Palladium-Catalysed Enolate Arylation in the Synthesis of Isoquinolines

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by

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For Grandad

Declaration

This thesis and the work described herein is entirely my own, except where the help of coworkers is acknowledged or where reference is made to a published source or thesis.

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Abstract

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Alice E. Gatland, Linacre College, Michaelmas 2014

Chapter 1. Introduction

Scientific background on the development of homogeneous palladium-catalysed cross coupling reactions, focusing on the α-arylation reaction of enolates and its application to the synthesis of heteroaromatic compounds. The classical syntheses of isoquinolines are discussed, followed by an account of modern methods for their synthesis, including the recent α-arylation-based methodology developed by the Donohoe group.

Chapter 2. Results and Discussion

2.1 Studies towards the development of a palladium-catalysed, C–H activation-based α-arylation reaction of ketones, resulting in a C–H bromination/α-arylation sequence for the synthesis of isoquinolines and isoquinoline *N*-oxides.

2.2 The one-pot, four component coupling of a ketone, an acetal-protected *ortho*-bromobenzaldehyde or ketone, an electrophile, and an ammonia source is described. This protocol, which ultimately provides C4-functionalised isoquinolines, is later extended to a novel α,α-heterodiarylation protocol to furnish C4-aryl isoquinolines.

2.3 It is shown that the synthesis of 3-aminoisoquinolines can be achieved *via* the α-arylation of nitriles. *tert*-Butyl cyanoacetate can act as a substitute for primary alkyl nitriles, with sequential α-arylation, *in situ* functionalisation, decarboxylation and cyclisation reactions provide C4-functionalised 3-aminoisoquinolines.

2.4 The synthetic utility of the α-arylation-based methodology for isoquinoline synthesis is exemplified by the total synthesis of the alkaloid berberine in 68% yield over five steps. This is followed by syntheses of pseudocoptisine, palmatine, dehydrocorydaline, and an unnatural fluorine-containing analogue, in yields of 46%, 73%, 60% and 37%, respectively.

2.5 Finally, preliminary investigations demonstrate the utility of palladium-catalysed enolate arylation in the synthesis of β-carbolines.

Abbreviations and Acronyms

Å	Ångström
Ac	Acetate
ACE	Angiotensin-converting enzyme
Ad	Adamantyl
Amphos	Di-*tert*-butyl(4-dimethylaminophenyl)phosphine
Ar	Aryl
atm	Atmosphere
B	Base
BINAP	2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
Bn	Benzyl
BQ	Benzoquinone
br.	Broad
Bu	Butyl
CAAC	Cyclic (alkyl)(amino)carbene
CHK1	Checkpoint kinase 1
cm^{-1}	Wavenumber
CMD	Concerted metallation-deprotonation
cod	1,5-Cyclooctadiene
COSY	Correlated spectroscopy
Cp*	1,2,3,4,5-Pentamethylcyclopentadienyl
Cy	Cyclohexyl
CyJohnPhos	(2-Biphenyl)dicyclohexylphosphine
d	Doublet
d.r.	Diastereomeric ratio
DABCO	1,4-Diazabicyclo[2.2.2]octane
DavePhos	2-Dicyclohexylphosphino-2’-(*N*,*N*-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarisation transfer
DG	Directing group
DIBAL-H	Diisobutylaluminium hydride
D*i*PrPf	1,1’-Bis(di-isopropylphosphino)ferrocene
DMA	*N*,*N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether

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^+	Generic electrophile
eq	Equivalent(s)
ESI	Electrospray ionisation
Et	Ethyl
FI	Field ionisation
FT	Fourier transform
FWHM	Full width half maximum
g	Gram
G	Gibbs free energy
h	Hour(s)
HMBC	Heteronuclear multiple-bond correlation
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HSQC	Heteronuclear single quantum correlation
HPLC	High performance liquid chromatography
Hz	Hertz
i	Iso
in situ	In position (Latin)
in vacuo	In a vacuum (Latin)
IR	Infrared
J	Scalar coupling constant
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
K	Kelvin
K_a	Acid dissociation constant
kJ	Kilojoule
L	Generic ligand
LCMS	Liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamide
Lit.	Literature report
M	Molar
[M]	Generic metal
m	Multiplet
m	*meta*
m.p.	Melting point
m/z	Mass to charge ratio
*m*CPBA	*meta*-Chloroperoxybenzoic acid
MDAP	Reverse phase mass-directed autopreparative HPLC

Me	Methyl
MePhos	2-Dicyclohexylphosphino-2’-methylbiphenyl
min	Minute(s)
mL	Millilitre
mm	Millimetre
mmol	Millimole
MMTS	Methyl methylthiomethylsulfoxide
mol	Mole
mol%	Molar percent
MS	Molecular sieves
MW	Molecular weight
n	Normal
nbd	Norbornadiene
NBS	*N*-Bromosuccinimide
NFSI	*N*-Fluorobenzenesulfonimide
NHC	N-Heterocyclic carbene
NIS	*N*-Iodosuccinimide
nm	Nanometre
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Nu	Generic nucleophile
[O]	Generic oxidant
o	*ortho*
p	*para*
PA-Ph	1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane
PET	Positron emission tomography
pH	$-\log[H_3O]^+$
Ph	Phenyl
piq	1-Phenylisoquinoline
Piv	Pivaloyl
pK_a	$-\log[K_a]$
pK_b	pK_a of conjugate acid
PMP	*p*-methoxyphenyl
ppm	Parts per million
Pr	Propyl
Py	Pyridyl
q	Quartet
QPA	Quaternary protoberberine alkaloid
quin.	Quintet
QUINAP	1-(2-Diphenylphosphino-1-naphthyl) isoquinoline
R	Molar gas constant = 8.314 J mol^{-1} K^{-1}

R	Generic alkyl group
Rf	Retention factor
rt	Room temperature
s	Singlet
sept.	Septet
T	Temperature
t	Triplet
TBAB	Tetrabutylammonium bromide
TBME	*tert*-Butyl methyl ether
tert/t	Tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMP	Tetramethylpiperidide
TMS	Trimethylsilyl
Tol	Tolyl
Tol-BINAP	2,2’-Bis(di-*p*-tolylphosphino)-1,1’-binaphthyl
tosyl/Ts	*para*-Toluenesufonyl
triflate/Tf	Trifluoromethanesulfonate
UPLC	Ultra performance liquid chromatography
VEGFR	Vascular enothelial growth factor receptor
via	By way of (Latin)
vs	Versus
VT	Variable temperature
w/w	By mass
X	Generic heteroatom, halide or leaving group
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl
µL	Microlitre
µW	Microwave irradiation
ν_{max}	Absorption maximum
ν	Resonant frequency
λ_{max}	Wavelength of maximum intensity
°C	Degrees Celsius

Chapter 1. Introduction

1.1 Palladium-catalysed cross-couplings in organic chemistry

1.1.1 Historical perspective to the metal-catalysed cross-coupling reaction

The field of metal-promoted coupling chemistry was established in 1869 when Glaser demonstrated that preformed copper or silver phenylacetylides underwent oxidative dimerisation.[1,2] Later, in 1901, Ullmann discovered that an external source of copper could similarly homodimerise 2-bromo- or 2-chloronitrobenzene;[3] such bond formation between halogenated carbon atoms was to become a recognisable feature of transition metal-promoted coupling processes. Further progress was made in 1924 when catalysis (here interpreted as the use of substoichiometric quantities of transition metals) was introduced by Job, who revealed that the amount of ethylene fixed by a nickel-promoted reaction with phenylmagnesium bromide and CO_2 was independent of the quantity of $NiCl_2$ added.[4,5] The final essential feature of modern coupling chemistry emerged in 1943 when Kharasch reported the $CoCl_2$-mediated selective heterocoupling, or cross-coupling, of two different carbon fragments, namely vinyl bromide and an aryl magnesium species.[6] A degree of competing homocoupling of the organohalide component remained, however, and was not eradicated until Cadiot and Chodkiewicz, and Castro and Stephens, reported the copper-promoted selective cross-coupling of alkynes with bromoalkynes and aryl or vinyl halides in 1955 and 1963 respectively.[7–9]

1.1.2 Palladium as a catalyst

In the one hundred years following the discovery of palladium by Wollaston in 1805,[10] its potential in organic synthesis remained largely unfulfilled whilst fellow group members nickel and platinum were investigated for their roles in the oxidation, reduction and hydrogenation of unsaturated compounds. Palladium’s affinity for double and triple bonds was eventually noted, however, and exploited in the heterogeneous hydrogenation of unsaturated systems using palladium on charcoal and Lindlar's catalyst.[11,12] Following shortly after were the development of the Wacker process,[13] for the industrial-scale oxidation of olefins, and the characterisation of palladium π-allyl complexes.[14]

Over the next 50 years, the versatility and synthetic utility of palladium in homogeneous catalysis would become apparent, particularly in the field of C–C bond forming cross-coupling reactions. As a greater understanding of the mechanisms and the role of ligands was gained, coupling reactions could be optimised to take place under mild conditions, with very low catalyst loadings, and with extensive coupling partner scope. New classes of cross-coupling reaction were discovered to form not only C–C bonds, but also C–N, C–O and C–S linkages. The importance and synthetic utility of this branch of organic chemistry cannot be understated; a fact 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.[15]

Elemental palladium has electronic configuration [Kr]$4d^{10}$ and is found at the heart of a group of catalytically-active transition metals towards the right of the d-block of the periodic table, which includes nickel, copper, ruthenium, rhodium, iridium and platinum. Palladium's popularity in organic synthesis can be partly attributed to its ability to effect a great number of coupling reactions, but its appeal is more wide ranging.[16] For example, despite being a very rare metal, palladium is considerably cheaper than its neighbours such as platinum, iridium and rhodium. Sensitivity to oxygen and moisture are usually less of a concern than with, for example, Ni(0) or Rh(I) species, though Pd(0)-catalysed reactions are often executed under anhydrous conditions as a precaution. Furthermore, palladium sources can be stored for a number of months without degradation, owing in part to the regular use of air- and moisture-stable Pd(II) precatalysts.

The most common oxidation states of palladium are Pd(0) and Pd(II), but Pd(IV) species are also known, especially in the field of C–H functionalisation.[17,18] Cross-coupling processes generally employ Pd(0) compounds as active catalysts, whilst Pd(II) is usually reserved for oxidative reactions such as the Wacker process, and for stable precatalysts which can be reduced to Pd(0) *in situ*, for example $Pd(OAc)_2$. Tetracoordinate Pd(II) possesses enhanced stability as a result of its d^8 configuration and associated low-energy square planar geometry. In the absence of ligands which can help form coordinatively saturated complexes, Pd(0) readily forms particles of palladium black which are insoluble in most organic solvents. Consequently, the use of ligands is crucial to the success of cross-coupling reactions. Ligands play the additional, equally important, role of influencing the rates of various steps of the catalytic cycle through their steric and electronic properties and it is, without doubt, the development of new ligands that has driven the success of palladium-catalysed cross-coupling in organic synthesis.

1.1.3 Prominent palladium-catalysed cross-couplings

Throughout the 1970s and 1980s a small group of chemists developed a number of palladium-catalysed cross-coupling reactions that have since found widespread use in synthetic chemistry.[19] The majority share three core components:

1) an organohalide coupling partner, usually aryl or alkenyl;
2) a transition metal, in catalytic quantity;
3) a stoichiometric organometallic coupling partner, either preformed or generated *in situ*.

A notable exception is the Mizoroki-Heck reaction, in which a stoichiometric metal is not required to activate the vinyl coupling partner. Nevertheless, the reactions share a common first step in their mechanism: the oxidative addition of the organohalide (or pseudohalide) coupling partner R–X to Pd(0) (**Figure 1**).

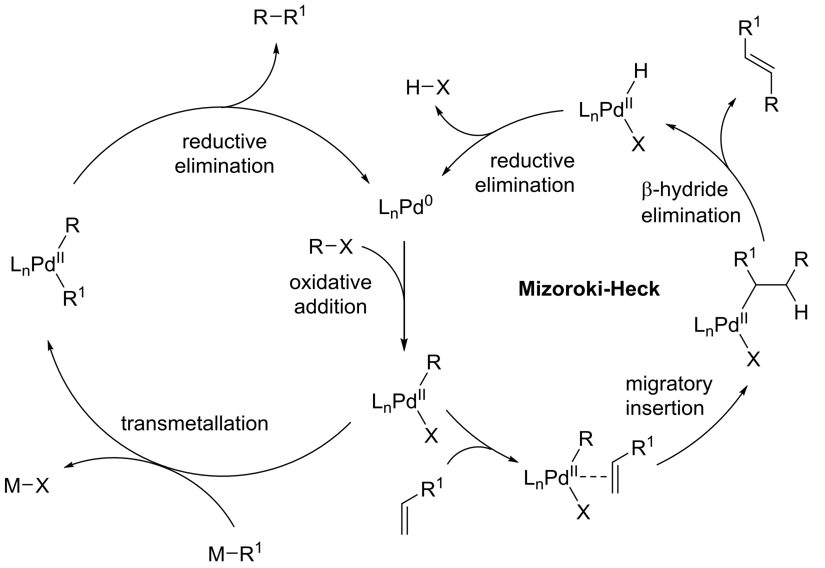


Figure 1. General catalytic cycles for palladium-catalysed cross-coupling reactions

During oxidative addition, the R–X bond is cleaved (hence the rate is inversely related to C–X bond strength) and two new bonds are formed to palladium by the arene or alkene R and the halide or pseudohalide (for example triflate) X, and in the process Pd(0) is oxidised to Pd(II). Oxidative addition is accelerated by electron rich palladium centres, that can be generated using good σ-donor ligands such as trialkylphosphines.

At this point the two cross-coupling mechanisms diverge, but both return the catalytically-active Pd(0) species by reductive elimination at the end of the catalytic cycle (**Figure 1**). Reductive elimination is a common final step in catalysis since the dissociation of the two coupling partners and concomitant reduction of Pd(II) to Pd(0) regenerates the coordinatively unsaturated catalyst. Since the process is concerted, the groups to be eliminated must be *cis*-disposed.[20] Bidentate ligands, which necessarily bind to palladium with their two coordination centres oriented *cis*, encourage reductive elimination by forcing the coupling partners to adopt a *cis* relationship (**Figure 2**). In addition, since the coordination number of palladium decreases during reductive elimination, steric crowding is reduced in the transition state and the relief of strain is maximised (and thus the rate enhanced) by using bulky ligands with a large bite angle.

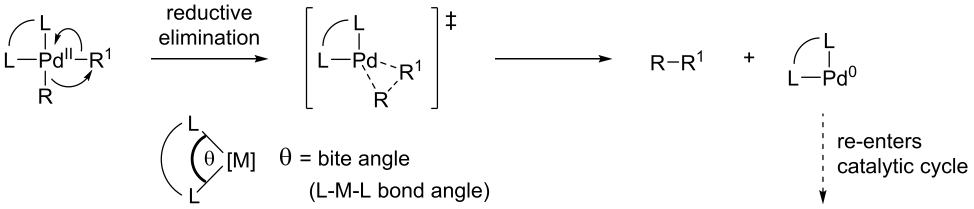
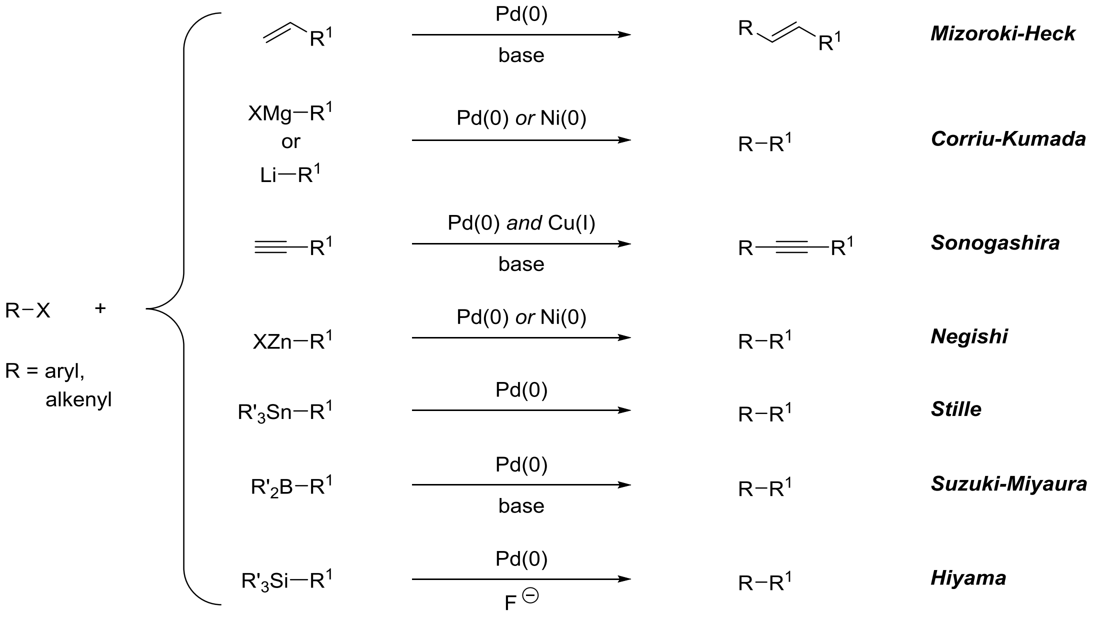


Figure 2. Reductive elimination

The intermediate mechanistic steps of the catalytic cycle will be discussed in the context of the prevalent palladium-catalysed cross-coupling reactions shown in **Scheme 1**.



Scheme 1. Notable C–C bond-forming palladium-catalysed cross-coupling reactions

Mizoroki-Heck reaction

Between 1968 and 1971, Mizoroki and Heck independently and simultaneously discovered the Pd(0)-catalysed coupling of aryl halides with alkenes.[21,22] Oxidative addition of the aryl halide onto Pd(0) is followed by coordination of the alkene and *syn* migratory insertion into the palladium-aryl bond. Such a reaction, where palladium and its carbon-bound ligand form σ-bonds to the two ends of the alkene, is often termed carbopalladation. The regioselectivity of insertion depends on the balance between the steric and electronic properties of the alkene.

Carbopalladation is followed by β-hydride elimination, which requires a *syn* disposition between the β-hydrogen and palladium, liberating the alkene product. Base-promoted reductive elimination of a hydrogen halide then regenerates the active Pd(0) catalyst.

Corriu-Kumada coupling

In 1972, Corriu and Kumada concurrently reported the nickel-catalysed coupling of aryl and alkenyl halides with Grignard reagents,[23] with Kumada using phosphine ligands to control the reactivity of nickel.[24] The subsequent introduction of palladium catalysis expanded the substrate scope to include organolithium reagents. Here, oxidative addition of R–X is followed by transmetallation with the organometallic partner and reductive elimination to liberate the product.

Sonogashira reaction

In 1975, Sonogashira published the palladium-catalysed coupling of acetylenes with aryl and vinyl halides. A copper co-catalyst and base formed a Cu(I) acetylide which underwent transmetallation with palladium.[25] Though conceptually similar to Castro and Stephens's early work,[9] Sonogashira's use of catalytic transition metals and ambient temperature represented a significant improvement in conditions.

Negishi coupling

In 1977, Negishi improved upon the Corriu-Kumada coupling by using nickel and palladium catalysts to couple less reactive organoaluminium and organozinc reagents with unsaturated organic halides.[26–28] The use of less electropositive-metal organometallic species (when compared to highly basic and nucleophilic Grignard reagents and organolithiums) expanded the functional group tolerance of the reaction.

Stille coupling

The coupling of aryl halides with organostannanes was first reported by Stille in 1978,[29] and then expanded in the early 1980s to include vinyl halide substrates.[30] A similar mechanism to that of the Corriu-Kumada coupling is proposed, proceeding by oxidative addition, transmetallation, and reductive elimination. However, a major disadvantage of the Stille reaction is the toxicity of organostannane reagents.

Suzuki-Miyaura coupling

The coupling of sp or sp^2 hybridised organoboranes with aryl halides was first reported by Suzuki and Miyaura in 1979.[31] Activation of the organoborane as the boronate is necessary for transmetallation, requiring the use of a base and aqueous conditions. Such conditions are convenient, however, and the organoboron starting materials are more stable and considerably less toxic than those of the Stille reaction.

Hiyama coupling

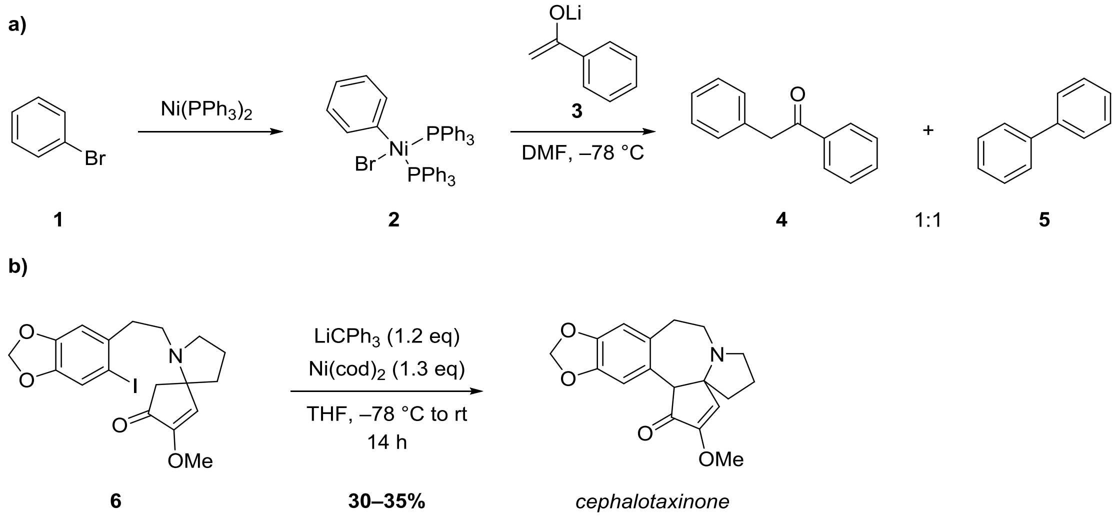
In 1988, Hiyama described the palladium-catalysed coupling of aryl halides and triflates with organosilanes which were activated towards transmetallation by a fluoride source, for example CsF, for formation of a pentavalent fluorosilicate intermediate.[32] Sensitive functional groups that did not withstand the strongly basic Suzuki-Miyaura conditions were now compatible.

Having established an invaluable cross-coupling toolkit for C–C bond formation using organometallic coupling partners, a second wave of cross-coupling research unlocked the potential of a new range of nucleophiles. Buchwald and Hartwig disclosed the coupling of aryl halides with amines in 1995, [33,34] and also made substantial contributions to the coupling reaction of enolates with aryl halides, whose application to heterocycle synthesis lies at the heart of this thesis.

1.2 Palladium-catalysed α-arylation of enolates

1.2.1 Early examples of metal-catalysed enolate arylation

The first, nickel-promoted, inter- and intramolecular arylation reactions of ketone enolates were reported by Semmelhack in 1973.[35] Treatment of bromobenzene **1** with $Ni(PPh_3)_4$ provided the isolable oxidative addition product **2**, to which was added the lithium enolate of acetophenone **3** either in a separate step or in one pot (**Scheme 2a**). The arylated ketone **4** and the homodimerisation product, biphenyl **5**, were obtained in a 1:1 ratio.



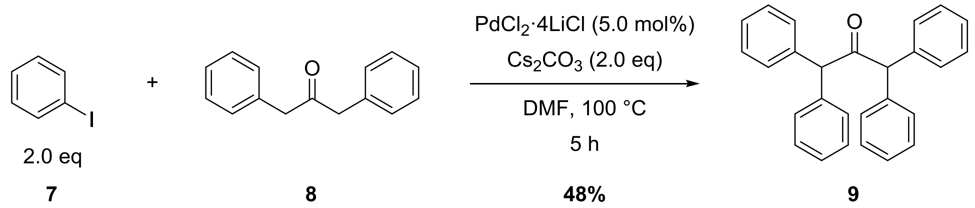
Scheme 2. Semmelhack's nickel-promoted enolate arylation reaction

The reaction was applied to the final intramolecular C–C bond-forming step in the synthesis of cephalotaxinone, where stoichiometric $Ni(cod)_2$ was required to provide the natural product in only 30% yield (**Scheme 2b**).[36] Nevertheless, and though not immediately followed-up, the results of Semmelhack demonstrated the viability of the concept of metal-promoted enolate arylation.

1.2.2 The pioneering work of Buchwald, Hartwig, and Miura

In 1997, Miura,[37] Buchwald,[38] and Hartwig[39] simultaneously published conditions for the direct intermolecular Pd(0)-catalysed arylation of ketone enolates.[40,41]

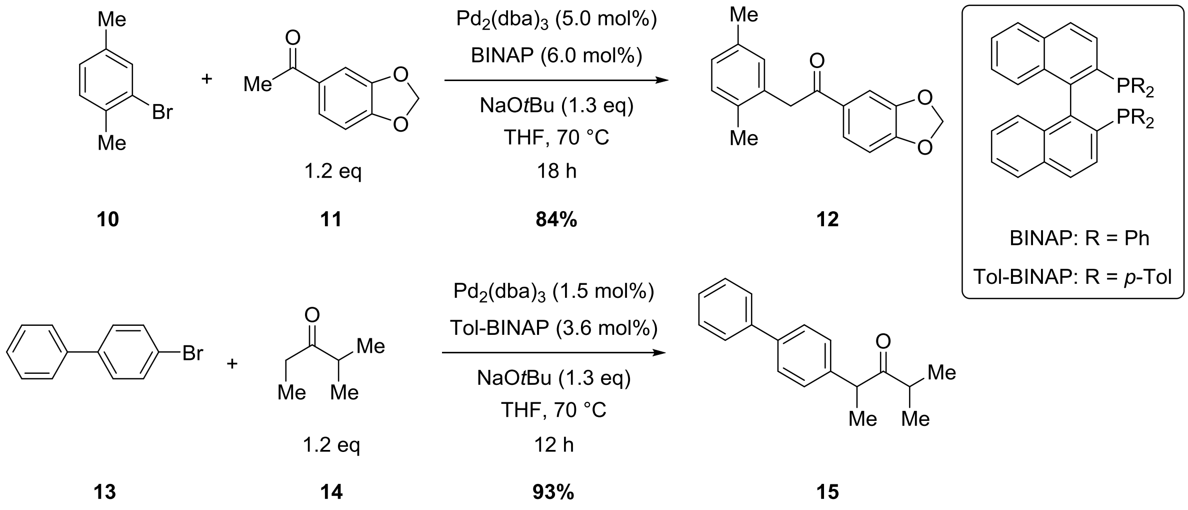
As a single example at the end of a publication primarily concerned with the arylation of phenols, Miura and coworkers used their newly-developed ligand-free conditions to arylate dibenzyl ketone **8** at both α positions (**Scheme 3**).[37]



Scheme 3. Miura’s ligand-free α-arylation of dibenzyl ketone **8**

Though product **9** was obtained in a modest yield of 48%, the intrinsic ability of Pd(0) to execute the coupling of aryl halides and ketones had been revealed.

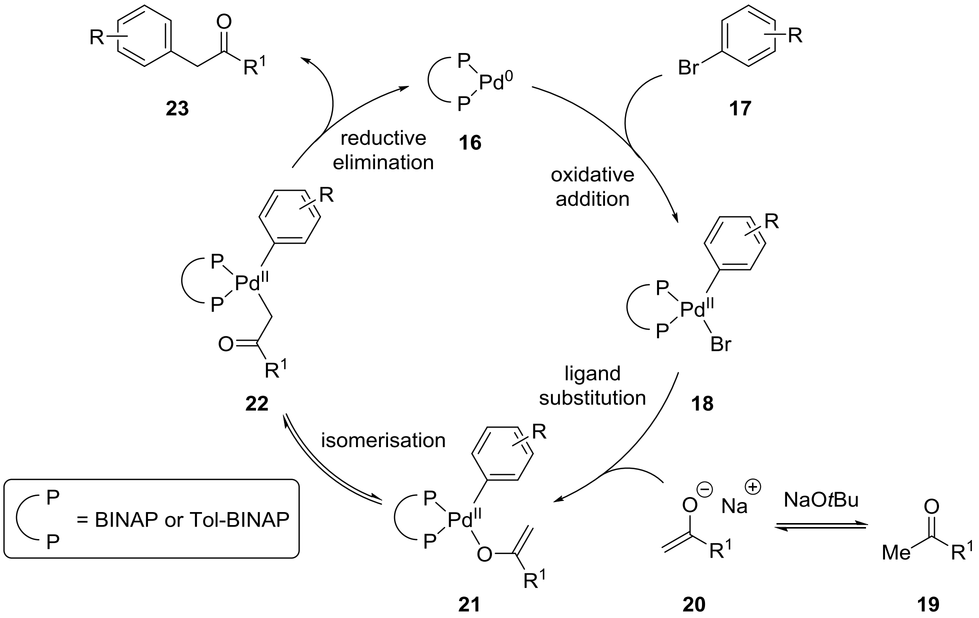
Buchwald and Hartwig, meanwhile, investigated the activity of a number of bisphosphine ligands which proved to be crucial for improving the yield of the reaction. Buchwald reported that in the presence of BINAP or Tol-BINAP, $Pd_2(dba)_3$ effectively catalysed the coupling of a range of aryl bromides and ketones in 63–93% yield (**Scheme 4**).[38]



Scheme 4. Buchwald’s α-arylation conditions

A variety of functional groups were compatible on the aryl bromide partner, including nitriles, ethers, imines, amides and acetals. Remarkable regioselectivity was observed, with ketones containing two enolisable α carbon centres undergoing selective arylation on the least-substituted side, even though it was less acidic. α,α-Diarylation was only observed for unhindered methyl ketones, and in small amounts (3–13%).

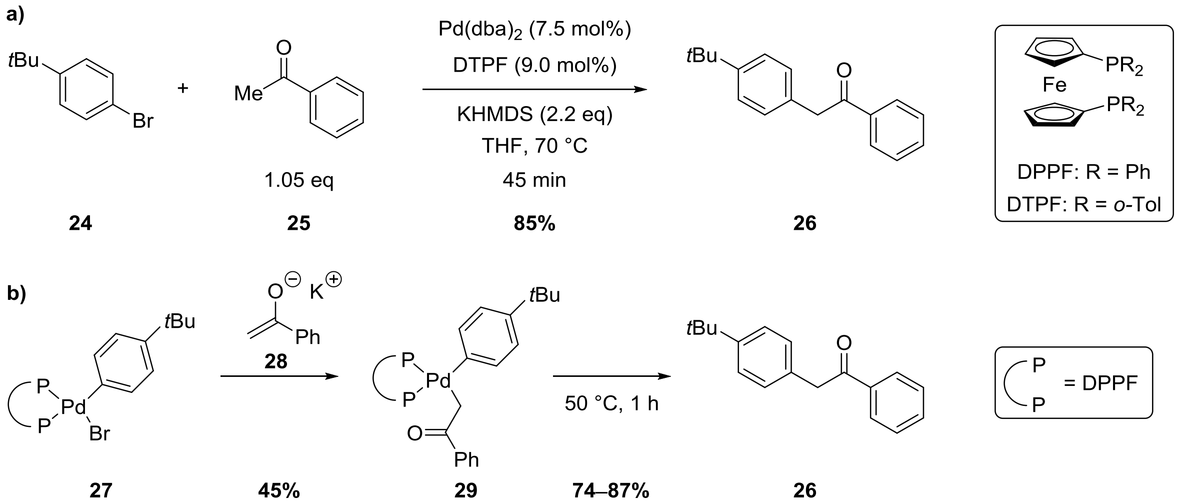
Mechanistically, Buchwald proposed that oxidative addition of the aryl bromide **17** to Pd(0) was followed by displacement of the bromide ligand by enolate **20** (formed *in situ* by deprotonation of ketone **19**) (**Scheme 5**). It was suggested that *O*-bound enolate complex **21** would be in equilibrium with *C*-bound species **22**, from which reductive elimination could occur to furnish α-arylated ketone **23** and regenerate Pd(0). The sterically bulky BINAP-based ligands were thought to play a crucial role in preventing β-hydride elimination in susceptible enolate complexes by denying the palladium centre open coordination sites.



Scheme 5. Proposed catalytic cycle for α-arylation

The formation of *O*-aryl enol ethers by direct reductive elimination from **21** has never been reported in these systems. Whilst reductive elimination to form a C–O bond is known, it is usually slow due to the high polarity and ionic nature of the Pd–O bond, and has been limited to special cases such as diaryl ether formation from phenoxide complexes.[42,43] In our case it is likely that isomerisation of **21** to the carbon-bound enolate complex **22** is followed by rapid reductive elimination, funnelling complex **21** through to α-aryl ketone **23**.

The procedure independently developed by Hartwig involved a catalytic system comprising Pd(dba)$_2$ and a chelating ferrocenyl bisphosphine ligand such as DPPF or DTPF (**Scheme 6a**). Good selectivity for monoarylation was observed when using KHMDS for electron rich or electron neutral aryl halides, and NaO*t*Bu for electron deficient aryl halides.



Scheme 6. Hartwig's α-arylation conditions and preliminary mechanistic investigations

Hartwig proposed an almost identical mechanism to Buchwald's, and conducted some initial mechanistic studies using isolable oxidative addition complex **27** (**Scheme 6b**).[44] Upon treatment with the potassium enolate of acetophenone, a new complex **29** was isolated, in 45% yield, which was shown to be *C*-bound by ^{31}P NMR spectroscopy. This complex underwent reductive elimination upon heating to form the α-aryl ketone **26** in 74–87% yield.

Buchwald and Hartwig both observed highly selective arylation on the less substituted side of ketones containing two enolisable α-positions. To gain some insight into the origin of this regioselectivity, Hartwig conducted further mechanistic studies using isolable DPPBz- and PPh$_2$Et-ligated arylpalladium enolate complexes (**Figure 3a**).[45] In DPPBz complexes, enolates from methyl or methylene ketones, such as **30**, were *C*-bound. In ketones with methyl *and* methylene groups, such as **31**, the enolate bound solely through the less-substituted methyl group. Branched enolates with two substituents at the α position, such as **32**, bound through oxygen.

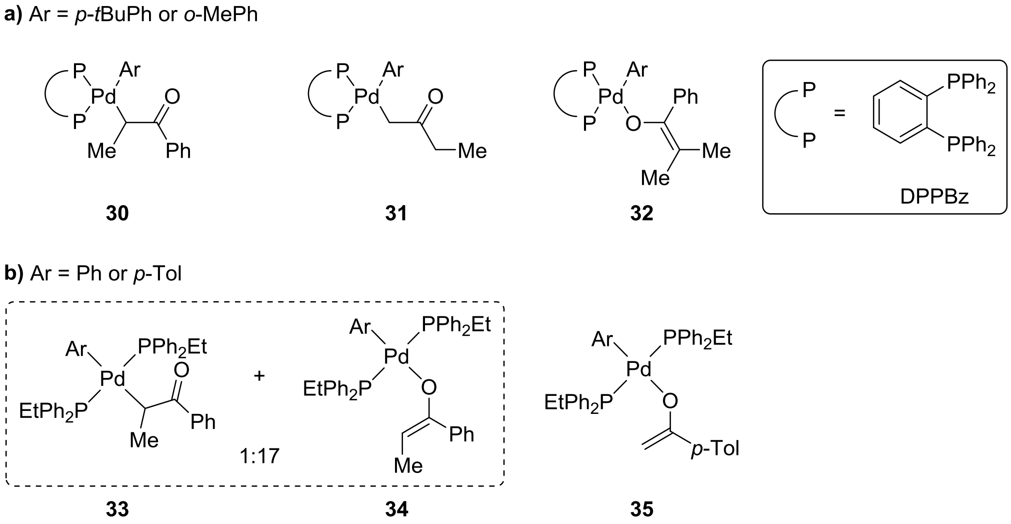


Figure 3. Stable aryl Pd(II) enolate complexes

Complexes with PPh_2Et as a ligand displayed a *trans* geometry between the aryl and enolate groups and showed a strong preference for the *O*-bound form (**Figure 3b**). Thus, it was concluded that *C*-bound enolates are favoured if the enolate is *trans* to a phosphine, but the *O*-bound form is favoured if *cis* to a phosphine. Therefore, binding through carbon might be encouraged by using a bidentate ligand. In all cases, complexes of α,α-disubstituted ketone enolates are more stable in the *O*-bound form.

The thermodynamic stabilities of the DPPBz enolate complexes **30**–**32** were assessed by equilibration with a competitive ketone enolate, and it was found that complexes with a greater number of substituents at the α position were more prone to collapse. Stability was largely independent of pK_a except for benzyl ketones, where the significantly enhanced acidity of the phenyl-substituted α position appeared to outweigh the effect of steric crowding. Subsequent experiments revealed that there was little variation in rate of reductive elimination from arylpalladium enolate complexes such as **30**–**32**, and so the major factor controlling the regioselectivity of the reaction was proposed to be the preferred formation of the most stable, least sterically-hindered *C*-bound enolate complex.

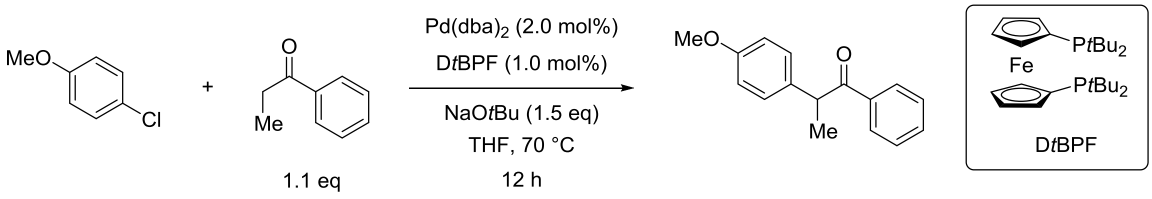
1.2.3 The role of base

Prashad and coworkers investigated the effect of the quantity of base on product distribution under ligand-free arylation conditions similar to those used by Miura.[46] Increasing the amount of NaO*t*Bu to 3.0 equivalents, when using 1.4 equivalents of ketone, suppressed the formation of α,α-diarylated side-products which had been previously observed by Buchwald.[38,47] Such over-reaction was a consequence of the greater acidity of the α protons in the product relative to the ketone starting material (acetophenone $pK_a = 24.7$,[48] deoxybenzoin $pK_a = 17.7$ in DMSO)[49] which resulted in preferential deprotonation of the product. This ketone was therefore susceptible to a second arylation unless excess base was present to fully deprotonate the starting material, which underwent faster arylation since it was both less hindered and higher in energy, to give selectively monoarylated products.

1.2.4 Ligand development

In 1999, Hartwig published the results of a study on the rational design and development of highly active catalysts for palladium-catalysed enolate arylation, focusing on the nature of the ligands.[50] It was hypothesised that sterically bulky ligands should increase the rate of reductive elimination, since a high-coordinate Pd(II) species is converted to a low-coordinate Pd(0) species,[51,52] and that chelation would prevent the intermediate enolate complex from undergoing β-hydride elimination.[53] Good σ-donor ligands ought to facilitate oxidative addition, and it was thought that alkyl phosphines would be more resistant towards P–C bond cleavage than aryl phosphines, thereby extending the lifetime of the catalyst.[54,55]

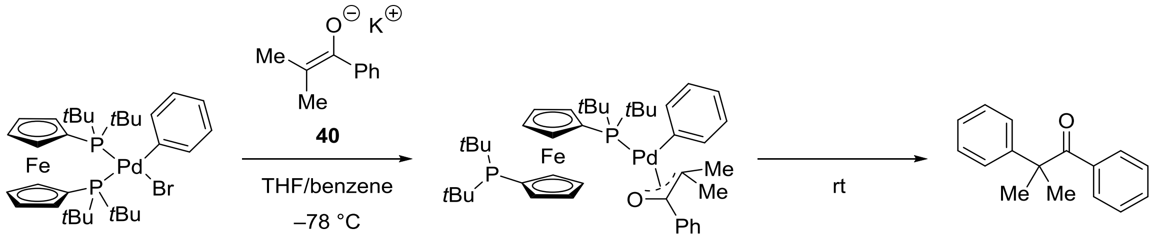
With this in mind, Hartwig and coworkers tested the sterically hindered bidentate ligand 1,1’-bis(di-*tert*-butylphosphino)ferrocene (D*t*BPF) and found it highly active in the coupling of a number of ketones with aryl bromides (**Scheme 7**).[56] For the first time, less-reactive aryl chlorides could also be used, and turnover numbers were as high 20,000.



36 **37** **38**

Scheme 7. Hartwig's use of D*t*BPF in the arylation of ketones using aryl chlorides

Stoichiometric mechanistic studies were once again conducted, this time using the D*t*BPF ligand and the potassium enolate of isobutyrophenone **40** (**Scheme 8**). A single product **41** was obtained, and whilst the coordination mode of the enolate in complex **41** could not be ascertained by ^{1}H NMR spectroscopy, ^{31}P NMR showed conclusively that only one phosphorus atom of D*t*BPF was bound to palladium. When warmed to room temperature, species **41** underwent reductive elimination in quantitative yield.



39 **41** **42**

Scheme 8. Monophosphine ligand coordination in intermediate enolate complex **41**

Hence, it was concluded that a bidentate ligand was not necessary, and that sterically hindered monophosphines may also effect the transformation. Indeed, P*t*Bu$_3$ and PCy$_3$ were shown to be extremely effective at promoting α-arylation with aryl bromides and chlorides, respectively.[56]

In 2000, Buchwald also demonstrated that a number of monodentate ligands were capable of mediating α-arylation reactions (**Figure 4**).[47] Substrate scope was comprehensive, including aryl bromides and chlorides with alkyl, alkoxy, nitrile, ester, amide and acetal substituents. When base-sensitive functional groups such as methyl esters were present, best results were obtained using K$_3$PO$_4$. Since it would not be expected that such a mild base would deprotonate a ketone (HPO_4^{2-} pK_a = 12.3,[57] *t*BuOH pK_a = 16.5 in H_2O),[58] it was proposed that prior coordination of the ketone oxygen atom to palladium may assist.

