Novel Palladium-Catalysed Routes to Aromatic Heterocycles

A thesis submitted to the Board of the Faculty of Physical Sciences in partial fulfilment of the requirements for the degree of

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by

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Declaration

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

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Abstract

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Chapter 1: Introduction

A brief summary of the use of palladium as a catalyst, the characteristic reactivity of palladium complexes and the commonly used palladium-catalysed cross-coupling reactions is given, with a special focus on the palladium-catalysed α-arylation of enolates and its application to the synthesis of aromatic heterocycles. The synthesis of aromatic heterocycles *via* both traditional methods and more recent metal-catalysed approaches is discussed in the context of isoquinolines.

Chapter 2: Results and Discussion

The palladium-catalysed oxidation of dihydrofurans bearing an *ortho*-bromophenyl group at the 2-position to the corresponding 2-phenyl furans is disclosed along with some preliminary mechanistic investigations. A novel synthetic route to isoquinolines is detailed involving the palladium-catalysed α-arylation of ketone enolates with an appropriate *ortho*-substituted aryl halide to furnish a protected 1,5-dicarbonyl intermediate. The versatility of these intermediates is demonstrated with their conversion into isoquinolines, isoquinoline *N*-oxides and naphthols. The scope of the synthetic procedure is fully exemplified across more than 30 different scaffolds covering the full spectrum of electron-rich to electron-deficient moieties.[I] The intermediates were shown to be amenable to functionalisation with electrophiles, leading to isoquinolines bearing additional substitution at the C4 position. Sequential one-pot procedures were developed allowing three and four component couplings to directly deliver highly-substituted isoquinolines from commercially available starting materials. This methodology was utilised in the total synthesis of the natural product berberine in 26% overall yield and a longest linear sequence of six steps.

Chapter 3: Experimental

Full experimental procedures and characterisation data for all compounds are reported.

I. Donohoe, T. J.; Pilgrim, B. S.; Jones, G. R.; Bassuto, J. A. *Proceedings of the National Academy of Sciences* **2012**, *109*, 11605-11608.

Acknowledgements

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Abbreviations and Acronyms

Å	Ångström
Ac	Acetyl
Amphos	Di-*tert*-butyl(4-dimethylaminophenyl)phosphine
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
br.	Broad
C	Celsius
c./conc.	Concentrated
CAAC	Cyclic alkyl-aminocarbene
C_{Ar}	Aromatic carbon atom
Cbz	Carboxybenzyl
cm^{-1}	Wavenumber
COD	Cyclooctadiene
COSY	Correlated spectroscopy
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
Cy	Cyclohexyl
CyJohnPhos	(2-Biphenyl)dicyclohexylphosphine
DavePhos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DCE	Dichloroethane
DEAD	Diethyl azodicarboxylate
de novo	Latin: beginning again
DEPT	Distortionless enhancement by polarisation transfer
DMA	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPBz	1,2-bis(diphenylphosphino)benzene
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
D*t*BPF	1,1'-Bis(di-*tert*-butylphosphino)ferrocene
DTPF	1,1'-Bis(di-*o*-tolylphosphino)ferrocene
e.g.	*exempli gratia* (Latin: for example)
en route	French: along the way
eq.	Equivalent(s)
ESI^+	Electrospray ionisation (positive ion detection)
Et	Ethyl
et al.	*et alii* (Latin: and others)
FI^+	Field ionisation (positive ion detection)
FWHM	Full width half maximum
g	Gram(s)
h	Hour(s)
HMDS	Hexamethyldisilazide

HMQC	Heteronuclear multiple quantum correlation
Hz	Hertz
i	*Iso*
in situ	Latin: in position
in vacuo	Latin: in a vacuum
IR	Infrared
J	Coupling constant (Hz)
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
Jr.	Junior
K_a	Acid dissociation constant
M	Molar
Me	Methyl
MePhos	2-Dicyclohexylphosphino-2′-methylbiphenyl
mg	Milligram(s)
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
mol%	Molar percent
m.p.	Melting point
m/z	Mass to charge ratio
n	*Normal*
N.B.	*Nota bene* (Latin: take notice)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NFSI	*N*-fluorobenzenesulfonimide
NHC	Nucleophilic heterocyclic carbene
NMR	Nuclear magnetic resonance
[Ox]	Oxidation
p	*Para*
PG	Protecting group
Ph	Phenyl
Phth	Phthalimide
pH	$-\log_{10}[H_3O^+]$
pK_a	$-\log_{10}[K_a]$
ppm	Parts per million
Pr	Propyl
QPhos	1,2,3,4,5-Pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene
R	Generic alkyl group
RCM	Ring Closing Metathesis
rt	Room temperature
S_EAr	Electrophilic aromatic substitution
Selectfluor® II	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
sept.	Septet

S_NAr	Nucleophilic aromatic substitution
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
$S_{RN}1$	Radical-nucleophilic aromatic substitution
t/tert	*Tertiary*
*t*BuMePhos	2-Di-*tert*-butylphosphino-2′-methylbiphenyl
*t*BuXPhos	2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl
Tf/Triflate	Trifluoromethanesulfonate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
tol-BINAP	2,2'-Bis(di-*p*-tolylphosphino)-1,1'-binaphthyl
Ts	Toluene-4-sulfonyl
unc.	Uncertain assignment
UV	Ultraviolet
via	Latin: by way of
vide infra	Latin: see below
vide supra	Latin: see above
w/w	Mass fraction
X	Generic heteroatom substituent, often a halogen/*pseudo*halogen
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-tri*iso*propylbiphenyl
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
α	Alpha
β	Beta
δ	Chemical shift
η	Hapticity
λ_{max}	Wavelength of maximum ultraviolet intensity
μ	Bridging ligand
μW	Microwave
π	Pi
σ	Sigma
υ_{max}	Infrared absorption maximum

Note

In a number of mechanistic schemes, neutral ligands on metal atoms are omitted for clarity.

Chapter 1: Introduction

1.1 An overview of palladium catalysis

1.1.1 Palladium as a catalyst

Palladium is a silvery-white metal located in the mid-right of the d-block of the periodic table. With electron configuration [Kr] $4d^{10}$, palladium sits in the midst of a cluster of catalytically-active transition metals including nickel, copper, ruthenium, rhodium, osmium and iridium. Palladium is undoubtedly the most versatile and valuable catalytic metal from this set, particularly in the context of organic synthesis. Palladium catalysts offer a plethora of possibilities for C-C bond formation, the most important disconnection in organic chemistry. The importance of palladium catalysts was recognised by the awarding of the 2010 Nobel Prize in Chemistry to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their work on palladium-catalysed cross couplings in organic synthesis.

Aside from the chemical ability of the metal itself to promote the key coupling reactions, a number of other factors have also contributed to the popularity of palladium catalysis.[1] Palladium catalysts and reagents are tolerant to many functional groups and so reactions can be carried out without protection of these moieties. Palladium reactions are generally carried out under anoxic and anhydrous conditions, however, this is often precautionary as palladium catalysts are frequently less sensitive to oxygen and moisture than most other metals (for example Pd(0) is much less sensitive to oxygen than Ni(0) or Rh(I)). This makes palladium reactions operationally simple. Palladium, although an expensive metal, is considerably cheaper than other transition metal catalysts such as platinum, rhodium, iridium or gold. In addition, many reactions can be optimised to an extent where catalyst loading is kept very low. Few toxicity issues from the use of palladium have been reported and these catalysts can be used in the production of fine chemicals on a commercial scale.

1.1.2 Characteristic reactivity of palladium compounds and complexes

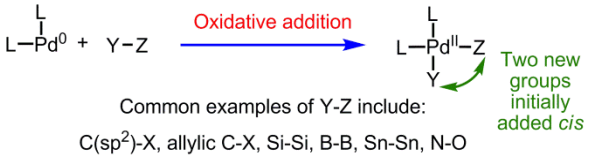
Palladium exists predominantly in the oxidation states Pd(0) and Pd(II), although Pd(IV) compounds are also known. In organic chemistry, it is generally Pd(0) complexes that are used as catalysts, whilst Pd(II) compounds find most usage as oxidising agents. However, as Pd(II) compounds are generally more stable than Pd(0) complexes (often due to their low energy d^8 square planar configuration), they are also used as the precursors to Pd(0) complexes. Reduction to Pd(0) occurs *in situ* with the concomitant oxidation of another reaction species such as a phosphine. Although active, unligated Pd(0) is very unstable and rapidly precipitates out of reactions as catalytically less active black Pd metal particles. Hence, the metal is almost always used in combination with one or more ligands to help form coordinatively saturated Pd(0) complexes which have a much longer lifetime. The steric and electronic properties of the ligands dominate the chemistry of the field through their influence on the various steps of the catalytic cycle. Although the presence of ligands on Pd(0) helps to stabilise this oxidation state (some Pd(0) sources such as the 16-electron $Pd(dba)_2$ or $Pd_2(dba)_3$, or the 18-electron $Pd(PPh_3)_4$ are commerically available) it can also lower their reactivity, as coordinatively unsaturated compounds are required for initiation of reactions.

In many catalytic reactions mediated by palladium, there are a number of common mechanistic steps that occur in the catalytic cycle. These are briefly summarised below.

1.1.2.1 Oxidative addition

Most palladium coupling reactions begin with oxidative addition. This is the addition of a molecule Y-Z to Pd(0) with cleavage of the Y-Z bond and formation of two new bonds to palladium. In this process palladium gains two new ligands and is oxidised from Pd(0) to

Pd(II). Stable 18-electron complexes of Pd(0) such as $Pd(PPh_3)_4$ are unable to undergo oxidative addition and are said to be coordinatively saturated. They must first undergo dissociation to form 14-electron or 16-electron complexes, with two free *cis* coordination sites in order to undergo oxidative addition. Oxidative addition can occur into a variety of bonds, but is most common with sp^2 hybridised C-X bonds, where X is a halogen or *pseudo*halogen, with the order of reactivity being C-I > C-Br > > C-Cl (due to increasing bond strength) (**Scheme 1**).[2]

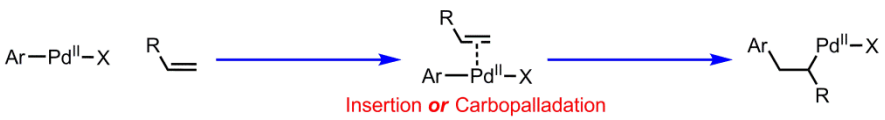


Scheme 1: *Oxidative addition*

Oxidative addition is promoted by high electron density on palladium, which can be achieved by the presence of ligands that are good σ-donors, with trialkylphosphines such as $P(tBu)_3$ being particularly proficient. Ligands that are good π-acceptors, such as CO, suppress oxidative addition.

1.1.2.2 Insertion

Various unsaturated ligands such as CO, alkenes and alkynes can undergo a formal insertion into a Pd-ligand σ-bond. This often occurs by prior coordination of the π-system of the unsaturated ligand to the palladium and then migration of the σ-bound ligand from palladium to one atom of the unsaturated ligand, with Pd becoming σ-bound to the other atom (an α,β-insertion). In the case of a *C*-bound ligand, this process is often termed a carbopalladation (**Scheme 2**).



Scheme 2: *Insertion*

The process is reversible, and rates of reaction are faster with cationic complexes, probably due to the more facile coordination of the π-ligand.[1] For insertion to take place, the σ-bound ligand and the π-bound ligand must be *cis*-coordinated about the Pd-centre. The insertion reaction occurs stereospecifically in a *syn*-manner across the unsaturated ligand.

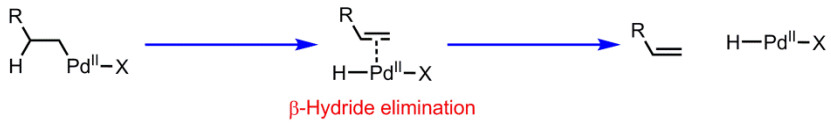
1.1.2.3 Transmetallation

Metal hydrides and organometallic compounds of main group and far right d-block metals, such as boron, tin, silicon, zinc, magnesium and aluminium, react with Pd(II) oxidative addition complexes *via* transmetallation. The organic group or hydride is transferred to palladium and the electronegative ligand on palladium to the metal, driven by the greater electropositivity of the main group metal (**Scheme 3**).

Scheme 3: *Transmetallation*

1.1.2.4 β-Hydride elimination

If an alkyl Pd(II) complex possesses a hydrogen in the β-position to Pd then a β-hydride elimination can take place to generate an alkene and a Pd(II) hydride (**Scheme 4**). This can also be referred to as a dehydropalladation.



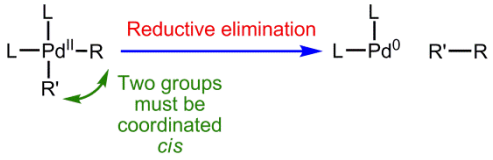
Scheme 4: *β-Hydride elimination*

During this process the coordination number of Pd increases by one and so this process requires a coordinatively unsaturated Pd complex, and hence can be retarded by bulky bidentate ligands that reduce space around the metal centre and discourage dissociation to form a free coordination site. The hydride to be eliminated must be *syn* to the Pd on the alkyl

chain for the reaction to take place. The Pd(II) hydride often then undergoes reductive elimination in the presence of a base to regenerate Pd(0).

1.1.2.5 Reductive elimination

Reductive elimination is the formal reverse of oxidative addition and results in the loss of two ligands from the palladium centre to give a single elimination product. In this process palladium reduces its coordination number and Pd(II) is reduced to Pd(0). This is a common final process in catalytic cycles which results in the extrusion of the product and regeneration of the active Pd(0) catalyst. In order for two ligands to undergo reductive elimination they must be *cis* to each other on the palladium centre (**Scheme 5**).[3]

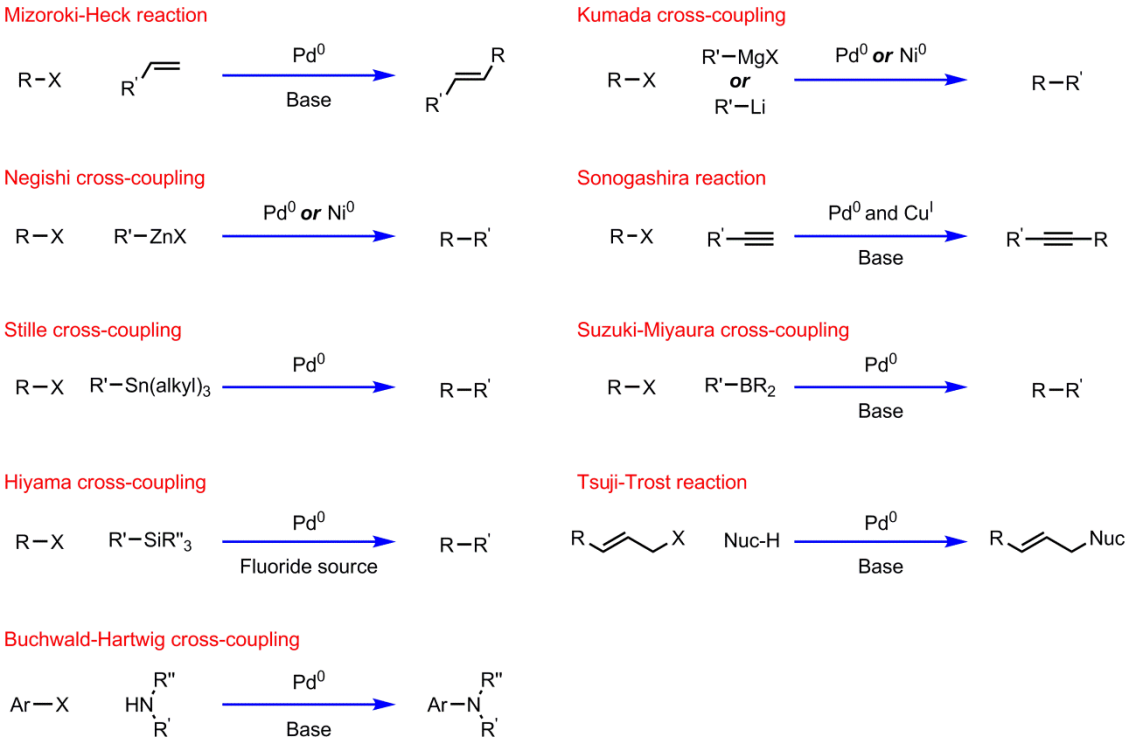


Scheme 5: *Reductive elimination*

Ligands that are *trans* orientated must first rearrange to *cis* before reductive elimination. Hence, bidentate ligands can help promote the reductive elimination of other species by forcing them to occupy *cis* positions on the palladium centre. As the coordination number of palladium is reduced in this process, bulky ligands that occupy a large volume of space (or bite angle) around the Pd centre are particularly effective at promoting reductive elimination due to the associated reduction in steric strain. Strong π-acceptor ligands that reduce the electron density on the Pd centre also help promote this process.

1.1.3 Notable palladium-catalysed cross-coupling reactions

A wide array of different palladium couplings are now known to the synthetic community. These are summarised in **Scheme 6**.



Scheme 6: *Commonly employed palladium-catalysed cross-couplings*

1.1.3.1 Mizoroki-Heck reaction

In the 1970s, Mizoroki[4] and Heck[5] both reported the coupling of aryl halides with alkenes. The reaction proceeded *via* oxidative addition of Pd(0) into the C-X bond of the aryl halide, a *syn*-insertion across the alkene, rotation about the C-C bond, a *syn*-β-hydride elimination and then reductive elimination of the Pd(II) halide to regenerate the Pd(0) catalyst.[6,7]

1.1.3.2 Kumada cross-coupling

In 1972, Kumada published the cross-coupling of Grignard reagents with aryl or alkenyl halides catalysed by a nickel-phosphine complex.[8] The reaction was later shown to be catalysed by palladium and the Grignard reagents could be replaced with organolithiums. The palladium-catalysed variant was believed to proceed *via* oxidative addition of Pd(0) into the C-X bond, transmetallation with the organometallic reagent and reductive elimination to form the C-C bond.

1.1.3.3 Negishi cross-coupling

Although the Kumada cross-coupling was a powerful synthetic transformation, the strong basicity of the organolithium and Grignard reagents limited the functional group tolerance of the reaction. Negishi discovered that organozinc compounds could be coupled with aryl, alkenyl or alkynyl halides under much milder conditions with palladium or nickel catalysis, following a similar postulated mechanism to the Kumada coupling.[9,10]

1.1.3.4 Sonogashira reaction

In 1975, Sonogashira published the coupling of acetylene with aryl halides to give disubstituted alkynes.[11] The Sonogashira reaction was believed to proceed *via* oxidative addition of Pd(0) into the C-X bond of an aryl or vinyl halide, generation of a Cu(I) acetylide by reaction of the Cu(I) salt and base with the terminal alkyne, transmetallation between the Cu(I) acetylide and the Pd(II) oxidative addition complex and then reductive elimination to form the C-C bond and regenerate the Pd(0).

1.1.3.5 Stille cross-coupling

In 1978, Stille reported the palladium-catalysed coupling of organostannanes with acyl chlorides.[12] Throughout the 1980s, Stille further developed this method to incorporate aryl and alkenyl halides and showed that aryl, alkenyl and allyl stannanes could be employed. Mechanistically, it is hypothesised the reaction proceeded *via* oxidative addition, transmetallation and reductive elimination. The reaction had a wide functional group tolerance and took place under mild conditions. However, the toxicity of the organostannanes was a drawback.

1.1.3.6 Suzuki-Miyaura cross-coupling

In 1979, Suzuki and Miyaura reported the palladium-catalysed coupling of alkenyl boranes with aryl halides.[13] A range of alkyl, allyl, alkynyl and aryl boranes were also later shown to be compatible. The organoborane required activation with a base to form a borate complex prior to coupling. After oxidative addition of the Pd(0) into the C-X bond, a metathesis occurred where the anionic X ligand on palladium was exchanged for the anion of the base. Transmetallation then occurred with the borate complex, followed by reductive elimination. The reaction occurred under mild conditions and had the benefit of using much safer reagents than the Stille cross-coupling.

1.1.3.7 Hiyama cross-coupling

In 1988, Hiyama published a similar protocol with organosilanes.[14] This coupling required pre-activation of the organosilane with a fluoride source to provide a pentavalent fluorosilicate species for the transmetallation step, but otherwise proceeded in an analogous fashion. It achieved similar scope to the Suzuki-Miyaura coupling, but without the need for strongly basic conditions.

1.1.3.8 Tsuji-Trost reaction

Building on earlier work by Tsuji,[15] in 1973 Trost reported that alkyl-substituted π-allyl palladium complexes could be coupled with soft carbon nucleophiles.[16] The Tsuji-Trost reaction coupled allyl halides with nucleophiles such as enolates, enamines and anions of dicarbonyl compounds. Mechanistically, Pd(0) coordinated to the alkene in the allyl halide and then underwent oxidative addition into the C-X bond to form an η^3 π-allyl complex. The allylic centre was then attacked by the nucleophile, affecting a formal substitution, followed

by reductive elimination from the Pd(II) complex, forming the bond between the nucleophile and the allylic moiety.

1.1.3.9 Buchwald-Hartwig cross-coupling

In 1995, Buchwald and Hartwig reported the palladium-catalysed coupling of aryl halides with amines in the presence of a strong base.[17,18] After oxidative addition of the Pd(0) into C-X bond of the aryl halide, coordination of the amine to the Pd(II) intermediate increased the N-H acidity and allowed it to be deprotonated by the base. This led to the displacement of the X anion from the Pd(II) centre with the amide anion. Reductive elimination then furnished the key C-N bond and regenerated the Pd(0).

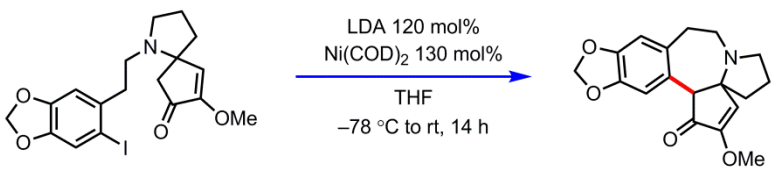
1.2 Palladium-catalysed α-arylation of enolates

Throughout the latter part of the 20th century, the development of palladium catalysis had caused a paradigm shift in the theory of molecular disconnection. Aryl halides had been successfully coupled with a host of nucleophilic entities; but the coupling of enolates, one of the most common classes of nucleophiles, had proven troublesome. The development of the palladium-catalysed α-arylation of enolates is now discussed in more detail.

1.2.1 Early research in the area

The α-aryl carbonyl compound is an important synthetic motif occurring in many biologically-active natural products and pharmaceutical agents.[19] However, prior to 1997, methods for arylating the α-carbon of a carbonyl compound were severely limited. It often required the stoichiometric use of toxic reagents, such as triarylbismuth diacetates,[20] aryllead triacetates[21] or trialkyltin fluorides.[22] In specific cases it was possible to form the bond *via* an S_NAr pathway, but this was obviously restricted to electron-deficient arenes and was most successful in intramolecular cases. It was also possible to form the bond *via* an $S_{RN}1$ pathway, but this was very substrate specific and often suffered from regioselectivity issues.[23] Addition of enolates to benzynes was also commonly employed, but this often required harsh reaction conditions.[24]

The first indication of a different mechanistic route to this motif was obtained in the 1970s by Semmelhack *et al.* during the total synthesis of cephalotaxinone (**Scheme 7**).[25]



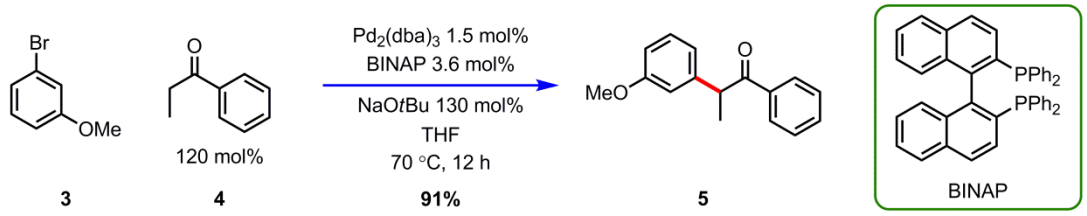
1 **30-35%** **2**

Scheme 7: *Nickel-promoted α-arylation in the synthesis of cephalotaxinone*

As this substrate was not expected to be proficient at S_NAr, it was proposed that activation of the C-I bond occurred by oxidative addition of Ni(0) and that the resultant species reacted with the enolate of the carbonyl compound that had been generated by the LDA, to form a cyclic organonickel intermediate. It was then proposed that reductive elimination from this Ni(II) intermediate formed the key C-C bond. The group subsequently switched to a photostimulated $S_{RN}1$ reaction to form this bond, which worked well in this case; and this mode of reactivity was not further investigated.

1.2.2 The seminal α-arylation papers of 1997

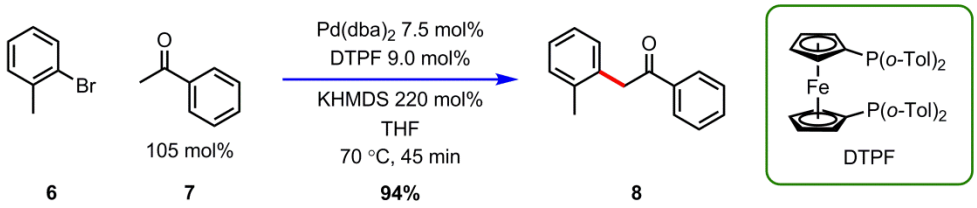
In 1997, the research groups of Buchwald,[26] Hartwig[27] and Miura[28] concurrently reported that the α-arylation of ketones could be performed intermolecularly in the presence of base and a catalytic quantity of Pd(0). In a representative example of Buchwald's procedure, aryl bromide **3** was coupled with propiophenone, **4** in 91% yield to furnish **5** (**Scheme 8**).



Scheme 8: *Buchwald's initial α-arylation conditions*

An array of aryl bromides and ketones could be employed as the coupling partners and the reaction was shown to be compatible with a range of functional groups on the aryl bromide including nitriles, ethers, non-enolisable imines, tertiary amides, aryl chlorides and acetals. The reaction also displayed high regioselectivity, with all ketones being preferentially arylated on the least-hindered side (i.e. preference for α-arylation: methyl > methylene > methine). Some of the less-hindered methyl ketones were observed to undergo small amounts of diarylation on the methyl position.

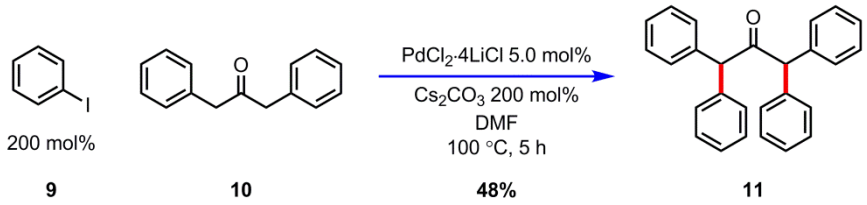
In Hartwig's independently developed protocol, chelating bisphosphines with a ferrocene backbone such as DTPF were employed. KHMDS was used as the base for the coupling of electron-neutral or electron-rich aryl halides such as **6**, and it was found that there was high selectivity for monoarylation (**Scheme 9**).



Scheme 9: *Hartwig's initial α-arylation conditions*

It was hypothesised that the sterically bulky chelating phosphines prevented the formation of an open coordination site on the catalyst, which would allow palladium-enolate complexes bearing a β-hydrogen to undergo β-hydride elimination. In stoichiometric studies, Hartwig showed by ^{31}P NMR spectroscopy that the enolate was *C*-bound and that such species could be converted through to the product.

In Miura's work, ketone **10** was coupled with iodobenzene, **9** in 48% yield to furnish **11**, where α-arylation had taken place at both methylene carbons (**Scheme 10**).

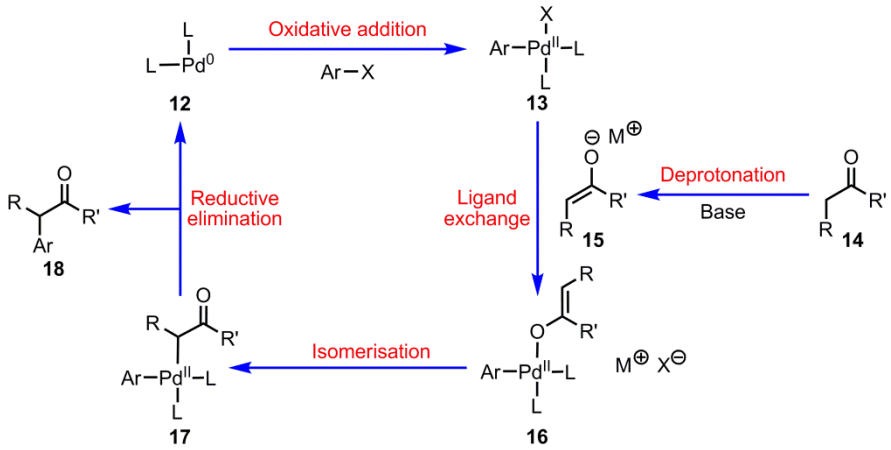


Scheme 10: *Miura's initial α-arylation conditions*

In this process it was clear that the reaction did not require the presence of phosphine ligands.

Buchwald and Hartwig both proposed similar mechanisms for this newly-discovered palladium-catalysed reaction (**Scheme 11**). The reaction began with oxidative addition of the Pd(0) catalyst **12** into the C-X bond of the aryl halide to furnish **13**. The ketone **14** was

deprotonated by the base to form enolate **15**. The enolate then underwent ligand exchange with the halide anion (X^-) to form a Pd(II) enolate complex. It was assumed that this was initially formed as the *O*-bound enolate complex **16** before isomerisation to the *C*-bound enolate complex **17**. Reductive elimination then occurred between the *cis*-coordinated *C*-bound enolate and aryl group to furnish the product **18** and regenerate the key Pd(0) catalyst **12**. If the *trans*-coordinated enolate complexes were formed, these were first required to isomerise to the *cis*-coordinated complexes prior to reductive elimination.



Scheme 11: *Proposed catalytic cycle for α-arylation*

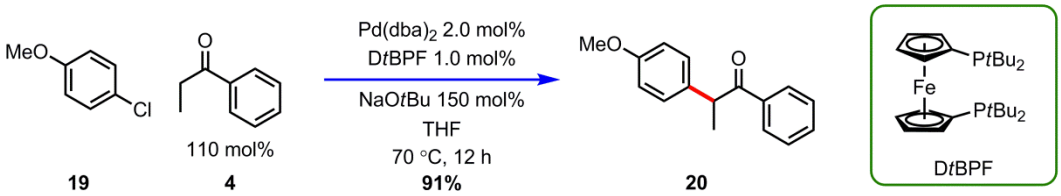
1.2.3 Further reaction development

Prashad *et al.* investigated the effect of base concentration under similar conditions to those used by Miura (i.e. without phosphine ligands).[29] It was shown that excess base was important to prevent the formation of diarylated products. This can be rationalised by considering the reaction of acetophenone with bromobenzene to form deoxybenzoin. The deoxybenzoin product has α protons that are significantly more acidic than those of acetophenone (pK_a data in DMSO: acetophenone 24.7,[30] deoxybenzoin 17.7),[31] meaning that the α-arylation product is deprotonated in preference to the unreacted ketone in the reaction mixture. (*N.B.* The majority of pK_a data for organic compounds in the literature are obtained in DMSO, however corresponding values in THF (where known) are typically higher by 2-3

pK_a units).[32] Thus, in reactions with only one equivalent of base, equilibration between enolates results in the reaction mixture containing enolate of only the monoarylated product and non-deprotonated ketone starting material. The addition of excess base ensures that enolates of both unreacted ketone starting material and α-arylated product are present. The ketone enolate now couples preferentially as it is much more nucleophilic, being both higher in energy due to the absence of a stabilising aryl group and less sterically-hindered than the enolate of the α-arylated product.

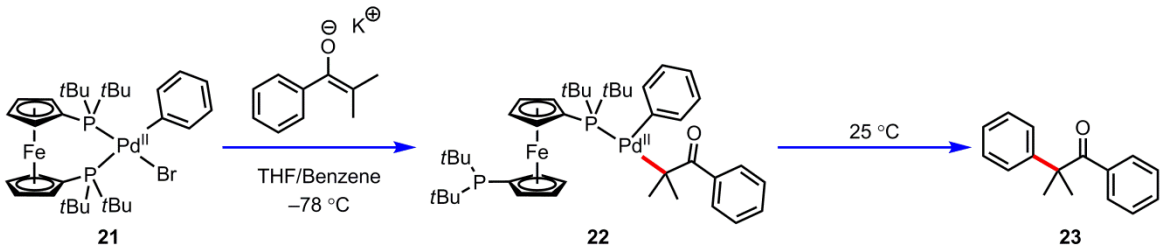
Hartwig and coworkers later demonstrated that the 1,1'-bis(di-*tert*-butylphosphino)ferrocene ligand (D*t*BPF) was highly active.[33] The D*t*BPF ligand had initially been synthesised in the 1980s by Cullen and coworkers as a scaffold to support rhodium hydrogenation catalysts.[34,35] It was thought that the sterically bulky nature of the ligand when coordinated to the reaction centre should help facilitate reaction steps such as reductive elimination, where a high-coordinate Pd(II) species is converted to a low-coordinate Pd(0) species. The strong σ-donor properties of the ligand were also expected to make the metal centre electron-rich, facilitating initial oxidative addition.[36] In addition, it was thought that alkyl phosphines should be more resistant to P-C bond cleavage than arylphosphines, which should allow higher turnover numbers.[37] It was also presumed that the chelating nature of the phosphine would ensure the Pd(II) intermediates did not undergo β-hydride elimination.[38]

The D*t*BPF ligand could achieve turnover numbers of 20,000 in α-arylation reactions with aryl bromides and in some cases the reactions took place at room temperature. The use of the D*t*BPF ligand also allowed aryl chlorides to be successfully coupled for the first time (**Scheme 12**).



Scheme 12: *Hartwig's successful α-arylation of aryl chlorides*

Hartwig then undertook some stoichiometric mechanistic studies with the D*t*BPF ligand (**Scheme 13**). When **21** (the oxidative addition complex of (D*t*BPF)Pd(0) with bromobenzene) was treated with the enolate of isobutyrophenone, it generated a single product **22** that was shown to undergo reductive elimination to **23** on warming to room temperature. The ^{31}P NMR spectrum of complex **22** indicated that only one of the phosphorous atoms in the D*t*BPF ligand was bound to Pd. It was not rigorously determined whether the enolate was *C*-bound (as shown here) or *O*-bound.

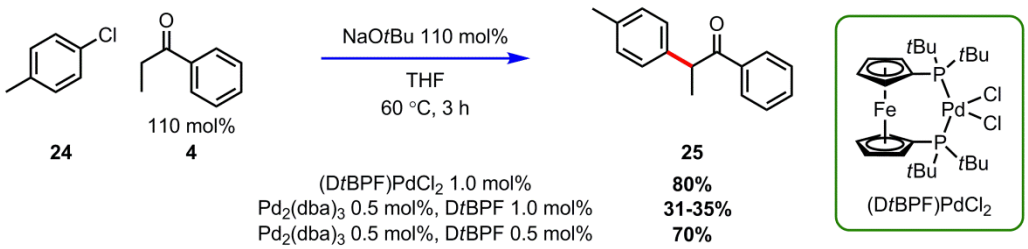


Scheme 13: *Hartwig's stoichiometric studies using ^{31}P NMR*

Hence, Hartwig concluded that sterically-hindered monophosphines could potentially promote α-arylation reactions. He subsequently showed that P(*t*Bu)$_3$ was an incredibly efficient ligand at promoting the α-arylation reaction. Turnover numbers of 20,000 were again achievable and the reaction amenable to both aryl bromides and chlorides.

In 2007, Colacot and coworkers published studies on the use of the air-stable Pd(II) pre-catalyst (D*t*BPF)PdCl$_2$ in α-arylation reactions,[39] (a complex that they had earlier shown to be efficient at promoting challenging Suzuki-Miyaura reactions).[40] The crystal structure of (D*t*BPF)PdCl$_2$ had a P-Pd-P bite angle of 104.22°, which was the largest in the bisphosphinoferrocene series. This, in addition to the bulky electron-rich nature of the

tert-butyl groups was believed to be key in explaining its superior activity. Studies of the catalytic reaction using ^{31}P NMR spectroscopy showed that one phosphorous-containing species predominated in the reaction, where both phosphorous atoms were in the same environment. This bidentate nature of the catalytic ground state (presumed to be the (D*t*BPF)Pd(0) complex), was in contrast to Hartwig's earlier studies that showed the Pd(II) enolate complex **22** had a monodentate D*t*BPF ligand. Interestingly, in the α-arylation of aryl chloride **24** with propiophenone, **4**, (D*t*BPF)$PdCl_2$ gave an 80% yield of product **25**, but the same Pd loading of $Pd_2(dba)_3$ and D*t*BPF gave yields only in the range 31-35% (depending on reaction concentration) (**Scheme 14**). When the Pd:D*t*BPF ratio was altered to 1:0.5 in the separate $Pd_2(dba)_3$ and D*t*BPF system, the yield increased to 70%. This was rationalised by the fact that use of the pre-formed catalyst ensured that there was always a high amount of the active (D*t*BPF)Pd(0) catalyst produced in the reaction. However, upon mixing separately, high amounts of inactive species such as the 18-electron $(DtBPF)_2Pd(0)$ could be formed. Hence, due to the sensitivity of these reactions to the Pd:Ligand ratio, the use of pre-formed air-stable catalysts was clearly beneficial. In addition, Colacot illustrated that in reactions with (D*t*BPF)$PdCl_2$, it was significantly easier to separate the product from the catalyst after the reaction. Residual amounts of Fe and Pd in the product were as low as 34 and 48 ppm respectively, after just a filtration through a pad of silica, and the Pd level could be as low as 6 ppm after one recrystallisation.[41]



Scheme 14: *Superior yields with pre-formed (DtBPF)PdCl₂*

Buchwald also showed that a range of monodentate biaryl ligands were highly efficient at promoting α-arylation reactions (**Figure 1**).[42] A wide substrate scope of ketones and aryl

halides was demonstrated with significant functional group tolerance including dimethylamino groups, nitro groups and free phenols. However, ketones with both enolisable methyl and methylene groups required bidentate ligands (such as XantPhos) to be arylated selectively. The use of XantPhos was also necessary for the arylation of ketones with electron-deficient aryl bromides. It was also shown that by the use of the milder base K_3PO_4, sensitive functionality such as methyl esters could be carried through the reaction.

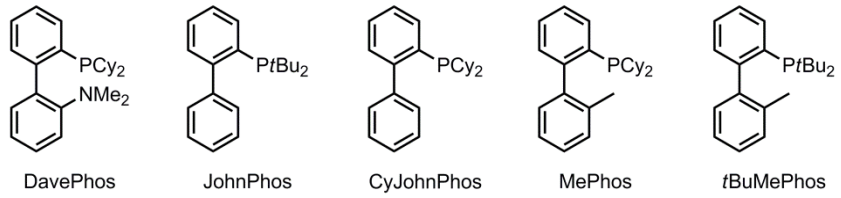
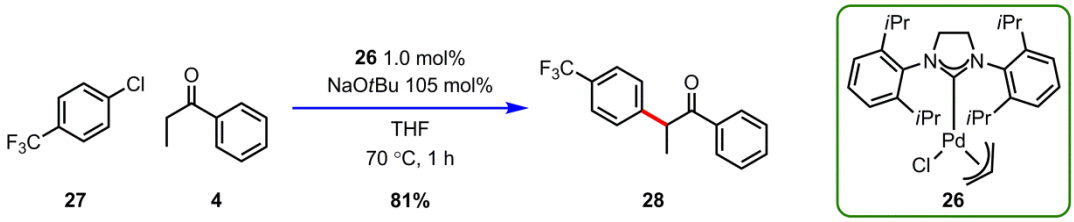


Figure 1: *Monodentate biaryl ligands developed by Buchwald*

Hartwig then carried out further investigations into the mechanism of the reaction by isolating and characterising stable aryl Pd(II) enolate complexes.[43] Complexes of the bidentate ligand DPPBz, (1,2-bis(diphenylphosphino)benzene), or of the monodentate ligand PPh_2Et, were analysed to determine the coordination mode of the enolate. With DPPBz, enolates from methyl or methylene positions were exclusively *C*-bound (and by necessity *cis* to the aryl group), and ketones with both methyl and methylene groups bound exclusively through the methyl group when deprotonated. Conversely, enolates from methine groups were *O*-bound. Complexes with PPh_2Et showed a *trans* geometry (between the enolate and aryl group) and were mostly *O*-bound, suggesting that for methyl and methylene enolates the *C*-bound enolate was favoured electronically if the enolate was positioned *trans* to a phosphine. The stability of the complexes was governed by the number of substituents at the α-carbon of the enolate (and not the pK_a of the starting ketone) with those with more substituents collapsing more readily as the temperature was raised. Hence, the regioselectivity of the α-arylation reaction derived from enhanced stability of the less sterically-hindered *C*-bound enolates, rather than from relative rates of reductive elimination.

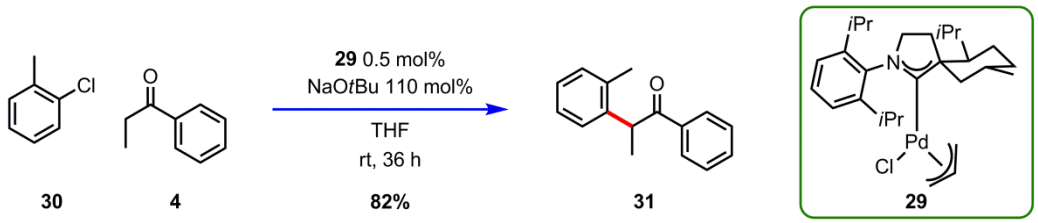
Until 2002, only tertiary phosphines had been employed as ligands for palladium. However, their relatively high cost and occasional difficulties in removing them during purification led to the search for alternative ligands. Nolan *et al.* discovered that N-heterocyclic carbene complexes (NHCs) could be employed as ligands for palladium.[44] The strong σ-donating abilities of these ligands facilitated oxidative addition and their steric bulk aided reductive elimination. Nolan used the air-stable Pd(II) pre-catalyst **26** to arylate propiophenone, **4** with aryl chloride **27** (**Scheme 15**). Ketones could be arylated with aryl chlorides, bromides and triflates in good yields with low palladium loadings in short reaction times.



Scheme 15: *α-Arylation of ketones with NHC catalyst **26***

Nolan later reported a number of other NHC ligands were also excellent at promoting these reactions, including a NHC-palladacycle complex.[45-47] It was also shown by Indolese and coworkers that a palladacycle stabilised by coordination with a secondary phosphine produced an efficient catalyst system.[48]

In 2005, Bertrand and coworkers reported the use of cyclic alkyl-aminocarbenes (CAACs) as ligands for palladium.[49] Compared to an NHC, the CAAC has a carbon in place of a more electronegative nitrogen atom, making it both more electron-rich (a better σ-donor) and creating a different steric environment due to the quaternary nature of the carbon. Bertrand found that palladium pre-catalysts such as **29** could promote the coupling of hindered aryl chloride **30** at room temperature (**Scheme 16**).



Scheme 16: *α-Arylation of ketones with CAAC pre-catalyst **29***

In 2006, Domínguez and coworkers demonstrated that PCP-bis(phosphinite) pincer complexes such as **32** (**Figure 2**) were active in the α-arylation reaction.[50] These combined the stability of palladacycles with the ability of the phosphinite ligands to modulate the steric and electronic properties of the catalyst.

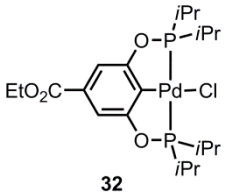


Figure 2: *Active PCP-bis(phosphinite) pincer complex **32***

Ackermann *et al.* reported that diaminochlorophosphines such as **33** (**Figure 3**) could also provide highly efficient catalytic systems. This can be rationalised by considering that after oxidative addition of Pd(0) to **33**, the corresponding phosphonium cation is isolobal to an NHC ligand.[51]

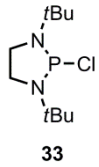
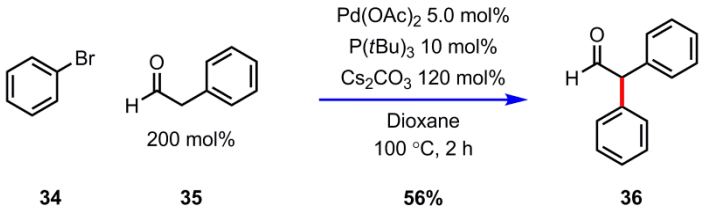


Figure 3: *Active diaminochlorophosphine **33***

1.2.4 α-Arylation of aldehydes

The α-arylation of aldehydes is considerably more challenging than the α-arylation of ketones. The less sterically-hindered aldehydes are much more prone to undergo aldol reactions under the basic reaction conditions. In addition, oxidative addition of the Pd(0) into

the formyl C-H bond can be a competing pathway.[52] Initial examples were limited to intramolecular cases,[53] where selection of solvent was important to prevent oxidative addition into the formyl C-H bond. In 2002, Miura *et al.* published the first successful intermolecular α-arylation of aldehydes.[54] Aldehyde **35** could be arylated in moderate yield with Cs_2CO_3 as the base in dioxane solvent (**Scheme 17**).



Scheme 17: *Miura's α-arylation of aldehydes*

The use of Cs_2CO_3 in dioxane was a common theme throughout subsequent papers on the α-arylation of aldehydes, with Buchwald reporting that BINAP or dialkylphosphinobinapthyl ligand **37** were efficient for the α-arylation of linear aldehydes and SPhos for branched aldehydes (**Figure 4**).[55]

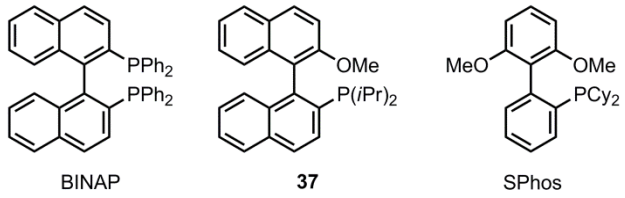
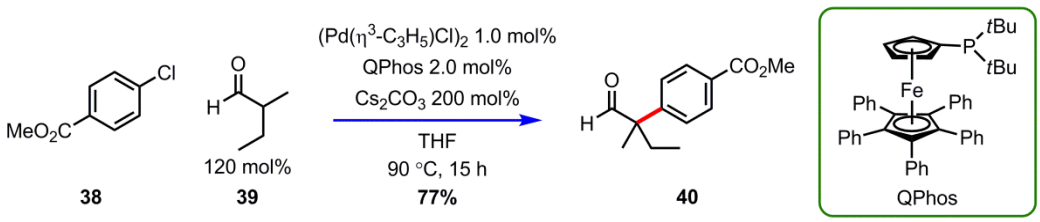


Figure 4: *Ligands employed by Buchwald in the α-arylation of aldehydes*

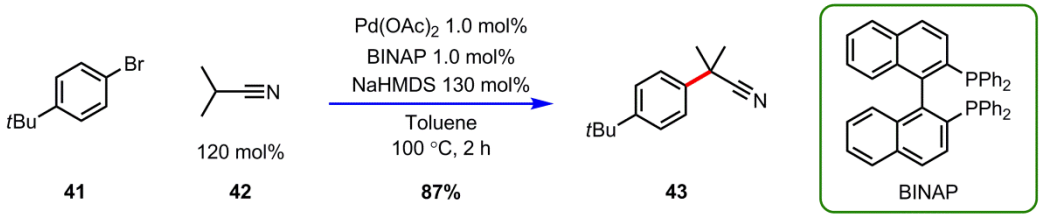
Hartwig also demonstrated that aryl chlorides **38** could be coupled with aldehydes **39** to furnish **40**, using QPhos as a ligand (**Scheme 18**).



Scheme 18: *Hartwig's α-arylation of aldehydes with aryl chlorides*

1.2.5 α-Arylation of nitriles

The α-arylation of nitriles is again a more challenging prospect than the α-arylation of ketones. The protons α to a nitrile are typically less acidic (pK_a data in DMSO: propiophenone 24.4,[31] propionitrile 32.5),[56] meaning stronger bases are often required. It is also possible for the anion of the nitrile to coordinate to palladium through the α carbon, the nitrogen, or to bridge between two metal centres in a μ^2-fashion.[57] Hartwig characterised a number of arylpalladium cyanoalkyl complexes and found that the majority of them were *C*-bound, except when other very bulky ligands were present, when they were *N*-bound. It was also possible for bridging cyanoalkyl complexes to form if other ligands on the palladium were labile.[58] Hartwig discovered that bulkier nitriles such as **42** coupled well with a range of aryl bromides using BINAP as the ligand and NaHMDS as the base (**Scheme 19**).

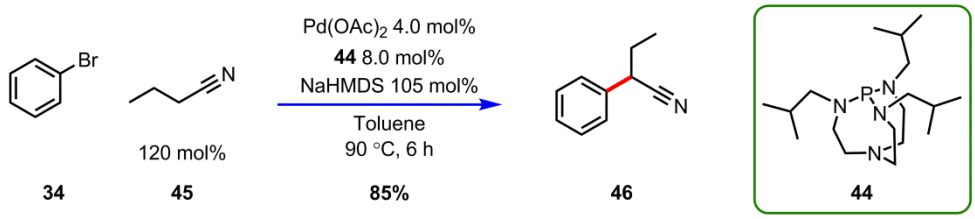


Scheme 19: *Hartwig's α-arylation of nitrile **42***

However, significant diarylation was observed with acetonitrile and butyronitrile. Compared to the product of ketone α-arylation, the product of nitrile α-arylation is considerably less sterically-hindered due to the linear nitrile substituent, and so this result with straight chain nitriles could be rationalised. The strongly basic reaction conditions limited the functional group tolerance of this reaction. Hartwig later developed two milder protocols for the α-arylation of nitriles.[59] In the first procedure, trimethylsilylnitriles were coupled with ZnF_2 as the stoichiometric fluoride source to promote the reaction. This gave high selectivity for monoarylation of primary nitriles and tolerated a range of functional groups including

ketones, esters and nitro groups. With secondary nitriles a procedure involving the generation of a zinc cyanoalkyl reagent proved more efficient.

In 2003, Verkade and coworkers disclosed a catalytic system for the α-arylation of nitriles based around the triaminophosphine **44**.[60] This worked efficiently to diarylate acetonitrile, or monoarylate primary nitriles such as **45** and secondary nitriles (**Scheme 20**).



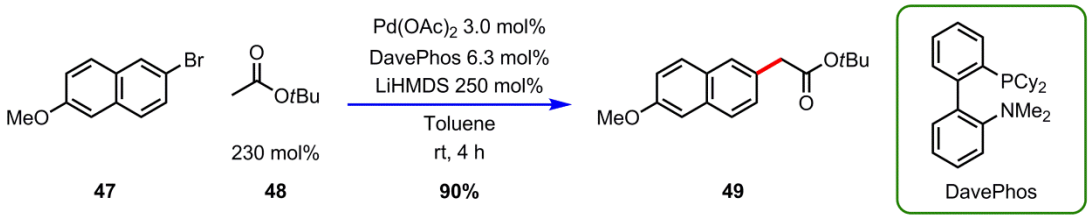
Scheme 20: *α-Arylation of nitrile **45** using a triaminophosphine*

1.2.6 α-Arylation of esters

Esters are significantly less acidic than the corresponding ketones and hence require stronger bases to deprotonate them. However, under basic conditions they also have the potential to undergo Claisen condensations, complicating an attempted α-arylation. In addition, ester enolates are vulnerable to decomposition to ketenes at elevated temperatures.[61] Isolated early examples of this disconnection, such as the coupling of *tert*-butyl acetate with iodobenzene in the presence of stoichiometric $NiBr_2$,[62] or the coupling of Reformatsky reagents with aryl triflates using stoichiometric Pd(0),[63] indicated promise in this area.

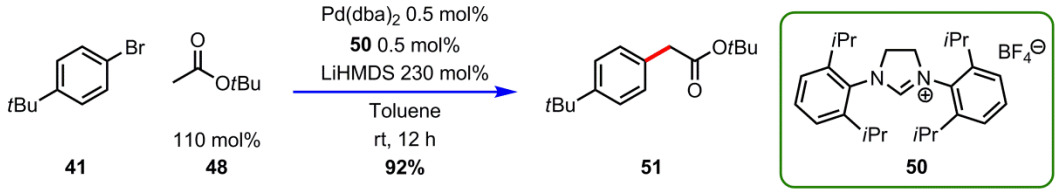
In 2001, Buchwald and coworkers published the room temperature coupling of *tert*-butyl acetate, **48** with aryl bromides (**Scheme 21**).[64] Key to the success of the reaction was the use of LiHMDS and toluene solvent, which prevented diarylation (postulated due to the more covalent nature of the Li-O bond). However, a significant excess of ester had to be employed to ensure full conversion of the aryl bromide, due to competing Claisen condensation of the

ester. This procedure was extendable to *tert*-butyl propionate by increasing the temperature to 80 °C. It was also shown possible to α-arylate ethyl esters and some methyl esters.



Scheme 21: *Buchwald's room temperature α-arylation of tert-butyl acetate,* ***48***

In 2002, Hartwig and coworkers published the room temperature palladium-catalysed α-arylation of esters with either P(*t*Bu)$_3$ or NHC precursor **50**.[65] They too worked predominantly with *tert*-butyl esters, which had been shown earlier by Rathke to generate much more stable enolates,[66,67] presumably due to slower Claisen condensation because of the more hindered carbonyl and slower decomposition to the ketene due to the worse leaving group ability of the *tert*-butoxide anion. Under these conditions with NHC precursor **50**, lower palladium loadings and fewer equivalents of ester could be employed (**Scheme 22**).



Scheme 22: *Hartwig's room temperature α-arylation of tert-butyl acetate,* ***48***

With P(*t*Bu)$_3$, it was shown that when LiNCy$_2$ was used as the base, yields were higher and there was a greater selectivity for monoarylation. The use of LiNCy$_2$ was also particularly important for the successful arylation of branched esters. The increased problem of diarylation with ester enolates is partly attributable to the less aggregated nature of the anion of the α-arylated product compared with the starting ester enolate.[68] The pK_a of dialkylamides is over 40 in DMSO,[69] meaning they can quantitatively deprotonate the ester, compared to the HMDS bases that are only able to produce small concentrations of the enolate at a time. Hartwig conducted studies that showed that the catalytic α-arylation

reaction with esters was much faster than proton transfer between the enolate of the starting ester and the α-arylation product, which explained the superior yields obtained with $LiNCy_2$. Hartwig later reported that superior yields could be obtained by replacing the $P(tBu)_3$ with the Pd(I) dimer $(P(tBu)_3PdBr)_2$.[70] He also published that esters could be α-arylated with catalytic palladium under milder conditions by the use of Reformatsky reagents, greatly improving functional group tolerance.[71]

1.2.7 α-Arylation in other systems

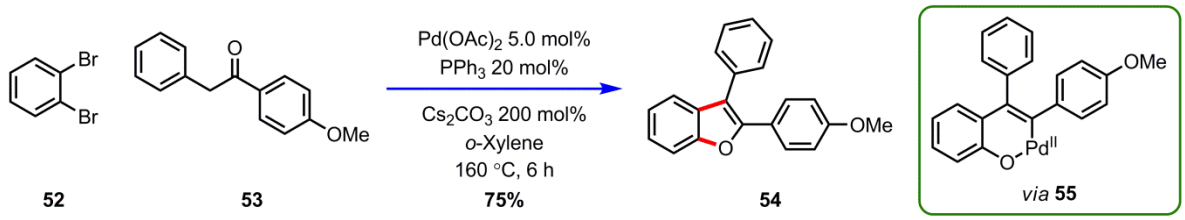
The α-arylation reaction has seen extension to a variety of other systems that are outside the scope of the discussion within this *Introduction*. These include the α-arylation of silyl enol ethers,[72-74] enol esters,[75] β-ketoesters,[76] β-cyanoesters,[77] malonates,[33] malonitriles,[78] diketones,[42] amides[79,80] and nitroalkanes.[42] Enantioselective α-arylations have also been reported.[81-83] In addition the reaction can be promoted with catalytic quantities of other metals including copper[84,85] and nickel.[86,87] There are two recent reviews on the area that cover these topics in detail.[88,89]

1.3 Synthesis of aromatic heterocycles utilising palladium-catalysed α-arylation

The palladium-catalysed α-arylation reaction has seen application to the synthesis of a number of 5,6-fused heterocyclic systems: namely benzofurans, benzothiophenes and indoles.

1.3.1 Benzofurans

In 1999, Miura and coworkers demonstrated that benzofuran **54** could be synthesised *via* the α-arylation of a suitable ketone enolate with *ortho*-dibromobenzene, **52** (**Scheme 23**).[90]

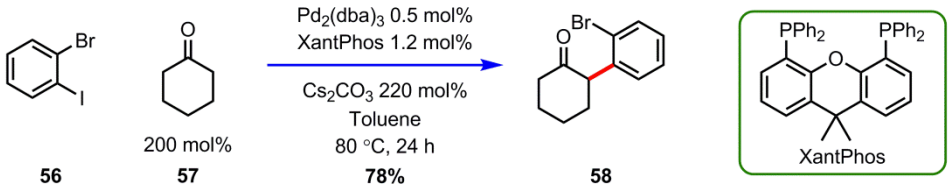


52 53 75% 54

Scheme 23: *Synthesis of benzofuran **54** from ortho-dibromobenzene, **52***

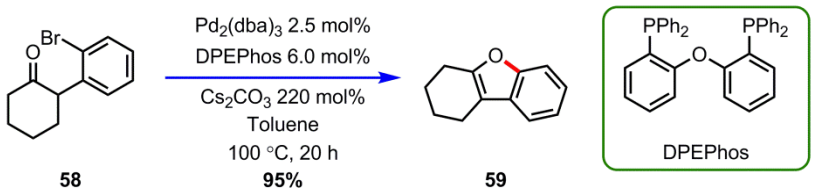
It was presumed that the reaction proceeded *via* initial formation of the enolate and *C*-arylation. This was followed by enolisation again at the same position. When the palladium inserted into the remaining C-Br bond, the oxygen atom of the enolate could now displace the bromide to form six-membered palladacycle **55**. Reductive elimination from a Pd(II) complex to form a C-O bond is generally much less favoured than to form a C-C bond, but has been demonstrated for alkoxides and phenoxides.[91-93] The usual preference of a Pd(II) enolate complex to reductively eliminate to form a C-C bond is clearly overridden in this case by the preferential formation of an unstrained benzofuran over a strained cyclopropene. This work was later further expanded by Domínguez and coworkers.[94]

The substrate scope of this protocol was significantly expanded by the work of Willis *et al.* by employing 1-bromo-2-iodobenzene, **56** in place of dibromobenzenes. Initial coupling occurred at the C-I bond to furnish α-arylated ketone **58** (**Scheme 24**).



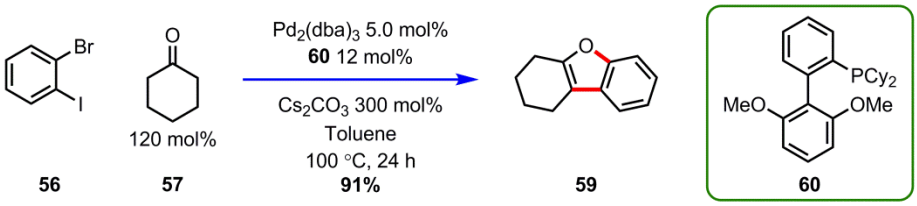
Scheme 24: *α-Arylation of 1-bromo-2-iodobenzene,* ***56***

However, under these conditions conversion to the benzofuran was very low. It was found that by altering the ligand to DPEPhos, intermediate **58** could be converted in high yield to the corresponding benzofuran **59** (**Scheme 25**).



Scheme 25: *Conversion of intermediate* ***58*** *to benzofuran* ***59***

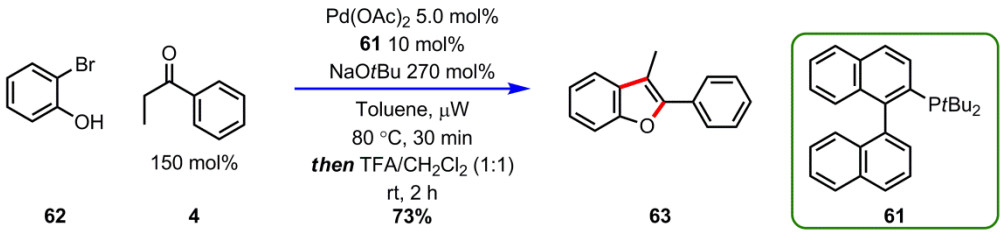
A range of cyclic ketones and alkyl aryl ketones were shown to be amenable to this procedure and it was also demonstrated that 1-chloro-2-iodobenzenes could be employed. Despite the similarity between XantPhos and DPEPhos, neither ligand could effect the other reaction. In a procedure where both ligands were added simultaneously to the reaction mixture, a yield of 51% of benzofuran **59** was obtained from **56**. It was later found that the dimethoxy-substituted dicyclohexylphosphine ligand **60**[95] could effect both processes, albeit in a higher loading (**Scheme 26**).



Scheme 26: *One-pot synthesis of benzofuran* ***59***

In 2008, Burch and coworkers disclosed a one-pot approach to benzofurans from *ortho*-bromophenols (**Scheme 27**).[96] The binaphthyl ligand **61** was found to be optimal for the α-arylation reaction, which took place in short reaction times under microwave

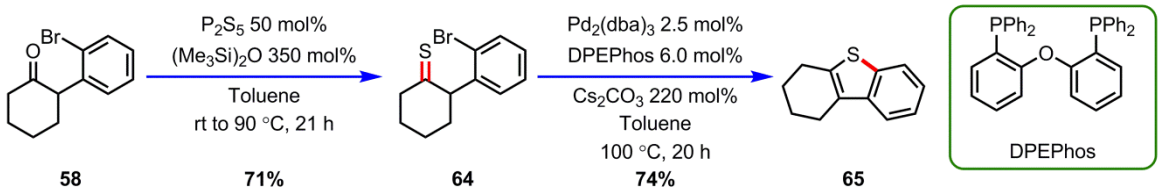
irradiation. Cyclisation could be promoted *in situ* by the addition of TFA. A wide variety of ketones were shown to be compatible with the procedure and a range of electron-neutral and electron-rich *ortho*-bromophenols could be employed.



Scheme 27: *One-pot synthesis of benzofuran **63** from ortho-bromophenol, **62***

1.3.2 Benzothiophenes

Although examples of palladium-catalysed C-S bond formation are known, they are generally much rarer than C-N and C-O bond forming examples.[97-99] Willis *et al.* demonstrated that the intermediates that were accessed *en route* to benzofurans could also be utilised in the synthesis of benzothiophenes. The α-arylated ketones were converted into the α-arylated thioketones by treatment with P_2S_5.[100] These could then be converted into the benzothiophenes under the same conditions used to synthesise the benzofurans (**Scheme 28**).

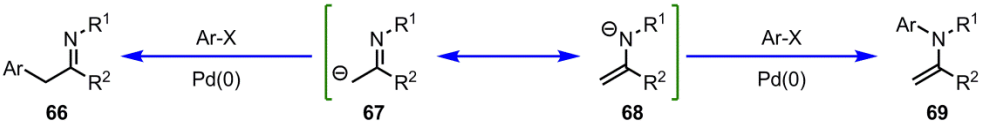


Scheme 28: *Synthesis of benzothiophene **65***

1.3.3 Indoles

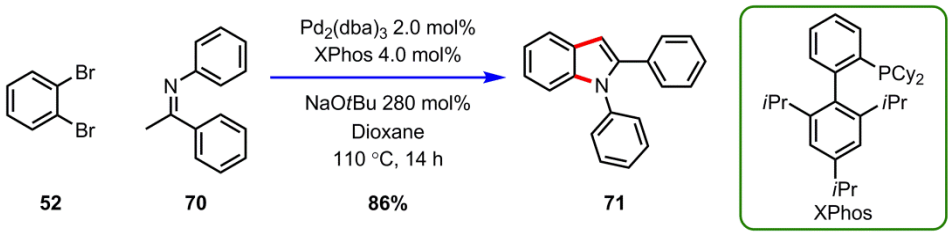
In 2007, Barluenga *et al.* described their studies on azaallylic anions, which could be generated from deprotonation of an imine bearing α-hydrogen atoms (and represented as **67** or **68**).[101] It was wondered whether in the presence of Pd(0) and an aryl halide, these anions would undergo *C*-arylation in a manner similar to the α-arylation of ketone/ester/amide

enolates to give **66** or *N*-arylation in a manner similar to a Buchwald-Hartwig amination[102,103] to give **69** (**Scheme 29**).



Scheme 29: *Possible reactivity of azaallylic anion*

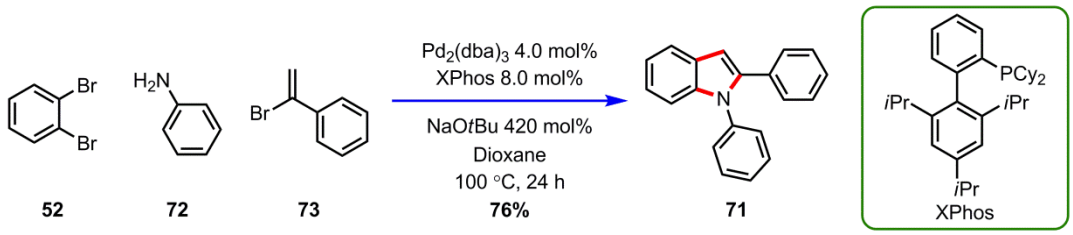
It was found that in the presence of suitable bases and ligands these azaallylic anions underwent exclusive *C*-arylation, and even with a large excess of aryl halide, no *N*-arylation was detected. Barluenga then reacted these anions with *ortho*-dibromobenzenes in an attempt to synthesis indoles. When imine **70** and 1,2-dibromobenzene, **52** were treated with NaO*t*Bu in the presence of XPhos, they underwent conversion to indole **71** in 86% yield (**Scheme 30**).



Scheme 30: *Barluenga's synthesis of indoles*

As in the benzofuran case, the new propensity for *N*-arylation was attributed to bias in the substrate. As before, it was presumed the reaction proceeded *via* initial *C*-arylation, deprotonation again at the same position and subsequent formation of a six-membered palladacycle. Reductive elimination to form a C-N bond and the five-membered indole was thermodynamically preferred rather than isomerisation to the *C*-bound enolate and elimination to form a cyclopropene. A range of ketones could be employed, and by the use of 1-chloro-2-bromoarenes, regioselectivity on the aryl partner could be achieved by initial α-arylation with the C-Br bond.[104]

In a separate study, Barluenga reported that the palladium-catalysed amination of haloalkenes with primary amines led to the synthesis of imines.[105] This protocol employed very similar conditions to those used in his synthesis of indoles and so work was undertaken to develop a three component coupling reaction. It was found that when bromoalkene **73**, aniline, **72** and 1,2-dibromobenzene, **52** were combined in a one-pot process, that a 76% yield of indole **71** was obtained (**Scheme 31**).



Scheme 31: *Barluenga's synthesis of indoles*

The success of this three component procedure was attributed to the higher reactivity of the bromoalkene over the bromoarene, ensuring that formation of the enamine occurred first, then tautomerisation to the imine, followed by the α-arylation (only once all of the alkenyl halide had been sequestered).

Analogous routes to indoles have also been achieved under the action of copper catalysis, although they are generally restricted to 1,3-ketoesters.[106-108]

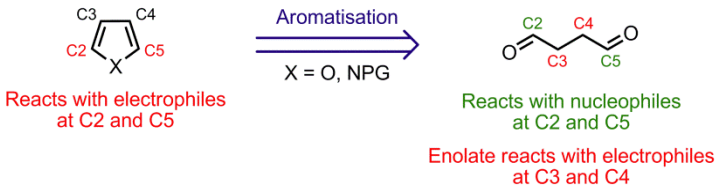
1.4 Synthetic strategies for substituted aromatic heterocycles

The importance of aromatic heterocycles needs no introduction. They are ubiquitous throughout natural products, pharmaceuticals and agrochemicals, and in organic materials.[109] The synthesis of substituted aromatic heterocycles is a mainstay of organic chemistry. However, in addition to selecting the correct class of heterocycle for a particular application, it is the nature and placement of the substituents around the heterocyclic core that is often key to achieving the desired properties. Unsurprisingly, there is a plethora of different ways to install substituents on aromatic heterocycles, however these many different reactions can be broadly classified into a few types.

The underlying reactivity of the heterocycle can be employed to install substituents once the heterocyclic motif itself has been formed. For example, the five-membered heterocycles pyrrole and furan have a natural reactivity with electrophiles at the C2 and C5 positions, allowing substituents to be incorporated *via* S_EAr reactions. Pyridine meanwhile reacts with nucleophiles particularly well at the C2 and C6 positions. This strategy has the advantage that substituents can be installed at the end of a synthesis, and therefore sensitive functionality does not need to be taken through multiple synthetic steps. However, the drawbacks are that regioisomeric mixtures of products can sometimes be produced and that certain relatively unreactive positions on the heterocycle (such as C3 of a pyridine) can be difficult to functionalise.

An alternative strategy is to install the substituent onto the non-aromatic precursor molecule, prior to its conversion to the heterocycle. A great advantage of this strategy is that the natural pattern of reactivity of the precursor is often very different to that of the heterocycle being synthesised. For example, a 1,4-dicarbonyl is a common precursor to a pyrrole or furan. Reactions such as nucleophilic addition to one of the carbonyl carbons, or formation of an

enolate of one of the carbonyls and reacting it with an electrophile are examples of reactivity modes that are much easier to perform on the precursor molecule than the final heterocycle (**Scheme 32**).



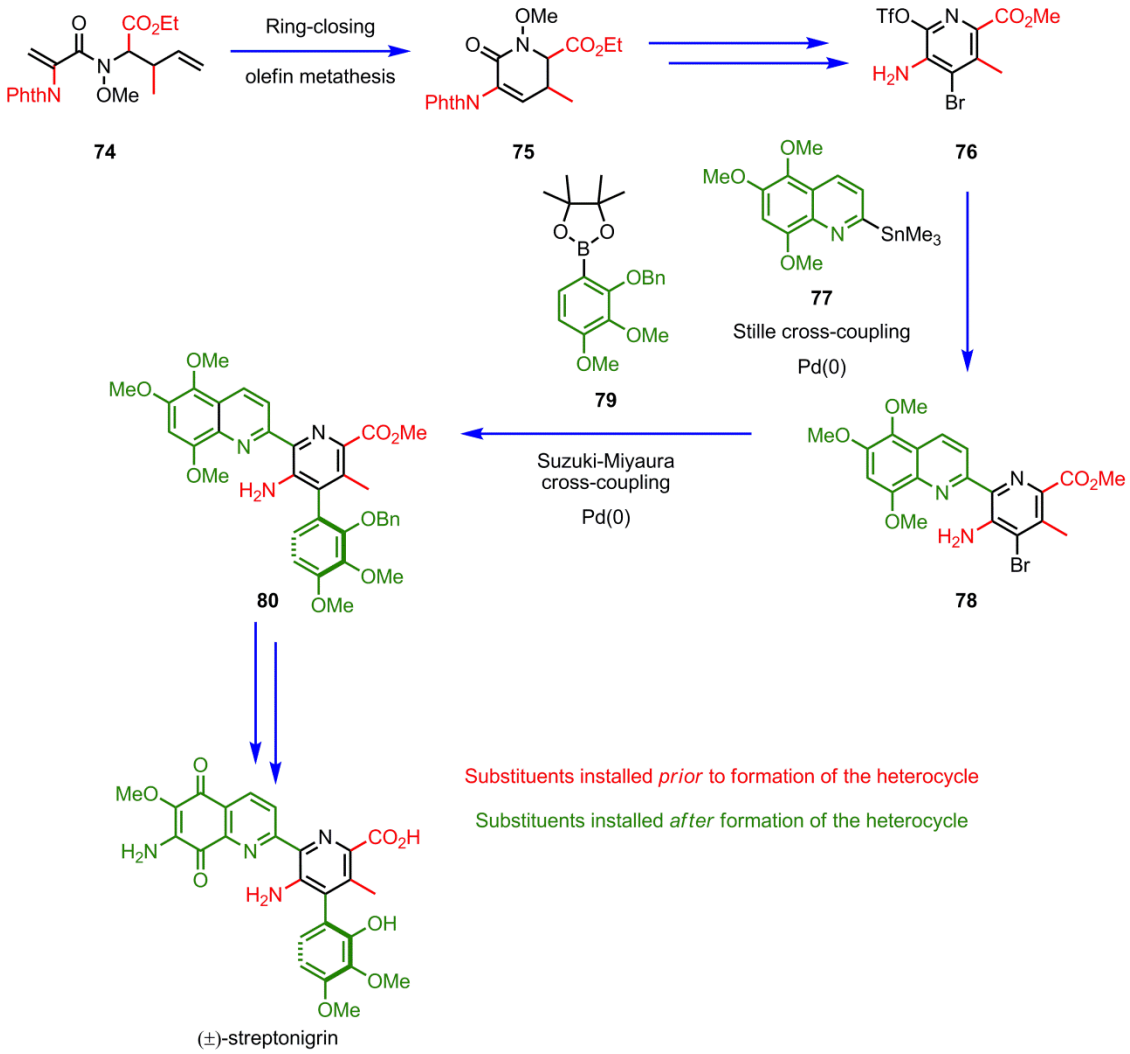
Scheme 32: *Contrasting reactivity of heterocycle precursor*

This often allows expedient incorporation of substituents at positions that would be otherwise difficult to manipulate. However, it means that the substituent often needs to be in place at an earlier stage at the synthesis.

It is also possible to incorporate a placeholder substituent at an appropriate position for later manipulation. For example, installation of a halogen atom (either on the non-aromatic precursor or directly onto the aromatic moiety itself) can provide the necessary handle on a molecule so that a substituent can later be appended to the aromatic ring with full regiocontrol, for example by employing a palladium-catalysed coupling reaction (*vide supra*).

These concepts are best illustrated by an example, such as the synthesis of (±)-streptonigrin by Donohoe *et al.* in 2011 (**Scheme 33**).[110] The synthesis of (±)-streptonigrin involved the construction of a pentasubstituted pyridine core, using a ring-closing olefin metathesis reaction. The metathesis precursor **74** was highly elaborated and already possessed three of the five substituents that were needed around the pentasubstituted pyridine in (±)-streptonigrin: a methyl group, a carboxylic acid (protected as the ester) and a primary amine (protected as the phthalimide). The position of these substituents was completely defined by the choice of starting materials to construct the metathesis precursor **74**. The

product of the metathesis reaction **75** was then converted in several steps to pyridine **76**. These transformations resulted in the incorporation of a bromine atom at C4 (using the reactivity of the enamine at this position) and the conversion of the amide moiety in **75** into a triflate at the C2 position, ready for the remaining substituents to be installed by cross-coupling reactions. Firstly a Stille cross-coupling with **77** appended the C2 quinoline substituent to furnish **78**. Afterwards a Suzuki-Miyaura cross-coupling with **79** attached the C4 aryl substituent to give **80**. Intermediate **80** could be converted into (±)-streptonigrin in several further steps.



Scheme 33: *Donohoe's synthesis of (±)-streptonigrin*

The combination of these strategies by Donohoe *et al.* enabled (±)-streptonigrin to be synthesised in a highly efficient manner, with the strengths of the different approaches being utilised to their full extent.

Modern metal-catalysed reactions (such as the ring-closing olefin metathesis reaction) have opened up new avenues for the synthetic chemist, making previously unfeasible disconnections into routine operations. *De novo* syntheses of aromatic heterocycles employing such methods often give unique opportunities for the incorporation of substituents on a motif prior to the generation of the fully aromatic heterocycle, due to fundamental differences in reactivity of the precursor. Compared to the often harsh conditions of traditional heterocyclic synthesis (such as high temperatures and strong acid), these newer methods also often occur under milder reaction conditions. This gives the potential for the development of highly regiospecific and convergent syntheses through application of these newer reactions. The ability to manipulate and functionalise precursor molecules should be a key factor to consider when designing new synthetic routes.

The importance of heterocycles and methods for their synthesis will now be discussed in more detail with reference to the isoquinoline skeleton, as an overview to a significant body of the work undertaken in this *Thesis*.

1.5 Isoquinolines

1.5.1 Structure and reactivity of isoquinoline

Isoquinoline is a 10π electron heterocyclic aromatic consisting of a benzene ring fused to a pyridine ring. Although the term isoquinoline formally refers to the fully aromatic system, it is also used more loosely when describing more saturated versions of the same scaffold (such as the di-, tetra- and decahydroisoquinolines) (**Figure 5**).

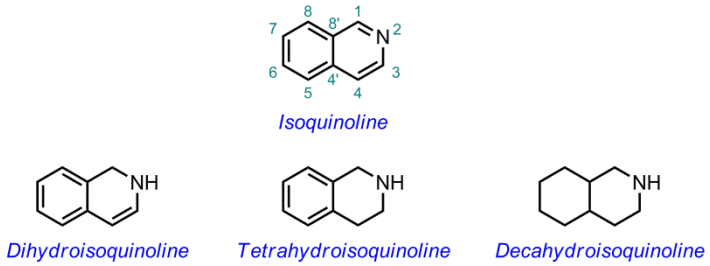


Figure 5: *Isoquinoline: structure and numbering*

Like pyridine, isoquinoline is a weakly basic (pK_b 5.4),[111] electron-deficient heterocycle. Hence, the reactivity profile for isoquinolines closely mirrors that of pyridines, with a strong propensity for the addition of nucleophilic reagents to the ring, but the general need for more forcing conditions in order to react with electrophilic reagents. The nitrogen lone pair can also add to electrophiles to form *N*-oxides and quaternary salts, as for pyridines. In terms of regioselectivity, the heterocyclic ring is significantly more electron-deficient than the carbocyclic ring. The addition of nucleophiles therefore takes place predominantly on the heterocyclic ring, with attack at the C1 position favoured. The propensity of halogen atoms on the heterocyclic ring to be displaced by nucleophilic substitution varies greatly, with those at C1 being highly labile, those at C3 intermediate in reactivity and those at C4 behaving as in a standard halobenzene.[112] Reaction with electrophiles, when it does takes place, occurs predominantly on the carbocyclic ring at C5, with also some reactivity at C8[113,114] (**Figure 6**).

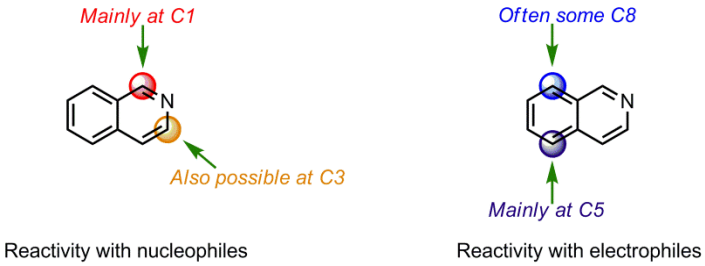


Figure 6: *Reactivity of isoquinolines*

1.5.2 Occurrence of isoquinolines

The isoquinoline motif occurs in a large array of natural products, which between them display an extensive range of biological activity. A large number of secondary metabolites are isoquinoline alkaloids.[115] Natural products containing isoquinolines or derivatives thereof include the opium poppy alkaloids such as morphine and papaverine (a potent vasodilator),[116] and the bright yellow dye berberine. Decumbenine B (isolated from the tubers of *Corydalis decumbens*)[117] inhibits intestinal contractions[118] and trabectedin, extracted from the sea squirt *Ecteinascidia turbinata*, (which contains three linked isoquinoline subunits) is used as an anti-tumour drug[119] (**Figure 7**).

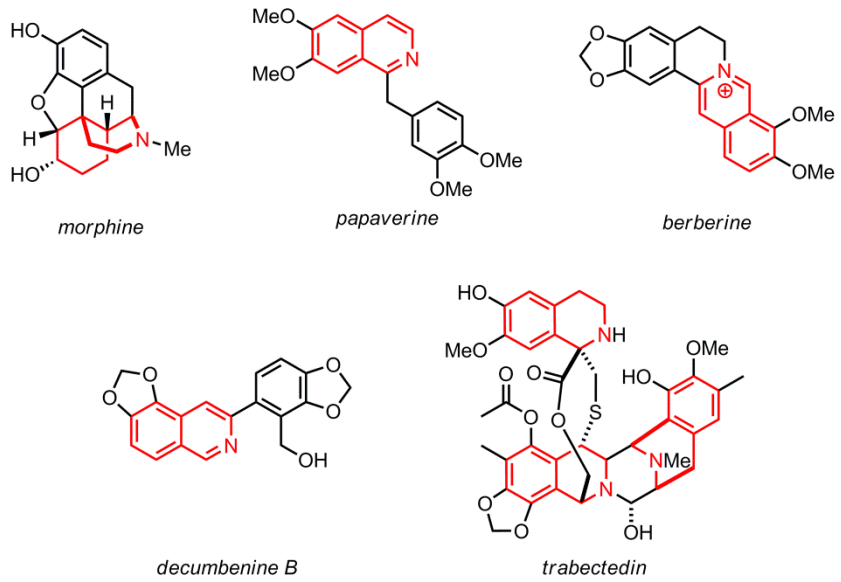
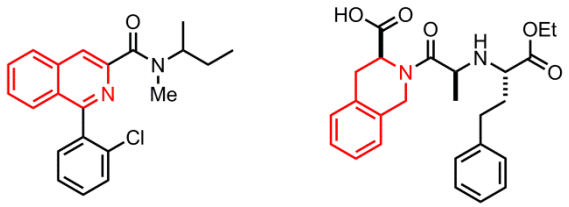


Figure 7: *Occurrence of the isoquinoline motif in natural products*

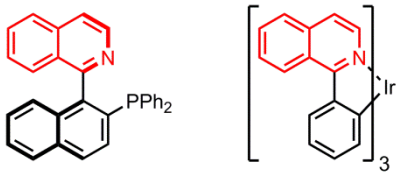
Isoquinolines have also been exploited in pharmaceuticals. The electron-deficient nature of the isoquinoline core is often a desirable property here, stabilising the drug molecule against oxidative degradation. The peripheral benzodiazepine receptor binder PK-11195[120] contains a fully aromatic isoquinoline, and quinapril, which is used in the treatment of heart failure and hypertension,[121] a tetrahydroisoquinoline (**Figure 8**).



PK-11195 *quinapril*

Figure 8: *Isoquinolines in pharmaceuticals*

Isoquinoline derivatives have also found application in a range of functional organic materials. This includes QUINAP, which can be employed as a chiral ligand,[122] and $Ir(piq)_3$, which is used in organic light emitting diodes (**Figure 9**).[123]



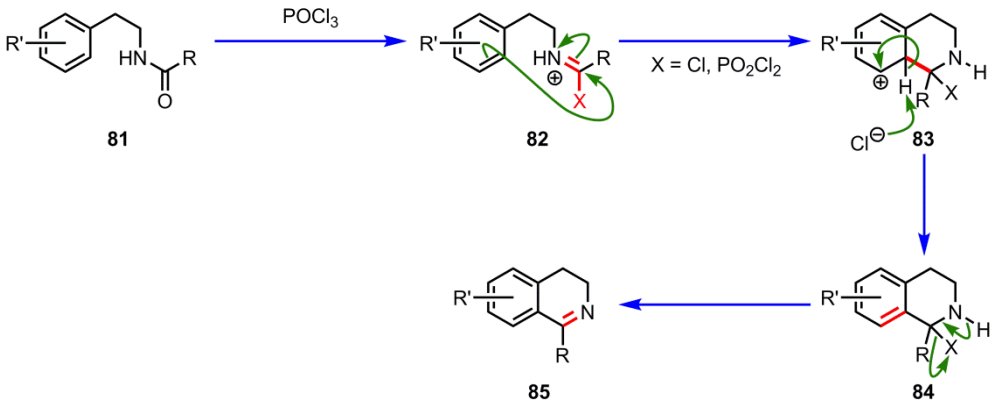
QUINAP *Ir(piq)3*

Figure 9: *Isoquinolines in functional organic molecules*

1.5.3 Traditional syntheses of isoquinolines

In 1893, Bischler and Napieralski published a synthetic route to isoquinolines that involved a key disconnection at the C1-C8' bond.[124] They showed that when acyl derivatives of a phenylethylamine **81** were treated with a dehydrating agent (such as $POCl_3$), a reactive electrophilic species **82** (now referred to as a Vilsmeier-type electrophile) was formed.[125] This was attacked by the pendant aromatic ring in an S_EAr reaction, forming the key C1-C8'

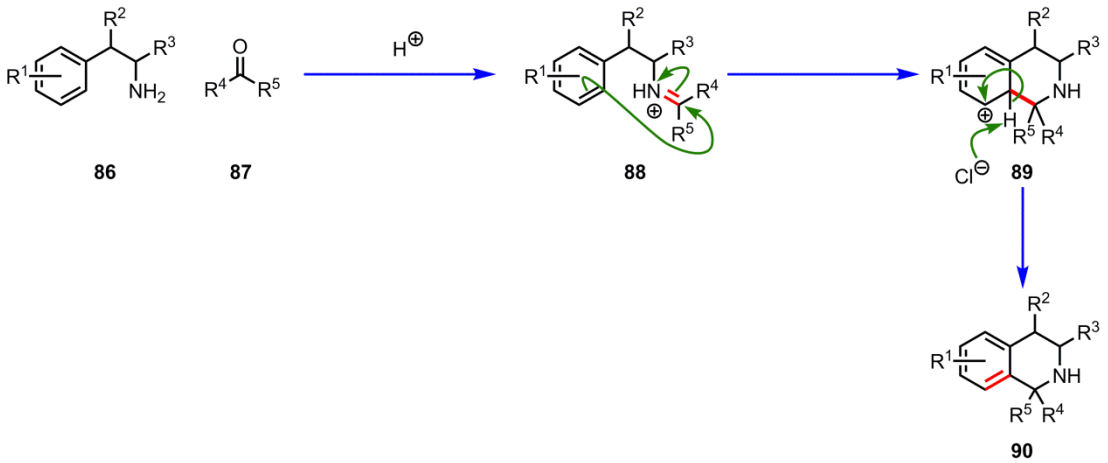
bond and delivering intermediate **83**. Rearomatisation to **84** and subsequent elimination furnished 3,4-dihydroisoquinoline **85** (**Scheme 34**).



Scheme 34: *Bischler-Napieralski isoquinoline synthesis*

If the starting compound contained a hydroxyl group on the tether linking the amide to the benzene ring, then an additional dehydration took place delivering the isoquinoline oxidation level directly. Considerable procedural improvements have taken place since this time, including the application of a variety of different dehydrating agents to the reaction.[126] It has also notably seen application in synthesis, including the first total syntheses of (±)-strychnoxanthine and (±)-melinonine-E.[127]

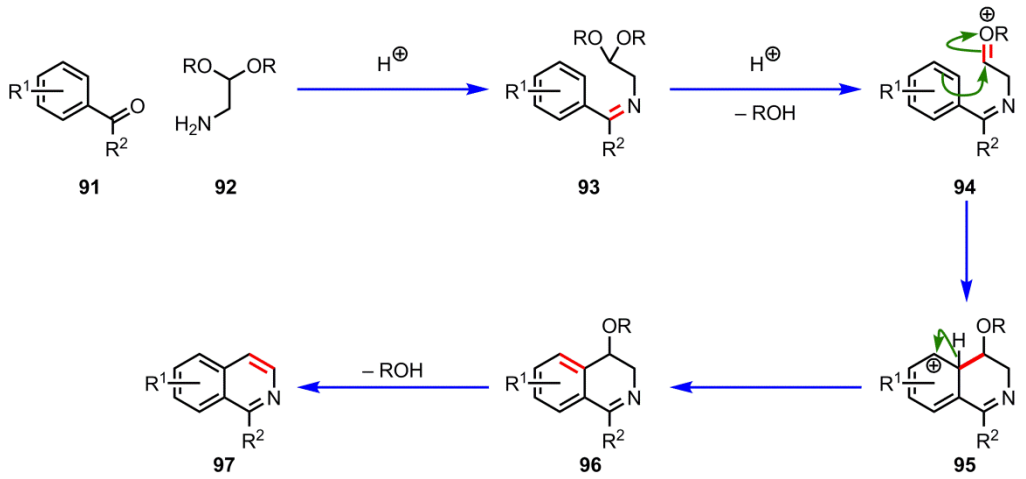
In 1911, Pictet and Spengler disclosed that the condensation of phenylethylamine with dimethoxymethane in the presence of conc. HCl delivered 1,2,3,4-tetrahydroisoquinoline.[128] The condensation of a β-arylethylamine with a carbonyl compound under acidic conditions to give substituted tetrahydroisoquinolines is known as the Pictet-Spengler reaction.[129] Under the acidic reaction conditions, amine **86** and carbonyl compound **87** condensed to form an imine, which existed protonated as the iminium ion **88** under the reaction conditions. This iminium ion was trapped by the aromatic ring *via* an S_EAr reaction to form **89**, which rearomatised to tetrahydroisoquinoline **90**, with the key bonds formed in this synthesis therefore being C1-C8' and C1-N (**Scheme 35**).[130]



Scheme 35: *Pictet-Spengler isoquinoline synthesis*

This is an analogous reactive intermediate to the Bischler-Napieralski synthesis. However, the iminium ion in this synthesis is less electrophilic and so the aromatic ring must be sufficiently electron-rich for the reaction to occur. Interestingly, this reaction can proceed under physiological conditions when there are two or more alkoxy or hydroxy groups on the benzene ring and this is often a key step in alkaloid biosynthesis.[131] This reaction has seen a number of applications in synthesis, particularly in the studies of Danishefsky and coworkers towards trabectedin.[132]

In 1893, Pomeranz and Fritsch both independently reported that the condensation of benzaldehyde with 2,2-diethoxyethylamine in conc. H_2SO_4 furnished an isoquinoline.[133,134] The benzaldehyde or aromatic ketone **91** condensed with the 2,2-dialkoxyethylamine **92** under acidic conditions to give benzalaminoacetal **93**. This was followed by formation of oxonium ion **94**, which was trapped by the aromatic ring to give intermediate **95**. Rearomatisation to **96** and then elimination furnished isoquinoline **97** (**Scheme 36**).



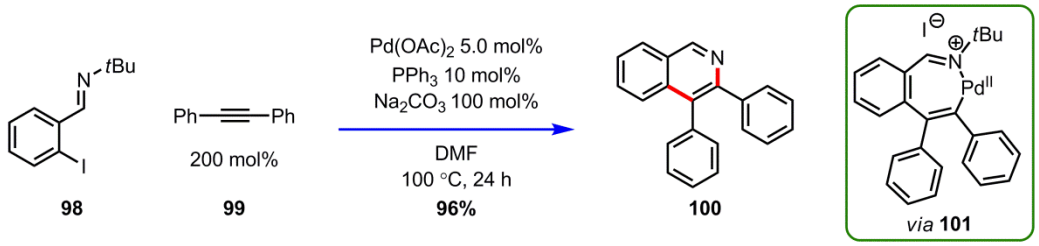
Scheme 36: *Pomeranz-Fritsch isoquinoline synthesis*

The key disconnections in this synthesis are therefore C4-C4' and C1-N. This synthesis, however, was poorly tolerant of substitution on the heterocyclic ring, with unsubstituted dialkoxyethylamines used almost exclusively, and reaction yields often low if a phenyl ketone was used instead of a benzaldehyde.[135] The reaction also required the presence of electron-donating substituents on the benzene ring. If electron-withdrawing substituents were present the corresponding oxazoles were obtained instead.[136] More recently the Schlittler-Müller modification (where a benzylamine was condensed with glyoxal hemiacetal) has allowed access to C1 substituted isoquinolines in far greater yield.[137]

All of these methods had their own individual strengths, but they also shared common limitations. In all cases the heterocyclic ring of the isoquinoline was closed by an S_EAr reaction and hence only worked well for electron-rich carbocyclic moieties and often failed entirely with electron-deficient carbocyclic systems. The methods also generally required reasonably harsh reaction conditions, such as strongly acidic conditions and/or the use of high temperatures, which significantly restricted the overall functional group tolerance of these reactions.

1.5.4 Approaches to isoquinolines using alkynes

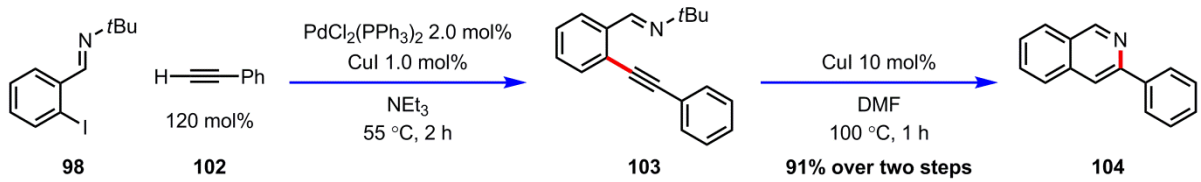
In 1998, Larock and coworkers reported the synthesis of isoquinolines *via* the palladium-catalysed iminoannulation of internal alkynes, formally a C4-C4' and C3-N disconnection (**Scheme 37**).[138]



Scheme 37: *Larock's synthesis of isoquinolines from internal alkynes*

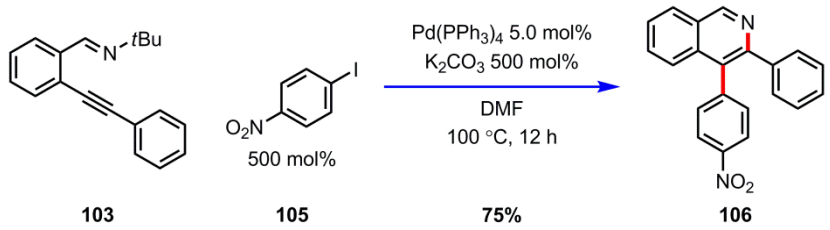
The reaction was proposed to proceed *via* oxidative addition of Pd(0) into aryl halide **98**, which then inserted across alkyne **99** to give a vinylic palladium intermediate. It was presumed that this was trapped by the nitrogen of the neighbouring imine to furnish seven-membered palladacycle **101**.[139] It was then suggested that reductive elimination of the palladium, followed by fragmentation by loss of the *tert*-butyl group (to relieve strain with the C3 substituent) gave isoquinoline **100**.

