL) and combined before being dried (MgSO$_4$), filtered and the solvent removed *in vacuo* to give the crude product which was purified via column chromatography to give the product as a clear oil (177 mg, 34%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (1H, d, *J* = 0.5 Hz, ArC*H*O), 7.82 (1H, dd, *J* = 7.7, 1.7 Hz, Ar*H*), 7.44 (1H, ddd, *J* = 8.2, 7.3, 1.8 Hz, Ar*H*), 7.32 – 7.22 (7H, m, Ar*H*), 7.20 – 7.14 (3H, m, Ar*H*), 7.11 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.04 (1H, d, *J* = 8.2 Hz, Ar*H*), 4.27 (4H, s, ArCH_2N).

Data in agreement with literature values[142]

2-Propoxybenzaldehyde 524[250]

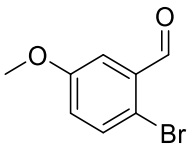


Potassium carbonate (1.40 g, 10.1 mmol) was suspended in DMF (10 mL) and salicyl aldehyde (0.85 mL, 8.0 mmol) was added. Bromopropane (2.0 mL, excess) was added and the mixture was heated to 80 °C for 18 h before being cooled to rt. The reaction was diluted with sat. $NaHCO_3$ solution (40 mL), then the organics were extracted with EtOAc (40 mL). The organic extract was washed with sat. $NaHCO_3$ solution (3 x 40 mL) then brine (40 mL). The organics were then dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to give the product as a faintly orange oil without further purification (1.173 g, 89%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (1H, d, *J* = 0.8 Hz, C*H*O), 7.83 (1H, dd, *J* = 7.7, 1.8 Hz, Ar*H*), 7.53 (1H, ddd, *J* = 8.5, 7.3, 1.8 Hz, Ar*H*), 7.03 – 6.95 (2H, m, Ar*H*), 4.04 (2H, t, *J* = 6.4 Hz, OCH_2), 1.93 – 1.83 (2H, m, OCH_2CH_2), 1.08 (3H, t, *J* = 7.4 Hz, $OCH_2CH_2CH_3$).

Data in agreement with literature values[250]

2-Bromo-5-methoxybenzaldehyde

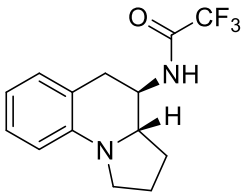


To m-anisaldehyde (0.73 mL, 6.0 mmol) in AcOH (15 mL) was added bromine (0.36 mL, 6.6 mmol). The resultant mixture was covered and stirred for 24 h at rt before being poured into ice water (100 mL) and stirred for 18 h. This formed a precipitate which was filtered off to isolate the product as an off-white solid (1.11 g, 86%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (1H, s, C*H*O), 7.52 (1H, d, *J* = 8.8 Hz, Ar*H*), 7.41 (1H, d, *J* = 3.2 Hz, Ar*H*), 7.03 (1H, dd, *J* = 8.8, 3.2 Hz, Ar*H*), 3.84 (3H, s, OC*H*$_3$). m.p. 73-74 °C Lit. 73-75 °C[251]

Data in agreement with literature values[252]

2,2,2-Trifluoro-N-((*anti*)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolin-4-yl)acetamide 550



To EtOAc (5.0 mL) and EtOH (5.0 mL) was added **358a** (75 mg, 0.34 mmol). The mixture was cooled to 0 °C and HCl (6 M, 1.2 mL) was added dropwise. Zinc dust (223 mg) was added and the mixture was stirred for 30 min, turning from yellow to colourless. The reaction mixture was then quenched ($NaHCO_3$ sat. solution), which caused the formation of a white precipitate. The precipitate was filtered through a short pad of Celite and washed with EtOAc (30 mL). The aqueous layer was separated and extracted with EtOAc (30 mL) and combined organic layers were dried ($MgSO_4$) and concentrated to give the crude amine as a colourless oil which was used directly.