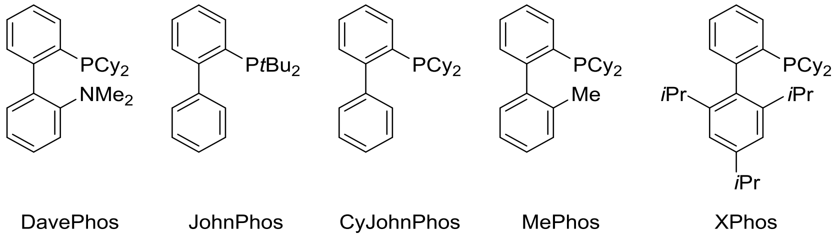
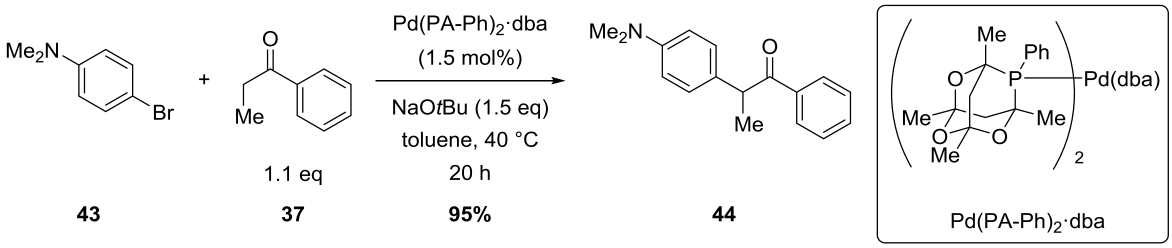


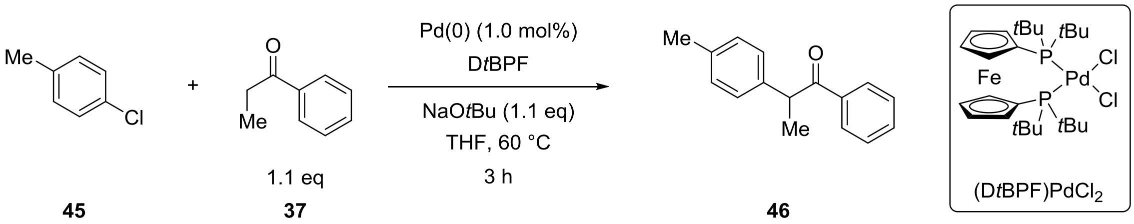
Figure 4. Buchwald's monodentate biaryl phosphine ligands

Capretta and coworkers used a bulky tertiary phosphine ligand bearing a phosphaadamantane group to effect the highly efficient α-arylation of propiophenone **37**, and isobutyrophenone, at low temperatures (**Scheme 9**).[59]



Scheme 9. Capretta's use of a phosphaadamantane ligand

In 2007, well-defined and air stable (D*t*BPF)PdX_2 complexes (X = Cl, Br), in which the P–Pd–P bite angle of the bidentate ligand is the largest (104.22°) in the series of bisphosphinoferrocene complexes of $PdCl_2$, were identified by Colacot and coworkers as active catalysts in α-arylation reactions of ketones (**Table 1**, Entry 3).[60]

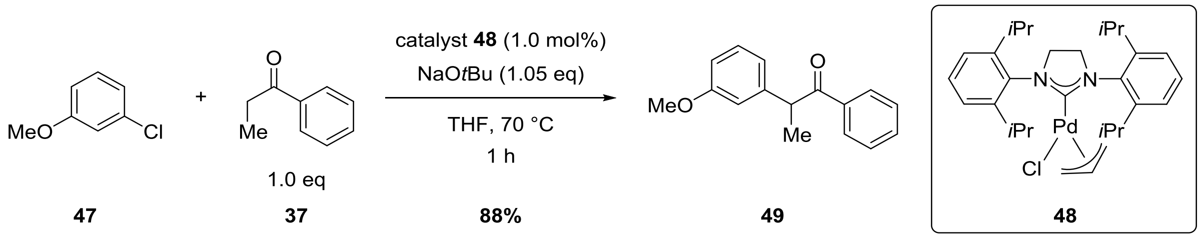


Entry	Pd source	Pd:D*t*BPF ratio	Conversion / %
1	$Pd_2(dba)_3$	2:1	70
2	$Pd_2(dba)_3$	1:1	31–35
3	(D*t*BPF)$PdCl_2$[a]	1:1	80

Table 1. Use of Pd(II) precatalyst (D*t*BPF)$PdCl_2$ vs $Pd_2(dba)_3$ plus D*t*BPF
[a] No additional D*t*BPF added

^{31}P NMR analysis of the reaction mixture indicated that the active catalytic species was (D*t*BPF)Pd(0). However the preformed Pd(II) precatalyst gave significantly better conversion than the equivalent mixture of $Pd_2(dba)_3$ and D*t*BPF (Entriy 3 vs Entry 2). This was hypothesised to be a result of the formation of inactive species, such as the 18-electron complex $(DtBPF)_2Pd(0)$, in addition to the active catalyst when palladium and ligand were mixed *in situ*. This was supported by the observation that, when added separately, the optimum Pd:ligand ratio was found to be 2:1. Using an excess of palladium ensured only monoligation by D*t*BPF, giving a higher concentration of the active (D*t*BPF)Pd(0) species.

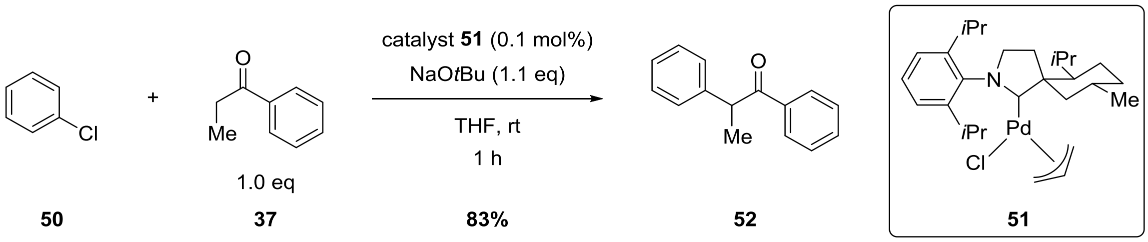
Though tertiary phosphines had become popular ligands, they were relatively expensive and could be difficult to remove during purification. Nolan and coworkers therefore investigated the use of N-heterocyclic carbenes (NHCs), which are also strong σ-donors, in the α-arylation of ketones.[61] Simple aryl bromides, chlorides and triflates could be coupled with ketones in short reaction times using low loadings of the air-stable precatalyst **48** (**Scheme 10**).



Scheme 10. α-Arylation using NHC complex **48**

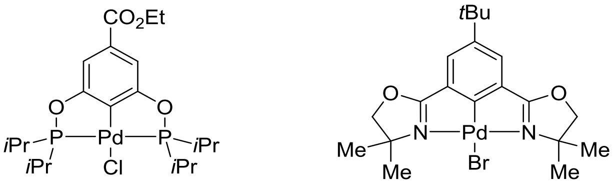
Nolan subsequently reported that a novel class of palladacycle-NHC complexes were also effective at promoting α-arylation reactions.[62]

A third class of active ligands was reported by Bertrand and coworkers in 2005.[63] Their stable cyclic (alkyl)(amino)carbenes (CAACs) were more electron rich than NHCs since one of the electronegative nitrogen atoms was replaced with carbon. Extremely low loadings of precatalysts such as **51** effectively coupled aryl chlorides with propiophenone at room temperature (**Scheme 11**).



Scheme 11. Bertrand’s CAAC ligand in α-arylation

Finally, pincer complexes such as PCP complex **53** and NCN complex **54**, developed by Domínguez and Connel respectively, were shown to be highly active in the selective α-monoarylation of ketones with *para*-substituted aryl bromides (**Figure 5**). [64,65]

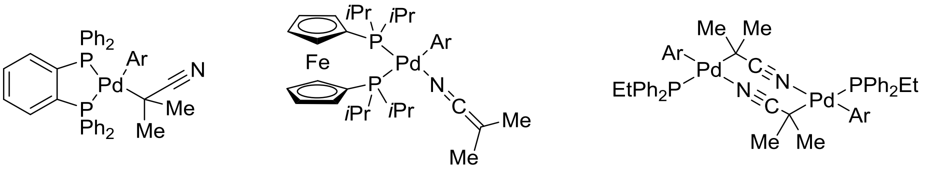


53 **54**

Figure 5. Active PCP and NCN pincer catalysts

1.2.5 α-Arylation of nitriles

The α-arylation reaction of nitriles is a significantly more challenging prospect than that of ketones. Nitriles are generally less acidic than ketones (propiophenone pK_a = 24.4,[49] propionitrile pK_a = 32.5 in DMSO),[66] requiring stronger bases which limit functional group tolerance. It is also possible for nitrile enolates to bind to palladium through carbon, nitrogen, or in a μ^2 bridging mode forming stable dinuclear structures. In 2002, Hartwig obtained X-ray crystal structures of a number of arylpalladium cyanoalkyl complexes and discovered that the nitrile anions were *C*-bound, as in **55**, unless a sterically-demanding ligand, such as D*i*PrPF in **56**, was present, when preferential coordination through nitrogen was observed (**Figure 6**).[67]

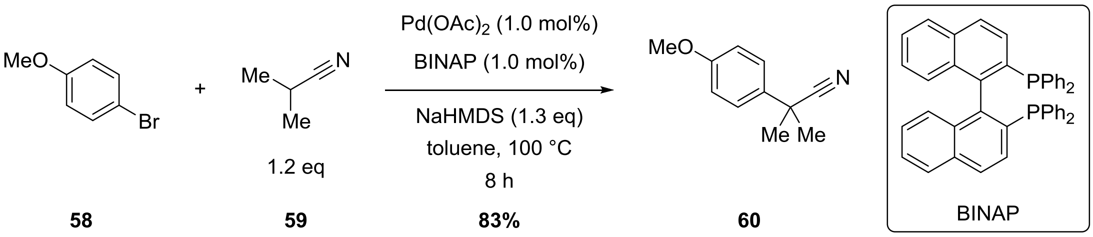


55 **56** **57**

Figure 6. The different coordination modes of alkyl nitrile anions

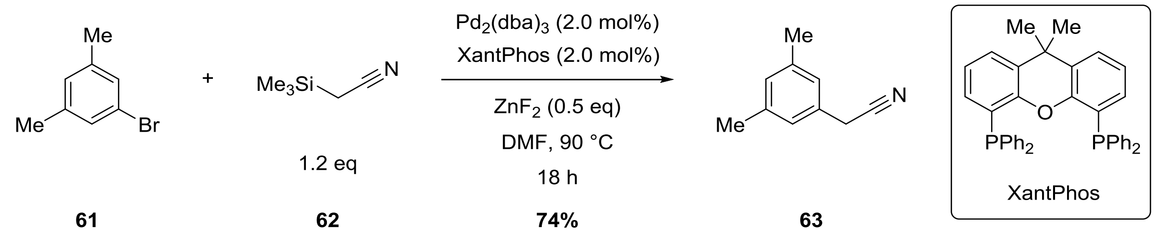
When a labile phosphine such as PPh_2Et was present, ligand displacement occurred and the nitrogen atom of a *C*-bound nitrile coordinated to a second palladium centre creating a μ^2 bridged complex such as **57**.

Furthermore, reductive elimination of nitriles is significantly slower than from ketone enolate complexes due to the strong inductive effect of the cyano group, which allows side reactions to compete with the desired coupling. Hartwig demonstrated that the arylation of α-disubstituted nitriles was possible, but only when using bulky ligands such as BINAP and P*t*Bu$_3$, and a strong metal HMDS base (**Scheme 12**).



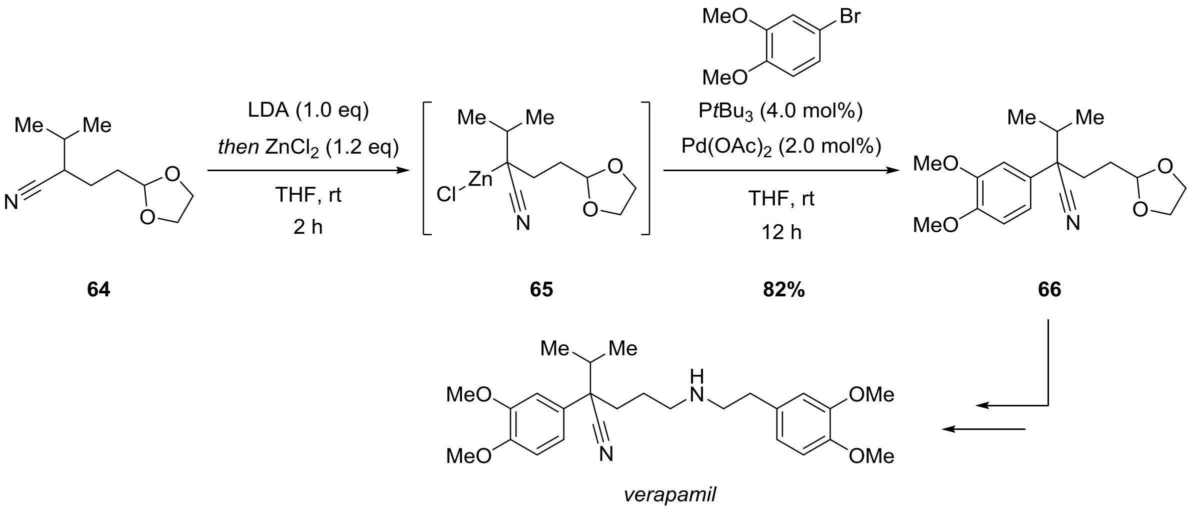
Scheme 12. Hartwig's α-arylation of branched alkyl nitrile **59**

The sensitivity of these conditions to moisture, and the propensity for unbranched α-alkyl nitriles to undergo diarylation due to the unhindered linear geometry of the nitrile group, limited the generality of the reaction. Hartwig therefore developed two new methods using nitrile enolate surrogates.[68] Firstly, α-silyl nitriles such as **62** were shown to undergo coupling with electron rich, electron deficient and electron neutral aryl bromides when activated with a stoichiometric amount of ZnF_2 (**Scheme 13**). The reactions of unhindered aryl halides were promoted by XantPhos, whilst *ortho*-substituted aryl halides required the use of P*t*Bu$_3$. Secondary nitrile derivatives were inert under these conditions.



Scheme 13. Arylation of α-silyl nitriles activated by ZnF_2

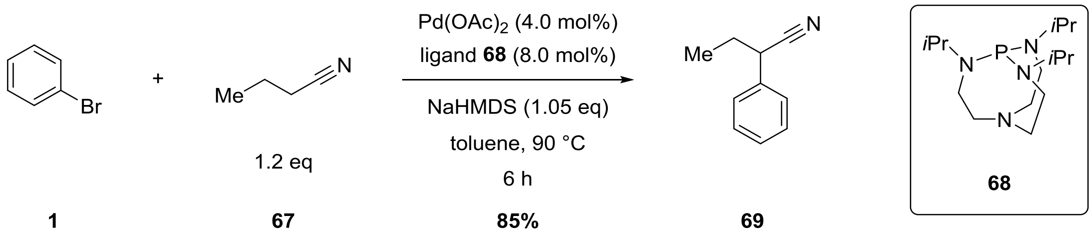
The absence of a free enolate likely results in a Hiyama-type mechanism involving transmetallation of the α-nitrile from silicon to palladium, possibly *via* a zinc cyanoalkyl derivative. Preformed zinc enolates were employed in Hartwig's second alternative procedure which could be used to α-arylate more hindered nitriles. Deprotonation of the nitrile was followed by the addition of $ZnCl_2$ to form a zinc cyanoalkyl species which was coupled with aryl bromides containing alkoxy, dimethylamino, acyl and ester groups, avoiding the need for strong bases. A short synthesis of the hypertension drug verapamil exemplified the method (**Scheme 14**).[69]



Scheme 14. Hartwig's zinc cyanoalkyl arylation in the synthesis of verapamil

Though the method was highly effective for the arylation of branched alkyl nitriles, it was not a practically amenable procedure as the use of air- and moisture-sensitive lithium amide bases and P*t*Bu$_3$ necessitated the use of a dry box.

In 2003, Verkade and coworkers reported that their bicyclic proazaphosphatranes were active catalysts in the α-arylation of branched and linear alkyl nitriles using aryl bromides and chlorides (**Scheme 15**).[70,71]



1 **67** **85%** **69**

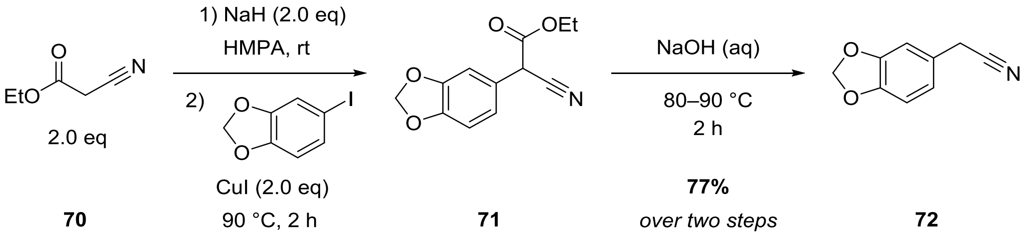
Scheme 15. Verkade's use of caged triaminophosphine ligands in the α-arylation of nitriles

Previously used as very strong bases and potent catalysts for other transformations, such as Suzuki-Miyaura reactions and aryl aminations, these ligands possessed a number of structural features which were key to their reactivity.[72] It was postulated that transannulation of the bridgehead nitrogen's lone pair enhanced the electron density on phosphorus, promoting oxidative addition.[73] Furthermore, the bicyclic framework was rigid yet strain-free, so resistant to cleavage, and the electronic and steric properties could be fine-tuned by attaching organic substituents to each PN_3 nitrogen atom. Once again, however, both the ligand (a viscous liquid) and base were air- and moisture-sensitive, requiring the use of a dry box.

1.2.6 α-Arylation of cyanoacetates

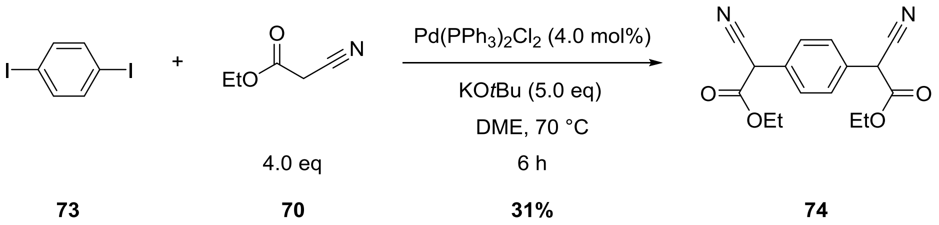
By virtue of the electron withdrawing ester moiety, cyanoacetates are considerably more acidic than alkyl nitriles (ethyl cyanoacetate $pK_a = 13.1$,[74] acetonitrile $pK_a = 31.3$ in DMSO)[66] and are therefore much more suitable candidates for α-arylation under mild conditions.

In 1983, Suzuki and coworkers reported the copper-mediated coupling of ethyl cyanoacetate **70** with aryl iodides and bromides (**Scheme 16**).[75] Subsequent decarboxylative hydrolysis upon treatment with aqueous NaOH provided the corresponding aryl acetonitrile **72**.



Scheme 16. Suzuki's copper-promoted arylation of ethyl cyanoacetate

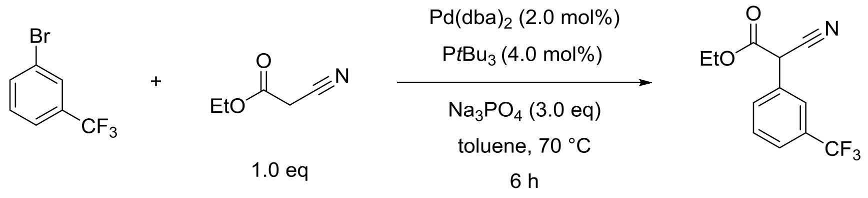
This was followed in 1985 by Takahashi's report of the first palladium-catalysed arylation of malononitrile and ethyl cyanoacetate using dihaloarenes, employing Pd(PPh$_3$)$_2$Cl$_2$ as a precatalyst and KO*t*Bu as the base, albeit in modest yields (**Scheme 17**).[76]



Scheme 17. Takahashi's early palladium-catalysed conditions for cyanoacetate arylation

In 2001, Hartwig used fluorescence resonance energy transfer in the high-throughput screening of precatalysts, ligands, bases and solvents for optimisation of the palladium-catalysed α-arylation of ethyl cyanoacetate.[77] A cyanoester containing a dansyl fluorophore tether was arylated with an aryl halide containing a pendant diazo chromophore. When coupled, and therefore sufficiently close in space, the fluorescence of the dansyl group was quenched by the diazo fragment. Emission intensity could be measured and the reaction yield was calculated using an inverse correlation.

As a result of these investigations, Hartwig found that Pd(dba)$_2$ and [Pd(allyl)Cl]$_2$ were the most active palladium sources when used with P*t*Bu$_3$ or P*t*Bu$_2$Ad ligands and Na$_3$PO$_4$ as a base (**Scheme 18**).



75 **70** **87%** **76**

Scheme 18. Hartwig’s optimised conditions for α-arylation of ethyl cyanoacetate

Subsequent experiments revealed that the ferrocenyl ligand QPhos could also be used in the coupling of ethyl cyanoacetate with aryl bromides and chlorides, and was particularly useful for the selective monoarylation of *para*-substituted electron deficient aryl bromides which had undergone varying amounts of diarylation with $\mathrm{P}t\mathrm{Bu}_3$.[78]

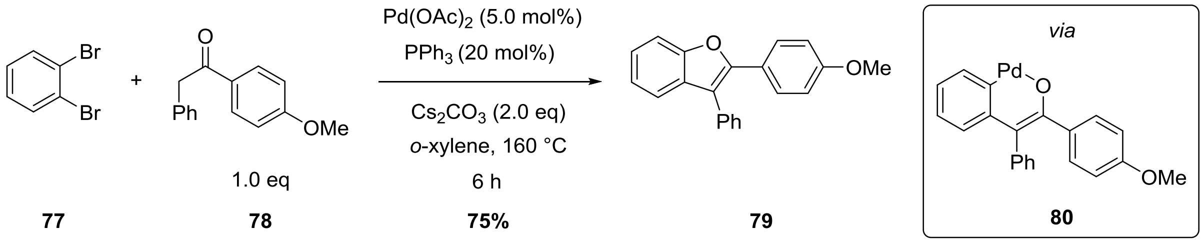
1.2.7 Palladium-catalysed α-arylation of other carbonyl systems

Similar to nitriles, esters are less acidic than ketones; they can undergo competing Claisen condensations under strongly basic conditions, and are vulnerable to decomposition to ketenes *via* deprotonation and acyl cleavage at elevated temperatures. Once again, Buchwald and Hartwig demonstrated that it was possible to overcome some of these difficulties, and arylated predominantly *tert*-butyl esters (which are less liable to undergo Claisen condensation) at room temperature using LiHMDS or $\mathrm{LiNCy_2}$, and bulky phosphine or NHC ligands.[79–81] Functional group tolerance was later improved when Hartwig used Reformatsky reagents which coupled under milder conditions.[82]

The α-arylation reactions of a variety of other systems have been reported, including aldehydes,[83–85] amides,[86,87] enolate equivalents such as silyl enol ethers,[88–90] β-difunctionalised carbonyls including β-ketoesters,[91] malonates,[50] malononitriles[92] and diketones,[47] and also nitroalkanes.[47] Good progress has also been made by those attempting to render the α-arylation reaction enantioselective.[93–95] These topics are discussed in depth in two comprehensive reviews.[40,41]

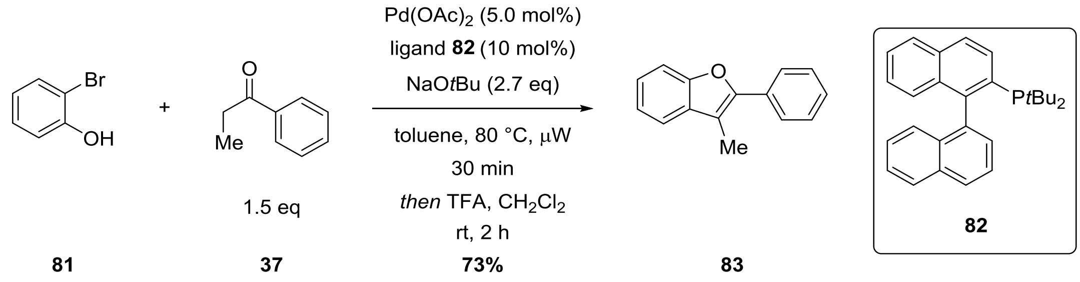
1.2.8 Palladium-catalysed α-arylation in the synthesis of heteroaromatic compounds

The palladium-catalysed α-arylation of ketones and imines has been applied to the synthesis of benzofurans, benzothiophenes and indoles. In 1999, Miura was the first to demonstrate this approach, by coupling benzyl phenyl ketone **78** with *o*-dibromobenzene **77** (**Scheme 19**).[96]



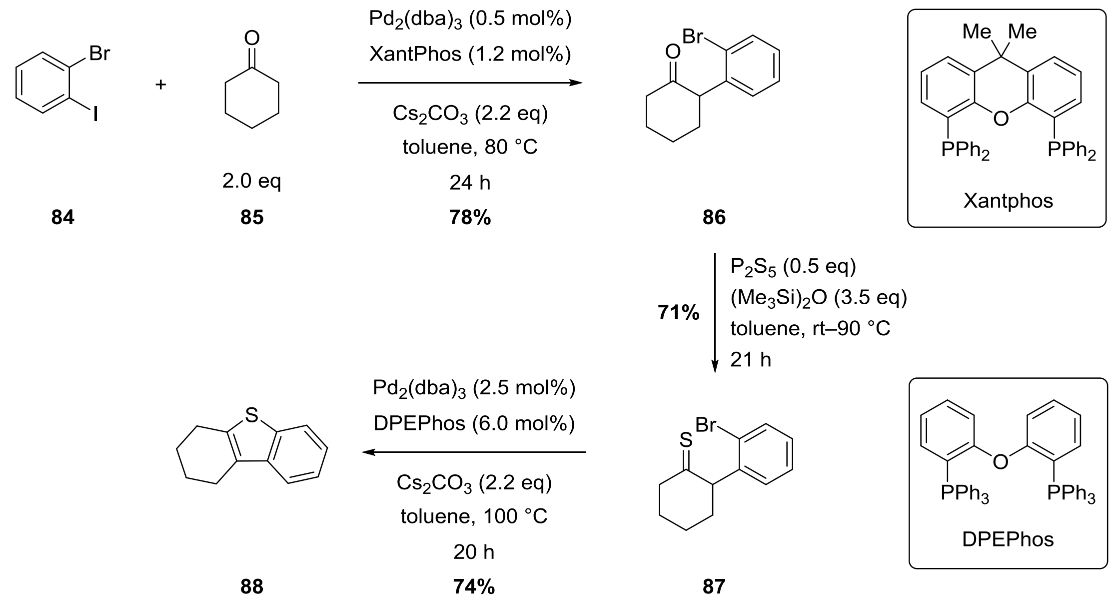
Scheme 19. Miura's benzofuran synthesis

It was suggested that the reaction proceeded *via* enolate arylation then oxidative addition of the second aryl C–Br bond to palladium and intramolecular displacement of bromide by the oxygen atom of the internal enolate, forming palladacycle **80**. Reductive elimination to form the C–O bond was favoured in this system as the alternative C–C bond formation would generate a strained, fused cyclopropene. This strategy was later expanded upon by Domínguez[97] and Willis.[98,99] In 2008, Burch reported that *ortho*-bromophenols could also be used as starting materials in the synthesis of benzofurans (**Scheme 20**).[100] Binaphthyl ligand **82** promoted the α-arylation of propiophenone **37** under microwave conditions, giving an intermediate phenolic benzyl ketone which could be cyclised by the addition of TFA.



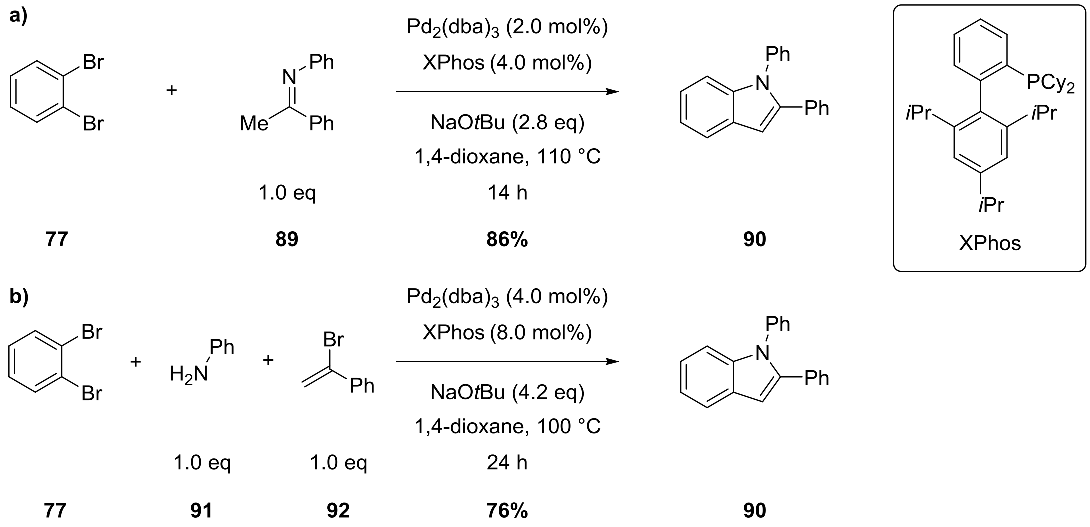
Scheme 20. Burch's synthesis of benzofuran **83** from *ortho*-bromophenol **81**

Willis and coworkers also applied their benzofuran methodology to the synthesis of benzothiophenes by treating the products of ketone α-arylation with P_2S_5 (**Scheme 21**).[99]



Scheme 21. Willis's use of ketone arylation in the synthesis of benzothiophene **88**

In 2007, Barluenga demonstrated that indoles were accessible by palladium-catalysed α-arylation, this time employing enolisable imines.[101,102] By careful choice of base and ligand, azaallylic anions underwent selective *C*-arylation (rather than *N*-arylation as in the Buchwald-Hartwig coupling),[33,34] followed by palladium-mediated annulation (**Scheme 22a**).



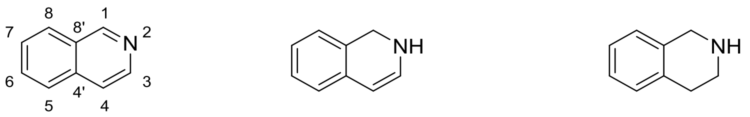
Scheme 22. Barluenga's catalytic two- and three-component indole syntheses

Having previously reported a synthesis of imines by palladium-catalysed amination of vinyl halides,[103] Barluenga was also able to execute a one-pot three-component coupling reaction providing indoles such as **90** (**Scheme 22b**).

1.3 Isoquinolines

1.3.1 Structure and reactivity

Isoquinoline, or 2-azanaphthalene, is a 10 π-electron benzopyridine in which the benzene ring is fused to the C3 and C4 atoms of pyridine (**Figure 7**).



isoquinoline *dihydroisoquinoline* *tetrahydroisoquinoline*

Figure 7. Isoquinoline and common partially-saturated derivatives

The nitrogen atom bears a lone pair of electrons not involved in aromatic bonding, enabling isoquinoline to act as a mild base (pK_b = 5.4).[104] The nitrogen atom can also be alkylated to form quaternary salts, or complexed to Lewis acids and metal catalysts. Oxidation of nitrogen with peroxy acids such as *m*CPBA affords the corresponding isoquinoline *N*-oxides.

In common with pyridine, isoquinoline is a π-electron deficient system due to the greater electronegativity and lower-energy 2p orbitals of nitrogen relative to carbon. As a result, isoquinolines react primarily with nucleophiles, especially on the heteroaromatic ring where attack adjacent to nitrogen is most common. Substitution at C1 is generally favoured since displacement at C3 involves temporary disruption of aromaticity in the benzenoid ring.

Electrophilic substitution reactions on simple isoquinoline derivatives are not common, but can take place on the less electron deficient carbocyclic ring under forcing conditions. In the presence of acid, for example during nitration and sulfonation, the nitrogen atom is protonated, which further deactivates the heteroaromatic ring towards the addition of electrophiles. When it does occur, electrophiles add predominantly at C5, with reaction also sometimes observed at C8 (**Figure 8**).

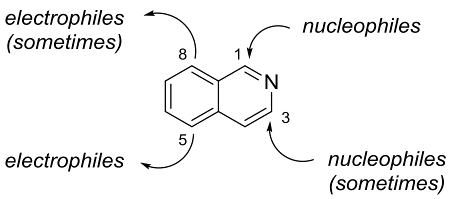
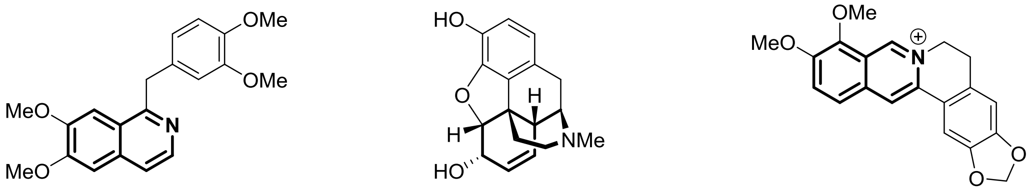
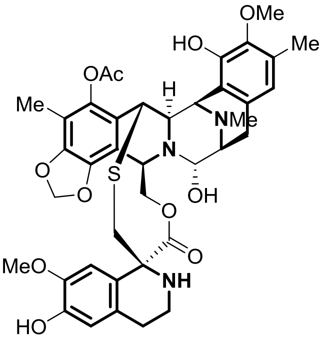


Figure 8. Reactivity of isoquinolines with nucleophiles and electrophiles

Isoquinolines and their partially-saturated derivatives form the core structures of a vast number of natural products, including over 400 isoquinoline alkaloids,[105] many of which are secondary metabolites, that possess potent biological activity.[106] These include the opium alkaloid morphine, and papaverine, which has found use as a vasodilator,[107–109] as well as the bright yellow dye berberine (**Figure 9**). Ecteinascidin 743 (also known as trabectedin), isolated from the Caribbean tunicate *Ecteinascidia turbinate,* contains three tetrahydroisoquinoline subunits and is used as an anti-tumour drug.[110]



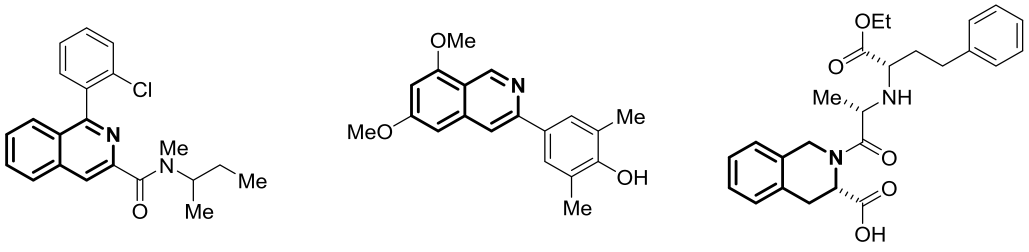
papaverine *morphine* *berberine*



ecteinascidin 743

Figure 9. Isoquinoline-containing natural products

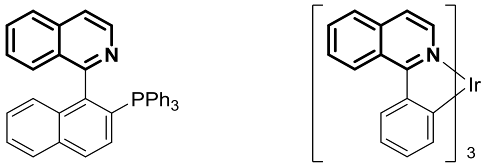
Isoquinolines are also found in many synthetic pharmaceutical agents, where their electron deficient nature is advantageous for the resistance of oxidative metabolism. The peripheral benzodiazepine receptor binder PK-11195 has been used in human brain imaging techniques such as positron emission tomography (PET),[111] and simple isoquinoline **93** is active in the treatment and prevention of cardiovascular disease (**Figure 10**).[112] The tetrahydroisoquinoline-containing compound quinapril is an angiotensin-converting enzyme (ACE) inhibitor used in the treatment of hypertension and heart failure.[113,114]



PK-11195 **93** *quinapril*

Figure 10. Isoquinoline-containing pharmaceutical compounds

In addition, isoquinolines have been used as ligands in both organic chemistry and materials applications, including QUINAP, a chiral ligand,[115] and Ir(piq)$_3$, a cyclometallated isoquinoline complex employed as a red-emissive dopant in organic light-emitting diodes (**Figure 11**).[116]



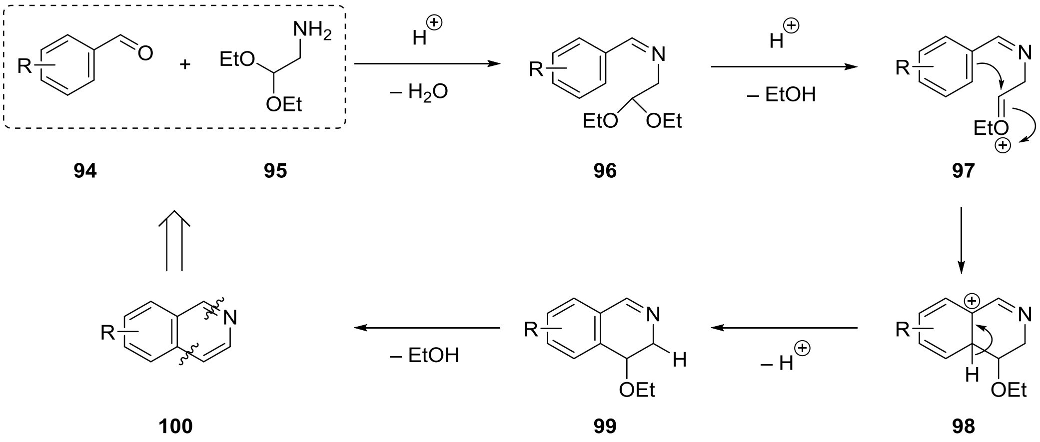
QUINAP Ir(piq)$_3$

Figure 11. Isoquinolines in functional organic molecules

1.3.2 Classical synthetic routes to isoquinolines

Pomeranz-Fritsch synthesis

In 1893, Pomeranz and Fritsch independently reported the condensation of aromatic aldehydes with aminoacetals such as 2,2-diethoxyethanamine **95**, to generate imines which, under acidic conditions, cyclised to isoquinolines (**Scheme 23**).[117,118]

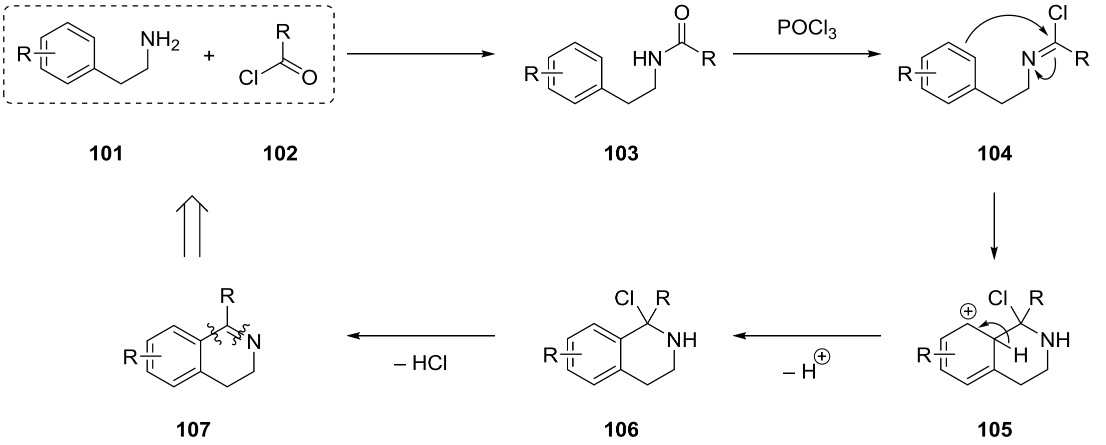


Scheme 23. Pomeranz-Fritsch isoquinoline synthesis

The formation of imine **96** was followed by partial acetal hydrolysis in concentrated H_2SO_4, providing oxonium ion **97**, which was trapped by the aromatic ring to form **98**. Full aromatisation by deprotonation then elimination of EtOH furnished isoquinoline **100**. Under such harshly acidic conditions, the competing hydrolysis of imine **96** limited the yield of the reaction, but this was later overcome by using trifluoroacetic anhydride and boron trifluoride instead of H_2SO_4 to cyclise imine **96**.[119] The process worked best for benzaldehyde-derived imines, rather than those formed from phenyl ketones, and required electron donating substituents on the benzene ring to encourage electrophilic attack on oxonium ion **97**. In their absence, the formation of oxazole side-products was observed.[120]

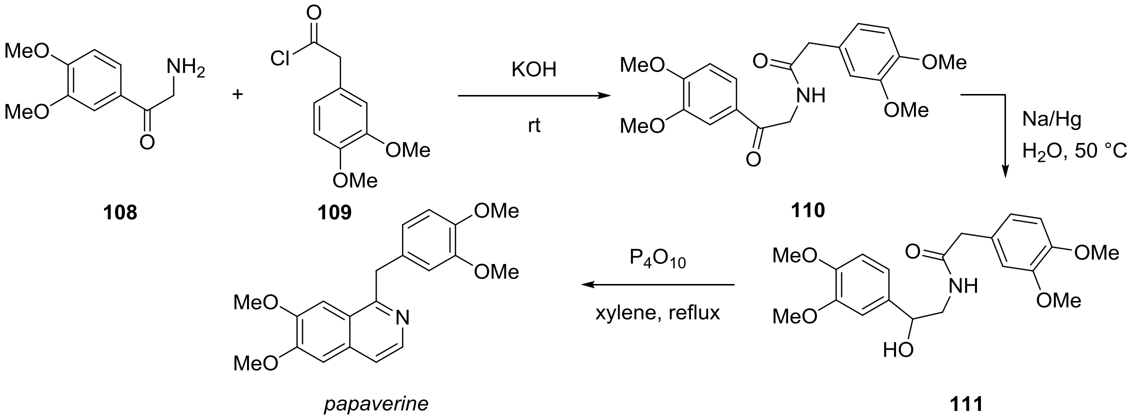
Bischler-Napieralski synthesis

Also developed in 1893, the Bischler-Napieralski isoquinoline synthesis employs a phenylethylamine **101** and a carboxylic acid chloride or anhydride **102** to form amide **103**, which is then activated as an electrophile by treatment with a reagent such as $POCl_3$, $SOCl_2$ or oxalyl chloride (**Scheme 24**).[121,122] Attack by the aromatic ring, followed by rearomatisation and elimination, provides dihydroisoquinoline **107** which can be readily dehydrogenated to the isoquinoline using, for example, palladium on carbon.