The reaction gave excellent yields, although sometimes mixtures of regioisomeric isoquinolines were produced, particularly with electron-rich imines. Also the reaction failed with dialkyl-substituted alkynes. Larock then extended the protocol to the coupling of terminal alkynes (**Scheme 38**).[140] The terminal alkyne **102** initially coupled with the aryl halide **98** to give imino alkyne **103**. After removal of solvents and precipitates, imino alkyne **103** was converted into isoquinoline **104**. A mixed palladium and copper catalyst system was found to be most efficient (although interestingly the authors noted that both metals could effect both steps).



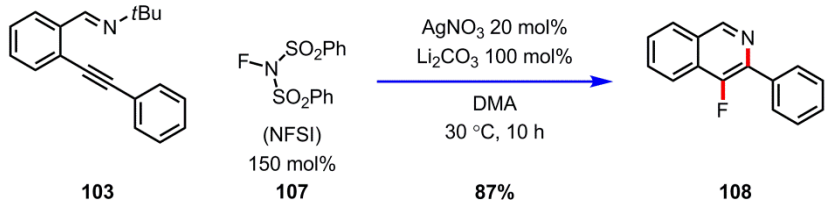
Scheme 38: *Larock's synthesis of isoquinolines from terminal alkynes*

Larock also later showed that the imino alkyne intermediates **103** could be converted into C4 substituted isoquinolines **106** *via* cyclisation with Pd(0) in the presence of aryl, allyl, alkynyl or vinyl halides (**Scheme 39**).[141,142]



Scheme 39: *Larock's synthesis of C4 substituted isoquinolines*

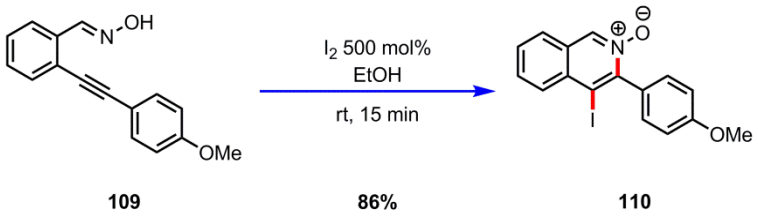
The synthetic approach of Larock was later adapted by Cheng and coworkers for use with nickel catalysis. This proceeded under milder conditions and had a greater functional group tolerance.[143] Larock later showed that the cyclisation of the intermediates could be promoted by electrophiles such as I_2, PhSeCl and PhSCl to give 4-heteroatom-substituted isoquinolines.[144] Meanwhile Liu and coworkers illustrated that the imino alkyne intermediates **103** could be cyclised under silver catalysis with NFSI, **107** to provide 4-fluoroisoquinolines **108** (**Scheme 40**).[145]



Scheme 40: *Liu's silver-catalysed cyclisation to 4-fluoroisoquinolines*

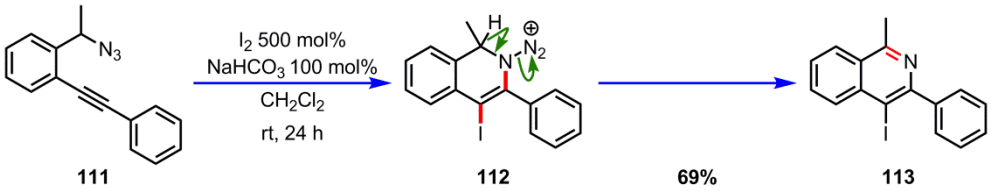
It was subsequently shown by Yamamoto and coworkers that I_2 could promote the cyclisation of related intermediate **109** (where the *tert*-butyl imine was replaced by an

oxime) to isoquinoline *N*-oxide **110** (**Scheme 41**).[146] As isoquinoline *N*-oxides are very versatile compounds, their direct synthesis in this manner was a significant advance.



Scheme 41: *Yamamoto's iodine-mediated cyclisation to isoquinoline N-oxides*

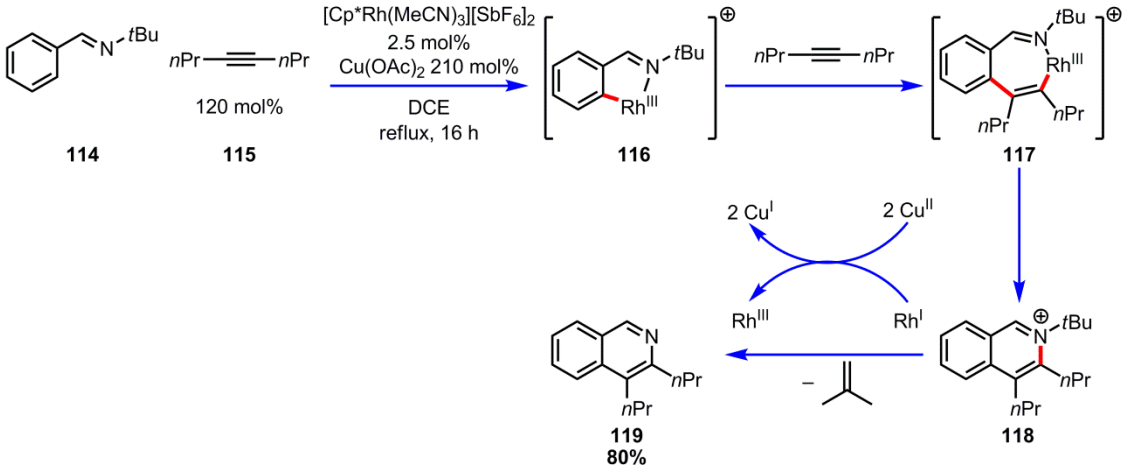
Yamamoto also disclosed that 2-alkynylbenzyl azides could be cyclised with iodine in a similar manner.[147,148] The reaction was believed to proceed *via* initial coordination of iodine to the alkyne in **111**, activating the triple bond towards nucleophilic ring closure by the azide to give **112**. Loss of a proton and nitrogen gas then delivered isoquinoline **113** (**Scheme 42**).



Scheme 42: *Yamamoto's iodine-mediated cyclisation of benzyl azides to isoquinolines*

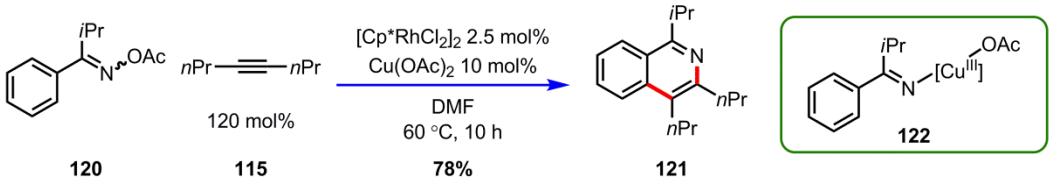
The Larock approach to isoquinolines (and subsequent modifications thereof), whereby an alkyne precursor provided the C3 and C4 isoquinoline carbons, was a landmark advance in the synthesis of isoquinolines. However, the need to employ difunctionalised starting materials limited the substrate scope. In 2009, Fagnou and coworkers adapted this synthesis to begin with a rhodium-catalysed C-H activation reaction at the *ortho*-position rather than an insertion of Pd(0) into a C-X bond.[149] Upon treatment of *tert*-butyl imine **114** with the active Rh(III) catalyst, it was proposed that a C-H activation occurred to give Rh(III) species **116**,[150] followed by carbometallation with alkyne **115** to give rhodacycle **117**. Reductive elimination of the rhodium furnished isoquinolinium ion **118** (which lost the *tert*-butyl group to give isoquinoline **119**) and Rh(I). The Rh(I) catalyst was then reoxidised by the Cu(II) (**Scheme 43**). The reaction had a reasonable substrate scope and occurred under mild

reaction conditions. Miura concurrently reported a similar procedure with benzophenone N-H imines.[151]



Scheme 43: *Fagnou's rhodium-catalysed approach to isoquinolines*

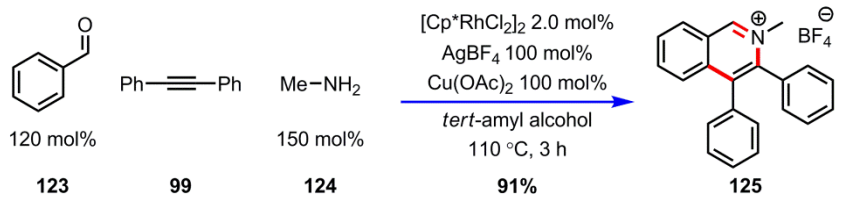
Chiba and coworkers later adapted this procedure and showed that *O*-acetyl oxime **120** could be coupled with alkyne **115** to deliver isoquinoline **121** in high yield (**Scheme 44**).[152]



Scheme 44: *Chiba's rhodium-catalysed approach to isoquinolines*

The use of the *O*-acetyl oxime also allowed the copper to be used in catalytic quantities as it was postulated by the authors that the reaction started with cleavage of the N-O bond to furnish **122**, which served as a reoxidant for Cu(I).

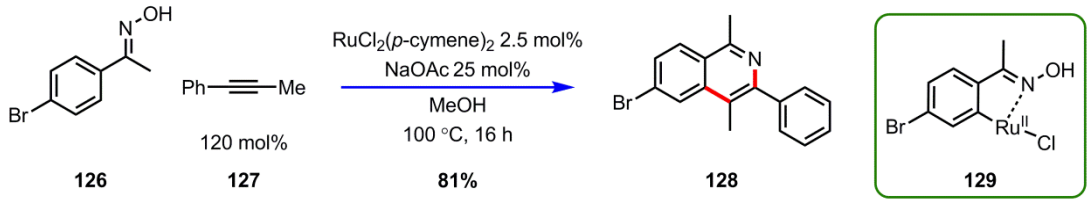
This work was later adapted to a one-pot synthesis of isoquinolinium salts by Cheng and coworkers.[153] The synthesis involved the three component coupling of benzaldehyde, **123**, an alkyne **99** and a primary amine **124** (**Scheme 45**).



Scheme 45: *Cheng's rhodium-catalysed approach to isoquinolinium salts*

The $AgBF_4$ was thought important for two reasons; it initiated the catalytic cycle by removal of a chloride from the rhodium catalyst and provided an inert anion necessary for the isolation of the isoquinolinium salt.

One major drawback of the rhodium-catalysed methods was that there was often poor regioselectivity when unsymmetrical alkynes were employed. More recently, it was shown that Ru(II) catalyst $RuCl_2(p\text{-cymene})_2$ could mediate similar reactions with $Cu(OAc)_2$ as the terminal oxidant, and Ackermann *et al.* employed this in the synthesis of isoquinilones.[154] Jeganmohan then applied these conditions to the synthesis of isoquinolines, where excellent regioselectivity was obtained with a range of internal and terminal alkynes.[155] The reaction showed a preference to place the aromatic or larger group at the C3 position, although the reasons for the high regioselectivity were not well understood. A range of functional groups were shown to be compatible, notably aryl halides (**126** → **128**) (**Scheme 46**).



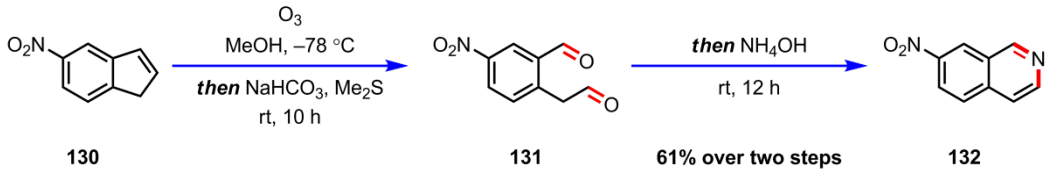
Scheme 46: *Jeganmohan's ruthenium-catalysed synthesis of isoquinolines*

Mechanistically, the reaction was believed to proceed in an analogous manner to the rhodium case. Initial coordination of the nitrogen of the oxime to the ruthenium was thought to be important in directing the C-H activation reaction. In stoichiometric studies, the authors isolated intermediate ruthenocycle **129** and showed that it could be converted to products, providing strong support for this pathway. After cyclisation, the cleavage of the N-O bond

was believed to assist the reoxidation of the ruthenium. It was later shown by Urriolabeitia and coworkers that benzylamines could also be coupled with alkynes under the action of the same ruthenium catalyst to furnish isoquinolines.[156]

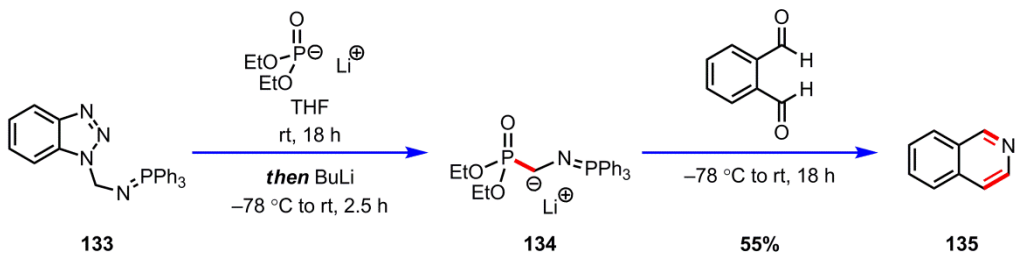
1.5.5 Other notable modern approaches

In 1980, Miller *et al.* disclosed a one-pot route to isoquinolines from the corresponding indenes (**Scheme 47**), disconnecting the C1-N and C3-N bonds.[157] Indene **130** was ozonolysed with a reductive work up to give dialdehyde **131**. Dialdehyde **131** was not isolated but converted into isoquinoline **132** *via* treatment with NH_4OH. This route was tolerant of substitution at all positions, and importantly did not depend on the electronic nature of the carbocyclic ring.



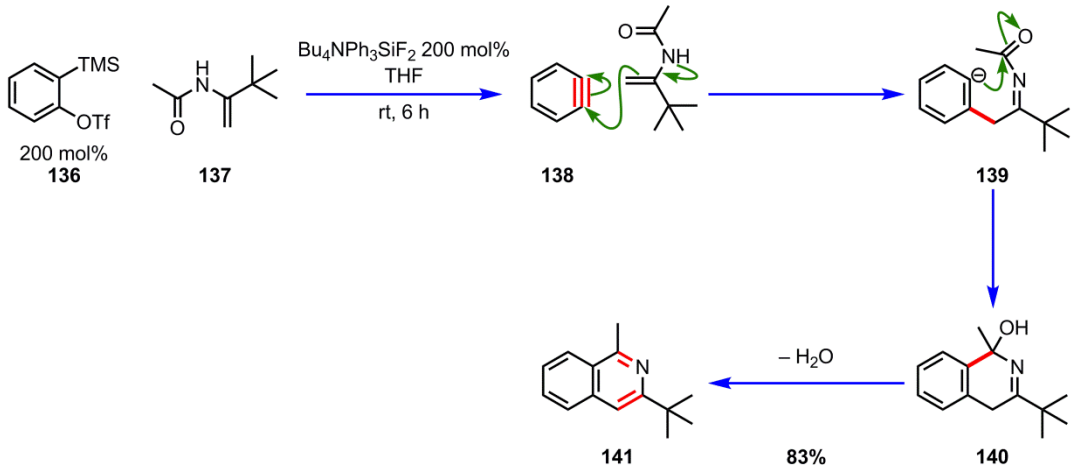
Scheme 47: *Synthesis of isoquinolines from indenes*

In 1993, Katritzky *et al.* reported a novel isoquinoline disconnection that involved breaking the C1-N and C3-C4 bonds.[158] In the synthetic sense, the reaction utilised a newly developed 1,2-monoazabisylid **134**, that was synthesised from the reaction of benzotriazole **133** with lithium diethylphosphite. This reagent, upon reaction with phthalic dicarboxaldehyde, delivered isoquinoline, **135** in 55% yield, *via* sequential Wittig and aza-Wittig reactions in one-pot (**Scheme 48**).



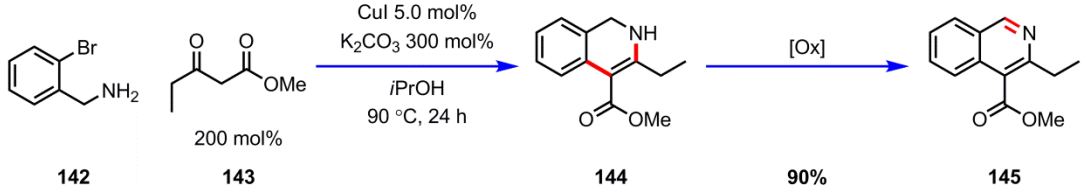
Scheme 48: *Katritzky's synthesis of isoquinolines*

Stoltz and coworkers demonstrated that isoquinolines could be synthesised from benzyne intermediates, formally a C1-C8' and a C4-C4' disconnection.[159] Upon treatment of silyl aryl triflate **136** with a source of fluoride, benzyne, **138** was formed, which was attacked by enamide **137** to furnish anion **139**. Anion **139** then underwent a dehydrative cyclisation (*via* **140**) to give isoquinoline **141** (**Scheme 49**).



Scheme 49: *Stoltz's isoquinoline synthesis utilising benzynes*

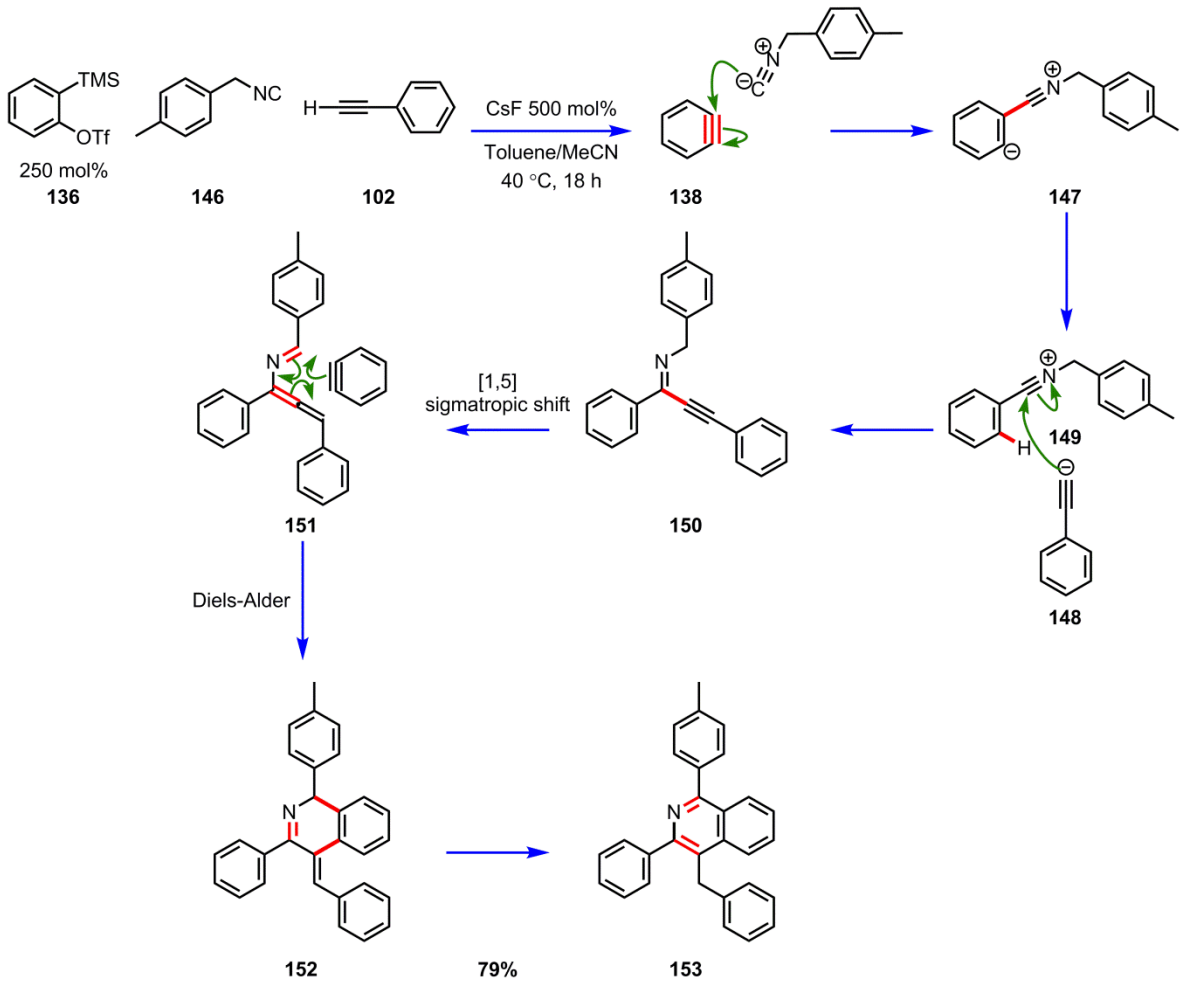
In 2008, Ma and coworkers published the copper-catalysed coupling of β-keto esters with 2-halobenzylamines to furnish isoquinolines.[160] The reaction proceeded *via* a copper-catalysed α-arylation of the enolate of keto ester **143** with aryl bromide **142**. Following this, intramolecular condensation of the benzylic amine on to the ketone gave dihydroisoquinoline **144**. These dihydroisoquinolines were found to oxidise spontaneously under an atmosphere of air (**Scheme 50**). Formally a C4-C4' and C3-N disconnection, the scope of this protocol was unfortunately limited by the requirement for an ester moiety at C4, and no C1 substituents could be incorporated.



Scheme 50: *Ma's copper-catalysed synthesis of isoquinolines*

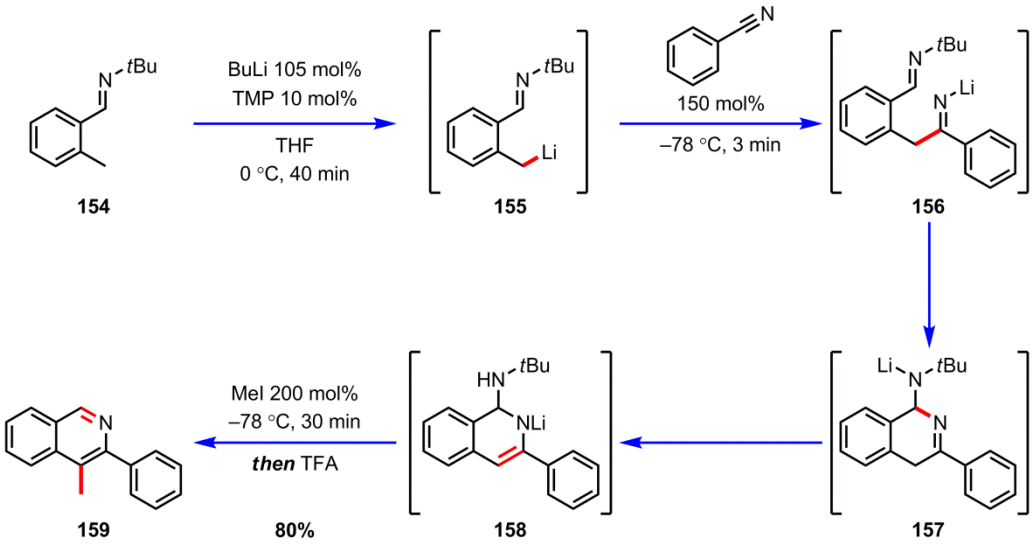
1.5.6 Multicomponent strategies

In 2009, Huang and coworkers adapted the benzyne strategy of Stoltz further into a four component coupling of two benzynes, an isocyanide and a terminal alkyne, with the disconnections being across C1-C8', C3-C4 and C4-C4'.[161] The authors proposed that the reaction began with the attack of the isocyanide **146** on benzyne, **138** to give zwitterion **147**. This deprotonated the alkyne **102**, activating it to nucleophilic anion **148**. This anion then attacked the nitrilium ion **149** to give intermediate **150**. Intermediate **150** underwent a [1,5]-sigmatropic shift to furnish intermediate **151**, which then reacted with another molecule of benzyne in a Diels-Alder reaction to give **152**, which isomerised to isoquinoline **153** (**Scheme 51**).



Scheme 51: *Huang's multicomponent isoquinoline synthesis utilising benzynes*

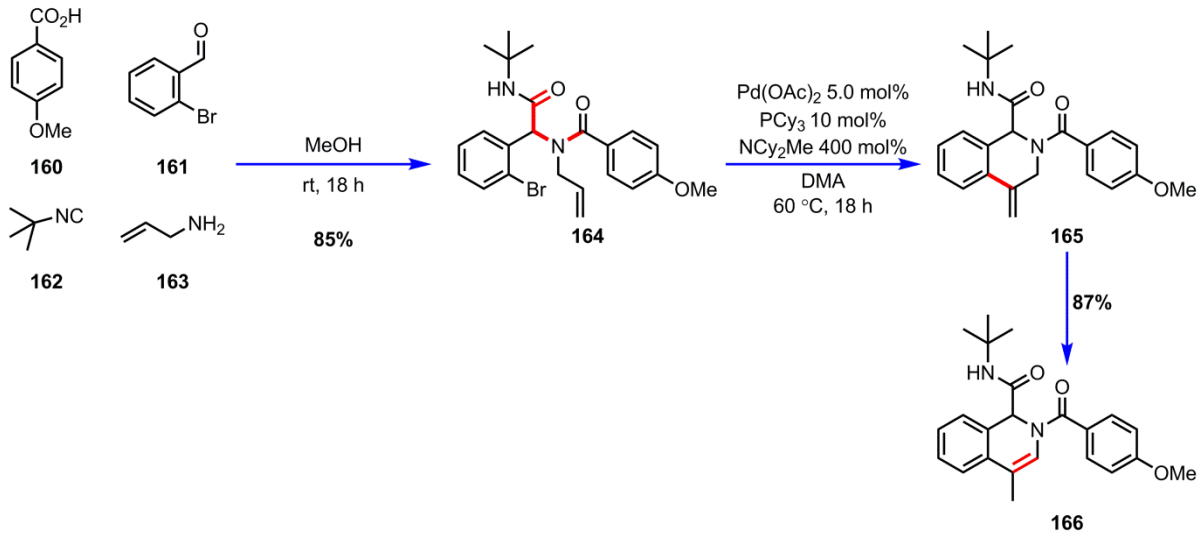
Myers and coworkers also published a multicomponent synthesis of isoquinolines, forming the C3-C4 and then the C1-N bonds in a one-pot operation.[162] Treatment of imine **154** with BuLi in TMP led to the formation of anion **155**. The authors then proposed that this anion attacked benzonitrile to give species **156**, which cyclised to species **157**. They then proposed an isomerisation to species **158**, presumably driven by the gain of extended conjugation. Upon addition of MeI, the anion was alkylated in the isoquinoline C4 position to give isoquinoline **159** on work up (**Scheme 52**). The protocol was shown to be applicable to a wide range of arenes, nitriles and electrophiles all in generally good yields.



Scheme 52: *Myers' multicomponent synthesis of isoquinolines*

A different multicomponent reaction was reported in 2004 by Yang and coworkers,[163] based upon the Ugi multicomponent[164] and Mizoroki-Heck reactions. The reaction began with an Ugi multicomponent reaction between carboxylic acid **160**, *ortho*halobenzaldehyde **161**, isocyanide **162** and allyl amine, **163**. This delivered Ugi product **164** in 85% yield (**Scheme 53**). Upon treatment of this Ugi product under reaction conditions for the Mizoroki-Heck reaction, a 6-*exo*-trig cyclisation took place, followed by β-hydride elimination to furnish intermediate **165**, which isomerised to the dihydroisoquinoline product **166** in good yield. The authors also showed that by moving the position of the halide from

ortho to the formyl group on the benzaldehyde to *ortho* to the carboxyl group on the acid, cyclisation could take place to furnish isoquinlones.



Scheme 53: *Synthesis of isoquinolines via the Ugi and Mizoroki-Heck reactions*

1.5.7 Outlook

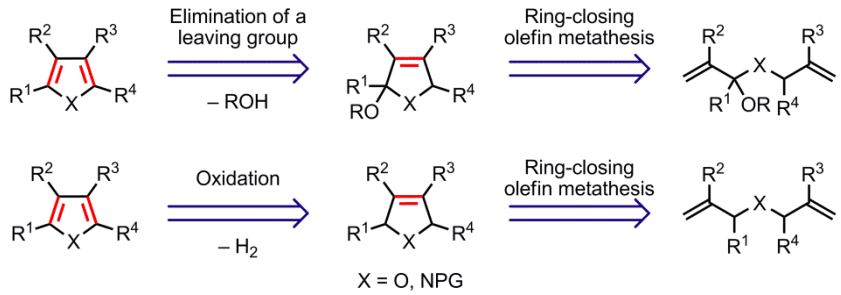
The advent of many novel synthetic approaches to isoquinolines in recent years has vastly increased the range of isoquinoline scaffolds readily accessible. Despite the discovery of many new routes, the variety of options available to synthesise an isoquinoline still lags significantly behind the range of options for many of the other common aromatic heterocycles. In addition, as all of these aforementioned reactions have their relative strengths and weaknesses, the search for new synthetic routes to isoquinolines (particularly those with general applicability, mild reaction conditions, a high functional group tolerance and an ability to access isoquinolines with electron-deficient carbocyclic rings) is a highly valuable endeavour.

Chapter 2: Results and Discussion

2.1 Palladium-catalysed oxidation of dihydrofurans and dihydropyrroles

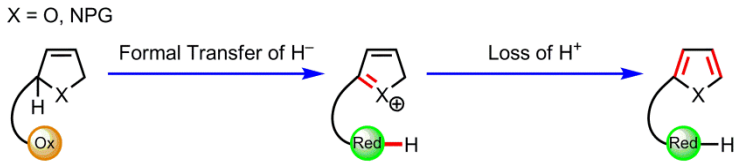
2.1.1 Concept

Ring-closing olefin metathesis has recently emerged as a powerful tool for the construction of aromatic heterocycles.[165] The cyclisation of linear precursors *via* such metathesis often delivers the heterocycle in the dihydro oxidation level, i.e. one level below that of the fully unsaturated system. Several strategies exist for the conversion of these intermediates to the aromatic systems. One common approach is to utilise the elimination of a pre-installed leaving group after the metathesis to introduce the final double bond.[166-170] However, perhaps the most obvious is a direct oxidation with an oxidising agent (**Scheme 54**). Occasionally this happens *in situ* under the reaction conditions,[171,172] driven presumably by the thermodynamic stability of the system gaining aromaticity. However, often more forcing oxidising agents such as $RuCl_3$[173] or oxygen gas with a metal catalyst are used.[174]



Scheme 54: *Ring-closing olefin metathesis strategies to aromatic heterocycles*

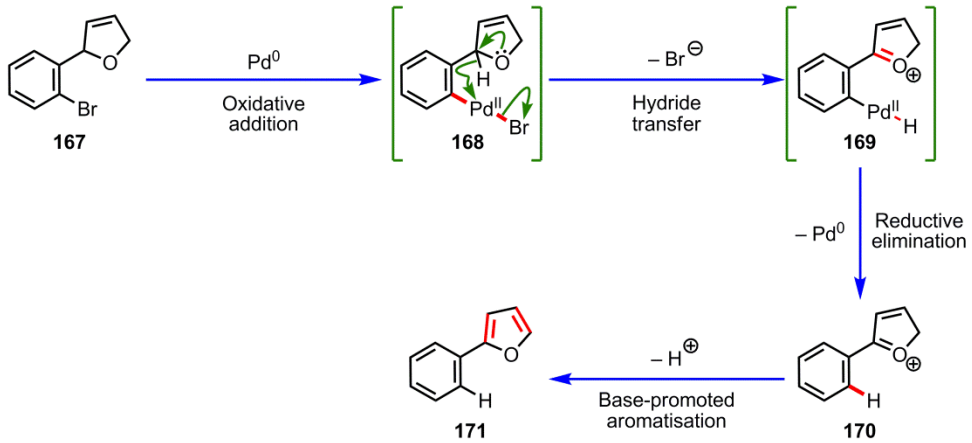
As a number of the direct oxidation methods in the literature were low yielding or required harsh conditions, a new variant of the oxidation method was desired whereby the oxidation could be rendered substrate controlled, i.e. the oxidising moiety would be tethered within the substrate itself. The oxidation involves removal of H_2, which can be imagined as the transfer of a hydride (onto a nearby oxidising moiety) followed by the loss of a proton (**Scheme 55**).



Scheme 55: *Substrate-controlled oxidation strategy*

It was envisaged that formal loss of a hydride could be achieved by the transfer of that hydride to a nearby Pd(II) oxidative addition complex. The resulting cationic heterocyclic species would then only require deprotonation with base to aromatise, and it was hoped that the resulting Pd(II) hydride would undergo reductive elimination, regenerating Pd(0), which would hence be catalytic.

Dihydrofuran **167**, bearing an *ortho*-bromophenyl group at the C2 position, was designed as the initial test substrate. Ample precedent from the known coupling chemistry of palladium suggested that oxidative addition of Pd(0) into the C-Br bond in **167** to generate Pd(II) intermediate **168** would be favourable (**Scheme 56**).[175]



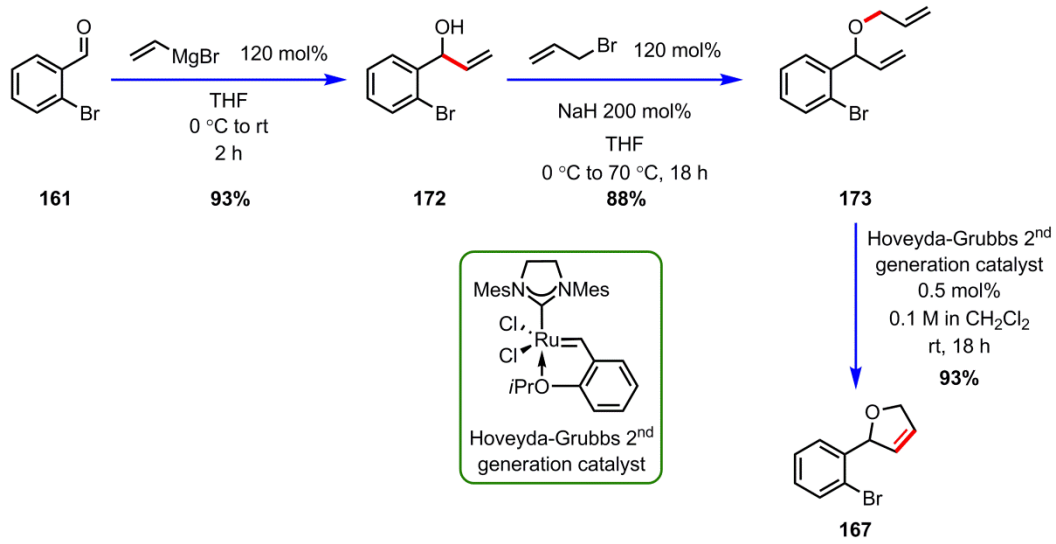
Scheme 56: *Palladium-catalysed oxidation strategy of **167** to **171***

It was then envisaged that a formal hydride transfer would occur to furnish Pd(II) hydride **169** (although the mechanism of this transformation may not be as simple as illustrated).[176,177] This transfer should be aided by the fact that the resultant cation would be benzylic, allylic and α to oxygen, and so low in energy. Reductive elimination of the Pd(II) hydride (again well-precedented in palladium catalysis, for example in the final step of the

Mizoroki-Heck reaction)[7] would give intermediate **170**, which would be expected to lose a proton under basic conditions to gain aromaticity and form furan **171**.

2.1.2 Initial screening

The initial test substrate dihydrofuran **167** was synthesised in three steps from 2-bromobenzaldehyde, **161**. Addition of vinyl magnesium bromide to a solution of **161** delivered allylic alcohol **172** in 93% yield (**Scheme 57**).



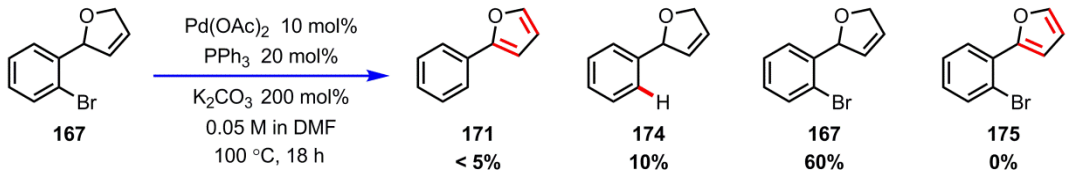
161 **93%** **172** **88%** **173** **167**

Scheme 57: *Synthesis of dihydrofuran **167***

Subsequent allylation of the alcohol with allyl bromide furnished allyl ether **173** in a very good yield of 88%. Allyl ether **173** was subjected to a ring-closing olefin metathesis reaction with Hoveyda-Grubbs 2nd generation catalyst. The reaction was performed at reasonably high dilution to discourage the formation of any polymeric side products. The reaction proceeded very well with a catalyst loading of just 0.5 mol%, delivering dihydrofuran **167** in a yield of 93%. The structure of **167** was confirmed by the appearance of only two olefinic multiplets in the ^{1}H NMR spectrum at 6.08-6.05 and 6.02-6.00 ppm.

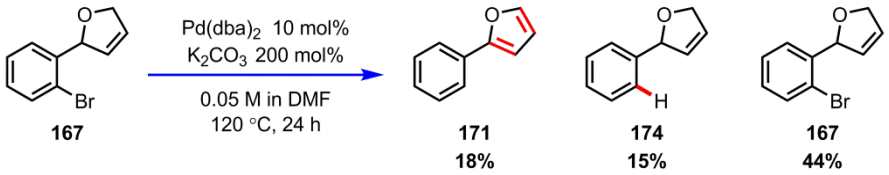
With dihydrofuran **167** in hand, attention turned to the palladium-catalysed oxidation. Dihydrofuran **167** was subjected to an initial set of oxidation conditions using $Pd(OAc)_2$ and

PPh_3 with K_2CO_3 as the base and in DMF solvent. Under these conditions, a very small amount (< 5% isolated yield) of the desired furan **171** was formed, along with some debrominated starting material **174** (10%), and a high proportion of starting material **167** was recovered (60%) (**Scheme 58**). No 2-(2-bromophenyl)furan, **175** was observed, strongly suggesting that the reduction of the C-Br bond to a C-H bond and the oxidation of the dihydrofuran to the furan were linked events. The presence of furan **171** was very clear in the ^{1}H NMR spectrum due to the distinctive double doublets from the protons at the C3 and C4 positions on the furan at 6.48 and 6.67 ppm respectively.



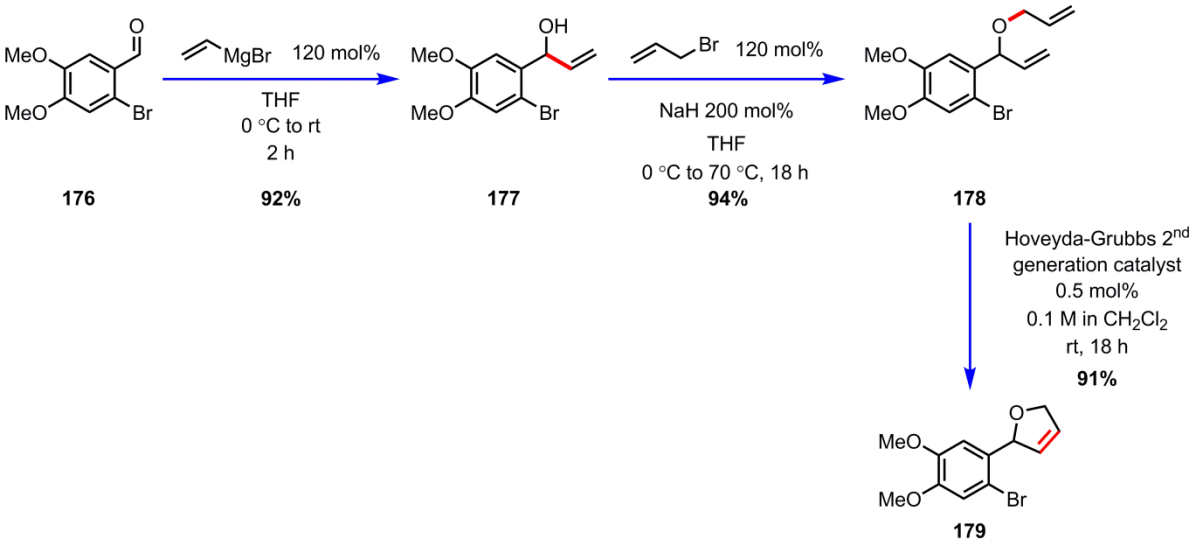
Scheme 58: *Initial conditions for the palladium-catalysed oxidation of dihydrofuran **167***

In a control reaction without any palladium, no furan **171** or debrominated starting material **174** were observed, suggesting that palladium was promoting this observed reactivity. In an attempt to boost the yield of furan a number of different phosphine ligands were screened in the reaction. However, the use of any other phosphine than PPh_3 led to no furan formation and large amounts of starting material recovery. This suggested that a relatively unligated palladium species may be necessary to promote the reaction. To examine this, the reaction was performed without a phosphine ligand (and a change of palladium source to $Pd(dba)_2$ to ensure that *in situ* reduction of Pd(II) to Pd(0) was not a problem without the phosphine). Under these conditions a 13% yield of furan **171** was obtained. The use of $Pd(dba)_2$ with phosphines still gave no furan, indicating that the oxidation state of the palladium source was not the issue in this reaction. Further screening showed that an increase in temperature to 120 °C and an increase in reaction time to 24 h led to a slight increase in yield, with now 18% of furan **171** being observed along with 15% debrominated starting material **174** and 44% recovered starting material **167** (**Scheme 59**).



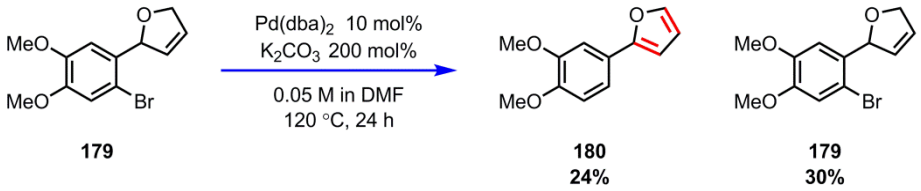
Scheme 59: *Improvements to the palladium-catalysed oxidation of dihydrofuran **167***

During these studies it was found that furan **171** was slightly volatile and so it was decided to continue the reaction screening with a more substituted dihydrofuran to eliminate this problem. It was also thought that an electron-rich benzene ring in the dihydrofuran precursor might help promote the reaction, particularly if the oxidation mechanism of the dihydrofuran began with the formal loss of a hydride to give a cationic intermediate. Dimethoxy-substituted dihydrofuran **179** was hence selected as the new target compound. It was synthesised in three steps from bromobenzaldehyde **176** in an analogous procedure to that for dihydrofuran **167** and all three steps proceeded in excellent yield (**Scheme 60**).



Scheme 60: *Synthesis of dihydrofuran **179***

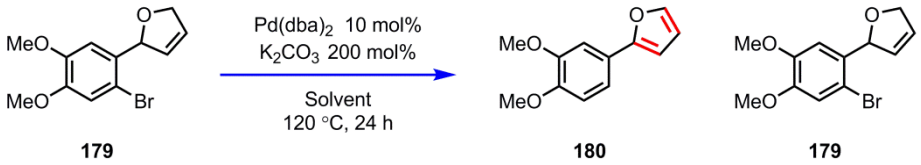
Dihydrofuran **179** underwent much cleaner conversion to furan **180** (24% yield), with none of the corresponding debrominated starting material observed (**Scheme 61**).



179 **180** **179**
24% **30%**

Scheme 61: *Oxidation of dihydrofuran **179** to furan **180***

Although the overall mass recovery from the reaction was disappointing, since the debrominated product had been eliminated it was decided to undertake more extensive screening on this system in an attempt to increase the conversion of **179** to **180**, and hopefully therefore the reaction yield and mass recovery as well. A variety of different solvents were examined first (**Scheme 62**).



179 **180** **179**

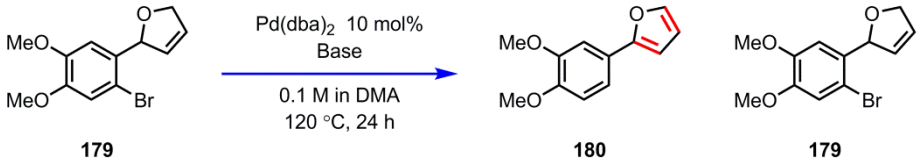
Scheme 62: *Solvent screen in the oxidation of dihydrofuran **179** to furan **180***

Entry	Solvent	Concentration	Isolated Yield of 180	Isolated Yield of 179
1	DMF	0.05 M	24%	30%
2	DMA	0.05 M	28%	27%
3	THF	0.05 M	0%	85%
4	1,4-Dioxane	0.05 M	0%	82%
5	MeCN	0.05 M	0%	80%
6	Benzene	0.05 M	0%	87%
7	Toluene	0.05 M	13%	38%
8	DMA	0.01 M	17%	32%
9	DMA	0.10 M	30%	15%
10	DMA	0.20 M	23%	11%

Table 1: *Solvent screen in the oxidation of dihydrofuran **179** to furan **180***

A screen of reaction solvent and concentration indicated that the reaction only proceeded well in DMF or DMA (**Table 1**, Entries 1 and 2), and that it failed completely in most other solvents (THF, 1,4-dioxane, MeCN and benzene), with only starting material being recovered (Entries 3-6). In toluene a reaction occurred, but the conversion was much lower

(Entry 7). As the highest yield was obtained in DMA solvent, some reactions were undertaken in DMA at different concentrations (Entries 8-10). It was found that an increase in concentration to 0.1 M led to an increase in yield of furan **180** to 30% (Entry 9). However, the total mass recovery was now only 45%, and it was thought that the electron-rich furan may not be stable at the high temperature of the reaction conditions. Resubjection of the furan to the reaction conditions and reisolation found that only 73% was recovered, indicating it was slowly degrading. However, it was hoped that further optimisation would lead to milder conditions that would reduce this problem. A screen of different bases in the reaction of **179** to **180** was then undertaken (**Scheme 63**).



179 **180** **179**

Scheme 63: *Base screen in the oxidation of dihydrofuran **179** to furan **180***

Entry	Base	Amount	Isolated Yield of 180	Isolated Yield of 179
1	K_2CO_3	200 mol%	30%	15%
2	Na_2CO_3	200 mol%	29%	21%
3	Cs_2CO_3	200 mol%	48%	0%
4	Cs_2CO_3	100 mol%	26%	12%
5	Cs_2CO_3	500 mol%	47%	0%
6	NCy_2Me	200 mol%	0%	54%
7	$NiPr_2Et$	200 mol%	15%	43%
8	NaO*t*Bu	200 mol%	26%	22%
9	KO*t*Bu	200 mol%	42%	0%
10	No base	-	0%	89%

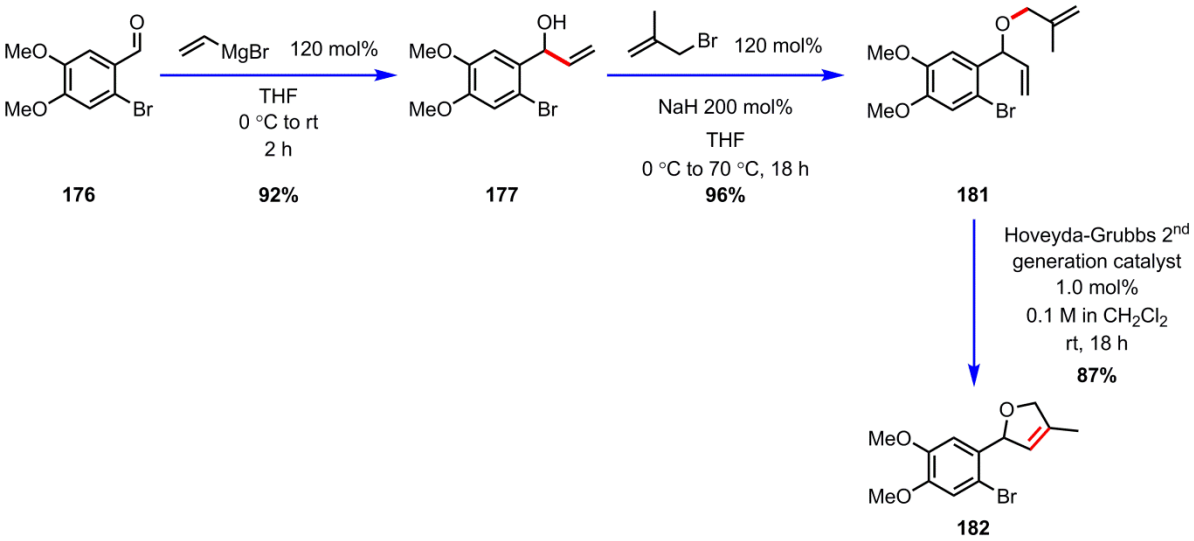
Table 2: *Base screen in the oxidation of dihydrofuran **179** to furan **180***

It was found that Na_2CO_3 gave a lower yield than K_2CO_3 (**Table 2**, Entries 1 and 2), but that Cs_2CO_3 performed much better (Entry 3), with a 48% isolated yield of **180** being obtained and no unreacted starting material remaining. It was found that 200 mol% of base was

necessary as reducing the amount to 100 mol% led to a significant reduction in yield (Entry 4). However, increasing the amount to 500 mol% did not lead to any further increase (Entry 5). Elsewhere, the *tertiary* amine bases NCy_2Me and $Ni Pr_2Et$ worked poorly (Entries 6 and 7). NaO*t*Bu was also reasonably poor (Entry 8), but KO*t*Bu gave better conversions, but not as good as Cs_2CO_3. The reaction did not proceed in the absence of base (Entry 10).

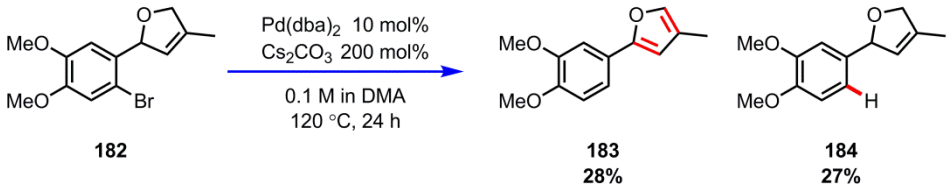
The high propensity of Cs_2CO_3 to promote this reaction may be due to its enhanced solubility in organic solvents compared to the other alkali metal carbonates and also the reduced ion pairing in solution. This is a well-established phenomenon for caesium cations in solution due to their large size.[178] Although the high conversion of **179** to **180** was now pleasing, the overall mass of material recovered from the reaction was low, often around 50%. It was thought possible that the dihydrofuran starting material might be undergoing Mizoroki-Heck[6,7] reactions leading to oligomerisation or polymerisation. However, it was thought more likely that decomposition of the furan product was the problem, possibly also *via* oligomerisation or polymerisation reactions.[179,180]

In an attempt to counteract this, it was decided to synthesise a more substituted dihydrofuran. Dihydrofuran **182**, bearing an additional methyl group at the C4 position was synthesised in a similar protocol to before, where 3-bromo-2-methylprop-1-ene was used in place of allyl bromide in the *O*-alkylation step (**Scheme 64**).



Scheme 64: *Synthesis of dihydrofuran **182***

It was also expected that the extra methyl group in **182** would further stabilise any cationic intermediate on the heterocyclic ring due to hyperconjugation and so hopefully also increase the rate of reaction. However, upon subjection of dihydrofuran **182** to the palladium-catalysed oxidation conditions, only a 28% yield of the desired furan **183** was obtained, with large amounts of debrominated starting material **184** also being recovered (**Scheme 65**).



Scheme 65: *Oxidation of dihydrofuran **182***

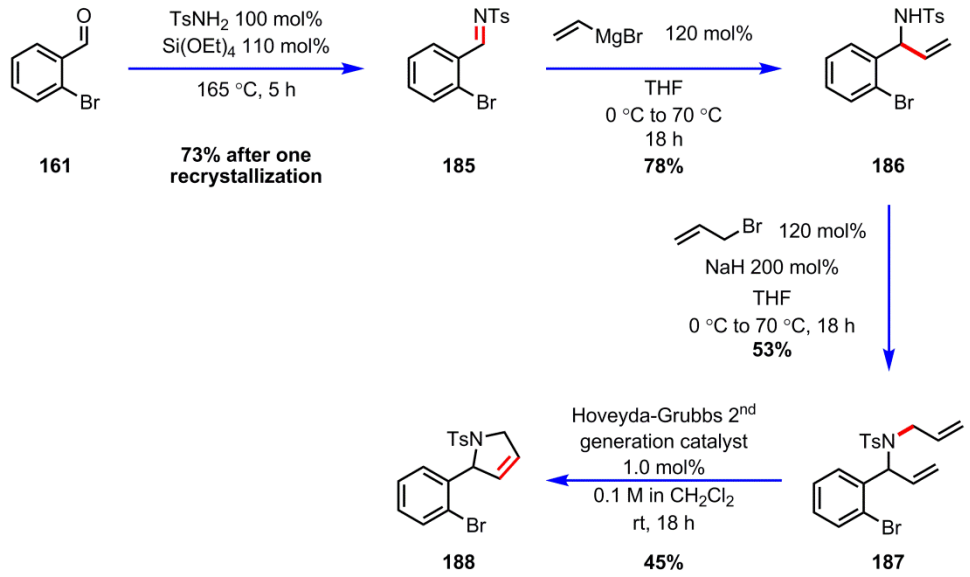
The yield of **183** was disappointing and gave certain insights into the reaction mechanism (*vide infra*). However, before examining the mechanism in more detail it was decided to further examine the scope of this methodology.

2.1.3 Oxidation of dihydropyrroles to pyrroles

So far only dihydrofurans had been oxidised to furans, however it was postulated that this route could be extended to the synthesis of other heterocyclic motifs. As dihydropyrroles

could also be accessed by the ring-closing olefin metathesis strategy, it was decided to investigate the conversion of dihydropyrroles to pyrroles. If successful, this would be an important advance due to the ubiquity of pyrroles in natural products and pharmaceuticals.[181]

Due to the high reactivity and polarity of unprotected pyrroles it was deemed necessary to protect the nitrogen atom of any dihydropyrrole precursor prior to attempting the oxidation reaction, and a sulfonamide protecting group was chosen to begin with. To this end, 2-bromobenzaldehyde, **161** was heated neat with *p*-toluenesulfonamide and tetraethoxysilane to furnish tosyl imine **185** in 73% yield (after one recrystallisation) (**Scheme 66**).[182]

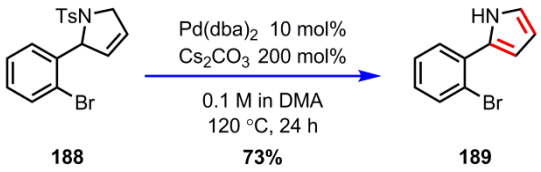


Scheme 66: *Synthesis of dihydropyrrole **188***

Addition of the vinyl group required more forcing conditions than for the analogous aldehyde, with the reaction requiring heating at reflux for 18 h. This delivered allyl sulfonamide **186** in a good yield of 78%. Allylation of the nitrogen atom proceeded less efficiently than for the corresponding alcohol to furnish *N*-allyl sulfonamide **187** in 53% yield. *N*-Allyl sulfonamide **187** underwent ring-closing olefin metathesis in a somewhat disappointing yield of 45% to deliver dihydropyrrole **188**, the low yield perhaps attributable to coordination of the nitrogen atom to the ruthenium, lowering the activity of the catalyst.

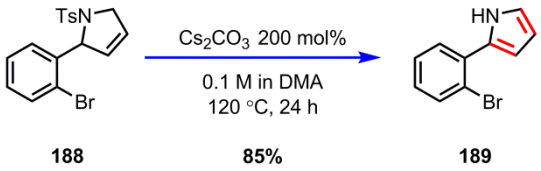
The structure of **188** was confirmed by the appearance of just two vinylic signals in the ^{1}H NMR spectrum as a multiplet from 5.72-5.69 ppm.

Upon subjection of dihydropyrrole **188** to the palladium-catalysed reaction conditions it was found that pyrrole **189** (which was obtained in 73% yield) still contained the bromine atom and had also lost its protecting group (**Scheme 67**).



Scheme 67: *Attempted oxidation of dihydropyrrole **188***

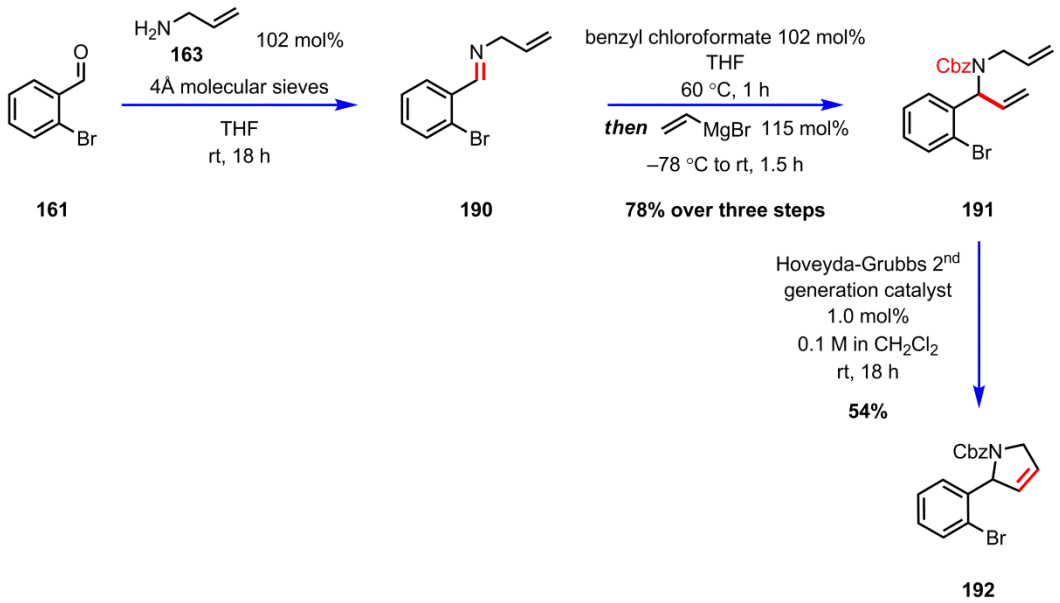
The structure of pyrrole **189** was confirmed by the presence of two quaternary aromatic signals in the ^{13}C NMR spectrum at 130.2 and 120.0 ppm, along with a consistent characteristic isotope pattern of the ^{79}Br and ^{81}Br isotopes in the mass spectrum. It was thought that at the high temperatures, an E2 elimination took place with the base deprotonating at the benzylic position with concomitant loss of the tosyl anion from the nitrogen. The resulting product had then presumably isomerised to the pyrrole driven by the gain in aromaticity. To confirm that this conversion of dihydropyrrole **188** to pyrrole **189** was just due to the basic reaction conditions, dihydropyrrole **188** was subjected to the reaction conditions without palladium. It was found that the same bromine-containing pyrrole **189** was obtained in 85% yield (**Scheme 68**).



Scheme 68: *Conversion of dihydropyrrole **188** to pyrrole **189** with base*

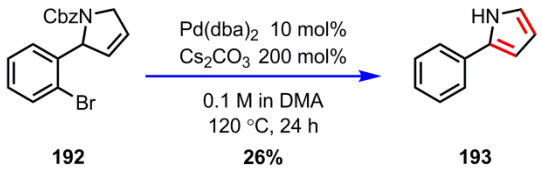
As the sulfonamide protecting group was not stable under the basic reaction conditions, it was decided to change the sulfonamide to a benzyl carbamate to help prevent a base-promoted elimination from competing with the palladium-catalysed oxidation. Using

the procedure of Sunderhaus *et al.*,[183] 2-bromobenzaldehyde, **161** was condensed with allyl amine, **163** in the presence of 4 Å molecular sieves to furnish allyl imine **190**. Imine **190** was not isolated but reacted on crude with benzyl chloroformate in THF. After 1 h at 60 °C the reaction was cooled to −78 °C before vinyl magnesium bromide was added. This furnished *N*-allyl carbamate **191** in a 78% yield over the three steps. The structure of **191** was confirmed by the signals from both the methine carbon attached to nitrogen and the methylene carbon attached to nitrogen (at 61.6 and 47.3 ppm respectively) in the ^{13}C NMR spectrum (**Scheme 69**). *N*-allyl carbamate **191** underwent ring-closing olefin metathesis to deliver dihydropyrrole **192** whose structure was confirmed by the appearance of just two olefinic signals (both multiplets) in the ^{1}H NMR spectrum at 5.94-5.90 and 5.87-5.85 ppm. The initial sample of dihydropyrrole **192** was strongly coloured and it was presumed that it was contaminated with ruthenium from the olefin metathesis catalyst or decomposition products thereof. Fortunately, following the work up procedure of Georg and coworkers,[184] where DMSO is added to decompose the catalyst into products that do not pass through silica gel, dihydropyrrole **192** was obtained as crystalline white prisms in a yield of 54%.



Scheme 69: *Synthesis of dihydropyrrole **192***

Subjection of dihydropyrrole **192** to the oxidation conditions delivered 2-phenylpyrrole, **193** in 26% yield, where the bromine atom had been removed and the carbamate protecting group had also been lost (**Scheme 70**). No 2-(2-bromophenyl)-pyrrole was detected.



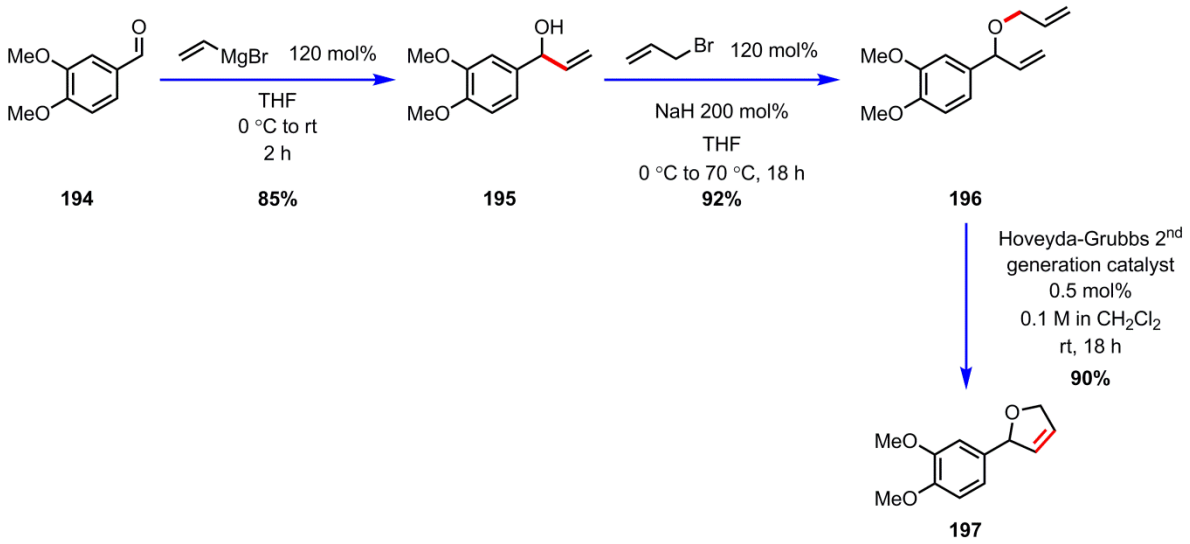
Scheme 70: *Oxidation of dihydropyrrole **192** to pyrrole **193***

The loss of the carbamate protecting group was confirmed by the presence of a broad singlet from the NH proton at 8.46 ppm in the ^{1}H NMR spectrum and the loss of the bromine atom confirmed by the symmetry in the phenyl ring in the product, resulting in only four signals in the ^{13}C NMR spectrum. It was thought that the palladium-catalysed oxidation occurred first, but then that this was followed by attack of a nucleophile at the carbamate carbonyl and subsequent loss of the pyrrole moiety (which would have a superior leaving group ability to that of the dihydropyrrole). The low yield of 26% was disappointing (no unreacted starting material remained at the end of the reaction), and it was thought that this might be because the free pyrrole was unstable under the reaction conditions. Resubjection of pyrrole **193** to the reaction conditions confirmed that this was the case, with only 53% recovered after a 24 h period. Due to the problems involved with synthesising pyrroles using this methodology it was decided to return to the dihydrofuran system and to undertake some preliminary investigations to gain insight into the mechanism of this reaction.

2.1.4 Mechanistic investigations

It was hoped that some understanding of the reaction mechanism would enable the design of a more potent catalytic system, thereby increasing the product yield and possibly leading to milder reaction conditions.

In order to determine whether the presence of a bromine atom was essential, dihydrofuran **197** was synthesised in three steps from benzaldehyde **194**. All three steps proceeded in excellent yield (**Scheme 71**).

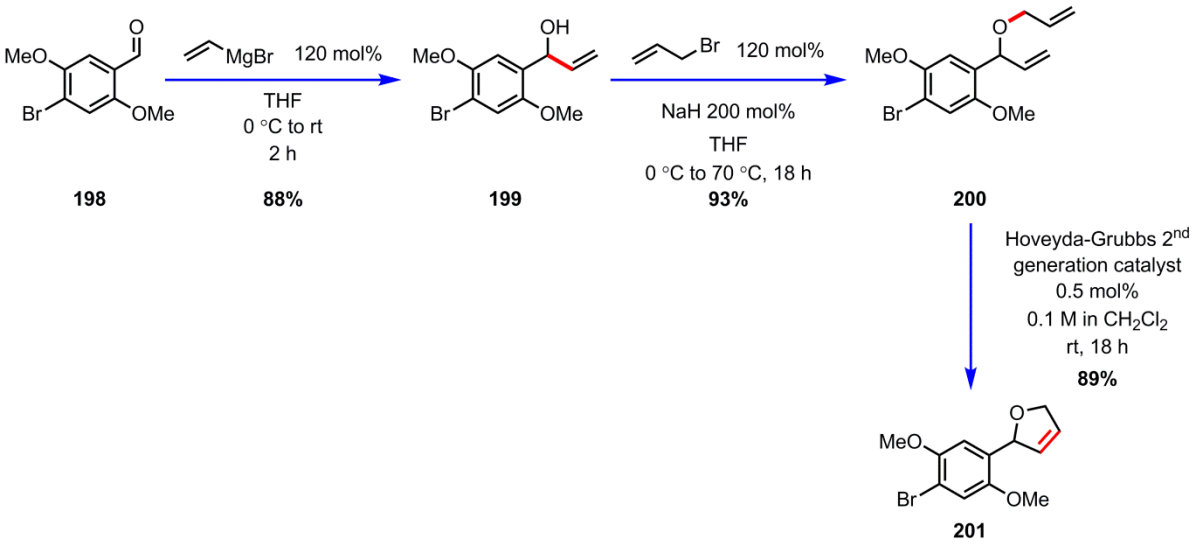


Scheme 71: *Synthesis of dihydrofuran **197***

Upon subjection of dihydrofuran **197** to the reaction conditions, no oxidation to furan **180** was observed, and dihydrofuran **197** was largely recovered unchanged (87%). This indicated that the presence of the bromine atom was essential in order for the oxidation of the dihydrofuran to the furan. It also eliminated the possibility of separate palladium-mediated dehalogenation of the aryl bromide and oxidation of the dihydrofuran to the furan (caused for example by dissolved oxygen in the reaction solvent *via* a radical oxidation pathway).

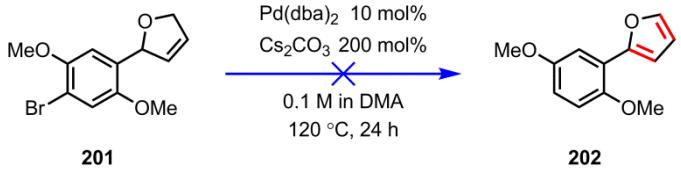
It was presumed that the first step of the reaction mechanism was insertion of the palladium into the C-Br bond. If the reaction was proceeding *via* an intramolecular pathway, then the position of the bromine atom would be crucial and presumably the reaction would only take place if the bromine was located *ortho* to the dihydrofuran. If however, the reaction was proceeding *via* an intermolecular mechanism then a palladium species inserted into a C-Br bond on any position of the benzene ring should be able to receive the hydride from the dihydrofuran moiety to cause the oxidation. To examine this, dihydrofuran **201** was

synthesised in three steps from 4-bromobenzaldehyde **198**, following the general procedure (**Scheme 72**). Again all steps proceeded in excellent yields.



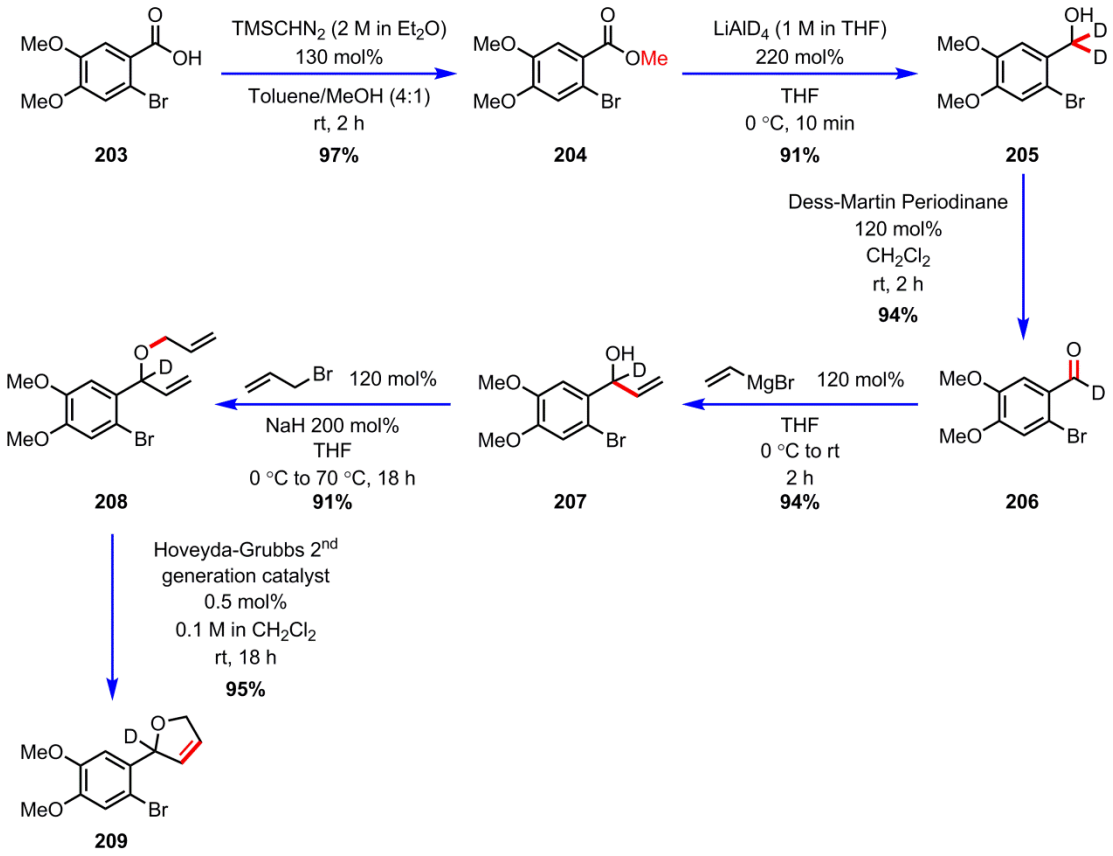
Scheme 72: *Synthesis of dihydrofuran **201***

Upon subjection of dihydrofuran **201** to the reaction conditions, no furan **202** was observed and instead 83% of dihydrofuran **201** was recovered (**Scheme 73**).



Scheme 73: *Attempted oxidation of dihydrofuran **201** to furan **202***

This provided strong evidence that the reaction was proceeding *via* an intramolecular mechanism. To try and further support this theory, it was decided to undertake a deuterium-labelling study where the hydrogen atom at the benzylic position of the dihydrofuran was replaced by deuterium. It could then be concluded whether the hydrogen atom in the new aryl C-H bond originated from the benzylic position of the dihydrofuran. To this end, deuterium-containing dihydrofuran **209** was synthesised in six steps from carboxylic acid **203** (**Scheme 74**).

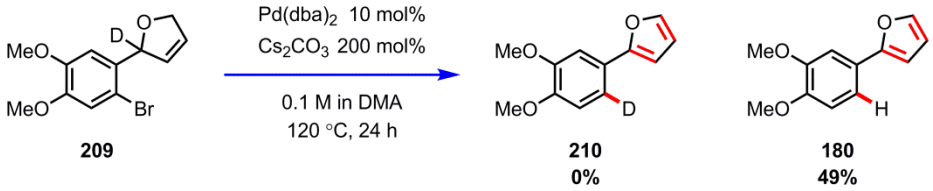


Scheme 74: *Synthesis of deuterium-containing dihydrofuran **209***

A solution of carboxylic acid **203** in toluene/MeOH was methylated with TMS-diazomethane in an excellent yield of 97% to furnish ester **204**. The deuterium atom which would be tracked in the key palladium oxidation was introduced by the reduction of the ester with lithium aluminium deuteride solution in THF to give benzylic alcohol **205** in high yield. The lithium aluminium deuteride reagent was quoted as 96% deuterated, and in benzylic alcohol **205** no signal was seen in the ^{1}H NMR spectrum in the region expected for a benzylic alcohol. Further confirmation was obtained in the ^{13}C NMR spectrum by the appearance of a distinctive quintet at 64.1 ppm. Oxidation of alcohol **205** to aldehyde **206** was accomplished with Dess-Martin Periodinane in excellent yield. Again the aldehydic proton signal in the ^{1}H NMR spectrum of **206** was absent but in the ^{13}C NMR spectrum the signal from the carbonyl carbon appeared as a triplet at 190.4 ppm. Aldehyde **206** was converted through to dihydrofuran **209** in three steps in the same manner as for the

non-deuterated example that had been synthesised previously. Confirmation that dihydrofuran **209** contained a deuterium atom at the benzylic centre was obtained from the ^{1}H NMR spectrum by the absence of the benzylic proton signal present in dihydrofuran **209** and also in the ^{13}C NMR spectrum where the benzylic carbon atom appeared as a triplet at 86.3 ppm.

With deuterium-labelled dihydrofuran **209** now in hand, it could be subjected to the palladium-catalysed oxidation conditions (**Scheme 75**).



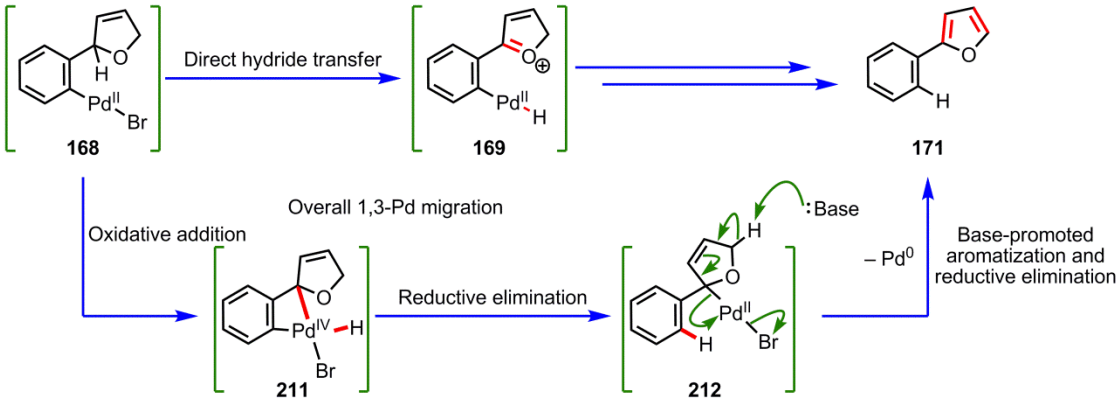
Scheme 75: *Deuterium labelling study*

However upon reaction, none of deuterated furan **210** was observed. Instead a 49% yield of the non-deuterated furan **180** was obtained. In the ^{1}H NMR spectrum of **180** from this reaction, the signal at 7.25 ppm (which is due to the proton on the carbon originally bearing the bromine atom in dihydrofuran **209**) did not show any reduction in intensity compared to the sample of furan **180** synthesised from the non-deuterated starting material. No other signals were reduced in intensity either. A ^{2}H NMR spectrum of the sample of **180** from this reaction also showed no signal.

The lack of deuterium transfer could be due to a number of reasons. It is known that palladium hydrides undergo fast exchange of the hydride bound to them in the presence of molecules bearing labile hydrogen atoms.[185] If the final step of the mechanism in this labelling experiment is a reductive elimination from the Pd(II) deuteride attached to the benzene ring, then exchange of this deuteride with extractable hydrogens from traces of water in the solvent or from HCO_3^- ions formed in the reaction may reduce the amount of

deuterium incorporated. This could also be coupled with a kinetic isotope effect in the reductive elimination step. However, it is unlikely that these processes would reduce the deuterium incorporation to zero. The reaction was repeated under more vigorously dry conditions where the DMA solvent had been pre-dried with 3 Å molecular sieves and where 3 Å molecular sieves were also added to reaction itself. This increased the reaction yield to 55% in the non-deuterated system. In the deuterated system a 53% yield was obtained, but again with no deuterium incorporation in the product.

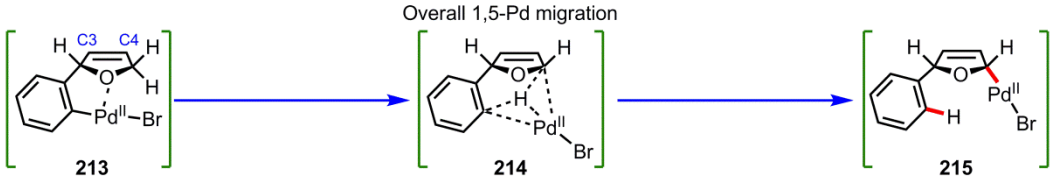
It had up to now been assumed that the benzylic hydrogen atom had been transferred to the benzene ring, either *via* a direct hydride transfer to palladium (analogous to the intermolecular transfer of a hydride to palladium in reductions with formic acid) or *via* a rearrangement process that involved a 1,3-Pd migration (**Scheme 76**).



Scheme 76: *Postulated mechanisms for transfer of the benzylic hydrogen atom*

Studies by Dedieu and coworkers indicated that in rearrangements involving a 1,3-Pd migration the energetically favoured pathway involved further oxidative addition to form a Pd(IV) complex such as **211**.[177] This was followed by reductive elimination to form the aryl C-H bond, which in this system would give Pd(II) intermediate **212**. Intermediate **212** could undergo a base-promoted aromatisation with concomitant reductive elimination from the Pd(II) to generate furan **171** and regenerate Pd(0). Both of these pathways would give deuterium incorporation.

However, it is possible that the C5 allylic hydrogen was transferred instead. Examination of molecular models indicated that once inserted into the C-Br bond, the molecule could adopt a conformation where the palladium atom could achieve close proximity to the allylic hydrogen. This conformation in particular could be stabilised by prior coordination of either the oxygen lone pair (such as in **213**) or the C3-C4 π-bond in the dihydrofuran to the palladium atom (**Scheme 77**).



Scheme 77: *Postulated mechanisms for transfer of the allylic hydrogen atom*

A 1,5-Pd migration could then take place that would furnish intermediate **215**, which presumably could undergo a base-promoted aromatisation with concomitant reductive elimination to generate the furan as in the previous case. The same studies by Dedieu indicated that this 1,5-Pd migration was more likely to take place *via* a concerted Pd(II) pathway (*via* **214** in this system). This mechanism would also explain why a lower yield of product furan was obtained with dihydrofuran **182** bearing a C4 methyl group, as the methyl group would presumably hinder coordination of the alkene π-bond to palladium and reduce the likelihood of the molecule adopting the reactive conformation. This would result in the Pd(II) insertion complex persisting for longer, possibly explaining why greater amounts of debrominated material were observed in this system. This mechanism may also explain why the reaction proceeded most efficiently in the absence of any phosphine ligand, as during the reaction a number of different atoms must coordinate to the palladium simultaneously which would require vacant coordination sites around the palladium centre.

A C5 deuterium-labelled dihydrofuran would enable this hypothesis to be examined, and this could presumably be synthesised with an appropriately-deuterated allyl bromide. The C5

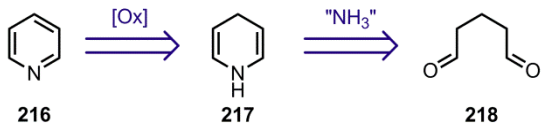
position could also be deliberately blocked to study whether this prevented the oxidation occurring. However, it was decided at this point to cease investigations in this project. Promising results had recently been obtained in another area of heterocyclic synthesis (*vide infra*) and it was felt that some of the limitations of this method that had been uncovered, such as the modest at best reaction yields on specific substrates, would limit its overall utility. However, the concept of achieving the oxidation of a dihydrofuran to a furan with an internal oxidising moiety had been successfully demonstrated.

2.2 Exploring isoquinoline synthesis by α-arylation

Work on the oxidation of dihydrofurans and dihydropyrroles had revealed an alternative method for manipulating the oxidation level of a heterocyclic scaffold post-cyclisation. However, if a synthetic route could access the fully unsaturated heterocyclic motif directly, it would likely be far more expedient than one requiring an oxidation after the cyclisation. The application of the ring-closing olefin metathesis reaction to the synthesis of aromatic heterocycles had demonstrated how modern metal-catalysed reactions enabled powerful new disconnections to be achievable. Thus, it was decided to examine the application of other metal-catalysed reactions in the *de novo* synthesis of other heterocycles.

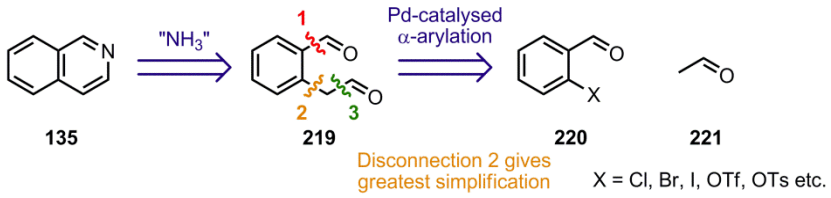
2.2.1 Retrosynthesis

It had been decided to target isoquinolines and to develop a new synthetic route towards the isoquinoline scaffold. It became helpful at this stage to consider one of the classic retrosynthetic strategies of a pyridine nucleus, **216**, whereby a 1,5-dicarbonyl **218** is condensed with a source of ammonia to form a dihydropyridine **217**, which is then oxidised to a pyridine (**Scheme 78**).



Scheme 78: *Classic retrosynthesis of a pyridine back to a 1,5-dicarbonyl*

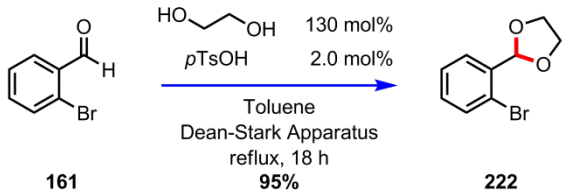
The addition of a fused benzene ring to the backbone of the 1,5-dicarbonyl formally increases the oxidation level by one, and so removes the need for a separate oxidation step in the synthesis. The appropriate 1,5-dicarbonyl **219**, (to condense with ammonia to form isoquinoline, **135**), can be further disconnected in several ways (**Scheme 79**).



Scheme 79: *Isoquinoline retrosynthesis via a 1,5-dicarbonyl*

In the view of the author, disconnection 2 gives the greatest simplification. Disconnection 1 still leaves an aryl fragment bearing two of the skeletal carbon atoms at different oxidation levels, whereas disconnection 3 leaves an aryl fragment with two *ortho*-substituted carbon substituents. Disconnection 2 leads back to an aryl component such as *ortho*-halobenzaldehyde **220** and a simple carbonyl compound possessing at least one alkyl substituent, **221**. It was postulated that these two components could be coupled in the synthetic sense by the palladium-catalysed α-arylation of an enolate. As this chemistry was most developed with aryl bromides, it was decided that the aryl component should be a bromide (i.e. X = Br).

As it was thought that an *ortho*-formyl group on the aryl bromide partner would not survive the α-arylation reaction conditions due to the likelihood of aldol condensation, it was deemed necessary to acetal-protect *ortho*-bromobenzaldehyde, **161**. The need to introduce a protecting group in chemical synthesis is always undesirable, but when necessary it should be noted that some protecting groups are more desirable than others. In this regard, acetals are among the 'best' protecting groups – only needing cheap reagents to both put on (a common alcohol solvent) and to take off (mild aqueous acid) and also offering robustness under reaction conditions (in this case the strong base needed to generate the enolate). As cyclic acetals offer additional stability over their acyclic counterparts and are easier to form, it was decided to react **161** with ethylene glycol. Refluxing **161** with a small excess of ethylene glycol and catalytic *para*-toluenesulfonic acid in toluene in a Dean-Stark apparatus for a period of 18 h led to full conversion to acetal **222** (**Scheme 80**).

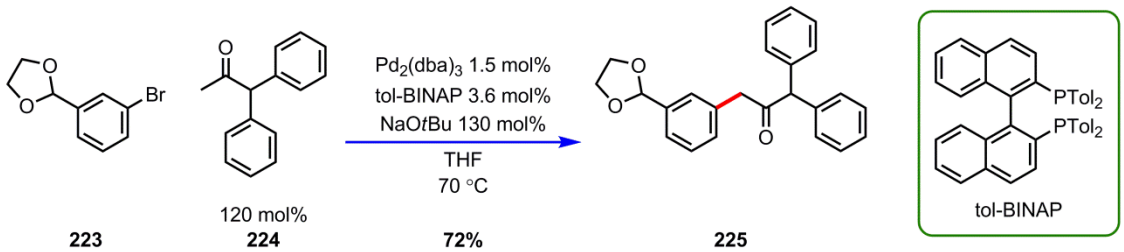


Scheme 80: *Synthesis of aryl bromide coupling partner **222***

This was evidenced in the ^{1}H NMR of the crude material by the complete disappearance of the aldehydic signal at 10.35 ppm and the emergence of a signal at 6.11 ppm, which was consistent with a proton at a benzylic centre flanked by two oxygen atoms. Upon purification, acetal **222** was isolated in 95% yield. Acetal **222** is actually itself a commercially available compound. However, as the acetals of more substituted aryl bromides are not commerically available, the fact that they could be made in a facile manner was an important result.

2.2.2 Exploring conditions for the α-arylation reaction

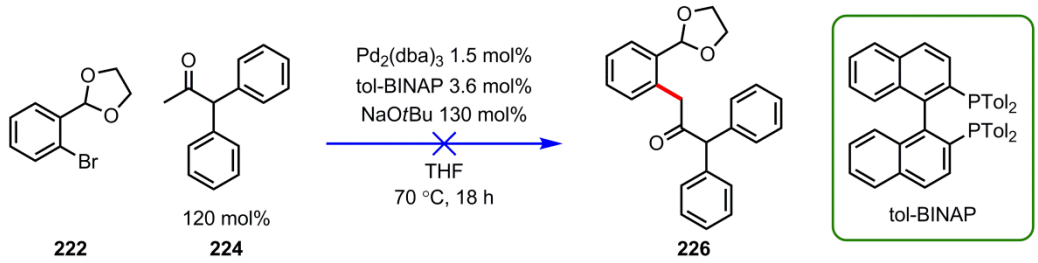
With acetal **222** in hand, attention turned to the α-arylation reaction itself. In Buchwald's seminal paper on the α-arylation of ketone enolates he demonstrated that acetal **223** (bearing a dioxolane acetal in the *meta*-position relative to the bromine atom) could be coupled with 1,1-diphenylacetone in 72% yield (**Scheme 81**).[26]



Scheme 81: *Buchwald's successful coupling of acetal **223***

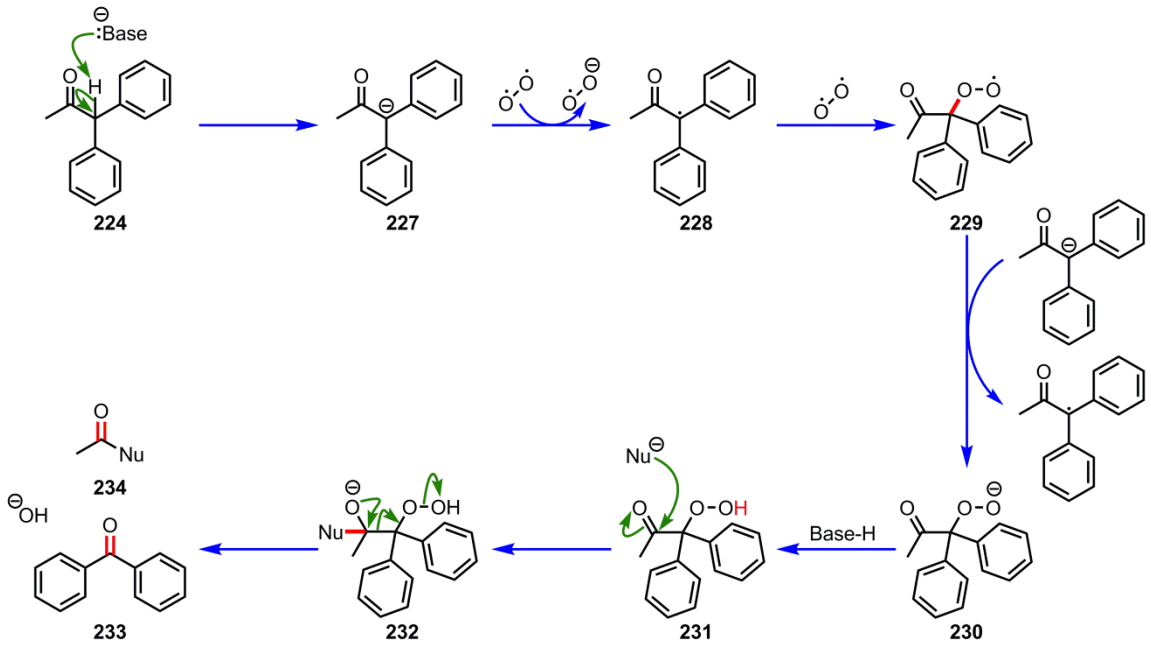
This was highly encouraging, illustrating that cyclic acetals were tolerated under the reaction conditions. However, it was anticipated that the coupling of *ortho*-acetal **222** would prove a far more challenging prospect due to increased steric hindrance and the possibility of intramolecular chelation of one of the acetal oxygen atoms to palladium. Nevertheless,

Buchwald's conditions were the obvious starting point and so acetal **222** was subjected to Buchwald's coupling protocol (**Scheme 82**). Analogously, 1,1-diphenylacetone was used as the ketone coupling partner as it had been shown to exhibit good selectivity for monoarylation, with no diarylated product observed.



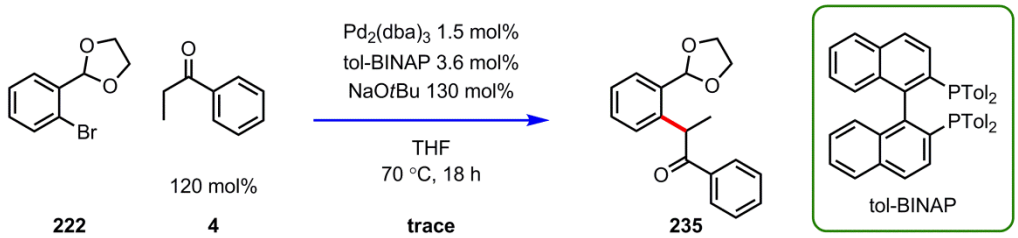
Scheme 82: *Attempted α-arylation of 1,1-diphenylacetone,* ***224***

Unfortunately, none of the product ketone **226** was observed. TLC analysis of the reaction mixture showed a number of spots and both the ^{1}H NMR and the ^{13}C NMR of the crude reaction mixture were complicated. However, significant amounts of benzophenone, **233**, could be detected. This unexpected product was postulated to have resulted from deprotonation of the doubly benzylic α-position in ketone **224** by the base to give enolate **227**, followed by single electron transfer between enolate **227** and oxygen to give radical **228** (**Scheme 83**). This then coupled with another oxygen molecule to give radical **229**, which could undergo single electron transfer with another molecule of enolate to give anion **230**. After protonation of anion **230** to form hydroperoxide **231**, attack of a nucleophile (such as another enolate) on the carbonyl of **231** would give tetrahedral intermediate **232** which presumably could collapse to give benzophenone, **233** and **234**. Although the reaction was performed under an atmosphere of argon provided by a balloon, it was likely that there was still oxygen dissolved in the THF solvent. Although it may have been possible to eliminate this product by applying more rigorously anoxic conditions, it was decided for ease of screening to switch to a ketone that would be less likely to suffer this problem.