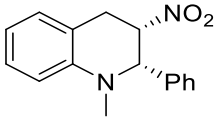
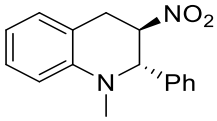
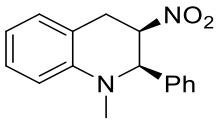
The crude amine was dissolved in DCM (7.0 mL) and cooled to -78 °C. DIPEA (0.18 mL, 1.0 mmol) and TFAA (0.14 mL, 1.0 mmol) were added and the mixture was stirred 10 min then warmed to rt. The reaction mixture was diluted with water (7.0 mL), then the organics were extracted in DCM (2 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The resultant crude material was purified via column chromatography (30% EtOAc in hexane) to give the product as an off-white waxy solid (45 mg, 46%).

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.11 (1H, t, *J* = 7.6 Hz, Ar*H*), 6.99 (1H, d, *J* = 7.4 Hz, Ar*H*), 6.61 (1H, t, *J* = 7.3 Hz, Ar*H*), 6.44 (1H, d, *J* = 8.1 Hz, Ar*H*), 6.12 (1H, s, N*H*), 4.08 (1H, ddd, *J* = 11.9, 9.7, 5.1 Hz, C*H*NCOCF$_3$), 3.40 (1H, td, *J* = 8.9, 2.1 Hz, NC*H*$_2$), 3.34 (1H, td, *J* = 9.9, 5.3 Hz, NC*H*), 3.29 (1H, dd, *J* = 16.4, 8.8 Hz, NC*H*$_2$), 3.08 (1H, dd, *J* = 15.2, 4.9 Hz, ArC*H*$_2$), 2.84 (1H, dd, *J* = 15.1, 11.9 Hz,

ArCH_2), 2.18 – 2.08 (2H, m, NCHCH_2, NCH$_2$CH_2), 1.92 (1H, dtd, *J* = 15.6, 12.2, 8.9 Hz, NCH$_2$CH_2), 1.75 (1H, ddd, *J* = 21.5, 11.7, 7.4 Hz, NCHCH_2) ^{13}C NMR (175 MHz, $CDCl_3$) δ 143.8 (Ar*C*), 129.0 (Ar*C*), 128.2 (Ar*C*), 118.6 (Ar*C*), 116.2 (Ar*C*), 110.8 (Ar*C*), 62.2 (N*C*H), 49.6 (*C*HNCOCF$_3$), 47.6 (N*C*H$_2$), 34.9 (Ar*C*H$_2$), 31.2 (NCH*C*H$_2$), 23.6 (NCH$_2$*C*H$_2$). IR (neat) 3220 C-H 3066 C-H 2927 C-H 2844 C-H 1710 C=O 1602 C=C 1555 C=C 1502 cm^{-1} C=C LRMS: 281.1 (10), 269.1 (20), 268.1 (100). HRMS: Expected: 281.0902 Found 281.0911

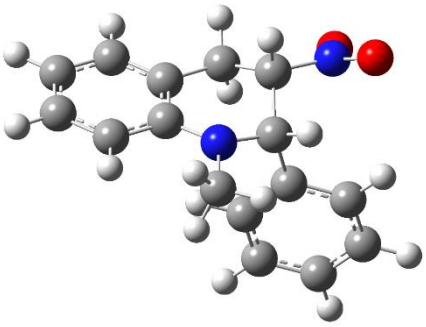
4. Appendices

4.1 Computational modelling for 1-methyl-3-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline arrangements in space

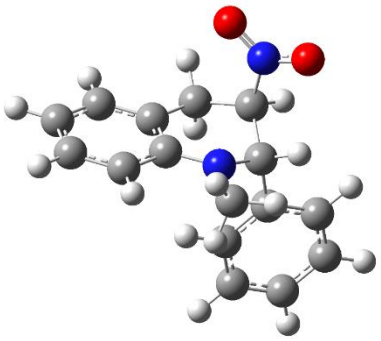
Isomer	Designation	Calc Energy	Relative Energy (Hartree)
	Quinoline1	-879.19455451	0.00017632
	Quinoline2	-879.19473083	0
	Quinoline3	-879.18771543	0.00701540

Energies calculated using B3LYP/6-31G*. Relative energies relative to lowest energy isomer. Quinoline4 is least stable. It is the only one with Ph equatorial. Energies are in Hartrees, 1 Hartree = 27.2114 eV.