Scheme 24. Bischler-Napieralski isoquinoline synthesis

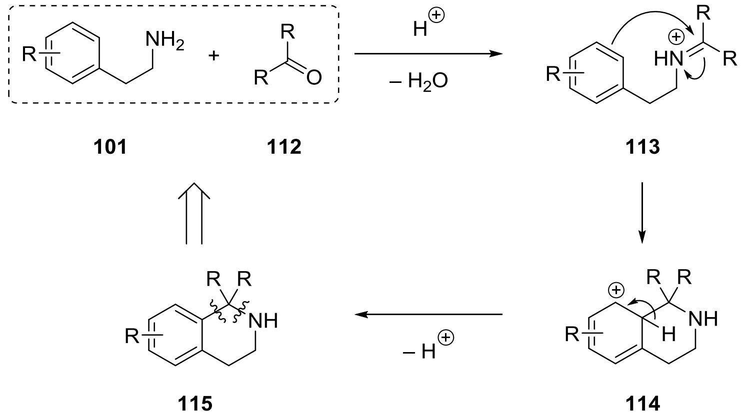
In the Pictet-Gams modification, a hydroxy group is included on the ethylamine tether, such that the elimination of water provides the fully aromatic isoquinoline.[123] The utility of this method was illustrated by the rapid synthesis of papaverine in 1909 (**Scheme 25**).



Scheme 25. The Pictet-Gams synthesis of papaverine. Yields were not disclosed

Pictet-Spengler synthesis

A similar phenylethylamine starting material was used by Pictet and Spengler in their 1911 isoquinoline synthesis.[124,125] Rather than adding to an activated acid (as in the Bischler-Napieralski reaction), a ketone **112** is used as the electrophile, generating a lower oxidation-level imine which is protonated under the acidic reaction conditions to give iminium **113** (**Scheme 26**). Consequently, the final product **115** is a tetrahydro- not a dihydroisoquinoline, though if not fully substituted, routine dehydrogenation furnishes the unsaturated species.



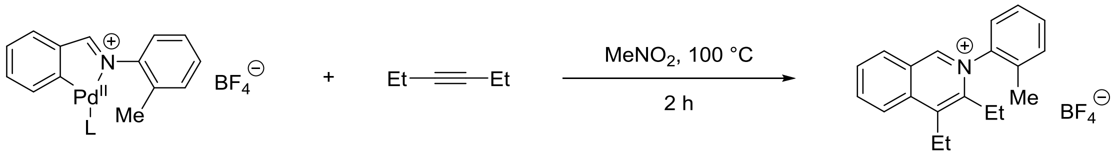
Scheme 26. Pictet-Spengler isoquinoline synthesis

The pendant Mannich-type electrophile in **113** is intrinsically less electrophilic than the imidoyl chloride **104** in the Bischler-Napieralski synthesis, hence a strongly electron donating substituent must be present on the benzene ring for efficient ring closure. Highly activated, hydroxylated aromatic rings permit Pictet-Spengler ring closure under very mild, physiological conditions, and the reaction is often invoked in alkaloid biosynthesis.[126]

The common disconnection shared by these methods is electrophilic aromatic substitution to form either the C8’–C1 or C4’–C4 bond, which restricts the scope of amenable starting materials to those possessing electron donating substituents. Functional group tolerance is further limited by the use of harsh, strongly acidic reaction conditions.

1.3.3 Synthesis of isoquinolines *via* metal-catalysed alkyne annulation

In 1988, Heck reported that internal alkynes underwent insertion into palladacycle complexes such as **116**, generated by warming an aryl imine with a Pd(II) source, to form isoquinolinium salts such as **118** in moderate yields (**Scheme 27**).[127]

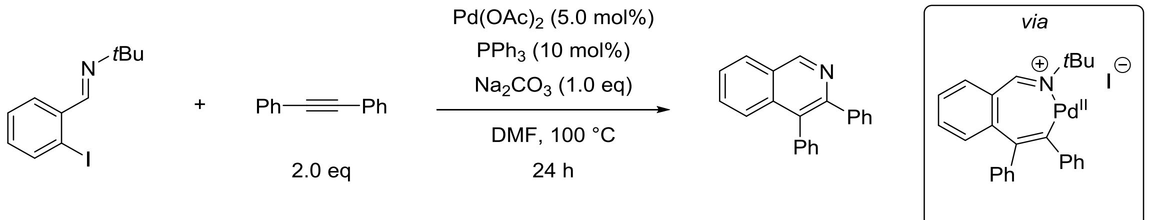


116 L = solvent **117** **60%** **118**

Scheme 27. Heck's stoichiometric synthesis of isoquinolinium salts

Each palladacycle-alkyne reaction pair required optimisation as a result of the sensitivity of the reaction to both temperature (due to decomposition of the palladacycle) and rate of addition of alkyne (which oligomerised if added too quickly). Attempts to make the reaction catalytic with respect to palladium were unsuccessful.

It was not until 1998 that Larock and coworkers reported a similar, but catalytic, synthesis of isoquinolines from *tert*-butyl aryl imines and internal alkynes (**Scheme 28**).[128,129]

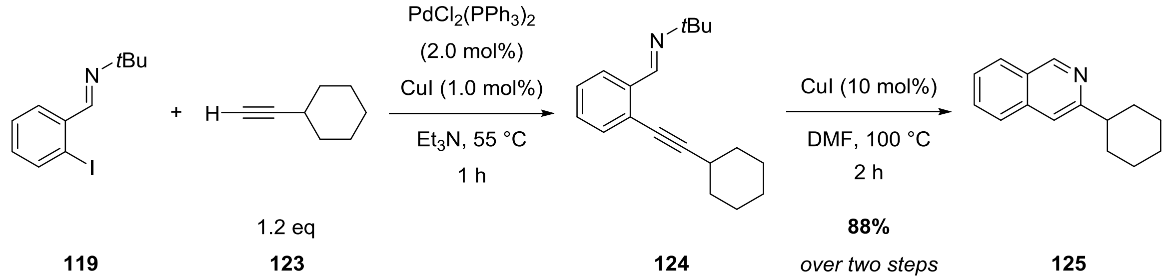


119 **120** **96%** **121** **122**

Scheme 28. Larock's catalytic synthesis of isoquinolines from internal alkynes

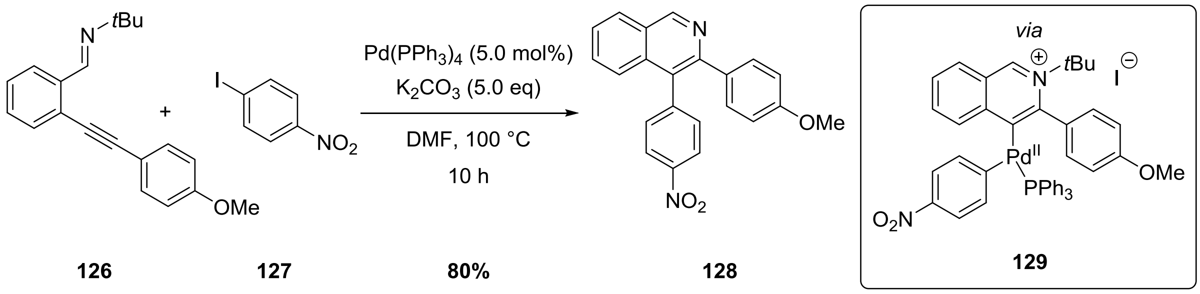
It was proposed that oxidative addition of the aryl halide **119** to Pd(0) produced an arylpalladium intermediate, into which inserted the alkyne, forming a vinylpalladium species. Coordination of the neighbouring imine formed seven-membered palladacycle **122**, from which reductive elimination and cleavage of the *tert*-butyl group (to relieve the strain resulting from proximity to the C3 substituent) occurred to afford isoquinoline **121**. With unsymmetrical alkynes, a mixture of regioisomers at C3 and C4 was obtained, especially when electron rich aryl imines were used. Attempts to annulate alkyl-alkyl alkynes failed.

Larock extended this approach by employing a variety of terminal alkynes in a tandem palladium/copper-catalysed reaction (**Scheme 29**).[130] Acetylenes such as **123** were coupled with aryl iodides or bromides to form the iminoacetylene **124**. Filtration and removal of the solvent was followed by copper-catalysed conversion to the isoquinoline in a procedure that was subsequently used for the synthesis of an 111-member combinatorial library of isoquinolines.[131]



Scheme 29. Synthesis of C3-substituted isoquinolines from acetylenes

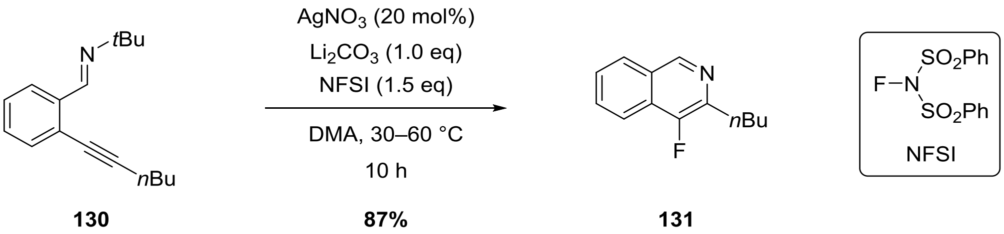
In the presence of aryl, allyl and alkynyl halides, additional groups could be installed regioselectively at C4 using tandem palladium-catalysed cross-couplings (**Scheme 30**).[132,133] It was proposed that coordination of an arylpalladium complex, generated by oxidative addition of **127** to Pd(0), activated the triple bond in **126** towards intramolecular nucleophilic attack by the imine, forming arylpalladium species **129**. Reductive elimination and *tert*-butyl cleavage liberated C4-functionalised isoquinoline **128**.



Scheme 30. Larock’s synthesis of 3,4-disubstituted isoquinolines

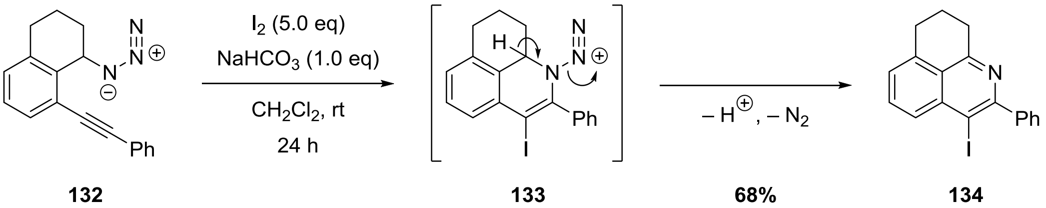
It was subsequently found that iminoalkynes such as **126** could be cyclised to isoquinolines using nonmetallic electrophiles including I_2, ICl and PhSeCl, which activated the alkyne towards intramolecular attack by nitrogen, and installed a heteroatom substituent at C4.[134]

Liu and coworkers demonstrated that fluorine could be incorporated at this position by using fluorinating agent NFSI in the silver-catalysed cyclisation of iminoalkynes (**Scheme 31**).[135]



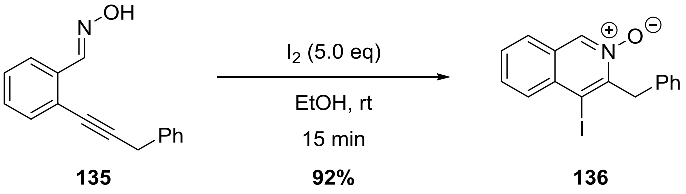
Scheme 31. Liu's silver-catalysed aminofluroination to give 4-fluoroisoquinolines

Yamamoto reported the synthesis of analogous C4-iodo isoquinolines but used alkynyl benzyl azides **132** as precursors (**Scheme 32**).[136,137] It was suggested that coordination of I_2 to the alkyne in **132** promoted nucleophilic ring closure by the azide and subsequent elimination of N_2 gas.



Scheme 32. Yamamoto's synthesis of 4-iodoisoquinolines

Aryl oximes underwent a similar iodine-mediated transformation, but the oxime-derived oxygen atom was retained, giving direct access to synthetically-versatile isoquinoline *N*-oxides (**Scheme 33**).[138]



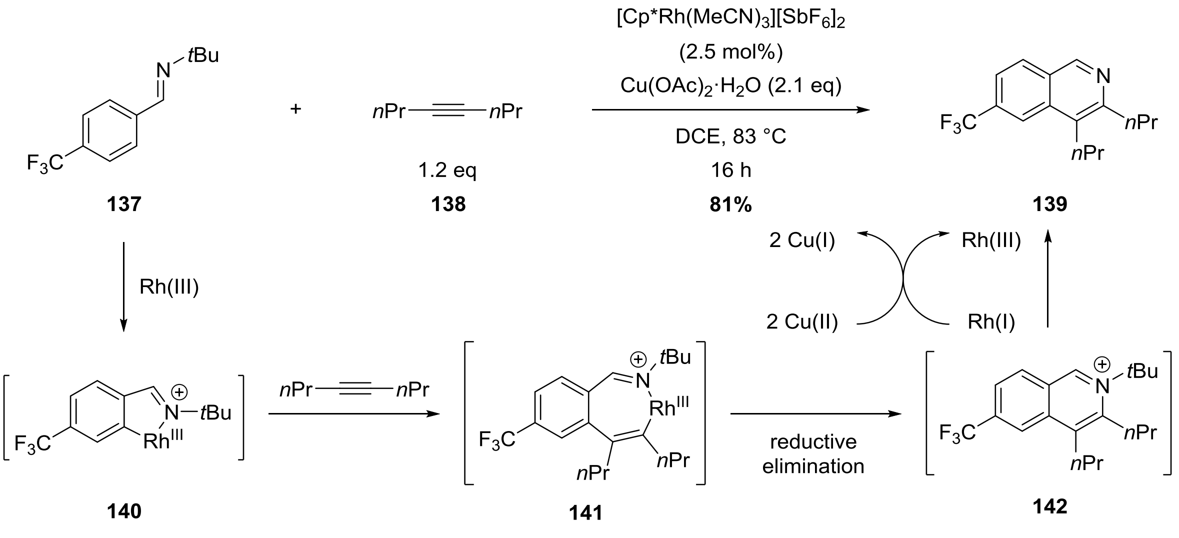
Scheme 33. Use of aryl oximes in the synthesis of 4-iodoisoquinoline *N*-oxides

1.3.4 Isoquinoline synthesis *via* C–H activation

These improved methods offered broader substrate scope, milder reaction conditions, and better functional group compatibilities than classical isoquinoline syntheses. However, the preinstallation of *ortho*-halo or -alkynyl groups limited the synthetic efficiency. Significant efforts were therefore made to exploit unreactive C–H bonds, allowing the use of minimally prefunctionalised starting materials.[139] The alkyne annulation strategy still prevailed, but the use of catalysts other than Pd(0), such as Rh(III), allowed the reaction to begin with a directed *ortho* C–H insertion rather than oxidative addition. Nitrogen-containing directing groups are well suited to isoquinoline synthesis as they can also act as the nitrogen source.

Imine directing groups

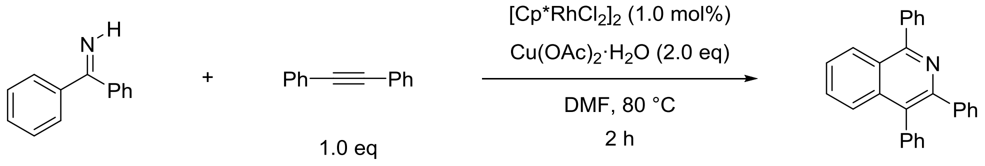
Seminal work was conducted in 2003 by Jun and coworkers who reported the Rh(I)-catalysed cyclisation of *N*-benzyl aromatic imines with diphenylacetylene, although the reaction required high temperature (150 °C) and gave a mixture of isoquinoline derivatives, whose mechanism of formation was unclear.[140] In 2009, Fagnou published an improved Rh(III)-catalysed coupling of *tert*-butyl imines with internal alkynes which gave the desired isoquinolines in 30–81% yield (**Scheme 34**).[141]



Scheme 34. Fagnou's Rh(III)-catalysed synthesis of isoquinolines

The reaction was believed to proceed *via* chelation-assisted insertion of Rh(III) into the *ortho* C–H bond of imine **137** to form complex **140**, followed by carbometallation with the alkyne giving seven-membered rhodacycle **141**. C–N bond-forming reductive elimination furnished isoquinolinium **142** which underwent strerically-driven loss of the *N*-*tert*-butyl group to provide isoquinoline **139**. The presence of Cu(II) was necessary for the oxidation of Rh(I) back to the active Rh(III) species.

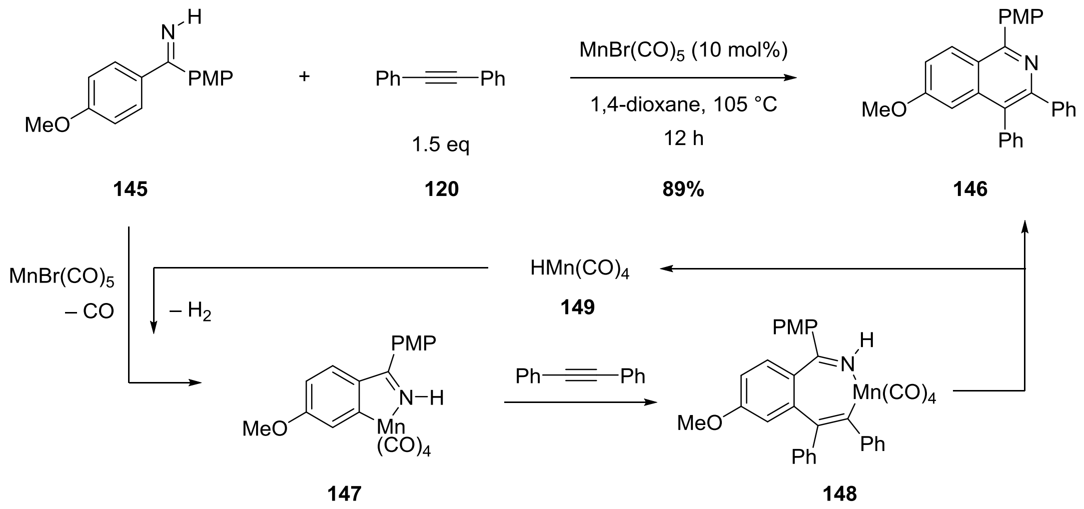
Satoh and Miura reported a set of similar conditions for the high-yielding synthesis of isoquinolines from unsubstituted benzophenone *N*–H imine **143** (**Scheme 35**).[142]



143 **120** **90%** **144**

Scheme 35. Miura's *N*–H imine directed annulation of alkynes

In 2014, unprotected *N*–H imines were also used by Wang and coworkers in their reoxidant-free manganese-catalysed annulation of both internal and terminal alkynes (**Scheme 36**).[143] Mechanistic investigations suggested that initial steps were analogous to those of Rh(III): cyclomanganation of imine **145** with $MnBr(CO)_5$ generated metallacycle **147**, into which inserted the alkyne to form the seven-membered manganacycle **148**. The extrusion of manganese hydride species **149** *via* a metathesis-type process then gave isoquinoline **146**. Finally, the coordinatively unsaturated manganese hydride **149** bound imine **145**, with the subsequent elimination of H_2 generating intermediate **147**.

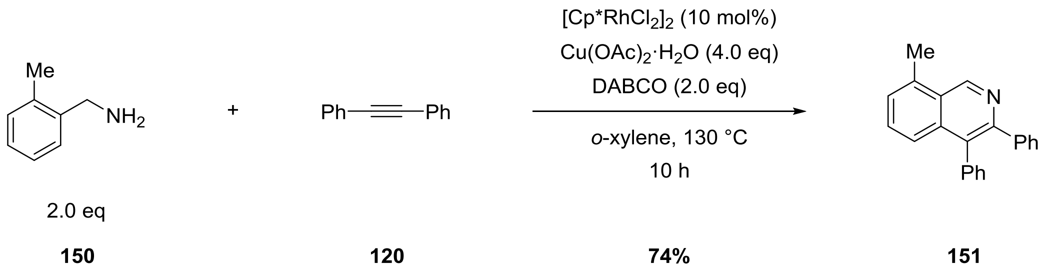


Scheme 36. Wang's manganese-mediated isoquinoline synthesis. PMP = *para*-methoxyphenyl

A wide range of functional groups were tolerated on the aryl imine starting material, but when electron donating *meta*-substituents were present, a mixture of regioisomeric isoquinolines was obtained.

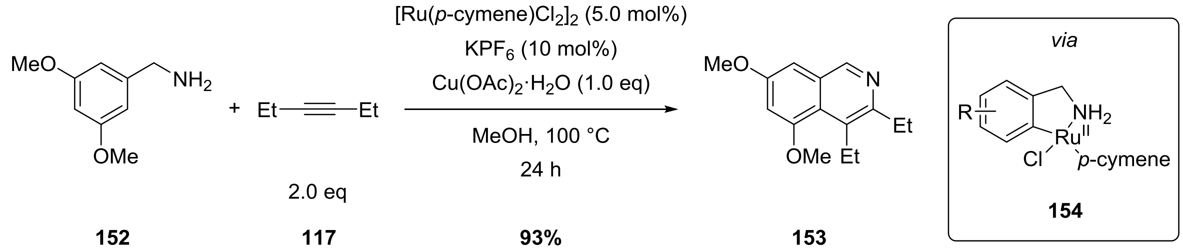
Amine directing groups

Satoh and Miura demonstrated that it was possible to oxidatively couple benzylamines in place of *N*–H imines with internal aromatic alkynes to access 3,4-diarylisoquinolines (**Scheme 37**).[144] It was proposed that rhodium-mediated dehydrogenation of the amine to the corresponding imine, for which the addition of DABCO was beneficial, occurred prior to C–H activation. The reaction required high temperature (130 °C) and yields were generally moderate.



Scheme 37. Miura and Satoh's dehydrogenative annulation of alkynes with benzylamines

In 2013, Urriolabeitia established a Ru(II)-catalysed synthesis of isoquinolines and derivatives using symmetrical benzylamines which appeared not to involve an *N*–H imine in the C–H insertion step.[145] Cycloruthenation of the amine was detected by ^{1}H NMR spectroscopy during the reaction, so it was proposed that the alkyne annulation of species **154** gave 1,2-dihydroisoquinolines which were then dehydrogenated to the corresponding isoquinolines (**Scheme 38**).



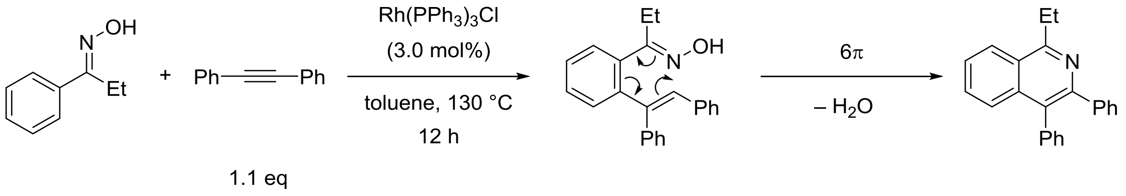
Scheme 38. Ru(II)-catalysed isoquinoline synthesis *via* benzylamine metallacycle **154**

Interestingly, minor side products were obtained in which the isoquinoline product had undergone a second C–H activation reaction with the alkyne, introducing a vinyl substituent at the C8 position. Such over-reaction was greatest for electron deficient benzylamines.

Almost concurrently, Jun and coworkers reported the Rh(III)-catalysed synthesis of isoquinolines from benzylamines and internal aliphatic alkynes. Again, the authors proposed the participation of the amine in the C–H activation step without prior oxidation to an *N*–H imine.[146]

Oxime directing groups

Unlike the oxidative couplings mentioned thus far, which generally require stoichiometric Cu(II) reoxidants, a novel redox-neutral strategy emerged that utilised the N–O bond of oximes as an internal oxidant for the formation of fully aromatic isoquinolines. In 2009, Cheng demostrated the synthesis of substituted isoquinolines from aromatic ketoximes and alkynes using Rh(I) catalysis (**Scheme 39**).[147] Isolation of *ortho*-vinylated oxime **156** and its subsequent rhodium-free conversion to the isoquinoline supported the authors' hypothesis of a 6π electrocyclisation mechanism for ring closure, followed by dehydrative aromatisation.

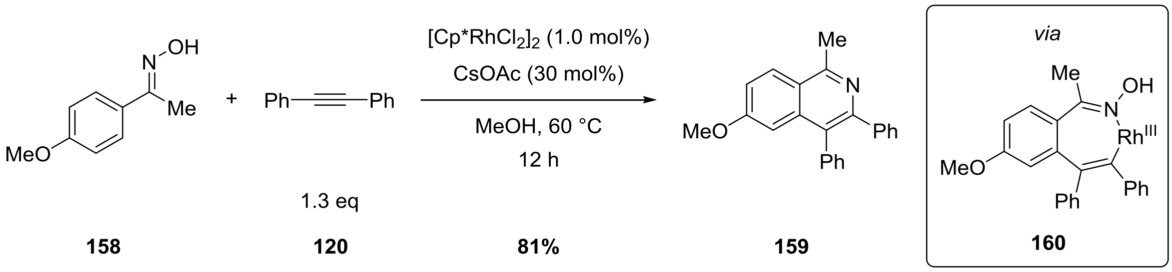


155 **120** **156** **87%** **157**

Scheme 39. Cheng's rhodium-catalysed isoquinoline synthesis from ketoximes

Benzaldehyde-derived oximes were unsuccessful in this protocol, presumably due to their kinetically favourable isomerisation to amides under Rh(I) catalysis.[148]

In 2011, Li and coworkers applied Rh(III) catalysis to the coupling of similar fragments, and obtained isoquinolines such as **159** at reduced temperature (60 °C) with the addition of a catalytic quantity of CsOAc (**Scheme 40**).[149]



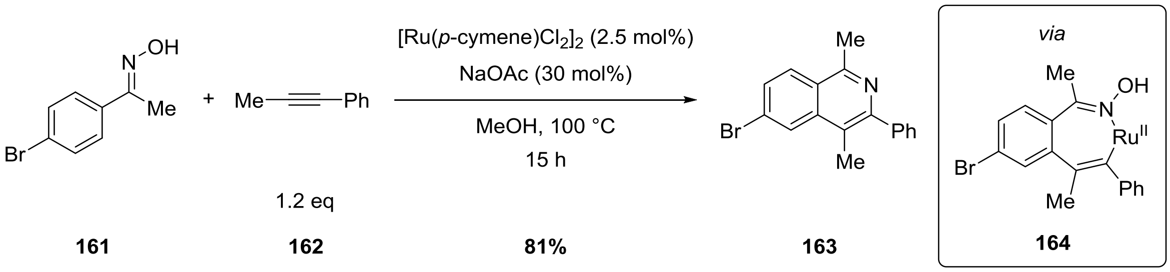
158 **120** **81%** **159** **160**

Scheme 40. Li's mild conditions for Rh(III)-catalysed isoquinoline synthesis

It was found that vinylated oximes analogous to **156** (**Scheme 39**), synthesised separately, did not undergo cyclisation to isoquinolines when subjected to Li's considerably milder reaction conditions. Instead, it was proposed that a different mechanism operated under these circumstances. Rather than protoderhodation of rhodacycle **160** (**Scheme 40**) to give an *ortho* vinyl aryl oxime, protonation and dehydration generated an iminyl Rh(V) rhodacycle from which C–N reductive elimination afforded isoquinoline **159** and regenerated Rh(III).

In 2012, the Hua group disclosed a one-pot, three-component coupling of simple phenyl ketones, hydroxylamine, and internal alkynes, also effected by [Cp*RhCl$_2$]$_2$, in which oximes were generated *in situ*.[150]

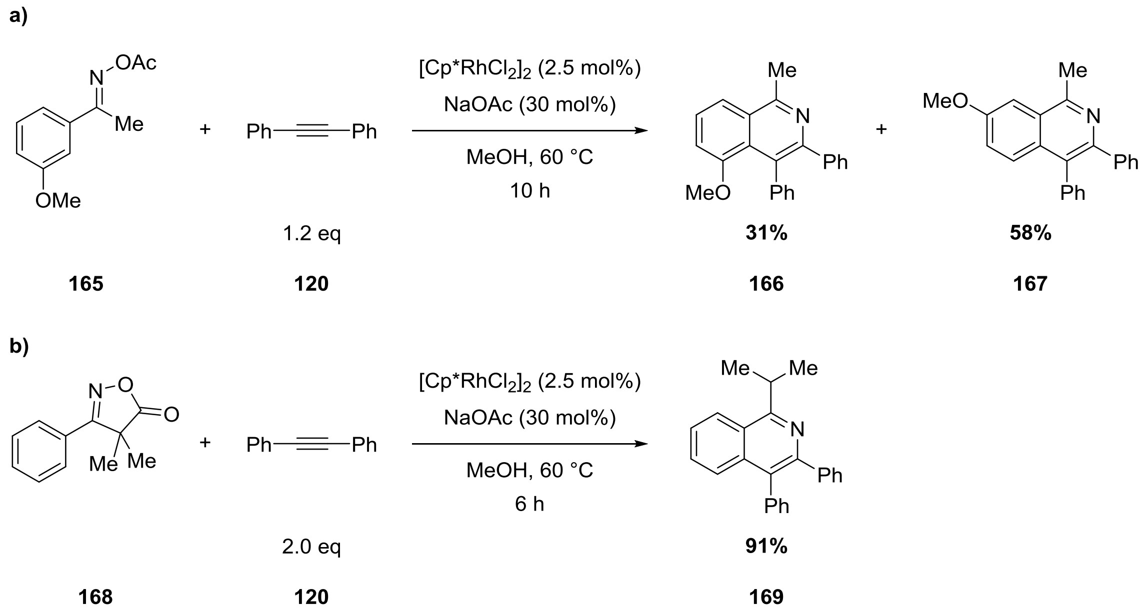
Also in 2012, Jeganmohan applied ruthenium catalysis to oxime-directed isoquinoline synthesis, achieving excellent regioselectivity when unsymmetrical alkynes were used, though the exact reasons for this were not well understood.[151] Impressive substrate scope was demonstrated, including sensitive functional groups on the aryl oxime such as halogen atoms. Both internal and terminal alkynes were compatible (**Scheme 41**).



Scheme 41. Jeganmohan’s ruthenium-catalysed isoquinoline synthesis

The mechanism was believed to be analogous to the Rh(III) case, proceeding *via* ruthenacycle **164**, with NaOAc assisting in the initial cleavage of the aromatic C–H bond. Shortly after this work, Ackermann reported a similar annulation using the same Ru(II) catalyst with KPF_6 as a co-catalytic additive.[152]

Chiba and coworkers employed the Rh(III)/NaOAc catalytic system in isoquinoline synthesis from *O*-acetyl ketoximes and internal alkynes.[153] With *meta*-substituted aryl oximes and unsymmetrical alkynes, a mixture of regioisomeric isoquinolines was formed (**Scheme 42a**). It was found that bulky ketoxime substituents gave a mixture of *anti*- (as in **165**) and *syn*-ketoximes, where the acetate and aryl groups were *cis* disposed across the C=N bond. The latter were inert to isoquinoline formation and this was attributed to the need for the nitrogen lone pair to be *syn* to the aryl moiety to direct the metal centre to the aryl group for C–H activation.

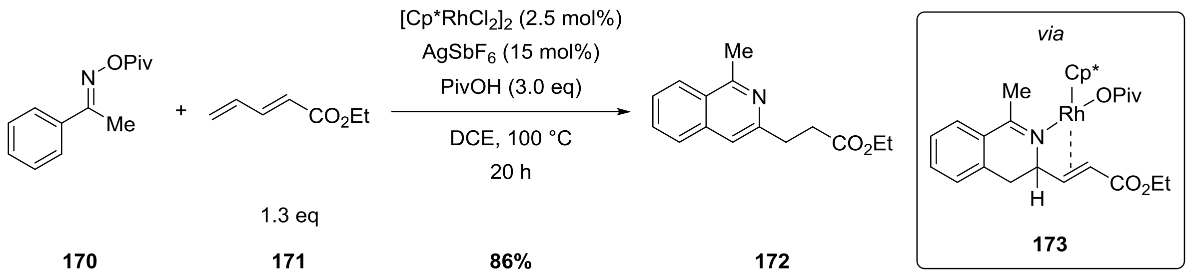


Scheme 42. Chiba's use of *O*-acetyl oximes and oxazol-5-ones

The issue was circumvented by replacing the oxime with an oxazol-5-one such as **168**, with the ring forcing the N–O bond to be *anti* to the aryl group (**Scheme 42b**). Alternatively, a Cu(I) co-catalyst could be added to reductively cleave the N–O bond, forming an iminyl-Rh(III) species which could freely isomerise.[154–157]

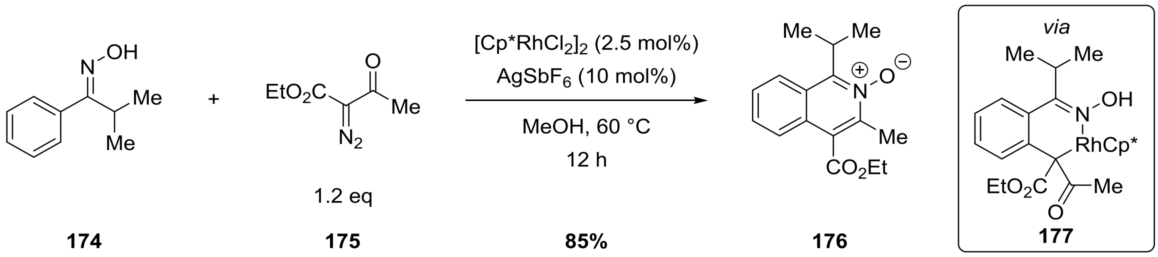
A nickel-catalysed annulation of internal alkynes with *O*-benzyl oximes was reported by Kurahashi and Matsubara in 2011.[158] The reaction gave isoquinolines in moderate yields, but if free *O*–H oximes were used instead, a mixture of isoquinolines and their *N*-oxides was obtained.

In 2014, Glorius demonstrated a complementary method to those relying on alkynes by coupling *O*-pivaloyl ketoximes and 1,3-dienes in a Rh(III)-catalysed C–H activation/cyclisation/isomerisation sequence (**Scheme 43**).[159] It was proposed that, following reductive elimination from a seven-membered rhodacycle, dihydroisoquinoline complex **173** underwent rhodium-mediated isomerisation, *via* repeated β-hydride abstraction and re-addition, to the fully aromatic isoquinoline **172**. Additive $AgSbF_6$ assisted in generation of the active catalyst by abstracting chloride from $[Cp^*RhCl_2]_2$.



Scheme 43. Glorius's rhodium-catalysed isoquinoline synthesis from 1,3-dienes

Glorius also showcased a method for the direct synthesis of isoquinoline *N*-oxides from free oximes and stabilised diazo compounds (**Scheme 44**).[160] Substrate scope was broad; a range of alkyl groups could be installed at C1 and alkyl, halide, methoxy and ester groups were tolerated on the carbocyclic ring, albeit with the usual regioselectivity issues when *meta* to the oxime.



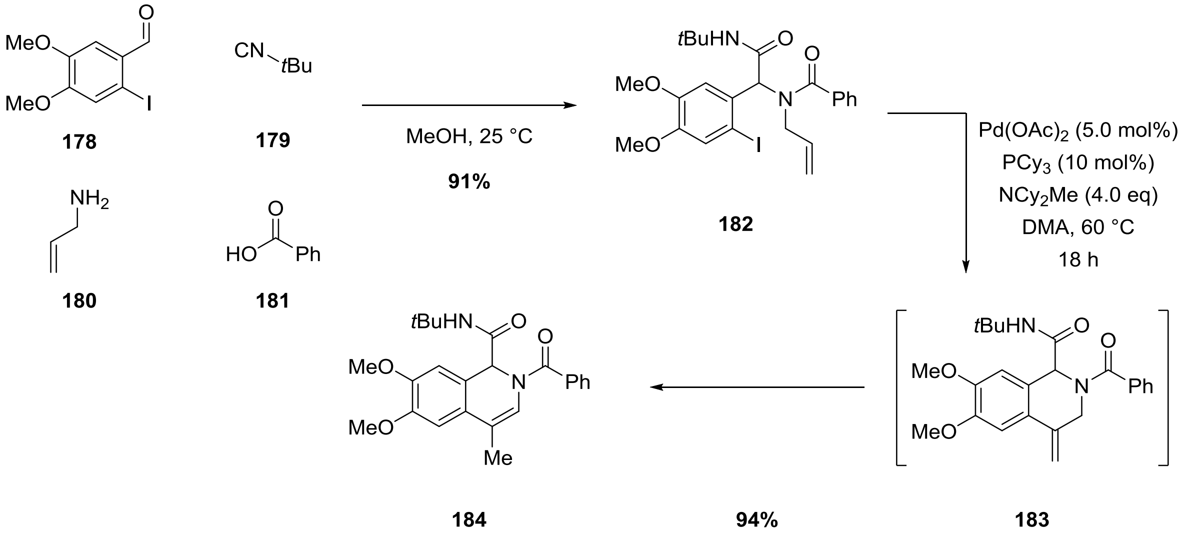
Scheme 44. Isoquinoline *N*-oxide **176** from oxime **174** and diazo compound **175**

Rhodacycle formation by insertion of Rh(III) into the *ortho* C–H bond, followed by coordination of diazo compound **175**, gave the carbene insertion complex **177**, from which protoderhodation and cyclisation occurred to furnish isoquinoline *N*-oxide **176**.

A number of other directing groups have been applied to the synthesis of isoquinolines, including amidines,[161] hydroximoyl halides,[162] hydrazones and azides.[163–166] This chemistry, along with C–H activation methods for the synthesis of isoquinolinium salts, is discussed in a 2014 review.[139]

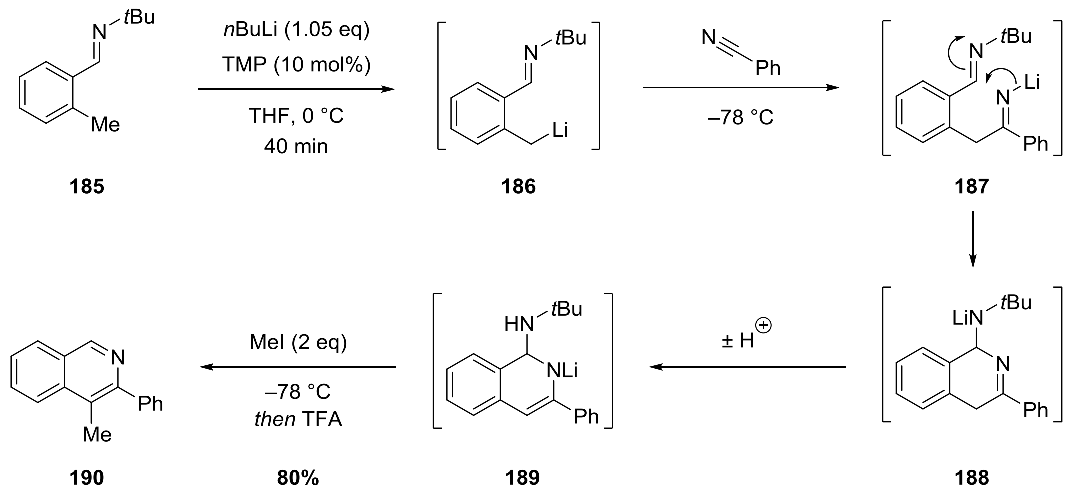
1.3.5 Other modern isoquinoline syntheses

In 2004, Yang and coworkers developed a multicomponent synthesis of dihydroisoquinolines, forming the C1–N, C3–C4 and C4–C4’ bonds using the Ugi four-component reaction[167] and an intramolecular Mizoroki-Heck coupling.[168] Ugi reaction between *ortho*-iodobenzaldehyde **178**, *tert*-butylisocyanide **179**, allyl amine **180**, and benzoic acid **181** afforded compound **182**, which underwent an intramolecular Mizoroki-Heck coupling to provide **183** (**Scheme 45**). Isomerisation of the exocyclic double bond, presumably mediated by palladium-catalysed reversible β-hydride elimination, provided dihydroisoquinoline **184**.



Scheme 45. Yang’s Ugi/Mizoroki-Heck multicomponent synthesis of dihydroisoquinolines

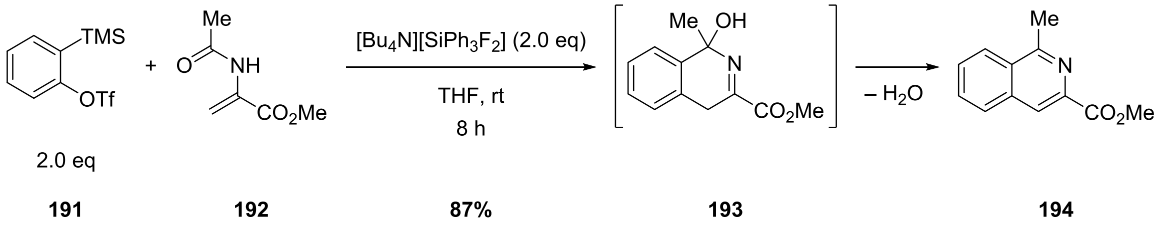
Myers also executed a multicomponent isoquinoline synthesis, whereby the benzylic anions of *ortho*-tolualdehyde *tert*-butyl imines such as **185** were added to nitriles to produce **187**, which cyclised then isomerised to enamine **189** (**Scheme 46**).[168] Upon the addition of an electrophile, enamine **189** was functionalised at C4 and an acidic workup prompted the elimination of *tert*-butylamine, producing isoquinoline **190**.



Scheme 46. Myers's synthesis of substituted isoquinolines from lithiated *o*-tolyl imines

A range of substituted aryl aldimines, nitriles and carbon- and heteroatom-centred electrophiles could be combined to give substituted isoquinolines in 40–80% yield.