Scheme 83: *Proposed mechanism to account for the formation of benzophenone,* ***233***

Propiophenone, **4**, had also been shown to couple well under Buchwald's conditions, albeit with a different aryl bromide, and was thought to be more tolerant to trace amounts of oxygen present in the reaction conditions. Upon attempting the coupling of **222** and **4** under these conditions, several new spots were observed by TLC analysis of the crude reaction mixture. In the mass spectrum (ESI^+) a peak was observed consistent with that of the product ion. In the ^1H NMR of the crude reaction mixture, a distinctive quartet was discernable at 5.12 ppm corresponding to the α-proton in product ketone **235** (**Scheme 84**).



Scheme 84: *Arylation of propiophenone under Buchwald's conditions*

However, due to the low amount formed, no purification was attempted. Upon changing the ketone partner to acetophenone, **7**, significantly more α-arylated product **236** was observed (**Scheme 85**, **Table 3**, Entry 1). Upon isolation and purification, a 43% yield was obtained.

The structure of **236** was confirmed by a characteristic singlet of relative intensity two at 4.51 ppm in the ^{1}H NMR spectrum from protons α to the carbonyl.

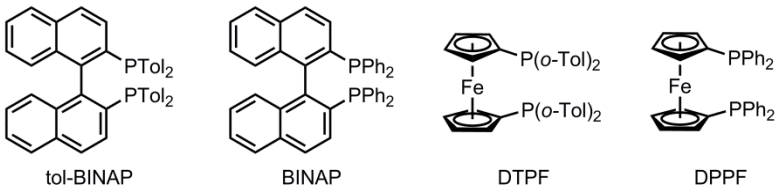
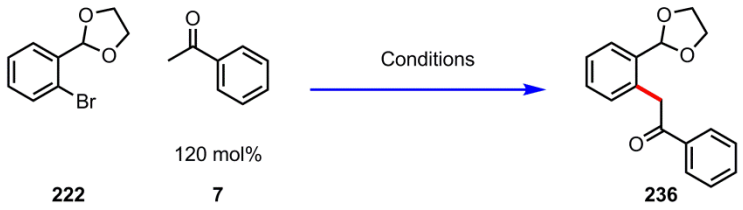


Figure 10: *Initial ligands employed in the α-arylation reaction*



Scheme 85: *Buchwald's and Hartwig's initial conditions in the α-arylation of acetophenone*

Entry	Pd Source	Ligand	Base	Conditions	Isolated Yield of 236
1	$Pd_2(dba)_3$ 1.5 mol%	tol-BINAP 3.6 mol%	NaO*t*Bu 130 mol%	THF, 70 °C, 18 h	43%
2	$Pd_2(dba)_3$ 1.5 mol%	BINAP 3.6 mol%	NaO*t*Bu 130 mol%	THF, 70 °C, 18 h	41%
3	$Pd(dba)_2$ 7.5 mol%	DTPF 9.0 mol%	KHMDS 220 mol%	THF, 70 °C, 18 h	trace
4	$Pd(dba)_2$ 7.5 mol%	DPPF 9.0 mol%	KHMDS 220 mol%	THF, 70 °C, 18 h	trace
5	$Pd(dba)_2$ 7.5 mol%	DTPF 9.0 mol%	NaO*t*Bu 220 mol%	THF, 70 °C, 18 h	34%

Table 3: *Buchwald's and Hartwig's initial conditions in the α-arylation of acetophenone*

It was decided to use acetophenone and aryl bromide **222** in a screen of a variety of other α-arylation conditions in an attempt to improve the yield. BINAP, also used by Buchwald in his seminal paper, gave similar amounts of product **236** to tol-BINAP (**Figure 10**, **Table 3**, Entry 2). Next it was decided to screen the conditions initially employed by Hartwig.[27] The use of DTPF (Entry 3) or DPPF ligands (Entry 4) with KHMDS gave only trace amounts of product and these reactions were not purified. However, the use of DTPF with NaO*t*Bu (Entry 5) did give a modest yield of 34%, but still less than for Buchwald's protocol.

In a later paper, Hartwig and coworkers reported that a catalytic system based on the monodentate P*t*Bu$_3$ ligand worked well.[33] In this reaction system, a 24% yield of product was

obtained (**Table 4**, Entry 1). The air-stable tetrafluoroborate salt of P*t*Bu$_3$ was employed rather than then air-sensitive P*t*Bu$_3$, as Fu and coworkers had previously demonstrated that this had similar activity once deprotonated *in situ*.[186]

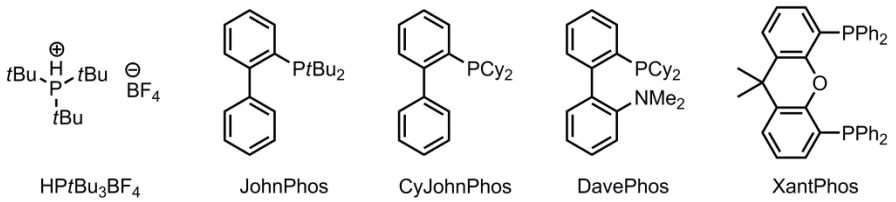
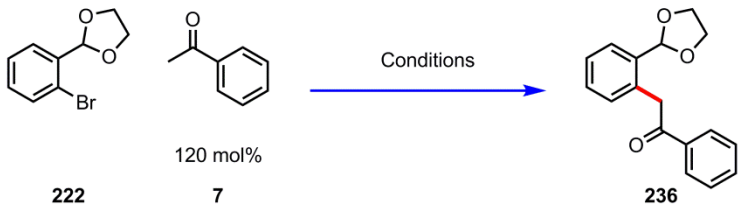


Figure 11: *Further ligands employed in the α-arylation reaction*



Scheme 86: *Further ligands and conditions employed in the α-arylation of acetophenone*

Entry	Pd Source	Ligand	Base	Conditions	Isolated Yield of 236
1	$Pd_2(dba)_3$ 1.5 mol%	HP*t*Bu$_3$BF$_4$ 7.2 mol%	NaO*t*Bu 250 mol%	THF, 70 °C, 18 h	24%
2	$Pd(OAc)_2$ 3.0 mol%	JohnPhos 6.0 mol%	NaO*t*Bu 130 mol%	Toluene, 70 °C, 18 h	0%
3	$Pd(OAc)_2$ 3.0 mol%	CyJohnPhos 6.0 mol%	NaO*t*Bu 130 mol%	Toluene, 70 °C, 18 h	0%
4	$Pd(OAc)_2$ 3.0 mol%	DavePhos 6.0 mol%	NaO*t*Bu 130 mol%	Toluene, 70 °C, 18 h	0%
5	$Pd(OAc)_2$ 3.0 mol%	JohnPhos 6.0 mol%	NaO*t*Bu 130 mol%	THF, 70 °C, 18 h	15%
6	$Pd(OAc)_2$ 3.0 mol%	CyJohnPhos 6.0 mol%	NaO*t*Bu 130 mol%	THF, 70 °C, 18 h	Trace
7	$Pd(OAc)_2$ 3.0 mol%	DavePhos 6.0 mol%	NaO*t*Bu 130 mol%	THF, 70 °C, 18 h	9%
8	$Pd_2(dba)_3$ 1.5 mol%	XantPhos 3.6 mol%	NaO*t*Bu 130 mol%	Toluene, 70 °C, 18 h	0%
9	$Pd_2(dba)_3$ 1.5 mol%	XantPhos 3.6 mol%	NaO*t*Bu 130 mol%	THF, 70 °C, 18 h	56%

Table 4: *Further ligands and conditions employed in the α-arylation of acetophenone*

Buchwald then also reported that bulky, electron-rich ligands with a biphenyl backbone (such as JohnPhos, CyJohnPhos and DavePhos) possessed high activity in α-arylation reactions.[42] When these conditions were applied to this system, no product was obtained (Entries 2-4). However, the reactions with these ligands had all employed toluene as a reaction solvent, as opposed to THF which had been used in all previous examples (Buchwald had not used these ligands with THF in his publication). When these ligands were used with THF, low yields of product were seen (Entries 5-7), where perhaps the increased polarity of THF in comparison to toluene promoted the desired reactivity. In the same paper, Buchwald had also reported that the bidentate ligand XantPhos was efficient at promoting certain classes of α-arylation reaction (those where the ketone possessed both an enolisable methyl and methylene group and those where electron-deficient aryl bromides were employed). In this system it proved ineffective with toluene as a reaction solvent (Entry 8), but gave a yield of 56% with THF (Entry 9).

Buchwald and coworkers later reported the high efficiency of the bulky electron-rich monophosphines XPhos and *t*BuXPhos (**Figure 12**) in the amination of aryl sulfonates,[187] and then later showed these to be effective ligands in the α-arylation of ketones with aryl sulfonates.[188] When applied to this system, XPhos gave a yield of 29% (**Table 5**, Entry 1) and *t*BuXPhos a yield of 17% (Entry 2). In 1998, Hartwig and coworkers had reported that sterically hindered chelating alkyl phosphines such as D*t*BPF gave large rate accelerations in the palladium-catalysed amination of aryl bromides.[36] Hartwig later showed that the D*t*BPF ligand was also highly active for enolate arylation,[33,189] in some cases giving turnovers of 20,000 at 70 °C. When the D*t*BPF ligand was applied in this system, a very high yield of 78% of α-arylated product **236** was obtained (Entry 3).

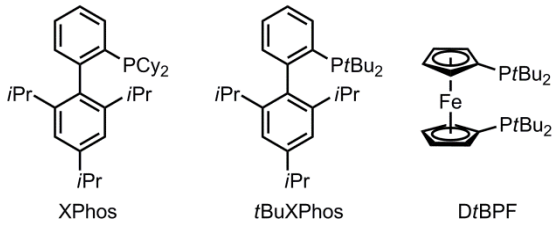
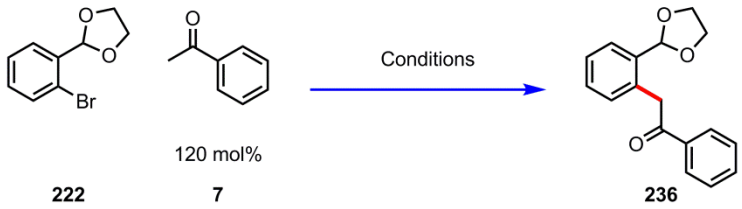


Figure 12: *XPhos, tBuXPhos and DtBPF ligands*



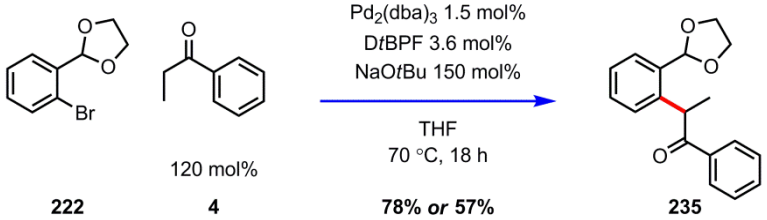
Scheme 87: *Screening of XPhos, tBuXPhos and DtBPF ligands in the α-arylation of acetophenone*

Entry	Pd Source	Ligand	Base	Conditions	Isolated Yield of 236
1	$Pd_2(dba)_3$ 1.5 mol%	XPhos 7.2 mol%	NaO*t*Bu 130 mol%	THF, 70 °C, 18 h	29%
2	$Pd_2(dba)_3$ 1.5 mol%	*t*BuXPhos 7.2 mol%	NaO*t*Bu 130 mol%	THF, 70 °C, 18 h	17%
3	$Pd_2(dba)_3$ 1.5 mol%	D*t*BPF 3.6 mol%	NaO*t*Bu 150 mol%	THF, 70 °C, 18 h	78%

Table 5: *Screening of XPhos, tBuXPhos and DtBPF ligands in the α-arylation of acetophenone*

2.2.3 Reaction optimisation

The D*t*BPF ligand had been by far the most successful and so it was decided to test it in the α-arylation of propiophenone, which seemed to be a far more challenging ketone to α-arylate. When the α-arylation of propiophenone was first carried out with the D*t*BPF ligand, a 78% yield of α-arylated product was obtained (**Scheme 88**). However, somewhat surprisingly, a repeat of the exact same reaction conditions only delivered a 57% yield of product.

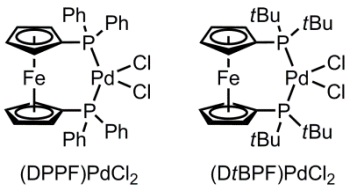


Scheme 88: *α-Arylation of propiophenone with **222** using DtBPF*

It was known in the literature for the case of D*t*BPF catalytic systems that complex equilibria existed in solution between various ligated species, with zero, one or two D*t*BPF ligands coordinated to the palladium centre in either a monodentate or a bidentate fashion.[41] It was hence postulated that the reaction might be extremely sensitive to the exact metal to ligand ratio. As these screening reactions had been performed on a *circa* 40 mg scale of aryl bromide, very low amounts of catalyst and ligand had to be measured out, giving the potential for quite large percentage errors in the metal to ligand ratio.

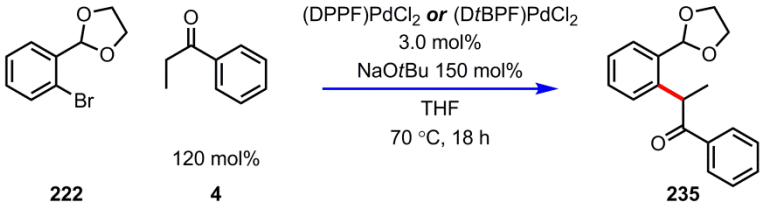
In 2004, Colacot reported that the Pd(II) complex, (D*t*BPF)$PdCl_2$ could itself be utilised as an air-stable Pd(II) precursor for Suzuki reactions,[40] with the active Pd(0) complex being formed *in situ*. Colacot then later reported that this same complex could be used as a highly active, air-stable pre-catalyst in the α-arylation of ketones.[39] The formation of the active Pd(0) species in this reaction system may occur from two enolates displacing the two chlorides on the palladium centre and then a reductive elimination between the two of them, or from the displacement of one chloride by an enolate, a β-hydride elimination and then a reductive elimination of HCl.

The now commercially available pre-catalysts (DPPF)$PdCl_2$ and (D*t*BPF)$PdCl_2$ (**Figure 13**) were thus applied to this system. A loading of 3.0 mol% of palladium was used, as before, and 150 mol% of NaO*t*Bu was used as the base (**Scheme 89**). To ensure that consistent results were being obtained, three separate runs were carried out with both preformed catalysts. The yields from these runs were in very good agreement with each other, suggesting that the previous source of inconsistency had been eliminated (**Table 6**). The (DPPF)$PdCl_2$ catalyst gave reasonable yields of α-arylated product and the (D*t*BPF)$PdCl_2$ catalyst gave excellent yields, averaging at 82%.



(DPPF)$PdCl_2$ (D*t*BPF)$PdCl_2$

Figure 13: *Preformed catalysts employed*



222 **4** **235**

Scheme 89: *Using preformed catalysts in the α-arylation of propiophenone*

Entry	Pd Source	Run 1	Run 2	Run 3	Average
1	(DPPF)$PdCl_2$	49%	49%	51%	50%
2	(D*t*BPF)$PdCl_2$	82%	81%	83%	82%

Table 6: *Using preformed catalysts in the α-arylation of propiophenone*

In the screening thus far, the amount of base used had been determined by which publication the procedure had been taken from, with different authors choosing anything from a slight excess to a significant excess. Prashad *et al.* had shown that excess base was important in certain cases to suppress diarylation.[29] Excess base often also increased product yield and was never observed to have a detrimental effect on yield. This is because the product of the α-arylation reaction contains a more acidic proton than the remainder of the ketone starting material and hence excess base is required to ensure that all of the starting ketone can fully be deprotonated. Hence, it was decided to increase the amount of base in this system up to 250 mol%. In another procedural change, reactions thus far had been performed in a resealable reaction tube, sealed with a rubber septum and under an atmosphere of argon provided by a balloon and needle. As some of the ketone partners were reasonably volatile, it was decided to set the reaction up under a septum, but to then replace the septum with a screw cap prior to putting the reaction on to heat. With these procedural modifications, excellent yields of product were obtainable (**Table 7**). Even with a low catalyst loading of

0.5 mol%, a good yield of product was attained (Entry 1). This could be slightly improved by increasing the amount of ketone (Entry 2). With 2.0 mol% catalyst, an 82% yield of product was achieved (Entry 3), which could be pushed up to 89% with 5.0 mol% catalyst and 200 mol% ketone (Entry 5).

Entry	Cat. Loading	Ketone	Time	Isolated Yield of 235
1	0.5 mol%	120 mol%	18 h	71%
2	0.5 mol%	200 mol%	18 h	74%
3	2.0 mol%	120 mol%	18 h	82%
4	2.0 mol%	200 mol%	18 h	83%
5	5.0 mol%	200 mol%	18 h	89%

Table 7: *Effect of catalyst loading in the optimised (DtBPF)PdCl$_2$ system with propiophenone*

It should be noted that applying the optimised α-arylation reaction conditions to the coupling of propiophenone with the unprotected 2-bromobenzaldehyde, **161** gave a complex mixture of products, with no α-arylated product detectable. Hence, the need to protect the formyl group during the α-arylation reaction was justified.

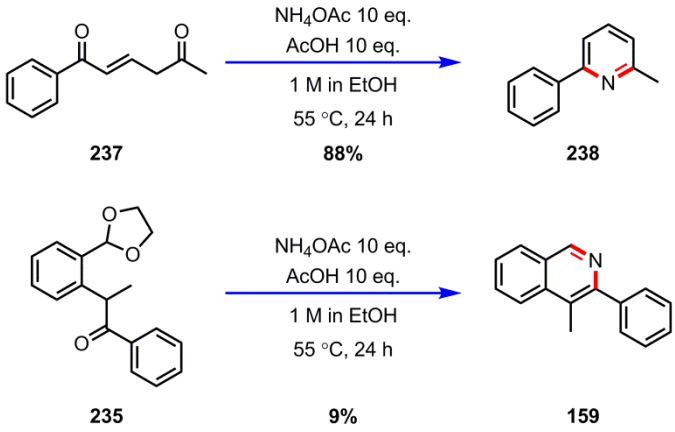
Before fully exemplifying the scope of the two partners for the α-arylation reaction (*vide infra*), it was decided to first focus upon optimising the cyclisation conditions.

2.2.4 Optimisation of the cyclisation conditions

With large amounts of intermediate **235** in hand, attention then turned towards cyclising to isoquinoline **159**. The exact mechanism by which substrate **235** would cyclise was not known, but it was presumed that the acetal-protected benzaldehyde would first need to be hydrolysed back to the free carbonyl form, followed by formation of an imine from one of the two carbonyls, attack of this nitrogen onto the other carbonyl carbon and then loss of water and aromatisation to give the isoquinoline. The reaction conditions thus needed a source of ammonia to provide the nitrogen atom and a source of aqueous acid to hydrolyse

the acetal. However, other factors such as solvent, temperature and concentration were thought to be important. For example, a greater proportion of water in the solvent mixture would likely favour acetal hydrolysis, but as the substrate is very lipophilic, also decrease substrate solubility.

Recent work in the group had demonstrated the cyclisation of unsaturated 1,5-dicarbonyls (which were assembled *via* olefin cross-metathesis) to form pyridines (**Scheme 90**).[190] Linear precursor **237** was converted in high yield to pyridine **238** by treatment with an NH_4OAc/AcOH mixture in EtOH solvent. As these conditions had been optimised for similarly lipophilic molecules, they were a good starting point for the conversion of intermediate **235** into the isoquinoline. However, upon treatment of **235** with these conditions, a disappointingly low yield of 9% of isoquinoline **159** was obtained.

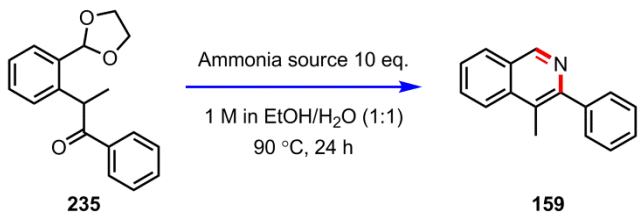


Scheme 90: *Donohoe's conditions for pyridine synthesis and application to isoquinolines*

The presence of isoquinoline **159** was very easy to detect in the ^{1}H NMR spectrum of the crude reaction mixture due to the characteristic singlet from the C1 proton at 9.22 ppm, in an otherwise clear region of the spectrum. Analysis of the mass spectrum showed a very strong peak at 220.1, consistent with the mass of the protonated isoquinoline. Upon purification, all other data for **159** matched that in the literature, confirming its synthesis. Hence, the postulated synthetic route was shown to be possible, and work began on optimising the deprotection/aromatisation sequence.

Further analysis of the initial attempt to cyclise intermediate **235** showed that most of the rest of the mass remaining at the end of the reaction was unreacted starting material, so it seemed that the hydrolysis of the acetal was the limiting step. Although no water was added to the initial reaction mixture, the use of solvent grade EtOH and AcOH meant there would have been some present in the reaction. The deliberate addition of more water (up to 1:1 EtOH/H_2O) in an effort to increase the rate of acetal hydrolysis did not lead to any improvement in yield. Increasing the reaction temperature to 90 °C led to an improvement to 29% yield of **159** after 24 h, but the majority of the mass recovered was still unreacted starting material.

It was postulated whether the reaction mixture was acidic enough to deprotect the acetal. As the reaction contained both AcOH (a weak acid) and NH_4OAc (the salt of a weak acid) it would be a buffered solution. The pH of this buffer would depend on the relative pK_as of the components: AcOH (4.76) and NH_4^+ (9.25), both in H_2O, 25 °C. As pK_a values are temperature and solvent dependent, it was decided to measure the pH of the reaction mixture at reaction temperature with pH paper. This was found to be the same as at room temperature and was only marginally more acidic than pH 7. In an effort to determine whether this was the problem, a number of other ammonia sources were screened (**Scheme 91**). As some of these other sources of ammonia were considerably less soluble in EtOH, a 1:1 mixture of EtOH/H_2O was chosen as the solvent mixture throughout in addition to a high temperature to ensure maximum conversion.



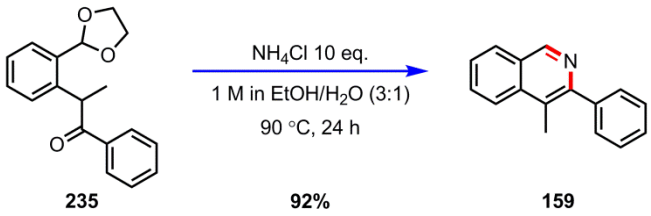
Scheme 91: *Screening of different ammonia sources for conversion to isoquinoline **159***

Depending on the source of ammonia chosen, the pH of the resulting solution was significantly different (pH measurements of solutions taken with pH paper at room temperature) (**Table 8**). The use of NH_4OAc (Entry 1) gave no isoquinoline **159**, neither did the more basic solutions of NH_4HCO_3 or NH_4OH (Entries 2 and 3), as expected. The use of an $(NH_4)_2SO_4$ solution (Entry 4) worked well, giving 63% of **159**. This solution has a pH of 5.5. The slightly more acidic solution of NH_4Cl (Entry 5) worked even better, delivering **159** in an excellent yield of 84%. As no commonly available sources of ammonia gave solutions that were very acidic, solutions of pH 3 and pH 1 (Entries 6 and 7) were obtained by further acidifying the NH_4Cl solution with HCl. These both gave high yields, although slightly less than at pH 5. At pH 1 a few other side products became observable by TLC, but these were not identified.

Entry	Source of Ammonia	pH at rt	Isolated Yield of 159
1	NH_4OAc	7.0	0%
2	NH_4HCO_3	9.0	0%
3	NH_4OH	12.0	0%
4	$(NH_4)_2SO_4$	5.5	63%
5	NH_4Cl	5.0	84%
6	NH_4Cl/HCl	3.0	81%
7	NH_4Cl/HCl	1.0	79%

Table 8: *Screening of different ammonia sources for conversion to isoquinoline **159***

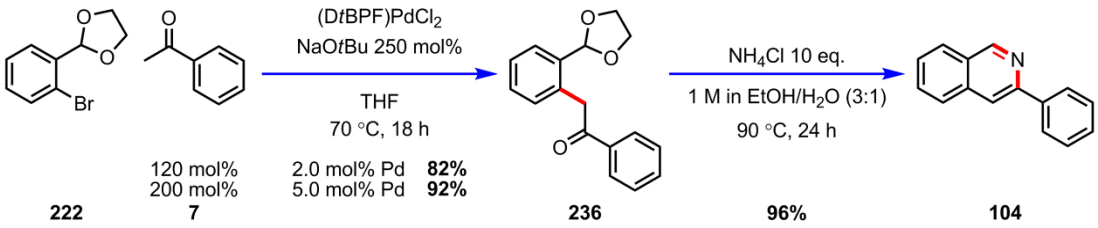
It was observed that substrate **235** was not completely soluble in the reaction solvent mixture at room temperature. In an effort to improve this, the solvent ratio was changed to 3:1 EtOH/H_2O, this being the proportion of water needed to fully dissolve the NH_4Cl to maintain a solution of 1 M concentration. Under these conditions an excellent yield of 92% of isoquinoline **159** was obtained (**Scheme 92**).



Scheme 92: *Optimised conditions for conversion to isoquinoline **159***

As the acetal protecting group was easy to install, survived fully intact during the α-arylation reaction and could be deprotected *in situ* during the aromatisation step, it had fulfilled the requirements of an ideal protecting group.

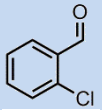
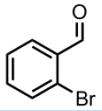
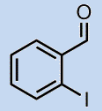
The optimised reaction sequence was subsequently tested with acetophenone as the ketone coupling partner (**Scheme 93**). The α-arylation reaction worked in excellent yield (82% with a 2.0 mol% loading of Pd and 92% with a 5.0 mol% loading of Pd) to give intermediate **236**. This intermediate cyclised in 96% yield, delivering isoquinoline **104**.



Scheme 93: α-*Arylation of acetophenone and cyclisation*

2.2.5 Aryl chlorides and iodides

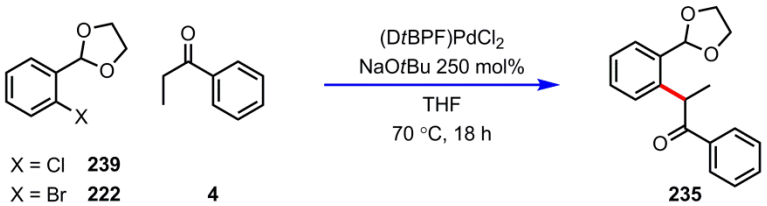
With the coupling of aryl bromide **222** now working well, it was decided to examine whether this procedure would also work with aryl chlorides and iodides. Most coupling reactions that work for aryl bromides do also work for aryl chlorides and iodides, although aryl chlorides are often far more challenging substrates. The benefits of extending this methodology to include aryl chlorides can be clearly seen from a comparison of the cost of the unsubstituted *ortho*-halobenzaldehyde starting material and the number of commercially available substituted variants of each of the *ortho*-halobenzaldehydes (**Table 9**).

Aldehyde	Cost of parent aldehyde per mole[a]	Commercially available substituted variants[b]
	£7.18	1614
	£106	731
	£10,900	174

[a]Based on the average price from the suppliers Sigma Aldrich and Alfa Aesar; [b]Based on a search of commercially available compounds on SciFinder®

Table 9: *Availability of different ortho-halobenzaldehydes*

The requisite aryl chloride and aryl iodide starting materials, **239** and **240** respectively, were synthesised from the corresponding benzaldehydes in an analogous manner to aryl bromide **222**, in 93% and 87% yields respectively. Under the optimised α-arylation reaction conditions, aryl iodide **240** gave a yield of 79% when coupled with propiophenone (**Table 10**, Entry 2), comparable to that of aryl bromide **222** (Entry 1).



Scheme 94: *Reactivity of different aryl halides with propiophenone*

Entry	X	Cat. Loading	Ketone	Isolated Yield of 235
1	Br	2.0 mol%	120 mol%	82%
2	I	2.0 mol%	120 mol%	79%
3	Cl	2.0 mol%	120 mol%	14%
4	Cl	5.0 mol%	200 mol%	30%

Table 10: *Reactivity of different aryl halides with propiophenone*

However, aryl chloride **239** was far more sluggish to react, giving only a 14% yield of product under identical conditions (Entry 3). Even under conditions with a higher catalyst loading and more ketone, only a 30% yield of product was obtained (Entry 4).

At this junction, the author was grateful to receive a donation of six different palladium pre-catalysts from Johnson Matthey (**Figure 14**) that had shown high activity in the α-arylation of aryl chlorides or in other coupling reactions of aryl chlorides. These pre-catalysts were screened in the reaction of propiophenone with aryl chloride **239** (**Scheme 95**).

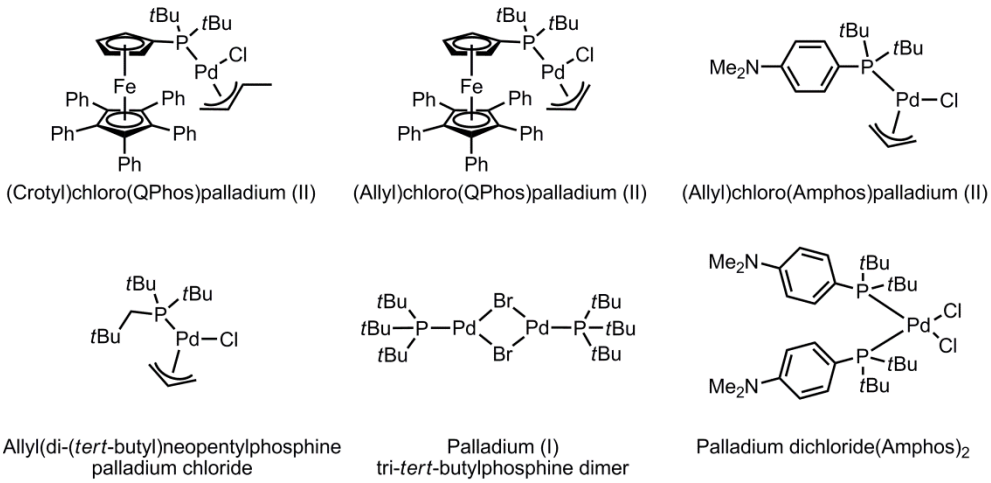
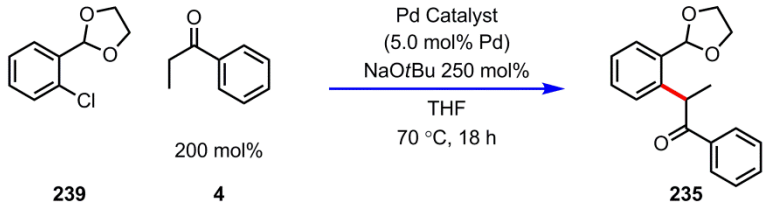


Figure 14: *Pre-catalysts screened in the coupling of propiophenone and aryl chloride **239***



Scheme 95: α-*Arylation of propiophenone with aryl chloride **239***

Entry	Catalyst	Isolated Yield of 235
1	(Crotyl)chloro(QPhos)palladium (II)	38%
2	(Allyl)chloro(QPhos)palladium (II)	39%
3	(Allyl)chloro(Amphos)palladium (II)	25%
4	Allyl(di-(*tert*-butyl)neopentylphosphine palladium chloride	17%
5	Palladium (I) tri-*tert*-butylphosphine dimer	22%
6	Palladium dichloride(Amphos)$_2$	45%

Table 11: *Reactivity of different pre-catalysts with aryl chloride **239***

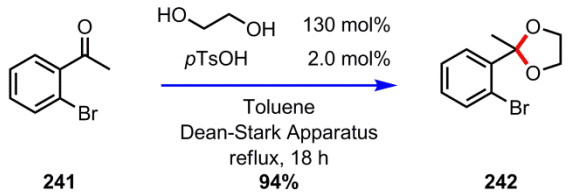
The pre-catalysts had varying activity (**Table 11**). Three of the six showed higher activity than that of (D*t*BPF)$PdCl_2$ (Entries 1, 2 and 6). Of these, $PdCl_2$(Amphos)$_2$ was the most active, giving a yield of 45%.

It was found that a higher yield of product could be obtained by using a higher loading of $PdCl_2$(Amphos)$_2$ catalyst and a longer reaction time. Adding two batches of 5.0 mol% catalyst, at 48 h intervals, (total reaction time 96 h) resulted in an overall yield of 74% of product. Hence, it had been shown that aryl chlorides were amenable to this reaction procedure, albeit being far more sluggish to react than aryl bromides. This illustrated again the challenging nature of the α-arylation reaction that was being performed here. It was found that $PdCl_2$(Amphos)$_2$ gave comparable yields to (D*t*BPF)$PdCl_2$ for aryl bromides and aryl iodides. Aryl bromides therefore clearly offered the best compromise between cost, commercial availability and reactivity, and so to further examine the substrate scope, other aryl bromides would be chosen for investigation.

2.2.6 C1 methyl isoquinolines, naphthols and naphthamines

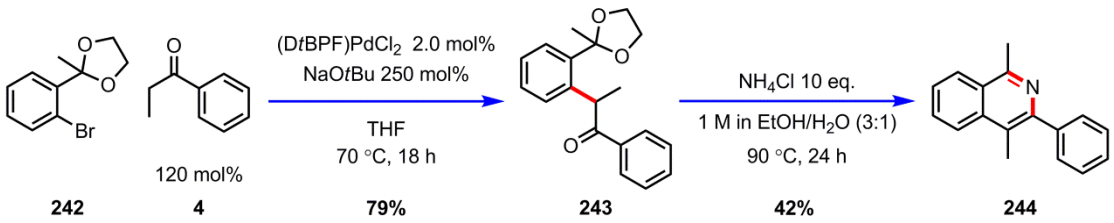
This synthetic route had thus far been limited to 2-halobenzaldehydes. If protected 2'-bromophenyl ketones could be employed as the aryl bromide partner then this would give facile access to isoquinolines bearing substitution at the C1 position. The extra steric hindrance induced by the presence of this group would provide a more challenging test of the both the α-arylation and cyclisation reactions in this synthetic methodology.

To this end, the acetal of 2'-bromoacetophenone was prepared (**Scheme 96**). The protection proceeded in an excellent yield of 94% and gave the aryl bromide coupling partner, **242**, necessary for synthesising isoquinolines bearing a methyl substituent at the C1 position.



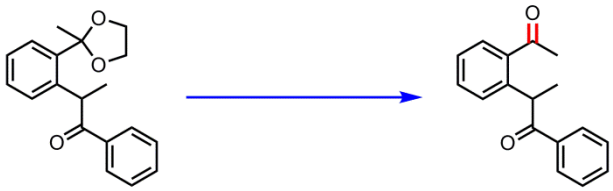
Scheme 96: *Preparation of acetal **242***

The α-arylation reaction with propiophenone worked in a high yield of 79% (**Scheme 97**). The fact that aryl bromide **242** proved to be a proficient coupling partner was surprising due to the fact that it contained such a bulky group at the *ortho*-position. However, the cyclisation of intermediate **243** proved far more sluggish under the recently optimised NH_4Cl conditions. A 42% yield of isoquinoline **244** was obtained under these conditions. Although **244** lacked the characteristic C1 proton singlet in the ^{1}H NMR spectrum of the other isoquinolines, it could be easily identified from the ^{13}C NMR spectrum by the two quaternary aromatic carbons bonded to nitrogen (C1 and C3) at 155.9 and 150.7 ppm.



Scheme 97: *Synthesis of C1-methyl isoquinoline **244***

Analysis of the reaction mixture by mass spectrometry and by TLC revealed that none of starting material **243** remained after the 24 h period and instead a large amount of the deprotected but uncyclised diketone **245** was present. This was isolated separately and characterised by the very intense absorption in the IR spectrum at 1682 cm^{-1}, from the stretching of the two carbonyls. As it was now apparent that the ideal conditions for deprotection and cyclisation might be different, it was decided to further investigate both steps of this process, starting solely with the deprotection of the acetal (**Scheme 98**, **Table 12**).



243 245

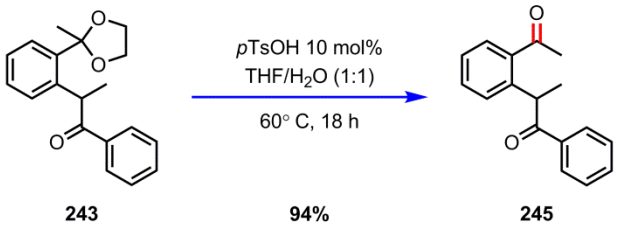
Scheme 98: *Optimisation of acetal deprotection*

Entry	Reagents and Conditions	Isolated Yield of 245
1	HCl 1 M in H_2O, rt, 18 h	0%
2	HCl 1 M in EtOH/H_2O (1:1), rt, 18 h	Trace
3	HCl 1 M in EtOH/H_2O (1:1), 60 °C, 18 h	45%
4	*p*TsOH (10 mol%), EtOH/H_2O (1:1), rt, 18 h	Trace
5	*p*TsOH (10 mol%), EtOH/H_2O (1:1), 60 °C, 18 h	69%
6	*p*TsOH (10 mol%), THF/H_2O (1:1), 60 °C, 18 h	94%

Table 12: *Screening of different conditions for conversion of **243** to **245***

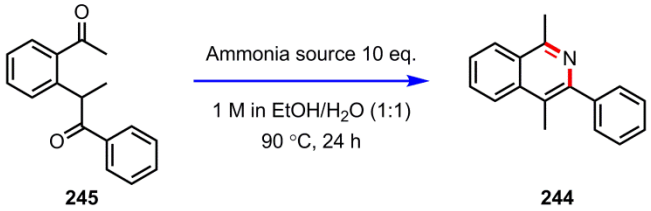
Initial attempts to cleave the acetal in **243** in 1 M aqueous HCl at room temperature were not successful (Entry 1), presumably hindered by the insolubility of lipophilic **243**. Dissolution of **243** in EtOH, prior to addition of 1 M aqueous HCl (Entry 2) did give some deprotection, but the process was sluggish. Increasing the temperature to 60 °C (Entry 3) aided the deprotection process and a 45% yield of diketone was obtained but there were also many other spots that were detected during analysis of the reaction mixture by TLC and so milder deprotection conditions were sought. The use of catalytic *p*TsOH (10 mol%) in EtOH/H_2O at room temperature (Entry 4) was slow and gave only trace amounts of product. Upon heating to 60 °C (Entry 5) the reaction proceeded in a 69% yield, but also remained relatively clean (with the majority of the material being product or acetal starting material). A switch of solvent to THF/H_2O (1:1) led to an increase in yield up to 94%.

With conditions optimised for the deprotection of **243** to diketone **245** (**Scheme 99**), work could now begin on the cyclisation of diketone **245**.



Scheme 99: *Deprotection of **243** under optimised conditions*

To determine the effect of pH on the cyclisation of diketone **245**, it was decided to screen the same range of ammonium salt solutions that were used to investigate the cyclisation of diketone **245** to isoquinoline **244** (*vide supra*) (**Scheme 100**, **Table 13**).



Scheme 100: *Cyclisation of diketone **245** to isoquinoline **244***

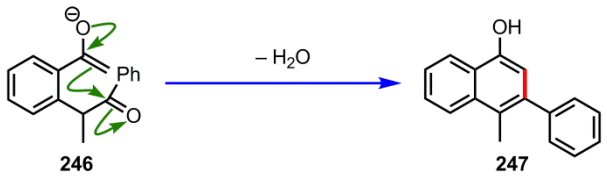
Entry	Source of Ammonia	pH	Isolated Yield of 244
1	NH_4OAc	7.0	78%
2	NH_4HCO_3	9.0	87%
3	NH_4OH	12.0	53%
4	$(NH_4)_2SO_4$	5.5	63%
5	NH_4Cl	5.0	56%
6	NH_4Cl/HCl	3.0	34%
7	NH_4Cl/HCl	1.0	12%

Table 13: *Screening of different ammonia sources for conversion of **245** to **244***

The results showed quite a marked contrast to the previous case. NH_4OAc (Entry 1) gave a high yield of 78% of isoquinoline **244**. The highest yield of 87% was seen at pH 9 with a solution of NH_4HCO_3 (Entry 2). However, the yield tailed off both at more basic (Entry 3) and at more acidic pHs (Entries 4-7).

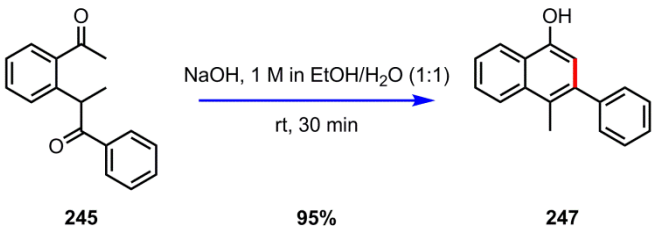
It was thus clear that the optimum pH for the cyclisation was mildly basic, around pH 9. At the more acidic pHs, the reactions remained clean and most of the mass recovery was

unreacted diketone. However, at pH 12 another very UV active spot was observed on the TLC plate. This spot was also observed, albeit at lower concentrations, at pH 9. Upon isolation and characterisation, it was discovered to be naphthol **247**, proposed to come from the intramolecular aldol condensation of the enolate **246** from diketone **245** under basic conditions (**Scheme 101**). A survey of the literature revealed precedent for cyclisation of similar substrates under basic conditions.[191]



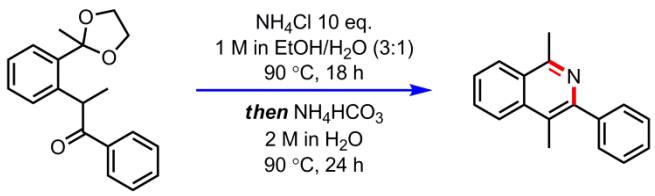
Scheme 101 *Aldol condensation to form naphthol **247***

The structure of naphthol **247** was confirmed by a broad O-H stretch in the IR spectrum at 3519 cm^{-1} and also the broad singlet from the OH proton at 5.48 ppm in the ^{1}H NMR spectrum. Although this naphthol was an undesired side product in the synthesis of isoquinoline **244**, it was a very interesting product in its own right. If the cyclisation conditions could be altered to reduce isoquinoline formation and promote formation of the naphthol, then this would be a valuable development, as polysubstituted naphthols are themselves valuable synthetic products. As a source of nitrogen is necessary for isoquinoline formation, it was obvious to first screen the reactivity of diketone **245** at different pHs under nitrogen-free conditions. It was discovered that treatment of **245** with 1 M NaOH in a mixture of EtOH/H_2O (1:1) led to very rapid conversion to naphthol **247**, a 95% yield being obtained after just 30 min at room temperature (**Scheme 102**).



Scheme 102: *Optimised conditions for the synthesis of naphthol **247***

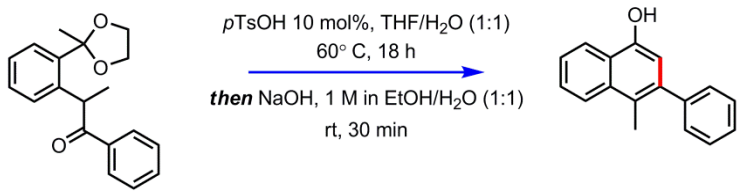
Returning to the synthesis of isoquinoline **244**, a good conversion had been obtainable from intermediate acetal **243** in two steps, but it was desired to carry out the conversion in a single operation, without needing to work up and isolate diketone intermediate **245**. The one-pot procedure would need to start at an acidic pH to cleave the acetal and then be altered to a more basic pH to promote isoquinoline formation, without becoming too basic to favour naphthol formation. It was decided to first subject intermediate **243** to the NH_4Cl cyclisation conditions, which were known to be capable of fully hydrolysing the acetal and not lead to the decomposition of diketone **245**, until TLC analysis showed the consumption of intermediate **243** and then cautiously add NH_4HCO_3 solution until the pH was just below 9, before putting the reaction back on to heat to form the isoquinoline (**Scheme 103**).



Scheme 103: *Optimised conditions for the synthesis of isoquinoline **244***

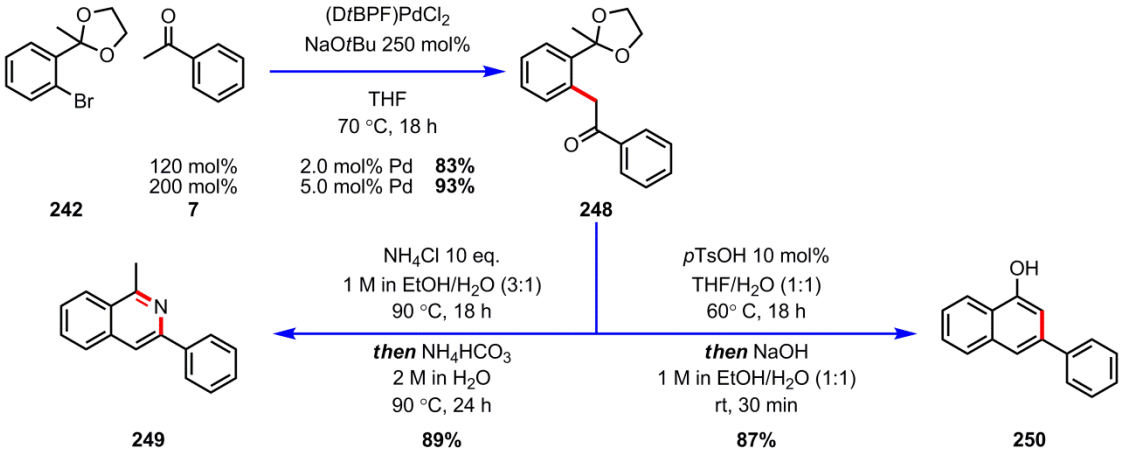
It was found that acetal hydrolysis was complete after around 18 h and so following this, aqueous 2 M NH_4HCO_3 was added to adjust the pH. The reaction required a further 24 h at 90 °C to go to completion, upon which an 84% yield of isoquinoline **244** was obtained after purification.

It also proved possible to synthesise naphthol **247** in a one-pot procedure from intermediate **243**. The deprotection of **243** was carried out as previously optimised, but rather than isolating the diketone intermediate, the reaction was cooled to room temperature and then a solution of NaOH (1 M in EtOH/H_2O (1:1)) was added. After 30 min the reaction was judged complete by TLC and upon work up and purification, an 84% yield of **247** was obtained (**Scheme 104**).



Scheme 104: *One-pot conditions for the synthesis of naphthol **247***

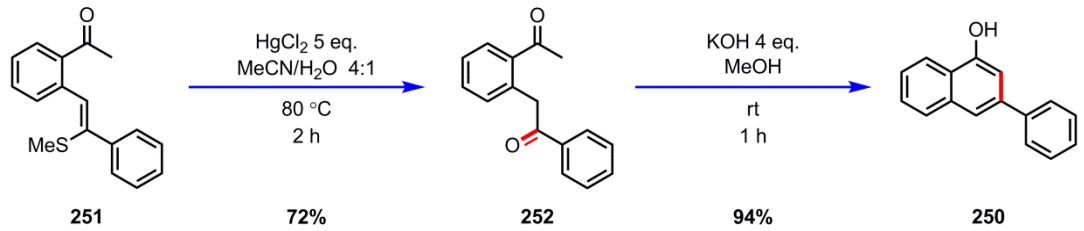
With optimised conditions for both isoquinoline and naphthol formation from intermediate **243**, attention returned to expanding the substrate scope of the α-arylation reaction. Thus, aryl bromide **242** was coupled with acetophenone to give intermediate **248** (**Scheme 105**).



Scheme 105: *Synthesis of isoquinoline **249** and naphthol **250***

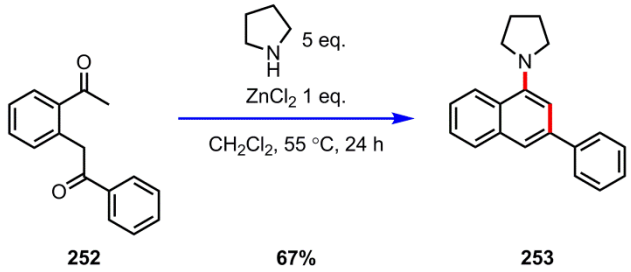
This proceeded in very high yield (83% with 2.0 mol% Pd and 93% with 5.0 mol% Pd). Intermediate **248** could be converted into isoquinoline **249** in an excellent yield of 89% and to naphthol **250** in a similarly excellent yield of 87%.

Shortly after this work had been carried out, the group of Willis published a similar route to naphthol **250** (**Scheme 106**).[192] Willis and coworkers accessed methyl vinyl sulfides such as **251** from the corresponding aryl methyl sulfides *via* a rhodium-catalysed alkyne carbothiolation. Vinyl sulfide **251** was hydrolysed to diketone **252** with an excess of mercury (II) chloride, which was then converted into naphthol **250** under very similar conditions and in almost identical yield to this work.



Scheme 106: *Approach of Willis and coworkers to naphthol **250***

The constraint of using superstoichiometric amounts of mercury to cleave the vinyl sulfides and the requirement for more specialised aryl methyl sulfide starting materials perhaps make the Willis route slightly less desirable than this route. Nevertheless, it was decided not to pursue further efforts in the naphthol series, but to concentrate efforts on isoquinolines. Before returning to discussion of the scope of the isoquinoline series however, it is notable that at a later date another Donohoe group member further demonstrated the great versatility of these diketone intermediates. For example, when diketone **252** was treated with pyrrolidine and $ZnCl_2$ (as a Lewis acid catalyst), it was converted to the corresponding naphthamine **253** in 67% yield (**Scheme 107**).[193]

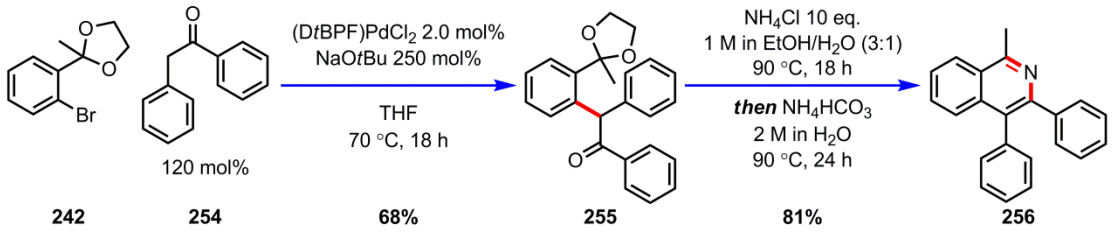


Scheme 107: *Conversion of diketone **252** to naphthamine **253** by another group member*

2.2.7 Exploring substitution accessible at C3 and C4 by varying the ketone partner

To this point, only propiophenone and acetophenone had been successfully employed as the ketone coupling partners in the α-arylation reaction. These gave respectively methyl and hydrogen as the substituents at the C4 position of the isoquinoline. The α-arylation of deoxybenzoin was attempted in an effort to incorporate a phenyl group at the isoquinoline

C4 position. The α-arylation of deoxybenzoin, **254**, proceeded in a good yield of 68% to give intermediate **255**. This intermediate then cyclised in an excellent yield of 81% to furnish isoquinoline **256** (**Scheme 108**).



Scheme 108: *Synthesis of a C4 phenyl isoquinoline **256***

The α-protons of deoxybenzoin are significantly more acidic (pK_a 17.7 in DMSO)[31] than those of acetophenone (pK_a 24.7 in DMSO)[194] due to the presence of the adjacent phenyl group. In fact their acidity is presumably comparable to the α-protons in the products of the α-arylation reaction of acetophenone, **236** or **248**, which were never observed to undergo a second arylation under the reaction conditions. The reluctance of **236** or **248** to undergo further arylation was therefore presumably due to the sterically bulky nature of the first aryl bromide partner that had been attached. Nevertheless, the fact that this more acidic ketone (and thereby less nucleophilic anion) could still be α-arylated, prompted investigation of some more functionalised ketone partners, to expand the scope of substitution available at the isoquinoline C4 position. The α-arylation reaction was attempted with a range of 2-heteroatom-substituted acetophenones; however none of these ketones gave any α-arylated product (**Figure 15**). A number of these ketones were observed to decompose under the reaction conditions. As many of these ketones possessed a good leaving group it is possible that once deprotonated by the NaO*t*Bu, they underwent an α-elimination to form a carbene. Whilst 2-nitroacetophenone was not observed to decompose, it is possible that the much greater acidity of the α-proton meant that the enolate was not sufficiently nucleophilic to couple with the palladium species.

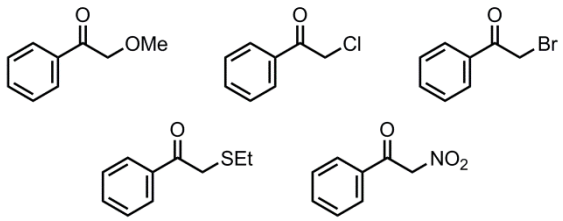


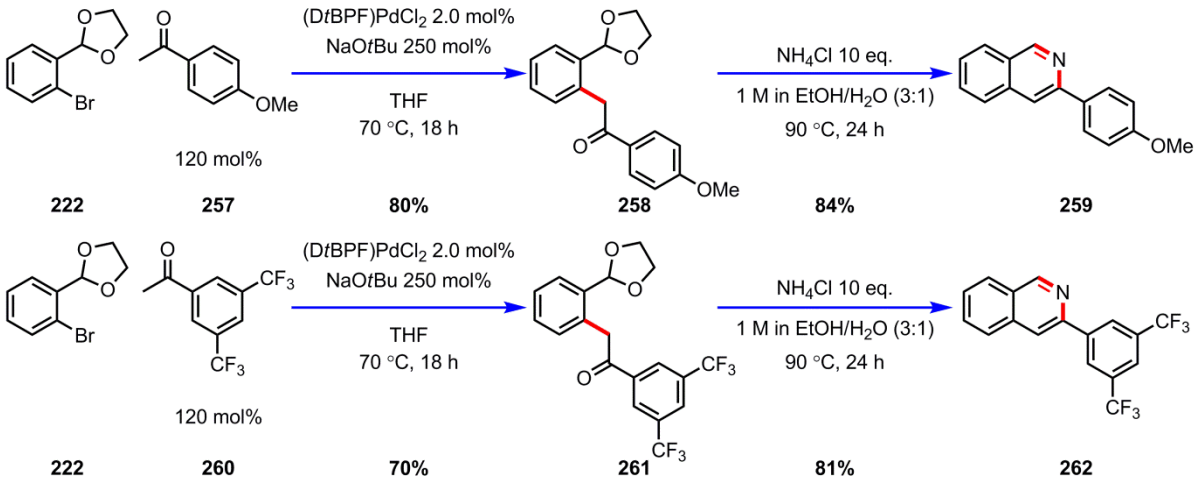
Figure 15: *Unsuccessful ketones used in arylations with acetal **222***

In a subsequent, more detailed study by another member of the group into the α-arylation of ketones bearing a heteroatom on the α-position (with a variety of different bases), it was found that 2-methoxyacetophenone could be successfully coupled with aryl bromide **222**, providing a mild base such as Cs_2CO_3 was used.[195] The α-arylation of all other α-heteroatom ketones was still unsuccessful even with milder bases.

So far only phenyl ketones had been successfully α-arylated, restricting the group at the C3 position to phenyl. The ability to vary the electronic and steric properties of an aryl substituent on a heteroarene ring is of high importance, particularly during lead development of any pharmaceutical or agrochemical compound and so it was decided to investigate what variation could be achieved in this system. The direct installation of the C3 aryl substituent in this methodology should be contrasted with the more traditional way of functionalising a preformed heteroarene, *via* reactions such as the Suzuki or Stille couplings onto 3-haloisoquinolines.

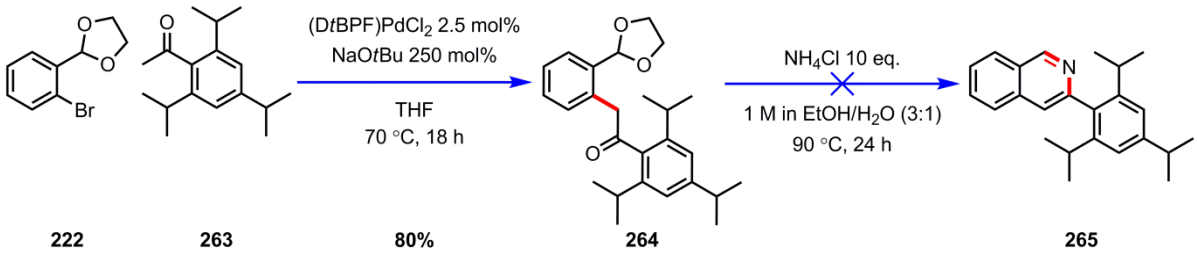
In order to install an electron-rich aryl ring at the C3 position, 4'-methoxyacetophenone, **257**, was used as the ketone component and coupled with acetal **222**. The α-arylation reaction proceeded in a high yield of 80% to form intermediate **258**, and this was then converted into isoquinoline **259** in 84% yield. Subsequently, 3',5'-bis(trifluoromethyl)acetophenone, **260**, was employed as the ketone coupling partner to incorporate an electron-deficient aryl ring at the C3 position. This too could be α-arylated in

a good yield of 70% with aryl bromide **222** to deliver intermediate **261**, which cyclised in 81% yield to isoquinoline **262** (**Scheme 109**).



Scheme 109: *Synthesis of electron-rich and electron-poor C3 aryl isoquinolines*

Next, it was attempted to integrate an aryl group that would be highly sterically demanding, and hence hard to install *via* cross coupling on a preformed isoquinoline. Pleasingly, 2',4',6'-tri*iso*propylacetophenone, **263**, coupled in an excellent yield of 80% with acetal **222** to give intermediate **264** (**Scheme 110**). However, upon treatment of **264** with the standard cyclisation conditions, none of isoquinoline **265** was detected.

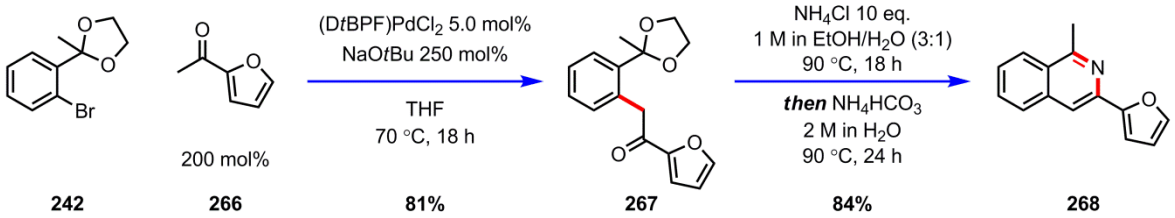


Scheme 110: *Attempted synthesis of an isoquinoline with a bulky C3 aryl group*

Increasing the reaction temperature and varying the pH of the cyclisation mixture both failed to give any isoquinoline. Analysis of the reaction showed a complex mixture of products, which included a small amount of free aldehyde, and the separation and purification of this mixture was not attempted. The fact that the first step proceeded in high yield but the second step failed may be due to the fact that the α-arylation reaction takes place at the α-carbon, whereas the isoquinoline synthesis requires attack at the carbonyl carbon, one position closer

to the bulky aryl group. The high yielding α-arylation reaction in this example may also be attributable to the fact that the rate-determining step of the catalytic cycle is believed to be reductive elimination, which could be accelerated by the bulky *iso*propyl groups giving a more crowded environment around the catalyst.

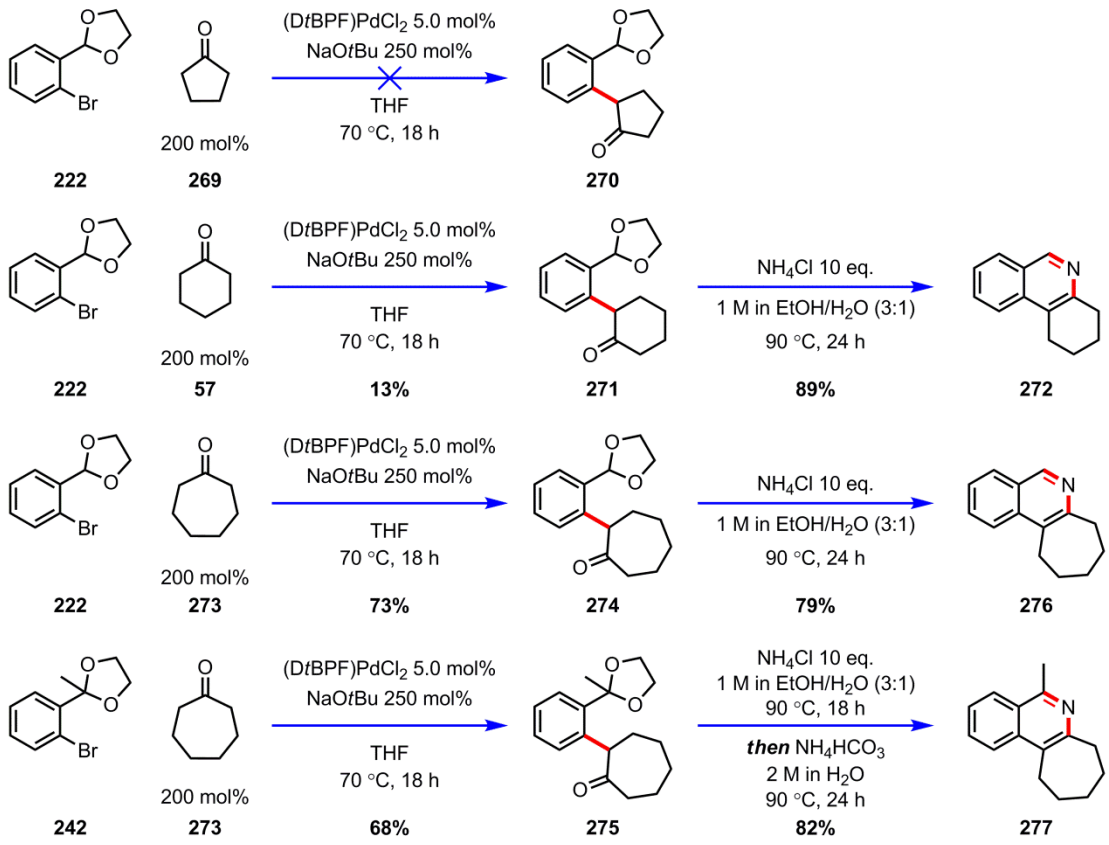
The coupling of 2-furyl methyl ketone, **266**, with acetal **242** was then attempted in an effort to deliver a C3 heteroaryl-substituted isoquinoline. The α-arylation reaction proceeded in an high yield of 81% to give intermediate **267**, which could be cyclised in an excellent yield of 84% to the corresponding isoquinoline **268** (**Scheme 111**). It should be noted that cross couplings between two heteroarenes in the *ortho*-position to both heteroatoms are typically very difficult to carry out,[196] and so this was deemed an important strength of this route.



Scheme 111: *Synthesis of a C3 furyl-substituted isoquinoline*

Continuing the investigation of the substrate scope, it was decided to examine whether cyclic ketones were amenable to this protocol. The successful α-arylation of cyclic ketones would eventually lead to tricyclic isoquinoline moieties (i.e. with alkyl substitution at both the C3 and C4 positions) and these would be useful products as they are challenging to synthesise by traditional methods. Upon subjection of cyclopentanone, **269**, to the reaction conditions, no α-arylated product **270** was observed (**Scheme 112**). The cyclopentanone was fully consumed under the reaction conditions and it was assumed that cyclopentanone may be undergoing an intermolecular aldol reaction in preference to α-arylation. The difficulty of carrying out an α-arylation reaction on smaller-membered cyclic ketones such as cyclopentanone had been noted by Buchwald.[42] With cyclohexanone, **57**, a small amount of

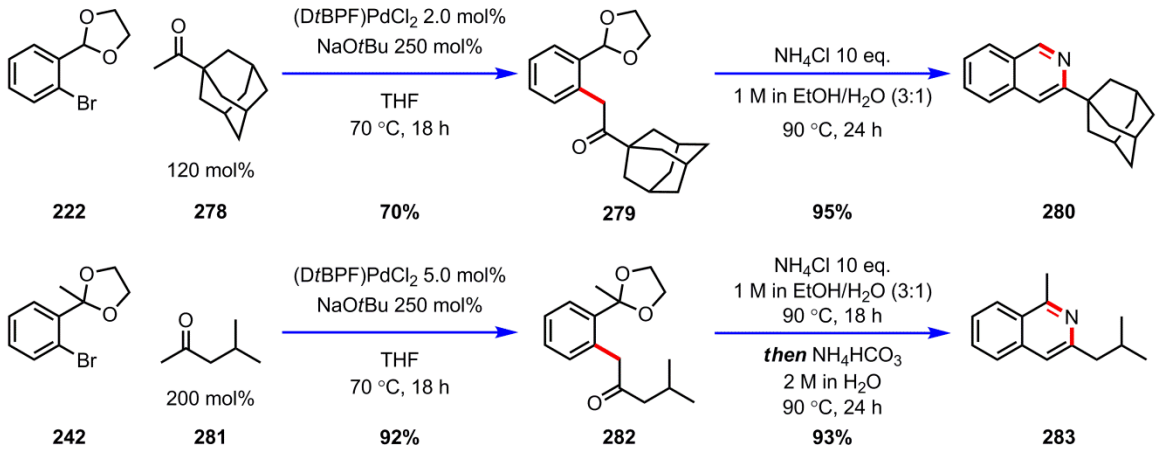
intermediate **271** was isolated, as evidenced by the α-proton appearing as a double doublet at 4.04 ppm in the ^{1}H NMR spectrum. Again, the cyclohexanone was presumed to be undergoing deleterious side reactions which reduced the yield of product, however intermediate **271** could be cyclised in high yield to the corresponding isoquinoline **272**. It was postulated that employing a more substituted cyclopentanone or cyclohexanone ring might retard the rate of aldol reaction and this was further investigated in the context of a steroid nucleus (*vide infra*). Cycloheptanone, **273**, proved a far more proficient ketone coupling partner and was successfully arylated with aryl bromides **222** and **242** in 73% and 68% yields respectively. Both intermediates **274** and **275** could be converted into the corresponding isoquinolines **276** and **277** in high yields (79% and 82% respectively).



Scheme 112: *Synthesis of tricyclic isoquinolines*

The successful coupling of cycloheptanone had illustrated that alkyl ketones were amenable to the reaction protocol and so investigation now turned to acyclic alkyl ketones. Ketones

bearing two alkyl substituents are a much more challenging class of substrate in the α-arylation reaction, due to increased likelihood for aldol condensations and issues of regioselectivity. The best partners are usually ketones bearing a bulky group on one side of the carbonyl. With this in mind, the α-arylation of adamantyl methyl ketone, **278**, was attempted and pleasingly this proceeded in a good yield of 70% to furnish intermediate **279**. This could be aromatised in very high yield to isoquinoline **280** (**Scheme 113**). This synthesis of **280** was a strength of this methodology as installation of an adamantyl group on a preformed arene ring is very challenging.



Scheme 113: *Investigating C3 alkyl substitution*

The structure of isoquinoline **280** was proven unambiguously by single crystal X-ray structure analysis (**Figure 16**).

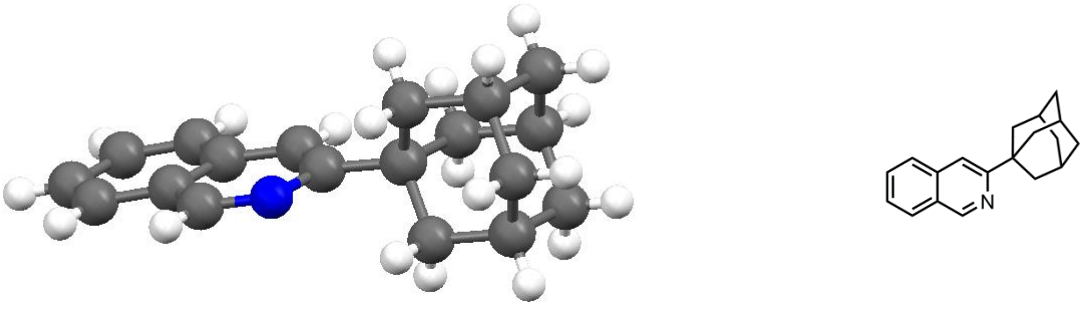


Figure 16: *Representation of the X-ray crystal structure of isoquinoline **280***

(solved by another group member)

*iso*Butyl methyl ketone, **281**, was investigated next. This could be α-arylated with aryl bromide **242** in an excellent yield of 92% to give intermediate **282**. Ketone **281** had been

arylated exclusively on the methyl group and this was evident from the ^{1}H NMR, where the α-aryl proton signal at 3.90 ppm existed as a singlet with the integration of two protons. Intermediate **282** could be converted in an excellent yield into isoquinoline **283**. Interestingly, the α-arylation of **281** with the less hindered aryl bromide **222** was much less clean, and was not pursued, indicating the sensitivity of the α-arylation of these alkyl ketones to sterics. The α-arylation of a number of other alkyl ketones was attempted, some of which are shown in **Figure 17**. Unfortunately, many of these were unstable under the reaction conditions, presumably due to competing aldol condensations.

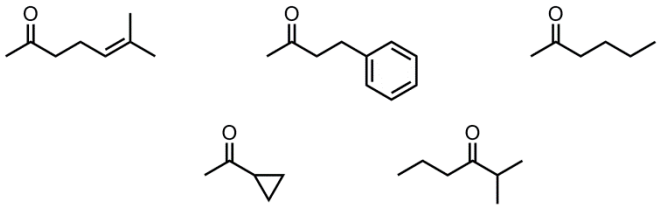
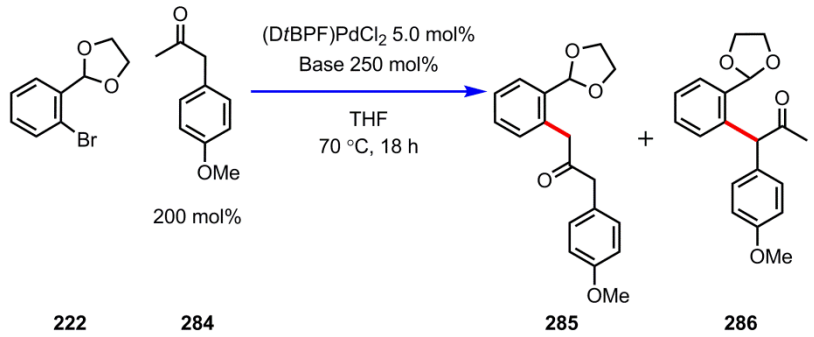


Figure 17: *Unsuccessful alkyl ketones used in the α-arylation reaction*

The successful α-arylation of linear ketones remains a very challenging problem, as shown by the recent paper by Stradiotto and coworkers that focussed solely on the α-arylation of acetone.[197]

Studies on the α-arylation reaction have shown that in general, on ketones with a choice of enolisable protons, it is the least sterically-hindered carbon that is selectively α-arylated (i.e. arylation preference: methyl > methylene > methine). It was decided to examine a case where the methylene carbon was significantly more acidic, to probe the importance of sterics versus proton acidity in determining the regiochemistry of the α-arylation. The ketone chosen for this was 4'-methoxyphenyl acetone, **284**. Upon subjection of **284** to α-arylation with **222** using NaO*t*Bu as the base, a mixture of two isomeric α-arylated products **285** and **286** was obtained (**Scheme 114** and **Table 14**, Entry 1). These two isomeric products could not be separated by column chromatography in any solvent system, however both displayed characteristic signals in distinctive and separate regions of the ^{1}H NMR spectrum allowing

clear identification and for a ratio of the two to be calculated. Intermediate **285** had two characteristic methylene singlets of equal intensity at 3.88 ppm and 3.65 ppm, whereas intermediate **286** exhibited a methine singlet at 5.67 ppm and a methyl singlet at 2.25 ppm in an intensity ratio of 1:3.

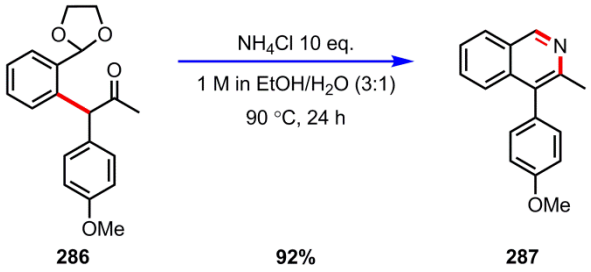


Scheme 114: *The effect of base on regioselectivity of the α-arylation of ketone **284***

Entry	Base	Yield of 285	Yield of 286
1	NaO*t*Bu	39%	27%
2	K_3PO_4	0%	74%
3	Cs_2CO_3	0%	98%
4	NaH	0%	0%
5	LDA	0%	0%

Table 14: *Bases screened in the α-arylation of 4'-methoxyphenylacetone*

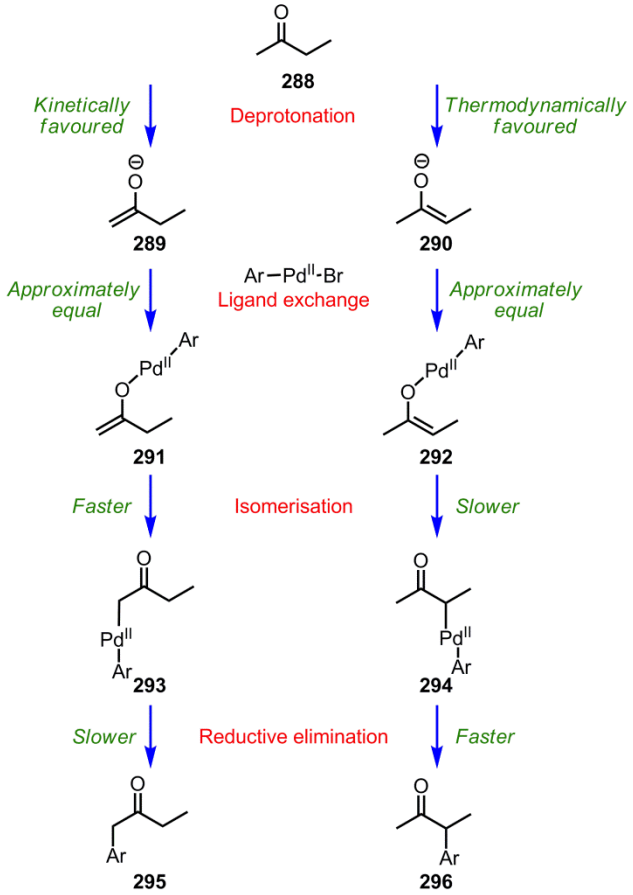
A number of bases were employed to see whether one of the two products could be formed selectively. With K_3PO_4, (Entry 2) intermediate **286** was produced with complete regioselectivity in 74% yield (from exclusive α-arylation at the methylene position). Cs_2CO_3 was also completely regioselective and gave an excellent yield (98%) of **286**. However, the use of NaH or LDA (Entries 4 and 5) led to none of either product being formed and solely to decomposition of starting material, suggesting that this particular ketone was not tolerant of strong bases. The full regiocontrol obtainable with the milder bases further illustrated the power of this synthetic route. Intermediate **286** could be smoothly converted into the corresponding isoquinoline **287** by the standard procedure (**Scheme 115**).



286 **92%** **287**

Scheme 115: *Conversion of intermediate **286** into isoquinoline **287***

There are clearly a number of factors that influence the regiochemistry of the α-arylation reaction and these merit further discussion here. Considering the α-arylation of butanone, **288** as a simple example (**Scheme 116**), deprotonation is favoured at the methyl group kinetically (to give **289**) due to reduced steric hindrance.



Scheme 116: *Factors affecting the regiochemistry of arylation of butanone, **288***

However, deprotonation at the methylene position is generally believed to be favoured thermodynamically, as the resulting enolate **290** is lower in energy due to greater hyperconjugation. However, House *et al.* have shown that this selectivity is highly

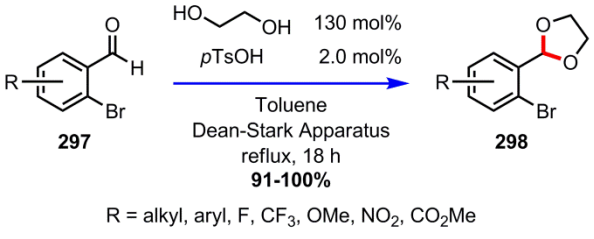
dependent on the solvent, the counterion and the nature of the specific ketone,[198] with the position of equilibrium often lying near the middle and occasionally on the side of the less substituted enolate. It is commonly thought that the α-arylation reaction proceeds by initial displacement of the halide on palladium by the oxygen of the enolate (**289** → **291** or **290** → **292**), the rate of this process likely similar for both enolates. Isomerisation of the *O*-bound enolate to the *C*-bound enolate would be fastest for the less substituted enolate (**291** → **293**) due to steric hindrance. However, reductive elimination from the *C*-bound enolate complexes would be fastest from the most substituted enolate (**294** → **296**) due to the greater relief of strain on going from a high-coordinate Pd(II) complex to a low coordinate Pd(0) complex.

The pK_a of *t*BuOH in DMSO is 32.2,[199] whereas the pK_as of dialkyl ketones are often in the mid-high twenties.[30] Hence, in the reaction of *iso*butyl methyl ketone **281** with NaO*t*Bu, the NaO*t*Bu is a strong base. Thus, substantial kinetic deprotonation of the methyl group is favoured due to sterics, and as displacement of the halide on palladium by the enolate is likely irreversible, the reaction proceeds to give α-arylation at the methyl position. This selectivity is probably increased by the very slow rate of *O*- to *C*-bound isomerisation of the more hindered enolate complex. With 4'-methoxyphenyl acetone, **284** the methylene protons are now significantly more acidic than the methyl protons (the pK_a of phenyl acetone is 19.8).[31] With NaO*t*Bu, the deprotonation still occurs kinetically, but now the far greater acidity of the methylene protons leads to a mixture of products forming. With the much weaker bases Cs_2CO_3 and K_3PO_4, they may only be sufficiently basic to enolise at the methylene position, and hence the more substituted product dominates despite the more difficult *O*- to *C*-bound enolate isomerisation.

Overall, it had been demonstrated that an array of functionality could be incorporated on the heterocyclic ring of the isoquinoline motif, including a hydrogen atom or a methyl group at C1, alkyl, aryl or heteroaryl groups at C3, and alkyl or aryl groups or a hydrogen atom at C4. The complete regiocontrol in this synthesis is a particular strength over many other synthetic routes (particularly those that employ an alkyne to install the C3 and C4 carbon atoms *vide supra*).

2.2.8 Exploring substitution accessible at C5-C8 by varying the aryl bromide partner

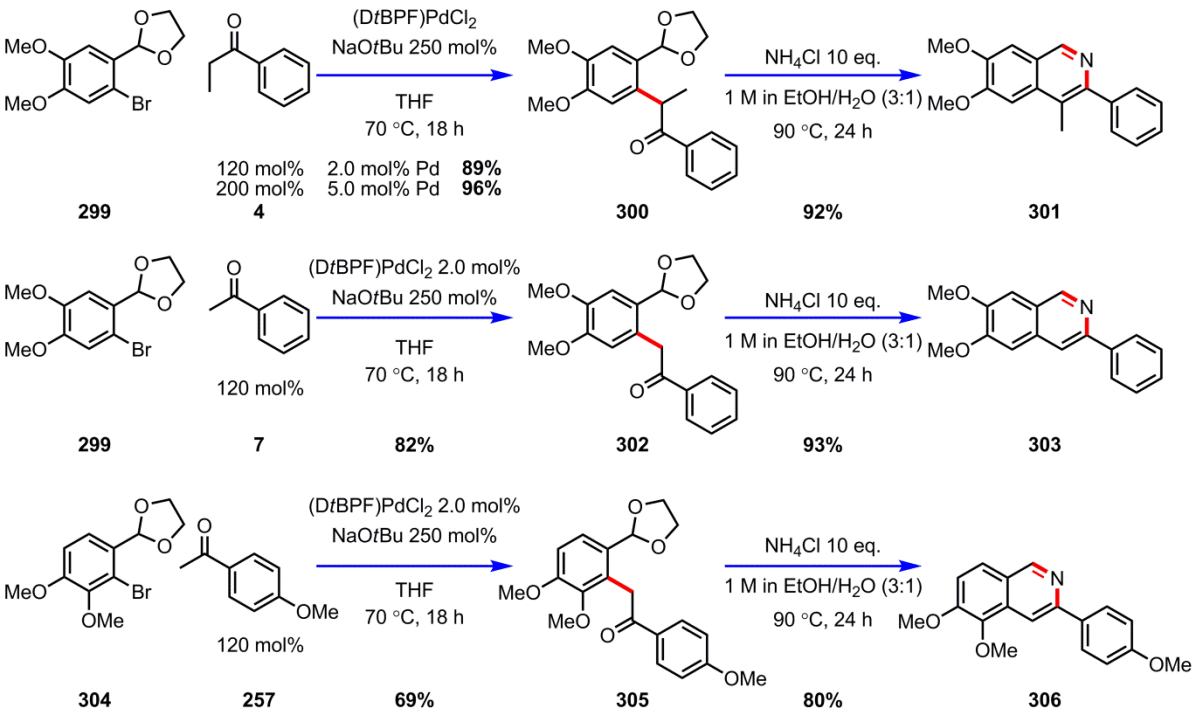
Attention then turned to investigate the scope of substitution that could be tolerated on the carbocyclic ring of the isoquinoline skeleton. This would involve the prior synthesis of a wide range of acetal-protected, substituted, *ortho*-bromobenzaldehydes **298**. These could all be made in a very facile manner and in excellent yields of 91-100% from the corresponding benzaldehydes **297** by the procedure previously used for the synthesis of **222** (**Scheme 117**). The acetals of the electron-poor and electron-neutral benzaldehydes were bench stable and showed no notable degradation after a period of several months. However, the acetals of the electron-rich benzaldehydes were susceptible to hydrolysis to the aldehyde over a period of weeks if left on the bench. Their shelf-life could be greatly increased by storage in a desiccator.



Scheme 117: *Synthesis of acetals of substituted benzaldehydes*

Dimethoxy-substituted acetal **299** was investigated first. In the α-arylation reaction with 120 mol% propiophenone and 2.0 mol% (D*t*BPF)$PdCl_2$, a high yield of 89% of intermediate **300** was obtained. The yield of **300** could be further increased up to an excellent 96% by the

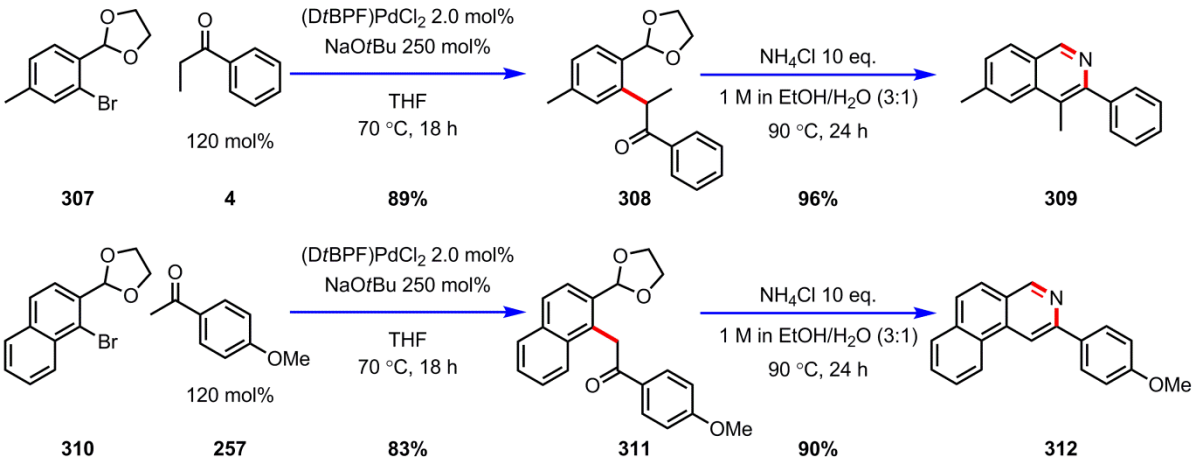
use of 200 mol% propiophenone and 5.0 mol% (D*t*BPF)$PdCl_2$. Intermediate **300** cyclised in an excellent yield of 92% to furnish the electron-rich isoquinoline **301** (**Scheme 118**). In a similar fashion, acetal **299** could also be coupled with acetophenone to deliver intermediate **302** in 82% yield and this intermediate could be cyclised in 93% yield to give isoquinoline **303**. Isomeric acetal **304** was also reacted with 4'-methoxyacetophenone, **257** in a yield of 69%. The successful coupling of acetal **304** is particularly noteworthy as this could be expected to be a very challenging α-arylation reaction. The aryl bromide is very sterically hindered with the C-Br bond being flanked by two *ortho*-substituents, both of which contain oxygen atoms that could possibly chelate to palladium and slow the rate of reductive elimination. Hence, the slightly reduced yield with acetal **304** compared to acetal **299** was perhaps unsurprising. Intermediate **305** also cyclised in a good yield of 80% to isoquinoline **306**.



Scheme 118: *Synthesis of electron-rich isoquinolines*

Alkyl- and aryl-substituted aryl halides were investigated next. Methyl-substituted aryl bromide **307** was coupled with propiophenone in an excellent yield of 89% to give

intermediate **308**, which went on to cyclise in an excellent yield of 96% to the corresponding isoquinoline **309** (**Scheme 119**).

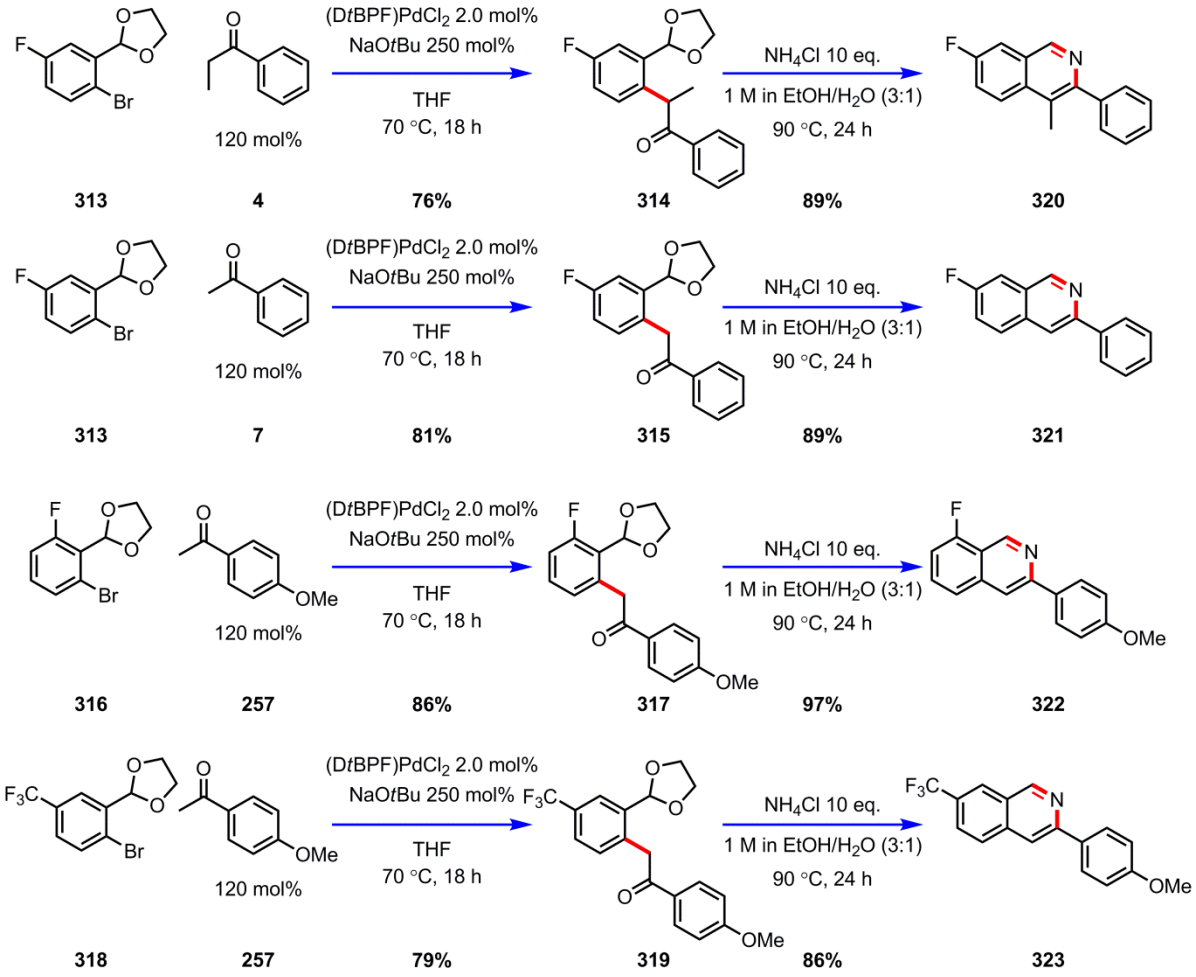


Scheme 119: *Alkyl- and aryl-substituted isoquinolines*

The acetal of 1-bromo-2-naphthaldehyde, **310**, was also found to couple in a high yield of 83% with 4'-methoxyacetophenone, **257** to furnish intermediate **311**. Again as this aryl bromide is 2,6-disubstituted, it was pleasing that it coupled to the ketone with such high efficiency. Intermediate **311** cyclised in an excellent yield of 90% to deliver isoquinoline **312**.

Fluorinated compounds are of huge importance in medicinal chemistry.[200] The replacement of an aromatic C-H bond with that of a C-F bond prevents oxidative degradation of the substrate to the corresponding phenol, whereas the replacement of a methyl group with that of a trifluoromethyl group helps to prevent the oxidation to the corresponding benzoic acid. A number of fluorinated aryl bromides were found to undergo this coupling procedure successfully (**Scheme 120**). Aryl bromide **313**, bearing a fluorine atom in the position to become C7 on the resulting isoquinoline was found to undergo coupling with both propiophenone and acetophenone (in 76% and 81% yields respectively) to furnish intermediates **314** and **315**. In a similar fashion, aryl bromide **316**, bearing a fluorine atom in the position to become C8 on the resulting isoquinoline coupled with

4'-methoxyacetophenone in an excellent yield of 86% to give intermediate **317**. Aryl bromide **318**, bearing a trifluoromethyl group at the position to become C7 on the resulting isoquinoline, coupled with 4'-methoxyacetophenone in a good yield of 79% to give intermediate **319**. All intermediates cyclised excellently (in yields of 86-97%) to the corresponding isoquinolines **320-323**.



Scheme 120: *Fluoro- and trifluoromethyl-substituted isoquinolines*

The structure of isoquinoline **322** was proven unambiguously by single crystal X-ray structure analysis (**Figure 18**).

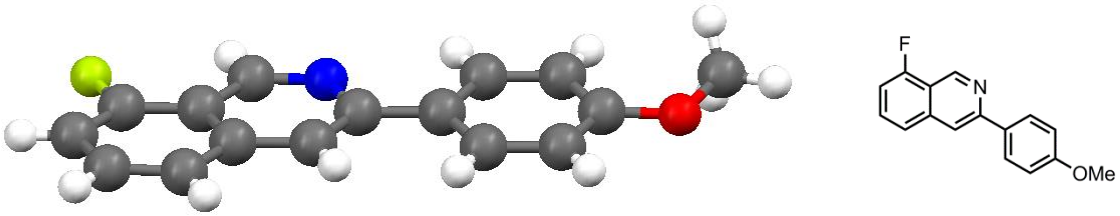
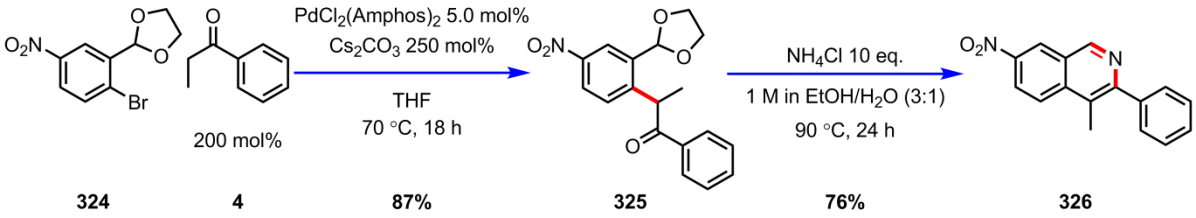


Figure 18: *Representation of the X-ray crystal structure of isoquinoline* ***322*** *(solved by another group member)*

At attempt to incorporate a trifluoromethyl group at the C4 position *via* the α-arylation of 1,1,1-trifluoroacetone was unsuccessful as this ketone decomposed under the reaction conditions.