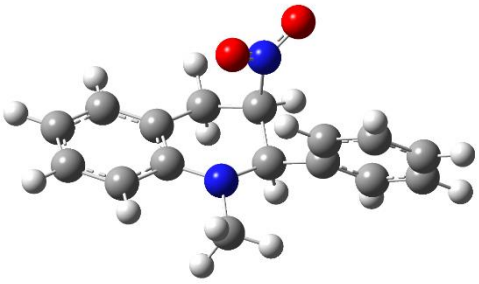
Quinoline1



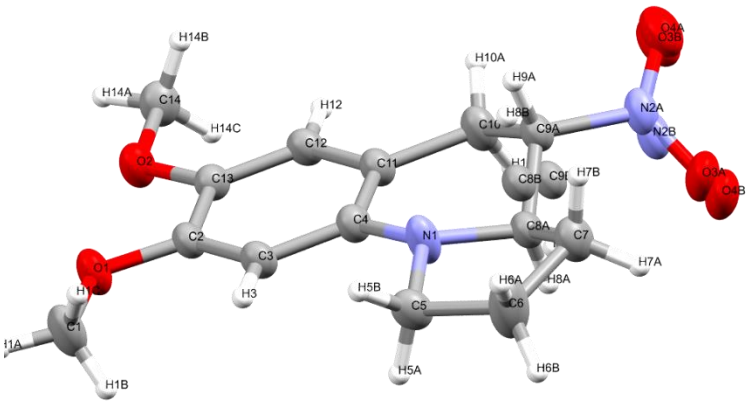
Quinoline2



Quinoline3



4.2 Crystal structure for (3a*S,4*R**)-7,8-dimethoxy-4-nitro-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline 539a as an example of the spatial arrangement of a 6,6,5 ring system.**



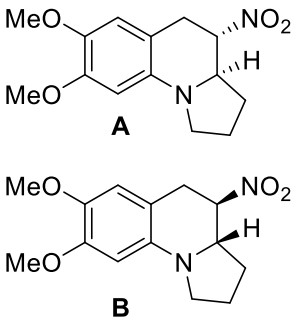


Table 14: Crystallographic data and structure refinement

Empirical formula	$C_{14}H_{18}N_2O_4$
Formula weight	278.3
Temperature/K	293(2)
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	11.0509(2)
b/Å	9.3888(2)
c/Å	12.9912(3)
α/°	90
β/°	97.989(2)
γ/°	90
Volume/Å^3	1334.82(5)
Z	4
ρ_{calc}g/cm^3	1.385
μ/mm^{-1}	0.849
F(000)	592.0
Crystal size/mm^3	0.056 × 0.110 × 0.160
Radiation	CuKα (λ = 1.54184)

2Θ range for data collection/°	9.856 to 133.146
Index ranges	-13 ≤ h ≤ 13, -11 ≤ k ≤ 10, -15 ≤ l ≤ 15
Reflections collected	18135
Independent reflections	2354 [R_{int} = 0.0302, R_{sigma} = 0.0146]
Data/restraints/parameters	2354/0/197
Goodness-of-fit on F^2	1.063
Final R indexes [I>=2σ (I)]	R_1 = 0.0429, wR_2 = 0.1118
Final R indexes [all data]	R_1 = 0.0459, wR_2 = 0.1144
Largest diff. peak/hole / e $Å^{-3}$	0.34/-0.23
Empirical formula	$C_{14}H_{18}N_2O_4$
Formula weight	278.3

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