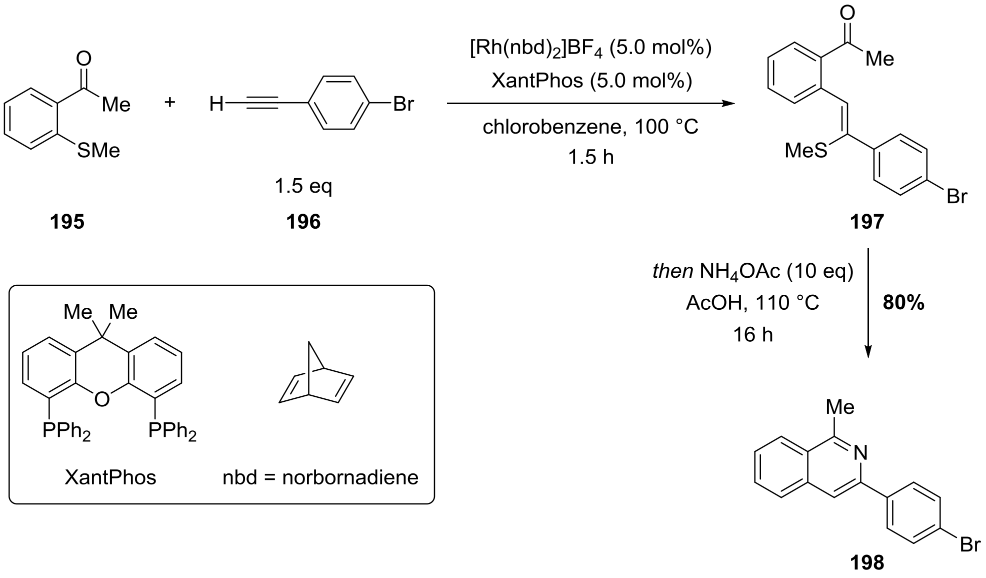
In 2008, Stoltz reacted benzyne intermediates, generated by treating silyl aryl triflates with a fluoride source, with *N*-acyl enamines such as **192** to furnish the formal product of [4+2] cycloaddition **193** (**Scheme 47**).[169] The elimination of water afforded isoquinoline **194**.



Scheme 47. Stoltz's isoquinoline synthesis *via* benzynes

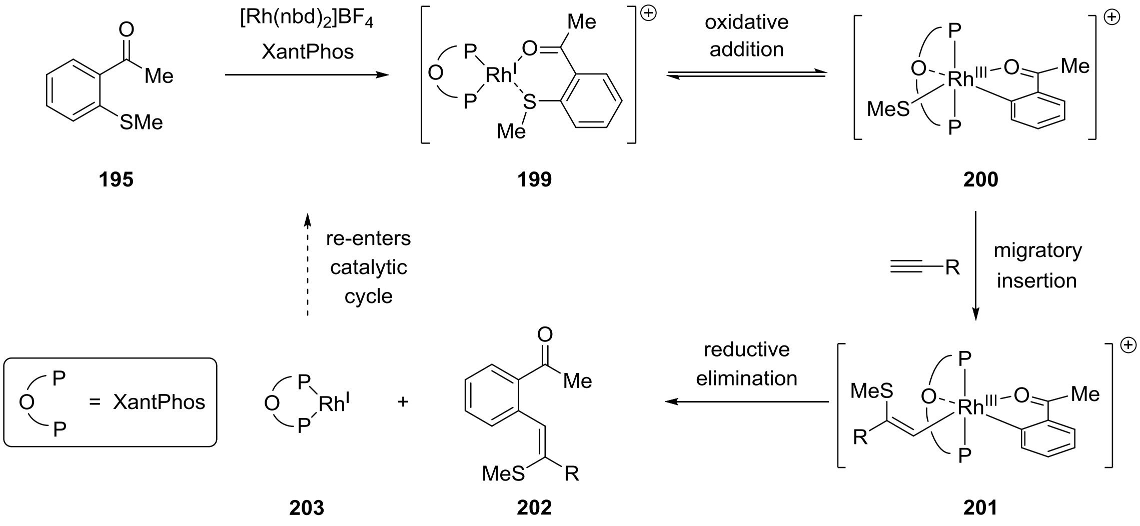
Huang and coworkers also employed benzyne intermediates in their multicomponent isoquinoline synthesis from silyl aryl triflates, benzylic isocyanides, and terminal alkynes.[170]

In 2013, the Willis group reported the application of their rhodium-catalysed carbothiolation methodology to the synthesis of isoquinolines, using the methyl sulfide activating group as a masked carbonyl (**Scheme 48**).[171] A range of alkynes bearing electron donating, electron withdrawing and aryl halide substituents were subjected to Rh(I)-catalysed carbothiolation to provide alkenyl sulfides such as **197**, which hydrolysed and cyclised to isoquinolines upon the addition of ammonium acetate in acetic acid.



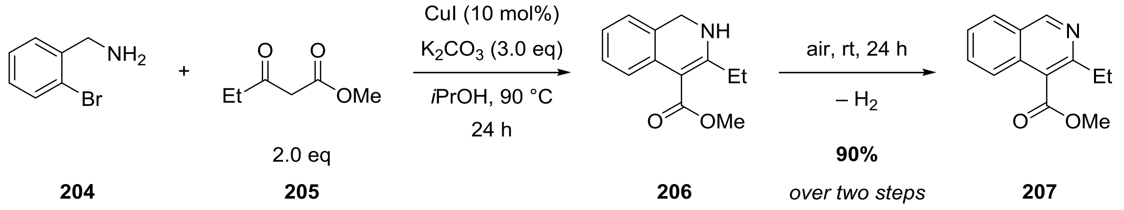
Scheme 48. Willis's synthesis of isoquinolines *via* carbothiolation

The mechanism of carbothiolation was believed to proceed *via* coordination of aryl methyl sulfide **195** to rhodium followed by oxidative addition of the Ar–S bond to form complex **200** (**Scheme 49**).[172] Migratory insertion of the alkyne into the rhodium sulfide species gave alkenyl complex **201** which furnished product **202** by reductive elimination.



Scheme 49. Rhodium-catalysed carbothiolation

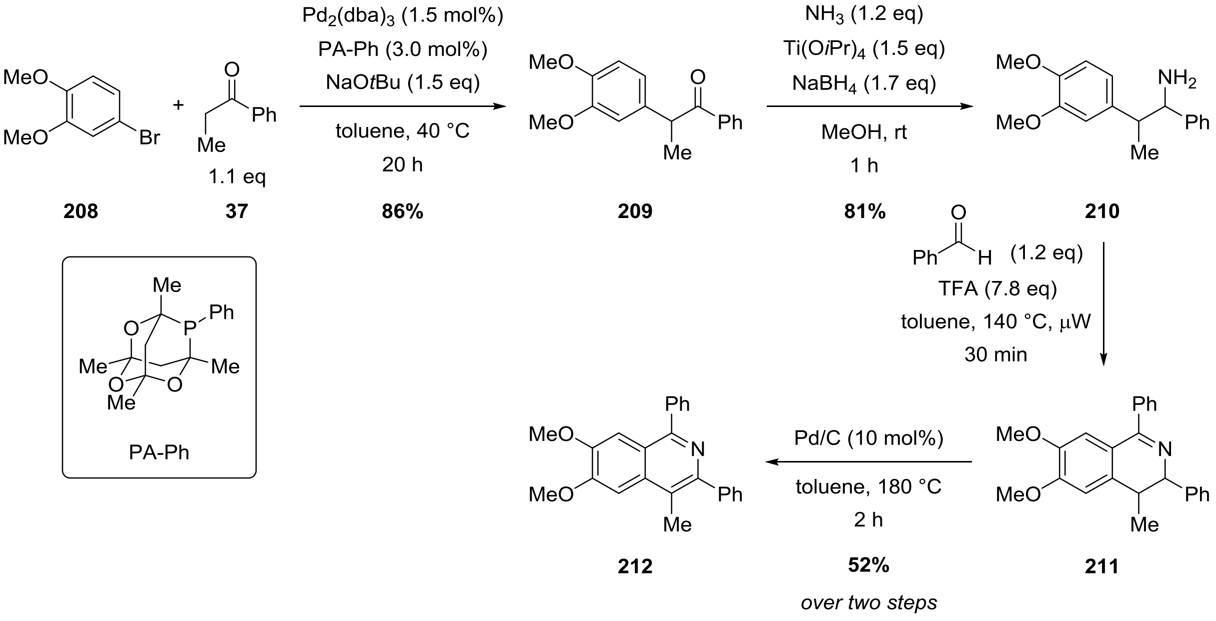
In 2008, the group of Ma published a copper-catalysed α-arylation approach to isoquinolines.[173] The coupling of simple *ortho*-halobenzylamines such as **204** with β-ketoesters was succeeded by intramolecular condensation to afford dihydroisoquinoline **206** (**Scheme 50**). Intermediate **206** was spontaneously oxidised to the corresponding isoquinoline **207** when stirred overnight under air.



Scheme 50. Ma’s copper-catalysed synthesis of isoquinolines

Only primary benzylamines were used, so the C1 position remained unsubstituted. Scope was further limited by the need for stabilised enolate starting materials, resulting in the unavoidable incorporation of an ester group at C4.

In 2011, Capretta and coworkers used their palladium-catalysed α-arylation conditions for the synthesis of isoquinolines.[174] Propiophenone **37** was coupled with aryl bromide **208** to give ketone **209** which was reductively aminated to provide β-arylethylamine **210** (**Scheme 51**). A microwave-assisted Pictet-Spengler reaction with benzaldehyde provided dihydroisoquinoline **211**, which was dehydrogenated to afford isoquinoline **212**.



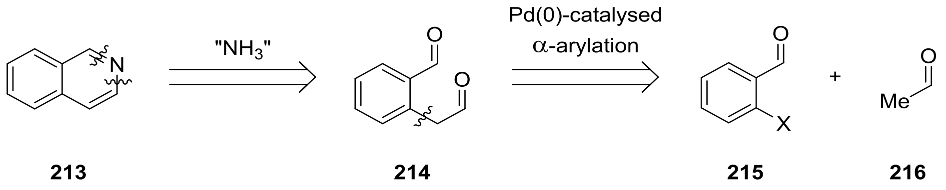
Scheme 51. Capretta’s α-arylation/reductive amination/Pictet-Spengler route to isoquinolines

1.4 Donohoe's synthesis of isoquinolines *via* palladium-catalysed α-arylation

Despite these advances in isoquinoline synthesis methodologies, the range of strategies available was still inferior to other heteroaromatic scaffolds. The reactions described thus far all have their drawbacks, namely the need for electron rich substrates in the classical syntheses, and regioselectivity issues when using either unsymmetrical alkynes or *meta*-substituted aromatic starting materials in C–H activation approaches. In 2010, the Donohoe group began investigations into the development of a novel synthetic route, with the aim of achieving high functional group tolerance, complete regioselectivity, and mild reaction conditions. The key C–C bond-forming reaction was to be the palladium-catalysed α-arylation of ketones.

1.4.1 Retrosynthetic strategy

A common tactic for the construction of fully aromatic heterocycles is the double condensation between a suitably connected dicarbonyl compound and a heteroatom-centred nucleophile. In the case of isoquinoline **213**, performing such disconnections reveals the 1,5-diketone **214**, containing a benzenoid ring fused to the backbone (**Scheme 52**).



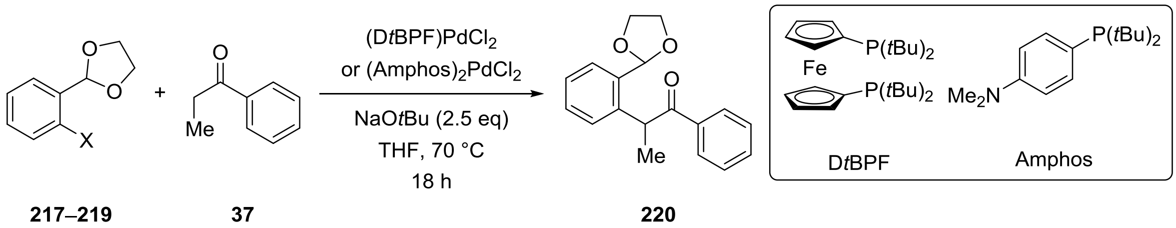
Scheme 52. Retrosynthetic analysis of isoquinoline **213** *via* 1,5-dicarbonyl **214**

It was noted that compound **214** is an α-aryl ketone bearing an *ortho*-aldehyde. Disconnection between the arene and the benzylic methylene carbon, which gives the greatest simplification, leads to fragments **215** and **216**, which could be coupled by the palladium-catalysed α-arylation of **216**.

In the forward sense, it was deemed necessary to protect the formyl group in **215** due to its propensity to undergo aldol condensation with ketone enolates. The use of a base-stable cyclic acetal would permit deprotection under mild conditions using an acidic source of ammonia, which would then condense with the two carbonyl groups to provide the isoquinoline.

1.4.2 Optimisation of the α-arylation reaction

Donohoe and coworkers reported the results of their endeavours in 2012.[175] The initial optimisation of the α-arylation reaction was conducted using propiophenone **37** and aryl bromide **217**, both commercially available (**Table 2**). A catalyst loading of 2.0 mol% of (D*t*BPF)PdCl$_2$ or (Amphos)$_2$PdCl$_2$, along with NaO*t*Bu and a slight excess of propiophenone **37**, gave arylated product **220** in very good yield (Entries 3 and 6) considering the steric hindrance introduced by the *ortho*-acetal. Increasing the catalyst loading to 5.0 mol% and adding two equivalents of propiophenone led to a small improvement (Entry 5).



Entry	X	Pd source	Catalyst loading / mol %	Ketone / eq	Yield / %
1	Br (**217**)	(D*t*BPF)PdCl$_2$	0.5	1.2	71
2	Br (**217**)	(D*t*BPF)PdCl$_2$	0.5	2.0	74
3	Br (**217**)	(D*t*BPF)PdCl$_2$	2.0	1.2	82
4	Br (**217**)	(D*t*BPF)PdCl$_2$	2.0	2.0	83
5	Br (**217**)	(D*t*BPF)PdCl$_2$	5.0	2.0	89
6	Br (**217**)	(Amphos)$_2$PdCl$_2$	2.0	1.2	82
7	I (**218**)	(D*t*BPF)PdCl$_2$	2.0	1.2	79
8	Cl (**219**)	(D*t*BPF)PdCl$_2$	5.0	2.0	30
9	Cl (**219**)	(Amphos)$_2$PdCl$_2$	5.0	2.0	45
10	Cl (**219**)	(Amphos)$_2$PdCl$_2$	2 × 5.0	2.0	74[a]

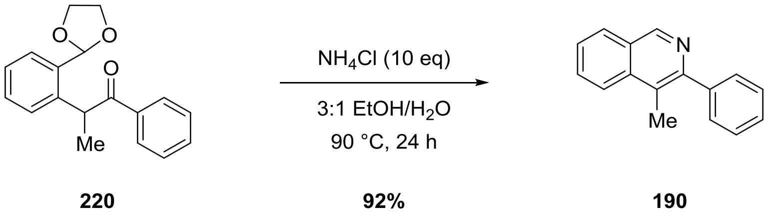
Table 2. Optimisation of the α-arylation of propiophenone with aryl halides **217–219**
[a] Reaction time 96 h instead of 18 h

The catalyst loading could be reduced to 0.5 mol% and good yields were still achievable (Entries 1 and 2). Aryl iodide **218** performed similarly to aryl bromide **217** (Entry 7 vs Entry 3), but aryl chloride **219** was less reactive (Entries 8 and 9). When using the latter, a good yield of product could be achieved, however, using two batches of catalyst over an extended reaction time of 96 hours (Entry 10). Since aryl bromides demonstrated the best combination of reactivity and commercial availability, these were the focus of subsequent investigations.

In agreement with the findings of Colacot,[60] it was found that the preformed Pd(II) precatalyst (D*t*BPF)PdCl$_2$ gave more consistent results over repeated reactions than the equivalent mixture of Pd$_2$(dba)$_3$ and D*t*BPF. It was proposed that formation of the active Pd(0) catalyst in this system could arise from the displacement of both chlorides by enolate molecules, followed by their reductive elimination.[176] Alternatively, displacement of one chloride by an enolate, then β-hydride elimination and reductive elimination of HCl, could also generate the active (D*t*BPF)Pd(0) species.

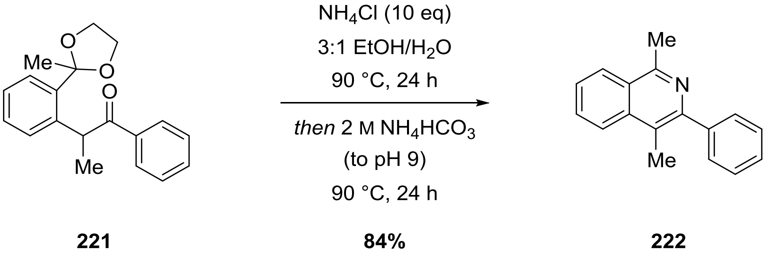
1.4.3 Optimisation of the isoquinoline-forming step

For the cyclisation and aromatisation of masked 1,5-dicarbonyls such as **220**, ethanolic solutions of a variety of ammonium salts, with different counterions and pHs, were screened. It was found that approximately pH 5 was sufficiently acidic for acetal hydrolysis at an acceptable rate, and consequently, heating intermediate **220** in a 1 M solution of ammonium chloride in 3:1 EtOH/H$_2$O, which was measured to be pH 5, effected deprotection, imine formation, and condensation to provide isoquinoline **190** in excellent yield (**Scheme 53**).



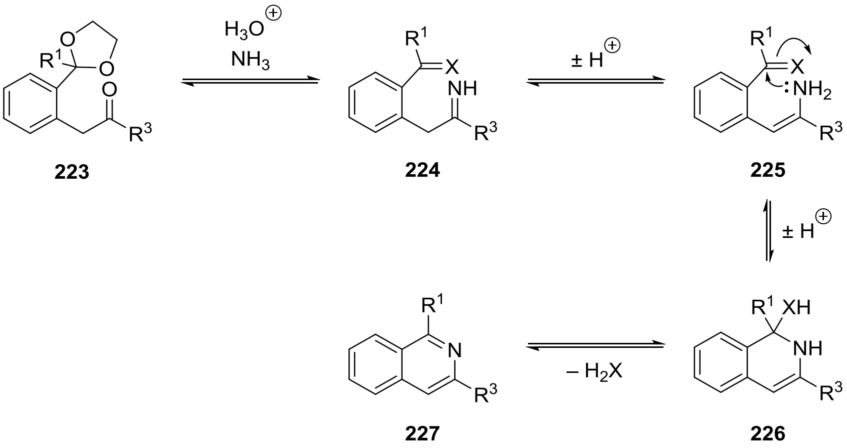
Scheme 53. Optimised conditions for the synthesis of isoquinoline **190** from **220**

Later, during studies into the scope of the synthesis, it was necessary to develop a second set of cyclisation conditions for acetals derived from methyl ketones, which installed a methyl group at C1 in the resulting isoquinoline. Subjecting intermediate **221** to the ammonium chloride conditions resulted in smooth hydrolysis of the acetal, but the resulting species did not cyclise until the reaction was basified to pH 9 by the addition of NH_4HCO_3 (**Scheme 54**).



Scheme 54. Cyclisation conditions for the synthesis of 1-methylisoquinolines

A proposed mechanism for cyclisation is shown in **Scheme 55**.[176] Imine formation from ketone **223**, and hydrolysis of the acetal, generates intermediate **224**, in which the unmasked carbonyl group may also have undergone imine formation by reaction with ammonia (therefore X = O or NH). Imine **224** tautomerises to (*Z*)-enamine **225**, which cyclises through nitrogen to provide aminal or hemiaminal **226**. Subsequent elimination of H_2X, which is thermodynamically driven by the generation of aromaticity, furnishes isoquinoline **227**.

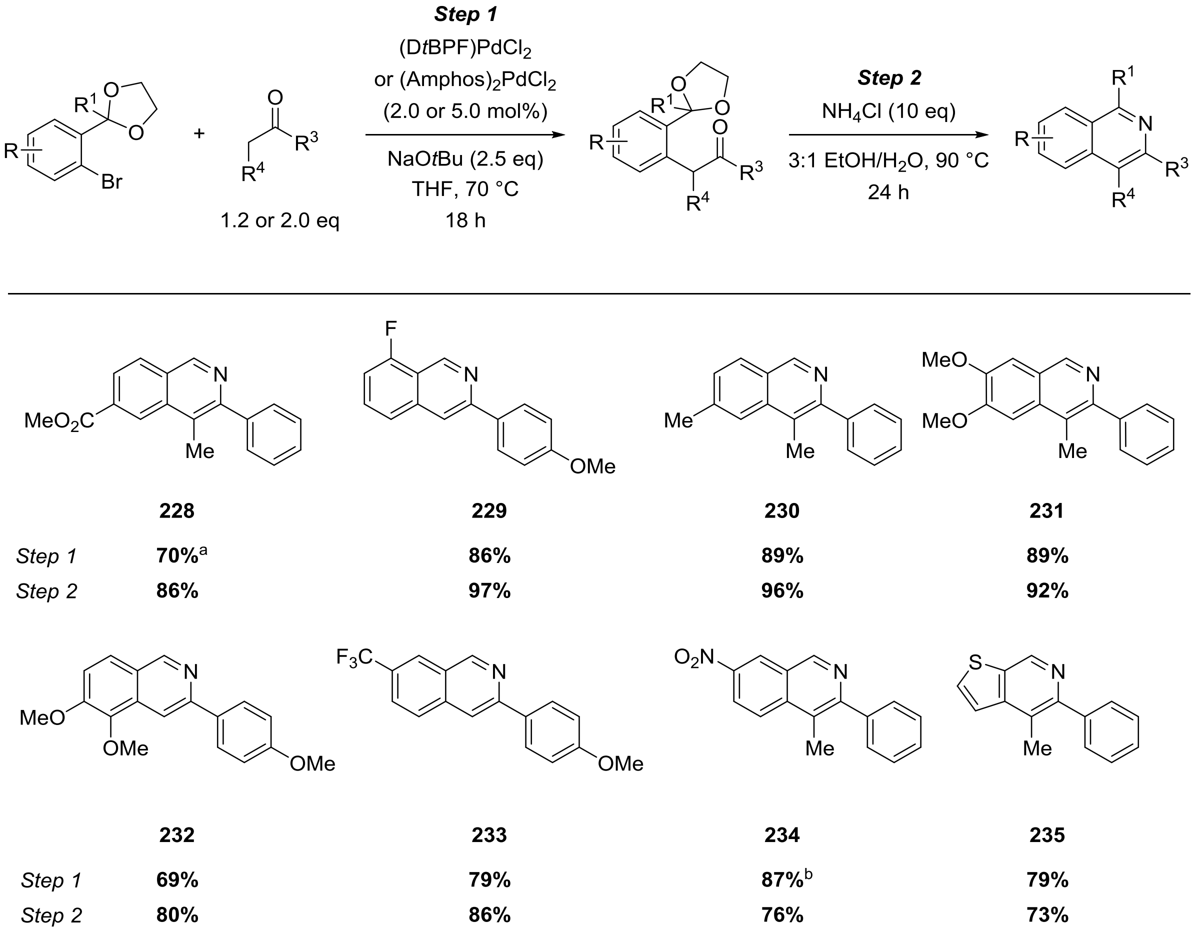


Scheme 55. Proposed mechanism for isoquinoline formation. X = O or NH

In the case of 1-methylisoquinolines (R^1 = Me instead of H), the formation of imine **224** is still likely to occur at pH 5. The need for basification most likely arises from the reduced reactivity of the carbonyl group (or imine) at C1, which means that deprotonation of nitrogen in enamine **225** is necessary to enhance its nucleophilicity and promote cyclisation.

1.4.4 Exploration of scope

The scope of accessible substitution patterns on the carbocyclic ring was tested by varying the functional groups present on the aryl bromide coupling partner (**Scheme 56**).



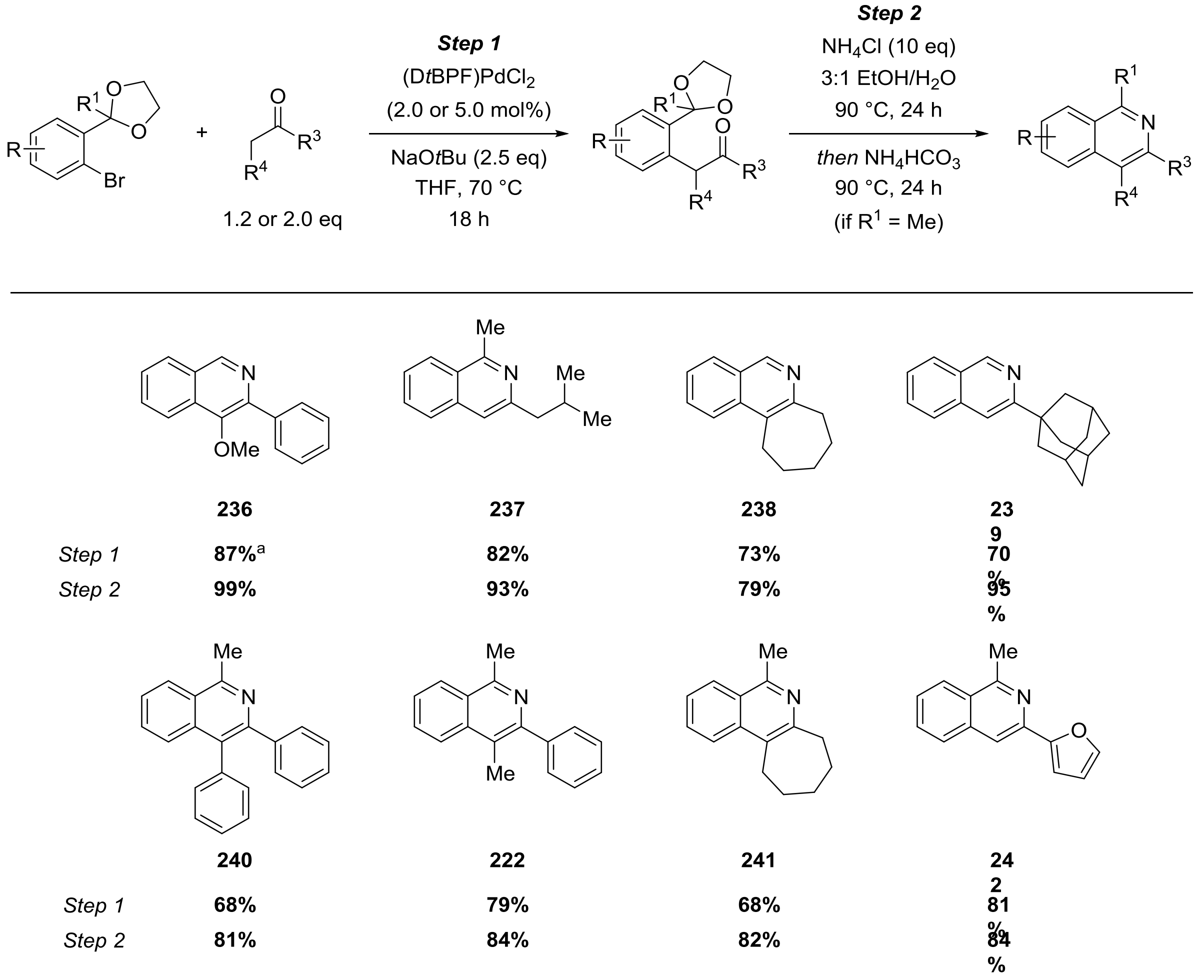
	228	229	230	231
Step 1	**70%**[a]	**86%**	**89%**	**89%**
Step 2	**86%**	**97%**	**96%**	**92%**

	232	233	234	235
Step 1	**69%**	**79%**	**87%**[b]	**79%**
Step 2	**80%**	**86%**	**76%**	**73%**

Scheme 56. Scope of substitution in aryl bromide coupling partner
[a] K_3PO_4 instead of NaO*t*Bu; [b] Cs_2CO_3 instead of NaO*t*Bu

A wide variety of substituents were tolerated, covering all four carbocyclic positions and including heteroatom, alkyl, electron donating and electron withdrawing substituents. The use of milder bases (K_3PO_4 or Cs_2CO_3) in the arylation step allowed sensitive functional groups such as a methyl ester (**228**) and a nitro group (**234**) to be carried through the synthesis. The benzenoid ring could also be replaced with thiophene for the synthesis of multiple heteroatom-containing bicycles (**235**).

The scope of the synthesis with respect to the C3 and C4 substituents on the heterocyclic ring was then explored by employing a range of different ketones (**Scheme 57**).



	236	**237**	**238**	**239**
Step 1	**87%**[a]	**82%**	**73%**	**70%**
Step 2	**99%**	**93%**	**79%**	**95%**

	240	**222**	**241**	**242**
Step 1	**68%**	**79%**	**68%**	**81%**
Step 2	**81%**	**84%**	**82%**	**84%**

Scheme 57. Exploring the scope of substituents R^1, R^3 and R^4
[a] K_3PO_4 instead of NaO*t*Bu

Aryl, heteroaryl and aliphatic ketones all underwent regioselective arylation in good yield. In the aryl bromide coupling partner, acetals of both aldehydes and ketones were tolerated, affording isoquinolines where R^1 = H or Me.

A number of additional ketones were tested but found to be unreactive due to decomposition under α-arylation conditions (presumably *via* carbene formation or aldol reaction), or, in the case of **243**, prohibitive steric hindrance (**Figure 12**).[176]

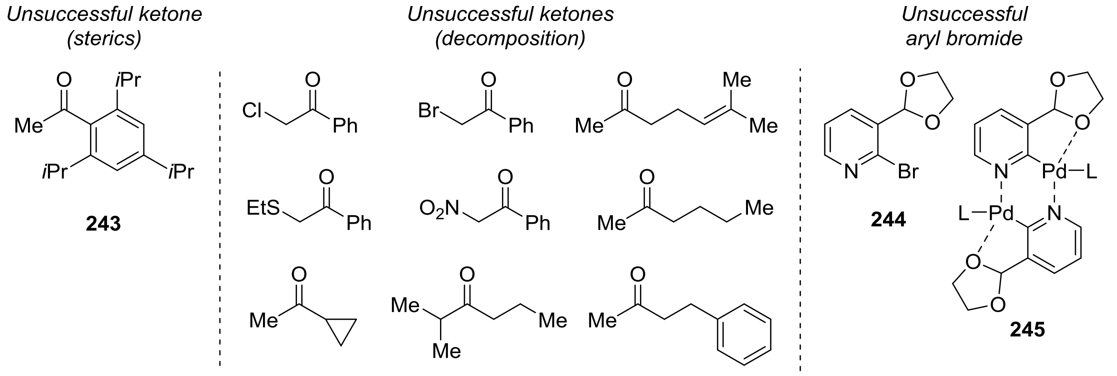
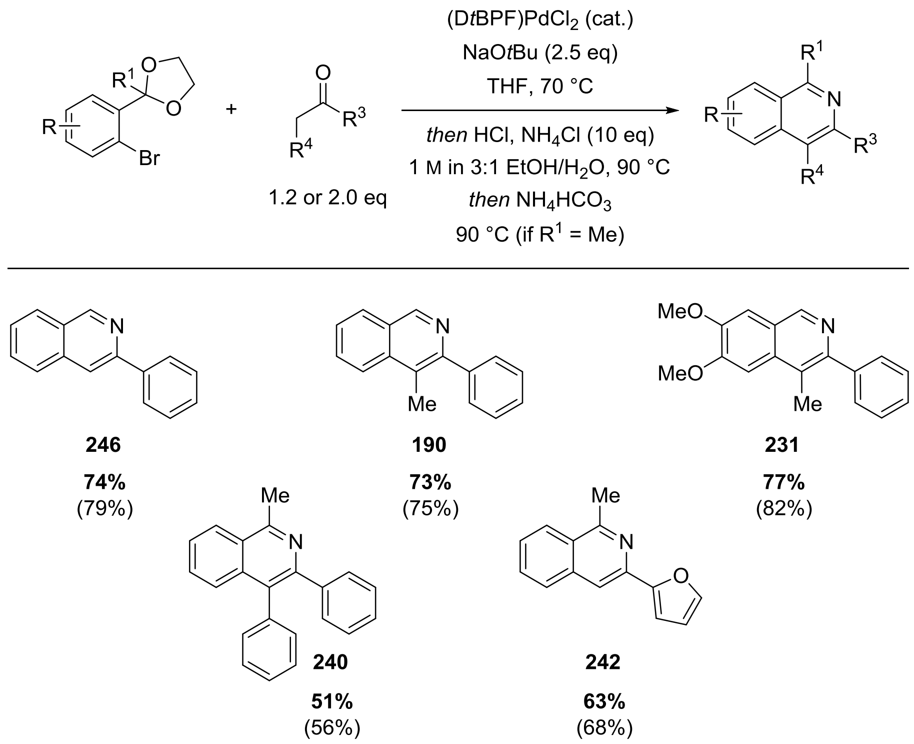


Figure 12. Failed aryl bromides and ketones

The 2-bromopyridyl acetal **244** was inert under α-arylation conditions,[176] despite the fact that Hartwig and coworkers had successfully employed 2-bromopyridine in their α-arylation reactions.[81] It is postulated that the failure of this reaction may be the result of the pyridine poisoning the catalyst by displacement of phosphine ligands by nitrogen[177–179] or, should oxidative addition occur, formation of stable dinuclear complex **245**. The chelating acetal was absent in Hartwig's system and, furthermore, the use of excess preformed lithium enolate may have allowed it to out-compete the pyridine for coordination to palladium.

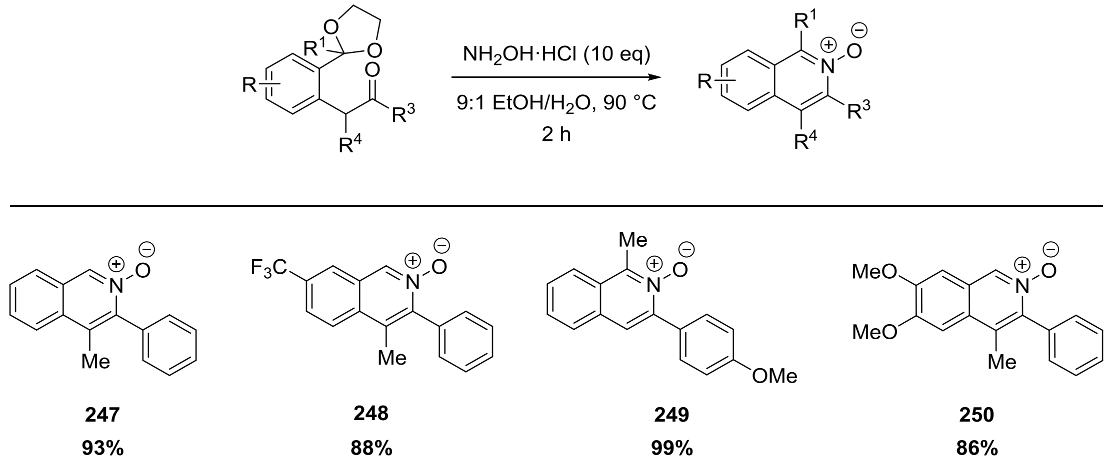
The miscibility of THF, EtOH, and water facilitated an operationally-simple one-pot protocol for the α-arylation and cyclisation reactions. Once TLC analysis indicated that the palladium-catalysed arylation was complete, the reaction mixture was acidified to pH 5 by the addition of 1 M aqueous HCl, and then a solution of ammonium chloride in 3:1 EtOH/H_2O was added. The reaction was heated as previously described to provide isoquinolines in yields that were comparable to those from the stepwise protocol (**Scheme 58**).



Scheme 58. One-pot synthesis of isoquinolines. Stepwise yields are in parentheses

1.4.5 Synthesis of isoquinoline *N*-oxides

It was also possible to directly convert the α-arylation products into isoquinoline *N*-oxides by replacing ammonium chloride in the cyclisation step with the hydrochloride salt of hydroxylamine (**Scheme 59**).[175,180] Conversion of the intermediates to *N*-oxides was faster than to the corresponding isoquinolines, presumably due to the α-effect enhancing the nucleophilicity of nitrogen and the inductive effect of the hydroxyl increasing N–H acidity.[181]

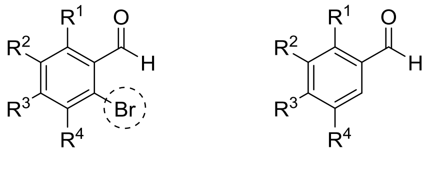


Scheme 59. Direct synthesis of selected isoquinoline *N*-oxides

Chapter 2. Results and Discussion

2.1 Palladium-catalysed α-arylation by C–H activation

During the past two decades, chelation-assisted direct C–H functionalisation has emerged as a powerful synthetic strategy due to its ability to bypass prefunctionalised starting materials.[182–188] Whilst significant progress has been made in the use of imines,[140–143] amines,[144–146] oximes,[147–160] and other nitrogen-centred directing groups for the synthesis of isoquinolines using the transition metal-catalysed annulation of alkynes, these methods tend to suffer from regioselectivity issues when using unsymmetrical alkynes, and the scope of substitution at C3 and C4 is limited by the commercial availability of the requisite alkyne starting materials.[139] Meanwhile, the α-arylation methodology developed by the Donohoe group for the synthesis of isoquinolines offered broad functional group tolerance and reliable regioselectivity but required difunctionalised precursors, specifically *ortho*-halobenzaldehydes or *ortho*-halo phenyl ketones, as starting materials.[175] It was therefore highly desirable to adapt this methodology into a C–H activation route, using simple, inexpensive benzaldehydes which are substantially more commercially abundant than their *ortho*-brominated congeners (**Figure 13**).

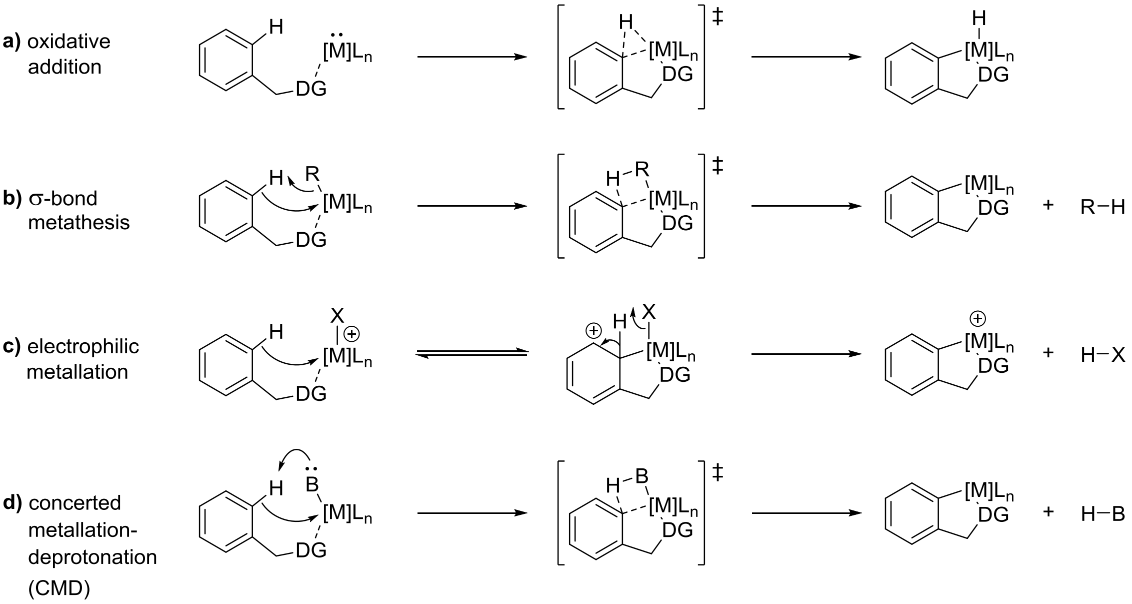


Price per mole:[a] ($R^1 = R^2 = R^3 = R^4 = H$)	£131.48	£3.22
Number of commercially available derviatives:[b]	1229	7016

Figure 13. Accessibility of benzaldehydes vs *ortho*-bromobenzaldehydes
[a] Average price from Sigma-Aldrich and Alfa Aesar; [b] Number of commercially available substances from SciFinder® substructure search

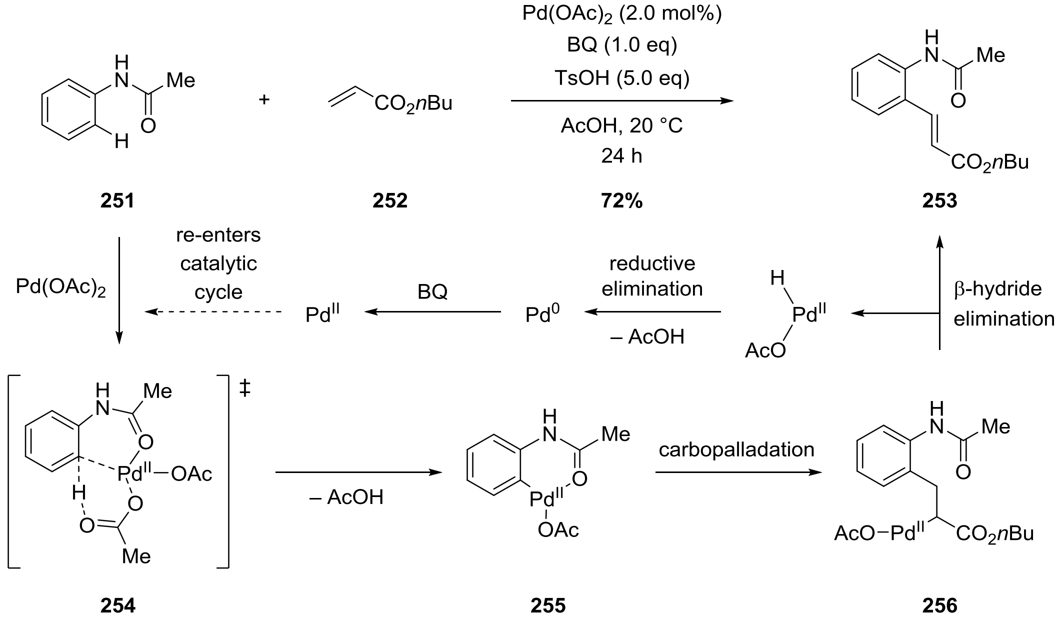
2.1.1 Mechanistic aspects of palladium-catalysed C–H activation

The exact mechanistic pathway of metal C–H bond insertion depends on the substrate, solvent, additives, transition metal and ligands present.[189] Four mechanisms are generally invoked: a) oxidative addition of C–H to electron rich, low-valent complexes of the late transition metals (**Scheme 60a**); b) σ-bond metathesis in early transition metals with d^0 configuration, for which oxidation is not possible (**Scheme 60b**);[190,191] c) electrophilic metallation in electron deficient late transition metal complexes (**Scheme 60c**) and d) base- or ligand-assisted concerted metallation-deprotonation (CMD), which is common in Pd(II)-catalysed C–H activation chemistry (**Scheme 60d**).[192]



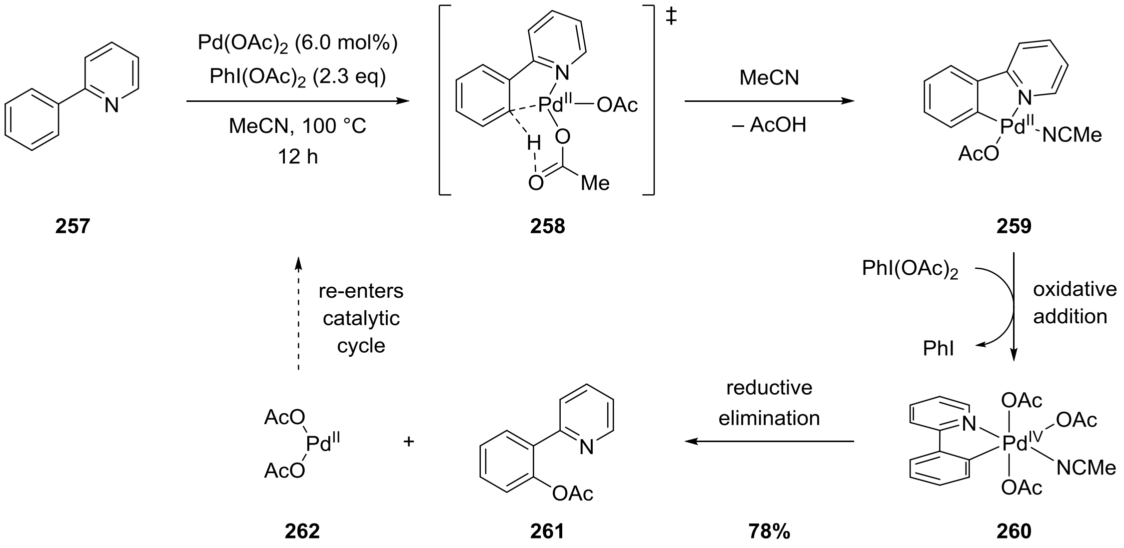
Scheme 60. Metal C–H insertion mechanisms. DG = directing group, B = base

Directing group-assisted C–H activation by Pd(II) generates cyclopalladated intermediates that can undergo functionalisation by two distinct mechanistic pathways.[182–186] The first involves a Pd(II)/(0) catalytic cycle which resembles a traditional cross-coupling mechanism. Palladacycle **255** undergoes ligand exchange by direct displacement, transmetallation (for example with a boronic acid)[187] or carbopalladation as in the Heck-like Fujiwara-Moritani reaction shown in **Scheme 61**.[193] β-Hydride elimination and/or reductive elimination furnish the product **253** and a Pd(0) species that requires reoxidation to Pd(II), commonly by the action of benzoquinone (BQ), Ag(I), or Cu(II) salts such as Ag_2CO_3, AgOAc, $Cu(OAc)_2$ or $Cu(OTf)_2$.