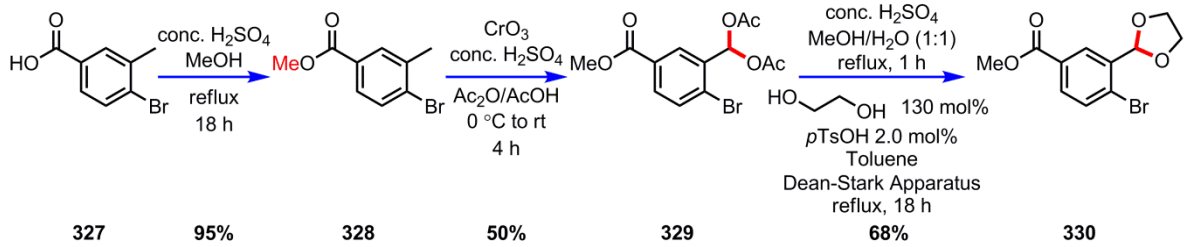
The successful incorporation of a trifluoromethyl group at the C7 position was a particularly notable result. Isoquinoline **323** is electron-poor and thus would be very difficult to synthesise by traditional synthetic approaches, which involve S_EAr approaches to synthesise the aromatic ring. To this end, it was decided to examine what other electron-deficient aryl bromides could be employed as coupling partners in the α-arylation reaction. The acetal of 2-bromo-5-nitrobenzaldehyde, **324**, was employed first. Under the standard α-arylation conditions with propiophenone, no α-arylated intermediate **325** was produced. It was observed that this reaction went a much darker brown colour upon addition of the aryl bromide than other α-arylation reactions. A closer examination of the literature examples where aryl nitro groups had been tolerated showed that it was often under conditions that were less basic, such as the fluoride-promoted coupling of silyl enol ethers[74] or the use of Reformatsky-type zinc enolates.[71] Hence, it was thought that the NaO*t*Bu conditions might be too harsh to tolerate the nitro group and so the milder bases K_3PO_4 and Cs_2CO_3 that had been used successfully with ketone **284** were employed. Both were found to work well, with Cs_2CO_3 giving the highest yield of intermediate **325** (87%) (**Scheme 121**).



Scheme 121: *Synthesis of 7-nitroisoquinoline **326***

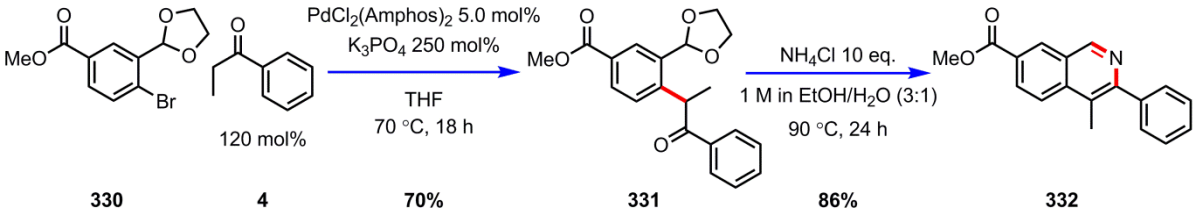
It was also found that $PdCl_2(Amphos)_2$ gave superior yields of product in this reaction with the milder bases than (D*t*BPF)$PdCl_2$. Intermediate **325** cyclised in good yield to corresponding isoquinoline **326**.

To continue the exploration of the scope of electron-poor aryl bromides that could be tolerated, it was desired to test an aryl bromide bearing an ester substituent. As the requisite *ortho*-bromobenzaldehyde was not commercially available, aryl bromide coupling partner **330** was synthesised in a short sequence as detailed in **Scheme 122**. Hence, benzoic acid **327** was converted into the corresponding methyl ester **328** by refluxing in MeOH with conc. H_2SO_4. Oxidation of the benzylic methyl group then followed with CrO_3 and conc. H_2SO_4 in Ac_2O/AcOH solvent. The oxidation stopped at the aldehyde oxidation level as the product was trapped out as diacetate **329**, indicated by the benzylic proton appearing as a singlet at 7.92 ppm in the ^{1}H NMR spectrum. Finally, the diacetate was hydrolysed to the aldehyde with conc. H_2SO_4 in a mixture of MeOH/H_2O which, without purification, was subjected to the standard reaction conditions to acetal protect the aldehyde, furnishing key coupling partner **330**, confirmed by the signal from the benzylic proton in the ^{1}H NMR moving to 6.10 ppm.



Scheme 122: *Synthesis of methyl ester-containing aryl bromide **330***

With aryl bromide **330** in hand, coupling was investigated with propiophenone. Again it was found that the methyl ester was not tolerated under the strongly basic NaO*t*Bu conditions. Use of the milder bases K_3PO_4 and Cs_2CO_3 again proved more fruitful, with K_3PO_4 giving superior yields of **331** (70%), with $PdCl_2(Amphos)_2$ as the catalyst (**Scheme 123**). Pleasingly, the methyl ester in **331** did not show any signs of hydrolysis to the corresponding carboxylic acid or transesterification to the ethyl ester (from the EtOH solvent) during the conversion of intermediate **331** into isoquinoline **332**. This was confirmed by the singlet signal from the methyl group of the ester in the ^{1}H NMR spectrum at 4.03 ppm. The fact that a methyl ester of a carboxylic acid could be successfully carried through both the α-arylation step and the subsequent cyclisation step illustrated the relatively mild conditions of this newly-developed methodology, especially in the presence of K_3PO_4 or Cs_2CO_3.

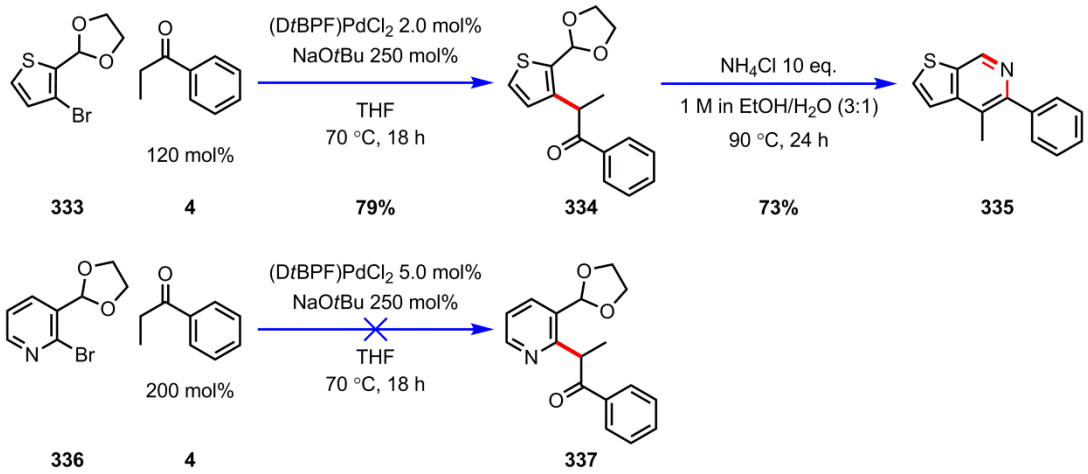


Scheme 123: *Synthesis of methyl ester bearing isoquinoline **332***

Hence, it had now been shown that this methodology was well suited to the synthesis of electron-deficient isoquinoline cores, with trifluoromethyl, nitro and ester moieties all tolerated in good yields. This is a key advantage of this method over traditional approaches. With these electron-deficient aryl bromides, it was conceivable that the α-arylation reaction proceeded *via* an S_NAr pathway, rather than by the typical palladium-catalysed coupling pathway. To confirm that this was not the case, control experiments with no palladium catalyst were run with aryl bromides **318**, **324** and **330** and no products were observed.

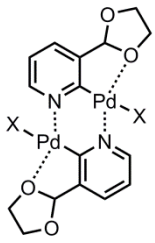
It was then decided to investigate whether heteroaryl bromides were amenable to this reaction protocol. If successful these had the potential to deliver arene units containing multiple heteroatoms, many of which are important pharmacological motifs. Subjecting the

acetal of 3-bromothiophene-2-carboxaldehyde, **333**, to the standard reaction conditions with propiophenone delivered α-arylated product **334** in a good yield of 79%, which itself cyclised in a good yield of 73% to produce thienopyridine **335** (**Scheme 124**). The structure of **124** was confirmed by the singlet from the C1 pyridine proton at 9.10 ppm in the ^{1}H NMR spectrum.



Scheme 124: *Investigating the scope with heteroaryl bromides*

However, the corresponding acetal of 2-bromopyridine-3-carbaldehyde, **336**, was unreactive under these reaction conditions and indeed any other reactions conditions tried (including the use of $PdCl_2(Amphos)_2$, different bases and higher temperatures). However, 2-bromopyridines had previously been shown to be competent reaction partners in α-arylation reactions by Hartwig and coworkers.[70] It is postulated that a reason for the unreactivity of this substrate might be the formation of a stable complex between the substrate and palladium under the reaction conditions, such as dimer **338** (**Figure 19**).



338

Figure 19: *Postulated dimer **338** for explaining the unreactivity of substrate **336***

Further exemplification with heteroaryl bromides was not undertaken due to the somewhat limited commercial availability/expense of the heteroaryl bromide staring materials. However, this is a worthwhile area for future study.

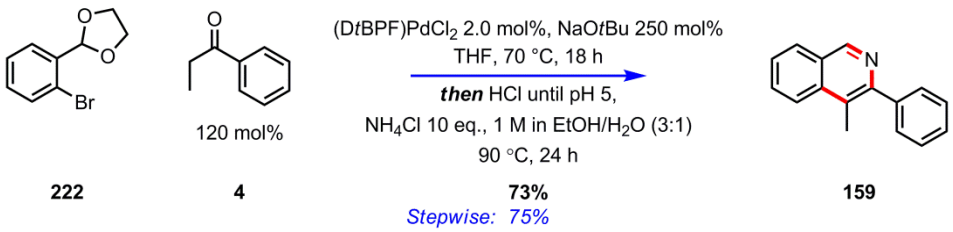
Overall it had been demonstrated that a range of electron-rich and electron-poor isoquinolines could be accessed in high yields. The synthetic protocol was tolerant to sensitive functional groups such as methyl esters and nitro groups. It had also now been established that substitution could be tolerated at all positions around the isoquinoline core. The versatility available from this *de novo* approach to isoquinolines made this a powerful piece of synthetic methodology.

2.2.9 Developing a one-pot procedure

A large range of isoquinolines had now been accessed and it was wondered whether the synthetic protocol could be altered to improve the operational simplicity of carrying out the reaction. The α-arylation had always been worked up directly and the intermediate purified before progressing onwards to synthesise the isoquinoline. However, as the THF solvent for the first reaction and EtOH/H_2O solvent for the second reaction are miscible, it was conceived that the α-arylation and subsequent aromatisation reactions could be performed sequentially in one-pot, hence eliminating one work up and instance of column chromatography from the reaction sequence.

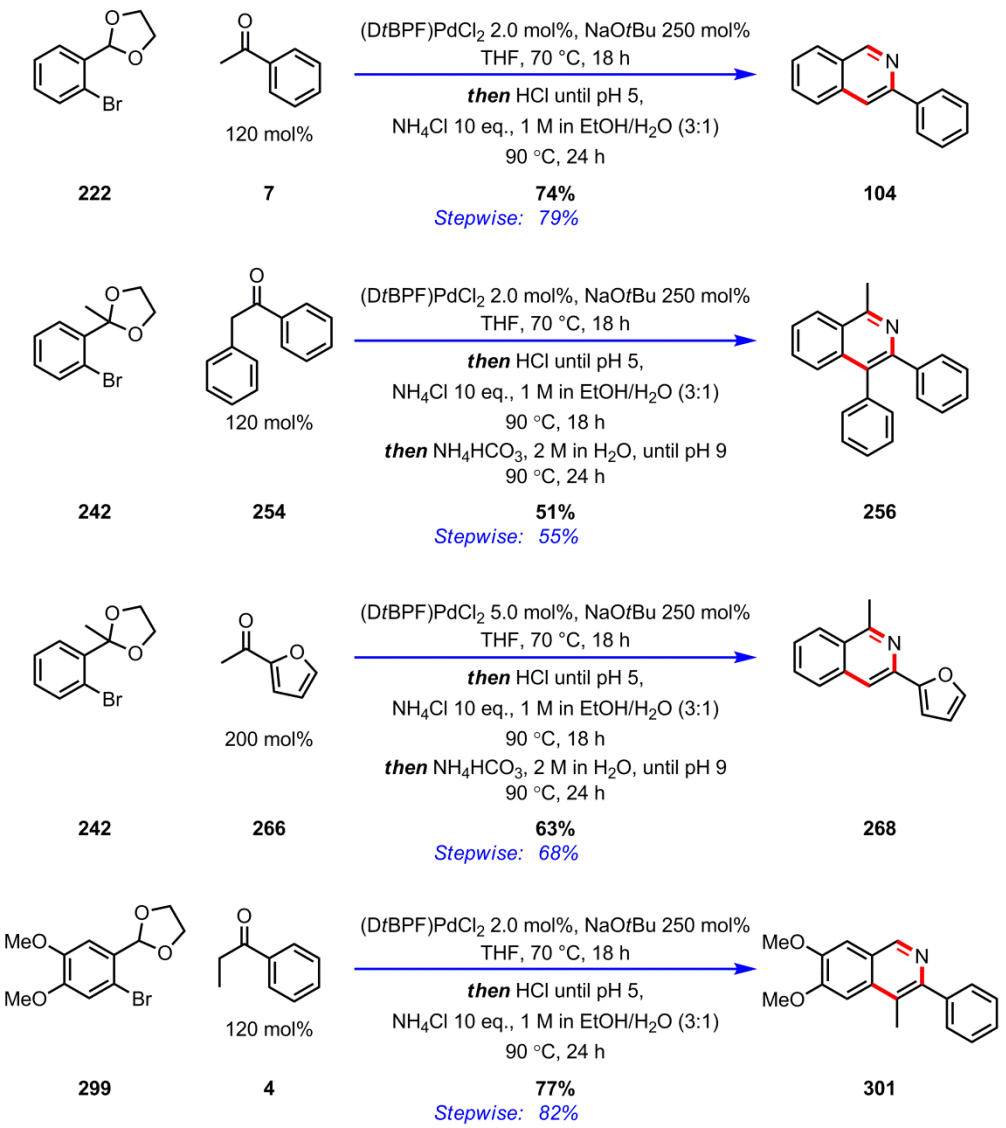
This one-pot protocol was first examined with aryl bromide **222** and propiophenone, **4**. The α-arylation reaction was carried out as previously optimised and after TLC analysis indicated complete reaction, the mixture was cooled to room temperature and the appropriate volume of the cyclisation solution was added. However, analysis of the pH of the reaction after addition of the ammonium chloride solution indicated that the reaction was not as acidic as

before. Presumably, the unreacted NaO*t*Bu deprotonated some of the NH_4^+ to NH_3 and the combination of NH_3 and NH_4^+ was causing buffering effects. To overcome this, it was decided to first quench the excess NaO*t*Bu and adjust the reaction mixture to pH 5 by the dropwise addition of aqueous 1 M HCl, before adding the appropriate volume of cyclisation solution and putting the substrate on to cyclise. This procedure delivered isoquinoline **159** in a superb yield of 73% (**Scheme 125**). The fact that the one-pot yield is only marginally less than the overall yield of 75% for the stepwise procedure to **159**, makes this protocol highly valuable to the synthetic chemist.



Scheme 125: *One-pot synthesis of isoquinoline **159***

A three component (aryl bromide, ketone, ammonia source), one-pot coupling had now been developed where three of the six heteroarene ring bonds were made in a single synthetic operation. This was further exemplified on four additional isoquinolines that had been previously synthesised in a stepwise fashion (**Scheme 126**). All isoquinolines were synthesised in good to excellent yields, which were again only slightly diminished when compared to the isolated stepwise yields, but had the benefit of involving one less synthetic procedure.



Scheme 126: *One-pot synthesis of isoquinolines*

2.2.10 Modifying biologically-active steroids via the one-pot procedure

A large number of pharmaceutical drugs are based around a steroid core. For example, finasteride is used to treat benign prostatic hyperplasia and male pattern baldness, fluticasone and budesonide are anti-inflammatories that are used to treat asthma and rhinitis and mometasone furoate is used to treat inflammatory skin disorders such as eczema. The steroidal skeleton is often most significantly modified on the five-membered D-ring, usually with the addition of extra heteroatom or heterocyclic functionality (**Figure 20**).

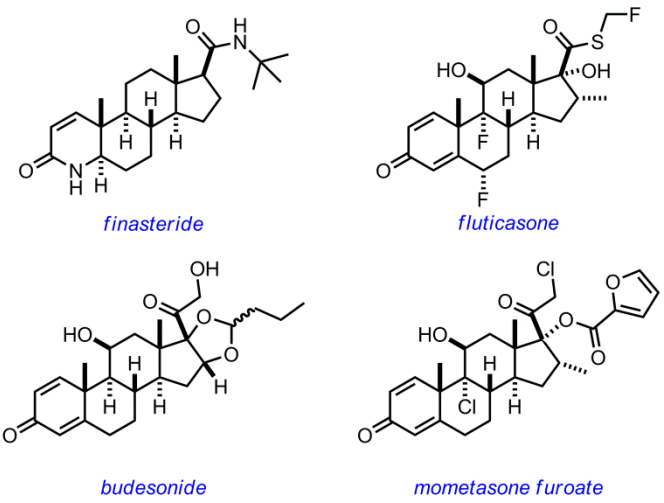


Figure 20: *Pharmaceutical drugs based on modified steroidal hormones*

It was thought that the one-pot protocol could potentially give access to isoquinoline-appended steroid skeletons and if successful would allow a diverse range of substrates to be quickly synthesised for medicinal screening. The steroidal hormones selected for exemplification of this procedure were estrone and androsterone. Estrone is one of the natural oestrogens (an important female reproductive hormone) and androsterone a male steroid hormone that can be readily converted into dihydrotestosterone (**Figure 21**).

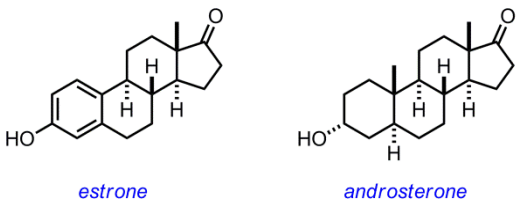
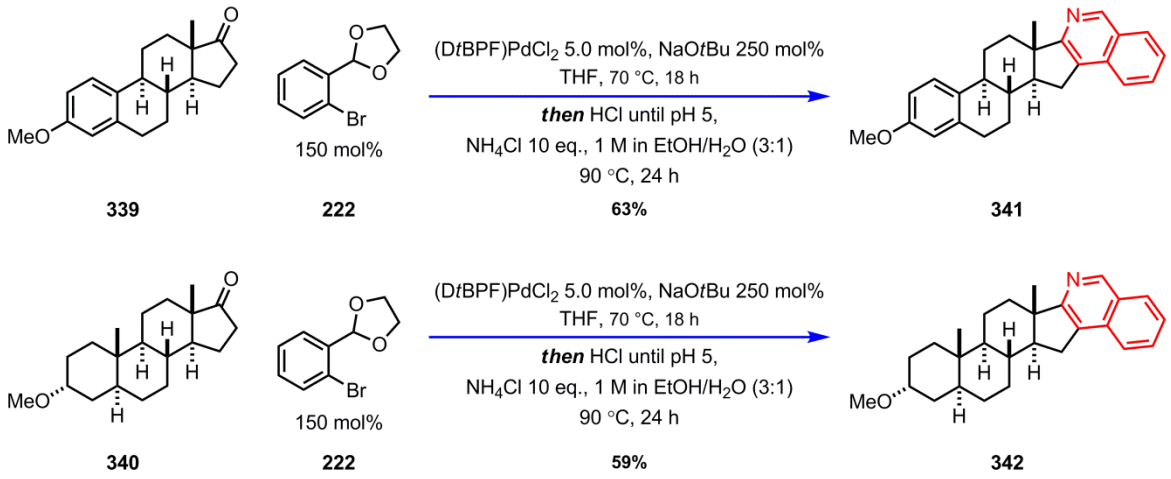


Figure 21: *Steroidal hormones chosen for investigation in this protocol*

A survey of the literature revealed that primary and secondary hydroxyl groups were not well tolerated in palladium-catalysed α-arylation reactions, presumably due to coordination of the oxygen to Pd(II) and then β-hydride elimination to give the carbonyl compound. Hence, the methyl ethers of estrone and androsterone were used. The methyl ether of estrone, **339**, is commercially available. The methyl ether of androsterone, **340**, was synthesised by addition of trimethyloxonium tetrafluoroborate to a solution of androsterone in CH_2Cl_2 in a yield of 99%. As the ketone partner was now the more costly reagent, this was

used as the limiting species, with the aryl bromide being used in excess (150 mol%) to try and ensure a high conversion of ketone to product. No evidence was ever observed to suggest the formation of any diarylated products under these conditions. Applying the one-pot procedure to **339** delivered a 63% yield of isoquinoline **341**, whilst **340** gave a 59% yield of isoquinoline **342** (**Scheme 127**).



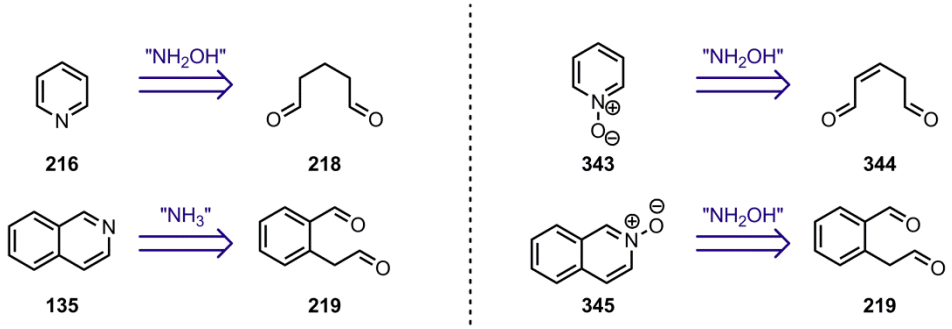
Scheme 127: *Derivatisation of estrone and androsterone under the one-pot conditions*

The fact that a highly complex hexacyclic motif (containing an isoquinoline moiety appended to a steroid) could be synthesised in such a facile manner was considered an important result. Variation in the aryl bromide partner would allow expedient access to an array of modified steroids, where important properties, such as the basicity of the isoquinoline nitrogen atom, could be readily adjusted by variation of the substituents around the isoquinoline scaffold. This protocol could thus be extremely valuable for the creation of libraries of target compounds in medicinal chemistry.

2.3 Altering the oxidation level of the isoquinoline framework

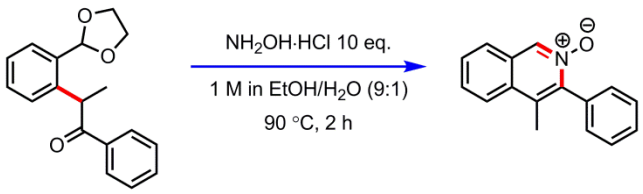
2.3.1 Isoquinoline N-oxides

It was decided to examine whether this methodology could be extended to allow access to the isoquinoline scaffold in different oxidation levels. In pyridine synthesis, whilst condensation of a 1,5-dicarbonyl with a source of ammonia leads to a dihydropyridine, condensation of the same 1,5-dicarbonyl **218** with a source of hydroxylamine delivers the pyridine **216** directly, with the cleavage of the N-O bond in the hydroxylamine providing the necessary oxidising power to increase the ring system from the dihydropyridine to the pyridine oxidation level. In this isoquinoline synthesis, the precursor **219** is such that condensation with a source of ammonia delivers the isoquinoline oxidation level directly. It was postulated therefore, that condensation of this isoquinoline precursor **219** with hydroxylamine might provide a direct route to isoquinoline *N*-oxides **345** (**Scheme 128**). A small amount of literature precedent revealed that analogous 1,5-dicarbonyls had been converted into the isoquinoline *N*-oxides directly by treatment with hydroxylamine,[201] however, no systematic study seemed to have been undertaken. In the pyridine series, there was surprisingly even less precedent for the conversion of unsaturated 1,5-dicarbonyls **344** directly to pyridine *N*-oxides **343** by treatment with hydroxylamine and so this definitely merited further study.



Scheme 128: *Accessing isoquinoline N-oxides directly*

Again intermediate **235** was chosen as the candidate for preliminary investigation. As before, the cyclisation conditions would need to be acidic in order to mediate acetal deprotection and it was thought this could be provided by a solution of $NH_2OH{\cdot}HCl$. Hence, a 1 M solution of $NH_2OH{\cdot}HCl$ was prepared in EtOH/H_2O (9:1) – again the minimum proportion of water needed to ensure complete solubility of the $NH_2OH{\cdot}HCl$. This solution was in the region of pH 4.5. This was slightly more acidic than the NH_4Cl solution (as might be expected by examining the relative pK_a data: NH_4^+ (9.25), NH_3OH^+ (8.05), both in H_2O, 25 °C. When intermediate **235** was heated in a solution of $NH_2OH{\cdot}HCl$ it underwent full conversion (to predominantly one new spot by TLC analysis) in a reaction time of just 2 h. Analysis of the ^{1}H NMR of the crude material indicated that predominantly isoquinoline *N*-oxide **346** had been synthesised (**Scheme 129**). Isoquinoline *N*-oxide **346** proved unstable to column chromatography on silica gel, but could be columned on basic alumina without degradation. After purification, an excellent yield of 93% of isoquinoline *N*-oxide **346** was obtained.



Scheme 129: *Conversion of intermediate **235** into isoquinoline N-oxide **346***

Confirmation that isoquinoline *N*-oxide **346** had been synthesised could clearly be observed by comparing its spectral data with that of the corresponding isoquinoline **159** (**Table 15**). In both the ^{1}H and ^{13}C NMR of **346**, a number of key signals were observed at values upfield of those of the corresponding isoquinoline **159**, as to be expected from the more electron-rich nature of the isoquinoline *N*-oxide.

Signal	Isoquinoline 159	Isoquinoline *N*-oxide 346
	^{1}H NMR chemical shift, δ/ppm	
C1	9.22	8.86
C5	8.01	7.73
C8	8.07	7.93
	^{13}C NMR chemical shift, δ/ppm	
C1	150.2	135.0
C3	151.9	146.3

Table 15: *Selected ^{1}H and ^{13}C NMR data for isoquinoline **159** and isoquinoline N-oxide **346***

The structure of isoquinoline *N*-oxide **346** was then proved unambiguously by X-ray crystal structure analysis (**Figure 22**).

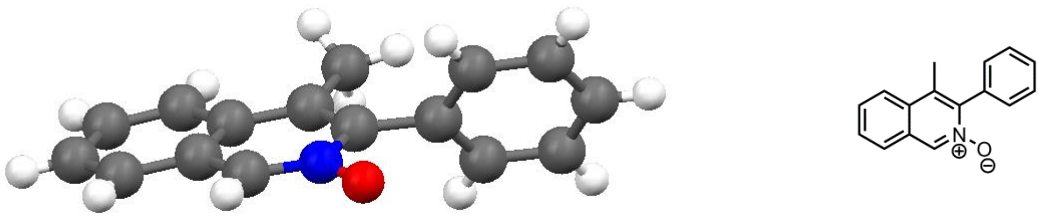
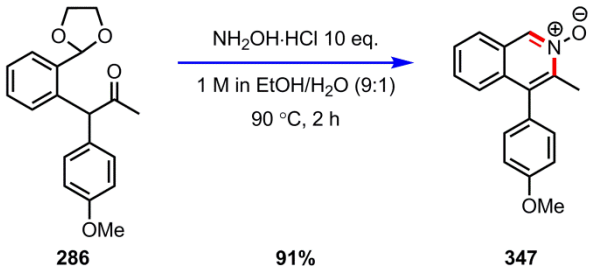


Figure 22: *Representation of the X-ray crystal structure of isoquinoline N-oxide **346** (solved by another group member)*

It was subsequently demonstrated that intermediate **286** could be converted into isoquinoline *N*-oxide **347** in a similarly high yield of 91% (**Scheme 130**).



286 **91%** **347**

Scheme 130: *Conversion of intermediate **286** into isoquinoline N-oxide **347***

This project was then taken onward for exemplification by a Part II student in the group under supervision of the author, where it was shown that a wide array of isoquinoline *N*-oxides could be synthesised in excellent yields from the corresponding α-arylated intermediates (**Figure 23**).[195,202]

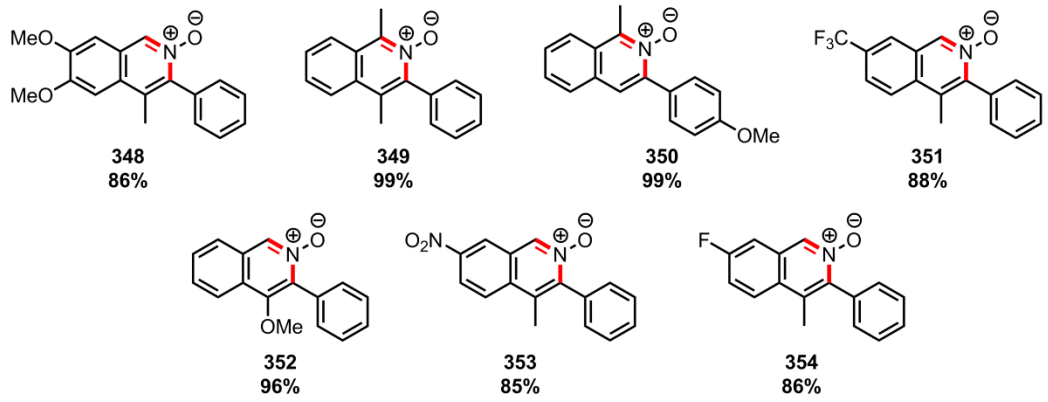
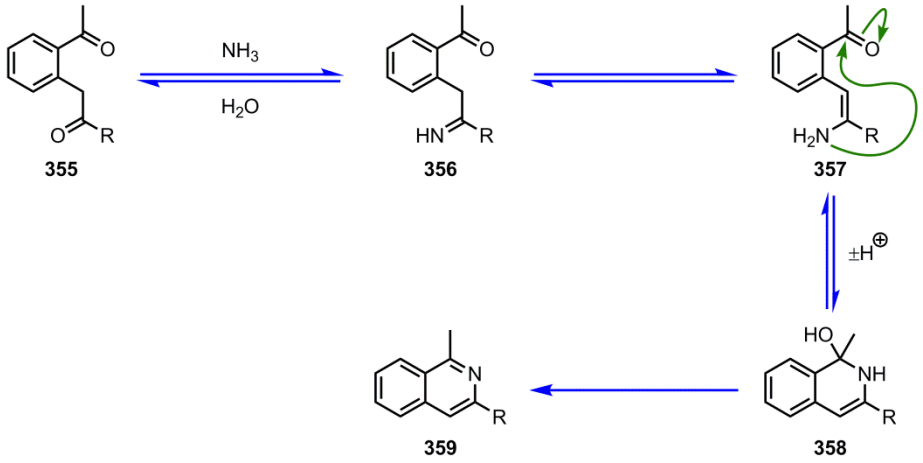


Figure 23: *Further isoquinoline N-oxides synthesised by another group member*

It was also later shown by the Part II student that isoquinoline *N*-oxides could be accessed in high yields directly from the aryl bromide precursors in an analogous one-pot procedure. It is pertinent to note that the reaction time to synthesise all isoquinoline *N*-oxides in **Figure 23** was only 2 h, and that isoquinoline *N*-oxides bearing a methyl substituent at C1 (such as **349** and **350**) could be synthesised in extremely high yields without needing to basify the reaction conditions after hydrolysis of the acetal as in the isoquinoline case. The ease of synthesising isoquinoline *N*-oxides is likely due to the increased nucleophilicity of the hydroxylamine-derived nitrogen atom relative to the ammonia-derived nitrogen atom. The enhanced nucleophilicity of an atom in a molecule due to the presence of an adjacent atom with a lone pair of electrons is called the alpha effect and was first observed by Jencks and Carriuolo in 1960.[203,204] Several reasons behind this effect have been put forward to date, including the stabilisation of the transition state for nucleophilic attack by the adjacent lone pair as the nucleophilic lone pair moves towards the substrate,[205] a destabilisation of the ground state due to repulsion between the adjacent lone pairs,[206] a greater thermodynamic product stability[207] and differing solvation properties.[208] This enhanced nucleophilicity is likely to be most important in the step of the mechanism where the heterocyclic ring is closed, as this is believed to be the slow step.

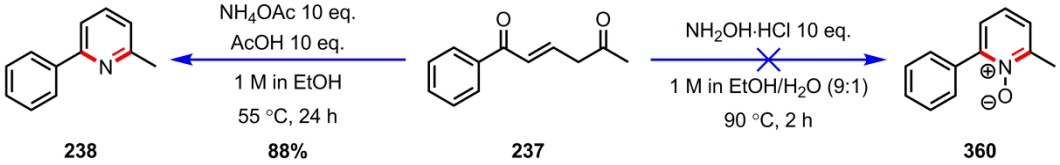
A proposed mechanism for isoquinoline synthesis is shown in **Scheme 131**, whereby imine formation occurs on the carbonyl to become C3 in the isoquinoline (**355** → **356**). Tautomerisation of imine **356** to *Z*-enamine **357** is necessary prior to cyclisation to **358**. Once cyclised, **358** loses water to form isoquinoline **359**, a reaction which presumably has a large thermodynamic driving force due to the generation of aromaticity.



Scheme 131: *Proposed mechanism for the formation of isoquinoline **359***

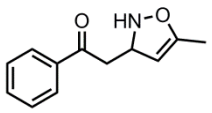
In the case of C1 methyl isoquinolines, where the optimum pH for their synthesis is around 9, it is likely that initial imine formation is not responsible for the need to basify the reaction, as this is widely accepted to be fastest at pH 4-6. It is presumed that the high pH is required to ensure the enamine nitrogen atom is fully deprotonated in order to attack the pendant ketone, which is thought to be the most difficult step. In the case of C1 unsubstituted isoquinolines, this results in a less sterically hindered tetrahedral intermediate and so is presumed less of an energetic barrier and thereby can take place at a lower pH. In the isoquinoline *N*-oxide case, the –OH group attached to the enamine nitrogen may both increase its nucleophilicity due to the alpha effect and also reduce its basicity – pK_a data: NH_4^+ (9.25), NH_3OH^+ (8.05), both in H_2O, 25 °C; hence facilitating cyclisation more rapidly and also at lower pH.

The enhanced nucleophilicity of hydroxylamine over ammonia may also explain why the direct synthesis of pyridine *N*-oxides from unsaturated 1,5-dicarbonyls is not well known. A sample of intermediate **237** was obtained from another member of the group (**237** can be synthesised readily *via* a literature procedure).[190] Previously the group had shown that intermediate **237** could be converted into pyridine **238** in high yield by treatment with NH_4OAc, however treatment of **238** with the optimised hydroxylamine conditions led to no formation of pyridine *N*-oxide **360** (**Scheme 132**).

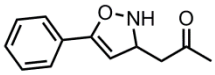


Scheme 132: *Failure of intermediate **237** to form pyridine N-oxide **360***

Instead, a complex mixture of inseparable products was formed in the reaction mixture. Analysis of the ^{1}H NMR of this crude material indicated that no pyridine or pyridine *N*-oxide was present. All starting material had been consumed and there were also no olefinic signals in the ^{1}H NMR spectrum. It was postulated that the nitrogen atom of hydroxylamine underwent conjugate addition onto intermediate **237**, followed by cyclisation of the oxygen atom of that hydroxylamine onto the adjacent carbonyl. This would give compounds such as **361** and **362** (**Figure 24**), which presumably would be dead end pathways *en route* to a pyridine *N*-oxide. The material from the reaction also quickly decomposed meaning no confirmatory evidence was obtained to support this hypothesis. However, this does suggest a reason as to why the reaction works well in the isoquinoline *N*-oxide series, as the aromaticity of the benzene ring makes the conjugate addition pathway both kinetically and thermodynamically unfavourable.



361



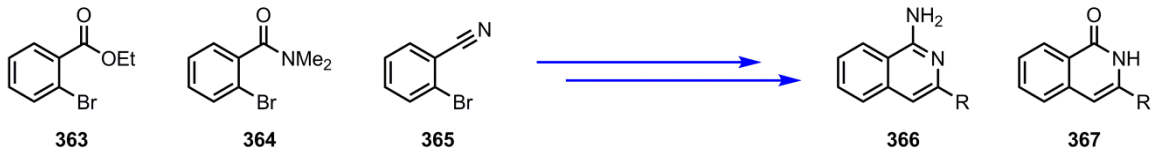
362

Figure 24: *Postulated compounds **361** and **362** to explain the lack of pyridine N-oxide formation*

Despite the failure in the pyridine *N*-oxide series, it was gratifying that a range of isoquinoline *N*-oxides could be obtained in such a facile manner. Direct access to isoquinoline *N*-oxides is of high value as their synthesis from the parent isoquinoline is not without its problems, often requiring harsh conditions that do not tolerate sensitive functionality in the molecule or employing non atom-economical reagents. Isoquinoline *N*-oxides are particularly useful if further substitution on the arene ring is desired after the ring synthesis. They are more electron-rich than the corresponding isoquinoline and so undergo S_EAr with much greater ease. They also show great propensity for C-H functionalisation reactions,[209-211] cycloadditions[212] and the addition of nucleophiles under milder conditions.[213]

2.3.2 Isoquinolines from higher oxidation level aryl bromides

The successful synthesis of isoquinoline *N*-oxides demonstrated that higher oxidation level isoquinoline scaffolds were accessible using this methodology through utilising a higher oxidation level reagent in the aromatisation step. An alternative possibility would be to use a higher oxidation level reagent in the initial α-arylation step, by replacing the acetal-protected *ortho*-bromobenzaldehyde with either an *ortho*-bromo ester **363**, amide **364** or nitrile **365** (**Scheme 133**). If carried through the synthesis, this could potentially lead to 1-aminoisoquinolines **366** or 1-hydroxyisoquinolines (which exist in the carbonyl tautomeric form as 1-isoquinilones **367**).[214,215]

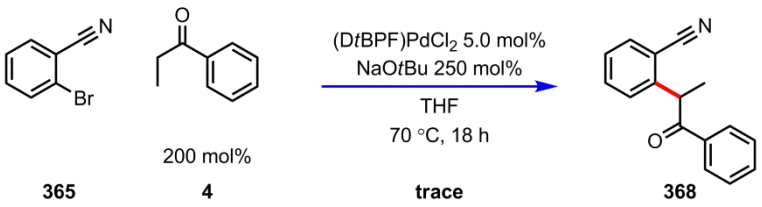


363 **364** **365** **366** **367**

Scheme 133: *Potential products from higher oxidation level aryl bromides*

As there was precedent for all of these functional groups surviving the α-arylation reaction conditions (esters,[42,74] amides,[26] nitriles[26,42,71,216,217]), no protecting group strategy was deemed necessary. Ester **363** and nitrile **365** were commercially available and *N*,*N*-dimethylamide **364** was synthesised from 2-bromobenzamide in 88% yield *via* a literature procedure.[218]

The α-arylation reaction of propiophenone with ester **363** was attempted with the bases NaO*t*Bu, Cs_2CO_3, K_3PO_4, and LiHMDS, with both (D*t*BPF)$PdCl_2$ and $PdCl_2$(Amphos)$_2$ catalysts. In all cases, no α-arylated product was observed. With Cs_2CO_3, K_3PO_4 and LiHMDS both propiophenone and ester **363** were recovered unreacted at the end of the reaction. With NaO*t*Bu, a complex mixture of products was obtained, but it was clear that the ethyl ester in **363** had not survived as the characteristic quartet and triplet signals of the OCH_2CH_3 group were absent in the ^{1}H NMR spectrum of the crude material. Amide **364** also proved to be completely unreactive under the α-arylation reaction conditions with propiophenone, with unreacted starting material returned in all cases. With nitrile **365** and propiophenone, no α-arylated product was observed with the weaker bases Cs_2CO_3 and K_3PO_4 and both starting materials were recovered unreacted. With LiHMDS, decomposition of the aryl bromide starting material occurred. Interestingly, with NaO*t*Bu, analysis of the NMR of the crude material from the reaction indicated that a small amount of α-arylated product **368** had been formed (**Scheme 134**).



Scheme 134: *α-Arylation of ortho-bromonitrile* ***365***

In the ^{1}H NMR spectrum a quartet was observable at 5.18 ppm from the α-aryl methine proton, and in the ^{13}C NMR spectrum a quaternary signal was observed at 117.9 ppm from the nitrile group. However, due to the similarity in polarity between the product and the starting material, purification of this small quantity of material was not possible. Higher palladium loadings, higher temperatures or longer reaction times failed to deliver any more of the α-arylated product.

The failure of the ester and amide to be good coupling partners in the α-arylation reaction could possibly be attributed to intramolecular coordination of the carbonyl oxygen to the palladium, stabilising the Pd(II) species formed after oxidative addition and making it less vulnerable to attack by the enolate. The linear geometry of the nitrile would prevent such intramolecular coordination, but it was possible that intermolecular coordination of the nitrogen of the nitrile to palladium was killing the catalytic activity of the palladium (**Figure 25**).

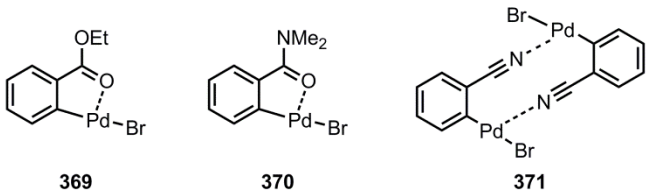


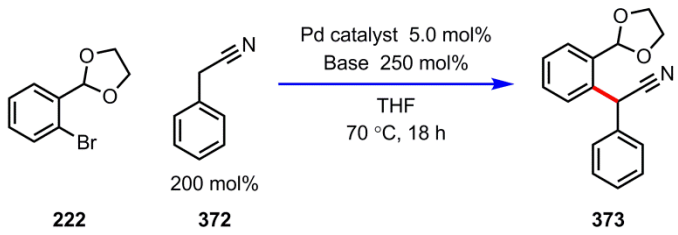
Figure 25: *Postulated complexes to explain the unreactivity of substrates* ***363***, ***364*** *and* ***365***

As these substrates contained electron-deficient aromatic rings there was the possibility of the coupling reaction taking place *via* an S_NAr mechanism, and indeed there was literature precedent for *ortho*-bromobenzonitriles coupling with carbon nucleophiles *via* an S_NAr

pathway.[219] However, control reactions without palladium indicated that this was not the case for any of these substrates under these reaction conditions.

2.3.3 α-Arylation of nitrile enolates

It was subsequently decided to investigate the α-arylation of higher oxidation level enolates. The successful α-arylation of ester or nitrile enolates could eventually lead through to 3-hydroxyisoquinolines or 3-aminoisoquinolines. The α-arylation of nitrile enolates was attempted first. As the protons α to a nitrile are typically less acidic than those α to the corresponding ketone (because delocalisation of the negative charge onto a nitrile nitrogen is less effective than a ketone carbonyl), it was decided to attempt the α-arylation reaction with 2-phenylacetonitrile, **372** due to the acidifying nature of the phenyl substituent (the pK_a of 2-phenylacetonitrile in DMSO is 21.9,[220] compared to 24.4 for propiophenone.[31]) The α-arylation reaction was attempted with aryl bromide **222** (**Scheme 135**).



Scheme 135: *α-Arylation of 2-phenylacetonitrile,* ***372***

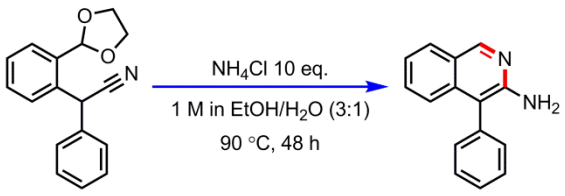
Entry	Palladium catalyst	Base	Isolated Yield of 373
1	(D*t*BPF)PdCl$_2$	NaO*t*Bu	17%
2	PdCl$_2$(Amphos)$_2$	NaO*t*Bu	24%
3	(D*t*BPF)PdCl$_2$	K$_3$PO$_4$	39%
4	PdCl$_2$(Amphos)$_2$	K$_3$PO$_4$	45%
5	(D*t*BPF)PdCl$_2$	Cs$_2$CO$_3$	64%
6	PdCl$_2$(Amphos)$_2$	Cs$_2$CO$_3$	69%

Table 16: *Screening of different catalysts and bases in the α-arylation of* ***372***

The α-arylation reaction was attempted with either (D*t*BPF)PdCl$_2$ or PdCl$_2$(Amphos)$_2$ and a variety of bases (**Table 16**). Upon reaction with (D*t*BPF)PdCl$_2$ and NaO*t*Bu (Entry 1), a

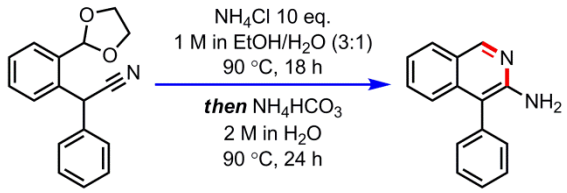
17% yield of α-arylated intermediate **373** was obtained. The structure of intermediate **373** was confirmed by the singlet at 5.95 ppm from the α-aryl methine proton in the ^{1}H NMR spectrum, and the C≡N stretch at 2244 cm^{-1} in the IR spectrum. With $PdCl_2(Amphos)_2$ a slightly higher yield of 24% was obtained (Entry 2). K_3PO_4 gave higher yields of **373** than NaO*t*Bu (Entries 3 and 4), but the best yields were obtained with Cs_2CO_3 (Entries 5 and 6).

With **373** in hand, attention turned towards its cyclisation to the isoquinoline. Under the optimised reaction conditions for the cyclisation of the intermediates from the α-arylation of ketones, intermediate **373** was much more sluggish to react. After an extended reaction time of 48 h, a 29% yield of 3-aminoisoquinoline **374** was obtained (**Scheme 136**).



Scheme 136: *Cyclisation of intermediate **373** to 3-aminoisoquinoline **374***

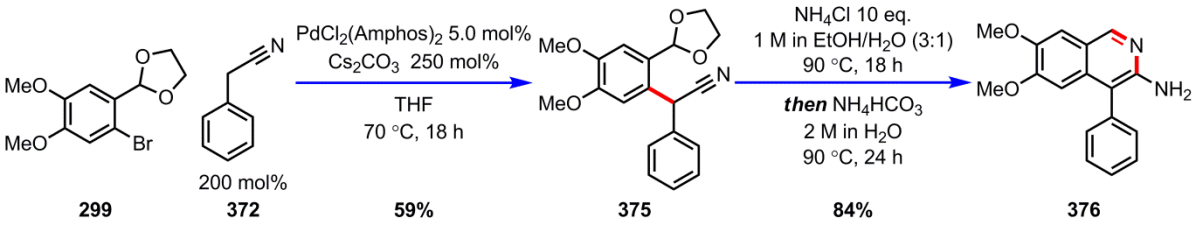
As little was known about the mechanism of cyclisation, it was conceivable that either a 3-aminoisoquinoline or a 3-hydroxyisoquinoline could have formed. Confirmation that a 3-aminoisoquinoline had been synthesised was evident in the ^{1}H NMR spectrum where there was a broad singlet at 4.42 ppm with the relative intensity of two. In addition, all the data obtained for **374** matched that in the literature.[221] Performing the cyclisation under more acidic conditions (pH 1) with the addition of 1 M HCl to the reaction mixture made the conversion to **374** even slower, indicating that acetal hydrolysis or protonation of a leaving group was unlikely to be the rate-determining step. Applying the cyclisation conditions optimised for C1 methyl isoquinolines was far more successful, with a 73% yield of **374** being obtained (**Scheme 137**).



Scheme 137: *Improved cyclisation of intermediate **373** to 3-aminoisoquinoline **374***

Further basification with NH_4OH did not further improve the reaction yield or increase the reaction speed. The fact that these intermediates only cyclised under more basic conditions hinted that having a fully deprotonated nitrogen atom in the cyclisation step may be key. However, details on the mechanism, including which (if any) nitrogen atom in **374** originated from the nitrile are unknown. Future work with the use of ^{15}N-labelled reagents and ^{1}H-^{15}N heteronuclear NMR correlation experiments could potentially shed more light on the mechanism of this cyclisation.

This protocol was then further exemplified in the coupling reaction between aryl bromide **299** and 2-phenylacetonitrile, **372** (**Scheme 138**). This proceeded in 59% yield to furnish intermediate **375**. Intermediate **375** could be converted in an excellent yield of 84% to 3-aminoisoquinoline **376**.

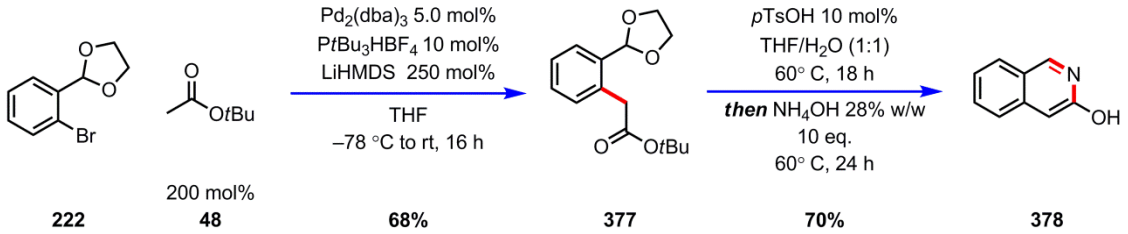


Scheme 138: *Synthesis of 3-aminoisoquinoline **376***

This reaction procedure was subsequently attempted with less acidic nitriles. Unfortunately, the use of propionitrile and butyronitrile was completely unsuccessful, even with a range of stronger bases. Hence in this reaction system, it seemed the coupling was limited to more acidic nitriles with pK_a values in the low to mid twenties and not too dissimilar from many of the ketones used, rather than nitriles such as propionitrile (with a pK_a of 32.5 in DMSO).[56]

2.3.4 α-Arylation of ester enolates

The α-arylation of ester enolates was investigated by the supervised Part II student, whereby it was found that the optimal conditions for the coupling of *tert*-butyl acetate, **48** with aryl bromide **222** employed LiHMDS as a base and P*t*Bu$_3$ as the ligand for palladium (**Scheme 139**), similar to conditions initially developed by Hartwig and coworkers for the α-arylation of esters.[222] As previously, the air stable tetrafluoroborate salt of P*t*Bu$_3$ was employed with the active P*t*Bu$_3$ being formed *in situ*. This delivered intermediate **377** in 68% yield. Intermediate **377** could be cyclised to deliver 3-hydroxyisoquinoline, **378**, in 70% yield, by firstly deprotecting the acetal under the previously optimised conditions and then basifying the reaction mixture with NH_4OH.[223] Unfortunately, the coupling of methyl and ethyl esters in this system was unsuccessful and *tert*-butyl esters of more sophisticated carboxylic acids coupled only in poor yields.



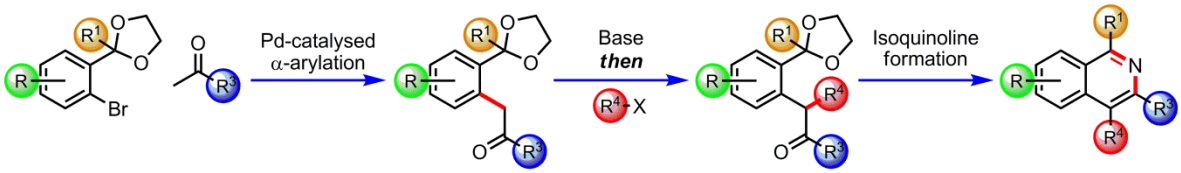
Scheme 139: *Synthesis of 3-hydroxyisoquinoline **378** by another group member*

Hence, the α-arylation of both nitrile and ester enolates had been achieved, albeit under higher palladium loading than for ketones, further expanding the scope of this methodology. Interestingly, the intermediates from nitrile arylation cyclised to furnish 3-aminoisoquinolines whereas those from ester arylation cyclised to 3-hydroxyisoquinolines. This may be indicative of the fact that the nitrile nitrogen and the ester carbonyl oxygen are retained in the corresponding isoquinolines, however, further investigations are needed to prove this.

2.4 Enhancing diversity at the C4 position by reaction with an electrophile

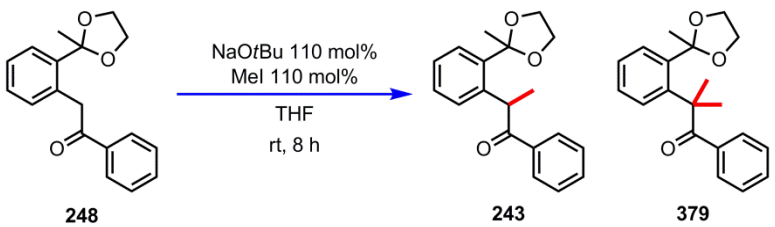
2.4.1 Initial investigations

The isoquinoline synthesis developed thus far had been a three component coupling protocol (the aryl bromide, ketone and ammonia source), carried out in either a two-pot operation or a one-pot operation. It was thought that the methodology could be further developed into a four component coupling procedure by deprotonating the initial product of the α-arylation reaction and then quenching the anion formed with an electrophile. This would allow a far greater variety of substitution to be possible at the C4 position of the resulting isoquinoline (**Scheme 140**). This would be of high synthetic importance as direct functionalisation of the C4 position of an isoquinoline skeleton is traditionally difficult, typically requiring addition to or reduction of the C1-N bond to give a dihydropyridine, reaction of the C3-C4 enamine with an electrophile at C4 and then elimination across or reoxidation of the C1-N bond.[224]



Scheme 140: *Strategy for obtaining further functionalisation at the C4 Position*

Intermediate **248** was chosen for initial study into further functionalisation and it was decided that iodomethane would be used as the electrophile. The desired product was a previously synthesised compound, which was thought to be useful when analysing the reaction (**Scheme 141**).

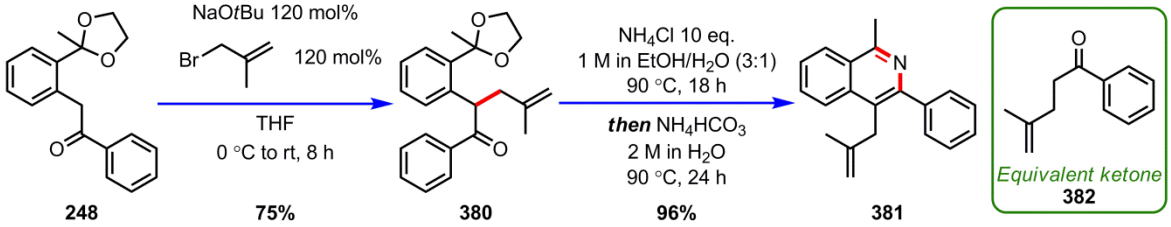


Scheme 141: *Initial methylation of ketone* ***248***

As it was known that the anion of **248** was stable under the α-arylation reaction conditions in the presence of NaO*t*Bu, this seemed the obvious choice as the base to employ to deprotonate the intermediate. Initial reaction conditions saw the ketone first deprotonated at room temperature with a slight excess of base, followed by dropwise addition of the electrophile. This appeared to give some of the desired methylated product **243**, but also some of the dimethylated product **379** and some unreacted starting material **248**, as evidenced by peaks in the mass spectrum with consistent masses to the corresponding molecular ions. Analysis of the reaction mixture by TLC showed three barely discernable spots that could not be fully separated from each other. Although dimethylated product **379** could presumably be separated at a later stage due to its inability to cyclise to the isoquinoline, the isoquinolines from **243** and **248** were also thought to be difficult to separate. A procedural change whereby the electrophile was added dropwise as a solution in THF at 0 °C and the reaction then warmed to room temperature seemed to reduce the amount of dimethylated product, but not eliminate it. Even reducing the amount of electrophile and base down to 95 mol% still led to some of **379**. The methylation had proved in principle that the intermediate could be functionalised with an electrophile, but it was thought that the sterically small nature of the methyl group actually made this one of the most challenging examples to perform selectively. As trapping this intermediate with iodomethane gave the product already available from the α-arylation of propiophenone it was decided to switch to a more complicated system for further investigation. A larger or more complicated electrophile would hopefully have the benefit of a more selective mono-trapping reaction, and also lead to products where the analogous ketone for their direct synthesis was unavailable.

2.4.2 Alkylation of intermediate 248 with larger electrophiles

It was decided to first attempt the alkylation of **248** with 3-bromo-2-methylpropene. Using a slight excess of both electrophile and base it was found that intermediate **380** could be obtained in a good yield of 75% (**Scheme 142**).

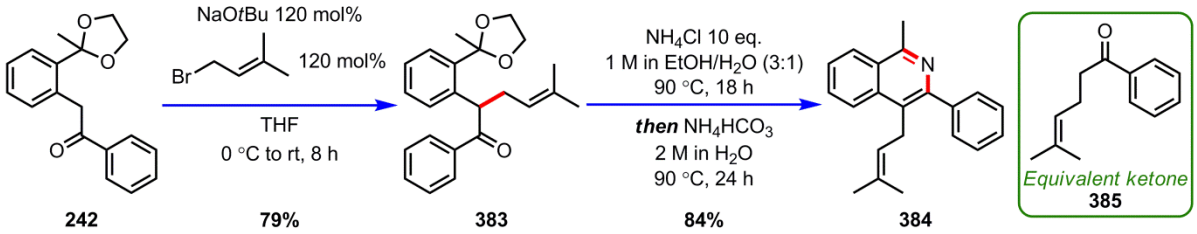


Scheme 142: *Alkylation of **248** with 3-bromo-2-methylpropene and cyclisation to **381***

The structure of **380** was confirmed by the methine proton α to the carbonyl appearing as a double doublet at 5.70 ppm in the ^{1}H NMR spectrum. The reaction conditions also appeared far more selective for monoalkylation, with no unreacted starting material remaining and only trace amounts of a spot on the TLC plate that was presumed to be the dialkylated product. It was presumed that the slightly lower reactivity of the electrophile and the more sterically hindered nature of the intermediate prevented dialkylation and as a result there was also sufficient electrophile to mono-alkylate all of the starting material. Intermediate **380** could be cyclised to isoquinoline **381** in an excellent yield of 96%, utilising the conditions that had been previously developed for the cyclisation of C1 methyl isoquinolines. The structure of **381** was validated by the singlet at 3.63 ppm in the ^{1}H NMR spectrum from the methylene group at the C4 position, and the corresponding lack of the singlet at 7.94 ppm which was known to originate from the analogous isoquinoline unsubstituted at that position. None of the isomeric isoquinoline, where the double bond had migrated into conjugation with the aromatic ring, was seen. This further illustrated the relatively mild nature of the reaction conditions. It is also important to note that this route involving an electrophilic

quench to isoquinoline **381** was equivalent to the direct α-arylation of a far more complicated ketone **382** that is not readily available.

In a similar fashion, the alkylation of **248** was also attempted with 1-bromo-3-methyl-2-butene (**Scheme 143**).



Scheme 143: *Alkylation of **242** with 1-bromo-3-methyl-2-butene and cyclisation to **384***

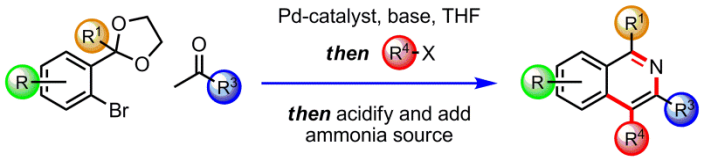
The alkylation proceeded in a high yield of 79% to give intermediate **383**, confirmed by the by the methine proton α to the carbonyl appearing as a triplet at 5.55 ppm in the ^{1}H NMR spectrum. Intermediate **383** cyclised in 84% yield to isoquinoline **384**, its structure proven by by the doublet at 3.69 ppm in the ^{1}H NMR spectrum from the methylene group, together with the lack of the signal from a proton at the C4 position. Again almost no dialkylation was observed.

2.4.3 Developing a four component, one-pot protocol

The α-arylation reaction and the alkylation of the resulting intermediate took place under very similar reaction conditions (with NaO*t*Bu in THF) and so it was postulated that the α-arylation reaction could be performed and then the electrophile added directly to quench the reaction. This was possible because the product of the α-arylation reaction has a significantly more acidic proton than the ketone starting material and so sits deprotonated as the anion *in situ* in the reaction mixture. Hence, after the α-arylation reaction has run to completion, the predominant species in the reaction is the anion of the α-arylation product,

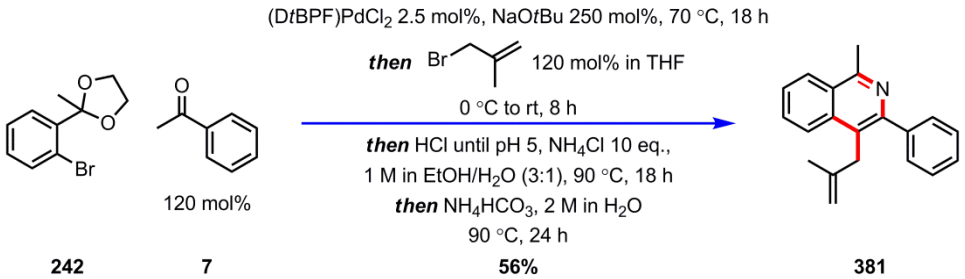
which is the species needed to react with the electrophile. A Part II student under supervision of the author demonstrated that this was possible on a couple of examples (*vide infra*).

It had also previously been demonstrated that three components (the aryl bromide, the ketone and the ammonia source) could be coupled together successfully in one-pot. It was postulated therefore that a three step (α-arylation, electrophile quench, cyclisation), four component (aryl bromide, ketone, electrophile, ammonia source) coupling could be carried out in a one-pot operation (**Scheme 144**).



Scheme 144: *One-pot, four component synthesis of isoquinolines*

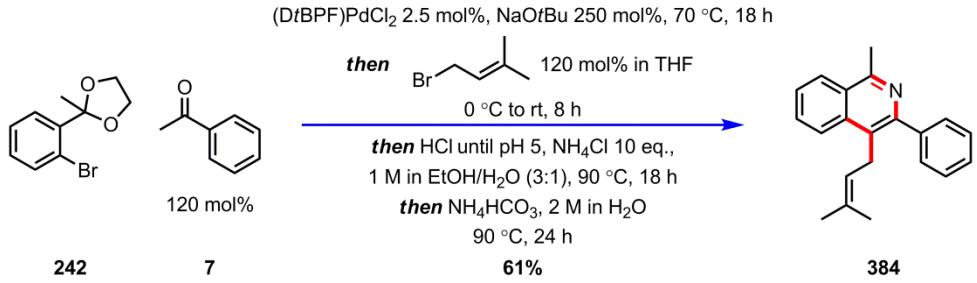
The procedure was first implemented with aryl bromide **242**, acetophenone and 3-bromo-2-methylpropene (**Scheme 145**). The α-arylation was carried out under standard conditions with 120 mol% ketone and 2.5 mol% catalyst. It was thought important not to use a large excess of ketone to try to increase the yield, to prevent competing alkylation of unreacted ketone in the next step. After this the reaction was cooled to 0 °C, the electrophile was added as a solution in THF (120 mol%) and the reaction left at room temperature for 8 h. The reaction was then acidified to pH 5 with 1 M aqueous HCl and the cyclisation procedure for C1 methyl isoquinolines was carried out as before.



Scheme 145: *One-pot synthesis of isoquinoline **381***

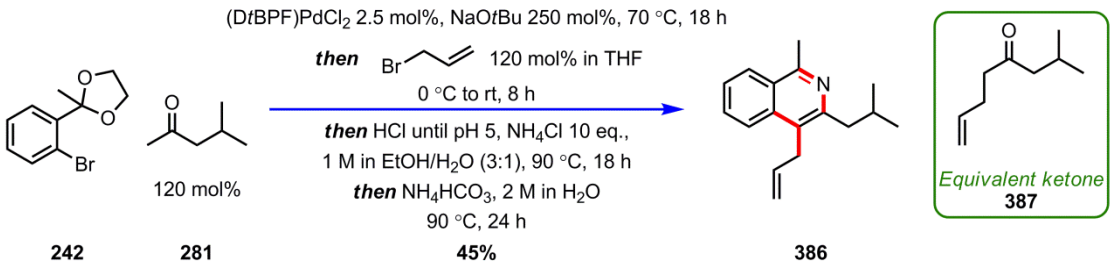
Pleasingly, a 56% yield of isoquinoline **381** was obtained after purification. This was an excellent yield for such a complicated protocol, and compared very well to the overall yield for the isolated stepwise procedure of 60% (with a 2.0 mol% Pd loading).

Implementing the one-pot procedure to synthesise isoquinoline **384** worked in a similarly high yield of 61% (**Scheme 146**). This is actually slightly higher than the 55% yield for the isolated stepwise procedure (with a 2.0 mol% Pd loading).



Scheme 146: *One-pot synthesis of isoquinoline **384***

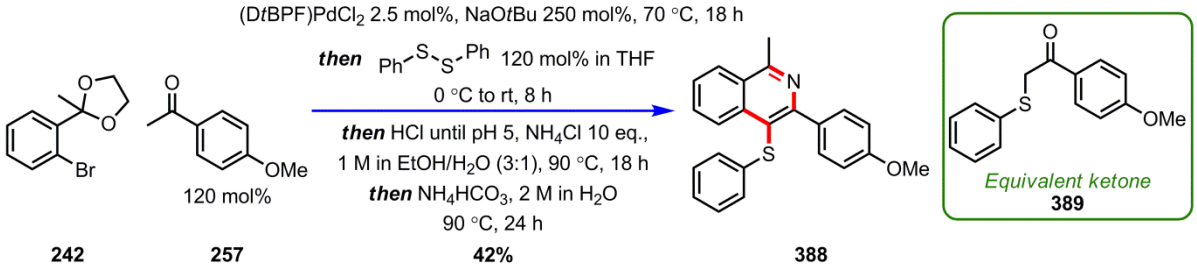
As the one-pot protocol was delivering isoquinolines in comparable yields to the stepwise sequence, it was decided to concentrate on the one-pot procedure from now on. The coupling of aryl halide **242**, *iso*butyl methyl ketone and allyl bromide delivered isoquinoline **386** in 45% yield (**Scheme 147**). Although slightly lower than the previous examples, this was still a good yield for the complexity of the transformation. The synthesis of isoquinoline **386** involving an electrophilic quench is also equivalent to the direct α-arylation of a ketone **387** with two flanking methylene groups, which would be difficult to arylate selectively.



Scheme 147: *One-pot synthesis of isoquinoline **386***

It was subsequently shown that diphenyldisulfide could be employed as the electrophile, delivering isoquinoline **388** in 42% yield (**Scheme 148**). The structure of **388** was confirmed

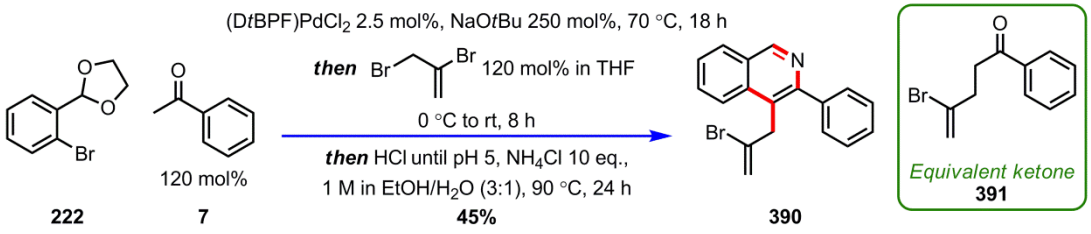
by the multiplet from 6.97-6.92 ppm in the ^{1}H NMR spectrum from the relatively electron-rich aromatic protons on the thiophenyl group.



Scheme 148: *One-pot synthesis of isoquinoline **388***

This was a particularly significant breakthrough, as heteroatom functionality had been installed at the C4 position, which had been previously very hard to do, for example the direct arylation of an enolate bearing thioether type functionality at the α-position had failed (*vide supra*).

Attention then turned to more highly functionalised electrophiles, in order to examine the functional group tolerance of this reaction. It was found that a vinylic bromide could be tolerated under the reaction conditions. The coupling of aryl bromide **222**, acetophenone and 2,3-dibromopropene delivered isoquinoline **390** in 45% yield (**Scheme 149**).



Scheme 149: *One-pot synthesis of isoquinoline **390***

The retention of the bromine atom in isoquinoline **390** was confirmed by the presence of only two vinylic signals in the ^{1}H NMR at 5.60 and 5.24 ppm (both quartets) along with a consistent characteristic isotope pattern of the ^{79}Br and ^{81}Br isotopes in the mass spectrum. No debrominated material was observed. The structure of isoquinoline **390** was then proved unambiguously by X-ray crystal structure analysis (**Figure 26**).

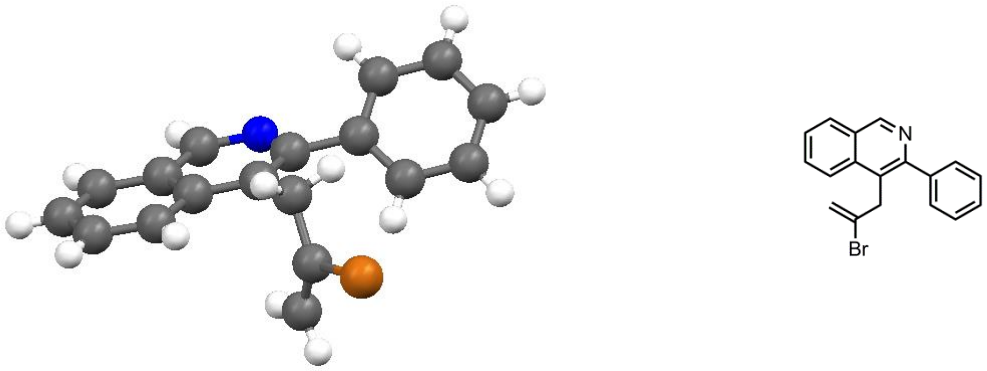
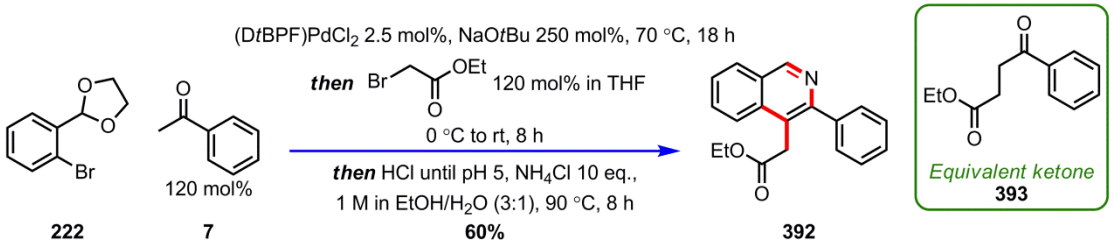


Figure 26: *Representation of the X-ray crystal structure of isoquinoline* ***390*** *(solved by another group member)*

Next it was considered whether an α-bromo ester would be a compatible electrophile with this protocol. To this end aryl bromide **222**, acetophenone and ethyl bromoacetate were subjected to the one-pot procedure and this furnished isoquinoline **392** in 60% yield (**Scheme 150**).



Scheme 150: *One-pot synthesis of isoquinoline* ***392***

The retention of the ester functionality in **392** was indicated by the characteristic stretch of the C=O group at 1729 cm^{-1} in the IR spectrum. During the cyclisation step of the one-pot procedure, traces of a very polar UV active spot were seen during TLC analysis of the reaction mixture. It was postulated that small amounts of the ester were being hydrolysed to the free acid during the cyclisation reaction and hence this reaction was stopped after 8 h (as opposed to the usual 24 h) as by then it was judged complete. The fact that an enolisable ethyl ester could survive both the basic and mildly acidic reaction conditions in such an excellent yield further demonstrated the capacity of this synthetic protocol.

This one-pot protocol was further exemplified by other members of the group (**Figure 27**).[225] Other successful alkyl electrophiles included benzyl bromide and ethyl iodide (to make **394** and **395** respectively). Halogen atoms could be installed at the C4 position in modest yields with Selectfluor® II and sulfuryl chloride (to make **108** and **396** respectively). Isoquinoline **397** was synthesised *via* a Michael addition to an enone electrophile. Other electrophiles that were not amenable to this synthetic protocol included epoxides, α-bromo ketones, some secondary and tertiary alkyl bromides, halogenating reagents such as NCS and NIS, chloroformates and DEAD.

It was also possible to perform two sequential but different α-arylation reactions on acetophenone in one-pot. The aryl bromide **222** (which is quite sterically hindered) was added first, followed by the addition of a second less hindered aryl bromide and reheating the reaction to 90 °C. This worked successfully to install electron-rich, electron-poor and reasonably hindered aryl groups at the C4 position (**398**, **399** and **400** respectively). Further work into this selective sequential diarylation is currently ongoing in the group.

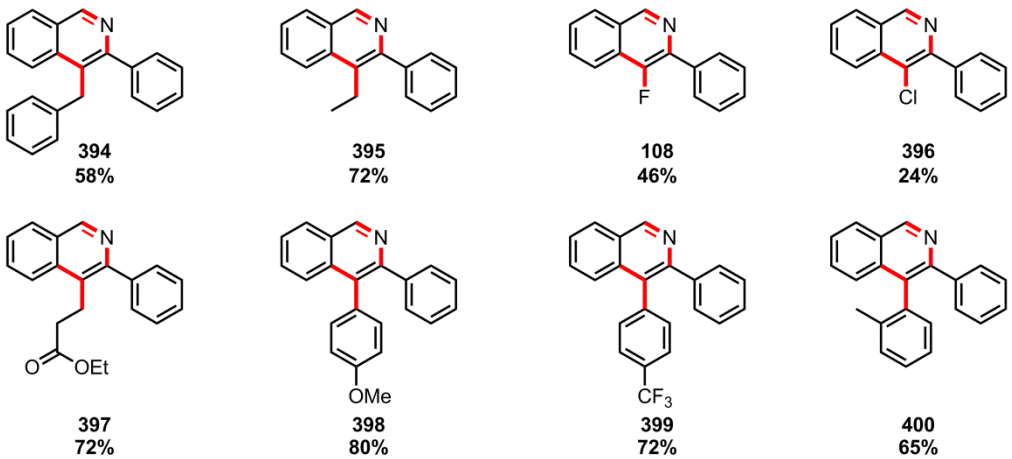


Figure 27: *Further isoquinolines synthesised by other group members*

Hence, a highly operationally simple synthetic procedure had been developed whereby complicated motifs could be synthesised in a one-pot operation from commerically available (or very readily accessible) starting materials. Significant extra diversity on the isoquinoline

scaffold could be obtained with the addition of an electrophilic quench to the reaction procedure, equivalent to the direct and completely regioselective α-arylation of highly complex ketones, which would be very challenging to do. This protocol greatly expanded the array of functional groups possible at the C4 position and the successful union of four components in three distinct synthetic steps should hopefully lend this procedure to many different applications.

2.5 The total synthesis of berberine chloride

2.5.1 Berberine

With the methodology for isoquinoline synthesis now well developed, it was decided to examine its use in the field of total synthesis of a natural product. The α-arylation reaction has only seen limited application in this field to date,[226-232] possibly due to the somewhat restricted functional group tolerance of this reaction, particularly for commonly-used protecting groups in synthesis.

An isoquinoline target was desired that would exemplify the methodology, but for which the synthesis of novel analogues would also be possible by this methodology (these could be important from a medicinal chemistry perspective). The natural product berberine was chosen (**Figure 28**).

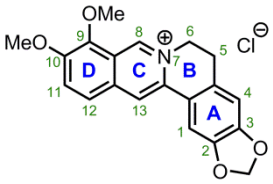


Figure 28: *Berberine chloride*

Berberine, a quaternary ammonium salt (often isolated as the chloride), is one of the isoquinoline alkaloids. It is found in the roots, stems and bark of numerous plants, including many of the *Berberis* genus (from which it takes its name). Berberine is brightly yellow coloured and *Berberis* plants have been used to dye wood, leather and wool (and still are today in certain parts of the world). Berberine exhibits a strong yellow fluorescence under UV light and is hence used for the staining of certain cell types. Berberine binds to nucleic acids and therefore has a very wide range of potential therapeutic properties.[233] It has shown antifungal,[234] antibacterial[235] and anti-inflammatory activity,[236] and is used both as a traditional medicine and a dietary supplement in some cultures. In addition, it has been used

in the treatment of diabetes,[237] for lowering blood cholesterol,[238] suppressing the growth of various types of cancer[239,240] and as an anti-depressant.[241]

2.5.2 Previous syntheses

Despite its wide ranging biological activity, there are surprisingly few total syntheses of berberine itself. As berberine is one of many closely related compounds, synthetic efforts have often focused on other members of the family. Initially, Perkin Jr. and coworkers (at the Dyson Perrins laboratory) focussed their efforts on oxyberberine (the derivative with a neutral nitrogen atom and carbonyl at C8) (**Figure 29**).[242,243]

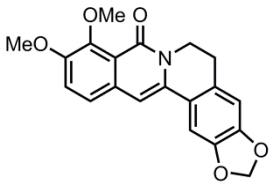
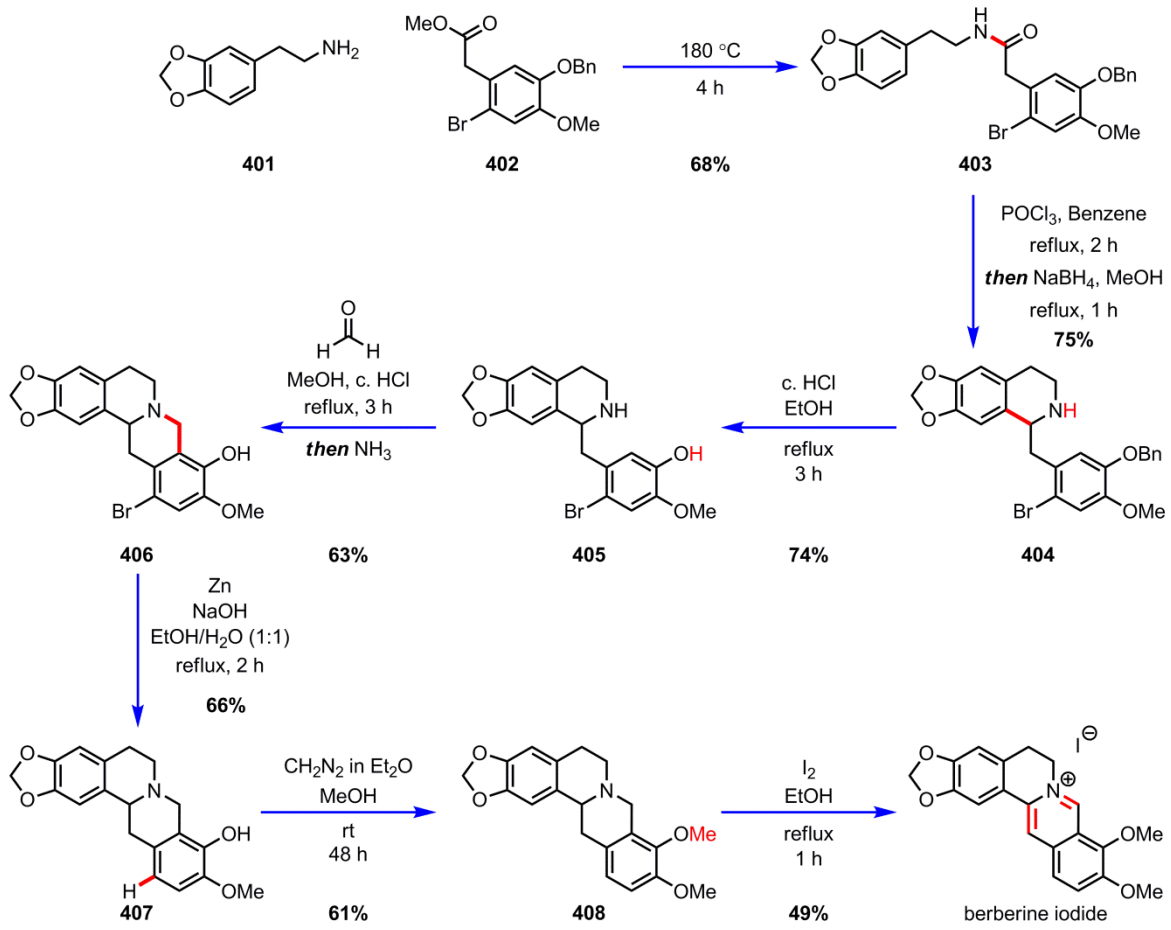


Figure 29: *Oxyberberine*

A total synthesis of berberine iodide was reported in 1969 by Kametani *et al.* (**Scheme 151**).[244] The synthesis began with the coupling of amine **401** and ester **402** to furnish amide **403**, which underwent a Bischler-Napieralski reaction with $POCl_3$ to form the B-ring of berberine and deliver intermediate **404**. Hydrolysis of the benzyl group to give **405** was followed by a Pictet-Spengler cyclisation (with formaldehyde as a one carbon skeletal component) to form the berberine C-ring and furnish intermediate **406**. The C-Br bond was then reduced with zinc to give **407**, followed by methylation of the phenol to give **408**. Finally oxidation of **408** with iodine delivered berberine iodide. The overall yield for the synthesis was 4.7%, but it should be noted that ester **402** is not commercially available and amine **401** is a costly starting material. In this synthesis, both the B-ring and the C-ring of berberine were formed by S_EAr reactions.

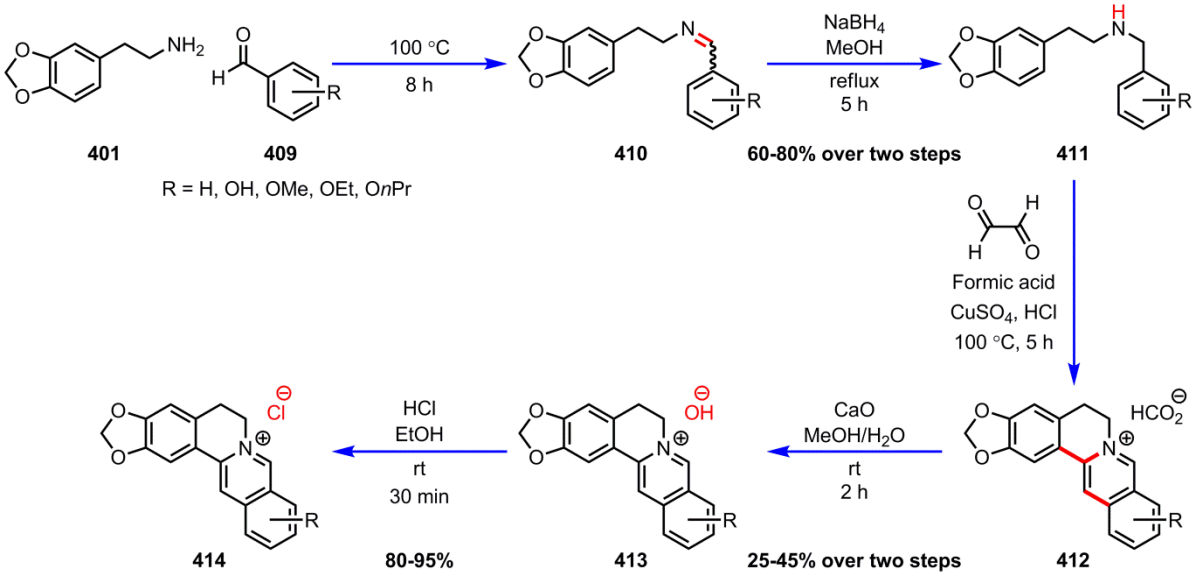


Scheme 151: *Kametani's total synthesis of berberine iodide*

More recently, attention has switched to the synthesis of berberine analogues in an effort to probe biological activity. Many of these analogues are synthesised semi-synthetically by the derivatisation of berberine itself and include analogues that are C9 *O*-alkylated,[245] C9 linked dimers,[246] C13 benzyl-substituted,[247] C9 *N*-substituted[248] and C2 and C3 hydroxy- and alkoxy-substituted.[249]

Another common synthetic route utilised glyoxal as a two carbon skeletal component.[250] This was employed by Song and coworkers to form a number of berberine analogues (**Scheme 152**).[251,252] Amine **401** was condensed with various benzaldehydes **409** to form imines **410** which were reduced *in situ* to the corresponding amines **411**. Upon treatment with glyoxal, a Pictet-Spengler reaction closed the B-ring and a Friedel-Crafts reaction

closed the C-ring to give **412** as a formate salt. Basification converted **412** to **413**, and upon treatment with HCl the chloride salt **414** was obtained.



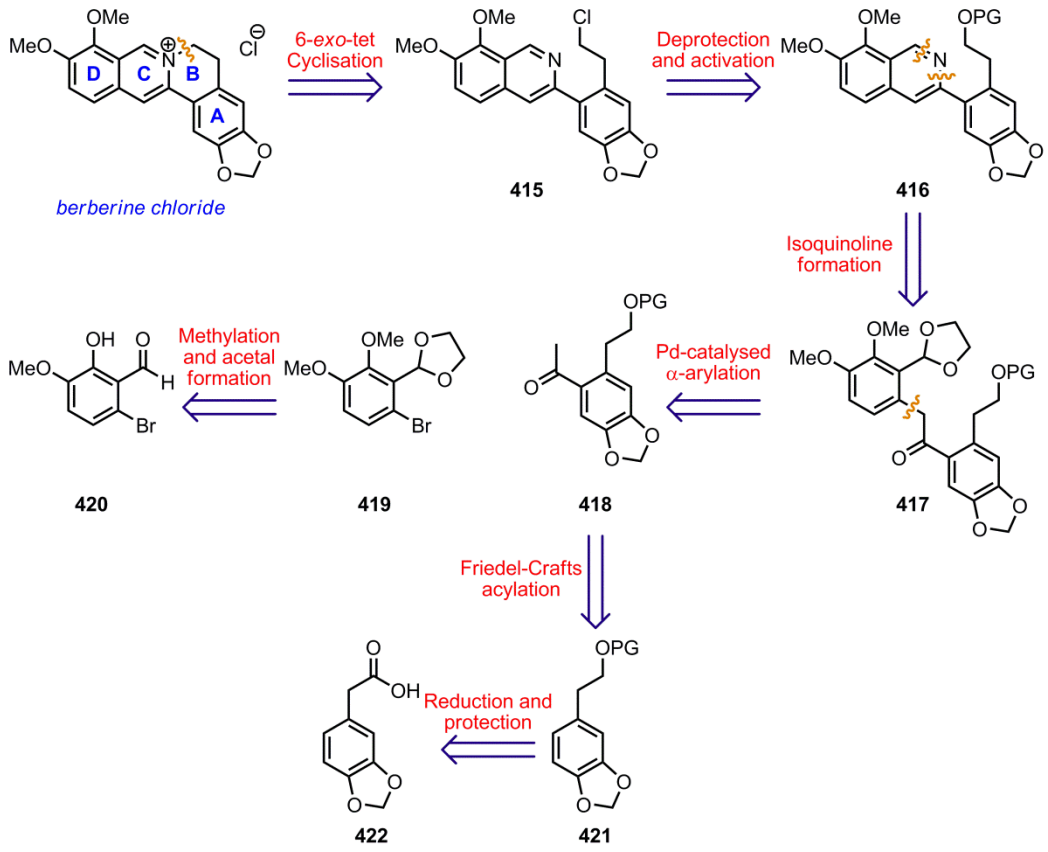
Scheme 152: *Route of Song and coworkers to berberine analogues*

Again, both the B-ring and C-ring were closed *via* S_EAr reactions. Although a number of other groups have made berberine analogues and there has been some optimisation of these routes in the patent literature, the dogma of synthesising the B and C-rings of these analogues utilising S_EAr chemistry still persists and has greatly limited the structural diversity of analogue scaffolds available, as it requires the A and D-rings to be electron-rich. In particular, berberine analogues with electron-deficient isoquinoline rings are not well documented. It was envisaged that application of the synthetic route to isoquinolines recently developed in this laboratory would avoid this restriction and would allow synthesis of both berberine itself and a range of electron-deficient analogues.

2.5.3 Retrosynthetic analysis

In the retrosynthetic analysis of berberine chloride, it was decided to save formation of the B-ring until the last synthetic step, due to the impracticality of handling isoquinolinium salts. It was proposed that this ring would be closed by the 6-*exo*-tet cyclisation of the nitrogen

atom in isoquinoline **415** onto the pendant primary chloride. This primary chloride would be masked as a protected primary hydroxyl group in **416** to be carried through the synthesis. Intermediate **416** would be the product of the aromatisation reaction of **417**, which would form the C-ring isoquinoline core of the molecule. Intermediate **417** would be delivered by the palladium-catalysed α-arylation reaction of ketone **418** with aryl bromide **419**. It was proposed that aryl bromide **419** could be formed in two steps from commercially available hydroxybenzaldehyde **420** *via* methylation and subsequent acetal formation. It was anticipated that ketone **418** would be synthesised from arene **421** by a Friedel-Crafts acylation reaction. Arene **421** would originate from the reduction and subsequent protection of the carboxylic acid group in the commercially available 3,4-(methylenedioxy)phenylacetic acid, **422** (**Scheme 153**).

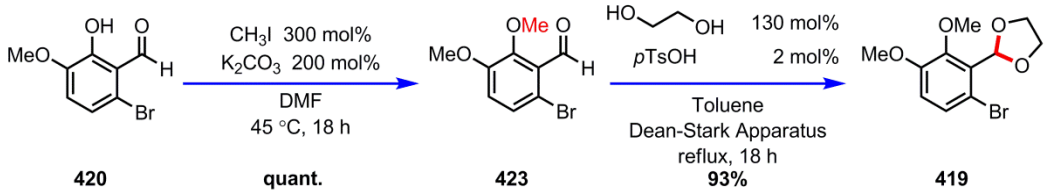


Scheme 153: *Retrosynthetic analysis of berberine chloride*

It was decided to use an acetate protecting group for the protection of the primary hydroxyl. It had already been shown that ester groups could survive the α-arylation reaction conditions and the aromatisation conditions (*vide supra* **322**, **392** and **397**), and it was thought that after the isoquinoline had been formed it would be a facile process to hydrolyse the acetate under aqueous basic conditions without affecting the rest of the molecule.

2.5.4 Synthesis of the aryl bromide partner

The synthesis of aryl bromide **419** commenced with the methylation of commercially available 6-bromo-2-hydroxy-3-methoxybenzaldehyde, **420** to form dimethoxyaldehyde **423**. This was achieved in quantitative yield by treatment of **420** with iodomethane and K_2CO_3 in DMF at 45 °C for a period of 18 h (**Scheme 154**), as evidenced by the appearance of two singlets at 3.92 and 3.88 ppm from the two methyl groups in the ^{1}H NMR spectrum. Aldehyde **423** was acetal-protected using the standard acetal formation conditions that had been used for all other aryl bromides, to deliver acetal **419** in an excellent yield of 93%. The formation of the acetal was confirmed by the appearance of a singlet at 6.34 ppm from the benzylic proton in the ^{1}H NMR spectrum.



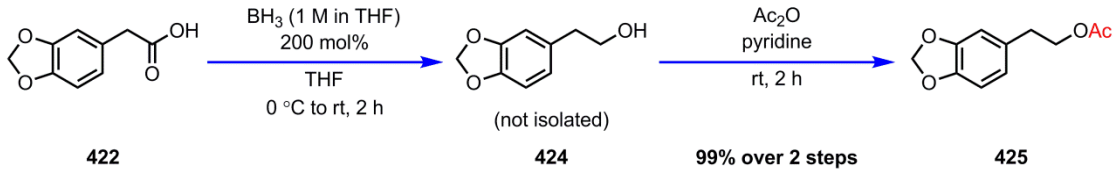
420 **quant.** **423** **93%** **419**

Scheme 154: *Synthesis of aryl bromide **419***

Both reactions to synthesise aryl bromide **419** were very clean and so in an effort to minimise column chromatography in the synthesis, both synthetic steps were subsequently performed without purifying intermediate aldehyde **423**. In this case, a yield of 98% for the two steps was obtained. This was higher than the overall yield for the stepwise procedure, possibly due a slight instability of aldehyde **423** towards oxidation to the benzylic acid.

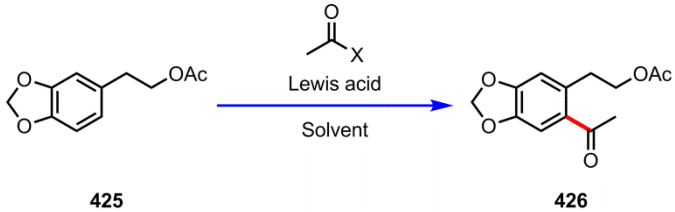
2.5.5 Synthesis of the ketone partner

Synthesis of the ketone coupling partner began with the reduction of 3,4-(methylenedioxy)phenylacetic acid, **422**. This was accomplished by the addition of borane-THF complex solution (1 M in THF) to a solution of **422** in THF at 0 °C, subsequent warming to room temperature and then stirring for 2 h. TLC analysis of the reaction mixture indicated full conversion and a very clean reaction so it was decided to take the crude material and acetylate it directly, hence reducing its polarity and aiding purification. Therefore, the crude product **424** was treated with acetic anhydride and pyridine to furnish arene **425** (**Scheme 155**). The structure of arene **425** was confirmed by the triplet at 4.22 ppm in the ^{1}H NMR spectrum from the two protons of the acetate-bearing methylene group.



Scheme 155: *Synthesis of arene **425***

Next, arene **425** was subjected to a Friedel-Crafts acylation reaction. As an electron-rich aromatic system, it was hoped that **425** would be an excellent substrate for a Friedel-Crafts reaction, and indeed there was ample literature precedent for benzene rings bearing a methylenedioxy group reacting without significant degradation reported.[253,254] However, the conversion of **425** to **426** proved troublesome (**Scheme 156**).



Scheme 156: *Friedel-Crafts acylation of **425***

Initially $SnCl_4$ was employed as the Lewis acid, and Ac_2O as the electrophile. Addition of the reagents at 0 °C and stirring the reaction at this temperature for a period of 4 h led only to an 8% yield of **426** on purification. The structure of **426** was confirmed by two strong absorptions in the IR spectrum, the C=O stretch of the ester at 1732 cm^{-1} and the ketone at 1676 cm^{-1}. In the ^1H NMR spectrum, the two aryl protons in **426** showed no coupling to each other, giving a strong indication that they were in a *para*-relationship and that the Friedel-Crafts reaction had proceeded with the expected regioselectivity to give a 1,2,4,5-substituted product. Purification of **426** was challenging, with the compound being highly sensitive to column chromatography both on silica and alumina, significant decomposition observed over a period of 30 min. Hence, all purification had to be performed quickly. Attempts to purify **426** by recrystallisation failed. The degradation products could not be identified. One possible decomposition pathway was an elimination to give the styrene, however in the ^1H NMR spectrum of the crude material, no vinylic protons were observed (it is of course possible the styrene was formed and then further decomposed to something else).

In an attempt to improve the yield of **426**, the reagents were added at 0 °C and then the reaction allowed to warm to room temperature and stirred for 4 h (**Table 17**, Entry 2). However, this still only gave a 13% yield of **426**, with significant amounts of starting material remaining. In addition, another more polar spot appeared on the TLC plate. Further analysis of this spot indicated it to be a mixture of several compounds close in polarity that could not be separated and were also unstable on silica or alumina for long periods. The ^{13}C NMR spectrum of this mixture revealed the presence of several new quaternary signals in the region of the spectrum corresponding to ester carbonyls and more than one signal in the region of acetal carbons, indicating that the methylenedioxy group had been opened by the Lewis acid and subsequently trapped out with excess acetylation reagent. Increasing the

reaction time to 18 h led to almost full consumption of starting material, a 31% yield of product, but also large amounts of the more polar impurity (Entry 3). Reducing the number of equivalents of reagents (Entry 4) resulted in a lower yield of product, with still large amounts of the polar impurity. Premixing the Lewis acid and electrophile made little difference. Replacement of the Ac_2O with the more reactive AcCl and maintaining the reaction at 0 °C for longer (Entry 5) still only gave a low yield of **426**, with some of the more polar impurity now being detected at the lower temperature of 0 °C. Use of AcCl and warming up to room temperature for 18 h gave a 28% yield of product, with traces of starting material still present with large amounts of the more polar impurity (Entry 6).

Entry	Lewis Acid	Electrophile	Reaction Conditions	Isolated Yield of 426
1	$SnCl_4$ 155 mol%	Ac_2O 130 mol%	CH_2Cl_2, 0° C, 4 h	8%
2	$SnCl_4$ 155 mol%	Ac_2O 130 mol%	CH_2Cl_2, 0° C to rt, 4 h	13%
3	$SnCl_4$ 155 mol%	Ac_2O 130 mol%	CH_2Cl_2, 0° C to rt, 18 h	31%
4	$SnCl_4$ 100 mol%	Ac_2O 100 mol%	CH_2Cl_2, 0° C to rt, 18 h	24%
5	$SnCl_4$ 155 mol%	AcCl 130 mol%	CH_2Cl_2, 0° C, 12 h	18%
6	$SnCl_4$ 155 mol%	AcCl 130 mol%	CH_2Cl_2, 0° C to rt, 18 h	28%

Table 17: *Friedel-Crafts reaction of **425** with $SnCl_4$*

It was thought that $SnCl_4$ may be too harsh a Lewis acid and so a variety of other Lewis acids were screened (**Table 18**). With $AlCl_3$ at 0 °C there was no reaction (Entry 1), but on allowing the reaction to warm up to room temperature, all of the starting material was consumed but only more polar impurities were detected and no product was observed (Entry 2), indicating $AlCl_3$ was an evener harsher Lewis acid than $SnCl_4$. A similar result was observed with $TiCl_4$. At 0 °C, largely unreacted starting material was recovered (Entry 3) but on warming to room temperature the methylenedioxy group was cleaved to give the more polar impurities (Entry 4). An alternative procedure using P_2O_5 as a dehydrating agent to transform AcOH into a reactive electrophile also returned no product and mainly starting material (Entry 5).[255] After this, ZnO was used as a solid-phase Lewis

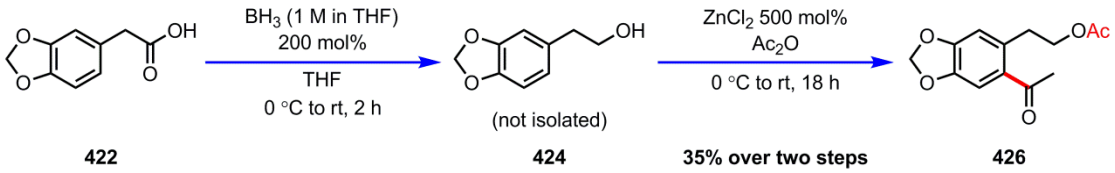
acid catalyst under solvent-free conditions, following a literature procedure (Entry 6).[256] After 4 h only a low conversion of 14% was seen (analogous electron-rich substrates in the literature typically reacted in 5-10 min), but the reaction was clean. Increasing the amount of ZnO and AcCl (with initial addition at 0 °C to prevent exotherms) increased both the conversion and the yield (Entries 7 and 8) but the more polar impurity reappeared. Replacing the ZnO with $ZnCl_2$ and the AcCl with Ac_2O (Entry 9) gave a 40% yield of product. It was deemed that this was sufficient at this stage to progress onwards with the synthesis.

Entry	Lewis Acid	Electrophile	Reaction Conditions	Isolated Yield of 426
1	$AlCl_3$ 150 mol%	AcCl 125 mol%	CH_2Cl_2, 0° C, 12 h	0%
2	$AlCl_3$ 150 mol%	AcCl 125 mol%	CH_2Cl_2, 0° C to rt, 4 h	0%
3	$TiCl_4$ 150 mol%	AcCl 125 mol%	CH_2Cl_2, 0° C, 12 h	0%
4	$TiCl_4$ 150 mol%	AcCl 125 mol%	CH_2Cl_2, 0° C to rt, 4 h	0%
5	P_2O_5 500 mol%	AcOH 150 mol%	CH_2ClCH_2Cl, rt, 18 h	0%
6	ZnO 50 mol%	AcCl 110 mol%	neat, rt, 4 h	14%
7	ZnO 500 mol%	AcCl 200 mol%	neat, 0° C to rt, 18 h	24%
8	ZnO 500 mol%	AcCl 1000 mol%	neat, 0° C to rt, 18 h	29%
9	$ZnCl_2$ 500 mol%	Ac_2O excess	neat, 0° C to rt, 18 h	40%

Table 18: *Friedel-Crafts reaction of **425** with other Lewis acids*

In order to quickly access significant quantities of ketone coupling partner **426**, given the low yield of the Friedel-Crafts reaction, a two step route from commercially available **422** was investigated without purification of intermediate **424** (**Scheme 157**). Reduction of the carboxylic acid group in **422** to the alcohol with borane-THF complex solution was carried out as previously described and after work up, an excess of Ac_2O was added to crude **424** at 0 °C, followed by portionwise addition of $ZnCl_2$. After warming to room temperature and stirring for 18 h, it was found that under these conditions the alcohol in **424** had been fully acetylated and that a significant amount of the material had undergone the Fridel-Crafts reaction. Upon purification a 35% yield of **426** was obtained over the two steps. This

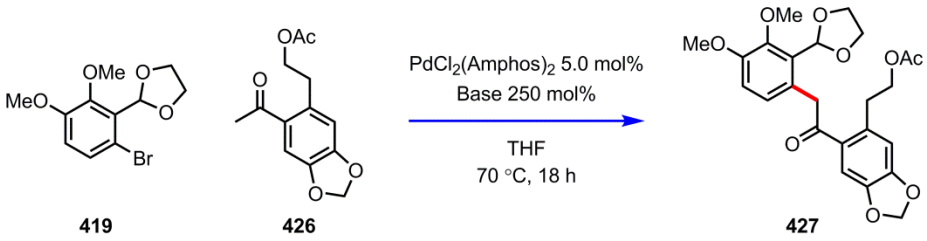
sequence could be performed on a reasonable scale, allowing approximately 500 mg to be synthesised in a single batch.



Scheme 157: *Two step synthesis of ketone precursor **426***

2.5.6 Coupling of the fragments via α-arylation

With the two fragments in hand, attention then turned to their unification utilising an α-arylation reaction. It was presumed that the highly-oxygenated nature of the two coupling partners would make this challenging, with multiple opportunities for coordination possibly reducing the activity of the palladium catalyst. It was decided to use a catalyst loading of 5 mol% Pd and 200 mol% of ketone **426** (**Scheme 158**, **Table 19**).



Scheme 158: *Coupling of fragments **419** and **426** via α-arylation*

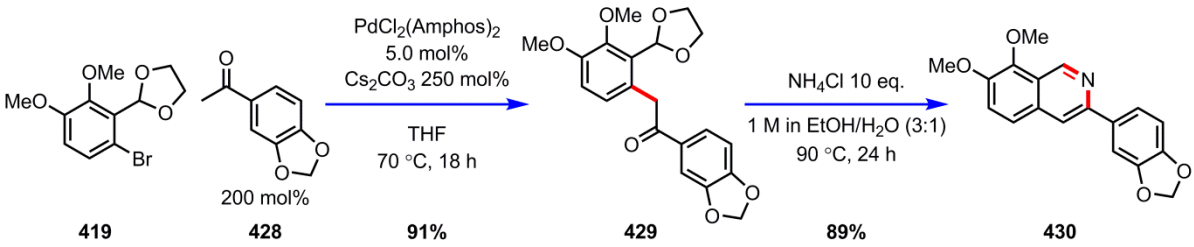
Entry	Base	Isolated Yield of 427
1	NaO*t*Bu	0%
2	K_3PO_4	24%
3	Cs_2CO_3	40%

Table 19: *Screening of bases for the α-arylation of **426** with **419***

The three bases that had been successfully employed in previous work were investigated. With NaO*t*Bu (Entry 1) no product was obtained and analysis of the reaction mixture indicated that the ketone partner had decomposed under these conditions. With K_3PO_4 (Entry 2) a 24% yield of product **427** was obtained, with significant amounts of both starting

materials still remaining. With Cs_2CO_3 (Entry 3) a higher yield of 40% was obtained, but again there were still significant amounts of both starting materials remaining. The structure of **427** was confirmed by the singlet at 4.26 ppm in the ^{1}H NMR spectrum from the methylene protons α to the carbonyl group, in addition to the singlet at 2.01 ppm indicating that the acetate group had been retained.

Although a modest yield had been obtained, this could not be increased by longer reaction times, and a catalyst loading of greater than 5 mol% was deemed undesirable. It was postulated that the instability of the primary acetate may be contributing to the low yield of **427**. To examine whether this was the case, aryl bromide **419** was coupled with 3′,4′-(methylenedioxy)acetophenone, **428** under identical conditions (**Scheme 159**).



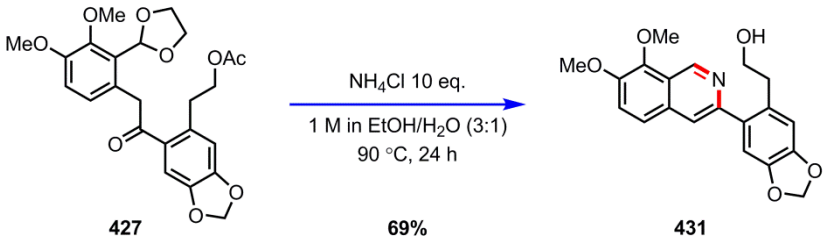
Scheme 159: *α-Arylation of ketone **428** with aryl bromide **419***

This α-arylation reaction proceeded in an excellent yield of 91% to give α-arylated ketone **429**. The structure of **429** was confirmed by the singlet at 4.34 ppm in the ^{1}H NMR spectrum from the methylene protons α to the carbonyl group. It was also subsequently shown that the α-arylated ketone **429** could be converted into the corresponding isoquinoline **430** in 89% yield. The high yield for the α-arylation of **428** with **419** indicated that aryl bromide **419** was a perfectly proficient coupling partner and that the methylenedioxy group on ketone **426** was not inhibiting the reaction either. The factor of sterics could also be ruled out for causing the low yield with ketone **426**, as it had previously been demonstrated that 2',4',6'-tri*iso*propylacetophenone could be arylated in high yield (*vide supra*). Hence, the primary acetate was causing the problem. It

was planned to address this issue later, as sufficient quantities of intermediate **427** had been obtained to progress forward with the synthesis.

2.5.7 Isoquinoline formation

Intermediate **427** was subjected to the standard cyclisation conditions to form the isoquinoline. After 24 h, it was observed that the reaction mixture had turned an intense yellow colour. One reasonably polar spot was observable *via* TLC and after purification a 69% yield of isoquinoline **431** was obtained, where the primary acetate had been deprotected to leave the primary alcohol (**Scheme 160**).



Scheme 160: *Isoquinoline formation*

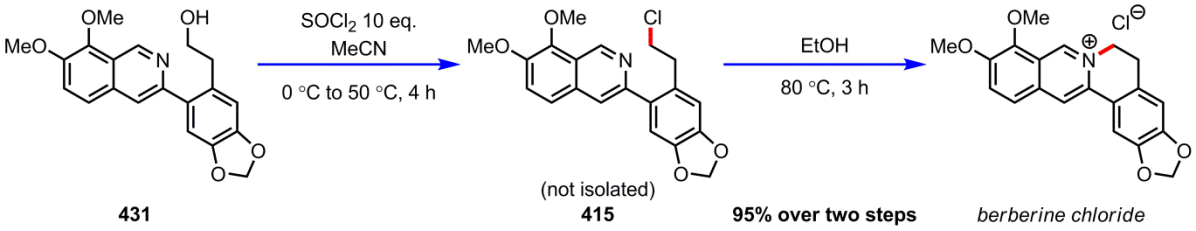
Isoquinoline formation was confirmed by the signal from the C1 proton at 9.54 ppm in the ^{1}H NMR spectrum. The IR spectrum showed a broad peak at 3191 cm^{-1}, indicating the presence of the free hydroxyl group. It had not been expected that the acetate would be deprotected under these conditions, given that ester moieties had previously been carried through the cyclisation step (*vide supra*). However, this acetate ester of a primary alcohol was probably less sterically-hindered/electronically-deactivated than previous esters and so its increased lability was understandable. As the subsequent step of the synthesis required deprotection of this group, its deprotection *in situ* could be viewed as advantageous. However, although a good yield of 69% had been obtained in this step, this was not as high as had come to be expected from the cyclisation step. The intense yellow colour that appeared during the reaction was transferred to the aqueous layer upon biphasic work up. Analysis of this solution by mass spectrometry gave an intense peak at 336.1, consistent with

the mass of the berberine cation. Unfortunately, concentration of the aqueous layer *in vacuo* with a toluene azeotrope and attempted extraction of the berberine from the inorganic salts remaining was unsuccessful and no further confirmatory evidence could be obtained. The direct formation of berberine under these reaction conditions can be rationalised by considering the order of events. If isoquinoline formation is complete before hydrolysis of the acetate then the isoquinoline nitrogen could quaternerise by displacing the acetate (a reasonable leaving group) in a 6-*exo*-tet cyclisation. However, if acetate hydrolysis occurs first, the resultant hydroxyl group is presumably a leaving group of insufficient quality to be displaced by the isoquinoline nitrogen once isoquinoline formation has taken place. This theory was supported by the resubjection of isoquinoline **431** to the cyclisation conditions, whereby the reaction solution did not turn intense yellow and mass spectrometric analysis of the aqueous layer after work up no longer showed a peak at 336.1.

2.5.8 Completing the total synthesis

The next step required conversion of the primary alcohol in isoquinoline **431** into primary chloride **415**. Addition of thionyl chloride to a solution of **431** in MeCN at 0 °C followed by warming to room temperature only led to a very slow rate of reaction. By increasing the reaction temperature to 50 °C, an increased rate of reaction was seen and TLC analysis indicated full conversion to another much less polar spot, presumed to be the chloride, in a period of 4 h. The solution had also turned yellow, suggesting that some of the chloride was cyclising *in situ* to form berberine. As some of the material had cyclised already and as the chloride was presumed to be reasonably labile, the separation and purification of **415** was not attempted. As berberine is an ionic salt, there would be a significant increase in polarity upon cyclisation of **415** to berberine and so it was thought that cyclisation would be favoured by a switch to a more polar solvent. To this end, the reaction mixture was concentrated *in*

vacuo and then redissolved in EtOH. Upon heating to 80 °C, TLC analysis suggested that **415** converted smoothly to berberine in 3 h. Upon concentration *in vacuo*, with no further purification needed, berberine chloride was obtained in a 95% overall yield from alcohol **431** (**Scheme 161**).



Scheme 161: *Completion of the synthesis*

The characteristic shift of the isoquinoline C1 proton (C8 in berberine numbering) at 9.76 ppm in the ^{1}H NMR spectrum indicated the isoquinoline nitrogen had quaternerised. The synthetic sample was compared with a sample of the natural product from Sigma-Aldrich, both by ^{1}H NMR and ^{13}C NMR spectroscopy, and was found to be identical. A mixture of the synthetic sample and the natural sample also showed only one set of signals in both the ^{1}H and ^{13}C NMR spectra, confirming the synthesis of berberine chloride.

As both coupling partners for the α-arylation reaction were synthesised in two steps, the calculation of the overall yield for the synthesis thus far depends upon which of the two commerically available starting materials the calculation is based upon. Of the starting materials **420** and **422**, the aryl bromide **420** is by far the more expensive, and derivative **419** is the limiting reagent in the α-arylation reaction. The overall yield of berberine chloride from aryl bromide **420** at this point was 26%, already making this synthesis at least comparable with previous syntheses of berberine and its analogues in the literature, if calculated this way. However, the use of two equivalents of ketone **426** in the α-arylation reaction and the two step yield of 35% to synthesise this ketone mean the overall yield is

considerably lower from starting material **422**, if calculated in this manner. Hence, further optimisation of this synthesis was required.

2.5.9 Future work on berberine

The acetate protecting group in the synthesis had proved troublesome. The low yield in the α-arylation reaction and the unwanted *in situ* formation of berberine during the cyclisation step were both attributed to the lability/instability of the acetate group under the reaction conditions. The Friedel-Crafts reaction to synthesise ketone **426** was also low yielding, possibly due to the relative instability of **426**.

One alternative to the acetate is the more bulky pivalate group, whose extra steric bulk may increase the stability of the ketone coupling partner. The pivalate group also lacks enolisable protons, which may have been a problem with the acetate protecting group in the α-arylation reaction. However, its leaving group ability is likely to be similar to that of acetate and so this may have a detrimental effect on the cyclisation yield if isoquinoline formation occurred faster than deprotection of the hydroxyl. Another alternative protecting group would be a benzyl ether. This would be expected to have much greater stability throughout the Friedel-Crafts alkylation, α-arylation and cyclisation, however would probably require the addition of a separate deprotection step to the synthesis after isoquinoline formation.

These modifications are currently being investigated by another member of the Donohoe group, who has recently taken up work on the optimisation of the total synthesis of berberine and the application of this synthetic route towards the synthesis of novel, electron-deficient berberine analogues.

2.6 Collated isoquinoline results

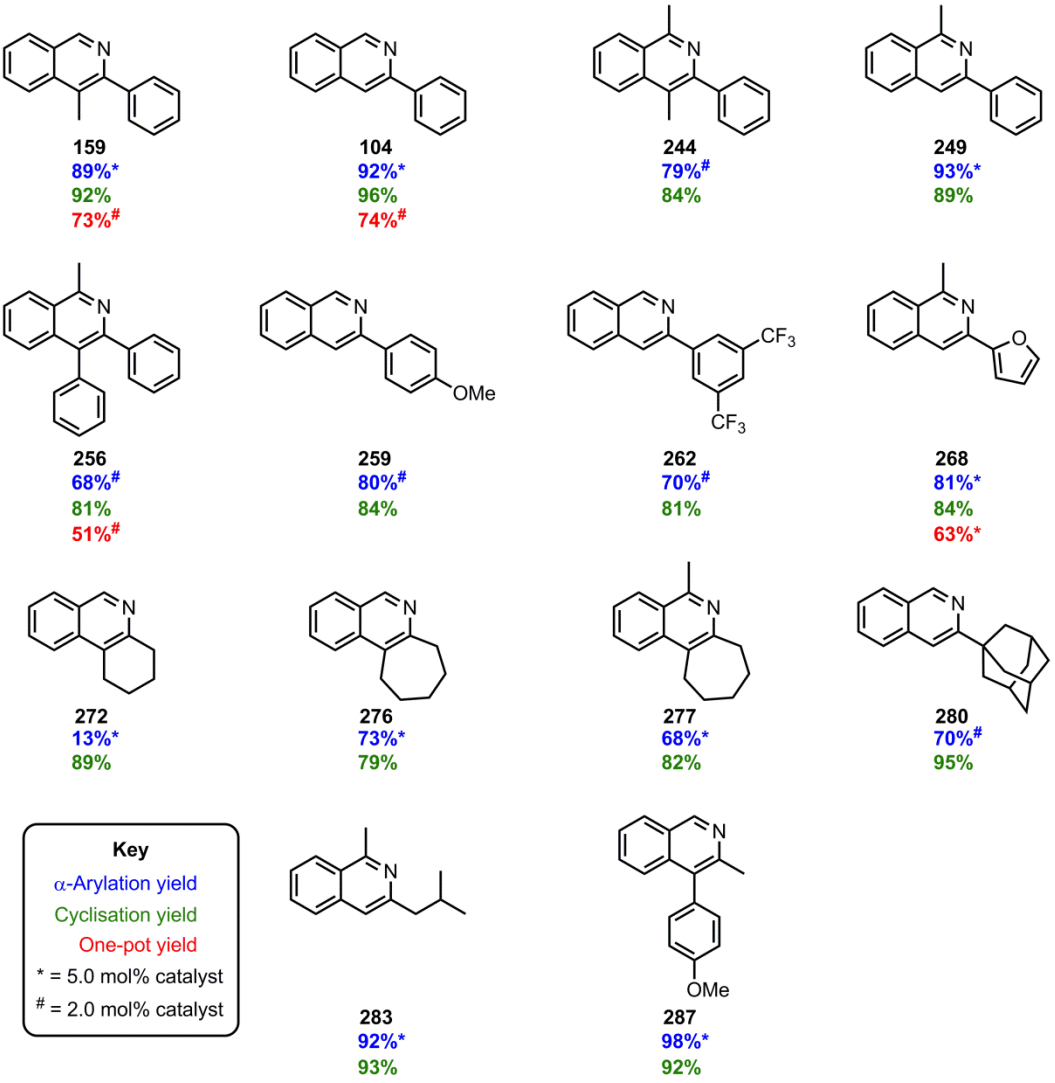


Figure 30: *C1, C3 and C4 substituted isoquinolines*

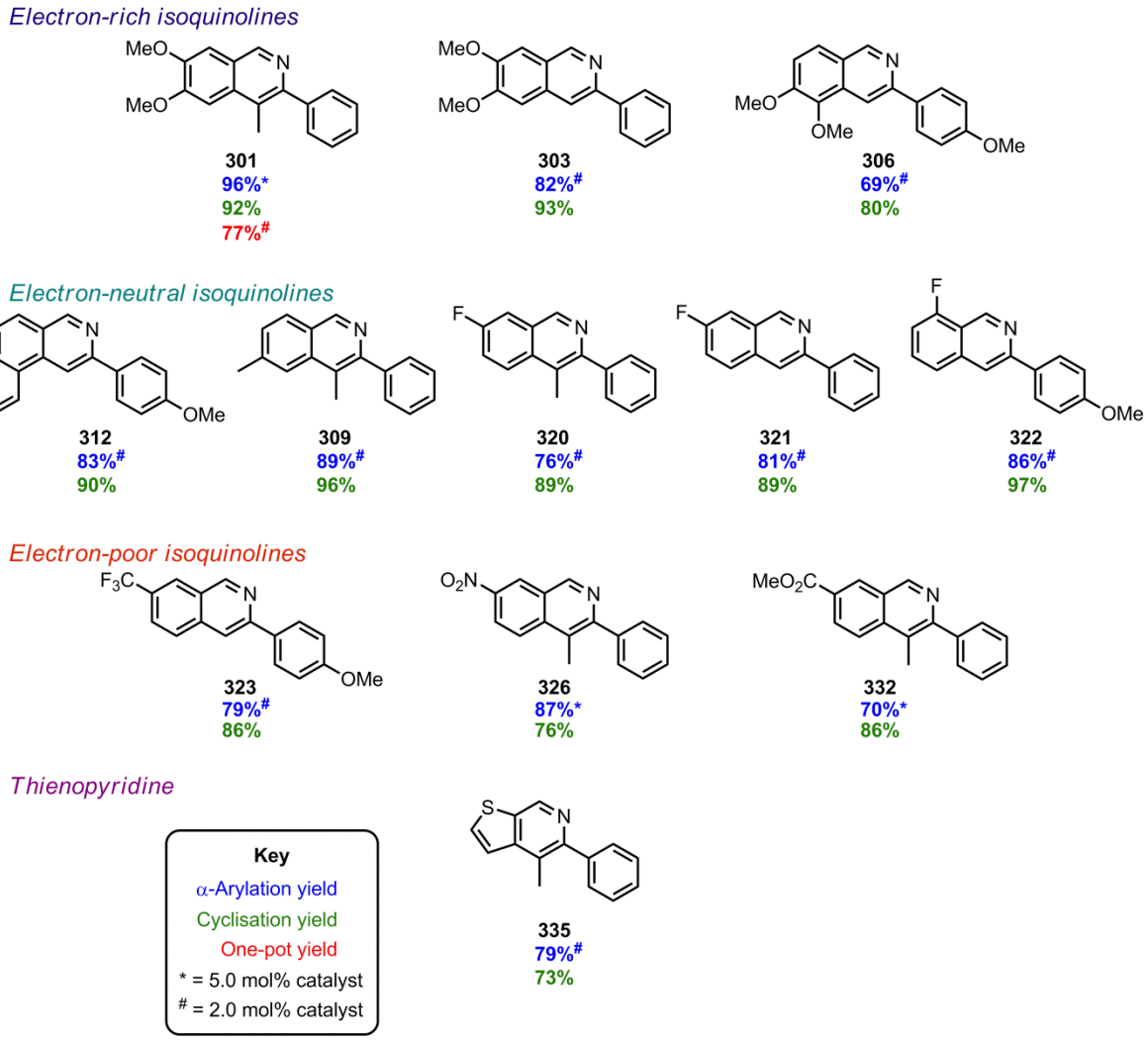


Figure 31: *C5, C6, C7 and C8 substituted isoquinolines*

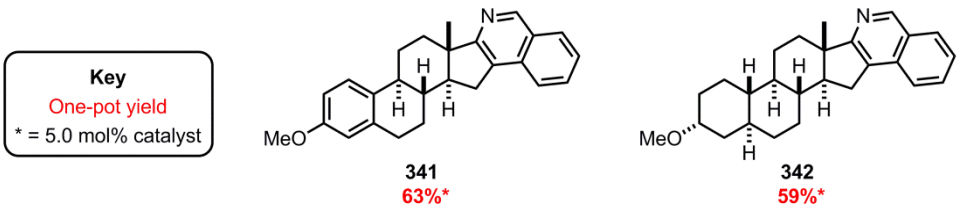


Figure 32: *Modified steroids*

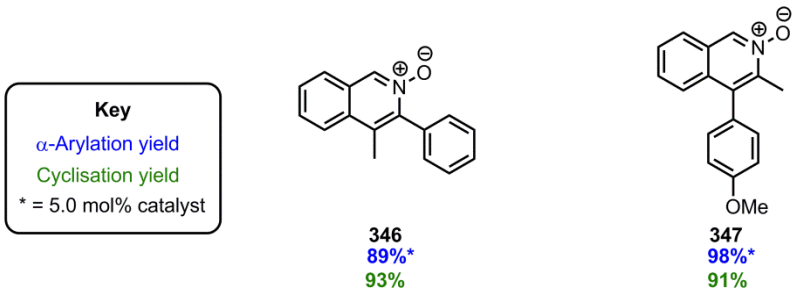


Figure 33: *Isoquinoline N-oxides*

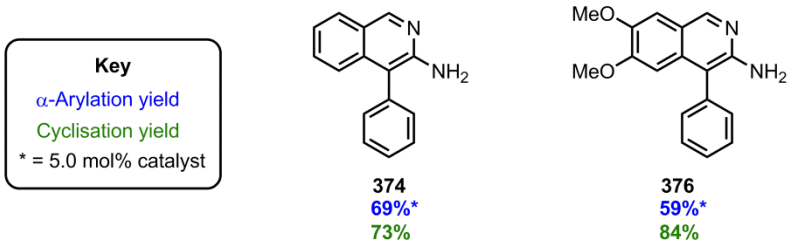


Figure 34: *3-Aminoisoquinolines*

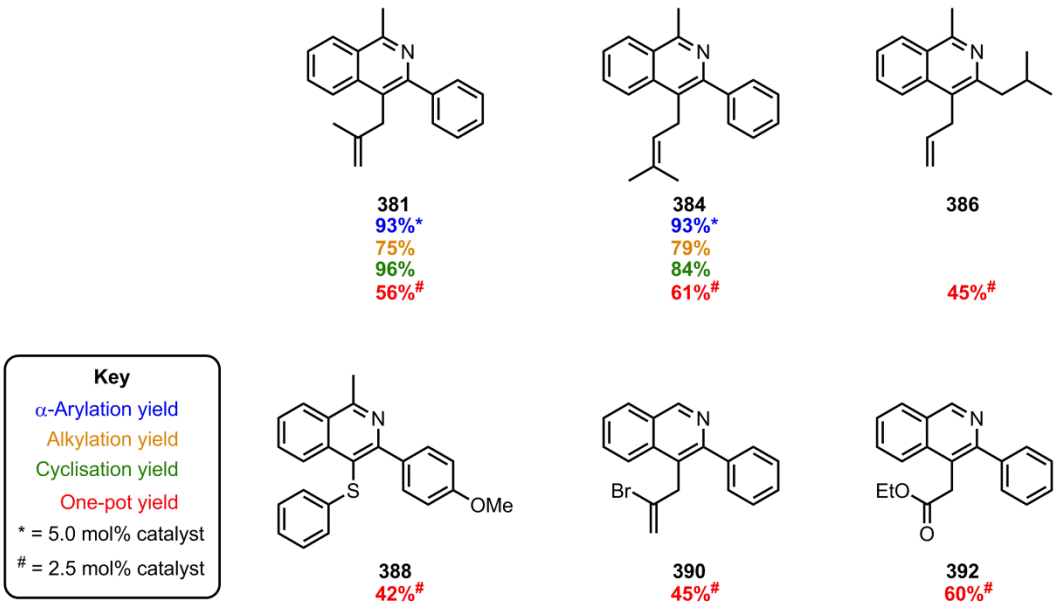


Figure 35: *C4 functionalised isoquinolines*

2.7 Conclusions

This work has demonstrated that dihydrofurans bearing an *ortho*-bromophenyl group in the 2-position can be converted in yields of up to 55% to the corresponding 2-phenyl furans by treatment with a catalytic amount of Pd(0) and a base, hence providing another pathway to access aromatic heterocycles from precursors assembled *via* ring-closing olefin metathesis. Some preliminary mechanistic studies have indicated an intramolecular mechanism, postulated to involve a 1,5-Pd migration.

This thesis has also described the development of an expedient and novel synthetic route that gives rapid access to polysubstituted isoquinolines from commercially available precursors. The palladium-catalysed α-arylation of a ketone enolate with a protected *ortho*halobenzaldehyde delivers a key protected-1,5-dicarbonyl intermediate, which can later be cyclised to an isoquinoline with an acidic source of ammonia, with both steps occurring in good to excellent yields. Intermediates from the α-arylation of protected 2'-bromoacetophenone can be also converted to naphth-1-ols *via* deprotection in acid and an intramolecular aldol condensation in base. Over 30 isoquinolines were synthesised, with a wide array of substituents tolerated in all positions, including nitro and ester moieties.[195] Importantly, the method was as equally applicable to electron-deficient isoquinolines as to electron-rich isoquinolines. The two synthetic steps could also be combined into a three component, one-pot procedure in yields up to 77%, greatly reducing the operational simplicity of the protocol.

Isoquinoline *N*-oxides could be accessed directly *via* this procedure by performing the cyclisation with hydroxylamine hydrochloride and 3-aminoisoquinolines or 3-hydroxyisoquinolines could be accessed from the cyclisation of the intermediates from the α-arylation of nitrile or ester enolates respectively.

The protected-1,5-dicarbonyl intermediates could be deprotonated with a base and alkylated by a suitable electrophile and then subsequently cyclised to furnish isoquinolines further functionalised at the C4 position, an equivalent process to the direct α-arylation of a complex ketone partner. It was shown that the α-arylation, functionalisation with an electrophile and cyclisation reactions could be performed sequentially in one-pot, giving a four component coupling procedure that delivered substituted isoquinolines in yields of up to 80%.

Two catalysts ((D*t*BPF)$PdCl_2$ and $PdCl_2(Amphos)_2$) were shown to be by far the most proficient at promoting these α-arylation reactions. Whilst upon first inspection they are structurally quite different, if (as certain aforementioned studies have shown)[33] the D*t*BPF ligand is only monodentate, then both ligands consist of an electron-rich bulky monophosphine bearing two *tert*-butyl groups and one electron rich arene, and hence are remarkably similar. Thus, it can reasonably be concluded that this class of α-arylation reaction requires a phosphine ligand that is both sterically bulky and electron-rich.

This methodology has been successfully applied to the total synthesis of berberine chloride in an overall yield of 26% from the aryl bromide starting material. The synthesis was completed in a total of eight synthetic steps, with a longest linear sequence of six steps and only four instances of column chromatography in the synthesis. This synthetic route still has the potential for considerable optimisation and the application to the synthesis of novel berberine analogues, particularly those with electron-deficient isoquinoline rings.

Chapter 3: Experimental

3.1 General methods

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

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

Low resolution mass spectra were recorded on a Fisons Platform II spectrometer under electrospray ionisation (ESI). Relative intensities of assignable peaks are quoted as percentage values. High resolution mass spectra are given to four decimal places and were recorded on a Bruker MicroTof (resolution = 10000 FWHM) under conditions of electrospray ionisation (ESI) or field ionisation (FI). Calibration was *via* the lock-mass of tetraoctyl ammonium bromide for positive ions and sodium dodecyl sulfate for negative ions.

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

Flash column chromatography was performed using silica gel (60 Å, 0.033-0.070 mm, BDH)[257] for all compounds apart from the isoquinoline *N*-oxides where it was performed using basic alumina (pH 9.5, 58 Å, 150 mesh, Sigma-Aldrich). TLC analyses were performed on Merck Kiesegel 60 F_{254} 0.25 mm precoated silica plates for all compounds apart from the isoquinoline *N*-oxides where analyses were performed on Macherey-Nagel Alugram Alox N/UV_{254} 0.20 mm precoated alumina plates. Product spots were visualized under UV light (λ_{max} = 254 nm) and/or by staining with potassium permanganate or vanillin solutions as deemed appropriate.

Reagents obtained from Sigma-Aldrich, Alfa, Fluorochem and TCI suppliers were used directly as supplied other than alkyl bromides which were first purified by being passed through a short plug of K_2CO_3. All palladium catalysts were obtained from Johnson Matthey. The palladium catalysts and bases were stored in a desiccator. Compounds that contained acetals of electron-rich benzaldehydes were found to undergo slow hydrolysis (over a period of weeks) due to atmospheric moisture and hence were also stored in a desiccator. This increased their lifetime to many months.

All anhydrous reactions were carried out in flame-dried glassware and under an inert atmosphere of argon provided by a balloon. All reactions were stirred with magnetic followers. Petrol refers to petroleum ether in the boiling range 40-60 °C. THF, toluene, CH_2Cl_2 and MeOH were dried by purification through two activated alumina purification columns.[258] Dry DMF and DMA were used directly from Sure/Seal® bottles from Sigma-Aldrich. Brine refers to a saturated aqueous solution of NaCl.

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

3.2 General procedures

3.2.1 General Procedure 1: Addition of vinyl Grignard to aldehydes

A solution of aldehyde (100 mol%) in THF (1.0 mL $mmol^{-1}$) was cooled to 0 °C. Vinyl magnesium bromide (1.0 M in THF, 120 mol%) was added dropwise and then the solution was warmed to room temperature and stirred for 2 h. The reaction was quenched by the dropwise addition of saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (100 mL). The organic layer was washed with aqueous 1.0 M HCl (25 mL), H_2O (25 mL), and brine (25 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude product which was purified as specified.

3.2.2 General Procedure 2: Allylation of alcohols

A solution of the alcohol (100 mol%) in THF (1.0 mL $mmol^{-1}$) was cooled to 0 °C. NaH (60% dispersion in mineral oil, 200 mol%) was added portionwise and the mixture stirred for 30 min at 0 °C. Allyl bromide (120 mol%) was added dropwise and then the reaction was warmed to room temperature and then heated at reflux for 18 h. The reaction was cooled to room temperature and then quenched by the dropwise addition of saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (100 mL). The organic layer was washed with H_2O (2 × 25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude product which was purified as specified.

3.2.3 General Procedure 3: Ring-closing olefin metathesis

The substrate (100 mol%) was dissolved in CH_2Cl_2 (10 mL $mmol^{-1}$) at room temperature and the solution degassed with a stream of argon gas (provided by a balloon and exit needle) for 15 min. Hoveyda-Grubbs 2nd generation catalyst (0.5 mol%) was added and the reaction stirred at room temperature for 18 h. The solvent was then removed *in vacuo* to give the crude product which was purified as specified.

3.2.4 General Procedure 4: Palladium-catalysed oxidation

The substrate (100 mol%) and DMA (10 mL $mmol^{-1}$) were added to a resealable reaction tube sealed with a rubber septum. The solution was degassed with a stream of argon (provided by a balloon and exit needle) for 15 min. $Pd(dba)_2$ (10 mol%) and Cs_2CO_3 (200 mol%) were added and the mixture was heated at 120 °C for 24 h. The mixture was cooled to room temperature and then Et_2O (50 mL) was added. The organic layer was washed with H_2O (3 × 25 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude product which was purified as specified.

3.2.5 General Procedure 5: Cyclic acetal protection of aldehydes/ketones

para-Toluenesulfonic acid monohydrate (2.0 mol%) was added to a solution of the aldehyde/ketone (100 mol%) and ethanediol (130 mol%) in toluene (10 mL $mmol^{-1}$) in a round-bottomed flask at room temperature. The flask was attached to a Dean-Stark apparatus and the solution was heated at reflux for 18 h. The reaction mixture was cooled to room temperature and quenched by addition of saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product, which was purified as specified.

3.2.6 General Procedure 6: Palladium-catalysed α-arylation of ketones

(D*t*BPF)$PdCl_2$ (2.0 mol%) and NaO*t*Bu (250 mol%) were added to a resealable reaction tube sealed with a rubber septum. The aryl halide (100 mol%) was dissolved in THF (5.0 mL $mmol^{-1}$) and the resulting solution was added *via* syringe to the tube at room temperature. The ketone (120 mol%) was then added *via* syringe to the tube. The rubber septum was then replaced with a screw cap and the tube was heated at 70 ^{o}C for 18 h. The reaction was then cooled to room temperature and quenched by the addition of H_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were

dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product, which was purified as specified.

3.2.7 General Procedure 7: Palladium-catalysed α-arylation of ketones

(D*t*BPF)$PdCl_2$ (5.0 mol%) and NaO*t*Bu (250 mol%) were added to a resealable reaction tube sealed with a rubber septum. The aryl halide (100 mol%) was dissolved in THF (5.0 mL $mmol^{-1}$) and the resulting solution was added *via* syringe to the tube at room temperature. The ketone (200 mol%) was then added *via* syringe to the tube. The rubber septum was then replaced with a screw cap and the tube was heated at 70 ^{o}C for 18 h. The reaction was then cooled to room temperature and quenched by the addition of H_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product, which was purified as specified.

3.2.8 General Procedure 8: Isoquinoline formation where C1 substituent = H

A solution of NH_4Cl (1000 mol%, 1.0 M in 3:1 EtOH/H_2O) was added to the cyclisation substrate (100 mol%) in a resealable reaction tube. The tube was sealed with a screw cap and heated at 90 °C for 24 h. The reaction was then cooled to room temperature and quenched by the addition of saturated aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product, which was purified as specified.

3.2.9 General Procedure 9: Deprotection of acetals

para-Toluenesulfonic acid monohydrate (10 mol%) was added to a solution of the acetal substrate (100 mol%) in THF/H_2O (1:1, 5.0 mL $mmol^{-1}$) in a resealable reaction tube at room temperature. The tube was sealed with a screw cap and heated at 60 °C for 18 h. The reaction was then cooled to room temperature and quenched by addition of saturated

aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product, which was purified as specified.

3.2.10 General Procedure 10: Naphthol formation

Aqueous NaOH (2 M, 5.0 mL $mmol^{-1}$) was added to a solution of the diketone (100 mol%) in EtOH (5.0 mL $mmol^{-1}$) and the reaction stirred at room temperature for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (25 mL) and diluted with Et_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product which was purified as specified.

3.2.11 General Procedure 11: Isoquinoline formation where C1 substituent = Me

A solution of NH_4Cl (1000 mol%, 1.0 M in 3:1 EtOH/H_2O) was added to the cyclisation substrate (100 mol%) in a resealable reaction tube. The tube was sealed with a screw cap and heated at 90 °C for 18 h. The reaction was cooled to room temperature then a solution of NH_4HCO_3 (2.0 M in H_2O) was added until the pH of the reaction mixture had been adjusted to approximately pH 9. The tube was resealed and heated for a further 24 h at 90 °C. The reaction was then cooled to room temperature and diluted by the addition of H_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product, which was purified as specified.

3.2.12 General Procedure 12: One-pot naphthol formation

para-Toluenesulfonic acid monohydrate (10 mol%) was added to a solution of the acetal substrate (100 mol%) in THF/H_2O (1:1, 5.0 mL $mmol^{-1}$) in a resealable reaction tube at room temperature. The tube was sealed with a screw cap and heated at 60 °C for 18 h. The

reaction was then cooled to room temperature and aqueous NaOH (2 M, 5.0 mL $mmol^{-1}$) and EtOH (5.0 mL $mmol^{-1}$) were then added and the reaction stirred at room temperature for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (25 mL) and diluted with Et_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product which was purified as specified.

3.2.13 General Procedure 13: One-pot isoquinoline formation where C1 substituent = H

(D*t*BPF)$PdCl_2$ (2.0 mol%) and NaO*t*Bu (250 mol%) were added to a resealable reaction tube sealed with a rubber septum. The aryl halide (100 mol%) was dissolved in THF (5.0 mL $mmol^{-1}$) and the resulting solution was added *via* syringe to the tube at room temperature. The ketone (120 mol%) was then added *via* syringe to the tube. The rubber septum was then replaced with a screw cap and the tube was heated at 70 ^oC for 18 h. The reaction was then cooled to room temperature and acidified to pH 5 by the addition of aqueous 1.0 M HCl. A solution of NH_4Cl (1000 mol%, 1.0 M in 3:1 EtOH/H_2O) was then added and the tube resealed and heated at 90 °C for 24 h. The reaction was then cooled to room temperature and quenched by the addition of saturated aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product, which was purified as specified.

3.2.14 General Procedure 14: One-pot isoquinoline formation where C1 substituent = Me

(D*t*BPF)$PdCl_2$ (2.0 mol%) and NaO*t*Bu (250 mol%) were added to a resealable reaction tube sealed with a rubber septum. The aryl halide (100 mol%) was dissolved in THF (5.0 mL $mmol^{-1}$) and the resulting solution was added *via* syringe to the tube at room temperature. The ketone (120 mol%) was then added *via* syringe to the tube. The rubber septum was then replaced with a screw cap and the tube was heated at 70 ^oC for 18 h. The reaction was then cooled to room temperature and acidified to pH 5 by the addition of

aqueous 1.0 M HCl. A solution of NH_4Cl (1000 mol%, 1.0 M in 3:1 EtOH/H_2O) was then added and the tube resealed and heated at 90 °C for 18 h. The reaction was then cooled to room temperature, a solution of NH_4HCO_3 (2.0 M in H_2O) was then added to adjust the pH to approximately 9 and the tube resealed and heated at 90 °C for 24 h. The reaction was then cooled to room temperature and diluted by the addition of H_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product, which was purified as specified.

3.2.15 General Procedure 15: Isoquinoline N-oxide formation

A solution of $NH_2OH.HCl$ (1000 mol%, 1.0 M in 9:1 EtOH/H_2O) was added to the cyclisation substrate (100 mol%) in a resealable reaction tube. The tube was sealed with a screw cap and heated at 90 °C for 2 h. The reaction was then cooled to room temperature and the solvent removed *in vacuo* using a toluene azeotrope to give the crude product which was purified as specified.

3.2.16 General Procedure 16: Palladium-catalysed α-arylation of nitriles

$PdCl_2(Amphos)_2$ (5.0 mol%) and Cs_2CO_3 (250 mol%) were added to a resealable reaction tube sealed with a rubber septum. The aryl halide (100 mol%) was dissolved in THF (5.0 mL $mmol^{-1}$) and the resulting solution was added *via* syringe to the tube at room temperature. The nitrile (200 mol%) was then added *via* syringe to the tube. The rubber septum was then replaced with a screw cap and the tube was heated at 70 ^oC for 18 h. The reaction was then cooled to room temperature and quenched by the addition of H_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product, which was purified as specified.

3.2.17 General Procedure 17: Alkylation of intermediates

The reaction substrate (100 mol%) was dissolved in THF (4.0 mL $mmol^{-1}$) and the mixture cooled to 0 °C. NaO*t*Bu (120 mol%) was added and the reaction stirred for 10 min. A solution of the electrophile (120 mol%) in THF (5.0 mL $mmol^{-1}$) was then added dropwise and the reaction warmed to room temperature and stirred for a further 8 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (25 mL) and H_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude product which was purified as specified.

3.2.18 General Procedure 18: One-pot, four component isoquinoline formation where C1 substituent = Me

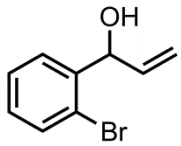
(D*t*BPF)$PdCl_2$ (2.5 mol%) and NaO*t*Bu (250 mol%) were added to a resealable reaction tube sealed with a rubber septum. The aryl halide (100 mol%) was dissolved in THF (5.0 mL $mmol^{-1}$) and the resulting solution was added *via* syringe to the tube at room temperature. The ketone (120 mol%) was then added *via* syringe to the tube. The rubber septum was then replaced with a screw cap and the tube was heated at 70 ^{o}C for 18 h. The reaction was then cooled to 0 °C and then a solution of the electrophile (120 mol%) in THF (5.0 mL $mmol^{-1}$) was added dropwise and the reaction warmed to room temperature and stirred for a further 8 h. The reaction was then acidified to pH 5 by the addition of aqueous 1.0 M HCl. A solution of NH_4Cl (1000 mol%, 1.0 M in 3:1 EtOH/H_2O) was then added and the tube resealed and heated at 90 °C for 18 h. The reaction was then cooled to room temperature, a solution of NH_4HCO_3 (2.0 M in H_2O) was then added to adjust the pH to approximately 9 and the tube resealed and heated at 90 °C for 24 h. The reaction was then cooled to room temperature and diluted by the addition of H_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product, which was purified as specified.

3.2.19 General Procedure 19: One-pot, four component isoquinoline formation where C1 substituent = H

(D*t*BPF)$PdCl_2$ (2.5 mol%) and NaO*t*Bu (250 mol%) were added to a resealable reaction tube sealed with a rubber septum. The aryl halide (100 mol%) was dissolved in THF (5.0 mL $mmol^{-1}$) and the resulting solution was added *via* syringe to the tube at room temperature. The ketone (120 mol%) was then added *via* syringe to the tube. The rubber septum was then replaced with a screw cap and the tube was heated at 70 ^{o}C for 18 h. The reaction was then cooled to 0 °C and then a solution of the electrophile (120 mol%) in THF (5.0 mL $mmol^{-1}$) was added dropwise and the reaction warmed to room temperature and stirred for a further 8 h. The reaction was then acidified to pH 5 by the addition of aqueous 1 M HCl. A solution of NH_4Cl (1000 mol%, 1.0 M in 3:1 EtOH/H_2O) was then added and the tube resealed and heated at 90 °C for 24 h. The reaction was then cooled to room temperature and quenched by the addition of saturated aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product, which was purified as specified.

3.3 Experimental details

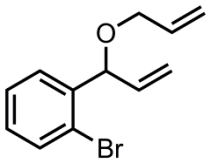
1-(2-Bromophenyl)prop-2-en-1-ol **172**



2-Bromobenzaldehyde (3.70 g, 20.0 mmol) was subjected to General Procedure 1. The crude product was purified by flash column chromatography [Petrol/EtOAc, 9:1 to 3:1] to furnish *vinyl alcohol* **172** (3.96 g, 18.6 mmol, 93%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.56-7.52 (2H, m, 2 × *H*C_{Ar}), 7.34 (1H, t, *J* 7.6, *H*C_{Ar}), 7.15 (1H, td, *J* 7.6, 1.1, *H*C_{Ar}), 6.03 (1H, ddd, *J* 16.7, 10.4, 5.5, C*H*=CH_2), 5.62-5.59 (1H, m, C*H*OH), 5.41 (1H, d, *J* 16.7, CH=C*H*$_a$H$_b$), 5.24 (1H, d, *J* 10.4, CH=CH$_a$*H*$_b$), 2.39 (1H, d, *J* 3.3, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 141.5 (*C*$_{Ar}$), 138.3 (*C*H=CH_2), 132.8, 129.2, 128.0, 127.8 (4 × H*C*$_{Ar}$), 122.6 (*C*$_{Ar}$), 115.7 (CH=*C*H_2), 73.5 (*C*HOH). Data were consistent with those previously reported.[259]

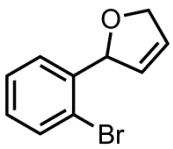
1-(1-(Allyloxy)allyl)-2-bromobenzene **173**



Vinyl alcohol **172** (3.28 g, 15.4 mmol) was subjected to General Procedure 2. The crude product was purified by flash column chromatography [Petrol/EtOAc, 19:1 to 9:1] to furnish *allyl ether* **173** (3.41 g, 13.5 mmol, 88%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.56-7.52 (2H, m, 2 × *H*C_{Ar}), 7.35 (1H, t, *J* 7.6, *H*C_{Ar}), 7.15 (1H, td, *J* 7.3, 1.3, *H*C_{Ar}), 6.01-5.87 (2H, m, 2 × C*H*=CH_2), 5.38-5.20 (5H, m, C*H*OR + 2 × CH=C*H*$_2$), 4.03 (1H, d, *J* 12.8, C*H*$_a$H$_b$OR), 3.97 (1H, d, *J* 12.8, CH$_a$*H*$_b$OR); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 140.1 (*C*$_{Ar}$), 137.0, 134.5 (2 × *C*H=CH_2), 132.7, 129.0, 128.3, 127.8 (4 × H*C*$_{Ar}$), 123.1 (*C*$_{Ar}$), 117.1, 116.6 (2 × CH=*C*H_2), 80.1 (*C*HOR), 69.6 (*C*H_2OR); **IR** υ_{max} (thin film)/cm^{-1} 3081m, 2924s, 2858s, 1731w, 1645w, 1568w, 1467m, 1439m, 1264w, 1195w, 1121s, 1070s, 1023s, 989m, 927s; **m/z** (EI/FI$^+$) $C_{12}H_{13}{}^{79}BrO$ predicted 252.0150, found 252.0150, (Δ + 0.0 ppm).

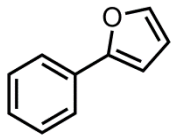
2-(2-Bromophenyl)-2,5-dihydrofuran **167**



Allyl ether **173** (3.35 g, 13.2 mmol) was subjected to General Procedure 3. The crude product was purified by flash column chromatography [Petrol/EtOAc, 24:1 to 4:1] to furnish *dihydrofuran* **167** (2.77 g, 12.3 mmol, 93%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.54 (1H, d, *J* 8.1, *H*C$_{Ar}$), 7.45 (1H, d, *J* 7.8, *H*C$_{Ar}$), 7.32 (1H, t, *J* 7.6, *H*C$_{Ar}$), 7.14 (1H, t, *J* 7.1, *H*C$_{Ar}$), 6.16-6.14 (1H, m, C*H*OR), 6.08-6.05 (1H, m, CHORCH=C*H*), 6.02-6.00 (1H, m, CHORC*H*=CH), 4.94 (1H, dd, *J* 12.9, 6.1, CH_aH$_b$OR), 4.85 (1H, dd, *J* 12.9, 1.3, CH$_a$*H*$_b$OR); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 141.4 (*C*$_{Ar}$), 132.6, 129.0 (2 × H*C*$_{Ar}$), 128.9 (CHORCH=*C*H), 127.8, 127.6 (2 × H*C*$_{Ar}$), 126.7 (CHOR*C*H=CH), 121.4 (*C*$_{Ar}$), 86.9 (*C*HOR), 76.2 (*C*H$_2$OR); **IR** υ_{max} (thin film)/cm^{-1} 3066m, 2927s, 1934w, 1790m, 1758s, 1588m, 1467s, 1433s, 1267m, 1222m, 1161w, 1024s, 868m, 755s; **m/z** (EI/FI$^+$) $C_{10}H_9{}^{79}BrO$ predicted 223.9837, found 223.9836, (Δ + 0.3 ppm).

2-Phenylfuran **171**

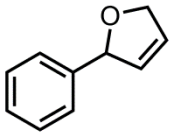


Dihydrofuran **167** (30.4 mg, 0.135 mmol) and DMF (2.7 mL) were added to a resealable reaction tube sealed with a rubber septum. The solution was degassed with a stream of argon (provided by a balloon and exit needle) for 15 min. $Pd(dba)_2$ (7.8 mg, 0.014 mmol) and K_2CO_3 (37.3 mg, 0.270 mmol) were added and the mixture was heated at 120 °C for 24 h. The mixture was cooled to room temperature and then Et_2O (50 mL) was added. The organic layer was washed with H_2O (3 × 25 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude product. Purification by flash column chromatography [Petrol/EtOAc, 99:1 to 19:1] furnished *furan* **171** (3.5 mg, 0.024 mmol 18%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.72-7.68 (2H, m, 2 × *H*C$_{Ar}$), 7.49 (1H, dd, *J* 1.9, 0.8, *H*C(5)), 7.43-7.37 (2H, m, 2 × *H*C$_{Ar}$), 7.30-7.23 (1H, m, *H*C$_{Ar}$), 6.67 (1H, dd, *J* 3.4, 0.8, *H*C(4)), 6.48 (1H, dd, *J* 3.4, 1.9, *H*C(3)); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 154.0 (*C*(2)),

142.0 (H*C*(5)), 130.9 (*C*$_{Ar}$), 128.7, 127.3, 123.8 (3 × H*C*$_{Ar}$), 111.6 (H*C*(4)), 104.9 (H*C*(3)). Data were consistent with those previously reported.[260]

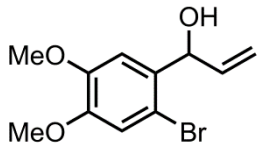
2-Phenyl-2,5-dihydrofuran **174**



Dihydrofuran **167** (30.4 mg, 0.135 mmol) and DMF (2.7 mL) were added to a resealable reaction tube sealed with a rubber septum. The solution was degassed with a stream of argon (provided by a balloon and exit needle) for 15 min. Pd(dba)$_2$ (7.8 mg, 0.014 mmol) and K_2CO_3 (37.3 mg, 0.270 mmol) were added and the mixture was heated at 120 °C for 24 h. The mixture was cooled to room temperature and then Et_2O (50 mL) was added. The organic layer was washed with H_2O (3 × 25 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude product. Purification by flash column chromatography [Petrol/EtOAc, 99:1 to 19:1] furnished *dihydrofuran* **174** (2.9 mg, 0.020 mmol 15%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.39-7.27 (5H, m, 5 × *H*C$_{Ar}$), 6.07-6.04 (1H, m, C*H*=CH), 5.93-5.89 (1H, m, CH=C*H*), 5.83-5.79 (1H, m, C*H*OR), 4.90 (1H, dddd, *J* 13.0, 6.0, 2.5, 1.5, C*H*$_a$H$_b$OR), 4.79 (1H, dddd, *J* 13.0, 4.0, 2.5, 1.5, CH$_a$*H*$_b$OR); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 142.0 (*C*$_{Ar}$), 130.0 (*C*H=CH), 128.5 (H*C*$_{Ar}$), 127.8 (CH=*C*H), 126.6, 126.4 (2 × H*C*$_{Ar}$), 87.9 (*C*HOR), 75.8 (*C*H$_2$OR). Data were consistent with those previously reported.[261]

1-(2-Bromo-4,5-dimethoxyphenyl)prop-2-en-1-ol **177**

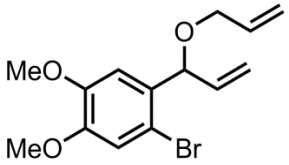


2-Bromo-4,5-dimethoxybenzaldehyde (1.23 g, 5.00 mmol) was subjected to General Procedure 1. The crude product was purified by flash column chromatography [Petrol/EtOAc, 9:1 to 3:1] to furnish *vinyl alcohol* **177** (1.25 g, 4.58 mmol, 92%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.03 (1H, s, *H*C$_{Ar}$), 6.99 (1H, s, *H*C$_{Ar}$), 5.99 (1H, ddd, *J* 16.8, 10.4, 5.3, C*H*=CH$_2$), 5.56-5.53 (1H, m, C*H*OH), 5.39 (1H, dd, *J* 16.8, 1.2,

CH=CH_aH$_b$), 5.22 (1H, dd, *J* 10.4, 1.2, CH=CH$_a$$H_b$), 3.87 (3H, s, OC$H_3$), 3.86 (3H, s, OC$H_3$), 2.22 (1H, br. s, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 148.9, 148.8 (2 × C_{Ar}), 138.5 (*C*H=CH$_2$), 133.5 (C_{Ar}), 115.3 (CH=*C*H$_2$), 115.2 (HC_{Ar}), 112.3 (C_{Ar}), 110.2 (HC_{Ar}), 73.3 (*C*HOH), 56.2, 56.0 (2 × OCH_3); **IR** υ_{max} (thin film)/cm^{-1} 3474br./s, 2932s, 2842m, 2285m, 1602w, 1503s, 1439m, 1380m, 1257s, 1207s, 1157s, 1032s; **m/z** (ESI$^+$) 295.0 [100, (M + Na)$^+$], 567.0 [80, (2M + Na)$^+$], $C_{11}H_{13}{}^{79}BrNaO_3$ predicted 294.9940, found 294.9943, (Δ − 1.1 ppm).

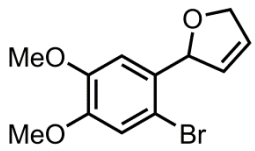
1-(1-(Allyloxy)allyl)-2-bromo-4,5-dimethoxybenzene **178**



Vinyl alcohol **177** (1.23 g, 4.52 mmol) was subjected to General Procedure 2. The crude product was purified by flash column chromatography [Petrol/EtOAc, 24:1 to 9:1] to furnish *allyl ether* **178** (1.34 g, 4.28 mmol, 94%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.99 (2H, s, 2 × *H*C$_{Ar}$), 5.99-5.85 (2H, m, 2 × C*H*=CH$_2$), 5.33 (1H, dd, *J* 17.2, 1.5, CH=CH_aH$_b$), 5.29 (1H, dd, *J* 17.2, 1.4, CH=CH_aH$_b$), 5.21-5.18 (3H, m, C*H*OR + 2 × CH=CH$_a$$H_b$), 3.99-3.96 (2H, m, C$H_2$OR), 3.87 (6H, s, 2 × OC$H_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 148.9, 148.9 (2 × C_{Ar}), 137.2, 134.6 (2 × *C*H=CH$_2$), 132.0 (C_{Ar}), 117.1, 116.2 (2 × CH=*C*H$_2$), 115.0 (HC_{Ar}), 113.1 (C_{Ar}), 110.4 (HC_{Ar}), 80.0 (*C*HOR), 69.5 (*C*H$_2$OR), 56.1, 56.0 (2 × OCH_3); **IR** υ_{max} (thin film)/cm^{-1} 3082m, 3004m, 2935s, 2842s, 2023w, 1601w, 1504s, 1463w, 1439m, 1380m, 1257s, 1209s, 1162s, 1068m, 1032m; **m/z** (ESI$^+$) 335.0 [100, (M + Na)$^+$], $C_{14}H_{17}{}^{79}BrNaO_3$ predicted 335.0253, found 335.0249, (Δ + 1.2 ppm).

2-(2-Bromo-4,5-dimethoxyphenyl)-2,5-dihydrofuran **179**

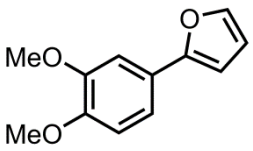


Allyl ether **178** (1.30 g, 4.15 mmol) was subjected to General Procedure 3. The crude product was purified by flash column

chromatography [Petrol/EtOAc, 24:1 to 4:1] to furnish *dihydrofuran* **179** (1.08 g, 3.79 mmol, 91%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.99 (1H, s, *H*C_{Ar}), 6.90 (1H, s, *H*C_{Ar}), 6.07-5.98 (3H, m, C*H*OR + C*H*=C*H*), 4.91 (1H, dd, *J* 12.9, 6.1, C*H*$_a$H$_b$OR), 4.82-4.78 (1H, m, CH$_a$*H*$_b$OR), 3.86 (6H, s, 2 × OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 148.9, 148.8, 133.2 (3 × *C*$_{Ar}$), 129.1, 126.6 (*C*H=*C*H), 115.3 (H*C*$_{Ar}$), 111.4 (*C*$_{Ar}$), 110.1 (H*C*$_{Ar}$), 86.0 (*C*HOR), 76.0 (*C*H$_2$OR), 56.2, 56.0 (2 × O*C*H$_3$); **IR** υ_{max} (thin film)/cm^{-1} 2934s, 2846s, 1732m, 1600m, 1506s, 1439m, 1383m, 1260s, 1209s, 1160s, 1076s, 1029m; **m/z** (ESI$^+$) 307.0 [100, (M + Na)$^+$], $C_{12}H_{13}{}^{79}BrNaO_3$ predicted 306.9940, found 306.9935, (Δ + 1.8 ppm); **m.p.** 45-47 °C (Petrol/CH_2Cl_2).

2-(3,4-Dimethoxyphenyl)furan **180**



Method A: Dihydrofuran **179** (57.2 mg, 0.201 mmol) was subjected to General Procedure 4. The crude product was purified by flash column chromatography [Petrol/EtOAc, 24:1 to 4:1] to furnish *furan* **180** (27.0 mg, 0.0955 mmol, 48%) as yellow plates.

Method B: As for ***Method A*** but with dihydrofuran **209** (48.6 mg, 0.170 mmol). Yield (23.7 mg, 0.0835 mmol, 49%) as yellow plates.

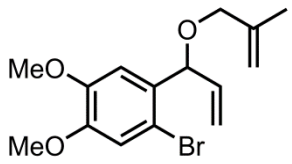
Method C: Cs_2CO_3 (183 mg, 0.562 mmol) and 3 Å molecular sieves (160 mg) were flame-dried under vacuum and then transferred to a resealable reaction tube sealed with a rubber septum. Dihydrofuran **179** (80.0 mg, 0.281 mmol) and DMA (2.8 mL) were added and the reaction degassed with a stream of argon (provided by a balloon and exit needle) for 15 min. $Pd(dba)_2$ (16.1 mg, 0.0281 mmol) was added and the reaction was heated at 120 °C for 24 h. The mixture was cooled to room temperature and then Et_2O (50 mL) was added. The organic layer was washed with H_2O (3 × 25 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography

[Petrol/EtOAc, 24:1 to 4:1] to furnish *furan* **180** (43.7 mg, 0.154 mmol, 53%) as yellow plates.

Method D: As for ***Method C*** but with dihydrofuran **209** (62.0 mg, 0.217 mmol). Yield (32.8 mg, 0.116 mmol, 53%) as yellow plates.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.44 (1H, d, *J* 1.4, *H*C(5)), 7.25 (1H, dd, *J* 8.4, 1.9, *H*C_{Ar}), 7.22 (1H, d, *J* 1.9, *H*C_{Ar}), 6.90 (1H, d, *J* 8.4, *H*C_{Ar}), 6.55 (1H, d, *J* 3.3, *H*C(3)), 6.47 (1H, dd, *J* 3.3, 1.4, *H*C(4)), 3.95 (3H, s, OCH_3), 3.91 (3H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 153.9 (*C*(2)), 149.1, 148.6 (2 × C_{Ar}), 141.4 (H*C*(5)), 124.2 (C_{Ar}), 116.5 (HC_{Ar}), 111.6 (H*C*(4)), 111.4, 107.2 (2 × HC_{Ar}), 103.7 (H*C*(3)), 55.9, 55.9 (2 × OCH_3); **m.p.** 59-60 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[260]

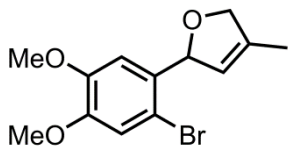
1-Bromo-4,5-dimethoxy-2-(1-(2-methylallyloxy)allyl)benzene **181**



Vinyl alcohol **177** (2.63 g, 9.64 mmol) was subjected to a modification of General Procedure 2 with 3-bromo-2-methylprop-1-ene (1.56 g, 11.6 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc, 24:1 to 19:1] to furnish *ether* **181** (3.03 g, 9.26 mmol, 96%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.00 (1H, s, *H*C_{Ar}), 6.98 (1H, s, *H*C_{Ar}), 5.88 (1H, ddd, *J* 16.7, 10.4, 5.8, C*H*=CH_2), 5.30 (1H, dt, *J* 16.7, 1.4, CH=CH_aH_b), 5.19-5.14 (2H, m, C*H*OR + CH=CH_aH_b), 4.99 (1H, s, CCH_3=CH_aH_b), 4.90 (1H, s, CCH_3=CH_aH_b), 3.85 (8H, s, 2 × OCH_3 + CH_2OR), 1.75 (3H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 148.9, 148.9 (2 × C_{Ar}), 142.0 (*C*CH_3=CH_2), 137.3 (*C*H=CH_2), 132.1 (C_{Ar}), 116.0 (CH=*C*H_2), 115.0 (HC_{Ar}), 113.0 (C_{Ar}), 112.2 (CCH_3=*C*H_2), 110.4 (HC_{Ar}), 79.7 (*C*HOR), 72.3 (*C*H_2OR), 56.1, 56.0 (2 × O*C*H_3), 19.6 (*C*H_3); **IR** υ_{max} (thin film)/cm^{-1} 3080m, 2935s, 2842s, 1656m, 1602s, 1504s, 1439s, 1379s, 1349m, 1257s, 1209s, 1162s, 1033s, 987m, 925m, 865m, 814m; **m/z** (ESI^+) 349.0 [100, $(M + Na)^+$], 675.1 [40, $(2M + Na)^+$], $C_{15}H_{19}{}^{79}BrNaO_3$ predicted 349.0410, found 349.0408, (Δ + 0.6 ppm).

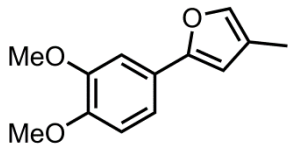
2-(2-Bromo-4,5-dimethoxyphenyl)-4-methyl-2,5-dihydrofuran **182**



Allyl ether **181** (2.92 g, 8.92 mmol) was subjected to a modification of General Procedure 3 with Hoveyda-Grubbs 2nd generation catalyst (55.9 mg, 0.0892 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc, 24:1 to 4:1] to furnish *dihydrofuran* **182** (2.32 g, 7.77 mmol, 87%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.97 (1H, s, *H*C$_{Ar}$), 6.92 (1H, s, *H*C$_{Ar}$), 6.01-5.98 (1H, m, C*H*=CCH$_3$), 5.61 (1H, m, C*H*OR), 4.74 (1H, dd, *J* 12.3, 5.6, C*H*$_a$H$_b$OR), 4.64 (1H, d, *J* 12.3, CH$_a$*H*$_b$OR), 3.85 (3H, s, OC*H*$_3$), 3.84 (3H, s, OC*H*$_3$), 1.79 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 148.8, 148.7 (2 × *C*$_{Ar}$), 136.5 (CH=*C*CH$_3$), 133.8 (*C*$_{Ar}$), 123.1 (*C*H=CCH$_3$), 115.3 (H*C*$_{Ar}$), 111.2 (*C*$_{Ar}$), 110.1 (H*C*$_{Ar}$), 87.2 (*C*HOR), 78.6 (*C*H$_2$OR), 56.2, 56.0 (2 × OCH$_3$), 12.2 (*C*H$_3$); **IR** υ_{max} (thin film)/cm^{-1} 3547w, 3083m, 2840s, 2693w, 2605w, 2254w, 2054m, 1767s, 1668s, 1601s, 1508s, 1382s, 1265s, 1065s, 961s, 922m, 864m; **m/z** (ESI$^+$) 321.0 [100, (M + Na)$^+$], 619.0 [95, (2M + Na)$^+$], $C_{13}H_{15}{}^{79}BrNaO_3$ predicted 321.0097, found 321.0097, (Δ − 0.1 ppm).

2-(3,4-Dimethoxyphenyl)-4-methylfuran **183**

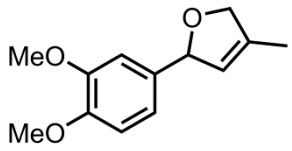


Dihydrofuran **182** (109 mg, 0.363 mmol) was subjected to General Procedure 4. The crude product was purified by flash column chromatography [Petrol/EtOAc, 99:1 to 19:1] to furnish *furan* **183** (22.0 mg, 0.101 mmol, 28%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.22-7.17 (3H, m, 2 × *H*C$_{Ar}$ + *H*C(5)), 6.88 (1H, d, *J* 8.0, *H*C$_{Ar}$), 6.42 (1H, s, *H*C(3)), 3.94 (3H, s, OC*H*$_3$), 3.91 (3H, s, OC*H*$_3$), 2.08 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 153.8 (*C*(5)), 149.1, 148.4 (2 × *C*$_{Ar}$), 138.2 (H*C*(2)), 124.4, 121.9 (*C*$_{Ar}$ + *C*(4)), 116.4, 111.4 (2 × H*C*$_{Ar}$), 107.1, 106.5 (H*C*$_{Ar}$ + H*C*(3)), 55.9, 55.9 (2 × OCH$_3$), 9.9 (*C*H$_3$); **IR** υ_{max} (thin film)/cm^{-1} 2962s, 1764s, 1662w, 1594m, 1515s,

1464m, 1419m, 1264s, 1141m, 1025s, 864m; **m/z** (ESI^+) 241.1 [100, $(M + Na)^+$], $C_{13}H_{14}NaO_3$ predicted 241.0835, found 241.0833, (Δ + 0.7 ppm).

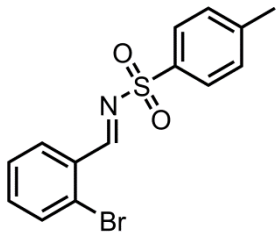
2-(3,4-Dimethoxyphenyl)-4-methyl-2,5-dihydrofuran **184**



Dihydrofuran **182** (109 mg, 0.363 mmol) was subjected to General Procedure 4. The crude product was purified by flash column chromatography [Petrol/EtOAc, 99:1 to 19:1] to furnish *dihydrofuran* **184** (21.6 mg, 0.0981 mmol, 27%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.87-6.84 (3H, m, 3 × *H*C_{Ar}), 5.74-5.71 (1H, m, C*H*OR), 5.51-5.49 (1H, m, C*H*=CCH_3), 4.71 (1H, dd, *J* 12.3, 5.5, C*H*$_a$H$_b$OR), 4.62-4.57 (1H, m, CH$_a$*H*$_b$OR), 3.89 (3H, s, OC*H*$_3$), 3.87 (3H, s, OC*H*$_3$), 1.84 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 149.1, 148.6 (2 × *C*$_{Ar}$), 136.7, 135.2 (*C*$_{Ar}$ + *C*CH_3), 123.9 (*C*H=CCH_3), 118.7, 111.0, 109.7 (3 × H*C*$_{Ar}$), 88.3 (*C*HOR), 78.2 (*C*H_2OR), 55.9, 55.8 (2 × O*C*H_3), 12.3 (*C*H_3); **IR** υ_{max} (thin film)/cm^{-1} 2999w, 2961s, 2936s, 2916s, 2837s, 1766w, 1668w, 1594m, 1516s, 1464s, 1420m, 1263s, 1234s, 1138m, 1028s, 975s; **m/z** (ESI^+) 243.1 [85, $(M + Na)^+$], 463.2 [100, $(2M + Na)^+$], $C_{13}H_{16}NaO_3$ predicted 243.0992, found 243.0992, (Δ − 0.1 ppm).

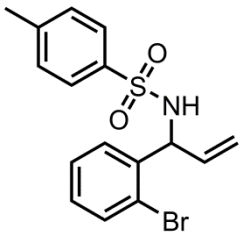
(*E*)-*N*-(2-Bromobenzylidene)-4-methylbenzenesulfonamide **185**



Tetraethoxysilane (4.58 g, 22.0 mmol) was added to 2-bromobenzaldehyde (3.70 g, 20.0 mmol) and *p*-toluenesulfonamide (3.42 g, 20.0 mmol) in a flask equipped with side-arm distillation apparatus. The mixture was stirred at 165 °C until EtOH finished distilling off (5 h). The mixture was cooled to room temperature to give the crude product. Recrystallisation (Petrol/EtOAc) furnished *sulfonamide* **185** (4.94 g, 14.6 mmol, 73% after one recrystallisation) as rods.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.44 (1H, s, *H*C=N), 8.15 (1H, dd, *J* 7.6, 2.0, *H*C_{Ar}), 7.91 (2H, d, *J* 8.3, 2 × *H*C_{Ar}), 7.67 (1H, dd, *J* 8.1, 1.5, *H*C_{Ar}), 7.46-7.31 (2H, d, *J* 8.3, 2 × *H*C_{Ar}), 7.36 (2H, d, *J* 8.3, 2 × *H*C_{Ar}), 2.46 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 169.2 (H*C*=N), 144.9 (*C*$_{Ar}$), 135.7 (H*C*$_{Ar}$), 134.6 (*C*$_{Ar}$), 133.8 (H*C*$_{Ar}$), 131.2 (*C*$_{Ar}$), 130.6, 129.9 (2 × H*C*$_{Ar}$), 128.9 (*C*$_{Ar}$), 128.3, 127.9 (2 × H*C*$_{Ar}$), 21.7 (*C*H$_3$); **m.p.** 139-141 °C (Petrol/EtOAc). Data were consistent with those previously reported.[262]

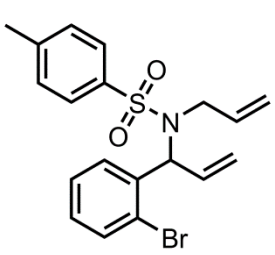
N-(1-(2-Bromophenyl)allyl)-4-methylbenzenesulfonamide **186**



A solution of sulfonamide **185** (2.77 g, 8.21 mmol) in THF (25 mL) was stirred at 0 °C. Vinyl magnesium bromide (1 M in THF, 9.86 mL) was added dropwise and then the solution was warmed up to room temperature and heated at 70 °C for 18 h. The reaction was cooled to room temperature and quenched by dropwise addition of saturated aqueous NH_4Cl (5 mL) and diluted with Et_2O (100 mL). The organic layer was washed with saturated aqueous NH_4Cl (25 mL), H_2O (25 mL) and brine (25 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude product. Purification by flash column chromatography [Petrol/EtOAc, 19:1 to 9:1] furnished *sulfonamide* **186** (2.34 g, 6.39 mmol, 78%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.63 (2H, d, *J* 8.0, 2 × *H*C_{Ar}), 7.42 (1H, d, *J* 7.8, *H*C_{Ar}), 7.16-7.14 (4H, m, 4 × *H*C_{Ar}), 7.07-7.03 (1H, m, *H*C_{Ar}), 5.87 (1H, ddd, *J* 16.9, 10.4, 5.4, C*H*=CH_2), 5.37 (1H, dd, *J* 7.9, 5.4, C*H*NH), 5.28 (1H, d, *J* 7.9, CHN*H*), 5.17 (1H, d, *J* 10.4, CH=C*H*$_a$H$_b$), 5.05 (1H, d, *J* 16.9, CH=CH$_a$*H*$_b$), 2.36 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 143.3, 138.2, 137.1 (3 × *C*$_{Ar}$), 136.0 (*C*H=CH_2), 133.1, 129.4, 129.2, 129.0, 127.6, 127.2 (6 × H*C*$_{Ar}$), 122.8 (*C*$_{Ar}$), 117.4 (CH=*C*H_2), 59.1 (*C*HNH), 21.5 (*C*H$_3$); **IR** υ_{max} (thin film)/cm^{-1} 3259s, 1438m, 1329s, 1159s, 1093m, 1022m, 915m; **m/z** (ESI$^+$) 388.0 [100, (M + Na)$^+$], 753.0 [90, (2M + Na)$^+$], $C_{16}H_{16}{}^{79}BrNNaO_2S$ predicted 387.9977, found 387.9982, (Δ − 1.1 ppm); **m.p.** 97-99 °C (Petrol/CH_2Cl_2).

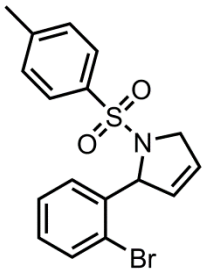
N-Allyl-*N*-(1-(2-bromophenyl)allyl)-4-methylbenzenesulfonamide **187**



Sulfonamide **186** (2.27 g, 6.20 mmol) was subjected to General Procedure 2. The crude product was purified by flash column chromatography [Petrol/EtOAc, 19:1] to furnish *N-allyl sulfonamide* **187** (1.34 g, 3.30 mmol, 53%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.61 (2H, d, *J* 8.1, 2 × *H*C_{Ar}), 7.48 (1H, d, *J* 7.8, *H*C_{Ar}), 7.34 (1H, dd, *J* 7.7, 1.2, *H*C_{Ar}), 7.22 (1H, t, *J* 7.1, *H*C_{Ar}), 7.18 (2H, d, *J* 8.1, 2 × *H*C_{Ar}), 7.11 (1H, td, *J* 7.8, 1.2, *H*C_{Ar}), 6.06 (1H, ddd, *J* 16.9, 10.4, 6.3, C*H*=CH_2), 5.84 (1H, d, *J* 6.3, C*H*NR_2), 5.66-5.56 (1H, m, C*H*=CH_2), 5.30 (1H, d, *J* 10.3, CH=CH_aH_b), 5.10 (1H, d, *J* 17.2, CH=CH_a*H*$_b$), 4.93 (1H, d, *J* 11.6, CH=C*H*$_a$H$_b$), 4.92 (1H, d, *J* 16.7, CH=CH_a*H*$_b$), 3.96 (1H, dd, *J* 17.3, 5.8, C*H*$_a$H$_b$$NR_2$), 3.87 (1H, dd, *J* 17.3, 6.4, CH_a*H*$_b$$NR_2$), 2.40 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 143.0, 137.7, 137.6 (3 × *C*$_{Ar}$), 135.0, 134.8, 133.1, 130.6, 129.3, 129.1, 127.6, 127.2 (6 × H*C*$_{Ar}$ + *C*H=*C*H), 125.0 (*C*$_{Ar}$), 119.1, 117.3 (2 × CH=*C*H_2), 63.8 (*C*HNR_2), 49.4 (*C*$H_2$$NR_2$), 21.5 (*C*$H_3$); **IR** υ_{max} (thin film)/cm^{-1} 3067m, 2923s, 1920w, 1598w, 1468m, 1439m, 1344s, 1160s, 1090s, 1206m, 927m, 813m; **m/z** (ESI$^+$) 428.0 [100, (M + Na)$^+$], 833.1 [80, (2M + Na)$^+$], $C_{19}H_{20}{}^{79}BrNNaO_2S$ predicted 428.0290, found 428.0292, (Δ − 0.3 ppm).

2-(2-Bromophenyl)-1-tosyl-2,5-dihydro-1*H*-pyrrole **188**

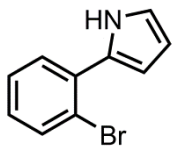


N-allyl sulfonamide **187** (920 mg, 2.26 mmol) was subjected to a modification of General Procedure 3 with Grubbs-Hoveyda 2nd generation catalyst (14.2 mg, 0.0226 mmol). The solvent was then removed *in vacuo* to give the crude product which was purified by flash column chromatography [Petrol/EtOAc, 19:1 to 9:1] to furnish *dihydropyrrole* **188** (384 mg, 1.02 mmol, 45%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.74 (2H, d, *J* 8.3, 2 × *H*C_{Ar}), 7.52-7.48 (2H, m, 2 × *H*C_{Ar}), 7.31 (2H, d, *J* 8.3, 2 × *H*C_{Ar}), 7.30-7.27 (1H, m, *H*C_{Ar}), 7.12 (1H, td, *J* 7.6, 1.0, *H*C_{Ar}), 5.88

(1H, dd, *J* 5.3, 2.5 C*H*NR_2), 5.72-5.69 (2H, m, C*H*=C*H*), 4.42 (1H, dd, *J* 14.7, 5.7, C*H*$_a$H$_b$$NR_2$), 4.32 (1H, dd, *J* 14.7, 2.7, CH$_a$*H*$_b$$NR_2$), 2.43 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 143.7, 140.2, 134.2, (3 × *C*$_{Ar}$), 132.5 (H*C*$_{Ar}$), 129.8 (*C*H=CH), 129.7, 129.0, 128.9, 127.9, 127.7 (5 × H*C*$_{Ar}$), 124.4 (CH=*C*H), 121.6 (*C*$_{Ar}$), 69.6 (*C*HNR_2), 56.2 (*C*H_2NR_2), 21.6 (*C*H_3); **IR** υ_{max} (thin film)/cm^{-1} 2920s, 2862m, 1730m, 1595m, 1466s, 1444m, 1340s, 1263w, 1157s, 1087m, 1059m, 814w; **m/z** (ESI$^+$) 400.0 [80, (M + Na)$^+$], 777.0 [100, (2M + Na)$^+$], $C_{17}H_{16}{}^{79}BrNNaO_2S$ predicted 399.9977, found 399.9978, (Δ − 0.2 ppm); **m.p.** 157-158 °C (Petrol/CH_2Cl_2).

2-(2-Bromophenyl)-1*H*-pyrrole **189**



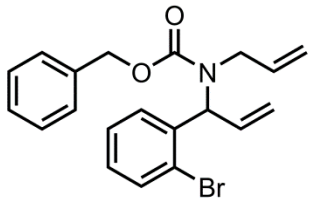
Method A: Dihydropyrrole **188** (42.4 mg, 0.112 mmol) was subjected to General Procedure 4. The crude product was purified by flash column chromatography [Petrol/EtOAc, 24:1 to 9:1] to furnish *pyrrole* **189** (18.2 mg, 0.0819 mmol, 73%) as a yellow oil.

***Method B*:** Dihydropyrrole **188** (36.3 mg, 0.0960 mmol) and DMA (0.96 mL) were added to a resealable reaction tube sealed with a rubber septum. The solution was degassed with a stream of argon (provided by a balloon and exit needle) for 15 min. Cs_2CO_3 (62.5 mg, 0.192 mmol) was added and the mixture was heated at 120 °C for 24 h. The mixture was cooled to room temperature and then Et_2O (50 mL) was added. The organic layer was washed with H_2O (3 × 25 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the crude product. Purification by flash column chromatography [Petrol/EtOAc, 24:1 to 9:1] furnished *pyrrole* **189** (18.1 mg, 0.0815 mmol, 85%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) $\delta_{H:}$ 8.98 (1H, br. s, N*H*), 7.63 (1H, d, *J* 8.1, *H*C$_{Ar}$), 7.53 (1H, dd, *J* 7.8, 1.3, *H*C$_{Ar}$), 7.33 (1H, t, *J* 7.6, *H*C$_{Ar}$), 7.10 (1H, td, *J* 8.3, 1.3, *H*C$_{Ar}$), 6.95-6.93 (1H, m, *H*C(5)), 6.59-6.57 (1H, m, *H*C(3)), 6.34 (1H, dd, *J* 5.8, 2.8, *H*C(4)); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 134.0 (H*C*$_{Ar}$), 133.3 (*C*(2)), 130.3 (H*C*$_{Ar}$), 130.2 (*C*$_{Ar}$), 127.8, 127.7 (2 × H*C*$_{Ar}$), 120.0 (*C*$_{Ar}$), 118.8 (H*C*(5)), 109.5 (*C*(3)), 109.3 (*C*(4)); **IR** υ_{max} (thin film)/cm^{-1} 3442s,

2963s, 2919s, 2850m, 1717w, 1592w, 1476m, 1261s, 1095s, 1020s, 919w, 864s; **m/z** (EI/FI$^+$) $C_{10}H_8{}^{79}BrN$ predicted 220.9840, found 220.9844, (Δ − 1.8 ppm).

Benzyl allyl(1-(2-bromophenyl)allyl)carbamate **191**

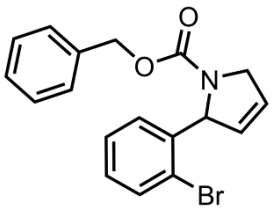


Allylamine (1.16 g, 20.4 mmol) was added to 2-bromobenzaldehyde (3.70 g, 20.0 mmol) and activated 4 Å molecular sieves (6.00 g) in THF (50 mL) and the resulting mixture was stirred at room temperature for 18 h. The mixture was filtered through Celite and the residue washed with Et_2O (2 × 25 mL). The filtrate was concentrated *in vacuo* to give the crude imine which was immediately redissolved in THF (60 mL). Benzyl chloroformate (3.48 g, 20.4 mmol) was added and the solution was heated to 60 °C for 1 h. The solution was cooled to −78 °C and vinyl magnesium bromide (1.0 M in THF, 23.6 mL) was added dropwise. The solution was warmed to room temperature and stirred for a further 1.5 h. The reaction was quenched by the dropwise addition of saturated aqueous NH_4Cl (5 mL), followed by the addition of H_2O (25 mL). The mixture was extracted with Et_2O (3 × 25 mL) and the combined organics were washed with saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography [Petrol/EtOAc, 24:1 to 4:1] to furnish *carbamate* **191** (5.99 g, 15.5 mmol, 78% over three steps) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.56 (1H, d, *J* 8.1, *H*C$_{Ar}$), 7.34-7.27 (7H, m, 7 × *H*C$_{Ar}$), 7.17 (1H, td, *J* 7.6, 1.7, *H*C$_{Ar}$), 6.12-6.04 (2H, m, C*H*NR$_2$ + C*H*=CH$_2$), 5.59-5.51 (1H, m, C*H*=CH$_2$), 5.36 (1H, d, *J* 9.1, CH=C*H*$_a$H$_b$), 5.23 (1H, d, *J* 11.9, C*H*$_a$H$_b$OR), 5.20 (1H, d, *J* 11.9, CH$_a$*H*$_b$OR), 5.15 (1H, d, *J* 15.4, CH=CH$_a$*H*$_b$), 4.83 (1H, d, *J* 10.1, CH=C*H*$_a$H$_b$), 4.75 (1H, d, *J* 16.9, CH=CH$_a$*H*$_b$), 3.95 (1H, dd, *J* 15.9, 4.8, C*H*$_a$H$_b$NR$_2$), 3.65 (1H, dd, *J* 15.9, 4.5, CH$_a$*H*$_b$NR$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 156.1 (*C*=O), 138.2, 136.7 (2 × *C*$_{Ar}$), 134.8, 134.2, 133.2, 130.2, 129.4, 128.4, 127.8, 127.8, 127.3 (7 × H*C*$_{Ar}$ + 2 × *C*H=CH$_2$), 125.9

(C_{Ar}), 117.1, 116.0 (2 × CH=CH$_2$), 67.3 (CH$_2$OR), 61.6 (CHNR$_2$), 47.3 (CH$_2$NR$_2$). Data were consistent with those previously reported.[183]

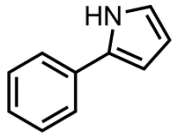
Benzyl 2-(2-bromophenyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate **192**



Carbamate **191** (2.56 g, 6.63 mmol) was dissolved in CH_2Cl_2 (66 mL) at room temperature and the solution degassed with a stream of argon gas (provided by a balloon and exit needle) for 15 min. Hoveyda-Grubbs 2nd generation catalyst (41.6 mg, 0.0663 mmol) was added and the reaction stirred at room temperature for 18 h. DMSO (0.235 mL) was added and the solution was stirred for a further 24 h. The solvent was removed *in vacuo* and the crude product subjected to flash column chromatography [Petrol/EtOAc, 19:1 to 9:1] to give *dihydropyrrole* **192** (1.27 g, 3.55 mmol, 54%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: (rotamers 60:40) 7.54 (1H, t, *J* 8.0, HC$_{Ar}$), 7.39-7.10 (7H, m, 7 × HC$_{Ar}$), 6.95-6.93 (1H, m, HC$_{Ar}$), 6.03-6.00 (1H, m, CHNR$_2$), 5.94-5.90 (1H, m, CHNCH=CH), 5.87-5.85 (1H, m, CHNCH=CH), 5.21 (0.4H, d, *J* 12.4, CH_aH$_b$OR), 5.11 (0.4H, d, *J* 12.4, CH$_a$$H_b$OR), 5.11 (0.6H, d, *J* 12.7, CH_aH$_b$OR), 4.99 (0.6H, d, *J* 12.7, CH$_a$$H_b$OR), 4.51-4.39 (2H, m, C$H_2NR_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: (rotamers) 154.4, 154.2 (C=O), 141.0, 140.1, 136.7, 136.5 (2 × C_{Ar}), 133.0, 132.7 (HC_{Ar}), 129.8, 129.8 (CH=CH), 128.8, 128.7, 128.5, 128.2, 128.2, 128.0, 128.0, 127.9, 127.5, 127.4, 127.2, 127.0 (6 × HC_{Ar}), 124.9, 124.8 (CH=CH), 121.9, 121.8 (C_{Ar}), 68.1, 67.4 (CHNR$_2$), 67.0, 66.7 (CH$_2$OR), 54.5, 54.2 (CH$_2$NR$_2$); **m.p.** 73-74 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[183]

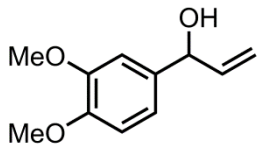
2-Phenyl-1*H*-pyrrole **193**



Dihydropyrrole **192** (115 mg, 0.321 mmol) was subjected to General Procedure 4. The crude product was purified by flash column chromatography [Petrol/EtOAc, 9:1 to 4:1] to furnish *pyrrole* **193** (12.0 mg, 0.0838 mmol, 26%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.46 (1H, br.s, N*H*), 7.51 (2H, d, *J* 7.2, 2 × *H*C$_{Ar}$), 7.39-7.34 (2H, m, 2 × *H*C$_{Ar}$), 7.24 (1H, m, *H*C$_{Ar}$), 6.90 (1H, m, *H*C(5)), 6.56 (1H, m, *H*C(3)), 6.33 (1H, m, *H*C(4)); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 132.8 (*C*$_{Ar}$), 132.1 (*C*(2)), 128.9, 126.2, 123.9 (3 × H*C*$_{Ar}$), 118.0 (H*C*(5)), 110.2 (H*C*(4)), 106.0 (H*C*(3)); **m.p.** 125-126 °C (CH_2Cl_2/EtOAc). Data were consistent with those previously reported.[263]

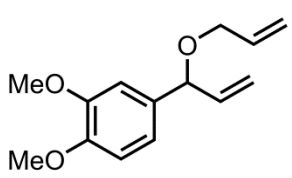
1-(3,4-Dimethoxyphenyl)prop-2-en-1-ol **195**



3,4-Dimethoxybenzaldehyde (1.66 g, 10.0 mmol) was subjected to General Procedure 1. The crude product was purified by flash column chromatography [Petrol/EtOAc, 9:1 to 3:1] to furnish *vinyl alcohol* **195** (1.65 g, 8.50 mmol, 85%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.90 (1H, s, *H*C$_{Ar}$), 6.88 (1H, d, *J* 8.1, *H*C$_{Ar}$), 6.82 (1H, d, *J* 8.1, *H*C$_{Ar}$), 6.03 (1H, ddd, *J* 16.9, 10.4, 5.8, C*H*=CH$_2$), 5.33 (1H, d, *J* 16.9, CH=C*H*$_a$H$_b$), 5.18 (1H, d, *J* 10.4, CH=CH$_a$*H*$_b$), 5.12 (1H, m, C*H*OH), 3.86 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 2.25 (1H, br. s, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 149.1, 148.5 (2 × *C*$_{Ar}$), 140.3 (*C*H=CH$_2$), 135.3 (*C*$_{Ar}$), 118.7 (H*C*$_{Ar}$), 114.9 (CH=*C*H$_2$), 111.0, 109.5 (2 × H*C*$_{Ar}$), 75.0 (*C*HOH), 55.9, 55.8 (2 × O*C*H$_3$). Data were consistent with those previously reported.[264]

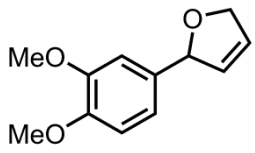
4-(1-(Allyloxy)allyl)-1,2-dimethoxybenzene **196**



Vinyl alcohol **195** (1.60 g, 8.24 mmol) was subjected to General Procedure 2. The crude product was purified by flash column chromatography [Petrol/EtOAc, 24:1 to 4:1] to furnish *allyl ether* **196** (1.77 g, 7.55 mmol, 92%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.88 (1H, s, *H*C$_{Ar}$), 6.86 (1H, d, *J* 8.1, *H*C$_{Ar}$), 6.82 (1H, d, *J* 8.1, *H*C$_{Ar}$), 5.99-5.88 (2H, m, 2 × C*H*=CH$_2$), 5.27 (1H, d, *J* 17.2, CH=C*H*$_a$H$_b$), 5.25 (1H, d, *J* 16.9, CH=C*H*$_a$H$_b$), 5.18 (1H, d, *J* 10.1, CH=CH$_a$*H*$_b$), 5.17 (1H, d, *J* 10.1, CH=CH$_a$*H*$_b$), 4.74 (1H, d, *J* 6.4, C*H*OR), 4.00-3.92 (2H, m, C*H*$_2$OR), 3.87 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 149.1, 148.5 (2 × *C*$_{Ar}$), 138.9, 134.9 (2 × *C*H=CH$_2$), 133.5 (*C*$_{Ar}$), 119.4 (H*C*$_{Ar}$), 116.8, 116.0 (2 × CH=*C*H$_2$), 110.9, 110.0 (2 × H*C*$_{Ar}$), 81.8 (*C*HOR), 69.1 (*C*H$_2$OR), 55.9, 55.8 (2 × OC*H*$_3$); **IR** υ_{max} (thin film)/cm^{-1} 3528w, 3079s, 2936s, 2836s, 2017w, 1854w, 1717m, 1645m, 1594s, 1514s, 1464s, 1418s, 1262s, 1139s, 1029s, 926s, 859m, 812m; **m/z** (ESI$^+$) 257.1 [80, (M + Na)$^+$], 491.3 [100, (2M + Na)$^+$], $C_{14}H_{18}NaO_3$ predicted 257.1148, found 257.1148, (Δ − 0.1 ppm).