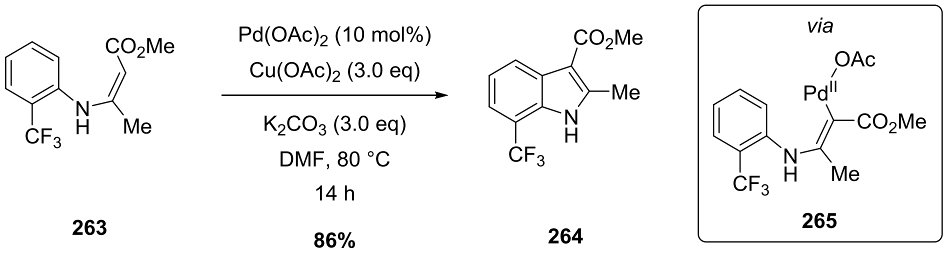
Scheme 61. Pd(II)/(0) catalytic cycle exemplified by the Fujiwara-Moritani reaction between **251** and **252**

Secondly, palladacycles can undergo mid-cycle oxidative addition of the second coupling partner, generating a Pd(IV) intermediate or a Pd(III)–Pd(III) dimer, depending on the nature of the ancillary ligands.[182–186] This mechanism is common in carbon-heteroatom bond formation, where reagents such as $PhI(OAc)_2$, $K_2S_2O_8$, Cl_2, *N*-chlorosuccinimide and CuX_2 (X = Cl, Br) are capable of oxidising Pd(II) and introducing heteroatom-bound ligands to palladium (**Scheme 62**).[194] Reductive elimination from **260** furnishes the functionalised product **261** along with Pd(II), ready to re-enter the catalytic cycle.



Scheme 62. Pd(II)/(IV) catalytic cycle in C–H acetoxylation

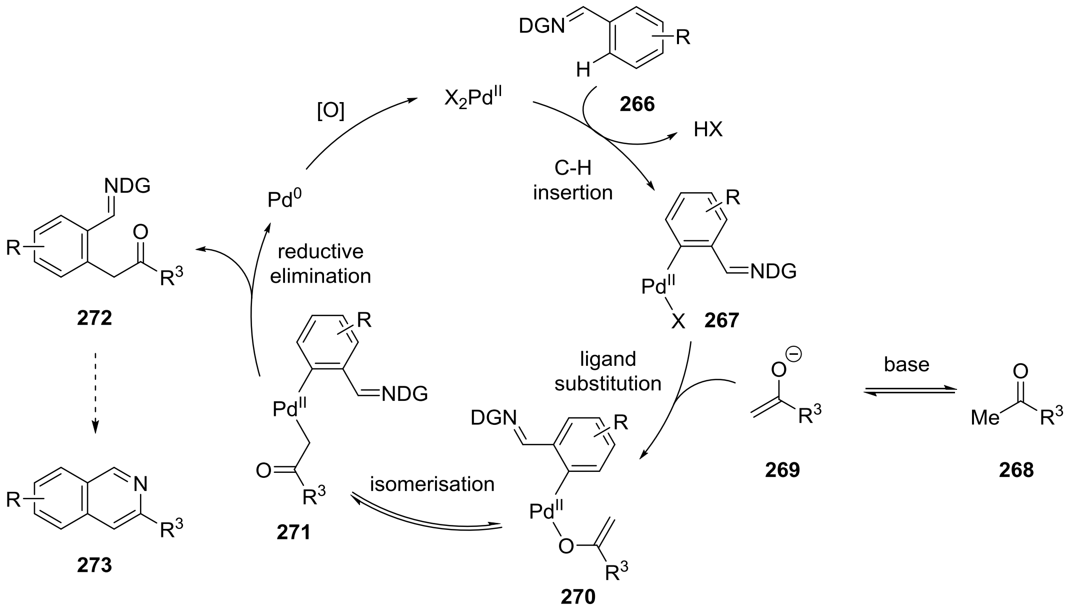
The use of carbonyl-derived nucleophiles, such as enamines, in transition metal-catalysed C–H functionalisation reactions has been limited to intramolecular palladium-, copper- and iron-catalysed arylation in the synthesis of aza-heterocycles such as indoles.[195–197] Glorius and coworkers proposed that indole formation from *N*-aryl enamines such as **263** was initiated by nucleophilic ligand displacement by the enamine on palladium, forming an α-palladated imine which then tautomerised to the enamine **265** (**Scheme 63**).[198–200] Only then did palladium insert intramolecularly into the *ortho* C–H bond to effect coupling.



Scheme 63. Glorius's Pd(II)-catalysed intramolecular enamine arylation in the synthesis of indoles

The arylation of nucleophilic carbonyl derivatives by C–H activation in an intermolecular fashion was completely unknown. Regardless of its potential for use in isoquinoline synthesis, the development of such a reaction would greatly expand the scope of C–H functionalisation chemistry and allow even greater exploitation of carbonyl compounds in organic synthesis.

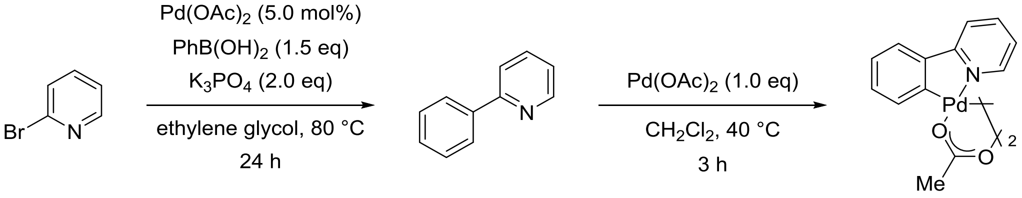
It was postulated that a suitable carbonyl protecting group in starting material **266** could act as a nitrogen directing group (NDG) for the insertion of Pd(II) into the *ortho* C–H bond, generating arylpalladium species **267** (**Scheme 64**). Ligand displacement by enolate **269**, isomerisation, and reductive elimination would furnish α-aryl ketone **272**, which could later be cyclised to isoquinoline **273**, making use of the nitrogen atom in the adjacent directing group. A reoxidant [O] would be required to regenerate the active Pd(II) catalyst from Pd(0).



Scheme 64. Postulated catalytic cycle for proposed α-arylation of ketones *via* C–H activation

2.1.2 Stoichiometric studies

Due to the lack of any precedent for a C–H activation/enolate cross-coupling reaction, it was decided to test the viability of the enolate arylation steps of the proposed catalytic cycle using a preformed arylpalladium complex. Initial studies focused on phenylpyridine **257** since pyridines were well-known to serve as highly effective directing groups for palladium-catalysed C–H bond functionalisation (**Scheme 65**).[201] 2-Phenylpyridine **257**, which can also be purchased, was synthesised by Suzuki coupling between 2-bromopyridine **274** and phenylboronic acid in 63% yield.[202]



274 **63%** **257** **95%** **275**

Scheme 65. Synthesis of dimeric palladacycle **275**

The effectiveness of the pyridine moiety as a directing group was demonstrated when 2-phenylpyridine **257** was treated with stoichiometric $Pd(OAc)_2$ in CH_2Cl_2 at 40 °C. After three hours, the solvent was removed and the residue triturated with Et_2O to provide the known C–H insertion product **275** as a yellow solid in 95% yield.[203] The insertion of palladium was confirmed by comparison of the NMR spectra of the substrate and product; specifically the loss of one aromatic proton from the ^{1}H NMR spectrum and the appearance of a new quaternary aromatic signal in the ^{13}C NMR spectrum. Single crystal X-ray diffraction confirmed the acetate-bridged dimeric structure of palladacycle **275** (**Figure 14**).

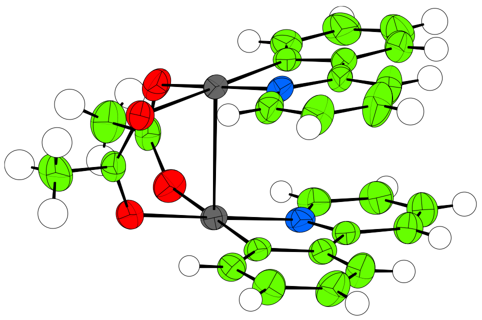
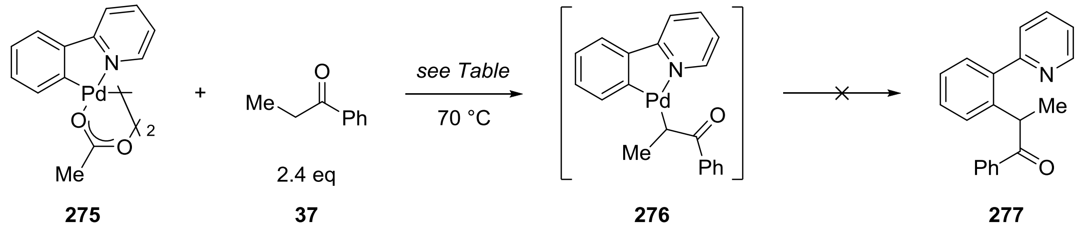


Figure 14. Representation of crystal structure of palladacycle **275**

Palladacycle **275** was then treated with propiophenone **37** and NaO*t*Bu – both of which had been used in the optimisation of Donohoe's α-arylation conditions – in the anticipation that the enolate of **37** would displace one of bridging acetate ligands to provide palladium enolate complex **276**, which would undergo reductive elimination to furnish α-aryl ketone **277** (**Table 3**, Entry 1).[175] The reaction was unsuccessful and, after workup, only propiophenone and traces of unidentifiable side products, most likely resulting from aldol condensation, were recovered.

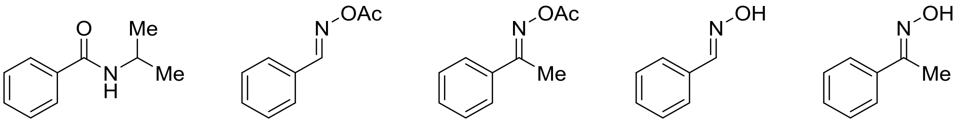


Entry	Base	Solvent	Additive	Time / h	Result
1	NaO*t*Bu	THF	–	20	No reaction
2	NaO*t*Bu	THF	D*t*BPF (2.0 eq)	20	No reaction
3	NaO*t*Bu	THF	P*t*Bu$_3$·HBF$_4$ (2.0 eq)	20	No reaction
4	–	Neat	–	24	Palladacycle recovered
5	–	AcOH	–	24	No reaction

Table 3. Unsuccessful attempts to arylate propiophenone using palladacycle **275**

It was envisaged that the addition of D*t*BPF (Entry 2) or the air-stable tetrafluoroborate salt of P*t*Bu_3 (Entry 3)[204] may promote the reaction of **257** with propiophenone by displacing the pyridyl directing group and encouraging reductive elimination, however no beneficial effect was observed. This was perhaps unsurprising, considering the catalyst-poisoning effect previously encountered with the use of pyridines in α-arylation.[176] Heating the palladacycle in neat propiophenone, or in acetic acid as a solvent, gave no trace of product **277** (Entries 4 and 5). It was apparent that the high stability of pyridyl palladacycle **275** may have been detrimental to the reaction due to the reluctance of the ligands to dissociate, retarding the displacement of acetate by the enolate and precluding the coordination of a bulky phosphine ligand. Furthermore, palladacycle **275** suffered from poor solubility in THF, which is generally the solvent of choice for α-arylation reactions.

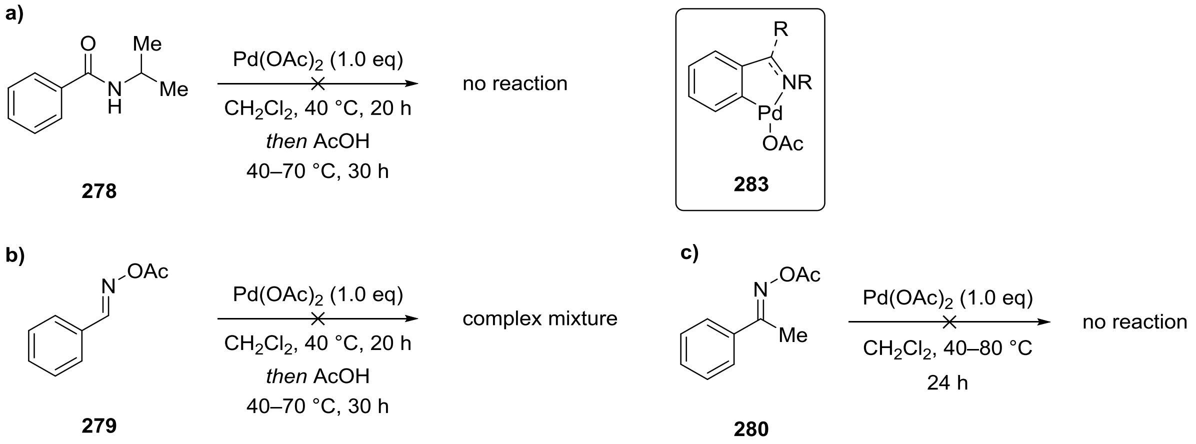
However, it was still desirable to continue stoichiometric studies using an isolable palladacycle in order to gain a deeper understanding of the ability of enolates to couple with such species. To this end, substrates **278–282** were synthesised from benzoyl chloride (**278**) or the corresponding aldehyde or ketone (**279–282**) (**Figure 15**). All of them contained a directing group with a benzylic nitrogen atom which could be exploited in isoquinoline syntheses at a later stage. The *O*-acetyl and *O*-H oximes **279–282** were chosen due to their prevalence in alkyne annulation chemistry for isoquinoline synthesis.[147–160]



278 **279** **280** **281** **282**

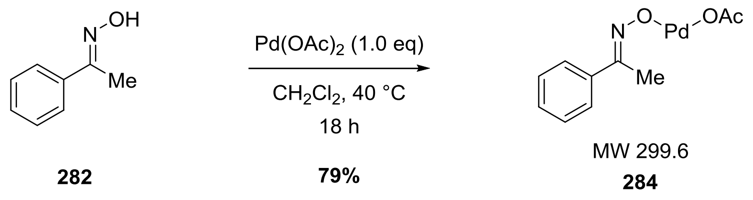
Figure 15. Substrates with alternative directing groups

Compounds **278–282** were then treated with $Pd(OAc)_2$, under the conditions used previously, in an attempt to form palladacycles with the general structure of **283** (**Scheme 66**). Upon removal of the solvent, ^{1}H NMR analysis showed that amide **278** was returned unchanged, along with Pd(OAc)$_2$, even when acetic acid was subsequently added and the temperature elevated to promote CMD (**Scheme 66a**). *O*-Acetyl oxime **279** gave a complex mixture of unidentifiable products (**Scheme 66b**), and acetophenone analogue **280** was unreactive (**Scheme 66c**).



Scheme 66. Unsuccessful attempts at palladacycle synthesis

Unsubstituted *O*–H oxime **281** was consumed upon reaction with Pd(OAc)$_2$, but ^{13}C NMR analysis of the crude residue still showed only three distinct tertiary aromatic carbon signals and one quaternary carbon signal at 184.5 ppm. A new singlet at 2.13 ppm in the ^{1}H NMR spectrum was consistent with the presence of the methyl group of an acetate, suggesting that the oxime had coordinated to palladium, displacing one acetate ligand, but the metal had not inserted into the *ortho* C–H bond. Oxime **282** met a similar fate, but in this case the reaction product **284**, which was obtained in 79% yield, was pure enough to permit full characterisation (**Scheme 67**). Once again, NMR spectroscopy indicated the presence of an acetate group, and the lack of an oxime O–H absorption band at 3200–3500 cm^{-1} in the IR spectrum suggested that the oxime was bound to palladium through oxygen.



Scheme 67. Formation of acetophenone oxime palladium complex **284**

Low resolution ESI$^+$ mass spectrometry gave a sodium adduct peak with a rather complex isotope pattern, indicating the presence of one or more palladium atoms (natural abundances: ^{104}Pd 11.1%, ^{105}Pd 22.3%, ^{106}Pd 27.3%, ^{108}Pd 26.5%, ^{110}Pd 11.7%),[205] centred around m/z = 921.9, equating to three times the molecular weight of complex **284** plus Na$^+$ ([M + Na]$^+$) (**Figure 16**). The [2M + Na]$^+$ ion was also observed around m/z = 1818.

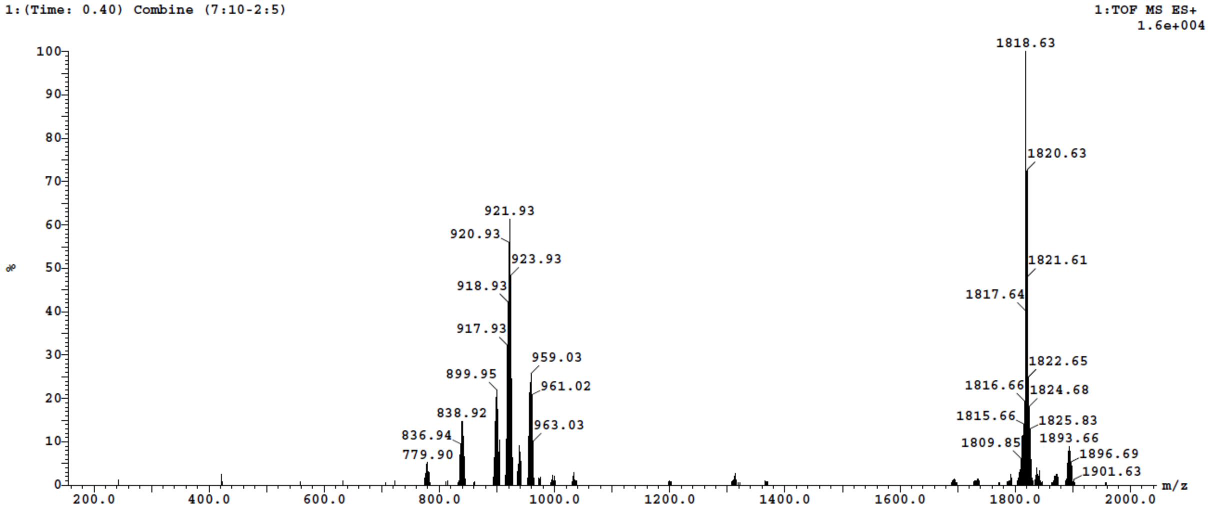


Figure 16. Low-resolution ESI$^+$ mass spectrum of complex **284**

The high resolution spectrum revealed the true complexity of the molecular ion peak (**Figure 17**). A compound containing a single palladium atom would be expected to show five peaks, one for each of the five most abundant palladium isotopes. If three indistinguishable palladium atoms were present, each of which may be one of five isotopes, the number of possible combinations would be 35. However, fewer than 35 molecular ion peaks are expected as several of the possible isotopic combinations would give the same total mass. The observed high resolution mass spectrum contained 16 peaks in the region m/z = 921, in agreement with the theoretical spectrum for a trinuclear palladium complex.

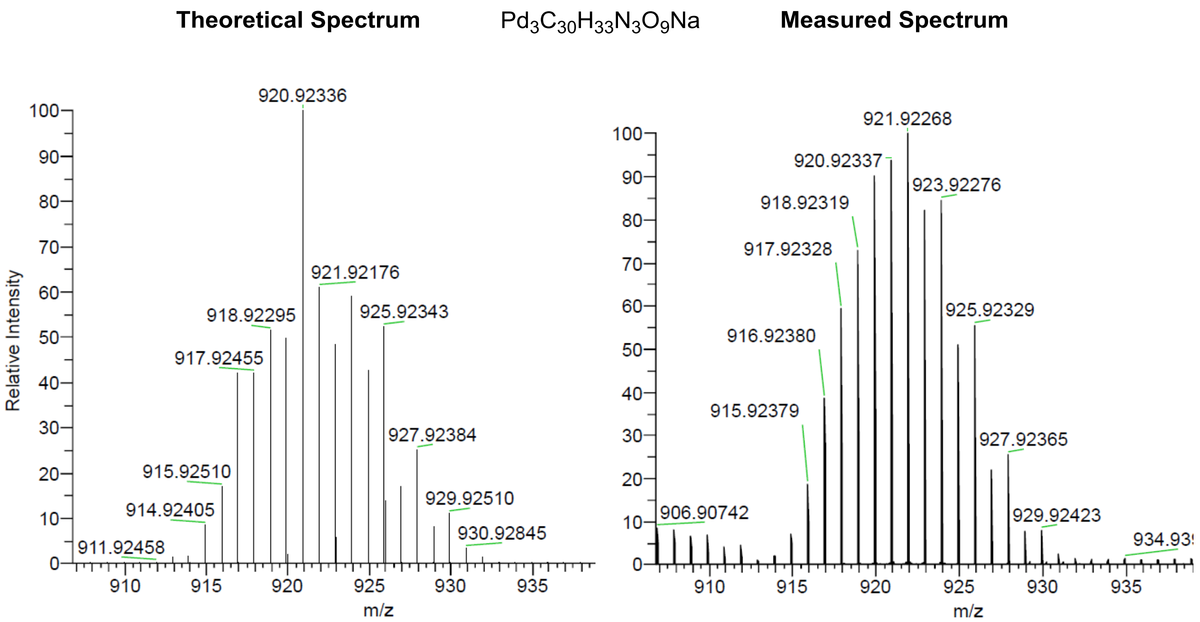
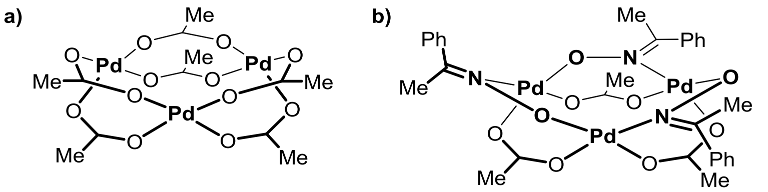


Figure 17. Theoretical and measured high resolution ESI$^+$ mass spectra of complex **284**

It was therefore proposed that the oxime palladium complex **284** was in fact trimeric, in an analogous manner to crystalline Pd(OAc)$_2$, which takes the form of an acetate-bridged trimer (**Figure 18a**).[206] Indeed, a literature search revealed that the formation of complex **284** had been reported by Kim and Gabbaï in 2004 when (*E*)-acetophenone oxime **282** was stirred with Pd(OAc)$_2$ in acetic acid at room temperature.[207] X-Ray crystallography by the authors revealed the trinuclear structure **286**, which can be derived from that of [Pd(OAc)$_2$]$_3$ by replacing three acetate ligands on one side of the Pd$_3$ plane by three *N*,*O*-coordinated oximate ligands (**Figure 18b**). The resulting structure has three coplanar Pd atoms, each with square planar geometry, connected by three μ^2 bridging acetate ligands on one side of the plane (the lower face in **Figure 18b**) and three *O*- and *N*-bound bridging oximate ligands on the other (upper) face.



285

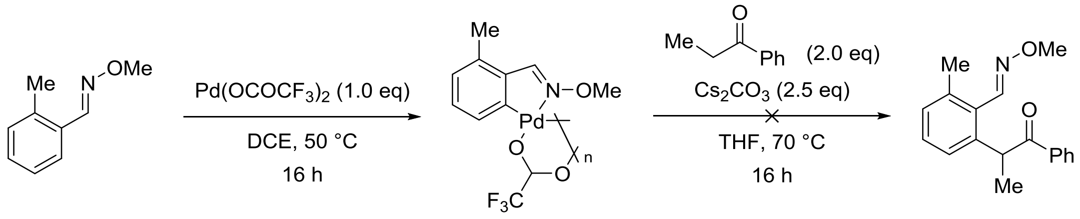
[Pd(μ-OAc)$_2$]$_3$

286

[Pd(μ-(*E*)-ON=C(CH$_3$)Ph)(μ-OAc)]$_3$

Figure 18. Trimeric structures of [Pd(OAc)$_2$]$_3$ and complex **286**

Though interesting, the formation of complex **286** did not lead to the identification of a suitable palladacycle, formed by C–H insertion, which would undergo coupling with the enolate of propiophenone. *O*-Methyl oxime **287**, in which one of the *ortho* positions was substituted with a methyl group, was the next substrate investigated, since it was thought that the methyl group would prevent complication of the α-arylation reaction by re-insertion of palladium into the product (**Scheme 68**). Reaction with $Pd(OCOCF_3)_2$ afforded palladacycle **288** in quantitative yield, as an oily 4:1 mixture of two species, most likely a monomeric and a dimeric palladacycle species. It was anticipated that the trifluoroacetate ligands would be more labile than acetate, promoting their displacement by an enolate.

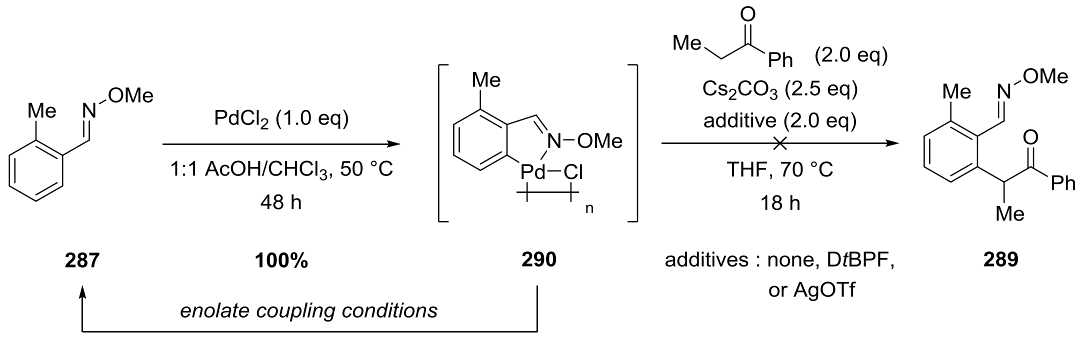


Scheme 68. Unsuccessful arylation attempt with palladacycle **288**

Benzaldoxime **287** was known to decompose in the presence of NaO*t*Bu, possibly *via* elimination of MeOH and nitrile formation, so the milder base Cs_2CO_3 was used in the reaction of palladacycle **288** with propiophenone, since it had previously been used successfully in α-arylation reactions of base-sensitive substrates.[175] However, not even traces of the product **289** were observed and a black solid, which could not be recrystallised or dissolved in deuterated solvents (most likely Pd(0)) precipitated from the reaction mixture.

Oxime **287** was then treated with $PdCl_2$ under literature conditions used for the synthesis of dimeric *O*–H and *O*–acetyloxime palladacycles,[208] providing an orange-brown solid, postulated to be chloride-bridged palladacycle **290** (**Scheme 69**). Suffering from poor solubility, the product could not be analysed by NMR spectroscopy but was subjected to a number of different enolate coupling conditions. In every case, including the addition of

Ag(I) to abstract chloride and generate a more electrophilic, positively charged palladium centre, only protodepalladation occurred, liberating oxime starting material **287**.

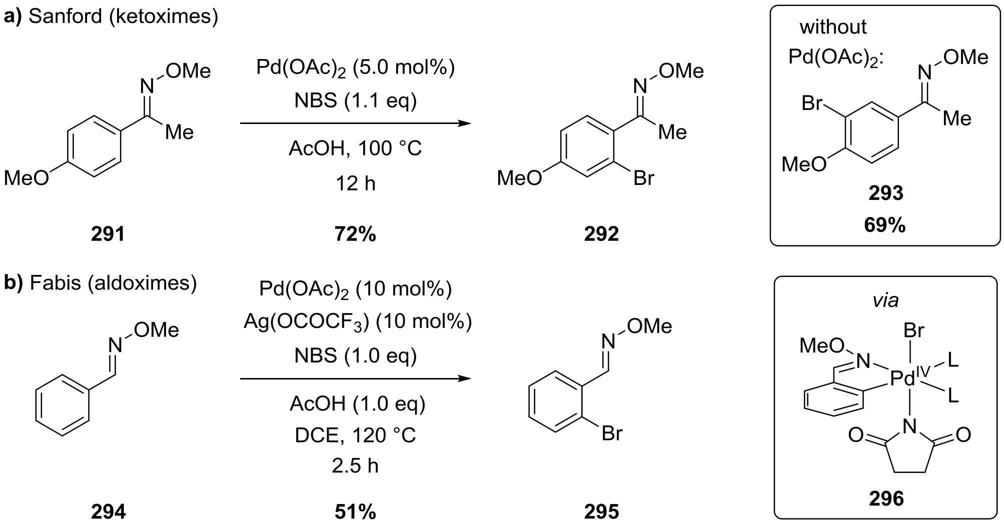


Scheme 69. Protodepalladation of palladacycle **290** under enolate coupling conditions

In light of these results, it was concluded that a ketone enolate would not react directly with a palladacycle generated by C–H activation in the same manner as it would with an arylpalladium complex formed by oxidative addition in the standard α-arylation reaction. It was therefore decided to explore an alternative approach.

2.1.3 Stepwise C–H activation/α-arylation

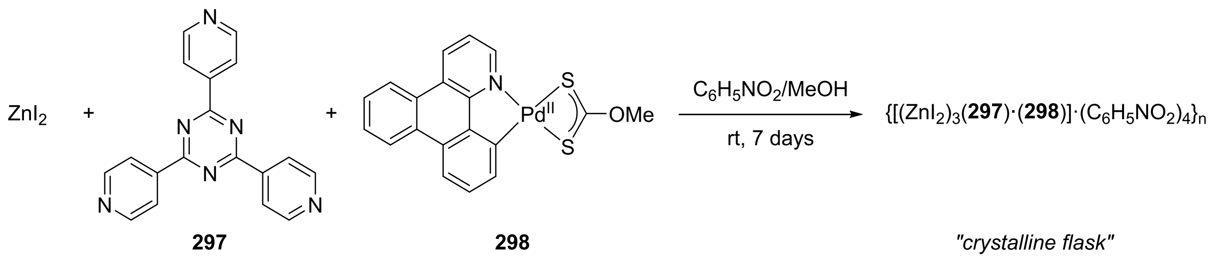
A known C–H halogenation reaction presented an opportunity for an alternative strategy to the direct coupling route. Procedures for the C–H bromination of aryl *O*-methyl oximes were reported by Sanford (**Scheme 70a**)[209] and Fabis (**Scheme 70b**)[210] in 2006 and 2011, respectively. Both authors proposed a Pd(II)/(IV) mechanism involving mid-cycle oxidation of Pd(II) by NBS to give octahedral Pd(IV) complexes like **296**. In the absence of $Pd(OAc)_2$, Sanford observed the formation of regioisomeric aryl bromide **293** (which is the expected product of electrophilic aromatic substitution based on the electronic properties of the starting material) in almost identical yield, confirming that the directed C–H insertion of palladium was responsible for the high *ortho*-selectivity in the formation of product **292**.



Scheme 70. Pd(II)-catalysed *O*-methyl oxime-directed C–H bromination

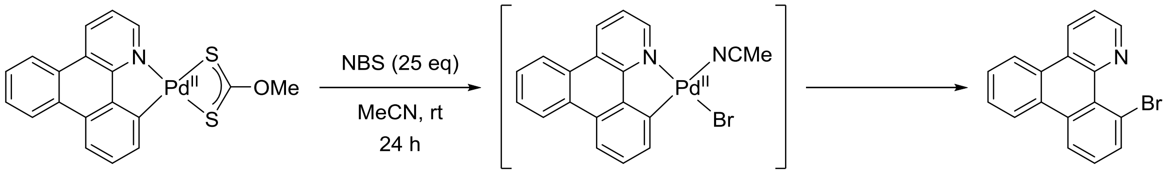
In 2009, Ritter isolated an acetate-bridged Pd(III)-Pd(III) chloride dimer, formed by two-electron oxidation of a dimeric benzoquinoline palladium acetate complex by $PhICl_2$, which gave the chlorinated arene by reductive elimination upon warming to room temperature, further supporting the hypothesis of mid-cycle oxidation of Pd(II).[211]

In 2014, Fujita and coworkers used X-ray snapshots to probe the mechanism of the bromination reaction of arylpalladium species **298** embedded in the pore of a “crystalline flask,” or porous crystalline coordination network, formed from ZnI_2 and tris(4-pyridyl)triazine **297** (**Scheme 71**).[212]



Scheme 71. Triazine **297** used with ZnI_2 by Fujita to form a “crystalline flask”

When localised palladacycle **298** was treated with NBS, the square planar aryl Pd(II) bromide complex **299** was observed, which underwent reductive elimination to form the aryl bromide product **300** (**Scheme 72**).

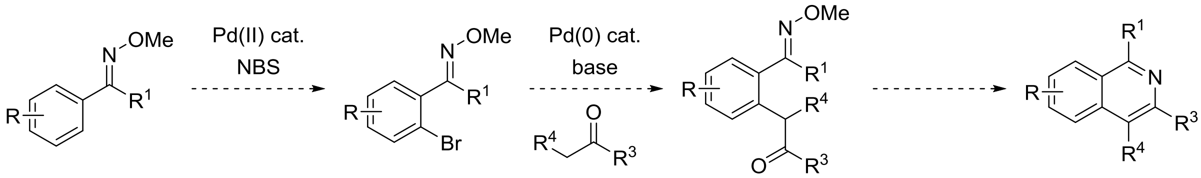


298 **299** **300**

Scheme 72. Pd(II) arylpalladium bromide complex **299** in C–H bromination

These observations suggested that Pd(II)-catalysed C–H bromination could occur *via* a Pd(II)/Pd(0) catalytic cycle, and that the dominant Pd(II)/(IV) mechanism was not exclusive. The authors conceded, however, that the crystalline state may bias the reaction pathway, since the inflexible cavities hinder the formation of octahedral Pd(IV) complexes and disallow the formation of Pd(III)–Pd(III) dimers. Furthermore, X-ray crystallography would only detect intermediates of sufficient lifetime, so the involvement of a transient higher oxidation state palladium species could not be ruled out.

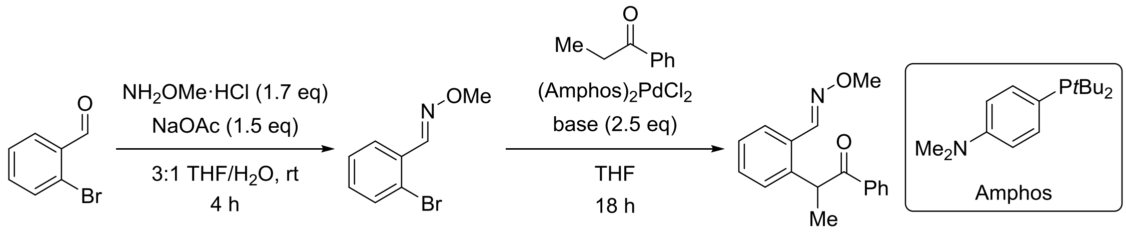
In light of these reports, an alternative strategy was proposed for the α-arylation of ketones *via* C–H activation, whereby the Pd(II)-catalysed C–H bromination of oxime **301** would afford aryl bromide **302**, which could then undergo Pd(0)-catalysed coupling with an enolate (**Scheme 73**). Though two steps, it was anticipated that the reactions could ultimately be combined in one pot, and the availability of starting materials would still be greatly enhanced.



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

Scheme 73. Proposed one-pot C–H activation/α-arylation route to isoquinolines

Before exploring the bromination reaction, it was necessary to test the compatibility of *O*-methyl oximes with the α-arylation reaction and subsequent isoquinoline formation, since only cyclic acetals had been used as protected carbonyl groups in Donohoe's previous work.[175] To this end, *ortho*-bromoaryl oxime **295** was obtained in near quantitative yield by treating commercially-available 2-bromobenzaldehyde **305** with methoxylamine hydrochloride under basic conditions (**Table 4**). Bromide **295** was then subjected to the palladium-catalysed α-arylation reaction with propiophenone under the optimised conditions developed previously in the Donohoe group (Entry 1).[175] Oxime **295** was rapidly consumed but a complex mixture of products was obtained with no trace of the *O*-methyl group by NMR analysis. It was concluded that **295** was destroyed by NaO*t*Bu, possibly by elimination of MeOH, thus the milder bases K_3PO_4 and Cs_2CO_3 (*t*BuOH $pK_a = 16.5$,[58] HPO_4^{2-} $pK_a = 12.3$,[57] HCO_3^- $pK_a = 10.3$ in H_2O)[213] were employed in combination with $(Amphos)_2PdCl_2$, which had previously exhibited greater activity than (D*t*BPF)$PdCl_2$ when weaker bases were used.[175]



305 99% **295** **306**

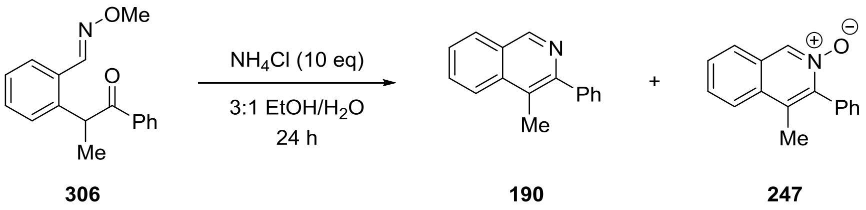
Entry	Catalyst loading / mol %	Base	Ketone / eq	Temperature / °C	Yield / %
1	5.0[a]	NaO*t*Bu	1.2	70	0
2	5.0	K_3PO_4	1.2	70	56
3	5.0	K_3PO_4	1.2	90	80
4	5.0	K_3PO_4	2.0	70	60
5	5.0	K_3PO_4	2.0	90	82
6	5.0	Cs_2CO_3	1.2	70	77
7	5.0	Cs_2CO_3	1.2	90	86
8	5.0	Cs_2CO_3	2.0	70	91
9	2.0	Cs_2CO_3	2.0	70	67
10	5.0[a]	Cs_2CO_3	2.0	70	18

Table 4. Optimisation of the α-arylation of propiophenone with aryl bromide **295**
[a] (D*t*BPF)$PdCl_2$ instead of $(Amphos)_2PdCl_2$

Pleasingly, oxime **295** survived treatment with K_3PO_4, and α-aryl ketone **306** was provided in 56% yield using 5.0 mol% $(Amphos)_2PdCl_2$ at 70 °C (Entry 2). The identity of **306** was confirmed by a quartet at 5.34 ppm in the ^1H NMR spectrum corresponding to the benzylic α-proton. A single oxime geometric isomer was obtained, which has been assigned as (*E*) by analogy to precursor **295**. Increasing the temperature to 90 °C gave a significant improvement in yield to 80% (Entry 3). It should be noted that these reactions were conducted in a sealed tube to allow the temperature to be elevated above the boiling point of THF (65 °C at a pressure of 1 atm). Using 2.0 equivalents of propiophenone rather than 1.2 equivalents gave little change in yield at both 70 °C and 90 °C (Entries 4 and 5). Less basic Cs_2CO_3 performed better than K_3PO_4, which may be due to the base-sensitivity of oxime **295**, but which could also be attributed to the superior solubility of Cs_2CO_3 in organic solvents (Entry 6 vs Entry 2). The latter could also explain the improvement in yield observed when increasing the amount of propiophenone from 1.2 to 2.0 equivalents (Entry 8 vs Entry 6), since a high concentration of Cs_2CO_3 in solution leads to a greater concentration of enolate when excess ketone is added. In the case of K_3PO_4, the enolate concentration is limited by the concentration of base in solution rather than the quantity of ketone. A higher concentration of enolate would accelerate the desired α-arylation reaction relative to any undesired decomposition pathways, and in addition, since the palladium catalyst has a limited active lifetime, a faster reaction would allow greater conversion within this period. Rates of reaction may also be enhanced by increasing the temperature, and indeed the yield improved from 77% to 86% upon elevating the temperature from 70 °C to 90 °C, even though only 1.2 equivalents of ketone were used (Entry 7 vs Entry 6).