2-(3,4-Dimethoxyphenyl)-2,5-dihydrofuran **197**

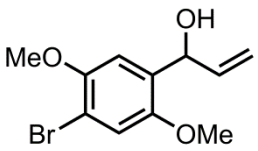


Allyl ether **196** (1.68 g, 7.16 mmol) was subjected to General Procedure 3. The crude product was purified by flash column chromatography [Petrol/EtOAc, 24:1 to 4:1] to furnish *dihydrofuran* **197** (1.33 g, 6.45 mmol, 90%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.85-6.82 (3H, m, 3 × *H*C$_{Ar}$), 6.05-6.03 (1H, m, C*H*=CH), 5.88-5.85 (1H, m, CH=C*H*), 5.74-5.71 (1H, m, C*H*OR), 4.87-4.82 (1H, m, C*H*$_a$H$_b$OR), 4.75-4.70 (1H, m, CH$_a$*H*$_b$OR), 3.87 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 149.1, 148.8, 134.5 (3 × *C*$_{Ar}$), 129.9, 126.8 (*C*H=*C*H), 118.9, 111.0, 109.7 (3 × H*C*$_{Ar}$), 87.7 (*C*HOR), 75.5 (*C*H$_2$OR), 55.9, 55.8 (2 × OC*H*$_3$); **IR** υ_{max} (thin film)/cm^{-1} 2937m, 2838s, 2282w, 1594w, 1515s, 1464m, 1420m, 1350w, 1263s, 1233s, 1157m,

1138m, 1061m, 1026m; **m/z** (ESI^+) 229.1 [100, $(M + Na)^+$], 435.2 [70, $(2M + Na)^+$], $C_{12}H_{14}NaO_3$ predicted 229.0835, found 229.0836, (Δ − 0.2 ppm); **m.p.** 38-39 °C (Petrol/CH_2Cl_2).

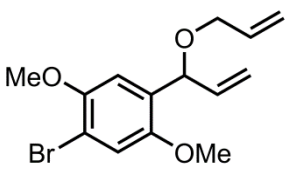
1-(4-Bromo-2,5-dimethoxyphenyl)prop-2-en-1-ol **199**



4-Bromo-2,5-dimethoxybenzaldehyde (2.45 g, 10.0 mmol) was subjected to General Procedure 1. The crude product was purified by flash column chromatography [Petrol/EtOAc, 19:1 to 9:1 to 3:1] to furnish *vinyl alcohol* **199** (2.41 g, 8.82 mmol, 88%) as needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.07 (1H, s, *H*C_{Ar}), 6.95 (1H, s, *H*C_{Ar}), 6.05 (1H, ddd, *J* 16.7, 10.6, 5.5, C*H*=CH_2), 5.41-5.38 (1H, m, C*H*OH), 5.31 (1H, d, *J* 16.7, CH=C*H*$_a$H$_b$), 5.17 (1H, d, *J* 10.6, CH=CH$_a$*H*$_b$), 3.85 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 2.74 (1H, br. s, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 150.8, 150.3 (2 × *C*$_{Ar}$), 138.9 (*C*H=CH_2), 131.1 (*C*$_{Ar}$), 116.2 (H*C*$_{Ar}$), 114.9 (CH=*C*H_2), 111.4 (H*C*$_{Ar}$), 110.4 (*C*$_{Ar}$), 70.5 (*C*HOH), 56.9, 56.2 (2 × O*C*H_3); **IR** υ_{max} (thin film)/cm^{-1} 3405br./s, 3083w, 3003s, 2941s, 2843s, 1640w, 1579w, 1492s, 1386s, 1210s, 1179m, 1151w, 1107s, 1035s, 926m; **m/z** (ESI^+) 295.0 [100, $(M + Na)^+$], 567.0 [50, $(2M + Na)^+$], $C_{11}H_{13}{}^{79}BrNaO_3$ predicted 294.9940, found 294.9941, (Δ − 0.4 ppm); **m.p.** 71-73 °C (Petrol/CH_2Cl_2).

1-(1-(Allyloxy)allyl)-4-bromo-2,5-dimethoxybenzene **200**

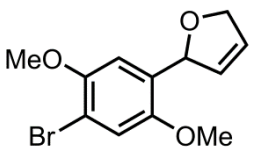


Vinyl alcohol **199** (2.30 g, 8.41 mmol) was subjected to General Procedure 2. The crude product was purified by flash column chromatography [Petrol/EtOAc, 19:1] to furnish *allyl ether* **200** (2.46 g, 7.85 mmol, 93%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.07 (1H, s, *H*C_{Ar}), 7.04 (1H, s, *H*C_{Ar}), 5.99-5.86 (2H, m, 2 × C*H*=CH_2), 5.29 (1H, dd, *J* 17.2, 1.3, C$_a$H=C*H*$_a$H$_b$), 5.27 (1H, d, *J* 17.1, C$_b$H=C*H*$_a$H$_b$),

5.22 (1H, d, *J* 5.8, C*H*OR), 5.17 (1H, d, *J* 11.9, C_aH=CH_aH_b), 5.15 (1H, d, *J* 11.8, C_bH=CH_aH_b), 4.04-3.94 (2H, m, CH_2OR), 3.86 (3H, s, OCH_3), 3.78 (3H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 151.0, 150.5 (2 × C_{Ar}), 137.7, 134.8 (2 × *C*H=CH_2), 129.8 (C_{Ar}), 116.8 (CH=*C*H_2), 116.2 (HC_{Ar}), 115.6 (CH=*C*H_2), 111.0 (HC_{Ar}), 110.3 (C_{Ar}), 75.1 (*C*HOR), 69.6 (*C*H_2OR), 56.8, 56.3 (2 × OCH_3); **IR** υ_{max} (thin film)/cm^{-1} 3080m, 2940s, 2845s, 1644w, 1580w, 1490s, 1464s, 1385s, 1333w, 1268w, 1211s, 1179m, 1110m, 1055s, 990m; **m/z** (ESI^+) 335.0 [100, $(M + Na)^+$], $C_{14}H_{17}{}^{79}BrNaO_3$ predicted 335.0253, found 335.0251, (Δ + 0.8 ppm).

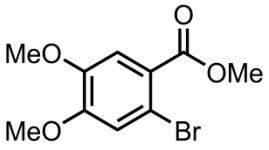
2-(4-Bromo-2,5-dimethoxyphenyl)-2,5-dihydrofuran **201**



Allyl ether **200** (2.34 g, 7.47 mmol) was subjected to General Procedure 3. The crude product was purified by flash column chromatography [Petrol/EtOAc, 24:1 to 4:1] to furnish *dihydrofuran* **201** (1.90 g, 6.66 mmol, 89%) as plates.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.06 (1H, s, *H*C_{Ar}), 6.99 (1H, s, *H*C_{Ar}), 6.05-6.03 (1H, m, C*H*OR), 5.99-5.95 (2H, m, C*H*=C*H*), 4.88 (1H, dd, *J* 13.0, 6.1, CH_aH_bOR), 4.82-4.78 (1H, m, CH_aH_bOR), 3.86 (3H, s, OCH_3), 3.82 (3H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 150.3, 150.3, 131.1 (3 × C_{Ar}), 129.2, 126.0 (2 × HC_{Ar}), 115.8, 110.6 (*C*H=*C*H), 110.0 (C_{Ar}), 82.5 (*C*HOR), 75.6 (*C*H_2OR), 56.9, 56.1 (2 × OCH_3); **IR** υ_{max} (thin film)/cm^{-1} 2847s, 1489s, 1463m, 1440m, 1386s, 1331w, 1209s, 1179w, 1072s, 1035m, 962w; **m/z** (ESI^+) 307.0 [100, $(M + Na)^+$], $C_{12}H_{13}{}^{79}BrNaO_3$ predicted 306.9940, found 306.9934, (Δ + 2.1 ppm); **m.p.** 103-104 °C (Petrol/CH_2Cl_2).

Methyl 2-bromo-4,5-dimethoxybenzoate **204**

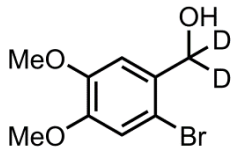


Trimethylsilyldiazomethane (2 M in Et_2O, 2.48 mL) was added dropwise to a solution of 2-bromo-4,5-dimethoxybenzoic acid

(997 mg, 3.82 mmol) in toluene (40 mL) and MeOH (10 mL) at room temperature and the solution was stirred for 2 h. The mixture was concentrated *in vacuo* to give the crude product which was purified by flash column chromatography [Petrol/EtOAc, 4:1] to furnish *ester* **204** (1.02 g, 3.71 mmol, 97%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.39 (1H, d, *J* 1.5, *H*C_{Ar}), 7.08 (1H, d, *J* 1.5, *H*C_{Ar}), 3.90 (3H, s, OC*H*$_3$), 3.89 (3H, s, CO_2C*H*$_3$), 3.88 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 165.8 (*C*O_2CH_3), 152.0, 147.8, 122.8 (3 × *C*$_{Ar}$), 116.9 (H*C*$_{Ar}$), 114.1 (*C*$_{Ar}$), 114.0 (H*C*$_{Ar}$), 56.3, 56.1 (2 × O*C*H_3), 52.2 (CO_2*C*H_3); **m.p.** 85-86 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[265]

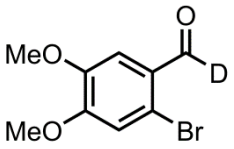
(2-Bromo-4,5-dimethoxyphenyl)dideuteriomethanol **205**



Lithium aluminium deuteride (1 M in THF, 6.97 mL) was added to a solution of ester **204** (871 mg, 3.17 mmol) in THF (160 mL) at 0 °C. After 10 min the reaction was quenched by the slow addition of MeOH (20 mL) and then H_2O (20 mL). The mixture was extracted with EtOAc (3 × 50 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo.* The crude product was purified by flash column chromatography [Petrol/EtOAc, 3:1] to furnish *alcohol* **205** (717 mg, 2.88 mmol, 91%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.99 (1H, s, *H*C_{Ar}), 6.99 (1H, s, *H*C_{Ar}), 3.86 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 2.23 (1H, br. s, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 148.9, 148.5, 131.8 (3 × *C*$_{Ar}$), 115.4 (H*C*$_{Ar}$), 112.5 (*C*$_{Ar}$), 111.9 (H*C*$_{Ar}$), 64.1 (quin., ^{1}J 22.4, *C*D_2OH), 56.2, 56.0 (2 × O*C*H_3); **IR** υ_{max} (thin film)/cm^{-1} 3220br./s, 3001s, 2844s, 2220m, 2098s, 1599m, 1501s, 1462m, 1439m, 1378s, 1324s, 1262s, 1202m, 1165s, 1090m, 1027s, 963m, 865s; **m/z** (ESI$^+$) 271.0 [100, $(M + Na)^+$], 519.1 [70, $(2M + Na)^+$], $C_9H_9{}^{79}BrD_2NaO_3$ predicted 270.9909, found 270.9910, (Δ − 0.2 ppm); **m.p.** 95-96 °C (Petrol/CH_2Cl_2).

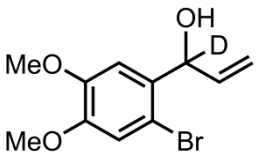
(2-Bromo-4,5-dimethoxy)deuteriobenzaldehyde **206**



Dess-Martin Periodinane (1.33 g, 3.13 mmol) was added to a solution of alcohol **205** (650 mg, 2.61 mmol) in CH_2Cl_2 (65 mL) at room temperature and the mixture stirred for 2 h. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography [Petrol/EtOAc, 9:1 to 3:1] to furnish *aldehyde* **206** (606 mg, 2.46 mmol, 94%) as needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.40 (1H, s, *H*C$_{Ar}$), 7.04 (1H, s, *H*C$_{Ar}$), 3.95 (3H, s, OC*H*$_3$), 3.91 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 190.4 (t, ^1J 27.6, *C*DO), 154.5, 148.9 (2 × *C*$_{Ar}$), 126.5 (t, ^2J 3.6, *C*$_{Ar}$), 120.3 (*C*$_{Ar}$), 115.4, 110.4 (2 × H*C*$_{Ar}$), 56.5, 56.1 (2 × O*C*H$_3$); **m.p.** 148-150 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[266]

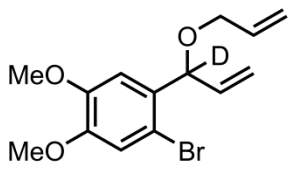
1-(2-Bromo-4,5-dimethoxyphenyl)-1-deuterioprop-2-en-1-ol **207**



Aldehyde **206** (559 mg, 2.27 mmol) was subjected to General Procedure 1. The crude product was purified by flash column chromatography [Petrol/EtOAc, 9:1 to 3:1] to furnish *vinyl alcohol* **207** (588 mg, 2.14 mmol, 94%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.02 (1H, s, *H*C$_{Ar}$), 6.99 (1H, s, *H*C$_{Ar}$), 5.99 (1H, dd, *J* 17.2, 10.4, C*H*=CH$_2$), 5.39 (1H, dd, *J* 17.2, 1.2, CH=C*H*$_a$H$_b$), 5.22 (1H, dd, *J* 10.4, 1.2, CH=CH$_a$*H*$_b$), 3.87 (3H, s, OC*H*$_3$), 3.86 (3H, s, OC*H*$_3$), 2.22 (1H, br. s, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 148.9, 148.8 (2 × *C*$_{Ar}$), 138.5 (*C*H=CH$_2$), 133.5 (*C*$_{Ar}$), 115.4 (CH=*C*H$_2$), 115.2 (H*C*$_{Ar}$), 112.3 (*C*$_{Ar}$), 110.3 (H*C*$_{Ar}$), 73.0 (t, ^1J 22.0, *C*DOH), 56.2, 56.0 (2 × O*C*H$_3$); **IR** υ_{max} (thin film)/cm^{-1} 3476br./s, 3085w, 3004m, 2936s, 2841m, 1602m, 1504s, 1463m, 1439m, 1378m, 1332m, 1257s, 1217m, 1163s, 1060m, 1023m, 991w, 928m; **m/z** (ESI$^+$) 296.0 [100, (M + Na)$^+$], 571.0 [80, (2M + Na)$^+$], $C_{11}H_{12}{}^{79}BrDNaO_3$ predicted 296.0003, found 296.0003, (Δ + 0.1 ppm).

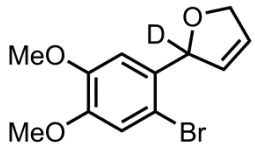
1-(1-(Allyloxy)-1-(deuterio)allyl)-2-bromo-4,5-dimethoxybenzene **208**



Vinyl alcohol **207** (556 mg, 2.03 mmol) was subjected to General Procedure 2. The crude product was purified by flash column chromatography [Petrol/EtOAc, 24:1 to 4:1] to furnish *allyl ether* **208** (582 mg, 1.85 mmol, 91%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.99 (1H, s, *H*C$_{Ar}$), 6.99 (1H, s, *H*C$_{Ar}$), 5.99-5.90 (1H, m, CH_2CH=CH_2), 5.89 (1H, dd, *J* 17.2, 10.4, C*H*=CH_2), 5.31 (1H, dd, *J* 17.2, 1.3, CH=C*H*$_a$H$_b$), 5.29 (1H, dq, *J* 17.2, 1.5, CH_2CH=C*H*$_a$H$_b$) 5.21-5.20 (1H, m, CH=CH$_a$*H*$_b$), 5.19-5.18 (1H, m, CH=CH$_a$*H*$_b$), 3.99-3.96 (2H, m, C*H*$_2$OR), 3.87 (6H, s, 2 × OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 148.9, 148.9 (2 × *C*$_{Ar}$), 137.2, 134.6 (2 × *C*H=CH_2), 132.0 (*C*$_{Ar}$), 117.1, 116.3 (2 × CH=*C*H$_2$), 115.0 (H*C*$_{Ar}$), 113.0 (*C*$_{Ar}$), 110.4 (H*C*$_{Ar}$), 79.5 (t, ^{1}J 22.4, *C*DOR), 69.4 (*C*H$_2$OR), 56.1, 56.0 (2 × OC*H*$_3$); **IR** υ_{max} (thin film)/cm^{-1} 3082w, 3004m, 2934s, 2908m, 2841s, 2361w, 1601m, 1504s, 1463m, 1439m, 1376m, 1334w, 1258s, 1219m, 1169s, 1083m, 1031m, 928m; **m/z** (ESI$^+$) 336.0 [100, (M + Na)$^+$], $C_{14}H_{16}{}^{79}BrDNaO_3$ predicted 336.0316, found 336.0320, (Δ − 1.1 ppm).

2-(2-Bromo-4,5-dimethoxyphenyl)-2-deuterio-5-hydrofuran **209**

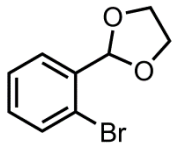


Allyl ether **208** (539 mg, 1.72 mmol) was subjected to General Procedure 3. The crude product was purified by flash column chromatography [Petrol/EtOAc, 24:1 to 4:1] to furnish *dihydrofuran* **209** (466 mg, 1.63 mmol, 95%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.99 (1H, s, *H*C$_{Ar}$), 6.90 (1H, s, *H*C$_{Ar}$), 6.02-5.97 (2H, m, C*H*=C*H*), 4.91 (1H, d, *J* 12.9, C*H*$_a$H$_b$OR), 4.80 (1H, d, *J* 12.9, CH$_a$*H*$_b$OR), 3.85 (6H, s, 2 × OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 148.9, 148.8, 133.2 (3 × *C*$_{Ar}$), 129.1, 126.7 (*C*H=*C*H), 115.3 (H*C*$_{Ar}$), 111.4 (*C*$_{Ar}$), 110.1 (H*C*$_{Ar}$), 86.3 (t, ^{1}J 23.2, *C*DOR), 76.0 (*C*H$_2$OR), 56.2, 56.0 (2 × OC*H*$_3$); **IR** υ_{max} (thin film)/cm^{-1} 3084w, 2954m, 2844s, 1601m, 1504s, 1439m, 1378s, 1333w, 1260s, 1221m, 1202m, 1167s, 1077s, 1010m, 934w; **m/z** (ESI$^+$)

308.0 [100, $(M + Na)^+$], $C_{12}H_{12}{}^{79}BrDNaO_3$ predicted 308.0003, found 308.0003, (Δ − 0.1 ppm); **m.p.** 44-46 °C (Petrol/CH_2Cl_2).

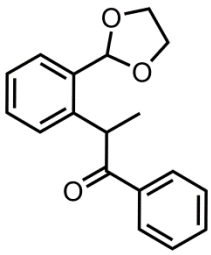
2-(2-Bromophenyl)-1,3-dioxolane **222**



2-Bromobezaldehyde (3.58 g, 19.4 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *acetal* **222** (4.22 g, 18.4 mmol, 95%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.61 (1H, d, *J* 7.8, *H*C_{Ar}), 7.58 (1H, d, *J* 7.9, *H*C_{Ar}), 7.35 (1H, t, *J* 7.0, *H*C_{Ar}), 7.27-7.21 (1H, m, *H*C_{Ar}), 6.11 (1H, s, C*H*$(OR)_2$), 4.19-4.13 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 4.12-4.05 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 136.6 (*C*$_{Ar}$), 133.0, 130.6, 127.8, 127.4 (4 × H*C*$_{Ar}$), 123.0 (*C*$_{Ar}$), 102.6 (*C*H$(OR)_2$), 65.5 (*C*H_2OR). Data were consistent with those previously reported.[267]

2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-phenylpropan-1-one **235**



Method A: Acetal **222** (56.0 mg, 0.244 mmol) was subjected to General Procedure 6 with propiophenone (39.4 mg, 0.293 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 14:1] to furnish *ketone* **235** (56.7 mg, 0.201 mmol, 82%) as prisms.

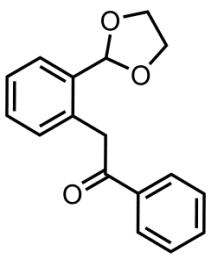
Method B: Acetal **222** (85.5 mg, 0.373 mmol) was subjected to General Procedure 7 with propiophenone (100 mg, 0.746 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 14:1] to furnish *ketone* **235** (93.4 mg, 0.331 mmol, 89%) as prisms.

Method C: As for ***Method A*** but with acetal **240** (70.2 mg, 0.254 mmol). Yield (56.6 mg, 0.200 mmol, 79%) as prisms.

Method D: A resealable reaction tube, containing a magnetic follower, was sealed with a rubber septum and flame dried under a flow of argon. $PdCl_2(Amphos)_2$ (13.8 mg, 0.0195 mmol) and NaO*t*Bu (93.5 mg, 0.973 mmol) were added to the tube. Acetal **239** (71.9 mg, 0.389 mmol) was dissolved in dry THF (2.0 mL) and the resulting solution was added *via* syringe to the tube. Propiophenone (105 mg, 0.779 mmol) was then added *via* syringe to the tube. The rubber septum was then replaced with a screw cap and the tube was heated at 70 ^oC for 48 h. Additional $PdCl_2(Amphos)_2$ (13.8 mg, 0.0195 mmol) was added and the tube was heated at 70 ^oC for a further 48 h. The reaction was then cooled to room temperature and quenched by the addition of H_2O (25 mL). The aqueous layer was extracted with Et_2O (3 × 25 mL) and the combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product. Purification by flash column chromatography [Petrol/EtOAc 19:1 grading to 14:1] furnished *ketone* **235** (80.8 mg, 0.286 mmol, 74%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.04 (2H, d, *J* 7.6, 2 × *H*C_{Ar}), 7.62-7.59 (1H, m, *H*C_{Ar}), 7.45 (1H, t, *J* 7.3, *H*C_{Ar}), 7.36 (2H, t, *J* 7.6, 2 × *H*C_{Ar}), 7.26-7.21 (2H, m, 2 × *H*C_{Ar}), 7.11-7.08 (1H, m, *H*C_{Ar}), 6.14 (1H, s, C*H*$(OR)_2$), 5.12 (1H, q, *J* 6.8, C*H*CH_3), 4.21-4.09 (4H, m, 2 × C*H*$_2$), 1.54 (3H, d, *J* 6.8, CHC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 200.9 (*C*=O), 140.6, 136.5, 133.7 (3 × *C*$_{Ar}$), 132.6, 129.8, 129.0, 128.4, 127.7, 127.4, 126.8 (7 × H*C*$_{Ar}$), 102.6 (*C*H$(OR)_2$), 65.3, 65.1 (2 × *C*H_2OR), 43.7 (*C*HCH_3), 19.2 (*C*H_3); **IR** ν_{max} (thin film)/cm^{-1} 3064w, 2976m, 2888m, 1682s, 1597w, 1581w, 1490w, 1449m, 1373w, 1222s, 1181w, 1111m, 1084s, 1057s, 1026w, 1002w, 968m, 950s; **m/z** (ESI$^+$) 305.1 [100, $(M + Na)^+$], 587.3 [60, $(2M + Na)^+$], $C_{18}H_{18}NaO_3$ predicted 305.1148, found 305.1148, (Δ + 0.2 ppm); **m.p.** 76-78 °C (Petrol/CH_2Cl_2).

2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-phenylethanone **236**

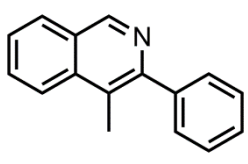


Method A: Acetal **222** (56.0 mg, 0.244 mmol) was subjected to General Procedure 6 with acetophenone (35.2 mg, 0.293 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *ketone* **236** (53.1 mg, 0.201 mmol, 82%) as prisms.

Method B: Acetal **222** (68.7 mg, 0.300 mmol) was subjected to General Procedure 7 with acetophenone (72.1 mg, 0.600 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *ketone* **236** (74.0 mg, 0.276 mmol, 92%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.06 (2H, dd, *J* 7.3, 0.8, 2 × *H*C_{Ar}), 7.58 (2H, td, *J* 8.0, 1.0, 2 × *H*C_{Ar}), 7.49 (2H, t, *J* 7.7, 2 × *H*C_{Ar}), 7.36-7.30 (2H, m, 2 × *H*C_{Ar}), 7.19 (1H, d, *J* 6.6, *H*C_{Ar}), 5.89 (1H, s, C*H*$(OR)_2$), 4.51 (2H, s, CH_2), 4.03-3.99 (2H, m, C$H_a$$H_bCH_a$$H_b$), 3.97-3.93 (2H, m, C$H_a$$H_bCH_a$$H_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 197.6 (*C*=O), 137.0, 135.6, 133.6 (3 × C_{Ar}), 133.0, 131.5, 129.2, 128.6, 128.4, 127.0, 127.0 (7 × HC_{Ar}), 102.8 (*C*H$(OR)_2$), 65.0 (*C*H_2OR), 42.6 (*C*H_2); **IR** ν_{max} (thin film)/cm^{-1} 2890w, 1687s, 1597w, 1580w, 1490w, 1448m, 1403w, 1333m, 1271w, 1214s, 1112m, 1073s, 1044w, 1023w, 993s, 943s; **m/z** (ESI^+) 291.1 [55, $(M + Na)^+$], 559.2 [100, $(2M + Na)^+$], $C_{17}H_{16}NaO_3$ predicted 291.0992, found 291.0994, (Δ - 0.7 ppm); **m.p.** 87-89 °C (Petrol/CH_2Cl_2).

4-Methyl-3-phenylisoquinoline **159**



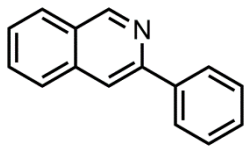
Method A: Ketone **235** (57.8 mg, 0.205 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 14:1 grading to 9:1] to furnish *isoquinoline* **159** (41.3 mg, 0.188 mmol, 92%) as prisms.

Method B: Acetal **222** (51.0 mg, 0.223 mmol) was subjected to General Procedure 13 with propiophenone (35.8 mg, 0.267 mmol). The crude product was purified by flash column

chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *isoquinoline* **159** (35.8 mg, 0.163 mmol, 73%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.22 (1H, s, *H*C(1)), 8.07 (1H, d, *J* 8.6, *H*C(8)), 8.01 (1H, d, *J* 8.3, *H*C(5)), 7.77 (1H, t, *J* 7.6, *H*C(7)), 7.65-7.60 (3H, m, *H*C(6) + 2 × HC_{Ar}), 7.50 (2H, d, *J* 8.6, 2 × HC_{Ar}), 7.42 (1H, t, *J* 7.3, HC_{Ar}), 2.67 (3H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 151.9 (*C*(3)), 150.2 (H*C*(1)), 141.3, 136.2 (2 × C_{Ar}), 130.4 (H*C*(7)), 129.9, 128.1 (2 × HC_{Ar}), 128.1 (H*C*(5)), 127.6 (HC_{Ar}), 127.3 (C_{Ar}), 126.6 (H*C*(6)), 124.0 (*C*(4)), 123.6 (H*C*(8)), 15.5 (*C*H_3); **m.p.** 96-98 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[138]

3-Phenylisoquinoline **104**

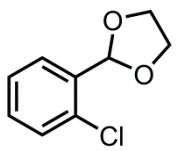


Method A: Ketone **236** (48.9 mg, 0.182 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *isoquinoline* **104** (35.9 mg, 0.175 mmol, 96%) as prisms.

Method B: Acetal **222** (66.7 mg, 0.291 mmol) was subjected to General Procedure 13 with acetophenone (42.0 mg, 0.349 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *isoquinoline* **104** (44.2 mg, 0.215 mmol, 74%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.36 (1H, s, *H*C(1)), 8.15 (2H, d, *J* 7.3, 2 × HC_{Ar}), 8.08 (1H, s, *H*C(4)), 8.01 (1H, d, *J* 8.1, *H*C(8)), 7.89 (1H, d, *J* 8.3, *H*C(5)), 7.71 (1H, t, *J* 7.6, *H*C(6)), 7.60 (1H, t, *J* 7.6, *H*C(7)), 7.53 (2H, t, *J* 7.7, 2 × HC_{Ar}), 7.43 (1H, t, *J* 7.4, HC_{Ar}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 152.4 (H*C*(1)), 151.3 (*C*(3)), 139.6, 136.7 (2 × C_{Ar}), 130.5 (H*C*(6)), 128.8, 128.5 (2 × HC_{Ar}), 127.8 (C_{Ar}), 127.6 (H*C*(8)), 127.1 (H*C*(7)), 127.0 (HC_{Ar}), 126.9 (H*C*(5)), 116.5 (H*C*(4)); **m.p.** 98-99 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[268]

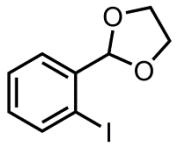
2-(2-Chlorophenyl)-1,3-dioxolane **239**



2-Chlorobenzaldehyde (2.04 g, 14.5 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *acetal* **239** (2.50 g, 13.5 mmol, 93%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.63 (1H, dd, *J* 5.7, 3.7, *H*C_{Ar}), 7.41-7.37 (1H, m, *H*C_{Ar}), 7.32-7.27 (2H, m, 2 × *H*C_{Ar}), 6.17 (1H, s, C*H*$(OR)_2$), 4.18-4.12 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 4.11-4.05 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 135.1, 133.5 (2 × *C*$_{Ar}$), 130.3, 129.7, 127.6, 126.8 (4 × H*C*$_{Ar}$), 100.7 (*C*H$(OR)_2$), 65.5 (*C*H_2OR). Data were consistent with those previously reported.[267]

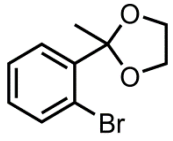
2-(2-Iodophenyl)-1,3-dioxolane **240**



2-Iodobenzaldehyde (500 mg, 2.16 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *acetal* **240** (518 mg, 1.87 mmol, 87%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.86 (1H, d, *J* 7.8, *H*C_{Ar}), 7.56 (1H, dd, *J* 7.8, 1.5, *H*C_{Ar}), 7.38 (1H, t, *J* 7.6, *H*C_{Ar}), 7.07 (1H, td, *J* 7.6, 1.5, *H*C_{Ar}), 5.93 (1H, s, C*H*$(OR)_2$), 4.20-4.14 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 4.13-4.07 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 139.7 (H*C*$_{Ar}$), 139.3 (*C*$_{Ar}$), 130.9, 128.2, 127.6 (3 × H*C*$_{Ar}$), 106.4 (*C*H$(OR)_2$), 97.1 (*C*$_{Ar}$), 65.5 (*C*H_2OR). Data were consistent with those previously reported.[269]

2-(2-Bromophenyl)-2-methyl-1,3-dioxolane **242**

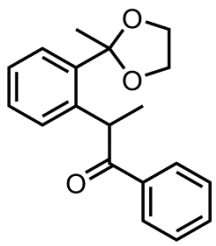


2'-Bromoacetophenone (1.98 g, 9.92 mmol) was subjected to General Procedure 5. The crude product was purified by flash column

chromatography [Petrol/EtOAc 49:1 grading to 24:1] to furnish *ketal* **242** (2.26 g, 9.31 mmol, 94%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.67 (1H, dd, *J* 7.9, 1.8, *H*C_{Ar}), 7.59 (1H, dd, *J* 8.1, 1.3, *H*C_{Ar}), 7.28 (1H, td, *J* 7.6, 1.1, *H*C_{Ar}), 7.13 (1H, td, *J* 7.6, 1.7, *H*C_{Ar}), 4.10-4.01 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 3.80-3.71 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$), 1.81 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 141.1 (*C*$_{Ar}$), 134.9, 129.5, 127.9, 127.1 (4 × H*C*$_{Ar}$), 120.5 (*C*$_{Ar}$), 108.7 (*C*(OR)$_2$), 64.2 (*C*H$_2$OR), 25.3 (*C*H$_3$). Data were consistent with those previously reported.[270]

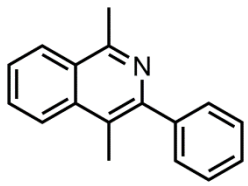
2-(2-(2-Methyl-1,3-dioxolan-2-yl)phenyl)-1-phenylpropan-1-one **243**



Acetal **242** (66.5 mg, 0.274 mmol) was subjected to General Procedure 6 with propiophenone (44.0 mg, 0.328 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 24:1] to furnish *ketone* **243** (63.9 mg, 0.216 mmol, 79%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.06-8.03 (2H, m, 2 × *H*C_{Ar}), 7.63 (1H, dd, *J* 7.9, 1.6, *H*C_{Ar}), 7.51 (1H, tt, *J* 7.4, 1.7, *H*C_{Ar}), 7.45-7.40 (3H, m, 3 × *H*C_{Ar}), 7.32 (1H, td, *J* 7.8, 1.5, *H*C_{Ar}), 7.24 (1H, td, *J* 7.6, 1.3, *H*C_{Ar}), 5.11 (1H, q, *J* 7.2, C*H*CH$_3$), 4.04-3.99 (1H, m, C*H*$_a$H$_b$CH$_a$H$_b$), 3.86-3.75 (2H, m, CH$_a$*H*$_b$C*H*$_a$H$_b$), 3.52-3.47 (1H, m, CH$_a$H$_b$CH$_a$*H*$_b$), 1.78 (3H, s, C*H*$_3$), 1.58 (3H, d, *J* 7.1, CHC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 202.1 (*C*=O), 140.0, 138.3, 137.2 (3 × *C*$_{Ar}$), 132.4, 129.4, 128.7, 128.4 (2 signals), 126.7, 126.4 (7 × H*C*$_{Ar}$), 109.3 (*C*(OR)$_2$), 64.4, 64.0 (2 × *C*H$_2$OR), 43.3 (*C*HCH$_3$), 28.1 (*C*H$_3$), 19.7 (CH*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2983w, 2889w, 1681s, 1597w, 1579w, 1481w, 1447m, 1374m, 1289w, 1189s, 1104w, 1035s, 967m, 951m, 867m; **m/z** (ESI$^+$) 319.1 [95, (M + Na)$^+$], 615.3 [100, (2M + Na)$^+$], $C_{19}H_{20}NaO_3$ predicted 319.1305, found 319.1307, (Δ - 0.8 ppm).

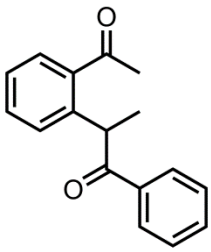
1,4-Dimethyl-3-phenylisoquinoline **244**



Ketone **243** (53.2 mg, 0.180 mmol) was subjected to General Procedure 11. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 19:1] to furnish *isoquinoline* **244** (35.2 mg, 0.151 mmol, 84%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.18 (1H, d, *J* 8.3, *H*C(8)), 8.07 (1H, d, *J* 8.3, *H*C(5)), 7.76 (1H, ddd, *J* 8.2, 6.8, 1.2, *H*C(6)), 7.64-7.58 (3H, m, *H*C(7) + 2 × *H*C_{Ar}), 7.50-7.47 (2H, m, 2 × *H*C_{Ar}), 7.40 (1H, tt, *J* 7.3, 1.3, 2 × *H*C_{Ar}), 3.00 (3H, s, C(1)C*H*$_3$), 2.61 (3H, s, C(4)C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 155.9 (*C*(1)), 150.7 (*C*(3)), 141.6, 136.3 (2 × *C*$_{Ar}$), 129.9 (2 signals) (H*C*$_{Ar}$ + H*C*(6)), 128.1, 127.4 (2 × H*C*$_{Ar}$), 126.3 (H*C*(7)), 126.2 (*C*$_{Ar}$), 126.1 (H*C*(8)), 124.1 (H*C*(5)), 122.2 (*C*(4)), 22.5 (C(1)*C*H$_3$), 15.5 (C(4)*C*H$_3$); **m.p.** 95-97 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[271]

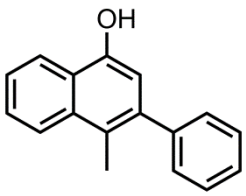
2-(2-Acetylphenyl)-1-phenylpropan-1-one **245**



Ketone **243** (72.3 mg, 0.244 mmol) was subjected to General Procedure 9. The crude product was purified by flash column chromatography [Petrol/EtOAc 39:1 grading to 19:1] to furnish *diketone* **245** (57.7 mg, 0.229 mmol, 94%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.99 (2H, dt, *J* 8.1, 1.5, 2 × *H*C_{Ar}), 7.76 (1H, dd, *J* 7.2, 1.3, *H*C_{Ar}), 7.47 (1H, tt, *J* 7.3, 2.0, *H*C_{Ar}), 7.43-7.37 (3H, m, 3 × *H*C_{Ar}), 7.30 (2H, t, *J* 7.9, 2 × *H*C_{Ar}), 5.69 (1H, q, *J* 6.8, C*H*CH$_3$), 2.65 (3H, s, C=OC*H*$_3$), 1.50 (3H, d, *J* 6.8, CHC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 202.2, 201.2 (2 × *C*=O), 141.2, 136.5, 136.2 (3 × *C*$_{Ar}$), 136.7, 132.3, 130.0, 129.0, 128.7, 128.5, 126.6 (7 × H*C*$_{Ar}$), 43.1 (*C*HCH$_3$), 29.8 (*C*H$_3$), 19.0 (CH*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2975w, 2931w, 1682s, 1597w, 1572w, 1486w, 1448m, 1356m, 1293w, 1256s, 1237s, 1180w, 1002w, 952m; **m/z** (ESI$^+$) 253.1 [100, (M + H)$^+$], 275.1 [40, (M + Na)$^+$], 527.3 [45, (2M + Na)$^+$], $C_{17}H_{16}NaO_2$ predicted 275.1043, found 275.1050, (Δ - 2.9 ppm).

4-Methyl-3-phenylnaphthalen-1-ol **247**

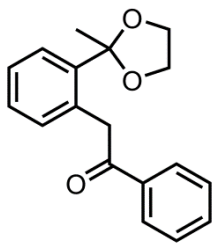


Method A: Diketone **245** (47.2 mg, 0.171 mmol) was subjected to General Procedure 10. The crude product was purified by flash column chromatography [Petrol/CH_2Cl_2 9:1 grading to 1:1] to furnish *naphthol* **247** (38.2 mg, 0.163 mmol, 95%) as plates.

Method B: Ketone **243** (61.4 mg, 0.207 mmol) was subjected to General Procedure 12. The crude product was purified by flash column chromatography [Petrol/CH_2Cl_2 9:1 grading to 1:1] to furnish *naphthol* **247** (40.9 mg, 0.175 mmol, 84%) as plates.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.31 (1H, d, *J* 8.1, *H*C$_{Ar}$), 8.10 (1H, d, *J* 8.5, *H*C$_{Ar}$), 7.63 (1H, ddd, *J* 8.3, 6.6, 1.3, *H*C$_{Ar}$), 7.56 (1H, ddd, *J* 8.1, 6.9, 1.0, *H*C$_{Ar}$), 7.50-7.46 (2H, m, 2 × *H*C$_{Ar}$), 7.43-7.38 (3H, m, 3 × *H*C$_{Ar}$), 6.76 (1H, s, *H*C$_{Ar}$), 5.48 (1H, br. s, O*H*), 2.56 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 149.2, 142.6, 138.9, 134.1 (4 × *C*$_{Ar}$), 129.7, 128.1, 126.9, 126.8, 124.9, 124.7 (6 × H*C*$_{Ar}$), 123.9, 123.4 (2 × *C*$_{Ar}$), 122.1, 111.1 (2 × H*C*$_{Ar}$), 15.8 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 3519br./s, 3058w, 2923w, 1624w, 1597s, 1497m, 1441w, 1390s, 1371m, 1358m, 1310w, 1232s, 1139s, 1074s, 1026w, 979w, 857w; **m/z** (ESI$^-$) 257.1 [100, $(M + Na)^+$], $C_{17}H_{14}NaO$ predicted 257.0937, found 257.0930, (Δ + 2.7 ppm); **m.p.** 184-186 °C (Petrol/CH_2Cl_2).

2-(2-(2-Methyl-1,3-dioxolan-2-yl)phenyl)-1-phenylethanone **248**

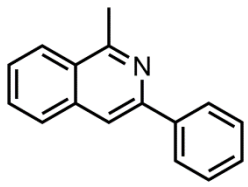


Acetal **242** (174 mg, 0.717 mmol) was subjected to General Procedure 6 with acetophenone (103 mg, 0.861 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 24:1] to furnish *ketone* **248** (189 mg, 0.670 mmol, 93%) as plates.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.08 (2H, dd, *J* 6.9, 1.5, 2 × *H*C$_{Ar}$), 7.65-7.63 (1H, m, *H*C$_{Ar}$), 7.61-7.58 (1H, m, *H*C$_{Ar}$), 7.51 (2H, t, *J* 7.5, 2 × *H*C$_{Ar}$), 7.35-7.28 (2H, m, 2 × *H*C$_{Ar}$), 7.18-7.16 (1H, m, *H*C$_{Ar}$), 4.55 (2H, s, C*H*$_2$), 3.89-3.85 (2H, m,

C*H*$_a$H$_b$C*H*$_a$H$_b$), 3.66-3.63 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$), 1.69 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 197.8 (*C*=O), 141.2, 137.4 (2 × *C*$_{Ar}$), 133.0, 132.8 (2 × H*C*$_{Ar}$), 132.3 (*C*$_{Ar}$), 128.6, 128.1, 128.1, 127.1, 126.4 (5 × H*C*$_{Ar}$), 109.0 (*C*(OR)$_2$), 64.2 (*C*H$_2$OR), 43.8 (*C*H$_2$), 27.7 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2988w, 2892w, 1690s, 1484w, 1447m, 1374w, 1331s, 1238m, 1214s, 1193s, 1124w, 1066s, 1034m, 995m, 951w, 868m; **m/z** (ESI$^+$) 305.1 [100, (M + Na)$^+$], 587.2 [95, (2M + Na)$^+$], $C_{18}H_{18}NaO_3$ predicted 305.1148, found 305.1140, (Δ + 2.8 ppm); **m.p.** 55-57 °C (Petrol/CH_2Cl_2).

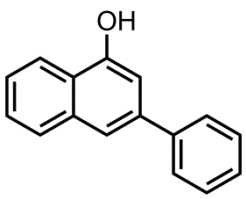
1-Methyl-3-phenylisoquinoline **249**



Ketone **248** (61.2 mg, 0.217 mmol) was subjected to General Procedure 11. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 19:1] to furnish *isoquinoline* **249** (42.3 mg, 0.193 mmol, 89%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.17-8.13 (3H, m, *H*C(8) + 2 × *H*C$_{Ar}$), 7.94 (1H, s, *H*C(4)), 7.87 (1H, d, *J* 8.3, *H*C(5)), 7.68 (1H, ddd, *J* 8.1, 7.1, 1.2, *H*C(6)), 7.58 (1H, ddd, *J* 7.9, 6.9, 1.3, *H*C(7)), 7.52 (2H, t, *J* 7.6, 2 × *H*C$_{Ar}$), 7.41 (1H, tt, *J* 7.4, 1.2, *H*C$_{Ar}$), 3.06 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 158.6 (*C*(1)), 150.0 (*C*(3)), 139.9, 136.8 (2 × *C*$_{Ar}$), 130.0 (H*C*(6)), 128.7, 128.3 (2 × H*C*$_{Ar}$), 127.6 (H*C*(5)), 127.0 (H*C*$_{Ar}$), 126.8 (H*C*(7)), 126.6 (*C*$_{Ar}$), 125.7 (H*C*(8)), 115.2 (H*C*(4)), 22.7 (*C*H$_3$). Data were consistent with those previously reported.[272]

3-Phenylnaphthalen-1-ol **250**

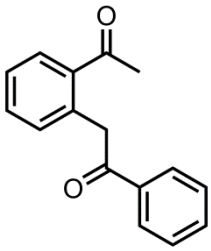


Method A: Diketone **252** (64.6 mg, 0.271 mmol) was subjected to General Procedure 10. The crude product was purified by flash column chromatography [Petrol/CH_2Cl_2 9:1 grading to 1:1] to furnish *naphthol* **250** (54.7 mg, 0.248 mmol, 92%) as needles.

Method B: Ketone **248** (48.6 mg, 0.172 mmol) was subjected to General Procedure 12. The crude product was purified by flash column chromatography [Petrol/CH_2Cl_2 9:1 grading to 1:1] to furnish *naphthol* **250** (32.9 mg, 0.149 mmol, 87%) as needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.20 (1H, d, *J* 7.8, *H*C_{Ar}), 7.88 (1H, dd, *J* 7.1, 1.7, *H*C_{Ar}), 7.71-7.66 (3H, m, 3 × *H*C_{Ar}), 7.55-7.46 (4H, m, 4 × *H*C_{Ar}), 7.39 (1H, tt, *J* 7.5, 1.5, *H*C_{Ar}), 7.10 (1H, d, *J* 1.4, *H*C_{Ar}), 5.61 (1H, br. s, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 151.8, 141.0, 138.9, 135.0 (4 × *C*$_{Ar}$), 128.9, 128.0, 127.5, 127.3, 126.9, 125.3 (6 × H*C*$_{Ar}$), 123.6 (*C*$_{Ar}$), 121.5, 118.7, 108.4 (3 × H*C*$_{Ar}$); **m.p.** 96-97 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[273]

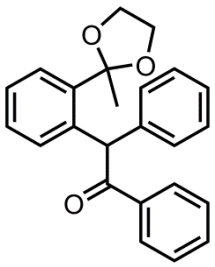
2-(2-Acetylphenyl)-1-phenylethanone **252**



Ketone **248** (90.2 mg, 0.319 mmol) was subjected to General Procedure 9. The crude product was purified by flash column chromatography [Petrol/EtOAc 39:1 grading to 19:1] to furnish *diketone* **252** (66.5 mg, 0.279 mmol, 87%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.07 (2H, d, *J* 7.3, 2 × *H*C_{Ar}), 7.88 (1H, d, *J* 7.6, *H*C_{Ar}), 7.59 (1H, t, *J* 7.3, *H*C_{Ar}), 7.53-7.48 (3H, m, 3 × *H*C_{Ar}), 7.43 (1H, t, *J* 7.6, *H*C_{Ar}), 7.27 (1H, d, *J* 7.5, *H*C_{Ar}), 4.68 (2H, s, C*H*$_2$), 2.59 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 201.2, 197.4 (2 × *C*=O), 137.3, 137.0, 135.2 (3 × *C*$_{Ar}$), 133.1, 133.0, 132.1, 130.2, 128.6, 128.2, 127.3 (7 × H*C*$_{Ar}$), 44.7 (*C*H$_2$), 28.7 (*C*H$_3$); **m.p.** 105-106 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[192]

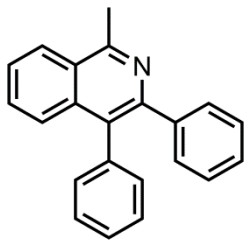
2-(2-(2-Methyl-1,3-dioxolan-2-yl)phenyl)-1,2-diphenylethanone **255**



Acetal **242** (244 mg, 1.00 mmol) was subjected to General Procedure 6 with deoxybenzoin (236 mg, 1.20 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 24:1] to furnish *ketone* **255** (233 mg, 0.677 mmol, 68%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.05 (2H, dd, *J* 7.4, 1.2, 2 × *H*C$_{Ar}$), 7.66-7.64 (1H, m, *H*C$_{Ar}$), 7.50 (1H, tt, *J* 7.4, 1.9, *H*C$_{Ar}$), 7.41 (2H, t, *J* 7.7, 2 × *H*C$_{Ar}$), 7.36-7.32 (2H, m, 2 × *H*C$_{Ar}$), 7.27-7.23 (5H, m, 5 × *H*C$_{Ar}$), 7.14-7.11 (1H, m, *H*C$_{Ar}$), 6.91 (1H, s, C*H*), 4.00-3.95 (1H, m, C*H*$_a$H$_b$CH$_a$H$_b$), 3.78-3.71 (2H, m, CH$_a$*H*$_b$C*H*$_a$H$_b$), 3.51-3.45 (1H, m, CH$_a$H$_b$CH$_a$*H*$_b$), 1.79 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 198.5 (*C*=O), 140.2, 139.6, 137.1, 136.5 (4 × *C*$_{Ar}$), 132.5, 132.2, 129.4, 128.9, 128.9, 128.5, 128.0, 127.0, 126.8, 126.1 (10 × H*C*$_{Ar}$), 109.2 (*C*(OR)$_2$), 64.4, 63.8 (2 × *C*H$_2$OR), 55.5 (*C*H), 28.3 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 3062w, 2989w, 2892w, 1686s, 1597w, 1580w, 1495w, 1479w, 1447m, 1374w, 1327w, 1274m, 1262m, 1207s, 1189s, 1100w, 1032s, 951w, 908w, 869s, 803m; **m/z** (ESI$^+$) 381.2 [25, (M + Na)$^+$], 739.3 [100, (2M + Na)$^+$], $C_{24}H_{22}NaO_3$ predicted 381.1461, found 381.1452, (Δ + 2.4 ppm); **m.p.** 134-136 °C (Petrol/CH_2Cl_2).

1-Methyl-3,4-diphenylisoquinoline **256**

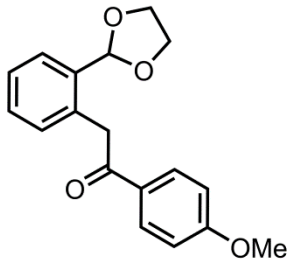


Method A: Ketone **255** (166 mg, 0.463 mmol) was subjected to General Procedure 11. The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 24:1] to furnish *isoquinoline* **256** (111 mg, 0.375 mmol, 81%) as plates.

Method B: Acetal **242** (40.7 mg, 0.167 mmol) was subjected to General Procedure 14 with deoxybenzoin (39.4 mg, 0.201 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 24:1] to furnish *isoquinoline* **256** (25.2 mg, 0.0853 mmol, 51%) as plates.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.24-8.20 (1H, m, *H*C(8)), 7.69-7.66 (1H, m, *H*C(5)), 7.63-7.58 (2H, m, *H*C(6) + *H*C(7)), 7.40-7.33 (5H, m, 5 × *H*C_{Ar}), 7.26-7.18 (5H, m, 5 × *H*C_{Ar}), 3.10 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 157.7 (*C*(1)), 149.4 (*C*(3)), 141.0, 137.6, 136.0 (3 × *C*$_{Ar}$), 131.4, 130.3 (2 × H*C*$_{Ar}$), 129.9 (H*C*(6)), 129.2 (*C*$_{Ar}$), 128.2, 127.6, 127.1, 126.9 (4 × H*C*$_{Ar}$), 126.5 (H*C*(7)), 126.2 (H*C*(5)), 126.2 (*C*(4)), 125.5 (H*C*(8)), 22.7 (*C*H$_3$); **m.p.** 150-152 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[274]

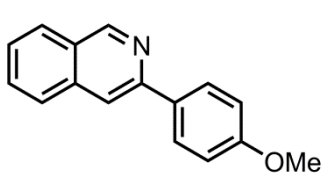
2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-(4-methoxyphenyl)ethanone **258**



Acetal **222** (51.8 mg, 0.226 mmol) was subjected to General Procedure 6 with 4'-methoxyacetophenone (40.7 mg, 0.271 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *ketone* **258** (53.8 mg, 0.180 mmol, 80%) as rods.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.04 (2H, d, *J* 8.9, 2 × *H*C_{Ar}), 7.59 (1H, dd, *J* 7.1, 1.8, *H*C_{Ar}), 7.34-7.28 (2H, m, 2 × *H*C_{Ar}), 7.18 (1H, dd, *J* 6.6, 2.0, *H*C_{Ar}), 6.95 (2H, d, *J* 8.9, 2 × *H*C_{Ar}), 5.90 (1H, s, C*H*(OR)$_2$), 4.45 (2H, s, C*H*$_2$), 4.06-3.94 (4H, m, 2 × C*H*$_2$OR), 3.87 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 196.2 (*C*=O), 163.4, 135.5, 134.0 (3 × *C*$_{Ar}$), 131.3, 130.7 (2 × H*C*$_{Ar}$), 130.0 (*C*$_{Ar}$), 129.2, 126.9, 126.9, 113.8 (4 × H*C*$_{Ar}$), 102.7 (*C*H(OR)$_2$), 65.0 (*C*H$_2$OR), 55.5 (OCH$_3$), 42.3 (*C*H$_2$); **IR** ν_{max} (thin film)/cm^{-1} 2894w, 2839w, 1679s, 1600s, 1575w, 1510s, 1420w, 1329w, 1258s, 1220m, 1170s, 1112w, 1074m, 1027m, 992m, 963m, 833m; **m/z** (ESI$^+$) 321.1 [45, (M + Na)$^+$], 619.2 [100, (2M + Na)$^+$], $C_{18}H_{18}NaO_4$ predicted 321.1097, found 321.1097, (Δ + 0.1 ppm); **m.p.** 131-133 °C (Petrol/CH_2Cl_2).

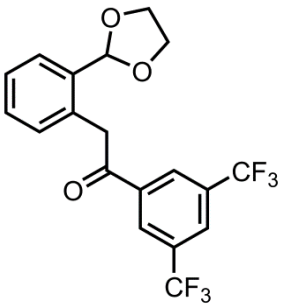
3-(4-Methoxyphenyl)isoquinoline **259**



Ketone **258** (121 mg, 0.406 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 14:1 grading to 9:1] to furnish *isoquinoline* **259** (79.8 mg, 0.339 mmol, 84 %) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.31 (1H, s, *H*C(1)), 8.10 (2H, dt, *J* 8.9, 2.4, 2 × *H*C_{Ar}), 7.99 (1H, s, *H*C(4)), 7.96 (1H, d, *J* 8.3, *H*C(8)), 7.83 (1H, d, *J* 8.1, *H*C(5)), 7.67 (1H, td, *J* 7.6, 1.1, *H*C(6)), 7.55 (1H, td, *J* 7.5, 0.9, *H*C(7)), 7.05 (2H, dt, *J* 8.9, 2.5, 2 × *H*C_{Ar}), 3.88 (3H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 160.1 (*C*$_{Ar}$), 152.3 (H*C*(1)), 151.0 (*C*(3)), 136.8, 132.2 (2 × *C*$_{Ar}$), 130.4 (H*C*(6)), 128.2 (H*C*$_{Ar}$), 127.5 (H*C*(8)), 127.4 (*C*$_{Ar}$), 126.7, 126.7 (H*C*(7) + H*C*(5)), 115.4 (H*C*(4)), 114.2 (H*C*$_{Ar}$), 55.4 (O*C*H_3); **m.p.** 99-101 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[268]

2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-(3,5-bis(trifluoromethyl)phenyl)ethanone **261**

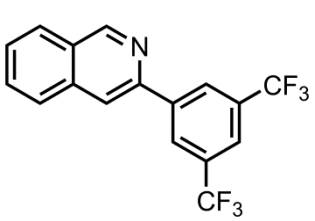


Acetal **222** (165 mg, 0.677 mmol) was subjected to General Procedure 6 with 3',5'-bis(trifluoromethyl)acetophenone (208 mg, 0.812 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 19:1] to furnish *ketone* **261** (191 mg, 0.472 mmol, 70%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.51 (2H, s, 2 × *H*C_{Ar}), 8.06 (1H, s, *H*C_{Ar}), 7.61-7.59 (1H, m, *H*C_{Ar}), 7.38-7.31 (2H, m, 2 × *H*C_{Ar}), 7.21-7.18 (1H, m, *H*C_{Ar}), 5.91 (1H, s, C*H*$(OR)_2$), 4.52 (2H, s, CH_2), 4.04-4.01 (2H, m, C$H_a$$H_bCH_a$$H_b$), 3.99-3.96 (2H, m, C$H_a$$H_bCH_a$$H_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 195.1 (*C*=O), 138.4, 135.4 (2 × *C*$_{Ar}$), 132.3 (q, ^{2}J 33.9, *C*$_{Ar}$), 132.1 (*C*$_{Ar}$), 131.1, 129.4 (2 × H*C*$_{Ar}$), 128.6 (q, ^{3}J 3.2, H*C*$_{Ar}$), 127.5, 127.5 (2 × H*C*$_{Ar}$), 126.1 (sept., ^{3}J 3.6, H*C*$_{Ar}$), 122.9 (q, ^{1}J 272.9, *C*F_3), 102.9 (*C*H$(OR)_2$), 64.9 (*C*H_2OR), 42.9 (*C*H_2); **^{19}F[^{1}H] NMR** (377 MHz, $CDCl_3$) δ_F: −62.9; **IR** ν_{max} (thin film)/cm^{-1} 2895w, 1699s, 1617w, 1381w, 1322w, 1277s, 1249w, 1173s, 1129s, 1077m,

1046w, 968w, 943w, 914w, 842w; **m/z** (ESI^+) 405.1 [100, $(M + H)^+$], 427.1 [35, $(M + Na)^+$], $C_{19}H_{14}F_6NaO_3$ predicted 427.0739, found 427.0732, (Δ + 1.7 ppm); **m.p.** 88-90 °C (Petrol/CH_2Cl_2).

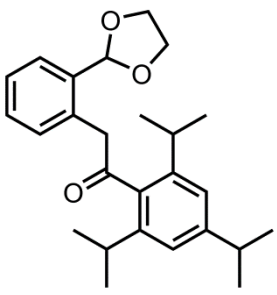
3-(3,5-Bis(trifluoromethyl)phenyl)isoquinoline **262**



Ketone **261** (39.2 mg, 0.0969 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 19:1] to furnish *isoquinoline* **262** (26.9 mg, 0.0788 mmol, 81 %) as needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.36 (1H, s, *H*C(1)), 8.62 (2H, s, 2 × *H*C_{Ar}), 8.16 (1H, s, *H*C(4)), 8.04 (1H, d, *J* 8.1, *H*C(8)), 7.95-7.92 (2H, m, *H*C(5) + *H*C_{Ar}), 7.77 (1H, ddd, *J* 8.2, 6.9, 1.3, *H*C(6)), 7.68 (1H, ddd, *J* 8.1, 7.0, 1.1, *H*C(7)); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 152.9 (H*C*(1)), 147.8 (*C*(3)), 141.6, 136.4 (2 × *C*$_{Ar}$), 132.1 (q, ^2J 33.1, *C*$_{Ar}$), 131.1 (H*C*(6)), 128.3 (*C*$_{Ar}$), 128.2 (H*C*(7)), 127.7 (H*C*(8)), 127.1 (H*C*(5)), 126.9 (q, ^3J 3.1, H*C*$_{Ar}$), 123.5 (q, ^1J 272.6, *C*F_3), 121.9 (sept., ^3J 3.8, H*C*$_{Ar}$), 117.3 (H*C*(4)); **^{19}F[^{1}H] NMR** (377 MHz, $CDCl_3$) δ_F: −62.8; **IR** ν_{max} (thin film)/cm^{-1} 2925w, 1628w, 1495w, 1391m, 1383m, 1336w, 1288s, 1212w, 1167s, 1125s, 1058m, 895m, 882m, 845w; **m/z** (ESI^+) 342.1 [100, $(M + H)^+$], 364.1 [10, $(M + Na)^+$], $C_{17}H_9F_6NNa$ predicted 364.0531, found 364.0523, (Δ + 2.4 ppm); **m.p.** 121-122 °C (Petrol/CH_2Cl_2).

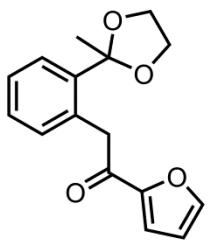
2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-(2,4,6-triisopropylphenyl)ethanone **264**



Acetal **222** (130 mg, 0.534 mmol) was subjected to General Procedure 6 with 2',4',6'-tri*iso*propylacetophenone (158 mg, 0.642 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 19:1] to furnish *ketone* **264** (169 mg, 0.429 mmol, 80%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.68 (1H, dd, *J* 7.1, 2.0, *H*C$_{Ar}$), 7.38-7.30 (2H, m, 2 × *H*C$_{Ar}$), 7.19-7.17 (1H, m, *H*C$_{Ar}$), 7.03 (2H, s, 2 × *H*C$_{Ar}$), 5.93 (1H, s, C*H*(OR)$_2$), 4.30 (2H, s, CH_2), 4.13-4.07 (2H, m, CH_aH$_b$CH_aH$_b$), 4.05-3.98 (2H, m, CH$_a$$H_bCH_a$$H_b$), 2.91 (1H, sept., *J* 6.9, C*H*(CH$_3$)$_2$), 2.78 (2H, sept., *J* 6.8, 2 × C*H*(CH$_3$)$_2$), 1.28 (6H, d, *J* 6.8, CH(CH_3)$_2$), 1.25 (12H, br. d, *J* 5.9, 2 × CH(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 207.3 (*C*=O), 149.7, 143.7, 137.6, 136.6, 132.2 (5 × *C*$_{Ar}$), 131.3, 129.0, 127.3, 126.1, 121.1 (5 × H*C*$_{Ar}$), 102.0 (*C*H(OR)$_2$), 65.1 (*C*H$_2$OR), 50.2 (*C*H$_2$), 34.4, 31.1 (2 × *C*H(CH$_3$)$_2$), 24.5 (br. CH(*C*H$_3$)$_2$), 24.0 (CH(*C*H$_3$)$_2$); **IR** ν_{max} (thin film)/cm^{-1} 2960s, 1700s, 1606m, 1460m, 1384m, 1363m, 1315m, 1213m, 1110s, 1071s, 985s, 944s, 910m, 878m; **m/z** (ESI$^+$) 395.3 [100, (M + H)$^+$], 417.2 [15, (M + Na)$^+$], $C_{26}H_{34}NaO_3$ predicted 417.2400, found 417.2387, (Δ + 3.2 ppm).

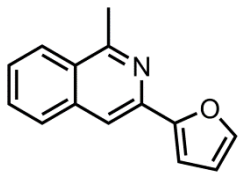
1-(Furan-2-yl)-2-(2-(2-methyl-1,3-dioxolan-2-yl)phenyl)ethanone **267**



Acetal **242** (83.1 mg, 0.342 mmol) was subjected to General Procedure 7 with 2-furyl methyl ketone (75.3 mg, 0.684 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 14:1] to furnish *ketone* **267** (75.8 mg, 0.278 mmol, 81%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.62-7.60 (2H, m, *H*C$_{Ar}$ + *H*C(5)), 7.32-7.26 (2H, m, 2 × *H*C$_{Ar}$), 7.24 (1H, d, *J* 3.5, *H*C(3)), 7.18-7.16 (1H, m, *H*C$_{Ar}$), 6.56 (1H, dd, *J* 3.6, 1.8 *H*C(4)), 4.40 (2H, s, CH_2), 3.90-3.86 (2H, m, CH_aH$_b$CH_aH$_b$), 3.65-3.62 (2H, m, CH$_a$$H_bCH_a$$H_b$), 1.68 (3H, s, C$H_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 186.9 (*C*=O), 152.8 (*C*(2)), 146.0 (H*C*(5)), 141.3 (*C*$_{Ar}$), 133.0 (H*C*$_{Ar}$), 131.4 (*C*$_{Ar}$), 128.1, 127.2, 126.4 (3 × H*C*$_{Ar}$), 116.6 (H*C*(3)), 112.1 (H*C*(4)), 109.0 (*C*(OR)$_2$), 64.2 (*C*H$_2$OR), 43.5 (*C*H$_2$), 27.6 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2959m, 2926m, 1680s, 1569m, 1468s, 1392w, 1375w, 1332w, 1243m, 1195m, 1156m, 1032s, 951w, 882m, 868m; **m/z** (ESI$^+$) 295.1 [80, (M + Na)$^+$], 567.2 [100, (2M + Na)$^+$], $C_{16}H_{16}NaO_4$ predicted 295.0941, found 295.0943, (Δ − 0.6 ppm); **m.p.** 85-88 °C (Petrol/CH_2Cl_2).

3-(Furan-2-yl)-1-methylisoquinoline **268**

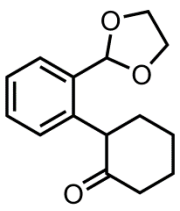


Method A: Ketone **267** (58.3 mg, 0.214 mmol) was subjected to General Procedure 11. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 14:1] to furnish *isoquinoline* **268** (37.6 mg, 0.180 mmol, 84%) as an oil.

Method B: Acetal **242** (47.9 mg, 0.197 mmol) was subjected to a modification of General Procedure 14 with 2-furyl methyl ketone (43.4 mg, 0.394 mmol) and (D*t*BPF)$PdCl_2$ (6.4 mg, 0.0099 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 19:1] to furnish *isoquinoline* **268** (25.8 mg, 0.123 mmol, 63%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.09 (1H, d, *J* 8.3, *H*C(8)), 7.88 (1H, s, *H*C(4)), 7.82 (1H, d, *J* 8.1, *H*C(5)), 7.65 (1H, ddd, *J* 8.1, 7.0, 1.1, *H*C(6)), 7.56-7.52 (2H, m, *H*C(7) + *H*C(5')), 7.13 (1H, d, *J* 3.3, *H*C(3')), 6.57 (1H, dd, *J* 3.3, 1.8, *H*C(4')), 3.00 (3H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 158.9 (*C*(1)), 154.4 (*C*(2')), 142.9 (H*C*(5')), 142.2 (*C*(3)), 136.5 (C_{Ar}), 130.2 (H*C*(6)), 127.8 (H*C*(5)), 126.7 (H*C*(7)), 126.6 (C_{Ar}), 125.8 (H*C*(8)), 113.0 (H*C*(4)), 112.0 (H*C*(4')), 108.0 (H*C*(3'), 23.0 (*C*H_3); **IR** ν_{max} (thin film)/cm^{-1} 3068w, 2920w, 1692w, 1621s, 1567s, 1488m, 1436m, 1389s, 1324m, 1287w, 1261w, 1239w, 1216w, 1157s, 1087m, 1006s, 970m, 937w, 882s, 834m, 812s; **m/z** (ESI$^+$) 210.1 [100, $(M + H)^+$], $C_{14}H_{12}NO$ predicted 210.0913, found 210.0921, (Δ − 3.5 ppm).

2-(2-(1,3-Dioxolan-2-yl)phenyl)cyclohexan-1-one **271**

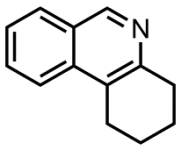


Acetal **222** (107 mg, 0.466 mmol) was subjected to General Procedure 7 with cyclohexanone (91.6 mg, 0.932 mmol). Purification by flash column chromatography [Petrol/EtOAc 49:1 grading to 9:1] furnished *ketone* **271** (15.4 mg, 0.0620 mmol, 13%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.53 (1H, dd, *J* 7.6, 1.5, *H*C_{Ar}), 7.36 (1H, dt, *J* 7.6, 1.5, *H*C_{Ar}), 7.27 (1H, dt, *J* 7.6, 1.2, *H*C_{Ar}), 7.21 (1H, dd, *J* 7.8, 1.2, *H*C_{Ar}), 5.87 (1H, s,

C*H*(OR)$_2$), 4.12 (1H, dd, *J* 12.5, 5.4, C*H*), 4.08-4.02 (2H, m, ROC*H*$_a$H$_b$C*H*$_a$H$_b$OR), 4.01-3.96 (2H, m, ROCH$_a$*H*$_b$CH$_a$*H*$_b$OR), 2.57-2.47 (2H, m, C*H*$_2$C=O), 2.34-2.13 (2H, m, C*H*$_2$CHC=O), 2.08-1.96 (2H, m, C*H*$_2$CH$_2$C=O), 1.88-1.78 (2H, m, C*H*$_2$CH$_2$CH$_2$C=O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 210.0 (*C*=O), 137.8, 135.4 (2 × C_{Ar}), 128.9, 128.8, 126.7, 126.3 (4 × HC_{Ar}), 102.3 (*C*H(OR)$_2$), 65.1, 65.0 (2 × *C*H$_2$OR), 53.0 (*C*HC=O), 42.5 (*C*H$_2$C=O), 35.3 (*C*H$_2$CHC=O), 27.9 (*C*H$_2$CH$_2$C=O), 26.0 (*C*H$_2$CH$_2$CH$_2$C=O); **IR** ν_{max} (thin film)/cm^{-1} 2936m, 2361w, 1708s, 1449w, 1224w, 1121m, 1079s; **m/z** (ESI$^+$) 247.1 [30, (M + H)$^+$], 269.1 [100, (M + Na)$^+$], $C_{15}H_{18}NaO_3$ predicted 269.1148, found 269.1145, (Δ + 1.0 ppm).

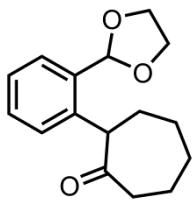
1,2,3,4-Tetrahydrophenanthridine **272**



Ketone **271** (12.9 mg, 0.0524 mmol) was subjected to General Procedure 8. Purification by flash column chromatography [Petrol/EtOAc 49:1 grading to 9:1] furnished *isoquinoline* **272** (8.6 mg, 0.047 mmol, 89%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.07 (1H, s, *H*C(1)), 7.95-7.92 (1H, m, *H*C(8)), 7.92-7.89 (1H, m, *H*C(5)), 7.70 (1H, dd, *J* 6.9, 1.2, *H*C(6)), 7.55 (1H, t, *J* 7.8, *H*C(7)), 3.13-3.07 (4H, m, 2 × C*H*$_2$C$_{Ar}$), 2.00-1.95 (4H, m, 2 × C*H*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 150.0 (H*C*(1)), 135.6 (*C*(3)), 130.3 (H*C*(6)), 128.2 (H*C*(8)), 126.9, 125.9, 124.9 (2 × C_{Ar} + *C*(4)), 124.8 (H*C*(7)), 121.9 (H*C*(5)), 31.8, 23.8 (2 × *C*H$_2$C$_{Ar}$), 22.0, 21.6 (2 × *C*H$_2$). Data were consistent with those previously reported.[275]

2-(2-(1,3-Dioxolan-2-yl)phenyl)cycloheptanone **274**

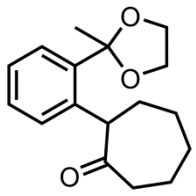


Acetal **222** (166 mg, 0.726 mmol) was subjected to General Procedure 7 with cycloheptanone (163 mg, 1.45 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *ketone* **274** (137 mg, 0.527 mmol, 73%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.53 (1H, dd, *J* 10.6, 1.0, *H*C$_{Ar}$), 7.37

(1H, td, *J* 7.4, 1.3 *H*C$_{Ar}$), 7.30 (1H, dd, *J* 7.8, 1.3, *H*C$_{Ar}$), 7.26 (1H, td, *J* 7.3, 1.5, *H*C$_{Ar}$), 6.01 (1H, s, C*H*(OR)$_2$), 4.36 (1H, dd, *J* 10.9, 2.6, C*H*), 4.12-3.99 (4H, m, 2 × C*H*$_2$OR), 2.73 (1H, dt, *J* 16.0, 4.8, C*H*$_a$H$_b$C=O), 2.61 (1H, ddd, *J* 15.7, 11.8, 3.8, CH$_a$*H*$_b$C=O), 2.12-1.90 (5H, m, 2 × C*H*$_2$ + C*H*$_a$H$_b$CH$_2$C=O), 1.83-1.71 (1H, m, CH$_a$*H*$_b$CH$_2$C=O), 1.63-1.52 (1H, m, C*H*$_a$H$_b$), 1.46-1.34 (1H, m, CH$_a$*H*$_b$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C: 213.0 (*C*=O), 140.1, 134.5 (2 × *C*$_{Ar}$), 129.0, 128.6, 126.4, 126.2 (4 × H*C*$_{Ar}$), 102.5 (*C*H(OR)$_2$), 65.1, 64.8 (2 × *C*H$_2$OR), 52.5 (*C*H), 43.6 (*C*H$_2$C=O), 33.0, 29.9, 29.4 (3 × *C*H$_2$), 24.3 (*C*H$_2$CH$_2$C=O); **IR** ν_{max} (thin film)/cm^{-1} 2926s, 2857m, 1701s, 1645m, 1606w, 1491m, 1454s, 1346m, 1295m, 1218m, 1179w, 1139m, 1117s, 1099s, 1029s, 974s, 950m, 911s; **m/z** (ESI$^+$) 283.1 [100, (M + Na)$^+$], 543.3 [100, (2M + Na)$^+$], $C_{16}H_{20}NaO_3$ predicted 283.1305, found 283.1306, (Δ − 0.4 ppm).

2-(2-(2-Methyl-1,3-dioxolan-2-yl)phenyl)cycloheptanone **275**

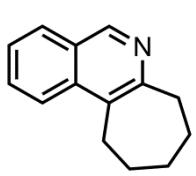


Acetal **242** (71.1 mg, 0.292 mmol) was subjected to General Procedure 7 with cycloheptanone (65.6 mg, 0.585 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 24:1] to furnish *ketone* **275** (54.6 mg, 0.199 mmol, 68%) as an oil.

^{1}H NMR (400 MHz, CDCl$_3$) δ_H: 7.55 (1H, dd, *J* 7.8, 2.4, *H*C$_{Ar}$), 7.32 (1H, td, *J* 7.5, 1.3 *H*C$_{Ar}$), 7.25 (1H, dd, *J* 7.9, 1.5, *H*C$_{Ar}$), 7.21 (1H, td, *J* 7.5, 1.5, *H*C$_{Ar}$), 4.66 (1H, dd, *J* 11.2, 2.8, C*H*), 3.98 (1H, td, *J* 7.2, 5.9, ROC*H*$_a$H$_b$CH$_a$H$_b$OR), 3.91 (1H, td, *J* 7.1, 5.6, ROCH$_a$H$_b$C*H*$_a$H$_b$OR), 3.70 (1H, td, *J* 7.6, 5.7, ROCH$_a$*H*$_b$CH$_a$H$_b$OR), 3.47 (1H, td, *J* 7.5, 6.0, ROCH$_a$H$_b$CH$_a$*H*$_b$OR), 2.77 (1H, dt, *J* 16.6, 4.3, C*H*$_a$H$_b$C=O), 2.54 (1H, ddd, *J* 16.5, 11.9, 4.3, CH$_a$*H*$_b$C=O), 2.09-1.96 (4H, m, 2 × C*H*$_2$), 1.94-1.82 (2H, m, C*H*$_2$), 1.73 (3H, s, C*H*$_3$), 1.68-1.57 (1H, m, C*H*$_a$H$_b$), 1.42-1.32 (1H, m, CH$_a$*H*$_b$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C: 213.3 (*C*=O), 139.5, 139.4 (2 × *C*$_{Ar}$), 129.7, 128.1, 126.3, 125.7 (4 × H*C*$_{Ar}$), 109.0 (*C*(OR)$_2$), 64.1, 63.8 (2 × *C*H$_2$OR), 52.8 (*C*H), 43.8 (*C*H$_2$C=O), 33.4, 30.4, 29.4 (3 × *C*H$_2$), 28.0 (*C*H$_3$), 23.8 (*C*H$_2$); **IR** ν_{max} (thin film)/cm^{-1} 2927m, 2856w, 1703s, 1482w, 1443w, 1375w, 1235m, 1189s, 1140w, 1098w, 1032s, 976w, 951w, 867m; **m/z** (ESI$^+$) 297.2 [90,

$(M + Na)^+$], 571.3 [100, $(2M + Na)^+$], $C_{17}H_{22}NaO_3$ predicted 297.1461, found 297.1450, (Δ + 3.6 ppm).

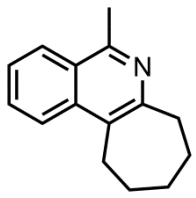
8,9,10,11-Tetrahydro-7H-cyclohepta[c]isoquinoline **276**



Ketone **274** (66.4 mg, 0.255 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 14:1 grading to 4:1] to furnish *isoquinoline* **276** (39.6 mg, 0.201 mmol, 79%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.01 (1H, s, *H*C(1)), 8.06 (1H, d, *J* 8.6, *H*C(8)), 7.93 (1H, d, *J* 8.3, *H*C(5)), 7.68 (1H, ddd, *J* 8.4, 6.8, 1.3, *H*C(7)), 7.51 (1H, td, *J* 7.5, 0.7, *H*C(6)), 3.28-3.25 (2H, m, CH_2C_{Ar}), 3.22-3.19 (2H, m, CH_2C_{Ar}), 1.98-1.92 (2H, m, CH_2), 1.78-1.70 (4H, m, 2 × C$H_2CH_2C_{Ar}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 156.5 (*C*(3)), 149.2 (H*C*(1)), 134.7 (C_{Ar}), 131.0 (*C*(4)), 129.9 (H*C*(7)), 128.2 (H*C*(5)), 127.2 (C_{Ar}), 125.5 (H*C*(6)), 122.3 (H*C*(8)), 38.9 (CH_2C_{Ar}), 32.4 (CH_2), 27.0, 26.7, 26.3 (CH_2C_{Ar} + 2 × $CH_2CH_2C_{Ar}$); **IR** ν_{max} (thin film)/cm^{-1} 2920s, 2851m, 1775w, 1698w, 1621s, 1575s, 1498m, 1454s, 1374s, 1260s, 1241s, 1221w, 1204w, 1154w, 1139w, 1093m, 1019s, 955s, 923w, 898m; **m/z** (ESI^+) 198.1 [100, $(M + H)^+$], $C_{14}H_{16}N$ predicted 198.1277, found 198.1280, (Δ − 1.6 ppm); **m.p.** 77-79 °C (Petrol/CH_2Cl_2).

5-Methyl-8,9,10,11-tetrahydro-7H-cyclohepta[c]isoquinoline **277**

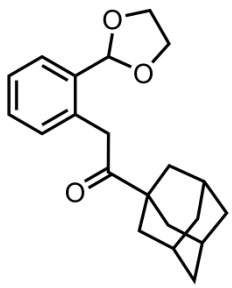


Ketone **275** (47.3 mg, 0.172 mmol) was subjected to General Procedure 11. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 19:1] to furnish *isoquinoline* **277** (29.9 mg, 0.142 mmol, 82%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.10 (1H, d, *J* 8.3, *H*C(5)), 8.06 (1H, d, *J* 8.9, *H*C(8)), 7.65 (1H, ddd, *J* 8.0, 6.8, 1.0, *H*C(7)), 7.49 (1H, t, *J* 7.7, *H*C(6)), 3.24-3.21 (2H, m, CH_2C_{Ar}),

3.18-3.15 (2H, m, CH_2C$_{Ar}$), 2.93 (3H, s, CH_3), 1.96-1.90 (2H, m, CH_2), 1.77-1.68 (4H, m, 2 × CH_2CH$_2$C$_{Ar}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 155.0, 154.8 (*C*(3) + *C*(1)), 134.8 (*C*$_{Ar}$), 129.5 (H*C*(7)), 129.2 (*C*$_{Ar}$), 126.2 (H*C*(5)), 125.8 (*C*(4)), 125.1 (H*C*(6)), 122.9 (H*C*(8)), 38.7 (*C*H$_2$C$_{Ar}$), 32.4 (*C*H$_2$), 26.8 (2 signals), 26.4 (*C*H$_2$C$_{Ar}$ + 2 × *C*H$_2$CH$_2$C$_{Ar}$), 22.3 (CH$_3$); **IR** ν_{max} (thin film)/cm^{-1} 3071w, 2921s, 2851s, 1699m, 1617m, 1566s, 1505w, 1450s, 1396s, 1339m, 1263m, 1227w, 1153w, 1026w, 988w, 971w, 956w, 832w; **m/z** (ESI$^+$) 212.1 [100, (M + H)$^+$], $C_{15}H_{18}N$ predicted 212.1434, found 212.1434, (Δ − 0.2 ppm); **m.p.** 65-67 °C (Petrol/CH_2Cl_2).

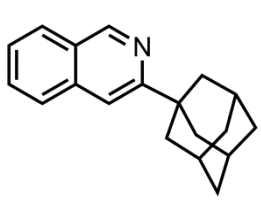
1-Adamantyl-2-(2-(1,3-dioxolan-2-yl)phenyl) ethanone **279**



Acetal **222** (175 mg, 0.766 mmol) was subjected to General Procedure 6 with methyl adamantyl ketone (164 mg, 0.919 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 19:1] to furnish *ketone* **279** (175 mg, 0.536 mmol, 70%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.59 (1H, dd, *J* 7.0, 2.2, *H*C$_{Ar}$), 7.33-7.26 (2H, m, 2 × *H*C$_{Ar}$), 7.06 (1H, dd, *J* 6.6, 2.2, *H*C$_{Ar}$), 5.83 (1H, s, C*H*(OR)$_2$), 4.09-4.03 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 4.03-3.97 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$), 4.00 (2H, s, C*H*$_2$C=O), 2.09 (3H, br. s, 3 × C*H*), 1.93 (6H, d, *J* 2.8, 3 × C*H*$_2$), 1.81-1.72 (6H, m, 3 × C*H*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 212.2 (*C*=O), 136.0, 133.8, (2 × *C*$_{Ar}$), 131.4, 128.8, 126.7, 126.1 (4 × H*C*$_{Ar}$), 102.1 (*C*H(OR)$_2$), 64.9 (*C*H$_2$OR), 46.7 (C=O*C*R$_3$), 40.3 (*C*H$_2$C=O) 38.5, 36.6 (2 × *C*H$_2$), 28.1 (*C*H); **IR** ν_{max} (thin film)/cm^{-1} 2904s, 2850s, 1701s, 1645w, 1491w, 1452m, 1390w, 1344m, 1327m, 1307m, 1223w, 1193w, 1157m, 1112m, 1074s, 1013s, 964m, 944m; **m/z** (ESI$^+$) 349.2 [10, (M + Na)$^+$], 675.4 [100, (2M + Na)$^+$], $C_{21}H_{26}NaO_3$ predicted 349.1774, found 349.1771, (Δ + 0.8 ppm); **m.p.** 69-71 °C (Petrol/CH_2Cl_2).

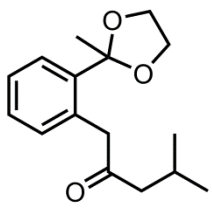
3-Adamantylisoquinoline **280**



Ketone **279** (30.4 mg, 0.0931 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 24:1] to furnish *isoquinoline* **280** (23.3 mg, 0.0885 mmol, 95%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.25 (1H, s, *H*C(1)), 7.92 (1H, d, *J* 8.1, *H*C(8)), 7.78 (1H, d, *J* 8.4, *H*C(5)), 7.64 (1H, ddd, *J* 7.9, 6.9, 1.1, *H*C(6)), 7.54-7.50 (2H, m, *H*C(4) + *H*C(7)), 2.18-2.14 (3H, m, 3 × C*H*), 2.11 (6H, d, *J* 2.7, RC(CH_2)$_3$), 1.84 (6H, t, *J* 3.0, 3 × CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 162.9 (*C*(3)), 151.8 (H*C*(1)), 136.6 (C_{Ar}), 129.9 (H*C*(6)), 127.3 (H*C*(8)), 127.0 (C_{Ar}), 126.6 (H*C*(5)), 126.3 (H*C*(7)), 114.3 (H*C*(4)), 42.0 (RC(*C*H_2)$_3$), 38.6 (R*C*(CH_2)$_3$), 36.9 (*C*H_2), 28.8 (*C*H); **IR** ν_{max} (thin film)/cm^{-1} 2902s, 2882s, 2848s, 1628s, 1585m, 1490m, 1451s, 1382w, 1366w, 1344w, 1316w, 1278w, 1260s, 1180w, 1099s, 1036s, 977m, 943m, 880s, 856w; **m/z** (ESI$^+$) 264.2 [100, (M + H)$^+$], $C_{19}H_{22}N$ predicted 264.1747, found 264.1742, (Δ + 1.7 ppm); **m.p.** 106-108 °C (Petrol/CH_2Cl_2).

4-Methyl-1-(2-(2-methyl-1,3-dioxolan-2-yl)phenyl)pentan-2-one **282**

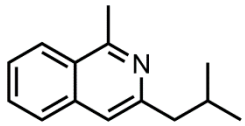


Acetal **242** (65.3 mg, 0.269 mmol) was subjected to General Procedure 7 with 4-methyl-2-pentanone (53.9 mg, 0.538 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 24:1] to furnish *ketone* **282** (64.7 mg, 0.246 mmol, 92%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.58 (1H, dd, *J* 6.6, 1.6, *H*C_{Ar}), 7.29-7.23 (2H, m, 2 × *H*C_{Ar}), 7.07 (1H, dd, *J* 6.8, 1.5, *H*C_{Ar}), 3.96-3.92 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 3.90 (2H, s, CH_2C_{Ar}), 3.65-3.62 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$), 2.43 (2H, d, *J* 6.8, CH_2CH), 2.19 (1H, sept., *J* 6.6, C*H*), 1.65 (3H, s, CH_3), 0.97 (6H, d, *J* 6.8, CH(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 207.6 (*C*=O), 140.9 (C_{Ar}), 132.8 (HC_{Ar}), 132.0 (C_{Ar}), 128.0, 126.9, 126.3 (3 × HC_{Ar}), 109.0 (*C*(OR)$_2$), 64.2 (*C*H_2OR), 51.4 (*C*H_2CH), 48.3 (*C*H_2C_{Ar}), 27.5 (*C*H_3), 24.3 (*C*H), 22.7

($CH(CH_3)_2$); **IR** ν_{max} (thin film)/cm^{-1} 2957s, 2895m, 1720s, 1469w, 1442w, 1419w, 1366m, 1319w, 1260m, 1241m, 1195s, 1143m, 1103m, 1036s, 952w, 870m; **m/z** (ESI^+) 285.2 [80, $(M + Na)^+$], 547.3 [100, $(2M + Na)^+$], $C_{16}H_{22}NaO_3$ predicted 285.1461, found 285.1453, (Δ + 3.0 ppm).

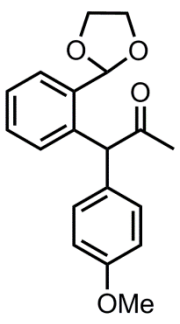
3-*iso*Butyl-1-methylisoquinoline **283**



Ketone **282** (42.0 mg, 0.160 mmol) was subjected to General Procedure 11. The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 14:1] to furnish *isoquinoline* **283** (29.5 mg, 0.148 mmol, 93%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.08 (1H, d, *J* 8.4, *H*C(8)), 7.73 (1H, d, *J* 8.0, *H*C(5)), 7.63 (1H, ddd, *J* 8.1, 6.9, 1.2, *H*C(6)), 7.52 (1H, ddd, *J* 8.2, 6.9, 1.3, *H*C(7)), 7.29 (1H, s, *H*C(4)), 2.96 (3H, s, CH_3), 2.76 (2H, d, *J* 7.3, CH_2), 2.21 (1H, sept., *J* 6.8, C*H*), 0.97 (6H, d, *J* 6.8, $CH(CH_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 158.0 (*C*(3)), 153.5 (*C*(1)), 136.5 (C_{Ar}), 129.8 (H*C*(6)), 126.8 (H*C*(5)), 126.0 (H*C*(7)), 125.8 (C_{Ar}), 125.5 (H*C*(8)), 117.6 (H*C*(4)), 47.3 (CH_2), 28.9 (*C*H), 22.5 ($CH(CH_3)_2$), 22.3 (CH_3); **IR** ν_{max} (thin film)/cm^{-1} 2954w, 2927w, 2867w, 1700m, 1625s, 1590s, 1568s, 1497m, 1464s, 1446s, 1390s, 1366s, 1338m, 1262w, 1165m, 1095w, 1026m, 955w, 879s, 849w, 818m; **m/z** (ESI^+) 200.1 [100, $(M + H)^+$], $C_{14}H_{18}N$ predicted 200.1434, found 200.1431, (Δ + 1.3 ppm).

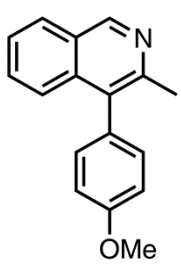
1-(2-(1,3-Dioxolan-2-yl)phenyl)-1-(4-methoxyphenyl)propan-2-one **286**



Acetal **222** (225 mg, 0.983 mmol) was subjected to a modification of General Procedure 7 with 4-methoxyphenylacetone (323 mg, 1.97 mmol) and Cs_2CO_3 (801 mg, 2.45 mmol) as the base. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 14:1] to furnish *ketone* **286** (301 mg, 0.965 mmol, 98%) as an oil.

^{1}H NMR (400 MHz, acetone-d_6) δ_H: 7.57 (1H, d, *J* 7.3, *H*C$_{Ar}$), 7.33 (1H, t, *J* 7.4, *H*C$_{Ar}$), 7.28 (1H, t, *J* 7.3, *H*C$_{Ar}$), 7.18 (2H, d, *J* 8.6, 2 × *H*C$_{Ar}$), 7.15 (1H, d, *J* 7.8, *H*C$_{Ar}$), 6.90 (2H, d, *J* 8.6, 2 × *H*C$_{Ar}$), 5.98 (1H, s, C*H*(OR)$_2$), 5.79 (1H, s, C*H*), 4.19-4.03 (4H, m, 2 × C*H*$_2$), 3.78 (3H, s, OC*H*$_3$), 2.18 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, acetone-d_6) δ_C: 206.0 (*C*=O), 159.6, 139.0, 136.5, 131.5 (4 × *C*$_{Ar}$), 131.2, 130.6, 129.6, 127.8, 127.4, 114.7 (6 × H*C*$_{Ar}$), 103.3 (*C*H(OR)$_2$), 65.8, 65.6 (2 × *C*H$_2$OR), 59.3 (*C*H), 55.5 (O*C*H$_3$), 30.0 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2956w, 2891w, 2837w, 1714s, 1609m, 1582w, 1510s, 1456w, 1408w, 1353m, 1303m, 1250s, 1181m, 1155m, 1109s, 1071s, 1031s, 970s, 945s; **m/z** (ESI$^+$) 335.2 [100, (M + Na)$^+$], $C_{19}H_{20}NaO_4$ predicted 335.1254, found 335.1238, (Δ + 4.6 ppm).

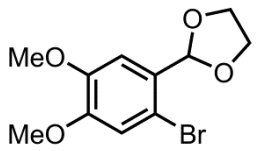
4-(4-Methoxyphenyl)-3-methylisoquinoline **287**



Ketone **286** (41.1 mg, 0.132 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 14:1] to furnish *isoquinoline* **287** (30.4 mg, 0.122 mmol, 92%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.21 (1H, s, *H*C(1)), 7.97 (1H, d, *J* 7.3, *H*C(8)), 7.58-7.50 (2H, m, *H*C(6) + *H*C(7)), 7.46 (1H, d, *J* 8.6, *H*C(5)), 7.22 (2H, d, *J* 8.6, 2 × *H*C$_{Ar}$), 7.06 (2H, d, *J* 8.5, 2 × *H*C$_{Ar}$), 3.91 (3H, s, OC*H*$_3$), 2.51 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 159.0 (*C*$_{Ar}$), 150.9 (H*C*(1)), 149.2 (*C*(3)), 136.2 (*C*$_{Ar}$), 131.1 (H*C*$_{Ar}$), 130.6, 129.7 (*C*$_{Ar}$ + *C*(4)), 130.3, 126.0 (H*C*(6) + H*C*(7)), 127.5 (H*C*(8)), 126.8 (*C*$_{Ar}$), 125.0 (H*C*(5)), 114.0 (H*C*$_{Ar}$), 55.3 (O*C*H$_3$), 23.0 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 3000w, 2956w, 2929w, 2836w, 1779w, 1723w, 1611m, 1573m, 1513s, 1456m, 1441m, 1379m, 1286m, 1242s, 1175m, 1106m, 1029s, 964m, 922w, 830s; **m/z** (ESI$^+$) 250.2 [100, (M + H)$^+$], $C_{17}H_{16}NO$ predicted 250.1226, found 250.1220, (Δ + 2.7 ppm); **m.p.** 96-98 °C (Petrol/CH_2Cl_2).