The best yield of 91% was achieved using 5.0 mol% catalyst and 2.0 equivalents of ketone at 70 °C (Entry 8), but a lower catalyst loading (2.0 mol%) still gave the product **306** in good yield (Entry 9). In agreement with earlier findings, the alternative precatalyst (D*t*BPF)$PdCl_2$ was significantly less active than $(Amphos)_2PdCl_2$ when using Cs_2CO_3 (Entry 10 vs Entry 8).

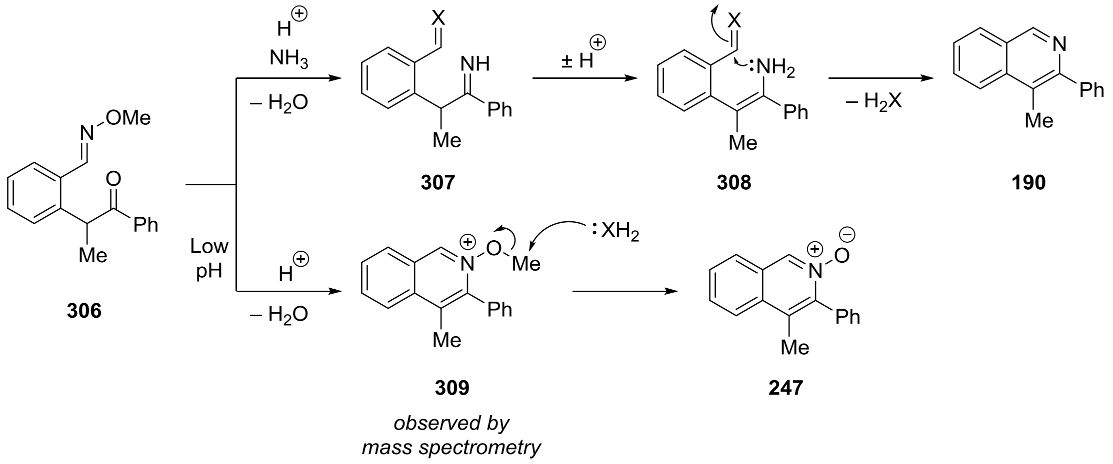
With α-arylation product **306** in hand, the development of suitable conditions for its cyclisation to the corresponding isoquinoline was required. The mildly acidic conditions used previously[175] generated a mixture of unreacted starting material **306**, isoquinoline **190** and the corresponding *N*-oxide **247** (**Table 5**, Entry 1). Increasing the temperature to 120 °C or decreasing the pH by acidification with aqueous HCl improved the conversion but increased the proportion of *N*-oxide (Entries 2, 3 and 4).



Entry	pH	Temperature / °C	306 : 190 : 247[a]
1	5	90	44 : 40 : 44
2	5	120	0 : 53 : 47
3	3[b]	90	24 : 48 : 29
4	1[b]	90	7 : 34 : 59

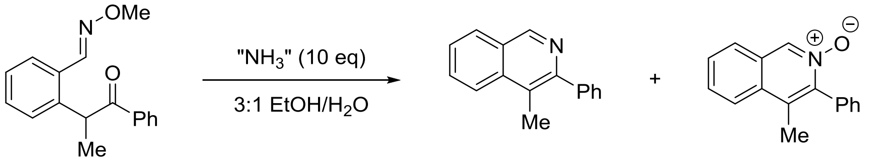
Table 5. Heterocycle formation from **306** under acidic conditions
[a] Ratio based on ^{1}H NMR; [b] Acidified with aqueous HCl

Presumably, desired isoquinoline **190** was formed *via* hydrolysis of the oxime and cyclisation of enamine **308** (**Scheme 74**). However under acidic conditions, a low concentration of free ammonia allowed cyclisation through the oxime nitrogen atom, which is relatively nucleophilic due to the α-effect,[181] to compete with hydrolysis and imine formation, leading eventually to *N*-oxide **247**. The generation and consumption of intermediate **309** could be followed by mass spectrometry during the reaction.



Scheme 74. Proposed mechanisms for competing isoquinoline and *N*-oxide formation under acidic conditions
X = O, NH, NOMe

It was therefore anticipated that the reaction could be optimised for sole isoquinoline formation by switching to a basic source of ammonia (**Table 6**).



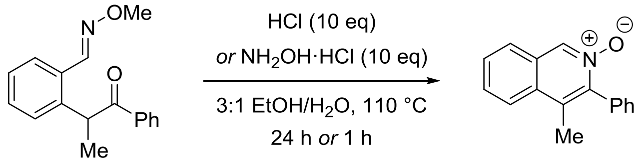
306 **88%** (Entry 10) **190** **247**

Entry	NH_3 source / M		pH	Temperature / °C	Time / h	306 : 190 : 247[a]
1	NH_4HCO_3	0.1[b]	9	90	24	100 : 0 : 0
2	NH_4OH	1.0	11	90	24	100 : 0 : 0
3	NH_4Cl/NH_4OH	1.0	8	90	24	62 : 38 : 0
4	NH_4Cl/NH_4OH	1.0	8	90	48	31 : 59 : 9
5	NH_4Cl/NH_4OH[c]	1.0	8	90	24	25 : 75 : 0
6	NH_4Cl/NH_4OH	1.0	10	90	24	38 : 62 : 0
7	NH_4Cl/NH_4OH	1.0	10	90	48	10 : 90 : 0
8	NH_4Cl/NH_4OH	1.0	10	90	64	6 : 94 : 0
9	NH_4Cl/NH_4OH	2.0	10	90	48	7 : 93 : 0
10	NH_4Cl/NH_4OH	1.0	10	110	24	0 : 100 : 0

Table 6. Optimisation of isoquinoline formation
[a] Ratio based on ^{1}H NMR; [b] Reduced concentration due to low solubility of NH_4HCO_3 in EtOH; [c] 20 eq

Pleasingly, under all basic conditions tested, the formation of *N*-oxide **247** was virtually eliminated, presumably due to the ketone in **306** remaining unprotonated and thus deactivated towards attack by the oxime nitrogen atom. No conversion was observed with just ammonium bicarbonate or ammonium hydroxide (Entries 1 and 2), but using a solution of ammonium chloride that had been basified to pH 8 by the addition of ammonium hydroxide gave 38% conversion to isoquinoline **190** in 24 hours (Entry 3), or 59% when reacted for 48 hours (Entry 4). A small amount of the *N*-oxide **247** was observed only after this extended reaction time. Increasing the pH by further addition of ammonium hydroxide gave greater conversion in the same time (Entries 6 and 7 vs Entries 3 and 4), but it was clear that the cyclisation reaction was more sluggish than the acid-mediated equivalent of the acetal-protected carbonyl compounds used in Donohoe's existing methodology.[175] No rate enhancement was observed upon doubling the ammonium chloride concentration (Entry 9), possibly due to limited solubility, but increasing the reaction temperature to 110 °C (again, a sealed tube was used) effected complete conversion in 24 hours, with isoquinoline **190** subsequently being isolated in 88% yield (Entry 10).

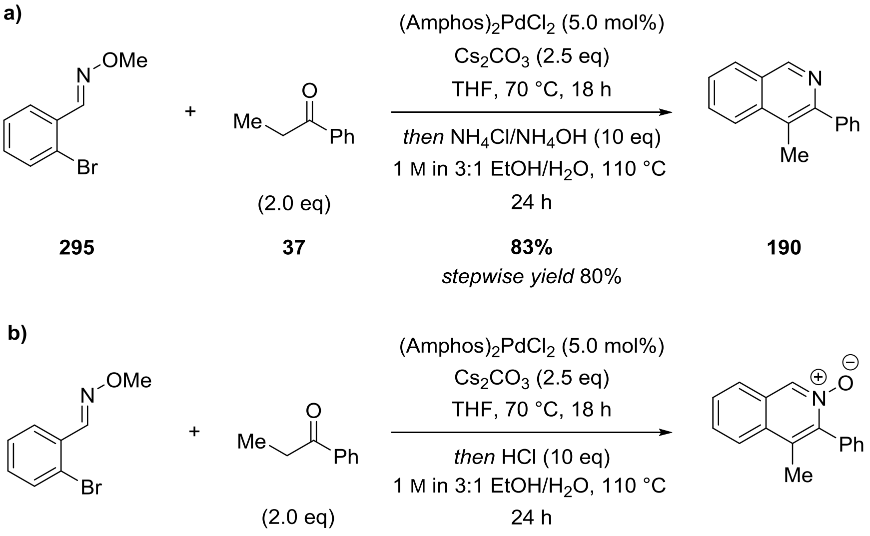
It was possible to exploit the pH dependence of the cyclisation reaction and selectively prepare isoquinoline *N*-oxide **247** in quantitative yield by treating precursor **306** with 1 M HCl (**Scheme 75**). This protocol was atom-efficient since, in contrast to many C–H activation reactions, the directing group is incorporated into the desired product, acting as the crucial N–O source, and is not cleaved in a subsequent step. *N*-Oxide **247** could be obtained more rapidly (in one hour) by adding hydroxylamine hydrochloride instead of HCl.[175]



306 **99%** **247**

Scheme 75. Selective synthesis of isoquinoline *N*-oxide **247**

Furthermore, the miscibility of THF, EtOH, and H_2O permitted the use of a one-pot protocol for the α-arylation and cyclisation reactions, providing isoquinoline **190** from aryl bromide **295** in an excellent yield of 83% using a convenient procedure (**Scheme 76a**).



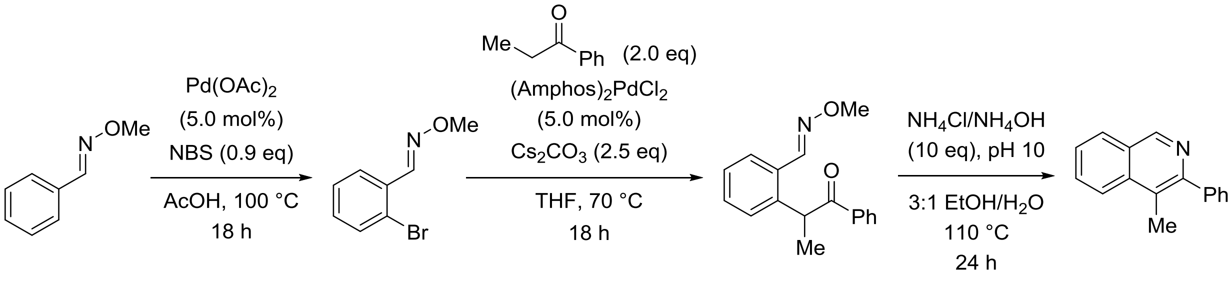
a) **295** **37** **83%** *stepwise yield* 80% **190**

b) **295** **37** **64%** *stepwise yield* 90% **247**

Scheme 76. One-pot α-arylation/cyclisation to provide isoquinoline **190** and *N*-oxide **247**

The corresponding *N*-oxide **247** could also be accessed in one pot, albeit in diminished yield (**Scheme 76b**).

Having proven the compatibility of *O*-methyl oximes with the α-arylation and isoquinoline-forming reactions, the overall route was completed with the Pd(II)-catalysed selective C–H bromination reaction of benzaldehyde oxime **294** (**Scheme 77**). Whilst the yield reported by Fabis (51%)[210] could not be reproduced in our hands, the desired *ortho* bromide was obtained in an identical yield under the conditions reported by Sanford.[209] Using NBS as the limiting reagent minimised the risk of forming polybrominated products, which had similar Rfs to the starting material **294** and the desired product **295**, and therefore complicated purification by flash column chromatography.



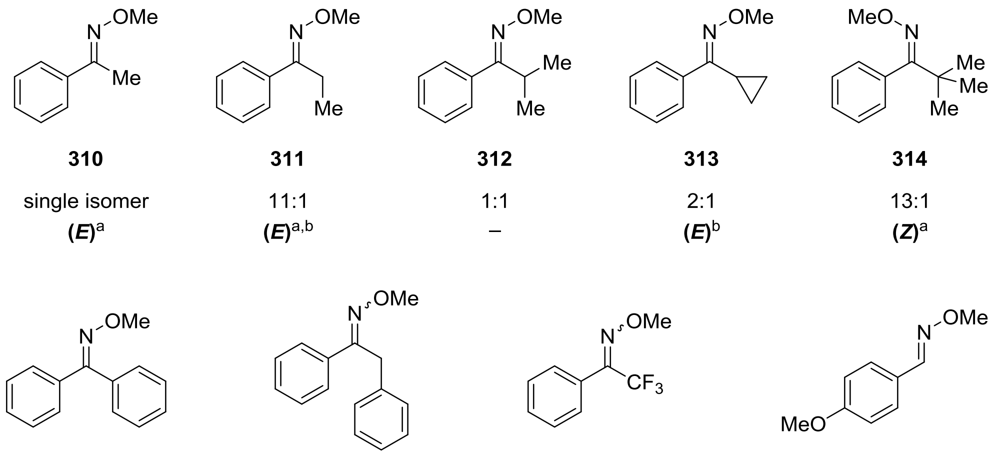
294 **51%** **295** **91%** **306** **88%** **190**

1.0 eq NBS **42%**
Fabis's conditions[a] **36%**

Scheme 77. Complete C–H activation/α-arylation route to isoquinoline **190**
[a] $Pd(OAc)_2$ (10 mol%), $Ag(OCOCF_3)$ (10 mol%), NBS (1.0 eq), AcOH (1.0 eq), DCE, 120 °C, 5 h

2.1.4 Exploration of scope

When investigating the scope of the synthesis, it was decided to focus on the C1 substituent of the resulting isoquinoline, since this was limited to hydrogen or methyl in the group's pre-existing methodology due to the difficulty of forming cyclic acetals from bulky phenyl ketones. A range of *O*-methyl oximes, for which the corresponding aromatic ketone or aldehyde were commercially available, were synthesised by treatment with methoxylamine hydrochloride (**Figure 19**).

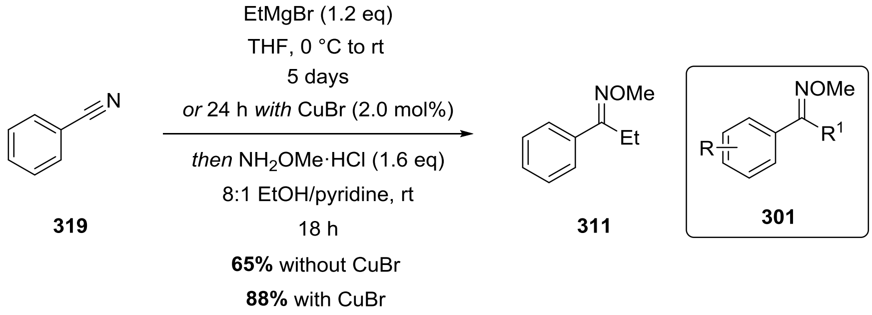


	310	**311**	**312**	**313**	**314**
d.r.	single isomer	11:1	1:1	2:1	13:1
major isomer	(***E***)[a]	(***E***)[a,b]	–	(***E***)[b]	(***Z***)[a]

	315	**316**	**317**	**318**
d.r.	–	single isomer	1.2:1.0	single isomer
major isomer	–	unknown[c]	unknown	(***E***)[d]

Figure 19. *O*-methyl oxime substrates synthesised from phenyl ketones or aldehydes
[a] Determined by comparison to literature data; [b] Determined by nOe experiments (see Appendix 1); [c] Could not be determined by nOe experiments; [d] Assigned by analogy to **294**

Meanwhile, with a view to accessing starting materials **301** with a wide range of substituents R^1, a new route to *O*-methyl oximes was developed which did not rely on the commercial availability of a phenyl ketone precursor (**Scheme 78**). Pleasingly, it was possible to synthesise propiophenone oxime **311** by the addition of ethylmagnesium bromide to benzonitrile **319**, followed by direct treatment with methoxylamine hydrochloride.

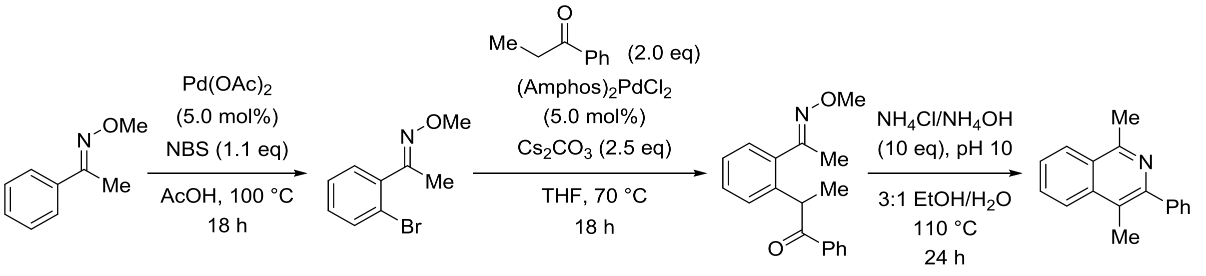


Scheme 78. Synthesis of propiophenone *O*-methyl oxime **311** by Grignard addition to benzonitrile

The addition of 2 mol% CuBr greatly accelerated the Grignard addition, giving complete consumption of benzonitrile **319** in 24 hours compared to five days in its absence.[214]

The ratio of (*E*) and (*Z*) isomers of oximes **310**–**318** (**Figure 19**) varied with the size of R^1, with the (*E*) isomer predominating except in the case of oxime **314**, where the sterically bulky *tert*-butyl substituent favoured orientation of the methoxy group over the phenyl ring. In all cases apart from ethyl oxime **311**, the geometric isomers were inseparable. This was of slight concern, since it was envisaged that an (*E*) geometry, where the lone pair on nitrogen is oriented *syn* to the aromatic ring, would be necessary to direct palladium for C–H activation, as was noted by Chiba in the Rh(III)-catalysed alkyne annulation.[153] However, ^{1}H NMR analysis revealed that the (*Z*) isomer of oxime **311**, which was separated upon repeated chromatography and subjected to nOe experiments to confirm its identity, isomerised to the (*E*) isomer when left to stand in $CDCl_3$. After four days at room temperature, the equilibrium ratio of 11:1 (*E*):(*Z*) was reached. It was decided, therefore, that isomerisation of unreactive (*Z*) oximes could occur under the acidic bromination conditions, and so their presence should not be detrimental to the yield.

Thus, the oximes shown in **Figure 19** were subjected to the isoquinoline synthesis route. Methyl oxime **310** underwent C–H bromination in a similar yield to benzaldoxime **294**, but the α-arylation reaction with propiophenone was poor, providing ketone **321** in only 29% yield, with a large amount of unreacted starting material observed (**Scheme 79**).

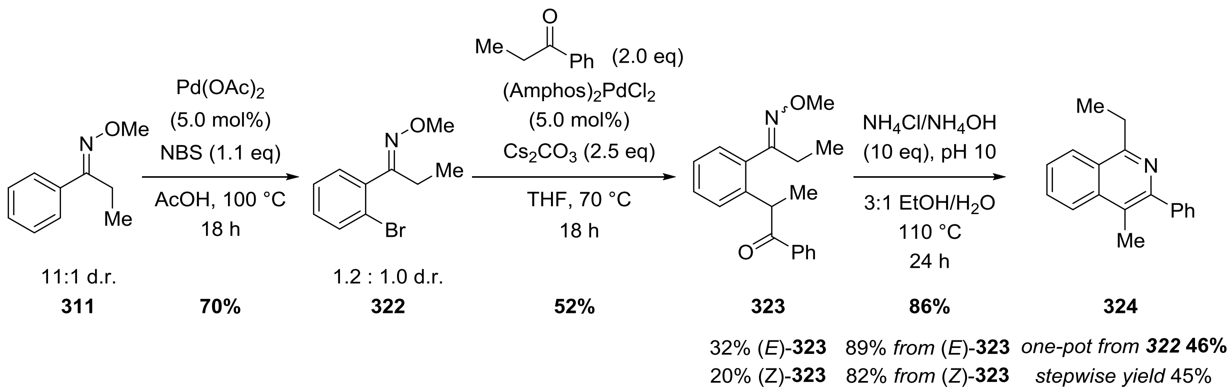


310 **55%** **320** **29%** **321** **84%** **222**

one-pot from ***320*** **25%**
stepwise yield 24%

Scheme 79. Synthesis of isoquinoline **222**

Intermediate **321** could be cyclised in 84% yield, however, preparing isoquinoline **222**, with the one-pot protocol giving a comparable result over two steps. Ethyl oxime **311** performed slightly better in both the bromination and α-arylation reactions (**Scheme 80**).



Scheme 80. Synthesis of C1-ethyl isoquinoline **324**

A mixture of isomers of aryl bromide **322** was formed, indicating that, if only the (*E*) isomer of oxime **311** could successfully undergo directed C–H activation, giving the (*E*) product, isomerisation of the oxime had subsequently occurred under the reaction conditions. Both (*E*) and (*Z*) isomers of α-aryl ketone **323** were obtained and interestingly, ^{1}H NMR analysis indicated that (*Z*)-**323** existed as a 2:1 mixture of conformers at room temperature, with coalescence of the signals occurring at 90 °C (see Appendix 2) (**Figure 20b**). Furthermore, the diastereotopic CH_2 protons of only the minor conformer were anisochronous.

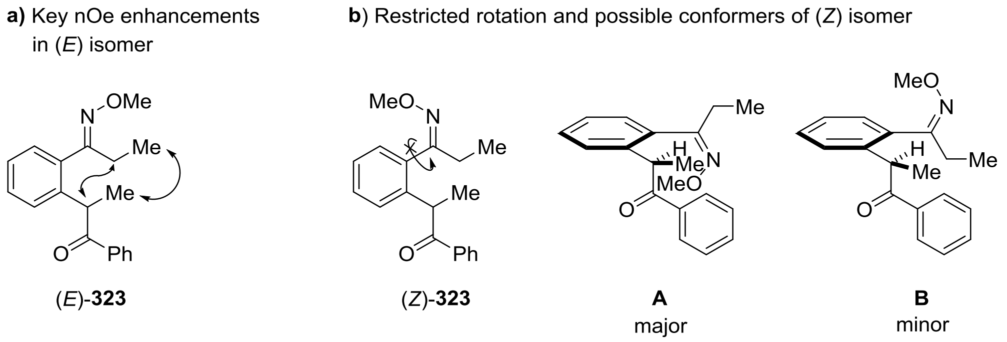
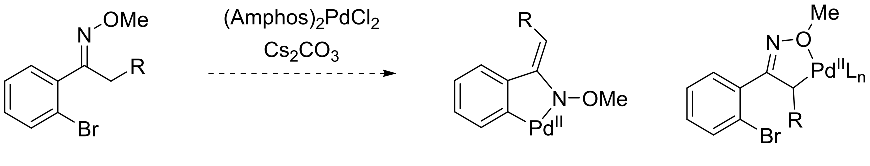


Figure 20. (*E*) and (*Z*) isomers of α-aryl ketone **323**

It is therefore proposed that unfavourable steric interactions between the OMe or ethyl group and the *ortho* ketone fragment restrict rotation about the arene-oxime bond in (*Z*)-**323**. In the two lowest energy conformations, it is likely that the C–H bond of the stereogenic centre lies in the plane of the central aromatic ring, with the trigonal oxime group perpendicular to this plane to minimise steric interactions. The C=N bond may point either down (**A**) or up (**B**) as drawn. In the latter, the electronic environments of the diastereotopic CH_2 protons are sufficiently different from each other, as a result of their proximity to the electron rich, anisotropic π system of the ketone phenyl ring, to possess different chemical shifts. In the former (**A**), however, the CH_2 group is more distant from this π system, and the two diastereotopic protons experience sufficiently similar shielding to render them isochronous.

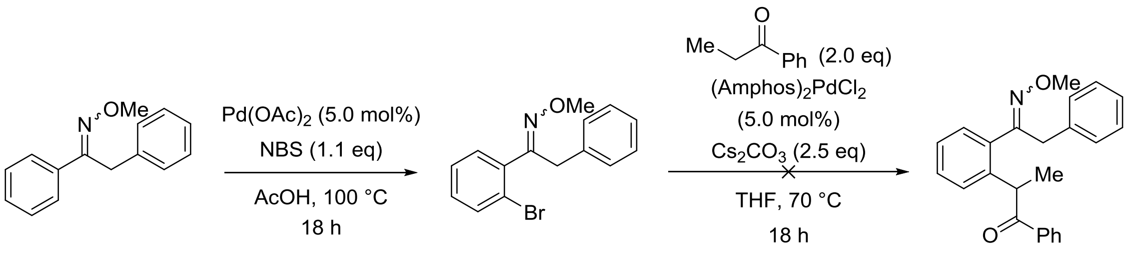
It was noted that a significant amount of unreacted starting material was recovered from the α-arylation reactions of methyl and ethyl oximes **320** and **322**, which were both poorly yielding. This may be a result of deprotonation α to the oxime, which would most likely be coordinated to palladium, under the basic reaction conditions, which could retard the reaction through the formation of stable, unreactive complex **326** (**Scheme 81**). Alternatively, if oxidative addition did not occur, the oxime enolate could sequester the Pd(II) precatalyst by binding in a bidentate fashion (**327**). Only 5.0 mol% of oxime **325** need be deprotonated and coordinated to palladium during the course of the reaction for the catalyst to be deactivated.



325 **326** **327**

Scheme 81. Possible dead-end complexes formed from deprotonated oxime **325**

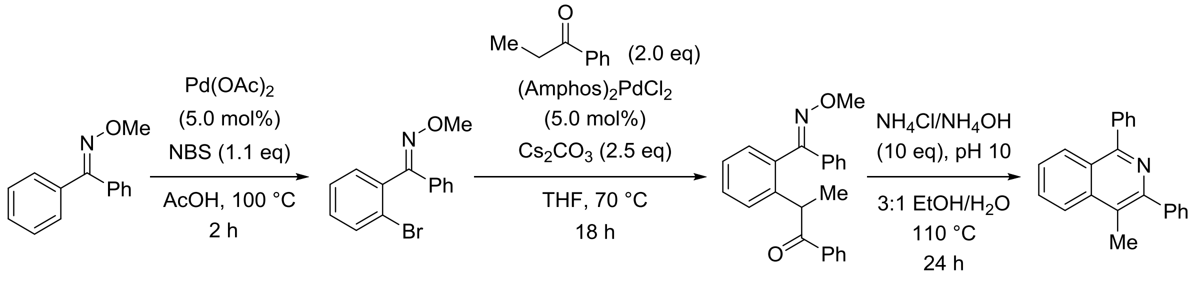
In support of this hypothesis, benzyl phenyl oxime **316**, the most acidic oxime prepared yet, underwent palladium-catalysed bromination in 70% yield (identical to ethyl oxime **311**) but was virtually unreactive in the α-arylation reaction, providing only a trace of product **329** by ^{1}H NMR analysis of the crude reaction mixture (**Scheme 82**).



316 **70%** **328** **329**

Scheme 82. Unsuccessful arylation of benzyl oxime **328**

Benzophenone oxime **315** was brominated in an excellent yield of 90% in just two hours (**Scheme 83**). With the absence of acidic protons, the α-arylation reaction was also highly successful, providing ketone **331** in 93% yield, which was then cyclised to isoquinoline **332**.



315 **90%** **330** **93%** **331** **84%** **332**

one-pot from ***330*** **69%**
stepwise yield 78%

Scheme 83. Synthesis of 1-phenylisoquinoline **332**

Brominated oxime **330**, an oil, was formed exclusively as the (*E*) isomer, whereas a 4:1 mixture of geometric isomers was obtained when 2-bromobenzophenone was treated with methoxylamine hydrochloride. The major isomer was isolated as a pure solid, with single crystal X-ray diffraction revealing it to be the (*Z*) isomer, with orthogonal phenyl rings in a propeller-like arrangement (**Figure 21**). The angle between the planes of the two aromatic systems was found to be 87.0°, suggesting that rotation of the aromatic rings would be restricted since the aromatic C–H groups would clash as they pass.

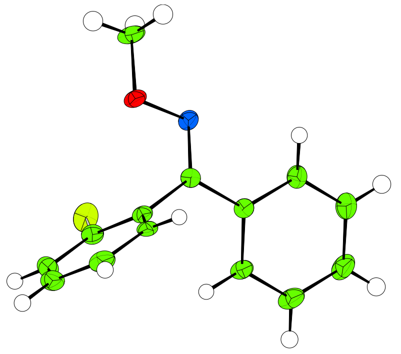
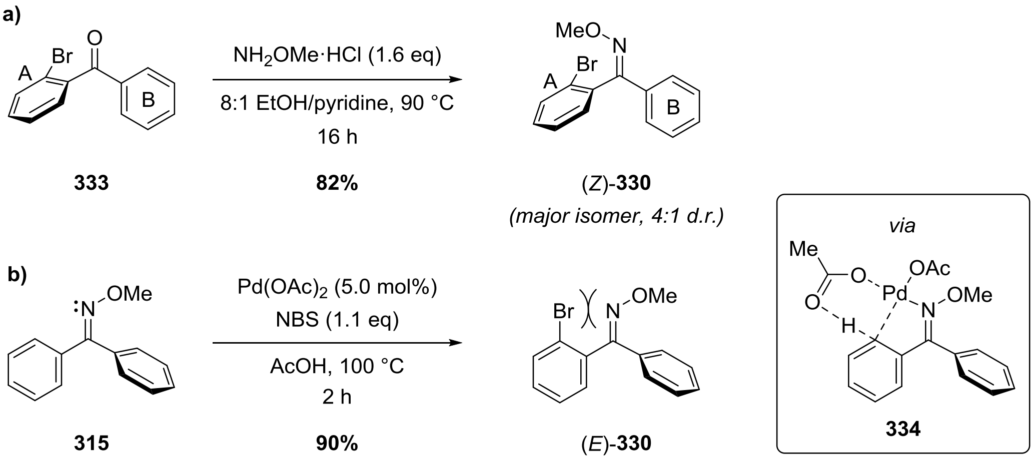


Figure 21. Representation of crystal structure of (*Z*)-**330**

It is proposed that it is thermodynamically preferred for the aromatic ring containing the large bromine atom (A), rather than the unsubstituted phenyl ring B, to be orthogonal to the plane of the carbonyl group in 2-bromobenzophenone **333** to minimise steric interactions

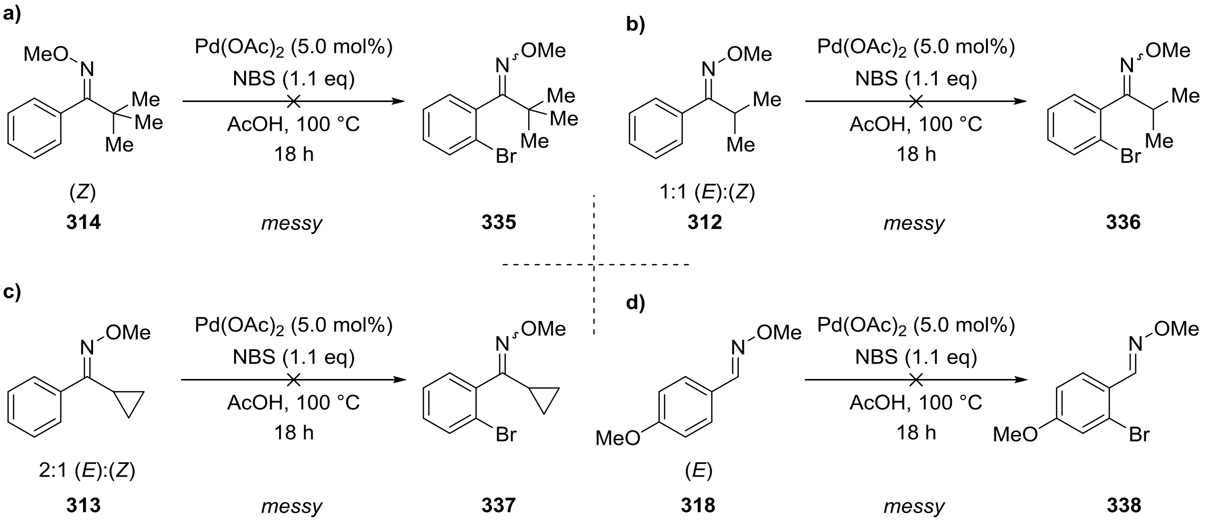
(**Scheme 84a**). Upon oxime formation, the methoxy group points over orthogonal ring A, forming the (*Z*) isomer (*Z*)-**330**. However in the oxime-directed bromination case, the bromine atom is necessarily installed on the aromatic ring which is *syn* to the nitrogen lone pair, and *anti* to the methoxy group, which is also likely to be coplanar with the oxime in **315** (**Scheme 84b**). Whilst the resulting (*E*) isomer (*E*)-**330** is higher in energy, the barrier to isomerisation is likely to be large since conversion into the lowest energy conformer of (*Z*)-**330** would require hindered rotation of both aromatic groups.



Scheme 84. Influence of synthetic route on oxime geometry

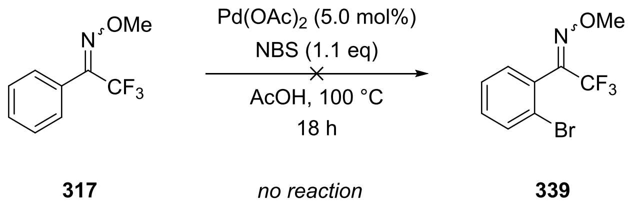
The preorganisation and conformational rigidity of **315**, which places the oxime nitrogen atom in close proximity to the C–H bond to be functionalised, may be responsible for the superior yield and rate of bromination of **315** (two hours) compared to methyl and ethyl oximes **310** (**Scheme 79**) and **311** (**Scheme 80**), which required 18 hours.

Perhaps unsurprisingly then, (*Z*)-*tert*-butyl oxime **314** was a poor substrate for C–H bromination, since the nitrogen lone pair is unable to direct palladium to the aryl C–H bond (**Scheme 85a**). TLC analysis showed a messy reaction mixture, from which the desired product **335** could not be isolated. Oxime **312** also gave a complex mixture of products, suggesting that the presence of (*Z*) oximes was problematic after all (**Scheme 85b**). The reaction of oxime **313** failed, possibly due to facile conjugate addition of nucleophiles *via* cyclopropane ring-opening (**Scheme 85c**), as did electron rich arene **318**, presumably due to bromination at other positions *via* electrophilic aromatic substitution (**Scheme 85d**).



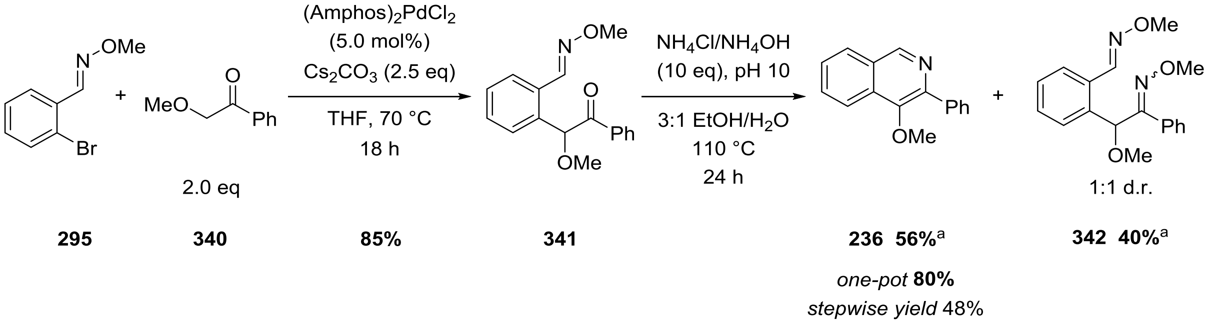
Scheme 85. Unsuccessful bromination attempts

Trifluoromethyl oxime **317** was completely unreactive under bromination conditions, most likely due to the inductive electron withdrawing effect of the fluorine atoms reducing the electron density, and therefore the directing group ability, of the nitrogen atom (**Scheme 86**).



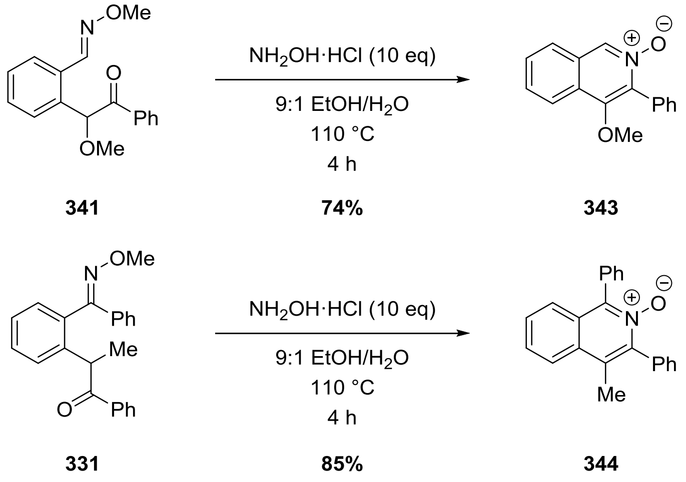
Scheme 86. Unreactivity of trifluoromethyl oxime **317** towards palladium-catalysed C–H bromination

Having found rather limited success when exploring the scope of the sequence with respect to the aryl coupling partner, it was decided to vary the ketone used in the α-arylation. Instead of propiophenone, 2-methoxyacetophenone **340** could be coupled with aryl bromide **295** in 85% yield, but the following cyclisation gave isoquinoline **236** in only 56% yield, along with 40% of bis-oxime **342** (**Scheme 87**). Here, the electron withdrawing methoxy group activated ketone **341** towards nucleophilic attack by the methoxylamine liberated during cyclisation of other molecules. The two isomers of **342** could be separated but began to re-equilibrate when left to stand in $CDCl_3$ at room temperature. Pleasingly, this issue was eliminated by using the one-pot protocol for α-arylation and cyclisation, since the excess 2-methoxyacetophenone **340** was able to mop up the extruded hydroxylamine.



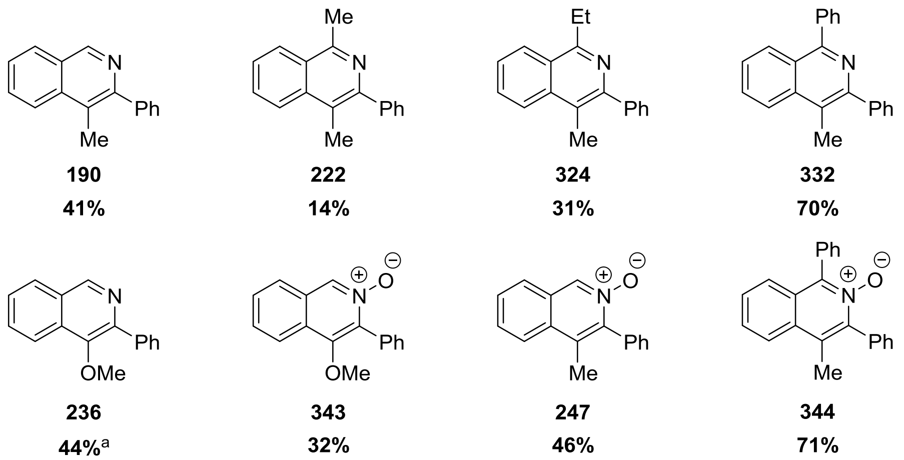
Scheme 87. Synthesis of 4-methoxyisoquinoline **236**.
[a] Isolated yield from stepwise synthesis

It was also possible to synthesise isoquinoline *N*-oxides **343** and **344** by treating arylated products **341** and **331** with hydroxylamine hydrochloride (**Scheme 88**).



Scheme 88. Synthesis of isoquinoline *N*-oxides **343** and **344** from intermediates **341** and **331**

To summarise this work, the isoquinolines and *N*-oxides shown in **Figure 22** were synthesised *via* a stepwise route involving *O*-methyl oxime-directed, Pd(II)-catalysed C–H activation/bromination, Pd(0)-catalysed α-arylation of ketones, and a final ammonia-mediated cyclisation/aromatisation. Hydrogen, methyl, ethyl and phenyl substituents were tolerated at the C1 position, demonstrating the expansion of the scope compared to the methodology previously developed in the Donohoe group.



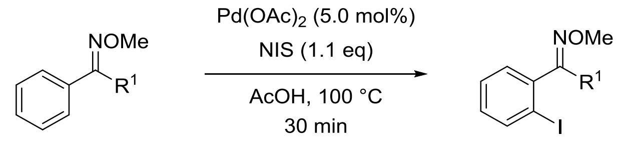
190 41%; **222** 14%; **324** 31%; **332** 70%

236 44%[a]; **343** 32%; **247** 46%; **344** 71%

Figure 22. Isoquinoline derivatives synthesised *via* C–H activation/bromination and α-arylation
[a] One-pot arylation/cyclisation. All other yields are over three steps

2.1.5 Comparison of aryl iodides with aryl bromides

It was decided to investigate the use of aryl iodides, rather than bromides, in the route to determine whether this would have a beneficial impact on the yields of the halogenation and α-arylation reactions. *O*-Methyl oximes **294** and **310–313** were treated with NIS in place of NBS under otherwise identical conditions (**Table 7**).



294 *and* **310–313** → **345–349**

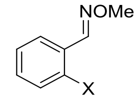
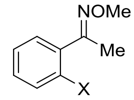
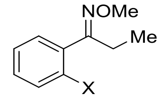
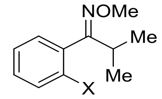
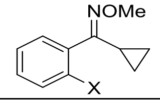
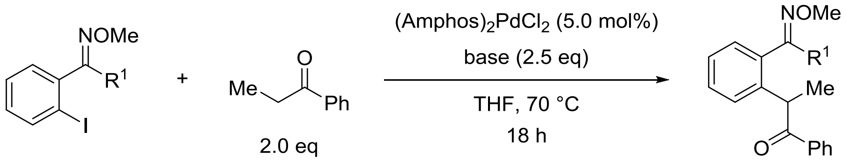
Entry	Product	X = I yield / %	X = Br yield / %
1		**345** 60	**295** 51
2		**346** 78	**320** 55
3		**347** 78	**322** 70
4		**348** 62	messy
5		**349** 45	messy

Table 7. Comparison of palladium-catalysed C–H iodination and bromination

For all substrates, iodination was much faster than the corresponding bromination, with starting material completely consumed in just 30 minutes. The yields were also improved, owing to cleaner reactions. Furthermore, the *ortho* iodides of secondary ketoximes (**348** and **349**) could be obtained, whereas the bromination reaction had been unsuccessful.

When subjected to the α-arylation reaction with propiophenone, however, the aryl iodides were generally found to be even less reactive than the corresponding aryl bromides (**Table 8**).



345, **346** *or* **348** **37** **306**, **321** *or* **350**

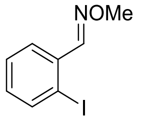
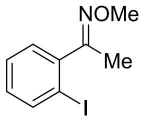
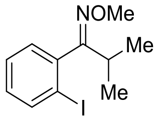
Entry	Aryl iodide		Base	Product	Yield / %	Yield from bromide / %
1		**345**	Cs_2CO_3	**306**	52	91
2			Cs_2CO_3[a]		54	18
3			K_3PO_4		44[b]	60
4			NaOPh		17[b]	–
5		**346**	Cs_2CO_3	**321**	11	29
6		**348**	Cs_2CO_3	**350**	24	messy

Table 8. Comparison of palladium-catalysed α-arylation with aryl iodides and bromides
[a] (D*t*BPF)$PdCl_2$ instead of $(Amphos)_2PdCl_2$; [b] conversion based on ^1H NMR.

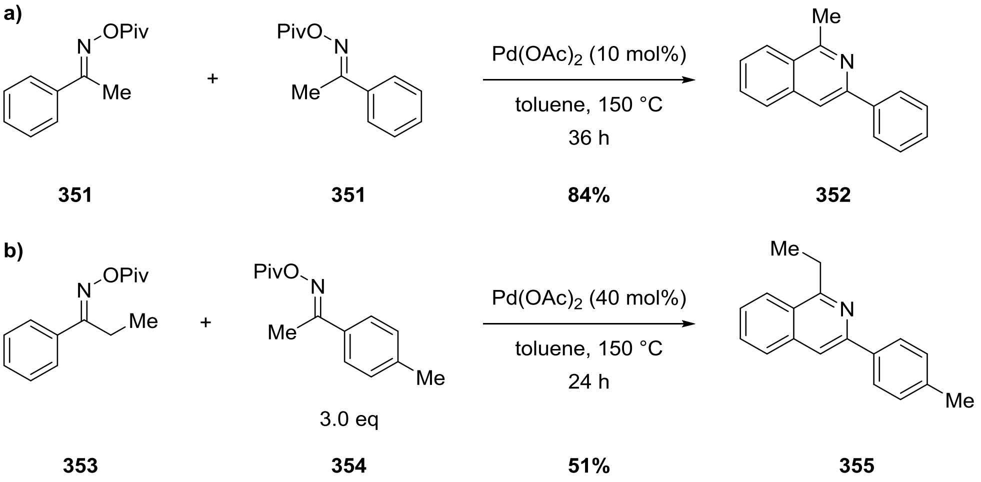
Under the standard α-arylation conditions using 5.0 mol% $(Amphos)_2PdCl_2$ and 2.5 equivalents of Cs_2CO_3, ketone **306** was provided in only 52% yield, compared to 91% when using the equivalent aryl bromide (Entry 1). Reduced sensitivity to the nature of the ligands was observed for iodide **345** though, with a similar result obtained when using (D*t*BPF)$PdCl_2$ (Entry 2). Changing the base to K_3PO_4 or NaOPh did not improve the conversion (Entries 3 and 4). Poor yields for α-arylation were also observed with methyl and isopropyl oximes **346** and **348** (Entries 5 and 6).

The low reactivity demonstrated by the iodides was initially surprising since it had been anticipated that the faster rate of oxidative addition, by virtue of the weaker C–I bond compared to the C–Br bond, might allow the α-arylation pathway to compete with deactivation of the catalyst. It is widely claimed that aryl iodides are very reactive substrates in palladium-catalysed cross-couplings, because oxidative addition is the rate determining step.[215] Indeed, in Mizoroki-Heck reactions in which palladium has an undefined coordination shell, iodides usually react better than bromides, and both are significantly more reactive than aryl chlorides. If oxidative addition was always the limiting step, however, the rate of reaction would also display a strong dependence on the electronic properties induced by substituents on the aryl halide, which is not the case. Where known, the Hammet reaction constants, ρ, which describe the sensitivity of a reaction to the electronic characteristics of substituents, are rather modest in value for palladium-catalysed reactions of aryl halides.[215,216] For so-called "type 3" Mizoroki-Heck reactions, which characteristically employ electron rich, bulky phosphine ligands to stabilise and activate palladium, the difference between electron rich and electron deficient substrates is not significant. Furthermore, aryl iodides are generally poor substrates. Hence, halide dependence stems not only from the kinetics of oxidative addition, but also from the ligand properties of halide ions. Iodide binds strongly to palladium and markedly influences the nature of palladium species, whereas chloride is a much more labile ligand.

By analogy to "type 3" Mizoroki-Heck reactions, which use very similar ligand systems to the α-arylation reaction, it is therefore proposed that the poor reactivity of aryl iodides observed here is a consequence of the strong binding of iodide to palladium, which retards its displacement by a ketone enolate. Chlorides are also poor substrates, as observed previously in the Donohoe group,[175,180] most likely because of the strength of the C–Cl bond and the ease of dissociation of chloride from palladium, which renders the oxidative addition complex more prone to decomposition. Attempts were made to encourage the displacement of iodide from palladium in the α-arylation reaction of **345** (**Table 8**) by adding *n*Bu$_4$NBr, AgBr or AgBF$_4$ to abstract the halogen, but these merely inhibited the reaction.

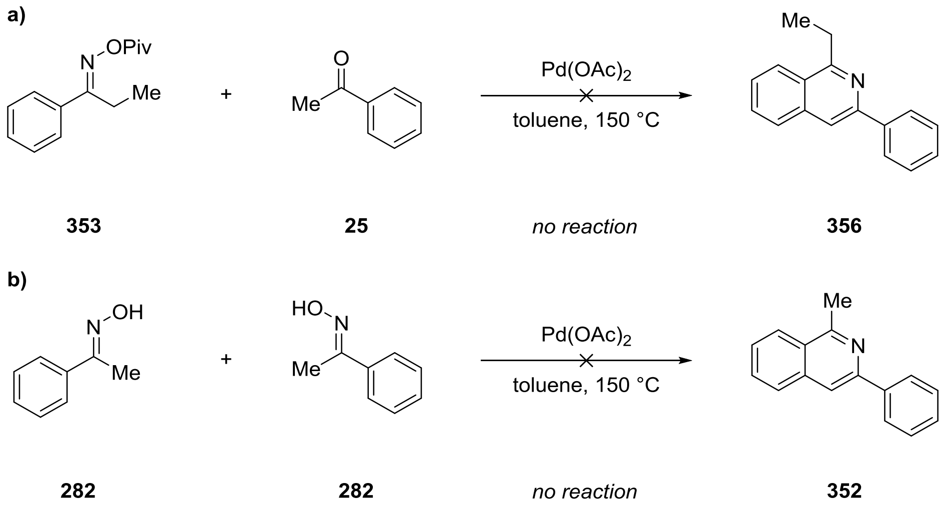
Although the synthesis of a number of isoquinolines and *N*-oxides had been achieved using a stepwise C–H activation/α-arylation protocol, it was decided to cease investigation into this project in light of the limitations which had emerged, such as the strong substrate dependence of the halogenation reaction and modest yields for the α-arylation reactions of alkyl oximes. Furthermore, regioselectivity issues with unsymmetrical aromatic starting materials were anticipated.

In 2014, two years after the conclusion of this project, a method was published by Yang and coworkers for the palladium-catalysed arylation of ketone derivatives by C–H activation.[217] The authors used Pd(OAc)$_2$ to homocouple methyl aryl *O*-pivaloyl oximes such as **351** under base-free conditions, giving isoquinolines such as **352** directly in 51–84% yield (**Scheme 89a**).



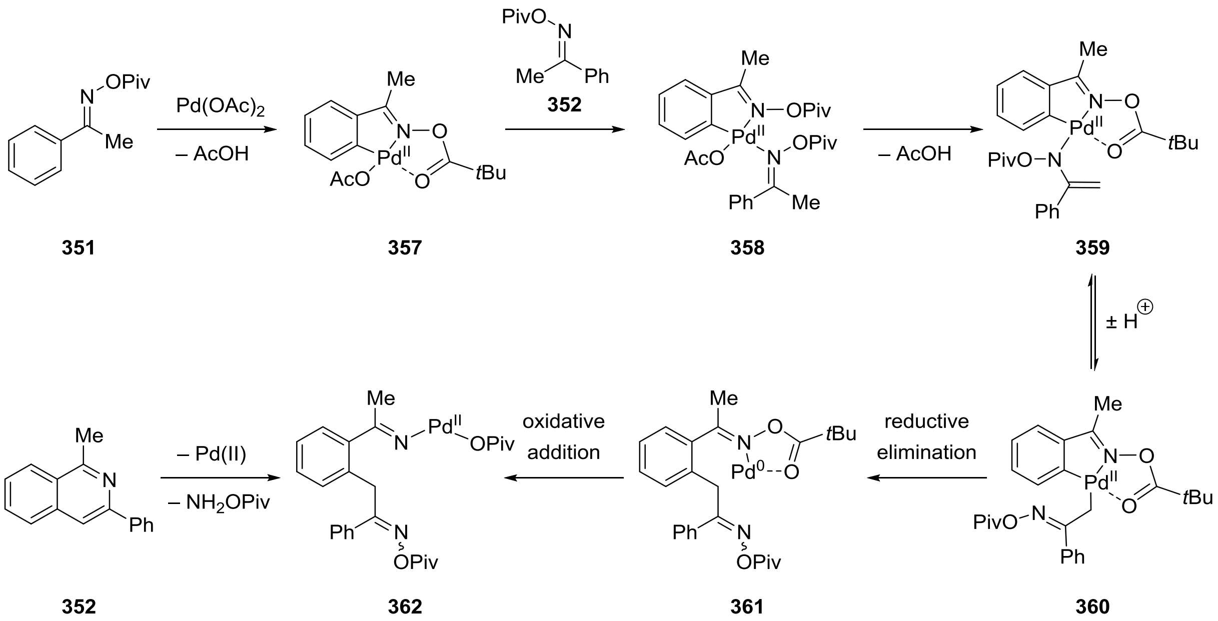
Scheme 89. Yang's isoquinoline-forming coupling of *O*-pivaloyl oximes

The methodology was extended to the cross-coupling of different aryl oximes, which relied on the use of one non-methyl, i.e. non-self-coupling, oxime such as **353**, but required very high catalyst loading (**Scheme 89b**). Counterintuitively, the authors chose to use oxime **354** in excess because of its competing homocoupling under the reaction conditions. Electron withdrawing, electron donating and halogen substituents were tolerated at the *ortho* and *para* positions of the C–H activated arene, but no *meta* substituents were included. A control experiment where *O*-pivaloyl oxime **353** and acetophenone **25** were subjected to the reaction conditions resulted in no reaction (**Scheme 90a**), as did the attempted homocoupling/cyclisation of free *O*–H oxime **282** (**Scheme 90b**), indicating that the presence of the *O*-pivaloyl oxime in both coupling partners was essential for a successful reaction.



Scheme 90. Control experiments demonstrating the importance of the *O*-pivaloyl oxime moiety. Detailed reaction conditions were not provided

The proposed mechanism for this transformation is depicted in **Scheme 91**. Oxime-directed C–H activation, assisted by bidentate coordination of the *O*-pivaloyl oxime, gives palladacycle **357**, to which coordinates a second oxime molecule through the nitrogen atom. Loss of acetic acid leads to complex **359**, which tautomerises in an analogous manner to the isomerisation step in the classical α-arylation reaction, to give *C*-bound oxime complex **360**. Thus the *O*-pivaloyl group is necessary to promote initial coordination of the oxime to palladium through nitrogen rather than oxygen. Reductive elimination from **360** furnishes α-aryl oxime **361**, which can undergo oxidative addition of the N–O moiety to form imido species **362**. Intramolecular condensation gives isoquinoline **352** and releases the Pd(II) catalyst.



Scheme 91. Proposed reaction mechanism for isoquinoline formation

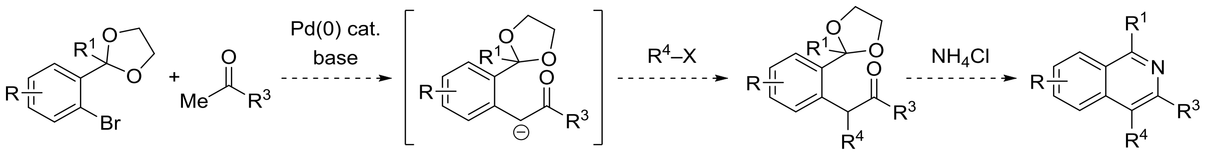
2.2 The synthesis of C4-substituted isoquinolines

2.2.1 *In situ* reaction with electrophiles

Following the conclusion of the C–H activation project, it was decided to further explore the α-arylation reaction of aryl halides and extend its use in isoquinoline synthesis, focusing on elaboration of the isoquinoline C4 position. This centre is notoriously unreactive and difficult to manipulate in preformed isoquinolines, since nucleophiles usually add to C1 and C3, with electrophiles reacting at C5 and C8. Functionalisation at C4 typically requires reduction or addition across the C1–N bond to form a 1,2-dihydroisoquinoline, followed by reaction of the resulting enamine with an electrophile at C4, and a final elimination or reoxidation of the C1–N bond.[218]

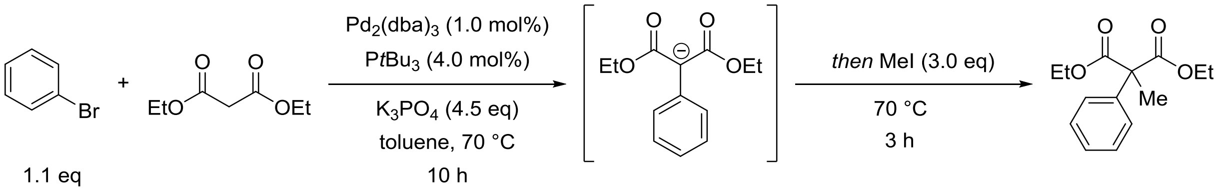
In the Donohoe group's α-arylation-based methodology for the synthesis of isoquinolines, the substituents at C3 and C4 were derived from the ketone coupling partner. Therefore, the facile incorporation of the desired C3 and C4 substitiuents into the isoquinoline was limited by the accessibility of the requisite ketones, and the compatibility of such ketones with the α-arylation conditions. In addition, the regioselectivity of the reaction for arylation at the least substituted position imparted fundamental restrictions on the relative orientation of the groups present at C3 and C4.

It was noted that the intermediate ketone, formed by α-arylation, in our synthetic route, was a prime candidate for further functionalisation at the α position *via* deprotonation and reaction with an electrophile. Furthermore, Prashad's conclusion that excess base is required to ensure complete monoarylation, as the α-arylation product is more acidic and preferentially deprotonated under the reaction conditions,[46] opened up the possibility of functionalising the product *in situ*, transforming the isoquinoline synthesis from a three component coupling (aryl bromide, ketone, and ammonia) to a four component coupling protocol (**Scheme 92**).



Scheme 92. Proposed *in situ* functionalisation and synthesis of C4-substituted isoquinolines

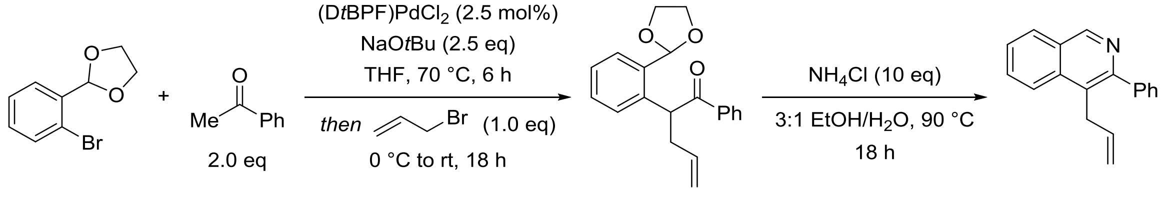
Supporting precedent was provided by Hartwig's use of iodomethane to trap the enolate of arylated diethylmalonate **364** (**Scheme 93**),[78] and our envisaged strategy bore resemblence to Myers's trapping of eneamido anions with electrophiles *en route* to substituted isoquinolines (Chapter 1.3.5).[168]



1 **363** **364** **91%** **365**

Scheme 93. Hartwig's arylation-methylation of diethylmalonate

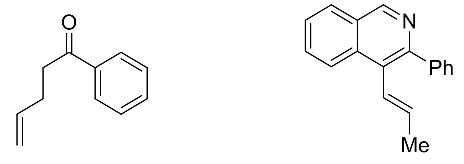
The strategy was first tested using allyl bromide as the electrophile, which was found to be highly effective (**Scheme 94**). Subjecting aryl bromide **217** and acetophenone **25** to coupling conditions using 2.5 mol% (D*t*BPF)PdCl$_2$ and 2.5 equivalents of NaO*t*Bu, then cooling and quenching the reaction with allyl bromide, delivered intermediate **366** in 78% yield. The structure of **366** was confirmed by the presence of a double doublet at 5.15 ppm in the ^{1}H NMR spectrum corresponding to the single proton α to the carbonyl group. When subjected to ammonium chloride conditions, **366** cyclised in excellent yield to give C4-functionalised isoquinoline **367**.



217 **25** **78%** **366** **96%** **367**

Scheme 94. Arylation-alkylation of acetophenone **25** and cyclisation to isoquinoline **367**

It is likely that the use of less than 2.0 equivalents of acetophenone **25**, and a slight excess of allyl bromide, would have provided **366** in a greater yield due to the minimisation of the competitive alkylation of unarylated acetophenone **25**. Nevertheless, it was demonstrated that enolate arylation and *in situ* functionalisation were valuable transformations *en route* to polysubstituted isoquinolines such as **367**. The same product would be obtained by directly arylating ketone **368**, which is not commercially available (**Figure 23**). The relatively mild nature of the reaction conditions was evidenced by the fact that none of the isomeric isoquinoline **369**, where the double bond had migrated into conjugation with the aromatic ring, was observed.



368

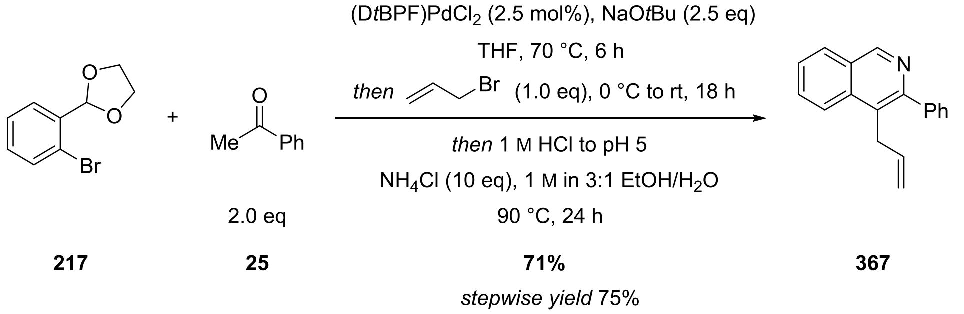
equivalent ketone for direct arylation

369

isomeric isoquinoline not observed

Figure 23. Commercially unavailable ketone **368** and isomeric isoquinoline **369**

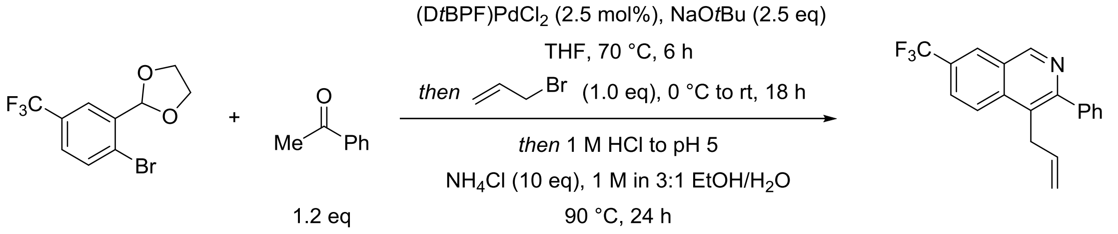
Since it had been previously demonstrated that a three component coupling (between the aryl bromide, ketone, and ammonia source) could be executed in one pot,[175] it was anticipated that the present protocol could be extended to the four component arylation-functionalisation-cyclisation sequence. As such, the coupling of **217** and **25** was repeated and, after quenching the α-arylation product with allyl bromide, the reaction mixture was acidified with HCl, ammonium chloride solution was added and the substrate was cyclised *in situ* (**Scheme 95**).



Scheme 95. One-pot synthesis of C4-functionalised isoquinoline **367**

Isoquinoline **367** was delivered in an excellent yield of 71% over three chemical transformations, which was comparable to the stepwise yield of 75%.

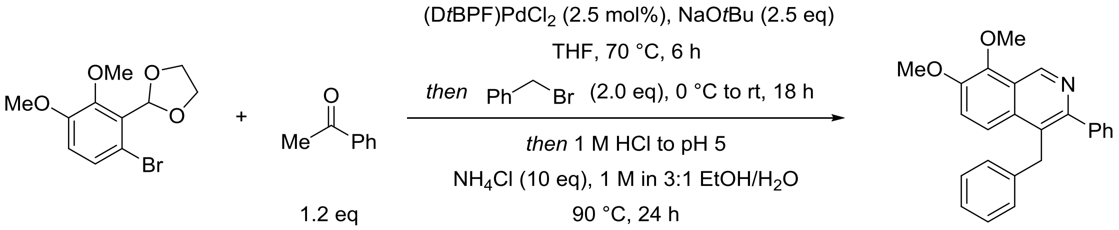
Electron deficient aryl bromide **370** was then subjected to an identical procedure, but this time using only 1.2 equivalents of acetophenone to limit competitive alkylation (**Scheme 96**). Isoquinoline **371** was obtained in 60% yield – equivalent to a calculated 84% for each of the three steps.



370 **25** **60%** **371**

Scheme 96. One-pot synthesis of electron deficient C4-functionalised isoquinoline **371**

Next, electron rich aryl bromide **372** was employed with an alternative electrophile, benzyl bromide (**Scheme 97**).



372 **25** **40%** **373**

Scheme 97. Synthesis of electron rich isoquinoline **373**

Although the yield of **373** was diminished compared to the preceding examples, it was still equivalent to a respectable calculated yield of 74% per step. Full exploration of the scope of the one-pot, four component isoquinoline synthesis was continued by a fellow group member and Part II student, who investigated which aryl bromides, ketones and electrophiles were compatible with this procedure.

2.2.2 Exploration of scope

A series of different electrophiles were tested by colleagues, and it was found that the method was broadly applicable to a range of both carbon- and halogen-centred electrophiles (E^+) (**Figure 24**).[219] α-Bromoesters and acrylates were found to be competent electrophiles, and the conditions were sufficiently mild to allow the ester moiety to be carried through the whole sequence to give ester-containing isoquinolines **376** and **377**, though the cyclisation reaction time was shortened to prevent hydrolysis. Vinyl bromide functionality could also be introduced, affording **378**, with no debromination observed which would theoretically be possible *via* oxidative addition of the palladium catalyst followed by protodepalladation. Halogen atoms could be installed at the C4 position in **379** and **380** by quenching with sulfuryl chloride and Selectfluor® II.[220]

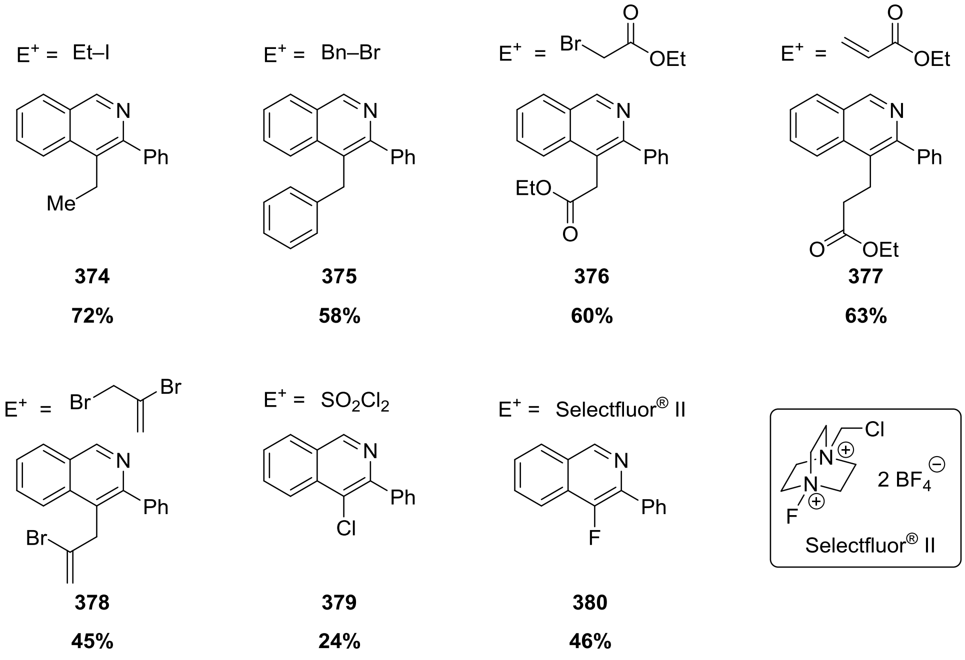


Figure 24. Additional isoquinolines synthesised by colleagues. E^+ = electrophile

Electrophiles that failed in this synthetic route included epoxides, α-bromoketones, hindered alkyl bromides, *N*-bromo- and -chlorosuccinimide, chloroformates, and DEAD.

The route was next extended towards isoquinolines bearing a methyl group at C1 by using the appropriate acetophenone-derived *ortho* acetal (**Figure 25**). For these substrates, the modified cyclisation conditions involving basification of the reaction mixture with NH_4HCO_3, were implemented for the final isoquinoline formation (Chapter 1.4.3).[175] Within this work, it was shown that diphenyldisulfide could also be employed as the electrophile, providing isoquinoline **383** in 42% yield, which was a pleasing result as the direct arylation of a ketone containing an α-thioether had previously failed.[176]

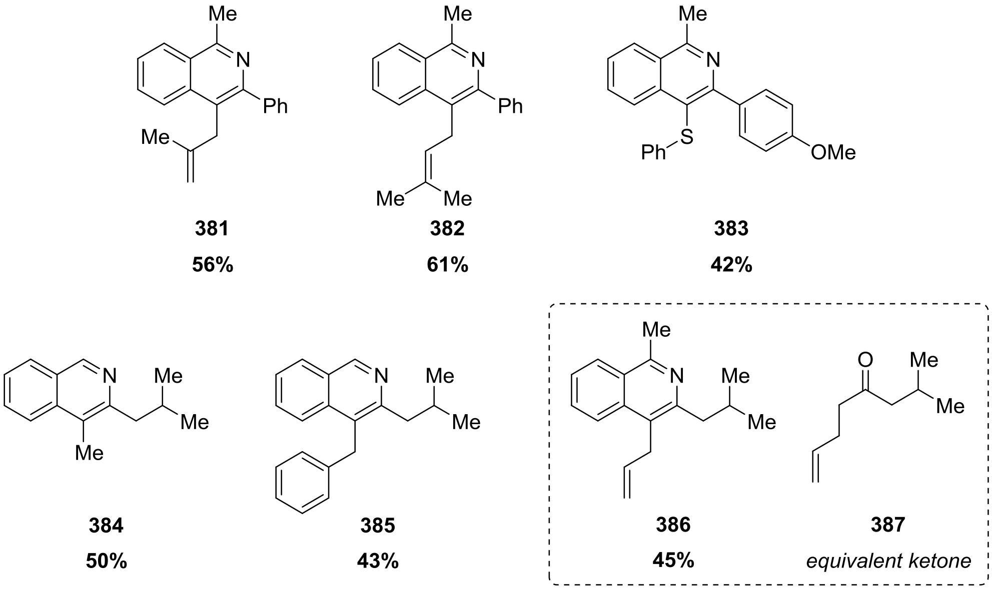
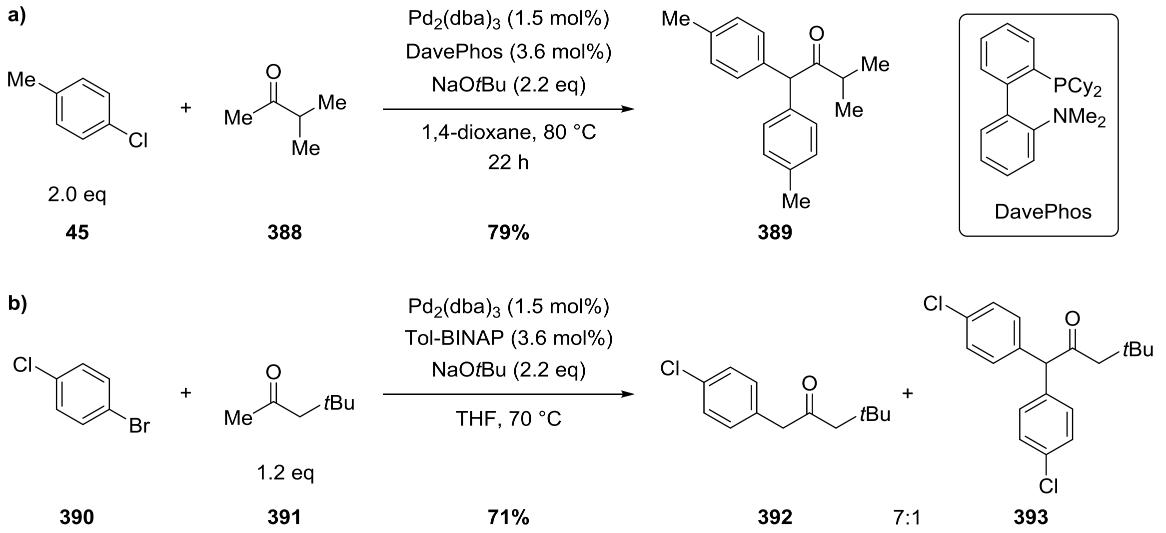


Figure 25. Isoquinolines synthesised by varying the aryl bromide and ketone coupling partners

Methyl isobutyl ketone was also compatible with the procedure, providing isoquinolines **384**–**386** with substitution patterns that would be difficult to access selectively from the direct arylation of the equivalent ketone. For example, ketone **387** has two secondary alkyl α carbon centres, both of which could potentially enolise and form similarly stable palladium enolate complexes, which would most likely result in poor regioselectivity.

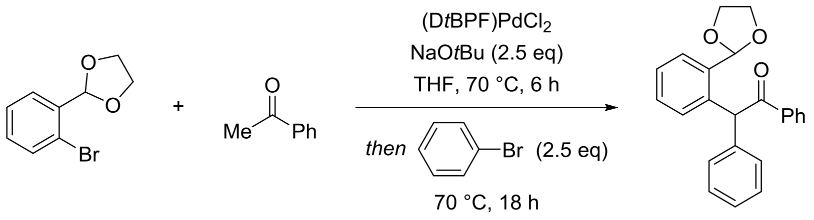
2.2.3 Palladium-catalysed α,α-heterodiarylation

Meanwhile, the possibility of incorporating an aryl group at C4 was explored, since the range of commercially available benzyl ketones, as the requisite α-arylation coupling partners for direct access to the desired isoquinolines, was limited. Thus it was envisaged that, by analogy to the *in situ* functionalisation described above, C4-aryl isoquinolines could be accessed *via* an α,α-diarylation of a methyl ketone, followed by acetal cleavage and cyclisation. Whilst the palladium-catalysed diarylation of methyl ketones had been reported previously, it was limited to homodiarylation using an excess of one unhindered aryl halide (**Scheme 98a**),[221–225] or was observed as an undesired over-reaction (**Scheme 98b**).[38,60,226,227]



Scheme 98. Buchwald's reports of α,α-diarylation reactions

In our experience of making isoquinolines *via* enolate arylation, the diarylation of a ketone with an aryl bromide bearing an *ortho* cyclic acetal was not observed, even though the monoarylated product was more acidic than the starting ketone (acetophenone pK_a = 24.7,[48] deoxybenzoin pK_a = 17.7 in DMSO),[49] presumably due to steric hindrance inhibiting the second coupling. It was therefore proposed that the enolate resulting from an initial α-arylation reaction and deprotonation could undergo a second α-arylation providing that a sufficiently unhindered aryl bromide was added second. Once more, it was anticipated that this second arylation could be executed *in situ* following the first. Pleasingly, this was found to be the case, and diarylated ketone **394** was obtained in 70% yield, using bromobenzene for the second arylation (**Table 9**, Entry 1). The identity of **394** was supported by the singlet at 6.73 ppm in the ^{1}H NMR spectrum, corresponding to the doubly-benzylic α proton.



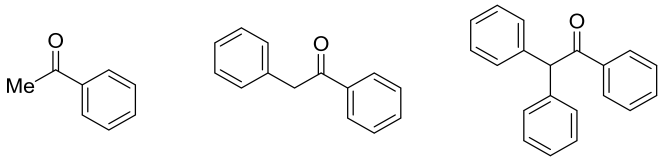
217 **25** **394**

Entry	Catalyst loading / mol%	Ketone / eq	Yield / %
1	2.5	2.0	70[a]
2	2 × 2.5[b]	2.0	74[a]
3	2.5	2.0	83
4	5.0	2.0	85
5	5.0	1.2	88

Table 9. Optimisation of the one-pot α,α-diarylation reaction
[a] First arylation 18 h instead of 6 h; [b] Second portion of catalyst added with PhBr after 18 h

It was thought that the catalyst may have been partially deactivated after 18 hours, so a second portion of 2.5 mol% was added alongside the second aryl bromide, but the effect on the yield was minimal (Entry 2). This may have been due to the fact that the reaction mixture was briefly exposed to the atmosphere when the catalyst was added, whereas the liquid bromobenzene could be added *via* syringe through the septum of a microwave vial. Instead, the first arylation was monitored more closely by TLC and found to be complete after just six hours, at which point bromobenzene was added. The second arylation reaction was then run for 18 hours to ensure complete conversion, and diarylated ketone **394** was provided in an excellent 83% yield (Entry 3). Increasing the catalyst loading to 5.0 mol% gave a small improvement (Entry 4), and product **394** could still be obtained in excellent yield when using only 1.2 equivalents of acetophenone **25** (Entry 5).

No triarylated product was observed, i.e. ketone **394** did not undergo further reaction. Whilst steric hindrance around the α position would likely render a third arylation incredibly slow, it is interesting to note that α,α-diaryl ketone **396** is less acidic than monoaryl ketone **395** (**Figure 26**).[49] It is sterically disfavoured for the two α-aryl rings to sit coplanar with the carbonyl group in **396**, so the π systems cannot achieve perfect orbital overlap with the enolate p orbitals and mesomeric stabilisation of the negative charge is reduced. It is therefore unlikely that diarylation product **394** would be fully deprotonated, hence complete reaction of the monoarylated ketone was possible using fewer than three equivalents of base. Though not explored in this study, it may be possible, in theory, to conduct the second arylation asymmetrically by employing a chiral ligand and only two equivalents of base.

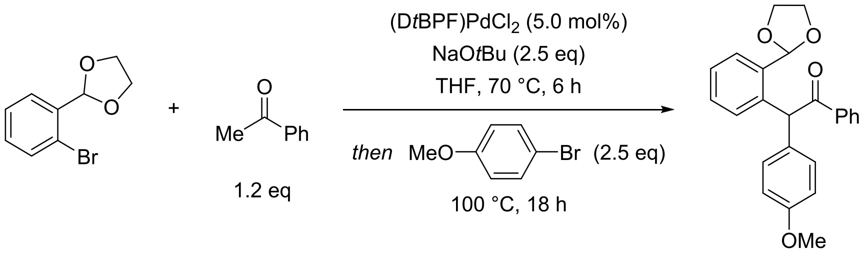


	25	**395**	**396**
pK_a (DMSO)	24.7	17.7	18.8

Figure 26. Acidity of un-, mono-, and diarylated acetophenone

To the best of our knowledge, this transformation was the first reported one-pot palladium-catalysed α,α-heterodiarylation reaction of a ketone, which was made possible by exploiting the steric dependence of the reaction.

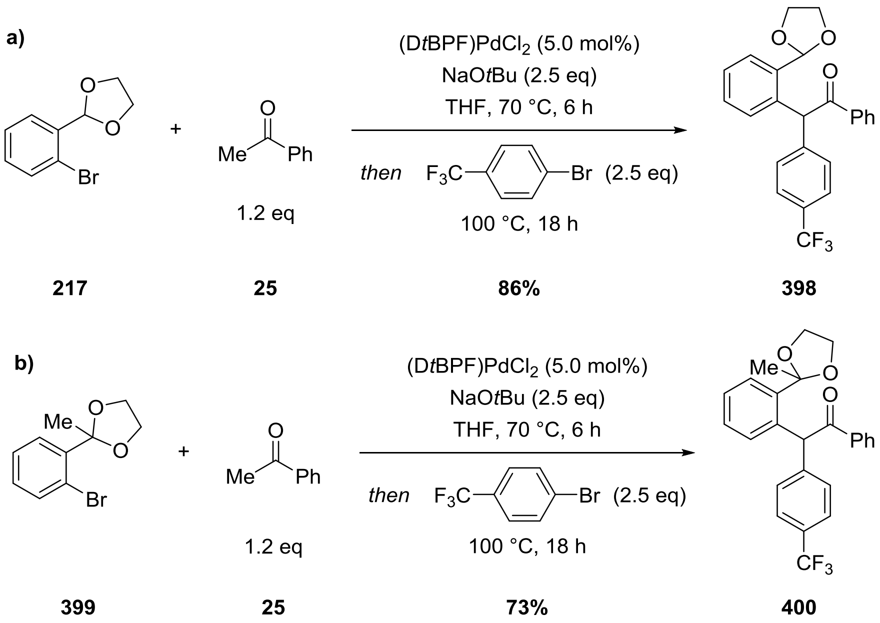
Next, the diarylation protocol was tested using 4-bromoanisole as the second aryl bromide coupling partner (**Scheme 99**). When the reaction mixture was stirred at 70 °C, as before, only monoarylated ketone was observed, possibly due to the reduced rate of oxidative addition of the electron rich aryl bromide. Increasing the temperature to 100 °C proved successful in driving the second α-arylation reaction to completion, and ketone **397** was obtained in an excellent yield of 97%.



217 **25** **97%** **397**

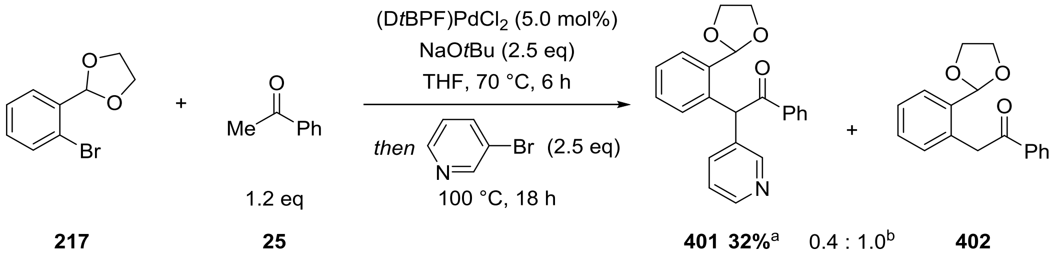
Scheme 99. Synthesis of ketone **397** *via* palladium-catalysed α,α-diarylation

Finally, electron deficient aryl bromide 4-bromobenzotrifluoride was employed in the reaction, using elevated temperature to ensure complete conversion, which provided **398** in 86% yield (**Scheme 100a**). The methyl ketone-derived aryl bromide **399** was also compatible, affording ketone **400** in very good yield (**Scheme 100b**).



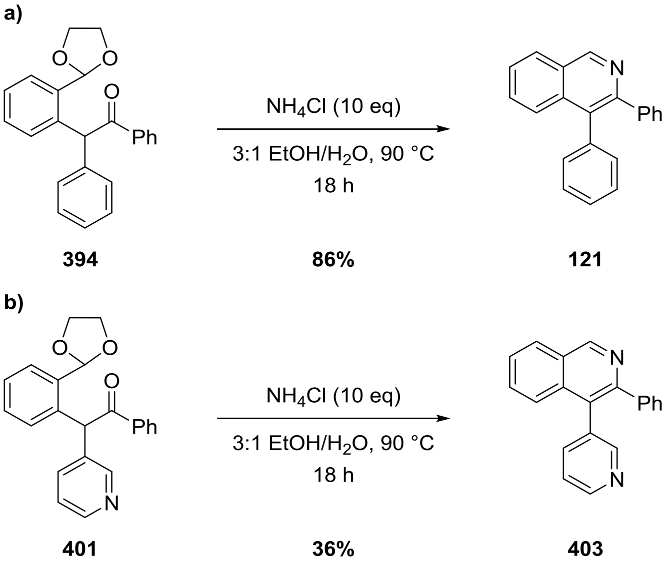
Scheme 100. Synthesis of diarylated ketones **398** and **400**

The possibility of employing a heteroaryl bromide in the second α-arylation was next explored. Though bromopyridines had previously been found to be unreactive (Chapter 1.4.4),[176] 3-bromopyridine was employed in the second arylation as it did not contain an acetal which might coordinate to palladium and contribute towards deactivation of the catalyst. Whilst some of the second arylation occurred, desired product **401** was isolated in only 32% yield, with a large amount of monoarylated ketone **402** observed by ^{1}H NMR analysis of the crude reaction mixture (**Scheme 101**).



Scheme 101. Low-yielding synthesis of ketone **401**. [a] Isolated yield; [b] Ratio based on ^{1}H NMR

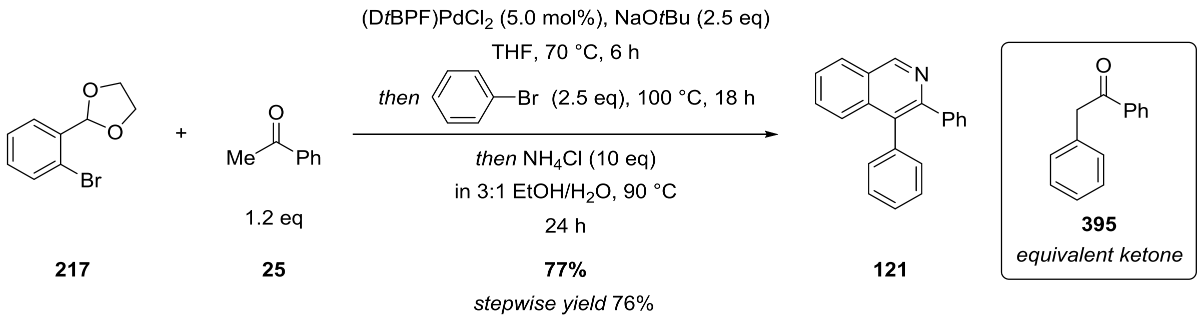
Having accessed a number of diarylated ketones, it only remained for their conversion to the corresponding isoquinolines. To this end, ketone **394** was subjected to standard ammonium chloride cyclisation conditions, affording isoquinoline **121** in 86% yield (**Scheme 102a**). Pyridine-containing intermediate **401**, however, did not undergo clean conversion to the C4-pyridyl isoquinoline **403**, probably due to protonation of the pyridine which could disfavour further protonation of the ketone, and also leave the pyridine susceptible to nucleophilic attack (**Scheme 102b**).