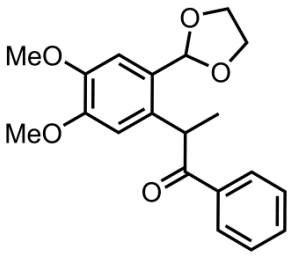
2-(2-Bromo-4,5-dimethoxyphenyl)-1,3-dioxolane **299**



2-Bromo-4,5-dimethoxybenzaldehyde (2.00 g, 8.15 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 9:1 grading to 4:1] to furnish *acetal* **299** (2.29 g, 7.91 mmol, 97%) as needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.11 (1H, s, *H*C_{Ar}), 7.01 (1H, s, *H*C_{Ar}), 5.99 (1H, s, C*H*$(OR)_2$), 4.19-4.16 (2H, m, C$H_aH_bCH_aH_b$), 4.07-4.04 (2H, m, C$H_aH_bCH_aH_b$), 3.89 (3H, s, OCH_3), 3.87 (3H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 150.2, 148.5, 128.2 (3 × C_{Ar}), 115.4 (HC_{Ar}), 113.4 (C_{Ar}), 110.1 (HC_{Ar}), 102.6 (*C*H$(OR)_2$), 65.4 (*C*H_2OR), 56.2, 56.0 (2 × OCH_3); **m.p.** 108-110 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[276]

2-(2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl)-1-phenylpropan-1-one **300**



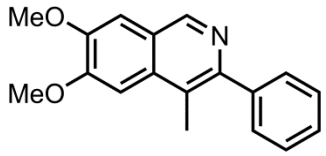
Method A: Acetal **299** (77.4 mg, 0.268 mmol) was subjected to General Procedure 6 with propiophenone (43.1 mg, 0.321 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *ketone* **300** (81.8 mg, 0.239 mmol, 89%) as plates.

Method B: Acetal **299** (103 mg, 0.356 mmol) was subjected to General Procedure 7 with propiophenone (95.5 mg, 0.712 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *ketone* **300** (117 mg, 0.343 mmol, 96%) as plates.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.02 (2H, dd, *J* 8.6, 1.5, 2 × *H*C_{Ar}), 7.46 (1H, tt, *J* 7.5, 1.6, *H*C_{Ar}), 7.36 (2H, t, *J* 7.6, 2 × *H*C_{Ar}), 7.14 (1H, s, *H*C_{Ar}), 6.56 (1H, s, *H*C_{Ar}), 6.09 (1H, s, C*H*$(OR)_2$), 5.03 (1H, q, *J* 6.8, C*H*CH_3), 4.24-4.18 (2H, m, C$H_aH_bCH_aH_b$), 4.15-4.09 (2H, m, C$H_aH_bCH_aH_b$), 3.87 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 1.51 (3H, d, *J* 6.9, CHCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 201.3 (*C*=O), 149.7, 147.5, 136.6, 133.1 (4 × C_{Ar}), 132.7,

128.9, 128.4 (3 × H*C*$_{Ar}$), 125.8 (*C*$_{Ar}$), 110.3, 110.2 (2 × H*C*$_{Ar}$), 102.1 (*C*H(OR)$_2$), 65.2, 65.1 (2 × *C*H$_2$OR), 55.8, 55.8 (2 × O*C*H$_3$), 43.2 (*C*H), 19.3 (CH*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2935m, 2892m, 1681s, 1597m, 1517s, 1450m, 1402w, 1343w, 1270s, 1225m, 1202m, 1178m, 1116s, 1081w, 1020m, 993m, 952m, 870w; **m/z** (ESI$^+$) 365.2 [30, (M + Na)$^+$], 707.3 [100, (2M + Na)$^+$], $C_{20}H_{22}NaO_5$ predicted 365.1359, found 365.1362, (Δ − 0.6 ppm); **m.p.** 89-91 °C (Petrol/CH_2Cl_2).

6,7-Dimethoxy-4-methyl-3-phenylisoquinoline **301**

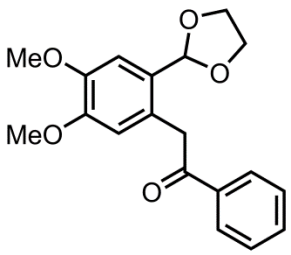


Method A: Ketone **300** (57.8 mg, 0.205 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 14:1 grading to 9:1] to furnish *isoquinoline* **301** (41.3 mg, 0.188 mmol, 92%) as needles.

Method B: Acetal **299** (46.8 mg, 0.162 mmol) was subjected to General Procedure 13 with propiophenone (26.1 mg, 0.194 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 14:1 grading to 9:1] to furnish *isoquinoline* **301** (34.6 mg, 0.124 mmol, 77%) as needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.01 (1H, s, *H*C(1)), 7.58 (2H, dd, *J* 8.3, 1.2, 2 × *H*C$_{Ar}$), 7.48 (2H, td, *J* 7.1, 1.7, 2 × *H*C$_{Ar}$), 7.39 (1H, tt, *J* 7.4, 1.2, *H*C$_{Ar}$), 7.25 (1H, s, *H*C(5)), 7.23 (1H, s, *H*C(8)), 4.08 (3H, s, OC*H*$_3$), 4.06 (3H, s, OC*H*$_3$), 2.61 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 152.9 (*C*(3)), 151.0, 149.8 (*C*(6) + *C*(7)), 147.6 (H*C*(1)), 141.6, 132.7 (2 × *C*$_{Ar}$), 129.8, 128.0, 127.3 (3 × H*C*$_{Ar}$), 123.4, 122.8 (*C*$_{Ar}$ + *C*(4)), 105.8 (H*C*(5)), 102.1 (H*C*(8)), 56.0, 56.0 (2 × O*C*H$_3$), 15.8 (*C*H$_3$); **m.p.** 155-157 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[139]

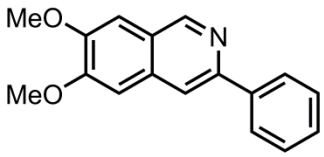
2-(2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl)-1-phenylethanone **302**



Acetal **299** (86.2 mg, 0.298 mmol) was subjected to General Procedure 6 with acetophenone (43.0 mg, 0.357 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 4:1] to furnish *ketone* **302** (79.9 mg, 0.243 mmol, 82%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.05 (2H, d, *J* 7.4, 2 × *H*C$_{Ar}$), 7.58 (1H, t, *J* 7.3, *H*C$_{Ar}$), 7.48 (2H, t, *J* 7.6, 2 × *H*C$_{Ar}$), 7.14 (1H, s, *H*C$_{Ar}$), 6.68 (1H, s, *H*C$_{Ar}$), 5.82 (1H, s, C*H*(OR)$_2$), 4.43 (2H, s, C*H*$_2$), 4.06-3.93 (4H, m, 2 × C*H*$_2$OR), 3.90 (3H, s, OC*H*$_3$), 3.84 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 197.8 (*C*=O), 149.2, 147.7, 136.9 (3 × *C*$_{Ar}$), 133.1, 128.6, 128.4 (3 × H*C*$_{Ar}$), 127.7, 125.9 (2 × *C*$_{Ar}$), 114.3, 110.1 (2 × H*C*$_{Ar}$), 102.4 (*C*H(OR)$_2$), 65.0 (*C*H$_2$OR), 55.9, 55.9 (2 × O*C*H$_3$), 42.1 (*C*H$_2$); **IR** ν_{max} (thin film)/cm^{-1} 2944w, 1684s, 1596w, 1573m, 1525m, 1466m, 1447s, 1349m, 1331m, 1273s, 1242m, 1215m, 1199m, 1115s, 1002s, 887m, 861m; **m/z** (ESI$^+$) 351.1 [75, (M + Na)$^+$], 679.2 [100, (2M + Na)$^+$], $C_{19}H_{20}NaO_5$ predicted 351.1203, found 351.1198, (Δ + 1.3 ppm); **m.p.** 97-99 °C (Petrol/CH_2Cl_2).

6,7-Dimethoxy-3-phenylisoquinoline **303**

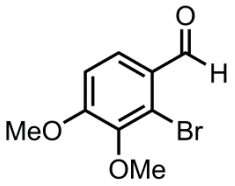


Ketone **302** (52.6 mg, 0.160 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 9:1 grading to 4:1] to furnish *isoquinoline* **303** (39.3 mg, 0.148 mmol, 93%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.11 (1H, s, *H*C(1)), 8.08 (2H, dt, *J* 7.4, 1.6, 2 × *H*C$_{Ar}$), 7.91 (1H, s, *H*C(4)), 7.49 (2H, t, *J* 7.6, 2 × *H*C$_{Ar}$), 7.39 (1H, tt, *J* 7.4, 1.3, *H*C$_{Ar}$), 7.19 (1H, s, *H*C(8)), 7.09 (1H, s, *H*C(5)), 4.02 (3H, s, OC*H*$_3$), 4.02 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 153.2 (*C*(3)), 150.3, 150.2 (*C*(6) + *C*(7)), 149.8 (H*C*(1)), 139.9, 133.3 (2 × *C*$_{Ar}$), 128.8, 128.2, 126.8 (3 × H*C*$_{Ar}$), 123.8 (*C*$_{Ar}$), 115.5 (H*C*(4)), 105.2 (H*C*(8)), 105.0 (H*C*(5)),

56.1, 56.1 (2 × O*C*H_3); **m.p.** 126-127 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[277]

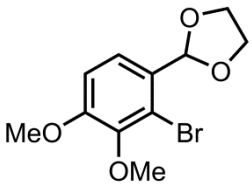
2-Bromo-3,4-dimethoxybenzaldehyde **E1**



Powdered NaOH (649 mg, 16.2 mmol) was stirred in DMSO (6.9 mL) for 5 min at room temperature. A solution of 2-bromo-3-hydroxy-4-methoxybenzaldehyde (1.50 g, 6.49 mmol) in DMSO (1.0 mL) and iodomethane (1.01 g, 7.14 mmol) were then added. The reaction was stirred for a further 30 min at room temperature and then poured onto 80 mL of 2 M aqueous HCl. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by flash column chromatography [Petrol/EtOAc 9:1 grading to 4:1] furnished *ether* **E1** (1.32 g, 5.39 mmol, 83%) as needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 10.25 (1H, s, C*H*O), 7.74 (1H, d, *J* 8.8, *H*C_{Ar}), 6.96 (1H, d, *J* 8.9, *H*C_{Ar}), 3.96 (3H, s, OCH_3), 3.89 (3H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 190.9 (*C*HO), 158.6, 146.4, 127.3 (3 × C_{Ar}), 126.5 (HC_{Ar}), 123.1 (C_{Ar}), 110.9 (HC_{Ar}), 60.6, 56.3 (2 × O*C*H_3); **m.p.** 82-84 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[278]

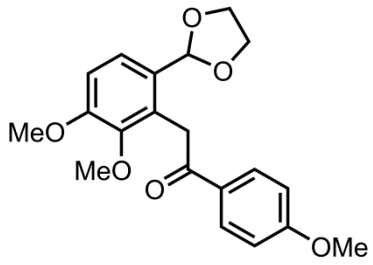
2-(2-Bromo-3,4-dimethoxyphenyl)-1,3-dioxolane **304**



2-Bromo-3,4-dimethoxybenzaldehyde (1.08 g, 4.42 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 9:1 grading to 4:1] to furnish *acetal* **304** (1.16 g, 4.02 mmol, 91%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.34 (1H, d, *J* 8.9, *H*C$_{Ar}$), 6.89 (1H, d, *J* 8.6, *H*C$_{Ar}$), 6.07 (1H, s, C*H*(OR)$_2$), 4.17-4.11 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 4.10-4.04 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$), 3.89 (3H, s, OC*H*$_3$), 3.86 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 154.3, 146.4, 129.5 (3 × *C*$_{Ar}$), 123.0 (H*C*$_{Ar}$), 118.8 (*C*$_{Ar}$), 111.0 (H*C*$_{Ar}$), 102.7 (*C*H(OR)$_2$), 65.4 (*C*H$_2$OR), 60.5, 56.1 (2 × O*C*H$_3$); **m.p.** 71-73 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[279]

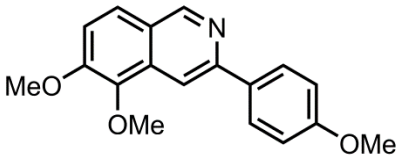
2-(6-(1,3-Dioxolan-2-yl)-2,3-dimethoxyphenyl)-1-(4-methoxyphenyl)ethanone **305**



Acetal **304** (146 mg, 0.509 mmol) was subjected to General Procedure 6 with 4'-methoxyacetophenone (91.8 mg, 0.611 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 9:1 grading to 4:1] to furnish *ketone* **305** (127 mg, 0.353 mmol, 69%) as plates.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.06 (2H, d, *J* 8.8, 2 × *H*C$_{Ar}$), 7.28 (1H, d, *J* 9.6, *H*C$_{Ar}$), 6.97 (2H, d, *J* 8.9, 2 × *H*C$_{Ar}$), 6.86 (1H, d, *J* 8.6, *H*C$_{Ar}$), 5.74 (1H, s, C*H*(OR)$_2$), 4.51 (2H, s, C*H*$_2$), 3.98-3.93 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 3.92-3.87 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$), 3.88 (3H, s, OC*H*$_3$), 3.88 (3H, s, OC*H*$_3$), 3.75 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 196.1 (*C*=O), 163.3, 153.2, 147.8, (3 × *C*$_{Ar}$), 130.4 (H*C*$_{Ar}$), 130.3, 128.7, 128.5 (3 × *C*$_{Ar}$), 122.8, 113.7, 110.4 (3 × H*C*$_{Ar}$), 103.0 (*C*H(OR)$_2$), 64.8 (*C*H$_2$OR), 60.6, 55.6, 55.5 (3 × O*C*H$_3$), 36.0 (*C*H$_2$); **IR** ν_{max} (thin film)/cm^{-1} 2940w, 2839w, 1680s, 1600s, 1576m, 1510m, 1495m, 1457m, 1421m, 1329w, 1308w, 1261s, 1230s, 1169s, 1093m, 1080m, 1035s, 995w, 960w, 938w, 831w, 813w; **m/z** (ESI$^+$) 359.2 [45, (M + H)$^+$], 381.1 [100, (M + Na)$^+$], 739.2 [100, (2M + Na)$^+$], $C_{20}H_{22}NaO_6$ predicted 381.1309, found 381.1307, (Δ + 0.4 ppm); **m.p.** 114-116 °C (Petrol/CH_2Cl_2).

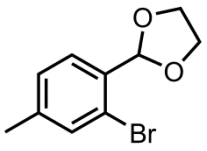
5,6-Dimethoxy-3-(4-methoxyphenyl)isoquinoline **306**



Ketone **305** (59.3 mg, 0.165 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 9:1 grading to 4:1] to furnish *isoquinoline* **306** (38.9 mg, 0.132 mmol, 80%) as plates.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.19 (1H, s, *H*C(1)), 8.21 (1H, s, *H*C(4)), 8.11 (2H, d, *J* 8.1, 2 × *H*C_{Ar}), 7.73 (1H, d, *J* 8.9, *H*C(8)), 7.32 (1H, d, *J* 9.1, *H*C(7)), 7.04 (2H, d, *J* 8.0, 2 × *H*C_{Ar}), 4.03 (6H, s, C(5)OCH_3 + C(6)OCH_3), 3.88 (3H, s, C_{Ar}OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 160.1 (C_{Ar}), 151.9 (H*C*(1)), 151.6, 151.0 (*C*(3) + *C*(6)), 141.6 (*C*(5)), 132.6, 132.5 (2 × C_{Ar}), 128.3 (HC_{Ar}), 124.4 (H*C*(8)), 123.6 (C_{Ar}), 115.0 (H*C*(7)), 114.1 (HC_{Ar}), 109.0 (H*C*(4)), 61.2 (C(5)O*C*H$_3$), 56.5 (C(6)O*C*H$_3$), 55.4 (C_{Ar}O*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2936w, 2837w, 1621m, 1606s, 1514s, 1488s, 1457s, 1425w, 1408w, 1385w, 1339w, 1318w, 1295m, 1278m, 1242s, 1169s, 1110s, 1064s, 1039m, 1024m, 986s, 939w, 870w, 834s, 801m; **m/z** (ESI$^+$) 296.1 [100, $(M + H)^+$], 318.1 [75, $(M + Na)^+$], 613.2 [75, $(2M + Na)^+$], $C_{18}H_{18}NO_3$ predicted 296.1281, found 296.1280, (Δ + 0.5 ppm); **m.p.** 101-102 °C (Petrol/CH_2Cl_2).

2-(2-Bromo-4-methylphenyl)-1,3-dioxolane **307**

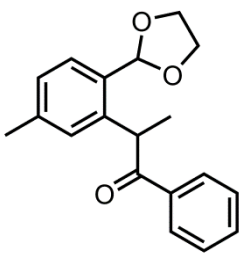


2-Bromo-4-methylbenzaldehyde (879 mg, 4.42 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 19:1] to furnish *acetal* **307** (1.07 g, 4.41 mmol, 100%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.48 (1H, d, *J* 7.8, *H*C_{Ar}), 7.40 (1H, s, *H*C_{Ar}), 7.15 (1H, d, *J* 7.8, *H*C_{Ar}), 6.08 (1H, s, C*H*$(OR)_2$), 4.17-4.11 (2H, m, C$H_a$$H_bCH_a$$H_b$), 4.10-4.04 (2H, m, CH$_a$$H_bCH_a$$H_b$), 2.34 (3H, s, C$H_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 140.9, 133.6 (2 × C_{Ar}), 133.4, 128.2, 127.6, (3 × HC_{Ar}), 122.7 (C_{Ar}), 102.7 (*C*H$(OR)_2$), 65.4 (*C*H$_2$OR), 20.8 (*C*H$_3$);

IR ν_{max} (thin film)/cm^{-1} 2885w, 1608m, 1567w, 1450w, 1381m, 1271m, 1218m, 1141m, 1086s, 1038s, 972m, 942s, 869m, 825s; **m/z** (EI/FI^{+}) $C_{10}H_{11}{}^{79}BrO_2$ predicted 241.9942, found 241.9943, (Δ − 0.2 ppm).

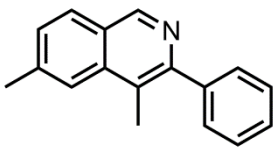
2-(2-(1,3-Dioxolan-2-yl)-5-methylphenyl)-1-phenylpropan-1-one **308**



Acetal **307** (177 mg, 0.729 mmol) was subjected to General Procedure 6 with propiophenone (117 mg, 0.875 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 19:1] to furnish *ketone* **308** (192 mg, 0.648 mmol, 89%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.07-8.04 (2H, m, 2 × *H*C$_{Ar}$), 7.49-7.43 (2H, m, 2 × *H*C$_{Ar}$), 7.36 (2H, tt, *J* 7.5, 1.1, 2 × *H*C$_{Ar}$), 7.04 (1H, d, *J* 7.6, *H*C$_{Ar}$), 6.89 (1H, s, *H*C$_{Ar}$), 6.10 (1H, s, C*H*(OR)$_2$), 5.08 (1H, q, *J* 6.8, C*H*CH$_3$), 4.21-4.15 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 4.14-4.08 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$), 2.23 (3H, s, C$_{Ar}$C*H*$_3$), 1.52 (3H, d, *J* 6.8, CHC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 201.0 (*C*=O), 140.4, 139.7, 136.5 (3 × *C*$_{Ar}$), 132.6 (H*C*$_{Ar}$), 130.6 (*C*$_{Ar}$), 129.0, 128.4, 128.2, 127.6, 127.5 (5 × H*C*$_{Ar}$), 102.8 (*C*H(OR)$_2$), 65.2, 65.1 (2 × *C*H$_2$OR), 43.6 (*C*HCH$_3$), 21.2 (C$_{Ar}$*C*H$_3$), 19.2 (CH*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2930w, 1682s, 1608w, 1597w, 1579w, 1449m, 1372w, 1334w, 1297w, 1259m, 1228s, 1211s, 1183w, 1115m, 1075s, 1057s, 1027m, 1001w, 958s, 817s; **m/z** (ESI^{+}) 319.1 [80, (M + Na)$^{+}$], 615.3 [100, (2M + Na)$^{+}$], $C_{19}H_{20}NaO_3$ predicted 319.1305, found 319.1303, (Δ + 0.6 ppm).

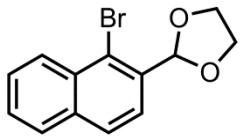
4,6-Dimethyl-3-phenylisoquinoline **309**



Ketone **308** (32.0 mg, 0.108 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 14:1] to furnish *isoquinoline* **309** (24.2 mg, 0.104 mmol, 96%) as plates.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.15 (1H, s, *H*C(1)), 7.88 (1H, d, *J* 8.3, *H*C(8)), 7.81 (1H, s, *H*C(5)), 7.62-7.59 (2H, m, 2 × *H*C_{Ar}), 7.51-7.47 (2H, t, *J* 7.6, 2 × *H*C_{Ar}), 7.45-7.39 (2H, m, *H*C(7) + *H*C_{Ar}), 2.63 (3H, s, C*H*$_3$), 2.61 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 151.9 (*C*(3)), 149.8 (H*C*(1)), 141.5, 140.7, 136.4 (2 × *C*$_{Ar}$ + *C*(6)), 129.9 (H*C*$_{Ar}$), 128.8 (H*C*(7)), 128.1, 127.9 (2 × H*C*$_{Ar}$), 127.5 (H*C*(8)), 125.7, 123.5 (*C*(4) + *C*$_{Ar}$), 122.7 (H*C*(5)), 22.5 (C(6)*C*H$_3$), 15.5 (C(4)*C*H$_3$); **m.p.** 96-98 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[280]

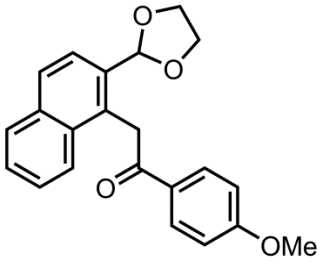
2-(1-Bromonaphthalen-2-yl)-1,3-dioxolane **310**



1-Bromo-2-naphthaldehyde (1.20 g, 5.08 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 19:1] to furnish *acetal* **310** (1.41 g, 5.03 mmol, 99%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.40 (1H, d, *J* 8.6, *H*C_{Ar}), 7.85 (1H, d, *J* 8.6, *H*C_{Ar}), 7.84 (1H, d, *J* 8.1, *H*C_{Ar}), 7.71 (1H, d, *J* 8.6, *H*C_{Ar}), 7.63 (1H, td, *J* 7.1, 1.3, *H*C_{Ar}), 7.56 (1H, td, *J* 8.3, 1.0, *H*C_{Ar}), 6.44 (1H, s, C*H*(OR)$_2$), 4.28-4.20 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 4.18-4.10 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 135.0, 134.6, 132.2 (3 × *C*$_{Ar}$), 128.2, 128.0, 127.6, 127.5, 127.2, 124.2 (6 × H*C*$_{Ar}$), 124.0 (*C*$_{Ar}$), 103.5 (*C*H(OR)$_2$), 65.7 (*C*H$_2$OR); **IR** ν_{max} (thin film)/cm^{-1} 2960w, 2885w, 1557w, 1501w, 1464w, 1399w, 1344w, 1324m, 1260m, 1224m, 1134m, 1094s, 1026m, 1000m, 961s, 943s, 864m, 818s; **m/z** (EI/FI$^+$) $C_{13}H_{11}{}^{79}BrO_2$ predicted 277.9942, found 277.9940, (Δ + 0.9 ppm).

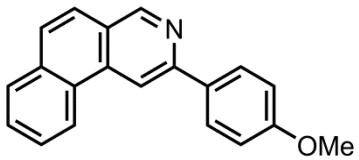
2-(2-(1,3-Dioxolan-2-yl)naphthalen-1-yl)-1-(4-methoxyphenyl)ethanone **311**



Acetal **310** (103 mg, 0.372 mmol) was subjected to General Procedure 6 with 4'-methoxyacetophenone (66.9 mg, 0.446 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 9:1] to furnish *ketone* **311** (108 mg, 0.310 mmol, 83%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.15 (2H, d, *J* 8.6, 2 × *H*C$_{Ar}$), 7.88-7.85 (2H, m, 2 × *H*C$_{Ar}$), 7.81-7.75 (2H, m, 2 × *H*C$_{Ar}$), 7.50-7.43 (2H, m, 2 × *H*C$_{Ar}$), 7.02 (2H, d, *J* 8.6, 2 × *H*C$_{Ar}$), 6.09 (1H, s, C*H*(OR)$_2$), 4.96 (2H, s, C*H*$_2$), 4.12-4.06 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 4.05-3.99 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$), 3.91 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 195.1 (*C*=O), 163.6, 134.0, 133.8, 133.0, 130.8 (5 × *C*$_{Ar}$), 130.5 (H*C*$_{Ar}$), 130.0 (*C*$_{Ar}$), 128.6, 127.7, 126.4, 126.0, 124.0, 123.7, 113.9 (7 × H*C*$_{Ar}$), 102.7 (*C*H(OR)$_2$), 65.2 (*C*H$_2$OR), 55.5 (OC*H*$_3$), 37.7 (*C*H$_2$); **IR** ν_{max} (thin film)/cm^{-1} 2961w, 2918w, 1681s, 1600s, 1574m, 1510s, 1463w, 1441w, 1419w, 1381w, 1320m, 1258s, 1216m, 1171s, 1096s, 1019s; **m/z** (ESI$^+$) 371.2 [30, (M + Na)$^+$], 719.3 [100, (2M + Na)$^+$], $C_{22}H_{20}NaO_4$ predicted 371.1254, found 371.1243, (Δ + 2.9 ppm); **m.p.** 129-131 °C (Petrol/CH_2Cl_2).

2-(4-Methoxyphenyl)benzo[f]isoquinoline **312**

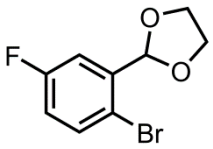


Ketone **311** (66.5 mg, 0.191 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 14:1] to furnish *isoquinoline* **312** (48.9 mg, 0.171 mmol, 90%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.27 (1H, s, *H*C(1)), 8.74-8.72 (2H, m, *H*C(4) + *H*C$_{Ar}$), 8.17 (1H, t, *J* 2.6, *H*C$_{Ar}$), 8.15 (1H, t, *J* 2.5, *H*C$_{Ar}$), 7.93-7.91 (1H, m, *H*C$_{Ar}$), 7.81-7.76 (2H, m, *H*C(7) + *H*C(8)), 7.73-7.69 (2H, m, 2 × *H*C$_{Ar}$), 7.10 (1H, t, *J* 2.4, *H*C$_{Ar}$), 7.07 (1H, t, *J* 2.6, *H*C$_{Ar}$), 3.91 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 160.3 (*C*$_{Ar}$), 153.1 (*C*(3)),

151.4 (H*C*(1)), 135.6, 133.8, 132.5 (2 × C_{Ar} + *C*(6)), 128.8 (HC_{Ar}), 128.7 (*C*(5)), 128.6, 128.4 (2 × HC_{Ar}), 127.8, 124.7 (H*C*(7) + H*C*(8)), 127.0 (HC_{Ar}), 125.5 (C_{Ar}), 123.1, 114.3 (2 × HC_{Ar}), 111.5 (H*C*(4)), 55.4 (OCH_3); **IR** ν_{max} (thin film)/cm^{-1} 2932w, 1607s, 1591s, 1519s, 1505s, 1480m, 1452s, 1385w, 1299w, 1248s, 1174s, 1030m, 834s, 815w; **m/z** (ESI$^+$) 286.1 [100, (M + H)$^+$], $C_{20}H_{16}NO$ predicted 286.1226, found 286.1228, (Δ − 0.7 ppm); **m.p.** 91-93 °C (Petrol/CH_2Cl_2).

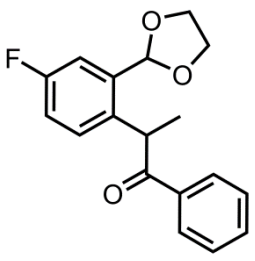
2-(2-Bromo-5-fluorophenyl)-1,3-dioxolane **313**



2-Bromo-5-fluorobenzaldehyde (1.98 g, 9.74 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *acetal* **313** (2.35 g, 9.53 mmol, 98%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.52 (1H, dd, *J* 8.4, 5.3, *H*C$_{Ar}$), 7.34 (1H, dd, *J* 9.3, 2.4, *H*C$_{Ar}$), 6.96 (1H, td, *J* 8.1, 2.3, *H*C$_{Ar}$), 6.04 (1H, s, C*H*(OR)$_2$), 4.17-4.06 (4H, m, 2 × CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 162.0 (d, ^1J 247.7, C_{Ar}), 139.0 (d, ^3J 8.0, C_{Ar}), 134.3 (d, ^3J 8.0, HC_{Ar}), 117.7 (d, ^2J 22.3, HC_{Ar}), 116.8 (d, ^4J 3.2, C_{Ar}), 115.1 (d, ^2J 25.4, HC_{Ar}), 102.0 (*C*H(OR)$_2$), 65.5 (*C*H$_2$OR); **^{19}F[^{1}H] NMR** (377 MHz, $CDCl_3$) δ_F: −113.9; **IR** ν_{max} (thin film)/cm^{-1} 2958w, 2889w, 1583m, 1468s, 1415m, 1390m, 1263s, 1221w, 1158s, 1118s, 1080s, 1029s, 964m, 941s, 880s, 814s; **m/z** (EI/FI$^+$) $C_9H_8{}^{79}BrFO_2$ predicted 245.9692, found 245.9691, (Δ + 0.3 ppm).

2-(2-(1,3-Dioxolan-2-yl)-4-fluorophenyl)-1-phenylpropan-1-one **314**

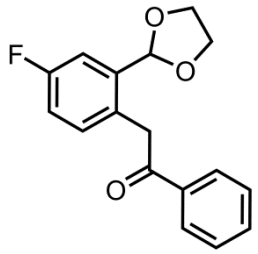


Acetal **313** (62.4 mg, 0.253 mmol) was subjected to General Procedure 6 with propiophenone (40.6 mg, 0.304 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc

24:1 grading to 14:1] to furnish *ketone* **314** (58.0 mg, 0.193 mmol, 76%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.01 (2H, dd, *J* 8.6, 1.3, 2 × *H*C_{Ar}), 7.47 (1H, tt, *J* 7.5, 1.3, *H*C_{Ar}), 7.37 (2H, t, *J* 7.6, 2 × *H*C_{Ar}), 7.34 (1H, dd, *J* 9.8, 3.0, *H*C_{Ar}), 7.08 (1H, dd, *J* 8.8, 5.5, *H*C_{Ar}), 6.93 (1H, td, *J* 8.5, 3.0, *H*C_{Ar}), 6.12 (1H, s, C*H*$(OR)_2$), 5.07 (1H, q, *J* 6.8, C*H*CH_3), 4.22-4.16 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 4.14-4.08 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$), 1.51 (3H, d, *J* 6.9, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 200.7 (*C*=O), 161.5 (d, ^{1}J 245.3, *C*$_{Ar}$), 136.5 (d, ^{3}J 6.4, *C*$_{Ar}$), 136.3 (*C*$_{Ar}$), 136.0 (d, ^{4}J 4.0, *C*$_{Ar}$), 132.8 (H*C*$_{Ar}$), 129.4 (d, ^{3}J 8.0, H*C*$_{Ar}$), 128.9, 128.5 (2 × H*C*$_{Ar}$), 116.4 (d, ^{2}J 21.5, H*C*$_{Ar}$), 114.1 (d, ^{2}J 23.2, H*C*$_{Ar}$), 101.3 (d, ^{4}J 1.6, (*C*H$(OR)_2$)), 65.4, 65.2 (2 × *C*H_2OR), 43.0 (*C*HCH_3), 19.2 (*C*H_3); **^{19}F[^{1}H] NMR** (377 MHz, $CDCl_3$) δ_F: −115.2; **IR** ν_{max} (thin film)/cm^{-1} 2977w, 2932w, 2891w, 1682s, 1595w, 1495m, 1449m, 1375w, 1338w, 1272s, 1222s, 1162s, 1114s, 1071m, 1054s, 1001m, 965s, 949s, 883s, 830m; **m/z** (ESI$^+$) 323.1 [100, $(M + Na)^+$], 623.3 [70, $(2M + Na)^+$], $C_{18}H_{17}FNaO_3$ predicted 323.1054, found 323.1044, (Δ + 3.2 ppm).

2-(2-(1,3-Dioxolan-2-yl)-4-fluorophenyl)-1-phenylethanone **315**

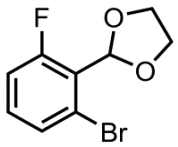


Acetal **313** (102 mg, 0.412 mmol) was subjected to General Procedure 6 with acetophenone (59.4 mg, 0.494 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 14:1] to furnish *ketone* **315** (95.0 mg, 0.332 mmol, 81%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.05 (2H, dd, *J* 8.0, 1.3, 2 × *H*C_{Ar}), 7.60 (1H, t, *J* 7.5, *H*C_{Ar}), 7.50 (2H, t, *J* 7.6, 2 × *H*C_{Ar}), 7.34 (1H, dd, *J* 9.7, 2.7, *H*C_{Ar}), 7.15 (1H, dd, *J* 7.9, 5.6, *H*C_{Ar}), 7.03 (1H, td, *J* 8.3, 2.8, *H*C_{Ar}), 5.86 (1H, s, C*H*$(OR)_2$), 4.46 (2H, s, C*H*$_2$), 4.03-3.98 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 3.97-3.93 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 197.3 (*C*=O), 161.8 (d, ^{1}J 245.2, *C*$_{Ar}$), 138.4 (d, ^{3}J 7.2, *C*$_{Ar}$), 136.8 (*C*$_{Ar}$), 133.2 (H*C*$_{Ar}$), 133.0 (d, ^{3}J 8.0, H*C*$_{Ar}$), 129.0 (d, ^{4}J 3.2, *C*$_{Ar}$), 128.7, 128.3 (2 × H*C*$_{Ar}$), 115.7 (d, ^{2}J 20.7, H*C*$_{Ar}$), 113.8 (d, ^{2}J 23.1, H*C*$_{Ar}$), 101.6 (d, ^{4}J 1.6, (*C*H$(OR)_2$)), 65.0 (*C*H_2OR), 41.8 (*C*H_2); **^{19}F[^{1}H]**

NMR (377 MHz, $CDCl_3$) δ_F: −115.2; **IR** ν_{max} (thin film)/cm^{-1} 3064w, 2929w, 1689s, 1639w, 1597m, 1499s, 1448m, 1382w, 1333m, 1257s, 1215m, 1159m, 1113m, 1066s, 1036s, 1014s, 962s, 907w, 873s, 834m, 812m; **m/z** (ESI^+) 309.1 [100, $(M + Na)^+$], 595.2 [85, $(2M + Na)^+$], $C_{17}H_{15}FNaO_3$ predicted 309.0897, found 309.0897, (Δ + 0.1 ppm); **m.p.** 63-65 °C (Petrol/CH_2Cl_2).

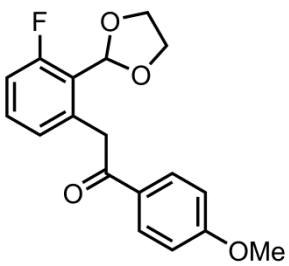
2-(2-Bromo-6-fluorophenyl)-1,3-dioxolane **316**



2-Bromo-6-fluorobenzaldehyde (991 mg, 4.88 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 19:1] to furnish *acetal* **316** (1.16 g, 4.69 mmol, 96%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.37 (1H, d, *J* 8.1, *H*C_{Ar}), 7.20 (1H, ddd, *J* 8.4, 8.1, 5.6, *H*C_{Ar}), 7.04 (1H, dd, *J* 9.6, 8.4, *H*C_{Ar}), 6.33 (1H, s, C*H*$(OR)_2$), 4.29-4.22 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 4.09-4.02 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 162.1 (d, ^1J 256.5, *C*$_{Ar}$), 131.4 (d, ^3J 10.3, H*C*$_{Ar}$), 129.2 (d, ^4J 3.9, H*C*$_{Ar}$), 124.3 (d, ^2J 12.8, *C*$_{Ar}$), 123.9 (d, ^3J 4.8, *C*$_{Ar}$), 115.9 (d, ^2J 23.2, H*C*$_{Ar}$), 102.0 (d, ^3J 2.4, *C*H$(OR)_2$), 66.0 (*C*H_2OR); **^{19}F[^{1}H] NMR** (377 MHz, $CDCl_3$) δ_F: −112.4; **IR** ν_{max} (thin film)/cm^{-1} 2969w, 2896w, 1602m, 1574m, 1457s, 1410m, 1391m, 1246s, 1209s, 1178w, 1167w, 1138w, 1096s, 1059s, 1027m, 959s, 941s, 881s, 804w; **m/z** (EI/FI^+) $C_9H_8{}^{79}BrFO_2$ predicted 245.9692, found 245.9689, (Δ + 1.1 ppm).

2-(2-(1,3-Dioxolan-2-yl)-3-fluorophenyl)-1-(4-methoxyphenyl)ethanone **317**

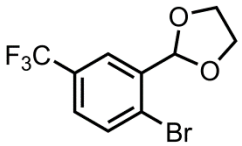


Acetal **316** (111 mg, 0.447 mmol) was subjected to General Procedure 6 with 4'-methoxyacetophenone (80.6 mg, 0.537 mmol). The crude product was purified by flash column

chromatography [Petrol/EtOAc 24:1 grading to 9:1] to furnish *ketone* **317** (122 mg, 0.387 mmol, 86%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.02 (2H, d, *J* 8.8, 2 × *H*C_{Ar}), 7.33-7.29 (1H, m, *H*C_{Ar}), 7.02-6.97 (2H, m, 2 × *H*C_{Ar}), 6.95 (2H, d, *J* 8.8, 2 × *H*C_{Ar}), 6.09 (1H, s, C*H*$(OR)_2$), 4.46 (2H, s, CH_2), 3.94-3.90 (4H, m, 2 × CH_2OR), 3.88 (3H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 195.8 (*C*=O), 163.3 (*C*$_{Ar}$), 162.3 (d, ^{1}J 249.3, *C*$_{Ar}$), 154.1 (d, ^{2}J 21.6, *C*$_{Ar}$), 137.5 (d, ^{3}J 2.4, *C*$_{Ar}$), 130.8 (d, ^{3}J 9.6, H*C*$_{Ar}$), 130.5 (H*C*$_{Ar}$), 129.9 (*C*$_{Ar}$), 128.0 (d, ^{4}J 3.2, H*C*$_{Ar}$), 114.4 (d, ^{2}J 23.2, H*C*$_{Ar}$), 113.8 (H*C*$_{Ar}$), 98.4 (d, ^{3}J 9.6, (*C*H$(OR)_2$)), 64.9 (*C*H_2OR), 55.5 (O*C*H_3), 42.4 (*C*H_2); **^{19}F[^{1}H] NMR** (377 MHz, $CDCl_3$) δ_F: −119.1; **IR** ν_{max} (thin film)/cm^{-1} 2935m, 1682s, 1601s, 1575m, 1510s, 1467s, 1420m, 1249s, 1216w, 1174s, 1085w, 1019s, 944m, 911m, 813m; **m/z** (ESI$^+$) 339.1 [30, $(M + Na)^+$], 655.2 [100, $(2M + Na)^+$], $C_{18}H_{17}FNaO_4$ predicted 339.1003, found 339.1006, (Δ − 0.9 ppm); **m.p.** 110-112 °C (Petrol/CH_2Cl_2).

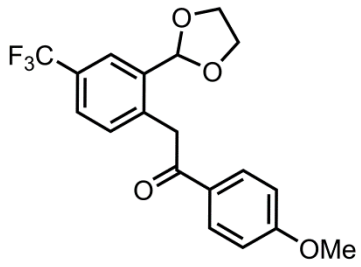
2-(2-Bromo-5-(trifluoromethyl)phenyl)-1,3-dioxolane **318**



2-Bromo-5-(trifluoromethyl)benzaldehyde (1.00 g, 3.97 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 99:1 grading to 49:1] to furnish *acetal* **318** (1.10 g, 3.69 mmol, 93%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.88 (1H, d, *J* 2.0, *H*C_{Ar}), 7.69 (1H, dd, *J* 8.0, 3.6, *H*C_{Ar}), 7.47 (1H, dd, *J* 8.4, 2.6, *H*C_{Ar}), 6.10 (1H, d, *J* 2.8, C*H*$(OR)_2$), 4.19-4.14 (2H, m, CH_aH$_b$CH_aH$_b$), 4.10-4.06 (2H, m, CH$_a$$H_bCH_a$$H_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 138.0 (*C*$_{Ar}$), 133.6 (H*C*$_{Ar}$), 129.9 (q, ^{2}J 32.7, *C*$_{Ar}$), 127.1 (q, ^{3}J 2.4, H*C*$_{Ar}$), 126.8 (q, ^{4}J 1.6, *C*$_{Ar}$), 124.9 (q, ^{3}J 4.0, H*C*$_{Ar}$), 123.7 (q, ^{1}J 272.4, *C*F_3), 101.8 (*C*H$(OR)_2$), 65.6 (*C*H_2OR); **^{19}F[^{1}H] NMR** (377 MHz, $CDCl_3$) δ_F: −62.7; **IR** ν_{max} (thin film)/cm^{-1} 2893w, 1608w, 1583w, 1476w, 1395w, 1326s, 1256s, 1199m, 1168s, 1123s, 1078s, 1027s, 975m, 944m, 900m, 828m; **m/z** (EI/FI$^+$) $C_{10}H_8{}^{79}BrF_3O_2$ predicted 295.9660, found 295.9671, (Δ − 3.8 ppm).

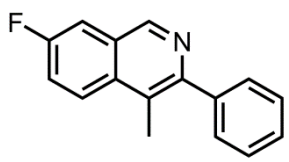
2-(2-(1,3-Dioxolan-2-yl)-4-(trifluoromethyl)phenyl)-1-(4-methoxyphenyl)ethanone **319**



Acetal **318** (115 mg, 0.388 mmol) was subjected to General Procedure 6 with 4'-methoxyacetophenone (69.9 mg, 0.465 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 14:1] to furnish *ketone* **319** (113 mg, 0.308 mmol, 79%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.03 (2H, dt, *J* 8.8, 2.4, 2 × *H*C$_{Ar}$), 7.89 (1H, s, *H*C$_{Ar}$), 7.58 (1H, dd, *J* 8.1, 1.3, *H*C$_{Ar}$), 7.30 (1H, d, *J* 7.9, *H*C$_{Ar}$), 6.97 (2H, dt, *J* 9.0, 2.4, 2 × *H*C$_{Ar}$), 5.91 (1H, s, C*H*(OR)$_2$), 4.51 (2H, s, CH_2), 4.06-4.01 (2H, m, CH_aH$_b$CH_aH$_b$), 4.00-3.95 (2H, m, CH$_a$$H_bCH_a$$H_b$), 3.88 (3H, s, C$H_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 195.2 (*C*=O), 163.7, 138.1, 137.0 (3 × *C*$_{Ar}$), 131.9, 130.6 (2 × H*C*$_{Ar}$), 129.6 (*C*$_{Ar}$), 129.2 (q, ^{2}J 32.5, *C*$_{Ar}$), 125.7 (q, ^{3}J 3.7, H*C*$_{Ar}$), 124.1 (q, ^{1}J 272.2, *C*F$_3$), 123.6 (q, ^{3}J 3.4, H*C*$_{Ar}$), 113.9 (H*C*$_{Ar}$), 101.6 (*C*H(OR)$_2$), 65.1 (*C*H$_2$OR), 55.5 (*C*H$_3$), 42.0 (*C*H$_2$); **^{19}F[^{1}H] NMR** (377 MHz, $CDCl_3$) δ_F: −62.5; **IR** ν_{max} (thin film)/cm^{-1} 2961w, 1679s, 1599s, 1575m, 1510m, 1421w, 1329s, 1266m, 1226m, 1164s, 1118s, 1085s, 1028m, 990m, 945m, 899m, 832s; **m/z** (ESI$^+$) 367.1 [70, (M + H)$^+$], 389.1 [100, (M + Na)$^+$], 755.1 [95, (2M + Na)$^+$], $C_{19}H_{17}F_3NaO_4$ predicted 389.0971, found 389.0970, (Δ + 0.3 ppm).

7-Fluoro-4-methyl-3-phenylisoquinoline **320**

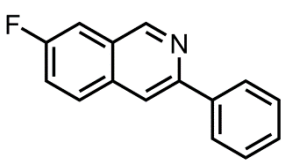


Ketone **314** (48.2 mg, 0.161 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 14:1] to furnish *isoquinoline* **320** (34.1 mg, 0.144 mmol, 89%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.16 (1H, s, *H*C(1)), 8.07 (1H, dd, *J* 9.4, 5.1, *H*C(5)), 7.61-7.58 (3H, m, *H*C(8) + 2 × *H*C$_{Ar}$), 7.55-7.48 (3H, m, *H*C(6) + 2 × *H*C$_{Ar}$), 7.42 (1H, tt, *J* 7.3, 1.5, *H*C$_{Ar}$), 2.66 (3H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 160.7 (d, ^{1}J 248.5, *C*(7)), 151.6 (d, ^{6}J 2.4, *C*(3)), 149.3 (d, ^{4}J 5.6, H*C*(1)), 141.0, 133.3 (2 × *C*$_{Ar}$), 129.8, 128.2

(2 × H*C*$_{Ar}$), 128.1 (d, ^{3}J 8.0, *C*$_{Ar}$), 127.7 (H*C*$_{Ar}$), 126.5 (d, ^{3}J 8.8, H*C*(5)), 124.2 (d, ^{5}J 1.6, *C*(4)), 120.7 (d, ^{2}J 25.5, H*C*(6)), 110.9 (d, ^{2}J 20.8, H*C*(8)), 15.7 (*C*H$_3$); **^{19}F[^{1}H] NMR** (377 MHz, $CDCl_3$) δ_F: −113.0; **IR** ν_{max} (thin film)/cm^{-1} 2925w, 2854w, 1682w, 1624w, 1565m, 1500s, 1445m, 1404w, 1373s, 1333m, 1274m, 1244m, 1224s, 1146s, 1098w, 1072w, 1007m, 953s, 921s, 859s, 835s; **m/z** (ESI$^+$) 238.1 [100, $(M + H)^+$], $C_{16}H_{13}FN$ predicted 238.1027, found 238.1025, (Δ + 0.7 ppm); **m.p.** 112-114 °C (Petrol/CH_2Cl_2).

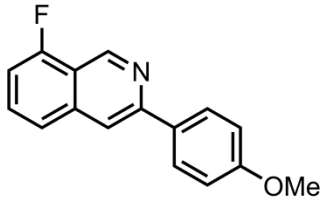
7-Fluoro-3-phenylisoquinoline **321**



Ketone **315** (58.2 mg, 0.203 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 14:1] to furnish *isoquinoline* **321** (40.4 mg, 0.181 mmol, 89%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.30 (1H, s, *H*C(1)), 8.12 (2H, dd, *J* 8.0, 1.6, 2 × *H*C$_{Ar}$), 8.06 (1H, s, *H*C(4)), 7.89 (1H, dd, *J* 9.0, 5.2, *H*C(5)), 7.60 (1H, dd, *J* 8.5, 2.3, *H*C(8)), 7.54-7.41 (4H, m, *H*C(6) + 3 × *H*C$_{Ar}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 160.8 (d, ^{1}J 249.3, *C*(7)), 151.6 (d, ^{4}J 5.6, H*C*(1)), 151.0 (d, ^{6}J 3.2, *C*(3)), 139.3, 133.7 (2 × *C*$_{Ar}$), 129.6 (d, ^{3}J 8.8, H*C*(5)), 128.8, 128.6 (2 × H*C*$_{Ar}$), 128.2 (d, ^{3}J 8.0, *C*$_{Ar}$), 126.9 (H*C*$_{Ar}$), 121.2 (d, ^{2}J 25.6, H*C*(6)), 116.2 (d, ^{5}J 1.6, H*C*(4)), 110.6 (d, ^{2}J 20.7, H*C*(8)); **^{19}F[^{1}H] NMR** (377 MHz, $CDCl_3$) δ_F: −111.3; **m.p.** 132-134 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[268]

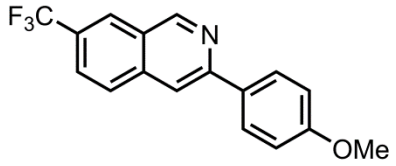
8-Fluoro-3-(4-methoxyphenyl)isoquinoline **322**



Ketone **317** (91.7 mg, 0.290 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 14:1] to furnish *isoquinoline* **322** (70.9 mg, 0.280 mmol, 97%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.58 (1H, s, *H*C(1)), 8.19 (2H, d, *J* 8.9, 2 × *H*C_{Ar}), 7.97 (1H, s, *H*C(4)), 7.62-7.58 (2H, m, *H*C(5) + *H*C(6)), 7.19-7.14 (1H, m, *H*C(7)), 7.05 (2H, d, *J* 8.9, 2 × *H*C_{Ar}), 3.89 (3H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 160.4 (C_{Ar}), 159.4 (d, ^{1}J 256.8, *C*(8)), 152.0 (*C*(3)), 146.0 (d, ^{3}J 4.8, H*C*(1)), 138.2 (d, ^{3}J 4.0, C_{Ar}), 131.8 (C_{Ar}), 130.7 (d, ^{3}J 8.8, H*C*(6)), 128.3 (HC_{Ar}), 122.6 (d, ^{4}J 4.0, H*C*(5)), 117.8 (d, ^{2}J 15.9, C_{Ar}), 114.6 (d, ^{4}J 3.2, H*C*(4)), 114.2 (HC_{Ar}), 110.4 (d, ^{2}J 19.2, H*C*(7)), 55.4 (OCH_3); **^{19}F[^{1}H] NMR** (377 MHz, $CDCl_3$) δ_F: −123.3; **IR** ν_{max} (thin film)/cm^{-1} 2961w, 1635m, 1605m, 1574s, 1512s, 1454s, 1438s, 1350m, 1282m, 1244m, 1174m, 1081m, 1032s, 906w, 829s; **m/z** (ESI$^+$) 254.1 [100, $(M + H)^+$], $C_{16}H_{13}FNO$ predicted 254.0976, found 254.0975, (Δ + 0.3 ppm); **m.p.** 132-134 °C (Petrol/CH_2Cl_2).

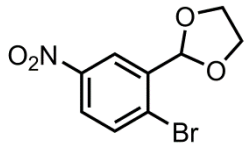
3-(4-Methoxyphenyl)-7-(trifluoromethyl)isoquinoline **323**



Ketone **319** (103 mg, 0.280 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 14:1] to furnish *isoquinoline* **323** (72.8 mg, 0.240 mmol, 86%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.38 (1H, s, *H*C(1)), 8.26 (1H, s, *H*C(8)), 8.11 (2H, dt, *J* 8.8, 1.9, 2 × *H*C_{Ar}), 8.02 (1H, s, *H*C(4)), 7.93 (1H, d, *J* 8.6, *H*C(5)), 7.82 (1H, dd, *J* 8.6, 1.5, *H*C(6)), 7.05 (2H, dt, *J* 8.9, 1.9, 2 × *H*C_{Ar}), 3.89 (3H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 160.6 (C_{Ar}), 153.1 (*C*(3)), 153.0 (H*C*(1)), 138.0, 131.4 (2 × C_{Ar}), 128.4 (HC_{Ar}), 128.4 (q, ^{2}J 32.7, *C*(7)), 127.9 (H*C*(5)), 126.0 (C_{Ar}), 126.0 (q, ^{3}J 3.2, H*C*(6)), 125.5 (q, ^{3}J 4.8, H*C*(8)), 123.9 (q, ^{1}J 272.4, *C*F_3), 114.8 (H*C*(4)), 114.3 (HC_{Ar}), 55.4 (OCH_3); **^{19}F[^{1}H] NMR** (377 MHz, $CDCl_3$) δ_F: −62.5; **IR** ν_{max} (thin film)/cm^{-1} 2918w, 2848w, 1635m, 1602s, 1574m, 1516s, 1452s, 1443s, 1396w, 1333s, 1313s, 1292m, 1273s, 1250s, 1217m, 1186s, 1174s, 1157s, 1121s, 1064s, 1038s, 1022m, 951w, 900m, 881s, 837s; **m/z** (ESI$^+$) 304.1 [100, $(M + H)^+$], $C_{17}H_{13}F_3NO$ predicted 304.0944, found 304.0945, (Δ − 0.5 ppm); **m.p.** 169-171 °C (Petrol/CH_2Cl_2).

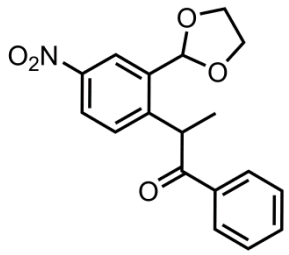
2-(2-Bromo-5-nitrophenyl)-1,3-dioxolane **324**



2-Bromo-5-nitrobenzaldehyde (978 mg, 4.25 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *acetal* **324** (1.10 g, 4.00 mmol, 94%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.44 (1H, d, *J* 2.8, *H*C$_{Ar}$), 8.08 (1H, dd, *J* 8.6, 2.8, *H*C$_{Ar}$), 7.76 (1H, d, *J* 8.9, *H*C$_{Ar}$), 6.10 (1H, s, C*H*(OR)$_2$), 4.24-4.16 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 4.16-4.08 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 147.3, 139.0, (2 × *C*$_{Ar}$), 134.1 (H*C*$_{Ar}$), 130.1 (*C*$_{Ar}$), 125.0, 123.0 (2 × H*C*$_{Ar}$), 101.5 (*C*H(OR)$_2$), 65.7 (*C*H$_2$OR); **m.p.** 95-96 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[281]

2-(2-(1,3-Dioxolan-2-yl)-4-nitrophenyl)-1-phenylpropan-1-one **325**

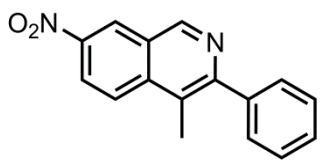


Acetal **324** (65.3 mg, 0.238 mmol) was subjected to a modification of General Procedure 7 with $PdCl_2(Amphos)_2$ (8.4 mg, 0.012 mmol), Cs_2CO_3 (194 mg, 0.595 mmol) and propiophenone (63.9 mg, 0.477 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *ketone* **325** (68.0 mg, 0.208 mmol, 87%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.49 (1H, d, *J* 2.3, *H*C$_{Ar}$), 8.10 (1H, dd, *J* 8.6, 2.5, *H*C$_{Ar}$), 8.00 (2H, d, *J* 7.7, 2 × *H*C$_{Ar}$), 7.50 (1H, t, *J* 7.3, *H*C$_{Ar}$), 7.39 (2H, t, *J* 7.6, 2 × *H*C$_{Ar}$), 7.32 (1H, d, *J* 8.6, *H*C$_{Ar}$), 6.17 (1H, s, C*H*(OR)$_2$), 5.21 (1H, q, *J* 6.8, C*H*CH$_3$), 4.25-4.11 (4H, m, 2 × C*H*$_2$), 1.56 (3H, d, *J* 6.9, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 199.6 (*C*=O), 147.6, 146.7, 136.4, 135.9 (4 × *C*$_{Ar}$), 133.2, 129.0, 128.8, 128.7, 124.4, 122.4 (6 × H*C*$_{Ar}$), 100.9 (*C*H(OR)$_2$), 65.5, 65.4 (2 × *C*H$_2$OR), 43.5 (*C*HCH$_3$), 19.0 (CH*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2894w, 1683s, 1614w, 1592m, 1564w, 1523s, 1485w, 1449m, 1346s, 1221s, 1177w, 1104s, 1072m, 1054m, 1026m, 1000m, 967m, 950m, 907s, 845w; **m/z** (ESI$^+$) 350.1 [85,

$(M + Na)^+$], 677.2 [100, $(2M + Na)^+$], $C_{18}H_{17}NNaO_5$ predicted 350.0999, found 350.0986, (Δ + 3.8 ppm).

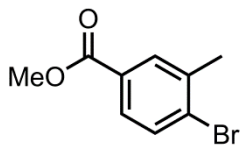
4-Methyl-7-nitro-3-phenylisoquinoline **326**



Ketone **325** (49.7 mg, 0.152 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *isoquinoline* **326** (30.5 mg, 0.116 mmol, 76%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.39 (1H, s, *H*C(1)), 8.95 (1H, d, *J* 2.3, *H*C(8)), 8.52 (1H, dd, *J* 9.5, 2.3, *H*C(6)), 8.22 (1H, d, *J* 9.1, *H*C(5)), 7.63-7.60 (2H, m, 2 × HC_{Ar}), 7.52 (2H, t, *J* 6.8, 2 × HC_{Ar}), 7.48 (1H, tt, *J* 7.0, 2.6, HC_{Ar}), 2.73 (3H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 155.5 (*C*(3)), 151.6 (H*C*(1)), 145.7, 140.2, 138.9 (*C*(7) + 2 × C_{Ar}), 129.8, 128.3, 128.3 (3 × HC_{Ar}), 125.9 (*C*(4)), 125.8 (H*C*(5)), 124.7 (H*C*(8)), 124.5 (C_{Ar}), 123.6 (H*C*(6)), 15.8 (CH_3); **IR** ν_{max} (thin film)/cm^{-1} 3030w, 1620s, 1588w, 1524s, 1486m, 1448w, 1384w, 1346s, 1248w, 1106w, 1091w, 1007m, 934m, 851w, 820w; **m/z** (ESI^+) 265.1 [80, $(M + H)^+$], 287.1 [100, $(M + Na)^+$], 551.2 [30, $(2M + Na)^+$], $C_{16}H_{13}N_2O_2$ predicted 265.0972, found 265.0970, (Δ + 0.7 ppm); **m.p.** 180-182 °C (Petrol/CH_2Cl_2).

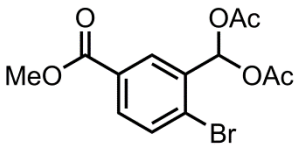
Methyl 4-bromo-3-methylbenzoate **328**



4-Bromo-3-methyl-benzoic acid (2.50 g, 11.6 mmol) and concentrated aqueous H_2SO_4 (2.0 mL) were added to MeOH (15 mL) at room temperature and the reaction heated at reflux for 18 h. The reaction was cooled to room temperature, the solvent was removed *in vacuo* and then the residue was taken up in EtOAc (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 and passed through a plug of silica to furnish *ester* **328** (2.54 g, 11.1 mmol, 95%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.89 (1H, d, *J* 1.7, *H*C_{Ar}), 7.69 (1H, dd, *J* 8.3, 2.0, *H*C_{Ar}), 7.59 (1H, d, *J* 8.3, *H*C_{Ar}), 3.90 (3H, s, OC*H*$_3$), 2.43 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 166.6 (*C*=O), 138.2 (*C*$_{Ar}$), 132.5, 131.7 (2 × H*C*$_{Ar}$), 130.4, 129.2 (2 × *C*$_{Ar}$), 128.3 (H*C*$_{Ar}$), 52.2 (O*C*H$_3$), 22.9 (*C*H$_3$); **m.p.** 38-39 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[282]

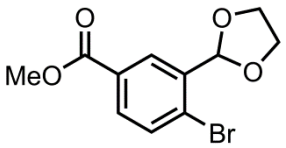
(2-Bromo-5-(methoxycarbonyl)phenyl)methylene diacetate **329**



Chromium trioxide (3.35 g, 33.5 mmol) was added portionwise over 30 min to a solution of ester **328** (2.40 g, 11.2 mmol), concentrated aqueous H_2SO_4 (2.0 mL) and acetic anhydride (14.7 g, 144 mmol) in AcOH (14 mL) at 0 °C. The reaction was warmed to room temperature and stirred for another 4 h. The mixture was poured on to iced H_2O (150 mL), stirred for 30 min and then filtered. The precipitate was taken up in EtOAc (150 mL), washed with H_2O (5 × 50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to furnish *diacetate* **329** (1.94 g, 5.61 mmol, 50%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.21 (1H, d, *J* 2.1, *H*C_{Ar}), 7.92 (1H, s, C*H*(OAc)$_2$), 7.91 (1H, dd, *J* 8.5, 2.0, *H*C_{Ar}), 7.68 (1H, d, *J* 8.4, *H*C_{Ar}), 3.94 (3H, s, OC*H*$_3$), 2.16 (6H, s, 2 × C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 168.4, 165.8 (2 × *C*=O), 135.5 (*C*$_{Ar}$), 133.5, 131.7 (2 × H*C*$_{Ar}$), 129.8 (*C*$_{Ar}$), 129.1 (H*C*$_{Ar}$), 127.8 (*C*$_{Ar}$), 88.6 (*C*H(OAc)$_2$), 52.5 (OC*H*$_3$), 20.7 (C*H*$_3$); **m.p.** 45-47 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[282]

Methyl 4-bromo-3-(1,3-dioxolan-2-yl)benzoate **330**

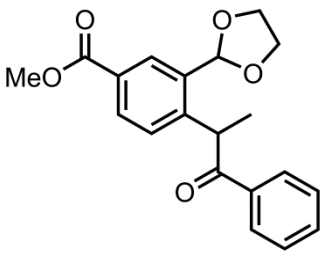


Diacetate **329** (1.78 g, 5.16 mmol) and concentrated aqueous H_2SO_4 (0.20 mL) in a solution of MeOH/H_2O (16 mL, 1:1) were heated at reflux for 1 h. The reaction mixture was diluted with H_2O

(50 mL) and then extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was then subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 14:1] to furnish *acetal* **330** (1.01 g, 3.52 mmol, 68%) as rods.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.23 (1H, d, *J* 2.3, *H*C_{Ar}), 7.87 (1H, dd, *J* 8.3, 2.3, *H*C_{Ar}), 7.64 (1H, d, *J* 8.3, *H*C_{Ar}), 6.10 (1H, s, C*H*$(OR)_2$), 4.20-4.13 (2H, m, C$H_a$$H_bCH_a$$H_b$), 4.12-4.05 (2H, m, C$H_a$$H_bCH_a$$H_b$), 3.91 (3H, s, OC$H_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 166.1 (*C*=O), 137.3 (C_{Ar}), 133.3, 131.3 (2 × HC_{Ar}), 129.5 (C_{Ar}), 129.0 (HC_{Ar}), 128.3 (C_{Ar}), 102.1 (*C*H$(OR)_2$), 65.6 (*C*H_2OR), 52.3 (O*C*H_3); **IR** ν_{max} (thin film)/cm^{-1} 2953w, 2890w, 1720s, 1436m, 1395w, 1292s, 1239s, 1203s, 1107s, 1086s, 1026s, 989m, 943m, 927m, 808w; **m/z** (ESI^+) 309.0 [100, $(M + Na)^+$], 595.0 [30, $(2M + Na)^+$], $C_{11}H_{11}{}^{79}BrNaO_4$ predicted 308.9733, found 308.9729, (Δ + 1.2 ppm); **m.p.** 69-71 °C (Petrol/CH_2Cl_2).

Methyl 3-(1,3-dioxolan-2-yl)-4-(1-oxo-1-phenylpropan-2-yl)benzoate **331**

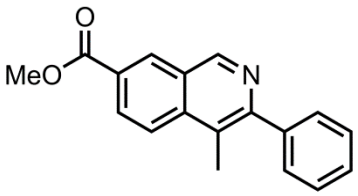


Acetal **330** (104 mg, 0.362 mmol) was subjected to a modification of General Procedure 7 with $PdCl_2(Amphos)_2$ (12.8 mg, 0.0181 mmol), K_3PO_4 (192 mg, 0.905 mmol) and propiophenone (58.2 mg, 0.434 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 4:1] to furnish *ketone* **331** (86.4 mg, 0.254 mmol, 70%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.27 (1H, d, *J* 1.8, *H*C_{Ar}), 8.02-7.99 (2H, m, 2 × *H*C_{Ar}), 7.90 (1H, dd, *J* 8.1, 2.1, *H*C_{Ar}), 7.45 (1H, tt, *J* 7.4, 1.3, *H*C_{Ar}), 7.35 (2H, tt, *J* 7.8, 1.5, 2 × *H*C_{Ar}), 7.17 (1H, d, *J* 8.1, *H*C_{Ar}), 6.14 (1H, s, C*H*$(OR)_2$), 5.15 (1H, q, *J* 6.8, C*H*CH_3), 4.24-4.17 (2H, m, C$H_a$$H_bCH_a$$H_b$), 4.16-4.09 (2H, m, C$H_a$$H_bCH_a$$H_b$), 3.87 (3H, s, OC$H_3$), 1.54 (3H, d, *J* 6.9, CHCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 200.3 (*C*=O), 166.6

(CO_2CH_3), 145.7, 136.2, 134.4 (3 × C_{Ar}), 132.8, 130.8, 128.9 (3 × HC_{Ar}), 128.7 (2 signals) (HC_{Ar} + C_{Ar}), 128.5, 128.0 (2 × HC_{Ar}), 102.0 ($CH(OR)_2$), 65.4, 65.2 (2 × CH_2OR), 52.1 (OCH_3), 43.8 ($CHCH_3$), 19.0 ($CHCH_3$); **IR** ν_{max} (thin film)/cm^{-1} 2892w, 1720s, 1683s, 1613w, 1437m, 1292s, 1211s, 1112s, 1074m, 1056m, 1000m, 967m, 950m; **m/z** (ESI^+) 363.1 [100, $(M + Na)^+$], 703.2 [90, $(2M + Na)^+$], $C_{20}H_{20}NaO_5$ predicted 363.1203, found 363.1210, (Δ − 1.9 ppm).

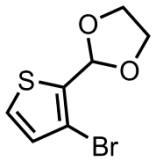
Methyl 4-methyl-3-phenylisoquinoline-7-carboxylate **332**



Ketone **331** (45.3 mg, 0.133 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *isoquinoline* **332** (31.7 mg, 0.114 mmol, 86%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.30 (1H, s, *H*C(1)), 8.76 (1H, s, *H*C(8)), 8.34 (1H, dd, *J* 8.9, 1.5, *H*C(6)), 8.11 (1H, d, *J* 8.9, *H*C(5)), 7.61 (2H, d, *J* 7.1, 2 × HC_{Ar}), 7.51 (2H, t, *J* 7.6, 2 × HC_{Ar}), 7.44 (1H, t, *J* 7.2, HC_{Ar}), 4.03 (3H, s, OCH_3), 2.69 (3H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 166.5 (*C*=O), 154.0 (*C*(3)), 151.3 (H*C*(1)), 140.8, 138.4 (2 × C_{Ar}), 131.1 (H*C*(8)), 129.8, 129.7 (H*C*(6) + HC_{Ar}), 128.2 (HC_{Ar}), 128.2 (C_{Ar}), 127.9 (HC_{Ar}), 126.5, 124.2 (*C*(4) + *C*(7)), 124.1 (H*C*(5)), 52.5 (OCH_3), 15.6 (CH_3); **IR** ν_{max} (thin film)/cm^{-1} 2999w, 2952w, 1720s, 1624m, 1572w, 1438m, 1379w, 1339w, 1295s, 1262s, 1203s, 1105m, 1007w, 992w, 973w, 940w, 839w, 806w; **m/z** (ESI^+) 278.1 [100, $(M + H)^+$], $C_{18}H_{16}NO_2$ predicted 278.1176, found 278.1179, (Δ − 1.2 ppm); **m.p.** 155-157 °C (Petrol/CH_2Cl_2).

2-(3-Bromothiophen-2-yl)-1,3-dioxolane **333**

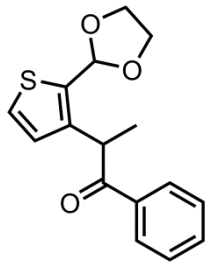


3-Bromothiophene-2-carboxaldehyde (867 mg, 4.53 mmol) was subjected to General Procedure 5. The crude product was purified by flash column

chromatography [Petrol/EtOAc 49:1 grading to 19:1] to furnish *acetal* **333** (1.02 g, 4.34 mmol, 96%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.31 (1H, d, *J* 4.5, *H*C(5)), 6.98 (1H, d, *J* 5.0, *H*C(4)), 6.14 (1H, s, C*H*$(OR)_2$), 4.20-4.12 (2H, m, C$H_a$$H_bCH_a$$H_b$), 4.07-3.99 (2H, m, C$H_a$$H_bCH_a$$H_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 136.0 (*C*(2)), 130.4 (H*C*(4)), 126.5 (H*C*(5)), 110.2 (*C*(3)), 99.5 (*C*H$(OR)_2$), 65.4 (*C*H_2OR). Data were consistent with those previously reported.[283]

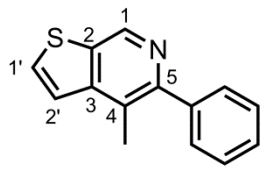
2-(2-(1,3-Dioxolan-2-yl)thiophen-3-yl)-1-phenylpropan-1-one **334**



Acetal **333** (118 mg, 0.500 mmol) was subjected to General Procedure 6 with propiophenone (80.5 mg, 0.600 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *ketone* **334** (114 mg, 0.396 mmol, 79%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.00 (2H, dd, *J* 7.4, 1.5, 2 × *H*C_{Ar}), 7.49 (1H, tt, *J* 7.4, 1.2, *H*C_{Ar}), 7.39 (2H, t, *J* 7.6, 2 × *H*C_{Ar}), 7.18 (1H, d, *J* 5.3, *H*C(5)), 6.85 (1H, d, *J* 5.0, *H*C(4)), 6.29 (1H, s, C*H*$(OR)_2$), 5.00 (1H, q, *J* 6.8, C*H*CH_3), 4.18-4.13 (2H, m, C$H_a$$H_bCH_a$$H_b$), 4.10-4.04 (2H, m, C$H_a$$H_bCH_a$$H_b$), 1.51 (3H, d, *J* 7.0, CHCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 200.2 (*C*=O), 139.8, 136.4, 135.2 (*C*$_{Ar}$ + *C*(2) + *C*(3)), 132.9, 128.7, 128.5 (3 × H*C*$_{Ar}$), 127.7 (H*C*(4)), 125.6 (H*C*(5)), 99.3 (*C*H$(OR)_2$), 65.3, 65.2 (2 × *C*H_2OR), 41.3 (*C*HCH_3), 18.7 (CH*C*H_3); **IR** ν_{max} (thin film)/cm^{-1} 2976w, 2933w, 2877w, 1682s, 1448w, 1426w, 1273w, 1218s, 1080m, 967s; **m/z** (ESI$^+$) 311.1 [100, $(M + Na)^+$], $C_{16}H_{16}NaO_3S$ predicted 311.0712, found 311.0724, (Δ − 3.6 ppm); **m.p.** 77-79 °C (Petrol/CH_2Cl_2).

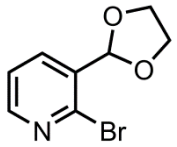
4-Methyl-5-phenylthieno[2,3-c]pyridine **335**



Ketone **334** (75.9 mg, 0.263 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *thienopyridine* **335** (43.5 mg, 0.193 mmol, 73%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.10 (1H, s, *H*C(1)), 7.75 (1H, d, *J* 5.5, *H*C(1')), 7.57 (2H, dd, *J* 7.1, 1.3, 2 × *H*C_{Ar}), 7.50-7.46 (3H, m, 2 × *H*C_{Ar} + *H*C(2')), 7.41 (1H, tt, *J* 7.4, 2.1, *H*C_{Ar}), 2.62 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 152.0 (*C*(5)), 146.0 (*C*$_{Ar}$), 141.6 (H*C*(1)), 140.6, 134.8 (2 × *C*$_{Ar}$), 131.8 (H*C*(1')), 129.6, 128.1, 127.6 (3 × H*C*$_{Ar}$), 124.6 (*C*(4)), 122.1 (H*C*(2')), 16.8 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 3058w, 2920w, 1567s, 1495m, 1445s, 1404s, 1380m, 1334m, 1253w, 1224s, 1152m, 1090w, 1073w, 1012s, 910w, 873w, 818m; **m/z** (ESI$^+$) 226.0 [95, $(M + H)^+$], 248.0 [100, $(M + Na)^+$], $C_{14}H_{12}NS$ predicted 226.0685, found 226.0688, (Δ − 1.2 ppm).

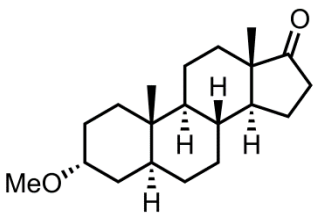
2-Bromo-3-(1,3-dioxolan-2-yl)pyridine **336**



2-Bromopyridine-3-carbaldehyde (1.02 g, 5.46 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *acetal* **336** (1.23 g, 5.35 mmol, 98%) as plates.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.37-8.35 (1H, m, *H*C(6)), 7.88 (1H, dd, *J* 7.6, 1.5, *H*C(4)), 7.29 (1H, dd, *J* 7.6, 5.4, *H*C(5)), 6.02 (1H, s, C*H*(OR)$_2$), 4.17-4.04 (4H, m, 2 × C*H*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 150.5 (*HC*(6)), 142.5 (*C*(2)), 136.4 (H*C*(4)), 134.2 (*C*(3)), 122.8 (H*C*(5)), 101.7 (*C*H(OR)$_2$), 65.6 (*C*H$_2$OR); **m.p.** 51-52 °C. Data were consistent with those previously reported.[284]

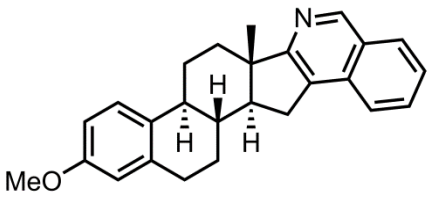
Androsterone-3-methyl ether **340**



Trimethyloxonium tetrafluoroborate (112 mg, 0.760 mmol) was added to a solution of androsterone (147 mg, 0.506 mmol) and *N*,*N*,*N*'*N*'-tetramethyl-1,8-naphthalenediamine (217 mg, 1.01 mmol) in CH_2Cl_2 (20 mL) at room temperature and the reaction was stirred for 18 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organics were dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product. Purification by flash column chromatography [Petrol/EtOAc 19:1] furnished *ketone* **340** (152 mg, 0.500 mmol, 99%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.44-3.42 (1H, m, C*H*OCH_3), 3.28 (3H, s, OC*H*$_3$), 2.42 (1H, dd, *J* 19.1, 8.8, C*H*$_a$H$_b$C=O), 2.05 (1H, dd, *J* 19.1, 8.8, CH$_a$*H*$_b$C=O), 1.95-1.88 (1H, m, unc.), 1.82-1.15 (17H, m, unc.), 1.00 (1H, ddd, *J* 17.2, 12.2, 4.9, unc.), 0.85 (3H, s, C*H*$_3$), 0.81-0.77 (1H, m, unc.), 0.80 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 221.6 (*C*=O), 75.4 (*C*HOCH_3), 55.7 (O*C*H$_3$), 54.3, 51.5 (2 × *C*H), 47.8 (*C*), 39.5 (*C*H), 36.0 (*C*), 35.9 (*C*H_2), 35.0 (*C*H), 32.8, 32.5, 31.6, 30.8, 28.3, 25.0, 21.7, 20.0 (8 × *C*H_2), 13.8, 11.4 (2 × *C*H_3); **m.p.** 120-122 °C (Petrol/CH_2Cl_2); **$[\alpha]_D^{20}$** + 88.8 (*c* 1.0, CH_2Cl_2). Data were consistent with those previously reported.[285]

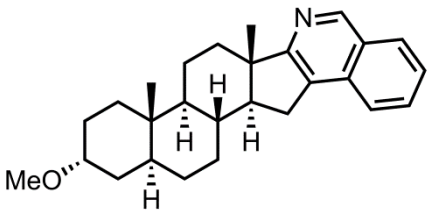
3-Methoxy-estra-1,3,5(10),16-tetraeno[17,16:3',4']isoquinoline **341**



Estrone-3-methyl ether (57.0 mg, 0.200 mmol) was subjected to a modification of General Procedure 13 with (D*t*BPF)$PdCl_2$ (6.5 mg, 0.010 mmol) and acetal **222** (68.7 mg, 0.300 mmol). The crude product was purifed by flash column chromatography [Petrol/EtOAc 24:1 grading to 9:1] to furnish *isoquinoline* **341** (46.4 mg, 0.126 mmol, 63%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.11 (1H, s, *H*C(1)), 7.98 (1H, d, *J* 8.1, *H*C(8)), 7.81 (1H, d, *J* 8.3, *H*C(5)), 7.70 (1H, ddd, *J* 8.1, 6.9, 1.1, *H*C(6)), 7.52 (1H, ddd, *J* 8.0, 6.9, 1.0, *H*C(7)), 7.29 (1H, d, *J* 8.6, *H*C_{Ar}), 6.77 (1H, dd, *J* 8.5, 2.7, *H*C_{Ar}), 6.70 (1H, d, *J* 2.5, *H*C_{Ar}), 3.81 (3H, s, OC*H*$_3$), 3.25 (1H, dd, *J* 14.6, 6.0, C*H*$_a$H$_b$C(4)), 3.08-2.93 (2H, m, C*H*$_2$$C_{Ar}$), 2.79 (1H, dd, *J* 14.1, 12.6, CH$_a$*H*$_b$C(4)), 2.57-2.51 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$CHC_{Ar}), 2.44 (1H, td, *J* 11.0, 4.2, C*H*C_{Ar}), 2.18-2.12 (1H, m, C*H*$_a$H$_b$CH$_2$$C_{Ar}$), 2.05 (1H, td, *J* 11.7, 6.4, C*H*CH$_2$C(4)), 1.95-1.75 (3H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$CHC_{Ar} + C*H*CHC_{Ar}), 1.60 (1H, dtd, *J* 18.6, 12.1, 6.7, CH$_a$*H*$_b$CH$_2$$C_{Ar}$), 1.07 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 166.0 (*C*(3)), 157.5 (*C*$_{Ar}$), 151.2 (H*C*(1)), 137.8, 134.0, 132.7 (3 × *C*$_{Ar}$), 130.1 (H*C*(6)), 129.6 (*C*(4)), 128.4 (H*C*(8)), 127.5 (*C*$_{Ar}$), 126.2 (H*C*$_{Ar}$), 125.7 (H*C*(7)), 123.2 (H*C*(5)), 113.9, 111.5 (2 × H*C*$_{Ar}$), 55.5 (*C*HCH$_2$C(4)), 55.2 (OC*H*$_3$), 46.3 (*C*), 44.6 (*C*HC$_{Ar}$), 37.6 (*C*HCHC$_{Ar}$), 34.1, 26.5 (*C*H$_2$*C*H$_2$CHC$_{Ar}$), 29.7 (*C*H$_2$C$_{Ar}$), 28.0 (*C*H$_2$C(4)), 27.6 (*C*H$_2$CH$_2$C$_{Ar}$), 17.8 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2927s, 2851m, 1736w, 1625m, 1610m, 1570m, 1500s, 1463m, 1369m, 1280m, 1256s, 1155w, 1103w, 1045m, 857w, 805m; **m/z** (ESI$^+$) 370.2 [100, (M + H)$^+$], $C_{26}H_{28}NO$ predicted 370.2165, found 370.2163, (Δ + 0.5 ppm); **m.p.** 219-221 °C (Petrol/CH_2Cl_2); **$[\alpha]_D^{20}$** + 34.8 (*c* 0.25, CH_2Cl_2).

3-Methoxy-(3β,5α)-estr-16-eno[17,16:3',4']isoqunoline **342**

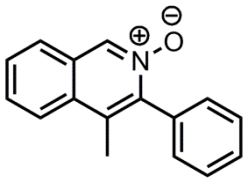


Ketone **340** (69.0 mg, 0.227 mmol) was subjected to a modification of General Procedure 13 with (D*t*BPF)$PdCl_2$ (7.4 mg, 0.011 mmol) and acetal **222** (77.9 mg, 0.340 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 9:1] to furnish *isoquinoline* **342** (52.0 mg, 0.133 mmol, 59%) as plates.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.06 (1H, s, *H*C(1)), 7.94 (1H, d, *J* 8.3, *H*C(8)), 7.75 (1H, d, *J* 8.3, *H*C(5)), 7.65 (1H, td, *J* 7.0, 1.1, *H*C(6)), 7.48 (1H, td, *J* 7.6, 0.9, *H*C(7)), 3.46-3.44 (1H, m, C*H*OCH$_3$), 3.30 (3H, s, OC*H*$_3$), 3.11 (1H, dd, *J* 15.1, 5.8, C*H*$_a$H$_b$C(4)), 2.63 (1H, dd, *J* 14.7, 11.4, CH$_a$*H*$_b$C(4)), 2.37-2.33 (1H, m, unc.), 1.92-1.76 (5H, m, unc.), 1.68-1.14 (11H,

m, unc.), 1.04-0.96 (1H, m, unc.), 1.02 (3H, s, CH_3), 0.90 (3H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 166.2 (*C*(3)), 151.0 (H*C*(1)), 133.9 (C_{Ar}), 130.0 (H*C*(6)), 129.7 (*C*(4)), 128.3 (H*C*(8)), 127.5 (C_{Ar}), 125.6 (H*C*(7)), 123.3 (H*C*(5)), 75.5 (*C*HOCH$_3$), 56.4 (*C*H), 55.7 (O*C*H$_3$), 55.1 (*C*H), 46.1 (*C*), 39.8 (*C*H), 36.3 (*C*), 34.4 (*C*H), 34.0, 32.9, 32.4, 31.7, 28.5 (5 × *C*H$_2$), 28.2 (*C*H$_2$C(4)), 25.1, 20.6 (2 × *C*H$_2$), 17.8, 11.5 (2 × *C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2924w, 2854w, 1626m, 1570m, 1445m, 1365m, 1259m, 1148w, 1089s, 1030m, 987w, 909s, 878w, 867w, 802s; **m/z** (ESI$^+$) 390.2 [100, (M + H)$^+$], $C_{27}H_{36}NO$ predicted 390.2791, found 390.2780, (Δ + 2.8 ppm); **m.p.** 178-180 °C (Petrol/CH_2Cl_2); **$[\alpha]_D^{20}$** + 7.90 (*c* 1.0, CH_2Cl_2).

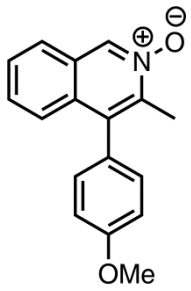
4-Methyl-3-phenylisoquinoline *N*-oxide **346**



Ketone **235** (50.6 mg, 0.179 mmol) was subjected to General Procedure 15. The crude product was purified by flash column chromatography [EtOAc/MeOH 99:1 grading to 19:1] to furnish isoquinoline *N*-oxide **346** (38.7 mg, 0.166 mmol, 93%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.86 (1H, s, *H*C(1)), 7.93 (1H, dd, *J* 5.0, 4.3, *H*C(8)), 7.74-7.72 (1H, m, *H*C(5)), 7.64-7.59 (2H, m, *H*C(6) + *H*C(7)), 7.54-7.45 (3H, m, 3 × *H*C$_{Ar}$), 7.39 (2H, d, *J* 7.3, 2 × *H*C$_{Ar}$), 2.42 (3H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 146.3 (*C*(3)), 135.0 (H*C*(1)), 133.0, 130.7 (2 × C_{Ar}), 130.0 (HC_{Ar}), 129.3 (C_{Ar}), 128.9, 128.8, 128.7 (H*C*(6) + H*C*(7) + HC_{Ar}), 128.6 (HC_{Ar}), 128.6 (*C*(4)), 125.3 (H*C*(5)), 124.0 (H*C*(8)), 16.1 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 1589w, 1495w, 1468w, 1425m, 1373w, 1314s, 1219m, 1182s, 1127s, 1034w, 1017m, 896w; **m/z** (ESI$^+$) 236.1 [70, (M + H)$^+$], 258.1 [80, (M + Na)$^+$], 493.1 [100, (2M + Na)$^+$], $C_{16}H_{13}NNaO$ predicted 258.0889, found 258.0893, (Δ − 1.6 ppm); **m.p.** 181-184 °C (MeOH/EtOAc).

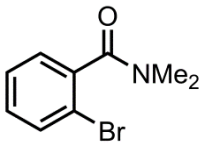
4-(4-Methoxyphenyl)-3-methylisoquinoline *N*-oxide **347**



Ketone **286** (48.7 mg, 0.156 mmol) was subjected to General Procedure 15. The crude product was purified by flash column chromatography [CH_2Cl_2/MeOH 99:1 grading to 39:1] to furnish *isoquinoline N-oxide* **347** (37.7 mg, 0.142 mmol, 91%) as prisms.

^{1}H NMR (400 MHz, CD_2Cl_2) δ_H: 8.88 (1H, s, *H*C(1)), 7.75 (1H, d, *J* 7.6, *H*C(8)), 7.55 (1H, t, *J* 7.5, *H*C(7)), 7.45 (1H, t, *J* 7.6, *H*C(6)), 7.35 (1H, d, *J* 8.6, *H*C(5)), 7.24 (2H, d, *J* 8.6, 2 × *H*C_{Ar}), 7.10 (2H, d, *J* 8.6, 2 × *H*C_{Ar}), 3.92 (3H, s, OC*H*$_3$), 2.40 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ_C: 160.0 (*C*$_{Ar}$), 145.1 (*C*(3)), 135.7 (*C*(4)), 135.4 (H*C*(1)), 131.1 (H*C*$_{Ar}$), 129.7, 128.6 (2 × *C*$_{Ar}$), 128.6, 128.4 (H*C*(6) + H*C*(7)), 128.3 (*C*$_{Ar}$), 126.0 (H*C*(5)), 124.8 (H*C*(8)), 114.6 (H*C*$_{Ar}$), 55.8 (O*C*H$_3$), 15.7 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2992w, 2955w, 2930w, 2832w, 1607m, 1593m, 1513s, 1490m, 1462m, 1423m, 1384m, 1315s, 1288s, 1243s, 1203m, 1164s, 1146s, 1107s, 1029m, 1002m, 970w, 943w, 894s, 872m, 850s; **m/z** (ESI$^+$) 266.2 [60, (M + H)$^+$], 288.1 [100, (M + Na)$^+$], $C_{17}H_{16}NO_2$ predicted 266.1176, found 266.1166, (Δ + 3.5 ppm); **m.p.** 237-238 °C (MeOH/EtOAc).

2-Bromo-*N*,*N*-dimethylbenzamide **364**

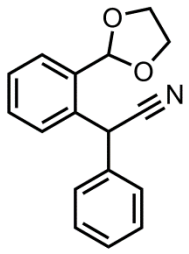


NaH (440 mg, 11.0 mmol, 60% dispersion in mineral oil) was added portionwise to a solution of 2-bromobenzamide (1.00 g, 5.00 mmol) in DMF (5.0 mL) at 0 °C and the resulting mixture stirred for 10 min. Iodomethane (2.13 g, 15.0 mmol) was added dropwise and then the reaction warmed to room temperature and stirred for a further 16 h. The reaction was quenched by the addition of H_2O (50 mL) and then extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give the crude product. Purification by flash column

chromatography [Petrol/EtOAc 9:1] furnished *benzamide* **364** (999 mg, 4.38 mmol, 88%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.55 (1H, d, *J* 8.0, *H*C_{Ar}), 7.34 (1H, td, *J* 7.6, 1.1, *H*C_{Ar}), 7.27-7.19 (2H, m, 2 × *H*C_{Ar}), 3.12 (3H, s, C*H*$_3$), 2.84 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 169.2 (*C*=O), 138.5 (C_{Ar}), 132.7, 130.1, 127.7, 127.7 (4 × HC_{Ar}), 119.1 (C_{Ar}), 38.2, 34.6 (2 × *C*H$_3$). Data were consistent with those previously reported.[218]

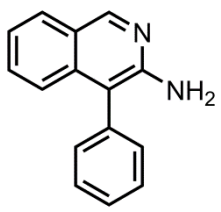
2-(2-(1,3-Dioxolan-2-yl)phenyl)-2-phenylacetonitrile **373**



Acetal **222** (82.2 mg, 0.359 mmol) was subjected to General Procedure 16 with 2-phenylacetonitrile (84.1 mg, 0.718 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 39:1 grading to 9:1] to furnish *nitrile* **373** (65.6 mg, 0.247 mmol, 69%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.62 (1H, d, *J* 7.7, *H*C_{Ar}), 7.45 (1H, d, *J* 8.2, *H*C_{Ar}), 7.42-7.32 (7H, m, 7 × *H*C_{Ar}), 5.95 (1H, s, C*H*C≡N), 5.90 (1H, s, C*H*$(OR)_2$), 4.16-4.03 (4H, m, 2 × C*H*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 135.8, 134.9, 134.7 (3 × C_{Ar}), 130.0, 129.7, 129.1, 128.3, 128.1, 127.9, 127.6 (7 × HC_{Ar}), 120.0 (*C*≡N), 102.3 (*C*H$(OR)_2$), 65.2, 65.1 (2 × *C*H$_2$OR), 37.8 (*C*HC≡N); **IR** ν_{max} (thin film)/cm^{-1} 2892w, 2244m, 1601w, 1494m, 1452m, 1406m, 1217m, 1112s, 1075s, 1043s, 970s, 943s, 894w; **m/z** (ESI$^+$) 288.1 [100, $(M + Na)^+$], 553.2 [50, $(2M + Na)^+$], $C_{17}H_{15}NNaO_2$ predicted 288.0995, found 288.0992, (Δ + 1.0 ppm).

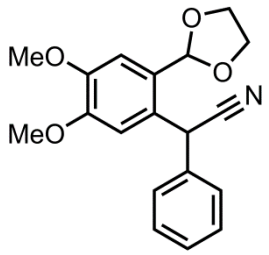
4-Phenylisoquinolin-3-amine **374**



Nitrile **373** (52.6 mg, 0.198 mmol) was subjected to General Procedure 11. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 2:1] to furnish isoquinoline **374** (32.1 mg, 0.146 mmol, 73%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.91 (1H, s, *H*C(1)), 7.83 (1H, d, *J* 8.1, *H*C(8)), 7.56 (2H, t, *J* 7.3, 2 × *H*C_{Ar}), 7.47 (1H, t, *J* 7.5, *H*C_{Ar}), 7.42-7.40 (3H, m, 2 × *H*C_{Ar} + *H*C(5)), 7.29 (1H, d, *J* 9.7, *H*C(6)), 7.25 (1H, d, *J* 7.1, *H*C(7)), 4.42 (2H, br. s, N*H*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 151.7 (*C*(3)), 151.2 (H*C*(1)), 137.3, 135.7 (2 × *C*$_{Ar}$), 130.6 (H*C*$_{Ar}$), 130.5 (H*C*(5)), 129.4 (H*C*$_{Ar}$), 127.9 (H*C*(8)), 127.9 (H*C*$_{Ar}$), 123.8 (*C*$_{Ar}$), 123.0, 122.7 (H*C*(6) + H*C*(7)), 111.6 (*C*(4)); **m.p.** 145-147 °C (CH_2Cl_2/EtOAc). Data were consistent with those previously reported.[221]

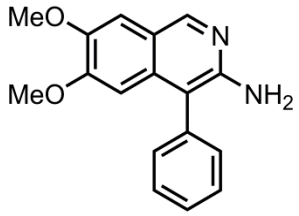
2-(2-(1,3-Dioxolan-2-yl)-4,5-dimethoxyphenyl)-2-phenylacetonitrile **375**



Acetal **299** (87.8 mg, 0.304 mmol) was subjected to General Procedure 16 with 2-phenylacetonitrile (71.2 mg, 0.607 mmol). The crude product was purified by flash column chromatography [Petrol/Et_2O 19:1 grading to 1:1] to furnish *nitrile* **375** (58.2 mg, 0.179 mmol, 59%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.37-7.36 (4H, m, 4 × *H*C_{Ar}), 7.34-7.31 (1H, m, *H*C_{Ar}), 7.11 (1H, s, *H*C_{Ar}), 6.84 (1H, s, *H*C_{Ar}), 5.82 (1H, s, C*H*$(OR)_2$), 5.82 (1H, s, C*H*C≡N), 4.17-4.02 (4H, m, 2 × C*H*$_2$), 3.91 (3H, s, OC*H*$_3$), 3.81 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 149.9, 148.6, 135.9 (3 × *C*$_{Ar}$), 129.0, 128.0, 127.6 (3 × H*C*$_{Ar}$), 127.4, 126.7 (2 × *C*$_{Ar}$), 120.0 (*C*≡N), 112.2, 110.1 (2 × H*C*$_{Ar}$), 101.8 (*C*H$(OR)_2$), 65.1, 65.0 (2 × *C*H_2OR), 56.0, 56.0 (2 × OC*H*$_3$) 37.4 (*C*HC≡N); **IR** ν_{max} (thin film)/cm^{-1} 2960w, 2893w, 2243w, 1609w, 1518s, 1494w, 1453m, 1402w, 1351w, 1290m, 1268s, 1201m, 1180m, 1114s, 1066s, 1030m, 1003s, 959m, 940m, 913m, 868m; **m/z** (ESI$^+$) 326.1 [40, $(M + H)^+$], 348.1 [70, $(M + Na)^+$], 673.2 [100, $(2M + Na)^+$], $C_{19}H_{19}NNaO_4$ predicted 348.1206, found 348.1203, (Δ + 0.9 ppm); **m.p.** 57-59 °C (Petrol/CH_2Cl_2).

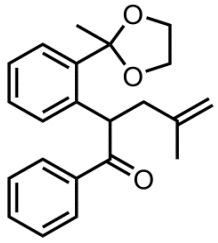
6,7-Dimethoxy-4-phenylisoquinolin-3-amine **376**



Nitrile **375** (40.6 mg, 0.125 mmol) was subjected to General Procedure 11. The crude product was purified by flash column chromatography [Petrol/EtOAc 4:1 grading to EtOAc/MeOH 39:1] to furnish *isoquinoline* **376** (29.5 mg, 0.105 mmol, 84%) as an oil.

^{1}H NMR (400 MHz, CD_3OD) δ_H: 8.59 (1H, s, *H*C(1)), 7.58 (2H, t, *J* 7.5, 2 × *H*C_{Ar}), 7.48 (1H, t, *J* 7.1, *H*C_{Ar}), 7.37 (2H, d, *J* 7.3, 2 × *H*C_{Ar}), 7.23 (1H, s, *H*C(8)), 6.49 (1H, s, *H*C(5)), 3.91 (3H, s, OCH_3), 3.65 (3H, s, OCH_3); **^{13}C NMR** (100 MHz, CD_3OD) δ_C: 154.3, 151.2, 148.0 (*C*(3) + *C*(6) + *C*(7)), 147.5 (H*C*(1)), 136.2, 134.9 (2 × C_{Ar}), 130.6, 129.6, 128.1 (3 × HC_{Ar}), 119.9, 112.3 (2 × C_{Ar}), 105.9 (H*C*(8)), 101.2 (H*C*(5)), 55.3, 54.9 (2 × OCH_3); **IR** ν_{max} (thin film)/cm^{-1} 3476m, 3375w, 3176m, 3001s, 2934w, 2830w, 2360w, 1627m, 1598m, 1579m, 1495s, 1452m, 1425s, 1401w, 1354w, 1246s, 1197w, 1160s, 1092w, 1031w, 1011w, 927w, 844w; **m/z** (ESI^+) 281.2 [100, $(M + H)^+$], 303.1 [50, $(M + Na)^+$], $C_{17}H_{17}N_2O_2$ predicted 281.1285, found 281.1292, (Δ − 2.7 ppm).

4-Methyl-2-(2-(2-methyl-1,3-dioxolan-2-yl)phenyl)-1-phenylpent-4-en-1-one **380**

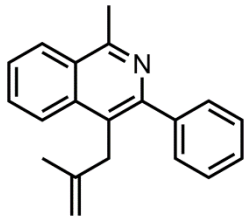


Ketone **248** (50.2 mg, 0.178 mmol) was subjected to General Procedure 17 with 3-bromo-2-methylpropene (28.8 mg, 0.214 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 19:1] to furnish *ketone* **380** (44.7 mg, 0.133 mmol, 75%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.10-8.07 (2H, m, 2 × *H*C_{Ar}), 7.61 (1H, dd, *J* 7.8, 1.5, *H*C_{Ar}), 7.45-7.39 (2H, m, 2 × *H*C_{Ar}), 7.35 (2H, tt, *J* 7.1, 1.4, 2 × *H*C_{Ar}), 7.20 (1H, td, *J* 7.5, 1.6, *H*C_{Ar}), 7.13 (1H, td, *J* 7.5, 1.3, *H*C_{Ar}), 5.70 (1H, dd, *J* 8.5, 5.5, C*H*), 4.67-4.65 (2H, m, R_2C=CH_2), 3.95 (1H, td, *J* 7.1, 6.4, C$H_a$$H_bCH_a$$H_b$), 3.80 (1H, td, *J* 7.3, 5.8, C$H_a$$H_bCH_a$$H_b$), 3.69 (1H, td, *J* 7.4, 6.1, C$H_a$$H_bCH_a$$H_b$), 3.40 (1H, td, *J* 7.5, 6.2, C$H_a$$H_bCH_a$$H_b$), 2.91 (1H, dd,

J 15.2, 8.6, C*H*$_a$H$_b$), 2.35 (1H, dd, *J* 15.0, 5.5, CH$_a$*H*$_b$), 1.69 (3H, s, CH$_2$=CC*H*$_3$), 1.66 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 201.4 (*C*=O), 143.4 (*C*$_{Ar}$), 140.2 (*C*R$_2$=CH$_2$), 137.7, 136.3 (2 × *C*$_{Ar}$), 132.5, 129.6, 128.8, 128.3, 128.3, 126.8, 126.6 (7 × H*C*$_{Ar}$), 112.0 (R$_2$C=*C*H$_2$), 109.3 (*C*(OR)$_2$), 64.3, 64.1 (2 × *C*H$_2$OR), 46.9 (*C*H), 42.1 (*C*H$_2$), 27.9 (*C*H$_3$), 23.2 (*C*H$_3$C=CH$_2$); **IR** ν_{max} (thin film)/cm^{-1} 3069w, 2967m, 2891m, 1682s, 1597w, 1580w, 1479w, 1447m, 1374m, 1233s, 1191s, 1104w, 1038s, 913m, 870m; **m/z** (ESI$^+$) 337.2 [95, (M + H)$^+$], 359.2 [100, (M + Na)$^+$], $C_{22}H_{24}NaO_3$ predicted 359.1618, found 359.1603, (Δ + 4.1 ppm).

1-Methyl-4-(2-methylallyl)-3-phenylisoquinoline **381**



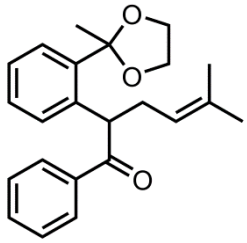
Method A: Ketone **380** (29.4 mg, 0.0874 mmol) was subjected to General Procedure 11. The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 19:1] to furnish *isoquinoline* **381** (23.0 mg, 0.0841 mmol, 96%) as an oil.

Method B: Acetal **242** (74.3 mg, 0.306 mmol) was subjected to General Procedure 18 with acetophenone (44.1 mg, 0.367 mmol) and 3-bromo-2-methylpropene (49.5 mg, 0.367 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 19:1] to furnish *isoquinoline* **381** (34.0 mg, 0.172 mmol, 56%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.18 (1H, d, *J* 8.6, *H*C(8)), 7.93 (1H, d, *J* 8.3, *H*C(5)), 7.70 (1H, ddd, *J* 8.3, 6.9, 1.2, *H*C(6)), 7.65-7.62 (2H, m, 2 × *H*C$_{Ar}$), 7.60 (1H, ddd, *J* 8.1, 6.9, 1.0, *H*C(7)), 7.45 (2H, tt, *J* 7.2, 1.5, 2 × *H*C$_{Ar}$), 7.40 (1H, tt, *J* 7.3, 1.6, *H*C$_{Ar}$), 4.90 (1H, m, CR$_2$=C*H*$_a$H$_b$), 4.36 (1H, m, CR$_2$=CH$_a$*H*$_b$), 3.63 (2H, s, C*H*$_2$), 3.02 (3H, s, C*H*$_3$), 1.86 (3H, s, C*H*$_3$C=CH$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 156.8 (*C*(1)), 151.4 (*C*(3)), 145.1 (*C*R$_2$=CH$_2$), 141.4, 136.2 (2 × *C*$_{Ar}$), 129.8 (H*C*(6)), 129.1, 128.1, 127.6 (3 × H*C*$_{Ar}$), 126.5 (H*C*(7)), 126.3 (*C*$_{Ar}$), 126.0 (H*C*(8)), 125.2 (H*C*(5)), 124.0 (*C*(4)), 112.5 (*C*H$_2$=CR$_2$), 37.3 (*C*H$_2$), 23.6 (*C*H$_3$), 22.6 (*C*H$_3$C=CH$_2$); **IR** ν_{max} (thin film)/cm^{-1} 3073m, 2923m, 1651w,

1615w, 1563s, 1504m, 1443s, 1392m, 1336m, 1030m, 892m; **m/z** (ESI^+) 274.2 [100, $(M + H)^+$], $C_{20}H_{20}N$ predicted 274.1590, found 274.1583, (Δ + 2.5 ppm).

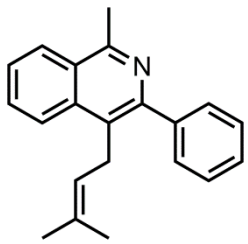
5-Methyl-2-(2-(2-methyl-1,3-dioxolan-2-yl)phenyl)-1-phenylhex-4-en-1-one **383**



Ketone **242** (53.7 mg, 0.190 mmol) was subjected to General Procedure 17 with 1-bromo-3-methyl-2-butene (33.9 mg, 0.228 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 19:1] to furnish *ketone* **383** (52.3 mg, 0.149 mmol, 79%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.06 (2H, dt, *J* 7.0, 1.7, 2 × *H*C_{Ar}), 7.60 (1H, dd, *J* 7.8, 1.5, *H*C_{Ar}), 7.56 (1H, dd, *J* 7.9, 1.1, *H*C_{Ar}), 7.52 (1H, dt, *J* 7.4, 1.5, *H*C_{Ar}), 7.44 (2H, tt, *J* 7.6, 1.4, 2 × *H*C_{Ar}), 7.33 (1H, td, *J* 7.6, 1.4, *H*C_{Ar}), 7.23 (1H, td, *J* 7.6, 1.2, *H*C_{Ar}), 5.55 (1H, t, *J* 7.5, C*H*), 5.11-5.07 (1H, m, *H*C=CR_2), 3.99 (1H, q, *J* 7.8, C*H*$_a$H$_b$CH$_a$H$_b$), 3.83-3.78 (1H, m, CH$_a$H$_b$C*H*$_a$H$_b$), 3.76-3.71 (1H, m, CH$_a$*H*$_b$CH$_a$H$_b$), 3.41 (1H, td, *J* 7.2, 6.1, CH$_a$H$_b$CH$_a$*H*$_b$), 2.89 (1H, dt, *J* 14.6, 7.4, C*H*$_a$H$_b$), 2.49 (1H, dt, *J* 14.7, 7.1, CH$_a$*H*$_b$), 1.73 (3H, s, C*H*$_3$), 1.63 (3H, d, *J* 0.8, CHR=CC$_a$*H*$_3$), 1.61 (3H, d, *J* 0.8, CHR=CC$_b$*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 201.9 (*C*=O), 140.4, 137.8, 136.7 (3 × *C*$_{Ar}$), 133.3 (*C*R_2=CHR), 132.5, 130.0, 128.8, 128.3, 128.2, 126.6, 126.3 (7 × H*C*$_{Ar}$), 122.0 (R_2C=*C*HR), 109.2 (*C*(OR)$_2$), 64.2, 63.9 (2 × *C*H_2OR), 48.6 (*C*H), 33.3 (*C*H_2), 28.0 (*C*H_3), 25.7, 17.9 (2 × *C*H_3C=CHR); **IR** ν_{max} (thin film)/cm^{-1} 3063w, 2968m, 2930m, 2361w, 1682s, 1597w, 1580w, 1480w, 1446m, 1375m, 1239m, 1191s, 1104w, 1037s, 950w, 869m; **m/z** (ESI^+) 351.2 [30, $(M + H)^+$], 373.2 [100, $(M + Na)^+$], $C_{23}H_{26}NaO_3$ predicted 373.1774, found 373.1767, (Δ + 1.8 ppm).

1-Methyl-4-(3-methylbut-2-enyl)-3-phenylisoquinoline **384**

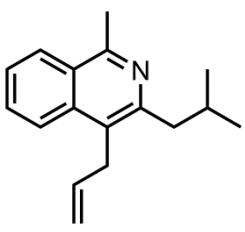


Method A: Ketone **383** (38.2 mg, 0.109 mmol) was subjected to General Procedure 11. The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 19:1] to furnish *isoquinoline* **384** (26.2 mg, 0.0912 mmol, 84%) as an oil.

Method B: Acetal **242** (68.7 mg, 0.283 mmol) was subjected to General Procedure 18 with acetophenone (40.7 mg, 0.339 mmol) and 1-bromo-3-methyl-2-butene (50.5 mg, 0.339 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 49:1 grading to 19:1] to furnish *isoquinoline* **384** (36.4 mg, 0.172 mmol, 61%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.19 (1H, d, *J* 8.3, *H*C(8)), 8.04 (1H, d, *J* 8.3, *H*C(5)), 7.74 (1H, ddd, *J* 8.3, 7.0, 1.4, *H*C(6)), 7.63-7.53 (3H, m, *H*C(7) + 2 × HC_{Ar}), 7.47 (2H, tt, *J* 7.3, 1.6, 2 × HC_{Ar}), 7.39 (1H, tt, *J* 7.2, 1.7, HC_{Ar}), 5.31-5.28 (1H, m, C*H*=CR_2), 3.69 (2H, d, *J* 6.1, CH_2), 3.00 (3H, s, CH_3), 1.72 (3H, d, *J* 0.9, CHR=CC_aH_3), 1.64 (3H, d, *J* 0.9, CHR=CC_bH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 156.2 (*C*(1)), 150.8 (*C*(3)), 141.6, 135.8 (2 × C_{Ar}), 132.1 (CR_2=CHR), 129.9 (H*C*(6)), 129.7, 128.2, 127.4 (3 × HC_{Ar}), 126.7 (*C*(4)), 126.3 (2 signals) (H*C*(7) + C_{Ar}), 126.2 (H*C*(8)), 124.7 (H*C*(5)), 123.7 (*C*HR=CR_2), 28.2 (CH_2), 25.7 (CH_3C=CHR), 22.6 (CH_3), 18.1 (CH_3C=CHR); **IR** ν_{max} (thin film)/cm^{-1} 3060w, 2967w, 2927w, 2856w, 1615w, 1564m, 1503m, 1438s, 1392s, 1375m, 1334m, 1261w, 1098w, 1073w, 1030m, 985w, 934w, 853w; **m/z** (ESI$^+$) 288.2 [100, $(M + H)^+$], $C_{21}H_{22}N$ predicted 288.1747, found 288.1736, (Δ + 3.7 ppm).

4-Allyl-3-*iso*butyl-1-methylisoquinoline **386**

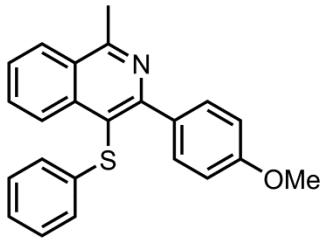


Acetal **242** (108 mg, 0.413 mmol) was subjected to General Procedure 18 with 4-methyl-2-pentanone (49.6 mg, 0.496 mmol) and allyl bromide (60.0 mg, 0.496 mmol). The crude product was purified by

flash column chromatography [Petrol/EtOAc 49:1 grading to 19:1] to furnish *isoquinoline* **386** (44.9 mg, 0.188 mmol, 45%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.10 (1H, d, *J* 8.3, *H*C(8)), 7.95 (1H, d, *J* 8.5, *H*C(5)), 7.65 (1H, ddd, *J* 8.3, 6.9, 1.2, *H*C(6)), 7.52 (1H, ddd, *J* 8.3, 6.8, 0.8, *H*C(7)), 6.04 (1H, ddt, *J* 17.1, 10.3, 5.6, C*H*=CH_2), 5.06 (1H, dq, *J* 10.2, 1.7, CH=CH_aH_b), 4.92 (1H, dq, *J* 17.1, 1.7, CH=CH_aH_b), 3.82-3.80 (2H, m, CH_2CH=CH_2), 2.94 (3H, s, CH_3), 2.82 (2H, d, *J* 7.3, CH_2CH(CH_3)$_2$), 2.28 (1H, sept., *J* 6.9, C*H*), 0.98 (6H, d, *J* 6.6, CH(CH_3)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 156.1 (*C*(3)), 151.7 (*C*(1)), 136.2 (*C*H=CH_2), 135.6 (C_{Ar}), 129.5 (H*C*(6)), 126.0 (H*C*(8)), 125.9 (C_{Ar}), 125.4 (H*C*(7)), 124.0 (H*C*(5)), 123.5 (*C*(4)), 116.0 (CH=*C*H_2), 43.9 (*C*H_2CH(CH_3)$_2$), 31.7 (*C*H_2CH=CH_2), 29.3 (*C*H(CH_3)$_2$), 22.6 (CH(*C*H_3)$_2$), 22.5 (*C*H_3); **IR** ν_{max} (thin film)/cm^{-1} 3073w, 2954s, 2867m, 1638m, 1618m, 1569s, 1504w, 1463m, 1391s, 1333m, 1166w, 1033w, 994w, 913s; **m/z** (ESI$^+$) 240.2 [100, $(M + H)^+$], $C_{17}H_{22}N$ predicted 240.1747, found 240.1752, (Δ − 2.2 ppm).

3-(4-Methoxyphenyl)-1-methyl-4-(phenylthio)isoquinoline **388**

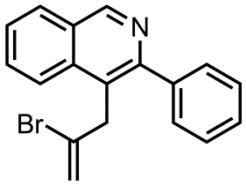


Acetal **242** (74.1 mg, 0.305 mmol) was subjected to General Procedure 18 with 4-methoxyacetophenone (54.9 mg, 0.366 mmol) and diphenyldisulfide (79.9 mg, 0.366 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 39:1 grading to 9:1] to furnish *isoquinoline* **388** (46.2 mg, 0.129 mmol, 42%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 8.43 (1H, d, *J* 8.1, *H*C(8)), 8.19 (1H, d, *J* 8.3, *H*C(5)), 7.69 (1H, ddd, *J* 8.3, 7.0, 1.2, *H*C(7)), 7.65-7.59 (3H, m, *H*C(6) + 2 × HC_{Ar}), 7.14 (2H, t, *J* 7.5, 2 × HC_{Ar}), 7.05 (1H, tt, *J* 7.2, 1.5, HC_{Ar}), 6.97-6.92 (4H, m, 4 × HC_{Ar}), 3.84 (3H, s, OCH_3), 3.08 (3H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 160.0, 159.6, 157.2 (*C*(3) + *C*(1) + C_{Ar}), 138.7, 138.3, 133.5 (*C*(4) + 2 × C_{Ar}), 131.2 (2 signals) (H*C*(7) + HC_{Ar}), 128.9 (HC_{Ar}), 127.1 (C_{Ar}), 127.0 (H*C*(6)), 126.8 (H*C*(8)), 126.3 (HC_{Ar}), 126.2 (H*C*(5)), 125.0 (HC_{Ar}), 118.9

(C_{Ar}), 113.2 (HC_{Ar}), 55.3 (OCH_3), 22.9 (CH_3); **IR** ν_{max} (thin film)/cm^{-1} 3001w, 2955w, 2835w, 1606m, 1581w, 1565w, 1545w, 1512s, 1478m, 1435m, 1390w, 1331m, 1288m, 1247s, 1176s, 1034s; **m/z** (ESI$^+$) 358.2 [100, $(M + H)^+$], $C_{23}H_{20}NOS$ predicted 358.1260, found 358.1255, (Δ + 1.3 ppm).

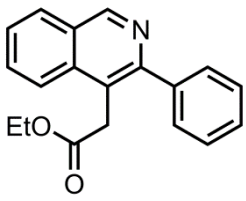
4-(2-Bromoallyl)-3-phenylisoquinoline **390**



Acetal **222** (113 mg, 0.493 mmol) was subjected to General Procedure 19 with acetophenone (71.1 mg, 0.591 mmol) and 2,3-dibromopropene (118 mg, 0.591 mmol). The crude product was purified by flash column chromatography [Petrol/EtOAc 24:1 grading to 9:1] to furnish *isoquinoline* **390** (71.7 mg, 0.221 mmol, 45%) as rods.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.31 (1H, s, *H*C(1)), 8.05 (1H, d, *J* 8.0, *H*C(8)), 7.97 (1H, d, *J* 8.5, *H*C(5)), 7.79 (1H, ddd, *J* 8.4, 6.9, 1.3, *H*C(6)), 7.67-7.63 (3H, m, *H*C(7) + 2 × *H*C_{Ar}), 7.53-7.43 (3H, m, 3 × *H*C_{Ar}), 5.60 (1H, q, *J* 1.8, CRBr=CH_aH_b), 5.24 (1H, q, *J* 2.0, CRBr=CH_aH_b), 4.17 (2H, t, *J* 1.7, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 153.0 (*C*(3)), 152.0 (H*C*(1)), 140.4, 135.6 (2 × C_{Ar}), 131.7 (*C*RBr=CH_2), 131.0 (H*C*(6)), 129.0, 128.4 (2 × HC_{Ar}), 128.3, 128.2 (H*C*(8) + HC_{Ar}), 127.6 (H*C*(7)), 127.1 (C_{Ar}), 124.1 (H*C*(5)), 123.9 (*C*(4)), 118.7 (*C*H_2=CRBr), 41.9 (CH_2); **IR** ν_{max} (thin film)/cm^{-1} 3058w, 2925w, 1623s, 1574s, 1497s, 1443s, 1369m, 1249m, 1233m, 1149w, 1111s, 1030w, 951w, 926w, 886s, 804w; **m/z** (ESI$^+$) 324.0 [100, $(M + H)^+$], $C_{18}H_{15}{}^{79}BrN$ predicted 324.0382, found 324.0390, (Δ − 2.3 ppm); **m.p.** 128-130 °C (Petrol/CH_2Cl_2).

Ethyl 2-(3-phenylisoquinolin-4-yl)acetate **392**

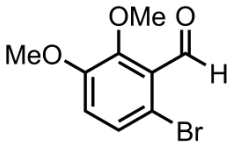


Acetal **222** (109 mg, 0.476 mmol) was subjected to General Procedure 19 with acetophenone (68.6 mg, 0.571 mmol) and ethyl bromoacetate (95.4 mg, 0.571 mmol). The crude product was purified by

flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *isoquinoline* **392** (82.6 mg, 0.284 mmol, 60%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.28 (1H, s, *H*C(1)), 8.03 (1H, d, *J* 8.0, *H*C(8)), 7.95 (1H, dd, *J* 8.6, 0.8, *H*C(5)), 7.77 (1H, ddd, *J* 8.4, 7.0, 1.3, *H*C(6)), 7.65-7.60 (3H, m, *H*C(7) + 2 × *H*C_{Ar}), 7.51-7.41 (3H, m, 3 × *H*C_{Ar}), 4.20 (2H, q, *J* 7.1, OC*H*$_2$CH$_3$), 4.07 (2H, s, C*H*$_2$) 1.25 (3H, t, *J* 7.2, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 171.7 (*C*=O), 153.4 (*C*(3)), 151.7 (H*C*(1)), 140.8, 135.9 (2 × *C*$_{Ar}$), 131.1 (H*C*(6)), 129.5 (H*C*$_{Ar}$), 128.4 (H*C*(8)), 128.3, 128.0 (2 × H*C*$_{Ar}$), 127.6 (*C*$_{Ar}$), 126.9 (H*C*(7)), 123.3 (H*C*(5)), 121.4 (*C*(4)), 61.2 (O*C*H$_2$CH$_3$), 35.6 (*C*H$_2$), 14.2 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2979w, 1729s, 1621w, 1574m, 1499w, 1444m, 1421w, 1369m, 1323m, 1251m, 1173s, 1026s, 954m, 924m, 895w, 858w; **m/z** (ESI$^+$) 292.2 [100, $(M + H)^+$], $C_{19}H_{18}NO_2$ predicted 292.1332, found 292.1334, (Δ − 0.7 ppm); **m.p.** 86-87 °C (Petrol/CH_2Cl_2).

6-Bromo-2,3-dimethoxybenzaldehyde **423**

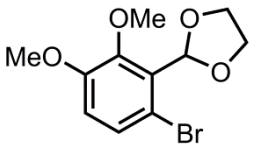


Iodomethane (907 mg, 6.39 mmol) was added to a solution of 6-bromo-2-hydroxy-3-methoxybenzaldehyde (492 mg, 2.13 mmol) and K_2CO_3 (589 mg, 4.26 mmol) in DMF (5.0 mL) at room temperature and then the mixture heated at 45 °C for 18 h. The reaction was cooled to room temperature and quenched by the addition of H_2O (20 mL) and then aqueous 1.0 M HCl (20 mL). The mixture was extracted with EtOAc (3 × 25 mL) and then the combined organics were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered and then concentrated *in vacuo*. Purification by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] furnished *aldehyde* **423** (521 mg, 2.12 mmol, 100%) as yellow needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 10.33 (1H, s, *H*C=O), 7.34 (1H, d, *J* 8.8, *H*C_{Ar}), 6.96 (1H, d, *J* 8.8, *H*C_{Ar}), 3.92 (3H, s, OC*H*$_3$), 3.88 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 190.5 (*C*=O), 152.8, 152.1 (2 × *C*$_{Ar}$), 129.4 (H*C*$_{Ar}$), 128.6 (*C*$_{Ar}$), 117.5 (H*C*$_{Ar}$), 112.8 (*C*$_{Ar}$),

62.4, 56.2 (2 × O*C*H_3); **m.p.** 81-82 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[229]

2-(6-Bromo-2,3-dimethoxyphenyl)-1,3-dioxolane **419**

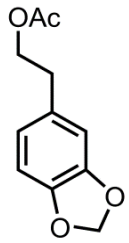


Method A: Aldehyde **423** (477 mg, 1.95 mmol) was subjected to General Procedure 5. The crude product was purified by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] to furnish *acetal* **419** (520 mg, 1.80 mmol, 93%) as prisms.

Method B: Iodomethane (860 mg, 6.06 mmol) was added to a solution of 6-bromo-2-hydroxy-3-methoxybenzaldehyde (467 mg, 2.02 mmol) and K_2CO_3 (558 mg, 4.04 mmol) in DMF (5.0 mL) and then the mixture heated at 45 °C for 18 h. The reaction was then cooled to room temperature and quenched by the addition of H_2O (20 mL) and then aqueous 1.0 M HCl (20 mL). The mixture was extracted with EtOAc (3 × 25 mL) and then the combined organics were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered and then concentrated *in vacuo*. The crude product was then subjected to General Procedure 5. Purification by flash column chromatography [Petrol/EtOAc 19:1 grading to 9:1] furnished *acetal* **419** (572 mg, 1.98 mmol, 98%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.28 (1H, d, *J* 8.6, *H*C_{Ar}), 6.80 (1H, d, *J* 8.8, *H*C_{Ar}), 6.34 (1H, s, C*H*$(OR)_2$), 4.29-4.25 (2H, m, C$H_a$$H_bCH_a$$H_b$), 4.06-4.02 (2H, m, C$H_a$$H_bCH_a$$H_b$), 3.84 (6H, s, 2 × O*C*$H_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 152.8, 150.1, 129.4 (3 × *C*$_{Ar}$), 129.1, 114.4 (2 × H*C*$_{Ar}$), 113.3 (*C*$_{Ar}$), 101.7 (H*C*$(OR)_2$), 65.9 (*C*H_2OR), 61.6, 56.0 (2 × O*C*H_3); **m.p.** 78-79 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[286]

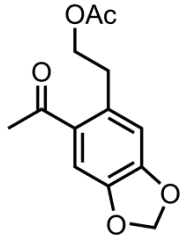
2-(Benzo[d][1,3]dioxol-5-yl)ethyl acetate **425**



Borane-THF complex solution (1.0 M in THF, 27.8 mL) was added dropwise to a solution of 3,4-(methylenedioxy)phenylacetic acid (2.50 g, 13.9 mmol) in THF (70 mL) at 0 °C. The reaction was warmed to room temperature and then stirred for a further 2 h. The reaction was quenched by the addition of aqueous 1.0 M NaOH (50 mL) and H_2O (50 mL) and then extracted with Et_2O (3 × 50 mL). The combined organics were dried over Na_2SO_4, filtered and then the solvent removed *in vacuo*. Pyridine (3.0 mL) and acetic anhydride (3.0 mL) were then added to the residue and the mixture stirred at room temperature for 2 h. The mixture was then concentrated *in vacuo* with aid of a toluene azeotrope. Purification by flash column chromatography [Petrol/EtOAc 19:1] furnished *acetate* **425** (2.88 g, 13.8 mmol, 99%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 6.73 (1H, d, *J* 8.0, *H*C_{Ar}), 6.70 (1H, d, *J* 1.6, *H*C_{Ar}), 6.65 (1H, dd, *J* 8.0, 0.9, *H*C_{Ar}), 5.91 (2H, s, ROC*H*$_2$OR), 4.22 (2H, t, *J* 7.1, C*H*$_2$OAc), 2.84 (2H, t, *J* 7.1, C*H*$_2$CH$_2$OAc), 2.03 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 170.9 (*C*=O), 147.7, 146.2, 131.6 (3 × *C*$_{Ar}$), 121.8, 109.3, 108.3 (3 × H*C*$_{Ar}$), 100.9 (RO*C*H$_2$OR), 65.1 (*C*H$_2$OAc), 34.8 (*C*H$_2$CH$_2$OAc), 20.9 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2958w, 2896w, 1734s, 1504m, 1489s, 1443m, 1387w, 1363w, 1246s, 1229s, 1187m, 1124w, 1101w, 1032s, 976w, 930m, 903w, 858w, 810m; **m/z** (ESI$^+$) 231.1 [100, (M + Na)$^+$], $C_{11}H_{12}NaO_4$ predicted 231.0628, found 261.0627, (Δ + 0.4 ppm).

2-(6-Acetylbenzo[d][1,3]dioxol-5-yl)ethyl acetate **426**



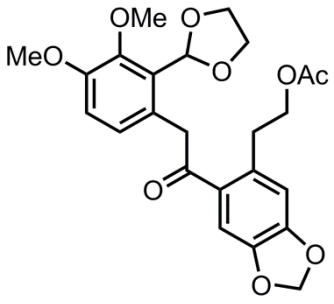
Method A: $ZnCl_2$ (553 mg, 4.06 mmol) was added portionwise to a solution of acetate **425** (203 mg, 0.811 mmol) in acetic anhydride (2.0 mL) at 0 °C. The reaction was then warmed to room temperature and stirred for a further 18 h. The reaction mixture was concentrated *in vacuo* and then the residue redissolved in Et_2O (100 mL). The organic layer was washed

with saturated aqueous $NaHCO_3$ (3 × 50 mL), water (50 mL) and brine (50 mL), and then dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [Petrol/EtOAc 19:1 to 9:1] furnished *ketone* **426** (82.0 mg, 0.327 mmol, 40%) as prisms.

Method B: Borane-THF complex solution (1.0 M in THF, 12.3 mL) was added dropwise to a solution of 3,4-(methylenedioxy)phenylacetic acid (1.11 g, 6.16 mmol) in THF (31 mL) at 0 °C. The reaction was warmed to room temperature and then stirred for a further 2 h. The reaction was quenched by the addition of aqueous 1.0 M NaOH (50 mL) and H_2O (50 mL) and then extracted with Et_2O (3 × 50 mL). The combined organics were dried over Na_2SO_4, filtered and then the solvent removed *in vacuo*. The crude product was then dissolved in acetic anhydride (10 mL) and the mixture cooled to 0 °C and stirred for 30 min. $ZnCl_2$ (4.20 g, 30.8 mmol) was added portionwise and then the reaction warmed to room temperature and stirred for a further 18 h. The reaction mixture was then concentrated *in vacuo* and then the residue redissolved in Et_2O (100 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), water (50 mL) and brine (50 mL), and then dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Purification by flash column chromatography [Petrol/EtOAc 19:1 to 9:1] furnished *ketone* **426** (541 mg, 2.16 mmol, 35%) as prisms.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.22 (1H, s, *H*C$_{Ar}$), 6.74 (1H, s, *H*C$_{Ar}$), 6.03 (2H, s, ROC*H*$_2$OR), 4.26 (2H, t, *J* 6.7, C*H*$_2$OAc), 3.16 (2H, t, *J* 6.8, C*H*$_2$CH$_2$OAc), 2.53 (3H, s, C*H*$_3$), 2.03 (3H, s, CO_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 199.2 (*C*=O), 171.0 (RO*C*=O), 150.1, 146.2, 134.9, 131.0 (4 × *C*$_{Ar}$), 112.1, 110.0 (2 × H*C*$_{Ar}$), 101.8 (ROCH$_2$OR), 65.1 (*C*H$_2$OAc), 33.7 (*C*H$_2$CH$_2$OAc), 29.5 (CO*C*H$_3$), 20.9 (CO_2CH_3); **IR** ν_{max} (thin film)/cm^{-1} 2900w, 1732s, 1676s, 1610m, 1506s, 1487s, 1434w, 1373s, 1231s, 1162w, 1111w, 1034s, 923s, 868s; **m/z** (ESI$^+$) 273.1 [45, (M + Na)$^+$], 523.2 [100, (2M + Na)$^+$], $C_{13}H_{14}NaO_5$ predicted 273.0733, found 273.0742, (Δ - 3.1 ppm); **m.p.** 42-44 °C (Petrol/CH_2Cl_2).

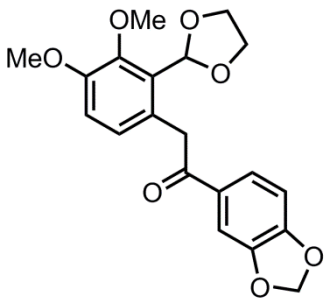
2-(6-(2-(2-(1,3-Dioxolan-2-yl)-3,4-dimethoxyphenyl)acetyl)benzo[d][1,3]dioxol-5-yl)ethyl acetate **427**



Acetal **419** (69.5 mg, 0.240 mmol) was subjected to a modification of General Procedure 7 with $PdCl_2(Amphos)_2$ (8.5 mg, 0.012 mmol), Cs_2CO_3 (195 mg, 0.600 mmol) and ketone **426** (120 mg, 0.480 mmol). The crude product was purified by flash column chromatography [Petrol/Et_2O 9:1 grading to 4:1] to furnish *ketone* **427** (43.8 mg, 0.0955 mmol, 40%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.32 (1H, s, *H*C$_{Ar}$), 6.95 (1H, d, *J* 8.3, *H*C$_{Ar}$), 6.91 (1H, d, *J* 8.6, *H*C$_{Ar}$), 6.77 (1H, s, *H*C$_{Ar}$), 6.12 (1H, s, C*H*(OR)$_2$), 6.04 (2H, s, ROC*H*$_2$OR), 4.30 (2H, t, *J* 6.9, C*H*$_2$OAc), 4.26 (2H, s, C*H*$_2$C=O), 3.87 (3H, s, OC*H*$_3$), 3.85-3.80 (2H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 3.83 (3H, s, OC*H*$_3$), 3.77-3.73 (2H, m, CH$_a$*H*$_b$CH$_a$*H*$_b$), 3.11 (2H, t, *J* 6.9, C*H*$_2$CH$_2$OAc), 2.01 (3H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 198.9 (*C*=O), 171.0 (RO*C*=O), 151.6, 149.7, 149.3, 146.1, 135.0, 131.3 (6 × *C*$_{Ar}$), 128.4 (H*C*$_{Ar}$), 127.4, 127.0 (2 × *C*$_{Ar}$), 113.1, 112.1, 108.8 (3 × H*C*$_{Ar}$), 101.8 (RO*C*H$_2$OR), 99.3 (*C*H(OR)$_2$), 65.3 (*C*H$_2$OAc), 64.6 (*C*H$_2$OR), 61.8, 55.8 (2 × O*C*H$_3$), 44.6 (CH$_2$C=O), 33.0 (*C*H$_2$CH$_2$OAc), 21.1 (*C*H$_3$); **IR** ν_{max} (thin film)/cm^{-1} 2895m, 2837m, 1735s, 1690m, 1611w, 1583w, 1492s, 1455w, 1432w, 1388m, 1367m, 1273s, 1238s, 1064s, 1042s, 978m, 959m, 932m; **m/z** (ESI$^+$) 481.2 [100, (M + Na)$^+$], $C_{24}H_{26}NaO_9$ predicted 481.1469, found 481.1452, (Δ + 3.5 ppm).

2-(2-(1,3-Dioxolan-2-yl)-3,4-dimethoxyphenyl)-1-(benzo[d][1,3]dioxol-5-yl)ethanone **429**

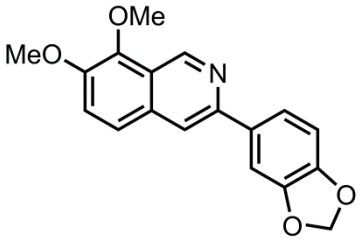


Acetal **419** (59.5 mg, 0.206 mmol) was subjected to a modification of General Procedure 7 with $PdCl_2(Amphos)_2$ (7.3 mg, 0.010 mmol), Cs_2CO_3 (168 mg, 0.515 mmol) and 3′,4’-(methylenedioxy)acetophenone (67.6 mg, 0.412 mmol). The crude product was purified by flash column chromatography

[Petrol/Et_2O 9:1 grading to 4:1] to furnish *ketone* **429** (70.0 mg, 0.188 mmol, 91%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 7.65 (1H, dd, *J* 8.1, 1.7, *H*C_{Ar}), 7.52 (1H, d, *J* 1.7, *H*C_{Ar}), 6.91 (1H, d, *J* 8.6, *H*C_{Ar}), 6.88 (1H, d, *J* 8.3 *H*C_{Ar}), 6.85 (1H, d, *J* 8.3 *H*C_{Ar}), 6.15 (1H, s, C*H*$(OR)_2$), 6.04 (2H, s, ROC*H*$_2$OR), 4.34 (2H, s, C*H*$_2$C=O), 3.90 (4H, s, 2 × C*H*$_2$OR), 3.86 (3H, s, OC*H*$_3$), 3.83 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 196.3 (*C*=O), 151.5, 151.4, 149.3, 148.1, 132.0 (5 × *C*$_{Ar}$), 127.9 (H*C*$_{Ar}$), 127.6, 127.0 (2 × *C*$_{Ar}$), 124.2, 113.2, 108.2, 107.9 (4 × H*C*$_{Ar}$), 101.8 (RO*C*H$_2$OR), 99.5 (*C*H$(OR)_2$), 64.8 (*C*H$_2$OR), 61.8, 55.8 (2 × O*C*H$_3$), 42.1 (CH_2); **IR** ν_{max} (thin film)/cm^{-1} 2943w, 1686s, 1604m, 1494s, 1443s, 1349w, 1318w, 1274s, 1255s, 1233s, 1092m, 1036s, 1011m, 987m, 934m, 869m, 831m, 815m, 802m; **m/z** (ESI$^+$) 373.2 [100, $(M + H)^+$], 395.1 [70, $(M + Na)^+$], $C_{20}H_{20}NO_7$ predicted 395.1101, found 395.1100, (Δ + 0.2 ppm).

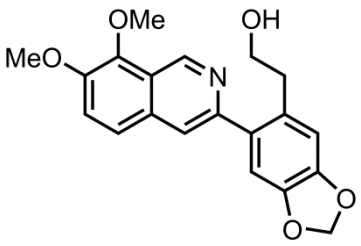
3-(Benzo[d][1,3]dioxol-5-yl)-7,8-dimethoxyisoquinoline **430**



Ketone **429** (42.3 mg, 0.114 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 14:1 grading to 5:1] to furnish *isoquinoline* **430** (31.2 mg, 0.101 mmol, 89%) as needles.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.58 (1H, s, *H*C(1)), 7.87 (1H, s, *H*C(4)), 7.64-7.61 (2H, m, 2 × *H*C_{Ar}), 7.59 (1H, d, *J* 8.8, *H*C(6)), 7.48 (1H, d, *J* 9.1, *H*C(5)), 6.95-6.93 (1H, m, *H*C_{Ar}), 6.03 (2H, s, ROC*H*$_2$OR), 4.08 (3H, s, OC*H*$_3$), 4.02 (3H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 149.3, 148.6, 148.2, 147.9, 144.0 (*C*(3), *C*(7), *C*(8) + 2 × *C*$_{Ar}$), 147.2 (H*C*(1)), 134.2, 132.6 (2 × *C*$_{Ar}$), 123.0 (H*C*(6)), 123.0 (*C*$_{Ar}$), 120.6 (H*C*$_{Ar}$), 120.3 (H*C*(5)), 115.1 (H*C*(4)), 108.5, 107.3 (2 × H*C*$_{Ar}$), 101.2 (RO*C*H$_2$OR), 61.7, 57.1 (2 × O*C*H$_3$); **m.p.** 140-142 °C (Petrol/CH_2Cl_2). Data were consistent with those previously reported.[287]

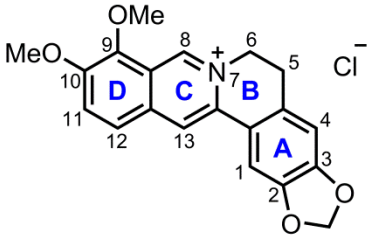
2-(6-(7,8-Dimethoxyisoquinolin-3-yl)benzo[d][1,3]dioxol-5-yl)ethanol **431**



Ketone **427** (35.7 mg, 0.0779 mmol) was subjected to General Procedure 8. The crude product was purified by flash column chromatography [Petrol/EtOAc 4:1 grading to 3:2] to furnish *isoquinoline* **431** (19.0 mg, 0.0537 mmol, 69%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 9.54 (1H, s, *H*C(1)), 7.73 (1H, s, *H*C(4)), 7.62 (1H, d, *J* 9.1, *H*C(6)), 7.55 (1H, d, *J* 9.0, *H*C(5)), 6.94 (1H, s, *H*C_{Ar}), 6.89 (1H, s, *H*C_{Ar}), 6.01 (2H, s, ROC*H*$_2$OR), 4.10 (3H, s, OC*H*$_3$), 4.04 (3H, s, OC*H*$_3$), 4.00 (2H, t, *J* 5.7, C*H*$_2$OH), 2.86 (2H, t, *J* 5.6, C*H*$_2$CH$_2$OH), not observed (O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 150.5, 149.0, 148.1, 146.1, 144.0 (*C*(3), *C*(7), *C*(8) + 2 × *C*$_{Ar}$), 145.5 (H*C*(1)), 133.6, 132.8, 132.7 (3 × *C*$_{Ar}$), 122.8 (H*C*(6)), 122.7 (*C*$_{Ar}$), 121.0 (H*C*(5)), 120.1 (H*C*(4)), 110.1, 110.1 (2 × H*C*$_{Ar}$), 101.2 (RO*C*H$_2$OR), 63.9 (*C*H$_2$OH), 61.8, 57.1 (2 × O*C*H$_3$), 35.3 (*C*H$_2$CH$_2$OH); **IR** ν_{max} (thin film)/cm^{-1} 3191br. m, 2963m, 2843m, 1683w, 1621w, 1588s, 1567m, 1504s, 1494s, 1466m, 1448m, 1374s, 1341w, 1263s, 1222s, 1115m, 1094m, 1062s, 1042s, 989m, 932m, 859w; **m/z** (ESI$^+$) 354.2 [100, (M + H)$^+$], $C_{20}H_{20}NO_5$ predicted 354.1336, found 354.1340, (Δ − 1.1 ppm).

Berberine chloride



Thionyl chloride (59.3 mg, 0.498 mmol) was added to a solution of isoquinoline **431** (17.6 mg, 0.0498 mmol) in MeCN (10 mL) at 0 °C. The reaction was warmed to room temperature and then heated at 50 °C for 4 h. The reaction was then cooled to room temperature and concentrated *in vacuo*. The residue was then redissolved in EtOH (25 mL) and then heated to 80 °C for 2 h. The reaction was cooled to room temperature and then concentrated *in vacuo* to furnish *berberine chloride* (17.6 mg, 0.0472 mmol, 95%) as prisms.

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 9.92 (1H, s, *H*C(8)), 8.97 (1H, s, *H*C(13)), 8.21 (1H, d, *J* 9.0, *H*C(11)), 8.02 (1H, d, *J* 8.9, *H*C(12)), 7.80 (1H, s, *H*C(1)), 7.10 (1H, s, *H*C(4)), 6.18 (2H, s, ROCH_2OR), 4.96 (2H, t, *J* 6.4, C(6)H_2), 4.11 (3H, s, OCH_3), 4.08 (3H, s, OCH_3), 3.23 (2H, t, *J* 6.3, C(5)H_2); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 150.3 (*C*(10)), 149.7 (*C*(3)), 147.5 (*C*(2)), 145.3 (H*C*(8)), 143.5 (*C*(9)), 137.3, 132.8, 130.5 (3 × C_{Ar}), 126.6 (H*C*(11)), 123.4 (H*C*(12)), 121.3, 120.3 (2 × C_{Ar}), 120.1 (H*C*(13)), 108.3 (H*C*(4)), 105.3 (H*C*(1)), 102.0 (RO*C*H_2OR), 61.9, 57.0 (2 × O*C*H_3), 55.1 (*C*(6)H_2), 26.3 (*C*(5)H_2); **m.p.** 209 °C decomposed (EtOH). Data were consistent with those previously reported.[288]

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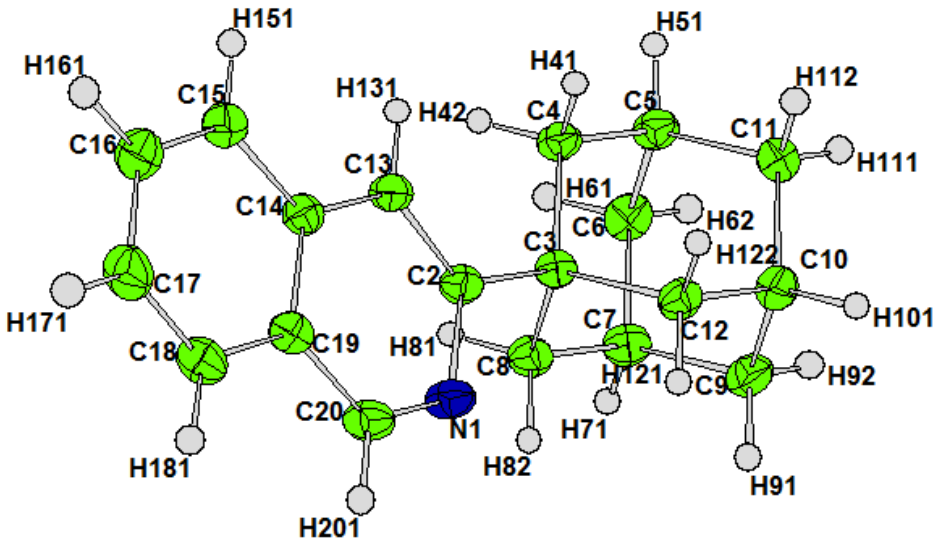
Appendix

Single crystal X-ray diffraction report for isoquinoline 280

Crystals of isoquinoline **280** were grown by Matthew Tatton and the structure was solved by Matthew Tatton.

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Structure



Crystal data

$C_{19}H_{21}N$	$F(000)$ = 284
M_r = 263.38	D_x = 1.216 Mg m^{-3}
Monoclinic, $P2_1$	Mo $K\alpha$ radiation, λ = 0.71073 Å
Hall symbol: P 2yb	Cell parameters from 1732 reflections
a = 6.5458 (1) Å	θ = 5–27°
b = 8.4459 (2) Å	μ = 0.07 mm^{-1}
c = 13.2079 (3) Å	T = 150 K
β = 99.9683 (9)°	Block, clear-colourless
V = 719.18 (3) Å^3	0.35 × 0.25 × 0.15 mm
Z = 2	

Data collection

Nonius KappaCCD diffractometer	1646 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.013$
ω scans	$\theta_{max} = 27.5°$, $\theta_{min} = 5.2°$
Absorption correction: multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	$h = -8 \rightarrow 8$
$T_{min} = 0.95$, $T_{max} = 0.99$	$k = -10 \rightarrow 10$
12150 measured reflections	$l = -17 \rightarrow 17$
1740 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Other
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.031$	H-atom parameters constrained
$wR(F^2) = 0.080$	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below*w*and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 42.7 69.9 42.4 18.6 4.79
$S = 0.93$	$(\Delta/\sigma)_{max} = 0.007$
1740 reflections	$\Delta\rho_{max} = 0.16$ e Å^{-3}
181 parameters	$\Delta\rho_{min} = -0.14$ e Å^{-3}
1 restraint	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
N1	0.09272 (19)	0.71691 (19)	0.65831 (10)	0.0281
C2	0.2652 (2)	0.67917 (19)	0.73005 (11)	0.0225
C3	0.2386 (2)	0.53520 (19)	0.79532 (11)	0.0212
C4	0.4390 (2)	0.4926 (2)	0.86934 (11)	0.0230
C5	0.4061 (2)	0.3470 (2)	0.93396 (12)	0.0251
C6	0.3422 (2)	0.2054 (2)	0.86279 (13)	0.0278
C7	0.1403 (2)	0.2453 (2)	0.78967 (12)	0.0265
C8	0.1734 (2)	0.3907 (2)	0.72506 (11)	0.0249
C9	−0.0315 (2)	0.2804 (2)	0.85236 (13)	0.0281
C10	0.0327 (2)	0.4220 (2)	0.92384 (11)	0.0263
C11	0.2351 (2)	0.3823 (2)	0.99696 (12)	0.0276
C12	0.0665 (2)	0.5677 (2)	0.85926 (11)	0.0244
C13	0.4440 (2)	0.76706 (19)	0.73966 (11)	0.0232
C14	0.4575 (2)	0.8983 (2)	0.67438 (10)	0.0228
C15	0.6397 (3)	0.9903 (2)	0.67754 (12)	0.0299
C16	0.6425 (3)	1.1123 (2)	0.60943 (13)	0.0357
C17	0.4658 (3)	1.1481 (2)	0.53586 (14)	0.0370
C18	0.2882 (3)	1.0622 (2)	0.53047 (12)	0.0312
C19	0.2809 (2)	0.9356 (2)	0.60025 (11)	0.0242
C20	0.1039 (2)	0.8385 (2)	0.59757 (12)	0.0288
H41	0.4810	0.5847	0.9155	0.0281*
H42	0.5500	0.4701	0.8293	0.0273*
H51	0.5381	0.3225	0.9810	0.0297*
H62	0.3204	0.1137	0.9035	0.0342*

H61	0.4520	0.1843	0.8214	0.0347*
H71	0.0970	0.1534	0.7426	0.0316*
H82	0.0398	0.4154	0.6777	0.0299*
H81	0.2845	0.3704	0.6859	0.0301*
H92	−0.0494	0.1857	0.8941	0.0349*
H91	−0.1637	0.3052	0.8055	0.0332*
H101	−0.0793	0.4438	0.9656	0.0306*
H112	0.2772	0.4730	1.0432	0.0338*
H111	0.2143	0.2887	1.0392	0.0330*
H122	0.1042	0.6572	0.9058	0.0299*
H121	−0.0661	0.5937	0.8115	0.0296*
H131	0.5649	0.7408	0.7898	0.0278*
H151	0.7589	0.9684	0.7281	0.0360*
H161	0.7664	1.1748	0.6114	0.0435*
H171	0.4680	1.2335	0.4888	0.0464*
H181	0.1705	1.0856	0.4787	0.0370*
H201	−0.0177	0.8628	0.5474	0.0340*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0224 (6)	0.0290 (7)	0.0305 (6)	0.0004 (6)	−0.0025 (5)	0.0033 (6)
C2	0.0212 (6)	0.0226 (7)	0.0231 (7)	0.0016 (6)	0.0018 (5)	−0.0002 (6)
C3	0.0192 (6)	0.0212 (7)	0.0226 (6)	0.0007 (5)	0.0016 (5)	−0.0003 (6)
C4	0.0187 (6)	0.0240 (7)	0.0251 (7)	0.0001 (5)	0.0006 (5)	0.0023 (6)
C5	0.0211 (7)	0.0251 (8)	0.0278 (7)	0.0008 (6)	0.0007 (5)	0.0034 (6)
C6	0.0262 (7)	0.0232 (8)	0.0339 (8)	0.0037 (6)	0.0050 (6)	0.0027 (7)
C7	0.0268 (7)	0.0229 (8)	0.0287 (7)	−0.0017 (6)	0.0021 (6)	−0.0036 (6)
C8	0.0252 (7)	0.0243 (7)	0.0245 (7)	−0.0016 (6)	0.0025 (6)	−0.0031 (6)
C9	0.0224 (7)	0.0285 (8)	0.0328 (8)	−0.0042 (6)	0.0028 (6)	0.0016 (7)
C10	0.0238 (7)	0.0288 (8)	0.0269 (7)	0.0004 (6)	0.0064 (6)	−0.0006 (6)
C11	0.0271 (7)	0.0316 (8)	0.0239 (6)	−0.0012 (6)	0.0042 (6)	0.0019 (6)
C12	0.0208 (7)	0.0252 (7)	0.0272 (7)	0.0022 (6)	0.0042 (5)	−0.0012 (6)
C13	0.0210 (6)	0.0259 (8)	0.0217 (6)	−0.0001 (6)	0.0005 (5)	−0.0010 (6)
C14	0.0236 (7)	0.0235 (8)	0.0215 (6)	0.0001 (6)	0.0041 (5)	−0.0030 (6)
C15	0.0288 (8)	0.0339 (9)	0.0266 (7)	−0.0049 (7)	0.0034 (6)	−0.0004 (7)
C16	0.0374 (9)	0.0365 (10)	0.0337 (8)	−0.0100 (8)	0.0073 (7)	0.0036 (8)
C17	0.0451 (10)	0.0338 (9)	0.0321 (8)	−0.0042 (8)	0.0070 (7)	0.0086 (7)
C18	0.0360 (8)	0.0284 (8)	0.0278 (7)	0.0029 (7)	0.0015 (6)	0.0041 (7)
C19	0.0255 (7)	0.0237 (7)	0.0230 (7)	0.0027 (6)	0.0027 (5)	−0.0010 (6)
C20	0.0257 (7)	0.0284 (8)	0.0297 (8)	0.0021 (6)	−0.0025 (6)	0.0036 (7)

Geometric parameters (Å, º)

N1—C2	1.3796 (18)	C9—H91	0.995
N1—C20	1.313 (2)	C10—C11	1.535 (2)
C2—C3	1.518 (2)	C10—C12	1.535 (2)
C2—C13	1.373 (2)	C10—H101	1.008
C3—C4	1.5365 (19)	C11—H112	0.988
C3—C8	1.548 (2)	C11—H111	0.991
C3—C12	1.5453 (19)	C12—H122	0.978
C4—C5	1.533 (2)	C12—H121	1.005
C4—H41	0.997	C13—C14	1.416 (2)
C4—H42	0.989	C13—H131	0.966
C5—C6	1.534 (2)	C14—C15	1.418 (2)
C5—C11	1.535 (2)	C14—C19	1.4153 (19)
C5—H51	0.995	C15—C16	1.370 (2)
C6—C7	1.533 (2)	C15—H151	0.953
C6—H62	0.968	C16—C17	1.409 (3)

C6—H61	0.992	C16—H161	0.964
C7—C8	1.532 (2)	C17—C18	1.362 (2)
C7—C9	1.536 (2)	C17—H171	0.954
C7—H71	1.004	C18—C19	1.418 (2)
C8—H82	1.005	C18—H181	0.958
C8—H81	0.978	C19—C20	1.415 (2)
C9—C10	1.536 (2)	C20—H201	0.965
C9—H92	0.990		

C2—N1—C20	118.35 (13)	C10—C9—H91	109.6
N1—C2—C3	114.50 (13)	H92—C9—H91	110.0
N1—C2—C13	121.43 (14)	C9—C10—C11	109.33 (14)
C3—C2—C13	124.06 (13)	C9—C10—C12	109.44 (12)
C2—C3—C4	112.33 (12)	C11—C10—C12	109.44 (13)
C2—C3—C8	109.76 (11)	C9—C10—H101	109.4
C4—C3—C8	108.27 (12)	C11—C10—H101	109.0
C2—C3—C12	109.51 (12)	C12—C10—H101	110.2
C4—C3—C12	108.46 (11)	C10—C11—C5	109.40 (12)
C8—C3—C12	108.42 (12)	C10—C11—H112	109.7
C3—C4—C5	110.82 (12)	C5—C11—H112	109.5
C3—C4—H41	108.8	C10—C11—H111	109.9
C5—C4—H41	109.6	C5—C11—H111	109.6
C3—C4—H42	109.3	H112—C11—H111	108.7
C5—C4—H42	109.3	C10—C12—C3	110.49 (12)
H41—C4—H42	109.1	C10—C12—H122	108.4
C4—C5—C6	109.50 (12)	C3—C12—H122	110.6
C4—C5—C11	109.37 (13)	C10—C12—H121	109.4
C6—C5—C11	109.65 (13)	C3—C12—H121	109.1
C4—C5—H51	108.9	H122—C12—H121	108.8
C6—C5—H51	109.6	C2—C13—C14	120.59 (13)
C11—C5—H51	109.7	C2—C13—H131	121.5
C5—C6—C7	109.18 (13)	C14—C13—H131	117.9
C5—C6—H62	109.5	C13—C14—C15	123.49 (13)
C7—C6—H62	109.4	C13—C14—C19	117.78 (13)
C5—C6—H61	109.3	C15—C14—C19	118.70 (14)
C7—C6—H61	108.7	C14—C15—C16	119.98 (15)
H62—C6—H61	110.7	C14—C15—H151	119.8
C6—C7—C8	109.75 (12)	C16—C15—H151	120.2
C6—C7—C9	109.53 (13)	C15—C16—C17	120.77 (16)
C8—C7—C9	109.43 (13)	C15—C16—H161	120.0
C6—C7—H71	109.9	C17—C16—H161	119.2
C8—C7—H71	109.1	C16—C17—C18	120.89 (16)
C9—C7—H71	109.2	C16—C17—H171	120.6
C3—C8—C7	110.42 (11)	C18—C17—H171	118.5
C3—C8—H82	109.2	C17—C18—C19	119.48 (15)
C7—C8—H82	108.8	C17—C18—H181	120.1
C3—C8—H81	107.5	C19—C18—H181	120.4
C7—C8—H81	110.1	C18—C19—C14	120.17 (14)
H82—C8—H81	110.7	C18—C19—C20	122.72 (14)
C7—C9—C10	109.50 (13)	C14—C19—C20	117.07 (13)
C7—C9—H92	108.2	C19—C20—N1	124.77 (14)
C10—C9—H92	109.5	C19—C20—H201	117.9
C7—C9—H91	110.1	N1—C20—H201	117.3

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C18—H181···N1^{i}	0.96	2.53	3.462 (2)	165 (1)

Symmetry code

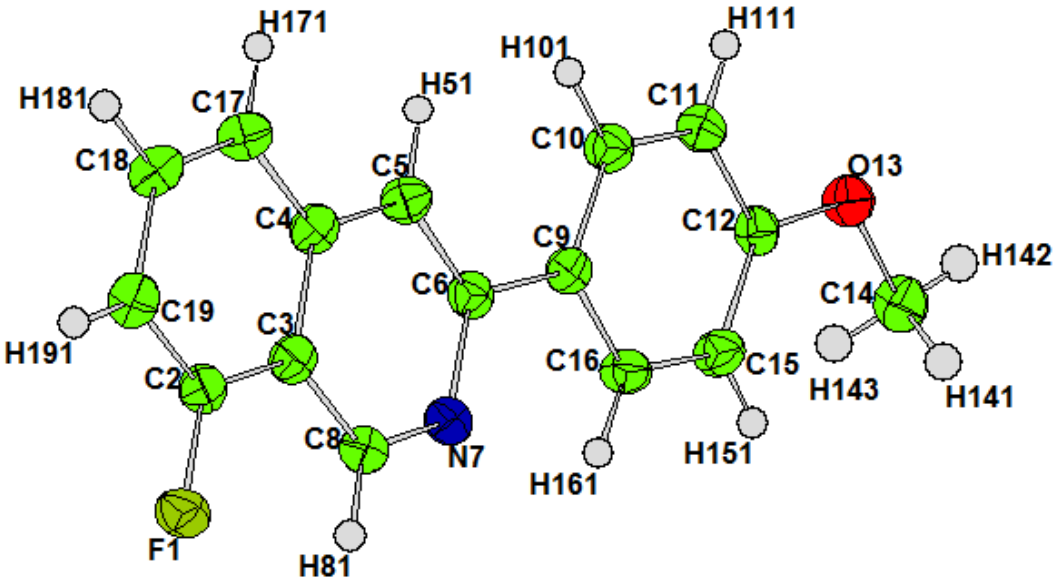
(i) −*x*, *y*+1/2, −*z*+1.

Single crystal X-ray diffraction report for isoquinoline 322

Crystals of isoquinoline **322** were grown by Matthew Tatton and the structure was solved by Matthew Tatton.

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomareet *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Structure



Crystal data

$C_{16}H_{12}FNO$	$F(000)$ = 528
M_r = 253.28	D_x = 1.429 Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, λ = 0.71073 Å
Hall symbol: -P 2yn	Cell parameters from 2517 reflections
a = 12.0003 (5) Å	θ = 5–26°
b = 5.4759 (2) Å	μ = 0.10 mm^{-1}
c = 17.9308 (8) Å	T = 150 K
β = 92.310 (2)°	Plate, clear-colourless
V = 1177.32 (8) Å^3	0.24 × 0.24 × 0.03 mm
Z = 4	

Data collection

Nonius KappaCCD diffractometer	1621 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.028$
ω scans	$\theta_{max} = 26.0°$, $\theta_{min} = 5.1°$
Absorption correction: multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	$h = -14 \rightarrow 14$
$T_{min} = 0.86$, $T_{max} = 1.00$	$k = -6 \rightarrow 6$
30505 measured reflections	$l = -22 \rightarrow 22$
2297 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: difference Fourier map
Least-squares matrix: full	H-atom parameters constrained
$R[F^2 > 2\sigma(F^2)] = 0.049$	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below*w*and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 22.4 34.8 18.3 5.09
$wR(F^2) = 0.150$	$(\Delta/\sigma)_{max} = 0.006$
$S = 1.03$	$\Delta\rho_{max} = 0.39$ e Å^{-3}
2296 reflections	$\Delta\rho_{min} = -0.36$ e Å^{-3}
172 parameters	Extinction correction: Larson (1970), Equation 22
0 restraints	Extinction coefficient: 0.000
Primary atom site location: Direct	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
F1	0.87532 (9)	0.7307 (2)	0.67661 (6)	0.0351
C2	0.82404 (15)	0.9113 (4)	0.63619 (10)	0.0280
C3	0.83963 (14)	0.9171 (3)	0.55917 (10)	0.0274
C4	0.78691 (15)	1.1080 (4)	0.51731 (10)	0.0277
C5	0.80337 (15)	1.1123 (4)	0.43942 (10)	0.0285
C6	0.86847 (14)	0.9380 (3)	0.40686 (10)	0.0264
N7	0.91895 (13)	0.7527 (3)	0.44819 (9)	0.0286
C8	0.90453 (15)	0.7462 (4)	0.52072 (11)	0.0291
C9	0.89043 (14)	0.9344 (3)	0.32612 (10)	0.0248
C10	0.85159 (15)	1.1178 (3)	0.27685 (11)	0.0288
C11	0.87392 (15)	1.1111 (4)	0.20197 (10)	0.0290
C12	0.93614 (14)	0.9206 (3)	0.17373 (9)	0.0251
O13	0.95433 (10)	0.9313 (2)	0.09846 (7)	0.0299
C14	1.01198 (17)	0.7300 (4)	0.06756 (11)	0.0341
C15	0.97531 (15)	0.7361 (3)	0.22074 (10)	0.0294
C16	0.95207 (15)	0.7450 (3)	0.29610 (11)	0.0288
C17	0.72073 (15)	1.2807 (4)	0.55411 (11)	0.0304
C18	0.70691 (16)	1.2631 (4)	0.62906 (11)	0.0315
C19	0.75928 (15)	1.0747 (4)	0.67193 (10)	0.0309
H51	0.7670	1.2420	0.4113	0.0343*
H81	0.9414	0.6196	0.5480	0.0354*
H101	0.8061	1.2516	0.2945	0.0341*
H111	0.8474	1.2341	0.1698	0.0359*

H142	1.0157	0.7681	0.0146	0.0492*
H141	1.0878	0.7143	0.0896	0.0491*
H143	0.9699	0.5825	0.0741	0.0494*
H151	1.0166	0.6032	0.2034	0.0359*
H161	0.9782	0.6199	0.3283	0.0340*
H171	0.6865	1.4107	0.5270	0.0347*
H181	0.6595	1.3763	0.6529	0.0373*
H191	0.7525	1.0688	0.7243	0.0371*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
F1	0.0390 (6)	0.0379 (7)	0.0282 (6)	0.0069 (5)	0.0009 (5)	0.0072 (5)
C2	0.0250 (8)	0.0316 (10)	0.0272 (9)	−0.0015 (8)	−0.0014 (7)	0.0022 (8)
C3	0.0239 (8)	0.0292 (10)	0.0289 (9)	−0.0021 (7)	−0.0014 (7)	−0.0005 (7)
C4	0.0242 (8)	0.0303 (10)	0.0284 (9)	−0.0011 (7)	−0.0022 (7)	−0.0014 (8)
C5	0.0274 (9)	0.0297 (10)	0.0281 (10)	0.0018 (7)	−0.0018 (7)	0.0000 (8)
C6	0.0247 (8)	0.0270 (9)	0.0273 (9)	−0.0025 (7)	−0.0002 (7)	0.0014 (7)
N7	0.0302 (8)	0.0294 (8)	0.0264 (8)	0.0014 (7)	0.0024 (6)	0.0034 (6)
C8	0.0296 (9)	0.0284 (9)	0.0292 (9)	0.0018 (7)	0.0012 (7)	0.0029 (8)
C9	0.0231 (8)	0.0261 (9)	0.0250 (9)	−0.0013 (7)	−0.0014 (7)	−0.0006 (7)
C10	0.0297 (9)	0.0284 (10)	0.0282 (9)	0.0012 (7)	0.0015 (7)	−0.0002 (8)
C11	0.0294 (9)	0.0298 (10)	0.0277 (9)	0.0016 (7)	0.0006 (7)	0.0039 (8)
C12	0.0250 (9)	0.0290 (9)	0.0212 (8)	−0.0029 (7)	0.0005 (7)	−0.0001 (7)
O13	0.0348 (7)	0.0325 (7)	0.0224 (6)	0.0031 (6)	0.0017 (5)	−0.0012 (5)
C14	0.0397 (10)	0.0359 (11)	0.0269 (9)	0.0007 (9)	0.0031 (8)	−0.0036 (8)
C15	0.0308 (9)	0.0295 (10)	0.0280 (9)	0.0051 (8)	0.0023 (7)	−0.0014 (8)
C16	0.0303 (9)	0.0279 (10)	0.0279 (9)	0.0039 (8)	−0.0009 (7)	0.0020 (8)
C17	0.0309 (9)	0.0301 (10)	0.0298 (9)	0.0033 (8)	−0.0035 (7)	−0.0036 (8)
C18	0.0276 (9)	0.0339 (10)	0.0327 (10)	0.0031 (8)	−0.0014 (7)	−0.0063 (8)
C19	0.0293 (9)	0.0382 (11)	0.0250 (9)	−0.0011 (8)	−0.0015 (7)	−0.0034 (8)

Geometric parameters (Å, º)

F1—C2	1.359 (2)	C11—C12	1.390 (3)
C2—C3	1.401 (3)	C11—H111	0.934
C2—C19	1.362 (3)	C12—O13	1.377 (2)
C3—C4	1.421 (3)	C12—C15	1.386 (3)
C3—C8	1.415 (3)	O13—C14	1.425 (2)
C4—C5	1.419 (3)	C14—H142	0.975
C4—C17	1.415 (3)	C14—H141	0.981
C5—C6	1.378 (3)	C14—H143	0.962
C5—H51	0.965	C15—C16	1.392 (3)
C6—N7	1.382 (2)	C15—H151	0.941
C6—C9	1.482 (2)	C16—H161	0.941
N7—C8	1.319 (3)	C17—C18	1.364 (3)
C8—H81	0.948	C17—H171	0.946
C9—C10	1.405 (3)	C18—C19	1.418 (3)
C9—C16	1.395 (3)	C18—H181	0.954
C10—C11	1.380 (3)	C19—H191	0.946
C10—H101	0.974		

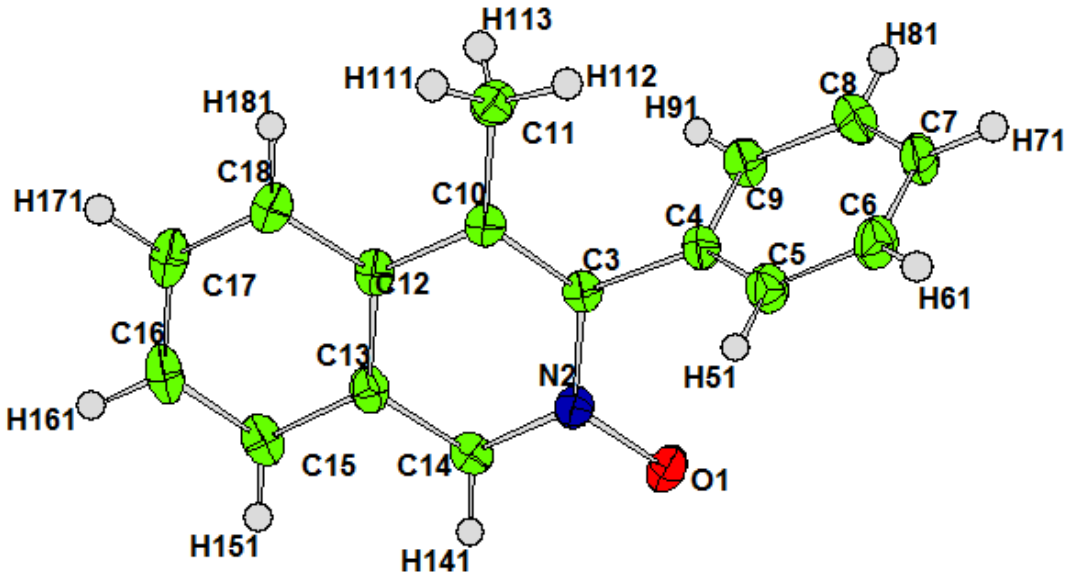
F1—C2—C3	117.81 (16)	C12—C11—H111	119.4
F1—C2—C19	118.81 (16)	C11—C12—O13	115.72 (15)
C3—C2—C19	123.38 (17)	C11—C12—C15	119.96 (16)
C2—C3—C4	117.58 (17)	O13—C12—C15	124.32 (16)
C2—C3—C8	124.27 (17)	C12—O13—C14	116.54 (14)
C4—C3—C8	118.15 (17)	O13—C14—H142	104.8
C3—C4—C5	117.09 (17)	O13—C14—H141	111.6
C3—C4—C17	119.46 (17)	H142—C14—H141	109.4
C5—C4—C17	123.44 (17)	O13—C14—H143	109.7
C4—C5—C6	120.64 (17)	H142—C14—H143	110.1
C4—C5—H51	116.7	H141—C14—H143	111.1
C6—C5—H51	122.7	C12—C15—C16	119.27 (17)
C5—C6—N7	121.68 (17)	C12—C15—H151	122.3
C5—C6—C9	123.32 (16)	C16—C15—H151	118.5
N7—C6—C9	115.00 (16)	C9—C16—C15	122.07 (17)
C6—N7—C8	118.45 (16)	C9—C16—H161	118.3
C3—C8—N7	123.99 (17)	C15—C16—H161	119.7
C3—C8—H81	119.1	C4—C17—C18	120.32 (18)
N7—C8—H81	116.9	C4—C17—H171	120.2
C6—C9—C10	122.50 (16)	C18—C17—H171	119.4
C6—C9—C16	120.33 (16)	C17—C18—C19	121.11 (18)
C10—C9—C16	117.17 (17)	C17—C18—H181	119.6
C9—C10—C11	121.36 (18)	C19—C18—H181	119.2
C9—C10—H101	120.6	C18—C19—C2	118.13 (17)
C11—C10—H101	118.0	C18—C19—H191	120.5
C10—C11—C12	120.17 (17)	C2—C19—H191	121.2
C10—C11—H111	120.4		

Single crystal X-ray diffraction report for isoquinoline N-oxide 346

Crystals of isoquinoline *N*-oxide **346** were grown by Matthew Tatton and the structure was solved by Matthew Tatton.

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Structure



Crystal data

$C_{16}H_{13}NO$	$F(000)$ = 496
M_r = 235.29	D_x = 1.347 Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, λ = 0.71073 Å
Hall symbol: -P 2yn	Cell parameters from 2550 reflections
a = 6.0190 (1) Å	θ = 5–27°
b = 8.0659 (2) Å	μ = 0.08 mm^{-1}
c = 23.9029 (5) Å	T = 150 K
β = 91.3683 (11)°	Block, colourless
V = 1160.12 (4) Å^3	0.60 × 0.25 × 0.25 mm
Z = 4	

Data collection

Nonius KappaCCD diffractometer	2075 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.027$
ω scans	$\theta_{max} = 27.5°$, $\theta_{min} = 5.1°$
Absorption correction: multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	$h = -7 \rightarrow 7$
$T_{min} = 0.77$, $T_{max} = 0.98$	$k = -10 \rightarrow 10$
17757 measured reflections	$l = -30 \rightarrow 30$
2619 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Other
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.045$	H-atom parameters constrained
$wR(F^2) = 0.116$	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below*w*and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 53.0 83.8 48.2 19.1 4.04
$S = 0.95$	$(\Delta/\sigma)_{max} = 0.001$
2618 reflections	$\Delta\rho_{max} = 0.33$ e Å^{-3}
163 parameters	$\Delta\rho_{min} = -0.33$ e Å^{-3}
0 restraints	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.62777 (18)	0.59686 (15)	0.62455 (5)	0.0324
N2	0.7662 (2)	0.65751 (16)	0.58910 (5)	0.0244
C3	0.9505 (2)	0.74904 (18)	0.60892 (6)	0.0221
C4	0.9725 (3)	0.76682 (19)	0.67065 (6)	0.0244
C5	0.8201 (3)	0.8597 (2)	0.70072 (6)	0.0306
C6	0.8502 (3)	0.8806 (2)	0.75800 (7)	0.0355
C7	1.0283 (3)	0.8064 (2)	0.78565 (7)	0.0360
C8	1.1785 (3)	0.7126 (2)	0.75633 (7)	0.0353
C9	1.1525 (3)	0.6941 (2)	0.69872 (6)	0.0294
C10	1.0993 (2)	0.81224 (18)	0.57175 (6)	0.0225
C11	1.2896 (3)	0.9175 (2)	0.59248 (7)	0.0298
C12	1.0723 (2)	0.77952 (18)	0.51305 (6)	0.0237
C13	0.8839 (3)	0.68766 (19)	0.49464 (6)	0.0258
C14	0.7341 (3)	0.6325 (2)	0.53448 (6)	0.0287
C15	0.8525 (3)	0.6491 (2)	0.43694 (6)	0.0315
C16	1.0057 (3)	0.7002 (2)	0.39936 (6)	0.0340
C17	1.1927 (3)	0.7921 (2)	0.41728 (7)	0.0340
C18	1.2252 (3)	0.8315 (2)	0.47256 (7)	0.0301
H51	0.6914	0.9099	0.6811	0.0380*

H61	0.7483	0.9466	0.7777	0.0427*
H71	1.0473	0.8188	0.8252	0.0431*
H81	1.3024	0.6601	0.7750	0.0422*
H91	1.2593	0.6331	0.6780	0.0356*
H111	1.3050	1.0152	0.5689	0.0449*
H112	1.2739	0.9514	0.6313	0.0444*
H113	1.4310	0.8550	0.5909	0.0459*
H141	0.6005	0.5752	0.5239	0.0356*
H151	0.7239	0.5910	0.4253	0.0389*
H161	0.9856	0.6750	0.3605	0.0389*
H171	1.2984	0.8299	0.3909	0.0411*
H181	1.3559	0.8921	0.4841	0.0366*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0313 (6)	0.0395 (7)	0.0268 (6)	−0.0072 (5)	0.0081 (4)	0.0016 (5)
N2	0.0245 (6)	0.0266 (6)	0.0222 (6)	−0.0001 (5)	0.0024 (5)	0.0010 (5)
C3	0.0233 (7)	0.0213 (7)	0.0217 (7)	0.0039 (5)	0.0006 (5)	0.0002 (5)
C4	0.0280 (7)	0.0248 (7)	0.0204 (7)	−0.0002 (6)	0.0021 (5)	−0.0002 (5)
C5	0.0314 (8)	0.0351 (9)	0.0256 (8)	0.0032 (7)	0.0035 (6)	−0.0026 (6)
C6	0.0392 (9)	0.0406 (9)	0.0271 (8)	−0.0020 (8)	0.0095 (7)	−0.0084 (7)
C7	0.0442 (10)	0.0454 (10)	0.0184 (7)	−0.0098 (8)	0.0020 (6)	−0.0024 (7)
C8	0.0372 (9)	0.0428 (10)	0.0258 (8)	0.0007 (8)	−0.0046 (7)	0.0023 (7)
C9	0.0317 (8)	0.0311 (8)	0.0253 (7)	0.0046 (7)	0.0002 (6)	−0.0004 (6)
C10	0.0241 (7)	0.0196 (7)	0.0239 (7)	0.0033 (5)	0.0011 (5)	0.0007 (5)
C11	0.0300 (8)	0.0293 (8)	0.0302 (8)	−0.0021 (7)	0.0035 (6)	−0.0020 (6)
C12	0.0276 (7)	0.0199 (7)	0.0236 (7)	0.0061 (6)	0.0028 (5)	0.0025 (5)
C13	0.0295 (8)	0.0266 (7)	0.0213 (7)	0.0054 (6)	0.0007 (6)	0.0017 (6)
C14	0.0276 (8)	0.0335 (8)	0.0249 (8)	−0.0037 (7)	−0.0015 (6)	−0.0016 (6)
C15	0.0370 (9)	0.0340 (9)	0.0233 (8)	0.0061 (7)	−0.0029 (6)	−0.0007 (6)
C16	0.0463 (10)	0.0369 (9)	0.0191 (7)	0.0124 (8)	0.0020 (6)	0.0014 (6)
C17	0.0403 (9)	0.0355 (9)	0.0268 (8)	0.0085 (7)	0.0112 (7)	0.0060 (7)
C18	0.0326 (8)	0.0289 (8)	0.0291 (8)	0.0022 (6)	0.0076 (6)	0.0029 (6)

Geometric parameters (Å, º)

O1—N2	1.2982 (16)	C10—C12	1.433 (2)
N2—C3	1.4056 (19)	C11—H111	0.975
N2—C14	1.3304 (19)	C11—H112	0.975
C3—C4	1.4851 (19)	C11—H113	0.990
C3—C10	1.374 (2)	C12—C13	1.416 (2)
C4—C5	1.397 (2)	C12—C18	1.415 (2)
C4—C9	1.391 (2)	C13—C14	1.400 (2)
C5—C6	1.387 (2)	C13—C15	1.422 (2)
C5—H51	0.983	C14—H141	0.957
C6—C7	1.382 (3)	C15—C16	1.366 (2)
C6—H61	0.946	C15—H151	0.941
C7—C8	1.382 (3)	C16—C17	1.406 (3)
C7—H71	0.954	C16—H161	0.957
C8—C9	1.390 (2)	C17—C18	1.368 (2)
C8—H81	0.958	C17—H171	0.956
C9—H91	0.957	C18—H181	0.961
C10—C11	1.501 (2)		

O1—N2—C3	119.44 (12)	C10—C11—H111	110.4
O1—N2—C14	120.22 (13)	C10—C11—H112	112.5
C3—N2—C14	120.34 (13)	H111—C11—H112	109.7
N2—C3—C4	115.89 (12)	C10—C11—H113	110.4
N2—C3—C10	119.87 (13)	H111—C11—H113	107.2
C4—C3—C10	124.22 (13)	H112—C11—H113	106.5
C3—C4—C5	121.26 (14)	C10—C12—C13	118.17 (13)
C3—C4—C9	119.25 (13)	C10—C12—C18	123.69 (14)
C5—C4—C9	119.45 (14)	C13—C12—C18	118.13 (14)
C4—C5—C6	120.07 (15)	C12—C13—C14	118.60 (13)
C4—C5—H51	119.7	C12—C13—C15	120.21 (14)
C6—C5—H51	120.2	C14—C13—C15	121.17 (15)
C5—C6—C7	120.07 (16)	C13—C14—N2	122.62 (14)
C5—C6—H61	119.2	C13—C14—H141	121.7
C7—C6—H61	120.7	N2—C14—H141	115.7
C6—C7—C8	120.24 (15)	C13—C15—C16	119.71 (16)
C6—C7—H71	120.1	C13—C15—H151	119.0
C8—C7—H71	119.7	C16—C15—H151	121.2
C7—C8—C9	120.10 (16)	C15—C16—C17	120.44 (15)
C7—C8—H81	121.2	C15—C16—H161	120.2
C9—C8—H81	118.7	C17—C16—H161	119.3
C4—C9—C8	120.04 (15)	C16—C17—C18	120.76 (15)
C4—C9—H91	119.4	C16—C17—H171	120.5
C8—C9—H91	120.5	C18—C17—H171	118.7
C3—C10—C11	120.03 (13)	C12—C18—C17	120.75 (16)
C3—C10—C12	120.28 (14)	C12—C18—H181	119.7
C11—C10—C12	119.69 (13)	C17—C18—H181	119.5

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C11—H113···O1^{i}	0.99	2.52	3.368 (2)	144 (1)
C11—H113···N2^{i}	0.99	2.57	3.556 (2)	172 (1)

Symmetry code:

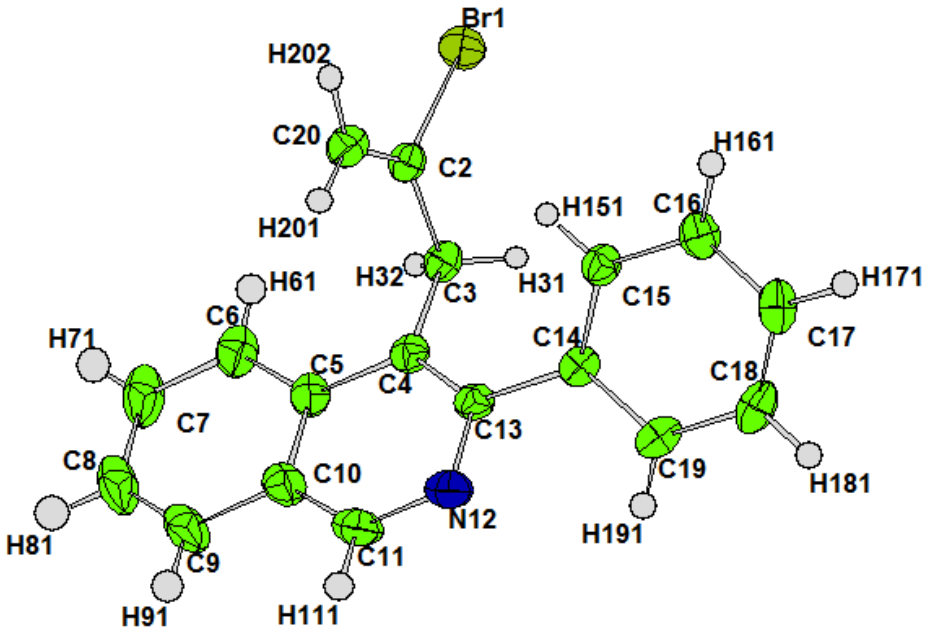
(i) $x+1, y, z$.

Single crystal X-ray diffraction report for isoquinoline 390

Crystals of isoquinoline **390** were grown by Matthew Tatton and the structure was solved by Matthew Tatton.

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

Structure



Crystal data

$C_{18}H_{14}BrN$	$F(000)$ = 656
M_r = 324.22	D_x = 1.507 Mg m^{-3}
Monoclinic, $P2_1/a$	Mo $K\alpha$ radiation, λ = 0.71073 Å
Hall symbol: -P 2yab	Cell parameters from 3388 reflections
a = 8.8066 (1) Å	θ = 5–27°
b = 13.3703 (2) Å	μ = 2.86 mm^{-1}
c = 12.5739 (2) Å	T = 150 K
β = 105.1056 (5)°	Block, colourless
V = 1429.38 (4) Å^3	0.40 × 0.20 × 0.20 mm
Z = 4	

Data collection

Nonius KappaCCD diffractometer	2943 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.013$
ω scans	$\theta_{max} = 27.5°$, $\theta_{min} = 5.2°$
Absorption correction: multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	$h = -11 \rightarrow 11$
$T_{min} = 0.32$, $T_{max} = 0.38$	$k = -16 \rightarrow 17$
44305 measured reflections	$l = -16 \rightarrow 16$
6127 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Other
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.033$	H-atom parameters constrained
$wR(F^2) = 0.077$	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below*w*and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 50.8 80.5 47.1 19.4 4.95
$S = 0.88$	$(\Delta/\sigma)_{max} = 0.0003$
3256 reflections	$\Delta\rho_{max} = 0.60$ e Å^{-3}
181 parameters	$\Delta\rho_{min} = -0.68$ e Å^{-3}
0 restraints	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
Br1	0.42787 (3)	0.359538 (17)	0.371865 (19)	0.0384
C2	0.3704 (2)	0.47635 (15)	0.28221 (16)	0.0277
C3	0.1991 (2)	0.47662 (15)	0.22107 (17)	0.0280
C4	0.1449 (2)	0.57205 (15)	0.15820 (16)	0.0271
C5	0.1705 (2)	0.58607 (17)	0.05149 (16)	0.0320
C6	0.2524 (3)	0.5164 (2)	0.00142 (19)	0.0398
C7	0.2714 (3)	0.5350 (3)	−0.1019 (2)	0.0528
C8	0.2111 (3)	0.6226 (3)	−0.1595 (2)	0.0568
C9	0.1325 (3)	0.6911 (2)	−0.11380 (19)	0.0495
C10	0.1102 (3)	0.6740 (2)	−0.00728 (18)	0.0383
C11	0.0285 (3)	0.74200 (19)	0.04279 (19)	0.0405
N12	0.0047 (2)	0.72991 (15)	0.14097 (16)	0.0361
C13	0.0650 (2)	0.64542 (15)	0.19939 (16)	0.0273
C14	0.0315 (2)	0.64095 (14)	0.30970 (17)	0.0274
C15	0.1464 (2)	0.61574 (16)	0.40517 (17)	0.0292
C16	0.1115 (3)	0.61492 (17)	0.50681 (18)	0.0340
C17	−0.0385 (3)	0.63846 (16)	0.51452 (19)	0.0352
C18	−0.1529 (3)	0.66455 (17)	0.4207 (2)	0.0377
C19	−0.1186 (2)	0.66622 (16)	0.31908 (19)	0.0336
C20	0.4777 (2)	0.54510 (17)	0.28264 (18)	0.0340
H31	0.1386	0.4657	0.2763	0.0340*
H32	0.1822	0.4198	0.1701	0.0337*
H61	0.2953	0.4566	0.0397	0.0497*

H71	0.3264	0.4884	−0.1341	0.0628*
H81	0.2256	0.6344	−0.2305	0.0660*
H91	0.0930	0.7501	−0.1531	0.0604*
H111	−0.0129	0.8005	0.0027	0.0497*
H151	0.2493	0.5997	0.4007	0.0352*
H161	0.1921	0.5981	0.5716	0.0410*
H171	−0.0642	0.6372	0.5848	0.0423*
H181	−0.2571	0.6811	0.4254	0.0452*
H191	−0.1984	0.6851	0.2550	0.0416*
H201	0.4504	0.6044	0.2404	0.0413*
H202	0.5818	0.5350	0.3263	0.0413*

Atomic displacement parameters ($Å^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Br1	0.04102 (13)	0.03410 (13)	0.04063 (13)	0.00645 (9)	0.01147 (9)	0.00709 (9)
C2	0.0281 (9)	0.0284 (10)	0.0282 (9)	0.0040 (8)	0.0099 (7)	−0.0021 (7)
C3	0.0265 (9)	0.0268 (9)	0.0318 (10)	−0.0011 (7)	0.0096 (8)	−0.0044 (8)
C4	0.0213 (8)	0.0314 (9)	0.0271 (9)	−0.0048 (7)	0.0039 (7)	−0.0033 (8)
C5	0.0254 (9)	0.0436 (12)	0.0255 (9)	−0.0092 (9)	0.0040 (7)	−0.0058 (8)
C6	0.0345 (11)	0.0531 (14)	0.0327 (10)	−0.0101 (10)	0.0106 (8)	−0.0124 (10)
C7	0.0446 (13)	0.083 (2)	0.0344 (12)	−0.0191 (14)	0.0172 (11)	−0.0214 (13)
C8	0.0457 (14)	0.102 (2)	0.0226 (10)	−0.0266 (15)	0.0082 (10)	−0.0047 (13)
C9	0.0393 (12)	0.0777 (19)	0.0264 (11)	−0.0184 (13)	−0.0007 (9)	0.0095 (11)
C10	0.0283 (10)	0.0551 (14)	0.0275 (10)	−0.0104 (10)	0.0000 (8)	0.0023 (9)
C11	0.0339 (11)	0.0448 (13)	0.0367 (11)	0.0000 (10)	−0.0020 (9)	0.0117 (10)
N12	0.0319 (9)	0.0385 (10)	0.0343 (9)	0.0031 (8)	0.0019 (7)	0.0046 (8)
C13	0.0227 (8)	0.0305 (10)	0.0264 (9)	−0.0015 (7)	0.0023 (7)	−0.0014 (7)
C14	0.0264 (9)	0.0247 (9)	0.0311 (10)	−0.0014 (7)	0.0076 (7)	−0.0038 (7)
C15	0.0277 (9)	0.0313 (10)	0.0295 (9)	0.0005 (8)	0.0091 (8)	−0.0045 (8)
C16	0.0401 (11)	0.0330 (10)	0.0302 (10)	−0.0023 (9)	0.0116 (9)	−0.0041 (8)
C17	0.0448 (12)	0.0286 (10)	0.0382 (11)	−0.0075 (9)	0.0214 (9)	−0.0071 (8)
C18	0.0341 (11)	0.0316 (10)	0.0534 (14)	−0.0021 (9)	0.0218 (10)	−0.0097 (10)
C19	0.0252 (9)	0.0322 (10)	0.0425 (12)	0.0014 (8)	0.0074 (8)	−0.0052 (9)
C20	0.0277 (10)	0.0372 (11)	0.0373 (11)	0.0010 (8)	0.0087 (8)	0.0015 (9)

Geometric parameters (Å, º)

Br1—C2	1.915 (2)	C10—C11	1.406 (4)
C2—C3	1.504 (3)	C11—N12	1.315 (3)
C2—C20	1.317 (3)	C11—H111	0.951
C3—C4	1.511 (3)	N12—C13	1.376 (3)
C3—H31	0.990	C13—C14	1.493 (3)
C3—H32	0.980	C14—C15	1.395 (3)
C4—C5	1.430 (3)	C14—C19	1.399 (3)
C4—C13	1.384 (3)	C15—C16	1.390 (3)
C5—C6	1.422 (3)	C15—H151	0.947
C5—C10	1.416 (3)	C16—C17	1.386 (3)
C6—C7	1.376 (3)	C16—H161	0.958
C6—H61	0.958	C17—C18	1.382 (4)
C7—C8	1.406 (5)	C17—H171	0.968
C7—H71	0.942	C18—C19	1.387 (3)
C8—C9	1.363 (5)	C18—H181	0.960
C8—H81	0.947	C19—H191	0.955
C9—C10	1.422 (3)	C20—H201	0.950
C9—H91	0.947	C20—H202	0.948

Br1—C2—C3	112.26 (14)	C5—C10—C11	118.0 (2)
Br1—C2—C20	119.16 (16)	C10—C11—N12	124.5 (2)
C3—C2—C20	128.55 (19)	C10—C11—H111	117.7
C2—C3—C4	114.04 (16)	N12—C11—H111	117.8
C2—C3—H31	107.0	C11—N12—C13	117.9 (2)
C4—C3—H31	109.7	C4—C13—N12	123.02 (19)
C2—C3—H32	107.1	C4—C13—C14	124.21 (18)
C4—C3—H32	109.8	N12—C13—C14	112.75 (18)
H31—C3—H32	109.1	C13—C14—C15	122.33 (18)
C3—C4—C5	119.74 (18)	C13—C14—C19	119.26 (19)
C3—C4—C13	121.65 (18)	C15—C14—C19	118.38 (19)
C5—C4—C13	118.57 (19)	C14—C15—C16	120.58 (19)
C4—C5—C6	123.5 (2)	C14—C15—H151	119.6
C4—C5—C10	118.0 (2)	C16—C15—H151	119.8
C6—C5—C10	118.5 (2)	C15—C16—C17	120.4 (2)
C5—C6—C7	120.0 (3)	C15—C16—H161	119.5
C5—C6—H61	120.2	C17—C16—H161	120.2
C7—C6—H61	119.8	C16—C17—C18	119.6 (2)
C6—C7—C8	121.0 (3)	C16—C17—H171	120.9
C6—C7—H71	119.2	C18—C17—H171	119.5
C8—C7—H71	119.8	C17—C18—C19	120.4 (2)
C7—C8—C9	120.5 (2)	C17—C18—H181	120.1
C7—C8—H81	119.9	C19—C18—H181	119.6
C9—C8—H81	119.6	C14—C19—C18	120.7 (2)
C8—C9—C10	119.9 (3)	C14—C19—H191	119.8
C8—C9—H91	119.9	C18—C19—H191	119.5
C10—C9—H91	120.2	C2—C20—H201	120.3
C9—C10—C5	120.0 (2)	C2—C20—H202	119.2
C9—C10—C11	122.0 (2)	H201—C20—H202	120.5