Scheme 102. Synthesis of C4-aryl isoquinolines **121** and **403**

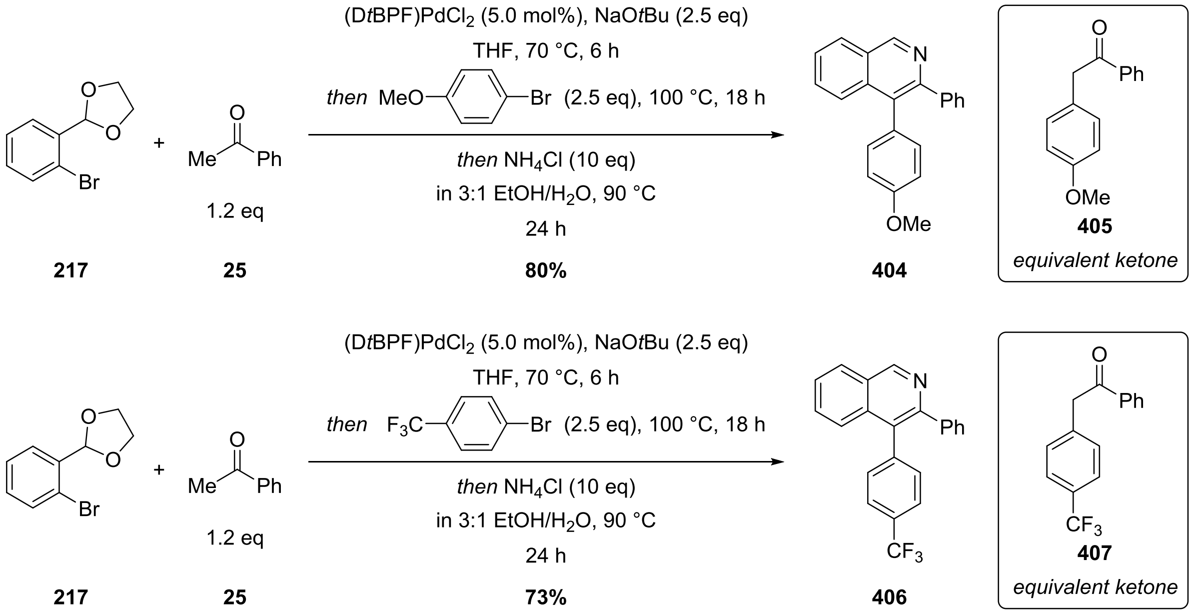
2.2.4 One-pot synthesis of C4-aryl isoquinolines

It was decided to attempt to simplify the synthesis of isoquinoline **121** by carrying out the four component coupling between aryl bromide **217**, acetophenone **25**, bromobenzene, and ammonia in one pot. Accordingly, it was found that adding ammonium chloride to the diarylation reaction mixture prompted deprotection and cyclisation, affording isoquinoline **121** in 77% yield (**Scheme 103**). Since the one-pot protocol afforded C4-aryl isoquinoline **121** in a yield that was marginally better than the stepwise sequence, it was decided to use this procedure for further exemplification of the route.[219] For consistency, all reactions were stirred at 100 °C during the second α-arylation.



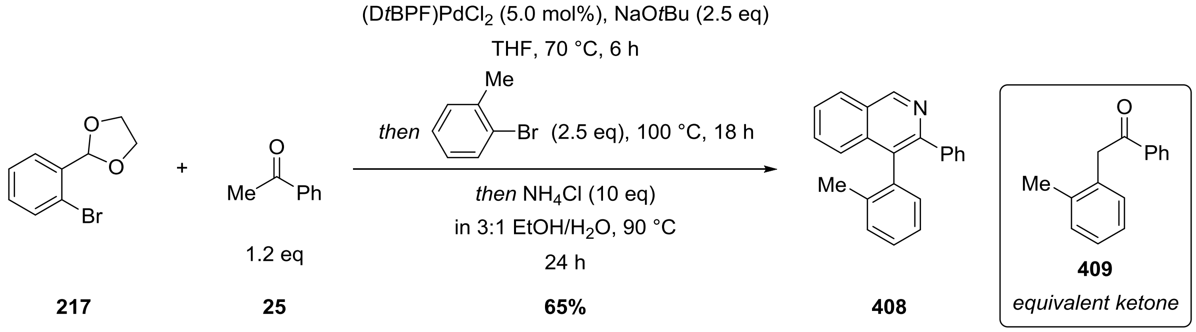
Scheme 103. One-pot, four component synthesis of C4-aryl isoquinoline **121**

The procedure was next implemented using *para*-substituted aryl bromides 4-bromoanisole and 4-bromobenzotrifluoride, giving isoquinolines **404** and **406** in excellent yields of 80% and 73% respectively following the one-pot procedure (**Scheme 104**). The characteristic signals of the C1 protons were observed at 9.25 and 9.42 ppm in the ^{1}H NMR spectrum, with thirteen other aromatic protons in each, confirming functionalisation with a monosubstituted aryl group. Neither of the equivalent ketones **405** and **406**, which would give the same product *via* monoarylation with **217**, were commercially available.



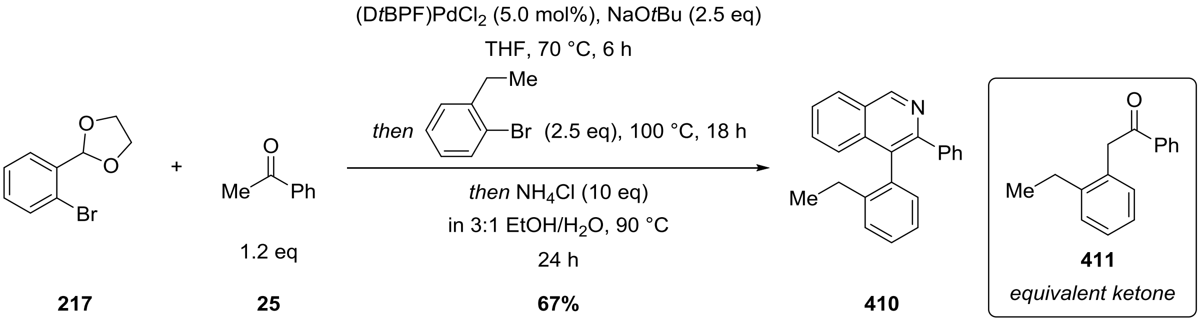
Scheme 104. Electron rich and electron poor aryl bromides in the one-pot isoquinoline synthesis

It was known, through the fact that aryl bromide **217** never diarylated acetophenone **25**, that only sufficiently unhindered aryl bromides could be installed in the second arylation step. Hence it was desirable to assess the level of tolerance for steric crowding, beginning by employing 2-bromotoluene in the reaction, which provided isoquinoline **408** in a pleasing yield of 65% (**Scheme 105**). Although a little lower than previous yields, this still equated to a theoretical yield of 87% for each of the three steps.



Scheme 105. Successful installation of an *ortho*-methylphenyl group at C4

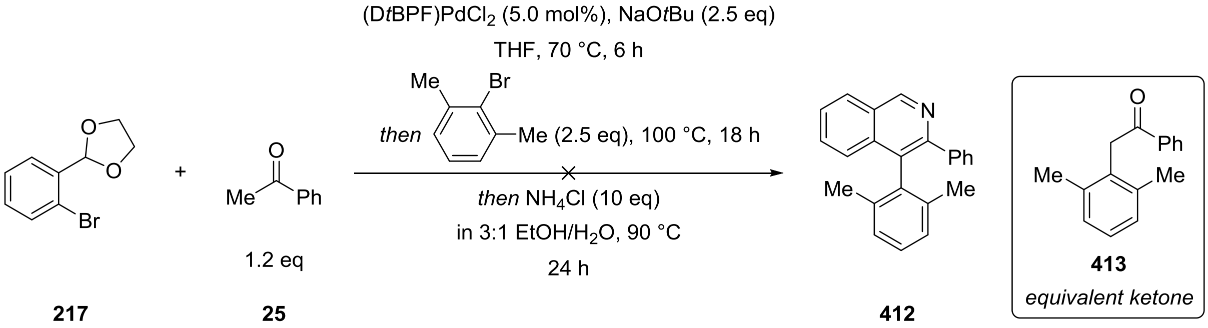
Next, 1-bromo-2-ethylbenzene was tested (**Scheme 106**). Isoquinoline **410** was obtained in 67% yield and it was noted that the CH_2 protons of the *ortho* ethyl group were diastereotopic, indicating that isoquinoline **410** posessed axial chirality, on the NMR timescale, at room temperature, by way of restricted rotation about the isoquinoline–aryl bond.



Scheme 106. Synthesis of chiral isoquinoline **410**

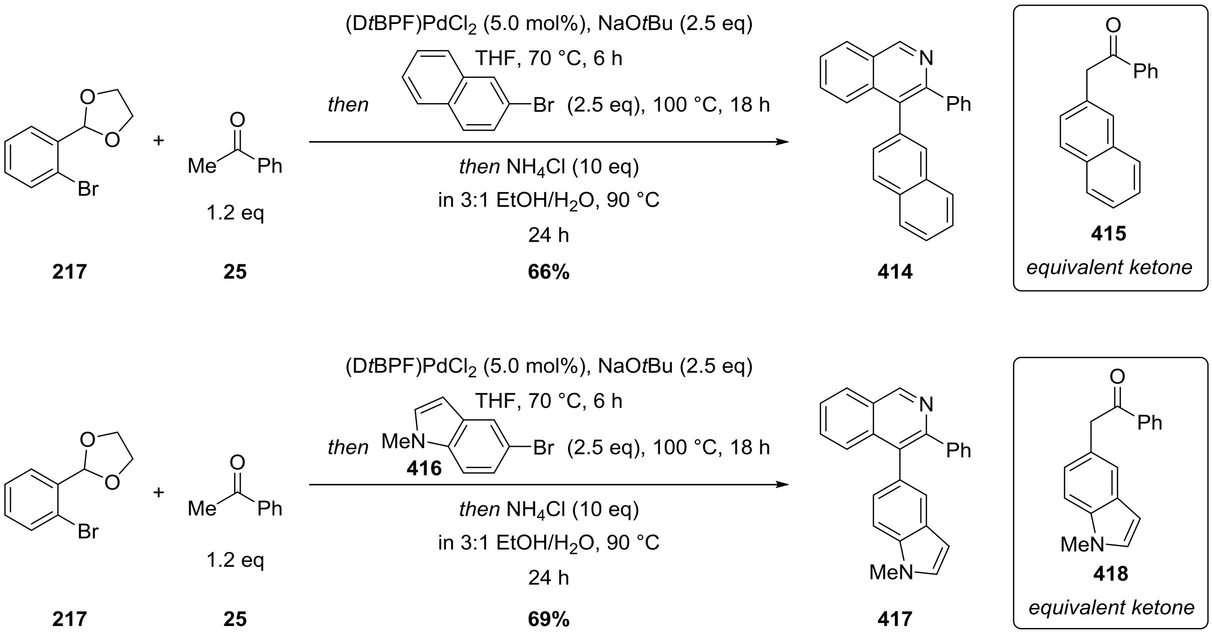
Variable temperature NMR spectroscopy was conducted in deuterated pyridine, and whilst the lineshape changed with temperature, the CH_2 multiplets did not coalesce to a single quartet even at 110 °C (see Appendix 2). That such a sterically crowded isoquinoline could be synthesised *via* this route was a powerful demonstration of its synthetic utility. If made electron rich by the inclusion of electron donating groups, such isoquinolines could potentially find use as chiral ligands.

The use of doubly *ortho* substituted aryl bromide 2-bromo-1,3-dimethylbenzene for the second arylation was unsuccessful, giving a complex mixture of products after attempted isoquinoline formation (**Scheme 107**).



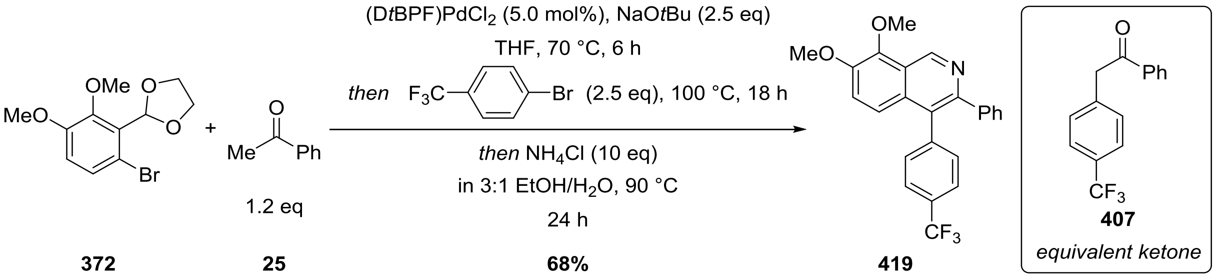
Scheme 107. Unsuccessful reaction of 2-bromo-1,3-dimethylbenzene

Attention then turned to the introduction of more complex benzo-fused aromatic substituents. The use of 2-bromonaphthalene for the second arylation led to isoquinoline **414**, and 5-bromo-*N*-methylindole gave isoquinoline **417**, both in very good yields for a one-pot, four component reaction (**Scheme 108**). It was deemed necessary to protect the acidic nitrogen atom of 5-bromoindole (indole pK_a = 21.0 in DMSO)[228] in order to prevent coordination to palladium and deactivation of the catalyst, therefore no unprotected indole derivatives were employed in this study.



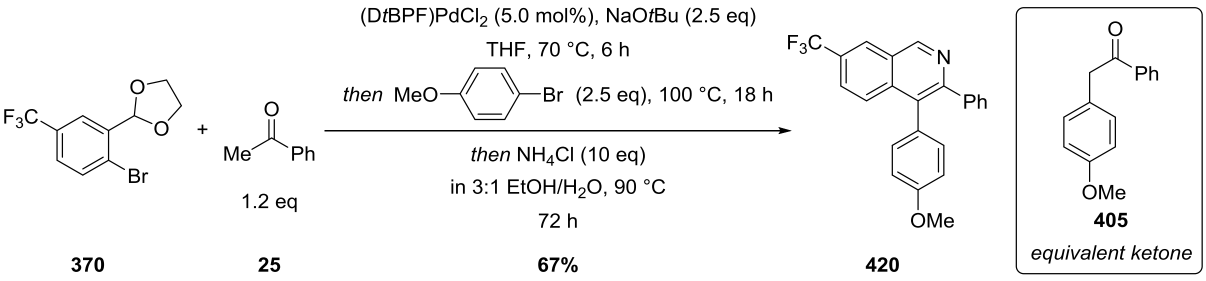
Scheme 108. One-pot synthesis of C4-biaryl isoquinolines **414** and **417**

Having established that aryl bromide **217** could provide access to a range of C4-aryl isoquinolines, it was decided to vary the aryl bromide coupling partner and synthesise isoquinolines containing additional functionality on the carbocyclic ring. Electron rich aryl bromide **372** was reacted with acetophenone, then with electron poor 4-bromobenzotrifluoride, providing isoquinoline **419** after cyclisation with ammonium chloride (**Scheme 109**). The efficacy of this route for preparing both electron rich and electron poor systems was demonstrated by the incorporation of two benzenoid rings with opposite electronic properties.



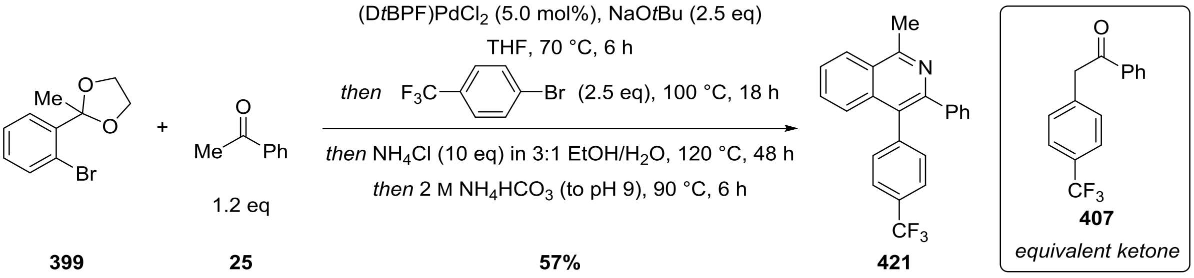
Scheme 109. Synthesis of electron rich isoquinoline **419** with electron deficient C4-aryl group

Isoquinoline **420**, with the reverse electronic arrangement, could also be efficiently synthesised (**Scheme 110**). When a nitro group was present in place of the trifluoromethyl moiety, however, the reaction was not clean due to decomposition of the nitro-containing starting material and intermediate.



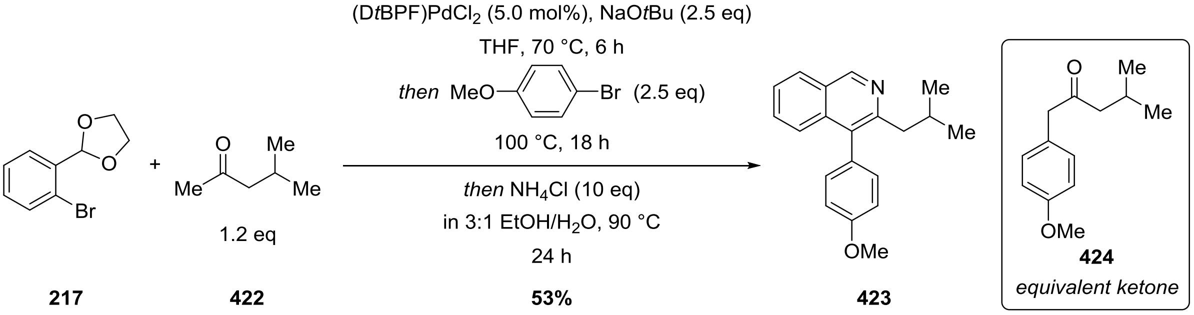
Scheme 110. Synthesis of electron deficient isoquinoline **419** with electron rich C4-aryl group

The procedure was then implemented using aryl bromide **399**, containing a methyl ketone-derived acetal (**Scheme 111**). The resulting intermediate necessitated the use of modified cyclisation conditions, with a higher temperature of 120 °C and extended reaction time required for acetal hydrolysis at pH 5. As it had previously been found that cyclisation of the resulting methyl ketone was sluggish under acidic conditions, ammonium bicarbonate was then added to effect isoquinoline formation, providing C1-methyl isoquinoline **421** in 57% yield (equivalent to a theoretical yield of 83% per step).



Scheme 111. One-pot synthesis of 1-methylisoquinoline **421**

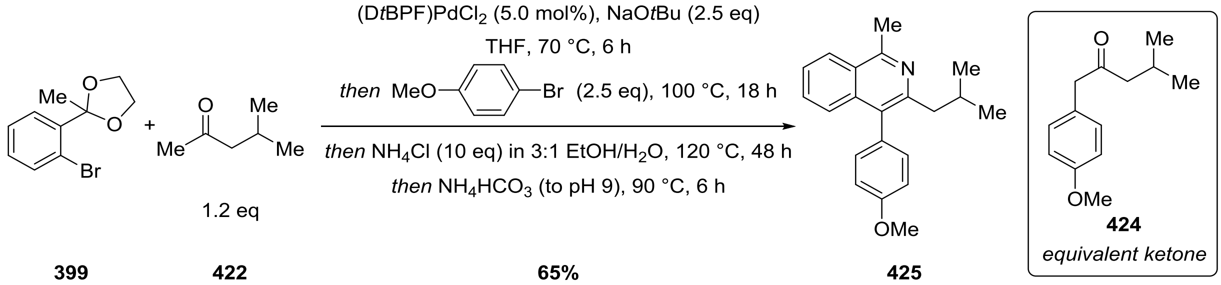
To this point, only acetophenone **25**, i.e. a phenyl ketone, had been employed in the arylation reaction, giving isoquinolines which all contained a phenyl group at C3. Whilst regioselectivity remains an issue with many linear alkyl ketones, selective arylation is possible if the two ketone substituents have sufficiently different steric properties, and if one group is bulky enough to discourage aldol condensation. Hence, methyl isobutyl ketone **422** was subjected to the diarylation-cyclisation protocol using 4-bromoanisole (**Scheme 112**). C3-Alkyl isoquinoline **423** was furnished in 53% yield. The regioselectivity of arylation was confirmed by the presence of a two-proton doublet at 2.65 ppm in the ^{1}H NMR spectrum, corresponding to the benzylic isobutyl methylene protons.



Scheme 112. Synthesis of isoquinoline **423** *via* α,α-heterodiarylation of alkyl ketone **422**

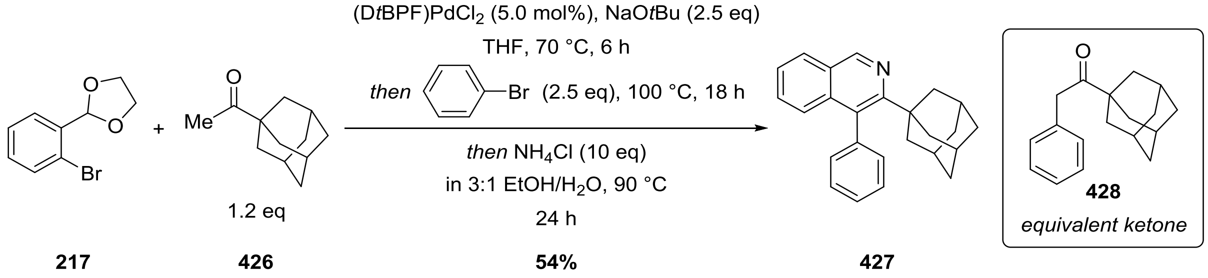
The reduced yield compared to previous examples may have been due to aldol condensation or some degree of competing α-arylation on the isobutyl side of the ketone. The analogous

C1-methyl isoquinoline **425** could be synthesised, and this reaction was slightly more successful, possibly due to the bulkier aryl bromide **399** reinforcing the preference of the reaction for initial arylation of the least substituted ketone α position (**Scheme 113**).



Scheme 113. One-pot synthesis of C3-alkyl isoquinoline **425**

Finally, the α,α-diarylation and cyclisation of adamantyl ketone **426** was attempted, and proceeded in a good yield of 54% to afford isoquinoline **427** (**Scheme 114**).



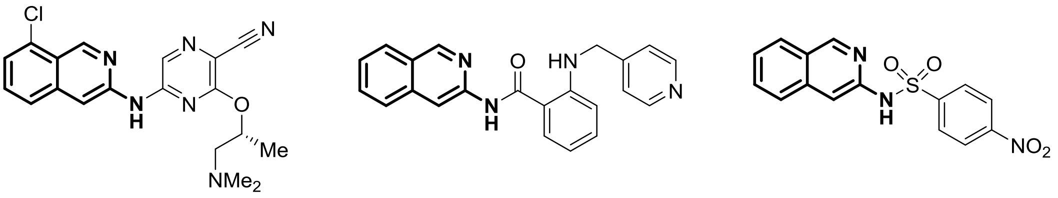
Scheme 114. Synthesis of C3-adamantyl, C4-aryl isoquinoline **427**

To summarise, a highly operationally simple procedure was developed for the synthesis of polysubstituted isoquinolines, whereby the product of regioselective ketone α-arylation was quenched with an electrophile to furnish C4-functionalised isoquinolines. This versatile methodology, which combined three chemical transformations between four reactive species in one pot, greatly expanded the range of substitution patterns that were accessible. Extending the *in situ* functionalisation strategy led to the development of the first α,α-heterodiarylation reaction of ketones, subsequently providing a range of C4-aryl isoquinolines with varying steric and electronic properties.

2.3 α-Arylation of nitrile enolates

2.3.1 Proposed route to 3-aminoisoquinolines

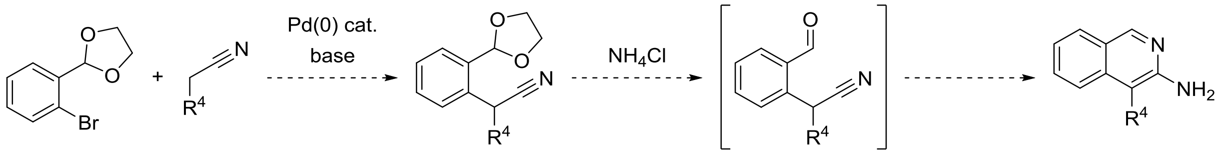
It was next decided to investigate the corresponding α-arylation of nitrile enolates, since this could eventually lead to the synthesis of higher oxidation level heterocycles, namely 3-aminoisoquinolines. Derivatives of these heterocycles are known to display significant biological activity, for example SAR-020106 is a checkpoint kinase 1 (CHK1) inhibitor that has been shown to enhance the antitumour activity of selected anticancer drugs (**Figure 27**).[229] Anthranilamide **429** has shown potential as an oral vascular endothelial growth factor receptor (VEGFR) kinase inhibitor with antiangiogenic and antitumour properties,[230] and sulfonamide **430** has demonstrated antimalarial activity.[231]



SAR-020106 **429** **430**

Figure 27. Biologically-active 3-aminoisoquinoline-containing compounds

It was postulated that the successful α-arylation of the enolate of nitrile **431**, using *ortho*-acetal aryl bromide **217**, would provide intermediate **432** which could undergo acetal hydrolysis and cyclisation in the presence of an ammonia source to provide 3-aminoisoquinoline **434** (**Scheme 115**).

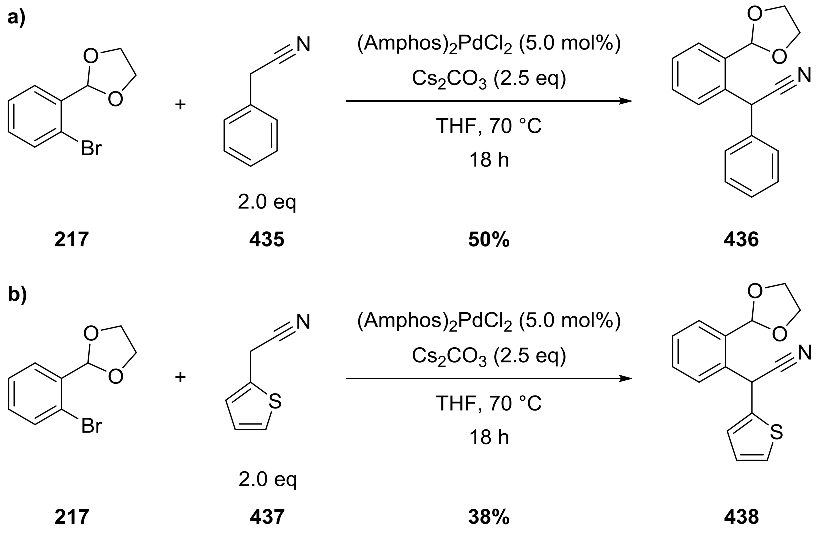


217 **431** **432** **433** **434**

Scheme 115. Proposed route to 3-aminoisoquinolines **433**

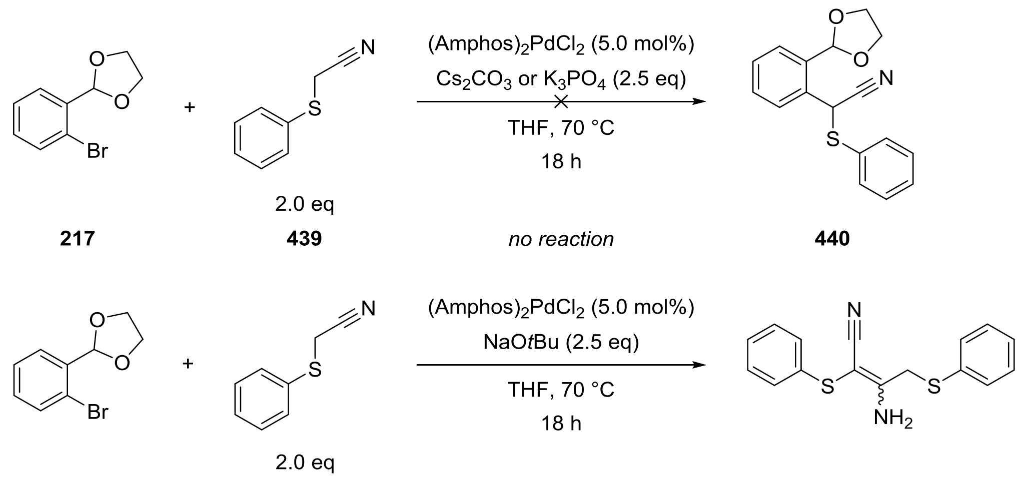
Due to the challenging nature of the α-arylation of nitrile enolates,[67,68] it was decided to begin this study with the coupling of the relatively acidic nitrile, benzylacetonitrile **435** (pK_a = 21.9

in DMSO)[232] with standard aryl bromide **217** (**Scheme 116a**). Preliminary experiments conducted by a Part II student in the Donohoe group revealed that the highest degree of conversion was achieved using (Amphos)$_2$PdCl$_2$ and Cs$_2$CO$_3$, while combinations of (DtBPF)PdCl$_2$, NaOtBu, or K$_3$PO$_4$ were less successful.[180] Applying these conditions to the α-arylation reaction afforded nitrile **436** in 50% yield. The identity of **436** was confirmed by the benzylic proton singlet at 5.91 ppm in the ^{1}H NMR spectrum, and the nitrile carbon peak at 119.9 ppm in the ^{13}C NMR spectrum. Nitrile **437** was also subjected to the reaction conditions, and the desired product **438** was isolated, but in a yield of only 38% (**Scheme 116b**).



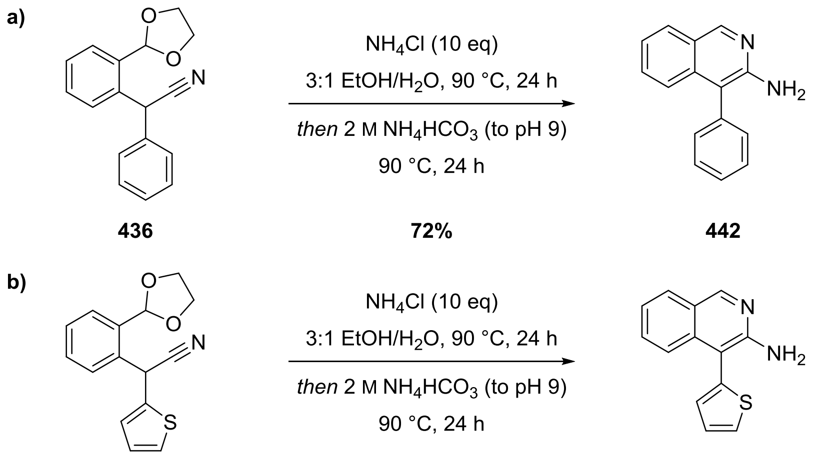
Scheme 116. Initial attempts towards nitrile arylation

The α-arylation of the slightly more acidic (phenylthio)acetonitrile **439** (pK_a = 20.8 in DMSO)[66] was then attempted using (Amphos)$_2$PdCl$_2$ (**Scheme 117**). When using the weaker bases Cs$_2$CO$_3$ or K$_3$PO$_4$, no reaction was observed, and in the presence of NaO*t*Bu, the nitrile **439** underwent a Thorpe reaction, furnishing enamine **441** in 94% yield.



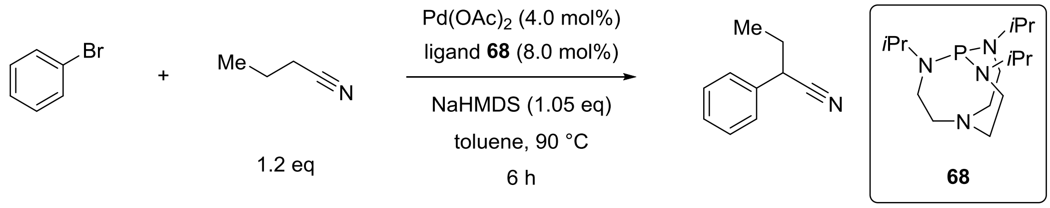
Scheme 117. Attempted α-arylation of nitrile **439**

Despite the low yields for the preliminary arylation attempts, it was decided to investigate the cyclisation of α-aryl nitriles **436** and **438** in order to test the viability of the proposed route to 3-aminoisoquinolines. Similar to the C1-methyl isoquinoline synthesis, it was found that treating nitrile **436** with ammonium chloride effected acetal hydrolysis but not isoquinoline formation. Adding ammonium bicarbonate to raise the pH then resulted in smooth converison to 3-aminoisoquinoline **442**, whose formation was supported by the broad NH_2 singlet at 4.41 ppm in the ^{1}H NMR spectrum (**Scheme 118a**). Spectroscopic data were also consistent with those reported in the literature.[233] An identical procedure afforded isoquinoline **443** from α-aryl nitrile **438** (**Scheme 118b**).



Scheme 118. Synthesis of 3-aminoisoquinolines **442** and **443**

Considering the limited success achieved when applying the ketone arylation conditions to the reaction of nitriles, it was decided to explore conditions developed by others. An attempt was made to reproduce a reaction reported by Verkade, who arylated butyronitrile **67** with bromobenzene **1** in 85% yield using proazaphophatrane ligand **68** (**Scheme 119**).[70]

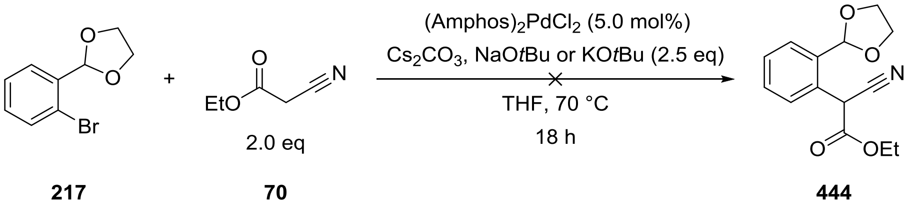


1 **67** **85%** **69**

Scheme 119. Verkade's α-arylation of butyronitrile **67**

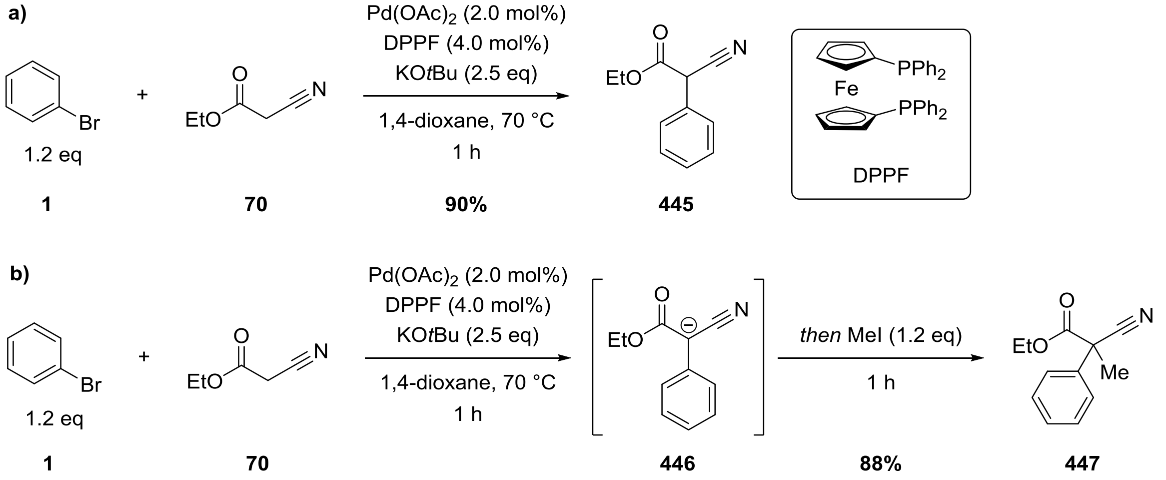
However, in our hands, no desired product could be detected, and the reaction gave a complex mixture of products with low mass recovery, highlighting the high sensitivity of the procedure. Conducted in a drybox by Verkade, the authors used solid NaHMDS, which we substituted with a solution in toluene, and air-sensitive ligand **68**, a viscous oil, proved difficult to add to the reaction mixture. The attempted α-arylation of alkyl nitrile **67** also gave a messy reaction when using combinations of (Amphos)$_2$PdCl$_2$ or (D*t*BPF)PdCl$_2$ and NaO*t*Bu, KO*t*Bu, NaHMDS, or Cs$_2$CO$_3$ in THF, 1,4-dioxane, or toluene.

In light of these difficulties, it was decided to focus efforts on the arylation of more acidic nitriles giving stabilised enolates. Ethyl cyanoacetate was chosen as it had been successfully arylated by Hartwig and others,[75–78] and with a pK_a of 13.1 in DMSO,[74] it was anticipated to be amenable to arylation under mildly basic conditions. The arylation of ethyl cyanoacetate **70** was therefore attempted using (Amphos)$_2$PdCl$_2$ and a number of bases (**Scheme 120**). When the reaction was performed at 70 °C (or at room temperature, before heating in the case of KO*t*Bu), a white precipitate was formed. After 18 hours, TLC analysis indicated the sole presence of aryl bromide **217** in the reaction mixtures. Filtration of the suspension, concentration of the filtrate *in vacuo*, and analysis by ^{1}H NMR spectroscopy confirmed the absence of ethyl cyanoacetate from the solution. It was concluded that the cyanoacetate enolate salt was insoluble in THF, so a new set of conditions were sought.



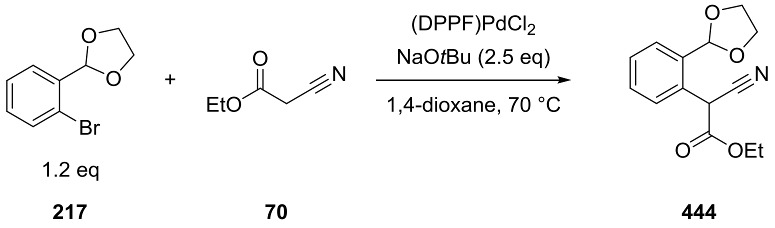
Scheme 120. Attempted arylation of ethyl cyanoacetate **70**

In 2007, having found the pre-existing methods of Hartwig and Verkade unsuitable for their purpose, Wang and coworkers developed a practical procedure for the palladium-catalysed arylation of ethyl cyanoacetate, using a catalyst system of Pd(OAc)$_2$, DPPF, and KO*t*Bu in 1,4-dioxane.[234] Using bromobenzene **1**, arylcyanoacetate **445** was obtained in 90% yield (**Scheme 121a**). Similar to the work described in Chapter 2.2, arylation could be combined with *in situ* alkylation to afford 2-aryl-2-alkylcyanoacetates such as **447** (**Scheme 121b**).



Scheme 121. Wang's conditions for the one-pot arylation-alkylation of ethyl cyanoacetate **70**

In this study, a modified version of Wang's conditions was applied to the coupling of ethyl cyanoacetate with aryl bromide **217** (**Table 10**). Given the discovery that Pd(II) precatalysts gave more consistent results than mixing a palladium source and ligand,[60] it was decided to use commercially available (DPPF)PdCl$_2$ in place of Pd(OAc)$_2$ and DPPF. Secondly, NaO*t*Bu was used instead of KO*t*Bu, since it is less hygroscopic. With 5.0 mol% catalyst loading, α-aryl cyanoacetate **444** was isolated in an excellent yield of 93% (Entry 1). Employing (D*t*BPF)PdCl$_2$ still gave product **444** in a very good yield, although it was slightly less effective than (DPPF)PdCl$_2$ (Entry 2 vs Entry 1).

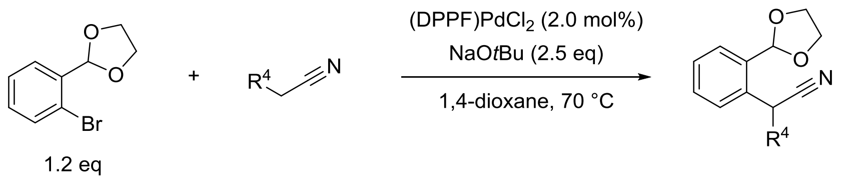


Entry	Catalyst loading / mol %	Time / h	Yield / %
1	5.0	18	93
2	5.0[a]	18	79
3	5.0	4	88
4	2.0	4	92
5	2.0[b]	4	90
6	0.5	4	87
7	0.1	4	7
8	0.5[c]	4	41

Table 10. Optimisation of conditions for the α-arylation of ethyl cyanoacetate with aryl bromide **217**
[a] (D*t*BPF)PdCl$_2$ instead of (DPPF)PdCl$_2$; [b] 300 mg scale based on **217**. All other entries 100 mg of **217**; [c] 1.0 eq **217** instead of 1.2 eq.

The reaction with (DPPF)PdCl$_2$ was repeated and followed more closely by TLC, when it was discovered that the ethyl cyanoacetate was consumed within four hours, giving **444** in similar yield to when left overnight (Entry 3 vs Entry 1). Reducing the catalyst loading to 2.0 mol%, and then to 0.5 mol%, gave essentially the same results (Entries 4 and 6), though reactivity dropped off sharply when using 0.1 mol% catalyst (Entry 7). A slight excess of aryl bromide **217** was necessary for optimal reaction outcome, as using just one equivalent reduced the yield significantly (Entry 8 vs Entry 6). The reaction could be scaled up, using 300 mg of aryl bromide **217**, with negligible impact on the yield (Entry 5 vs Entry 4).

The optimised procedure was then implemented using a variety of stabilised nitriles (**Table 11**). *tert*-Butyl cyanoacetate **448**, which would be expected to have a similar pK_a to ethyl cyanoacetate, was also arylated in excellent yield (Entry 2), as were (phenylsulfonyl)acetonitrile **449** (Entry 3) and malononitrile **450** (Entry 4).



217 **431** **432**

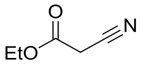
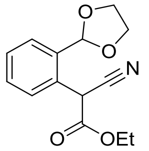
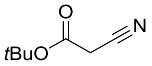
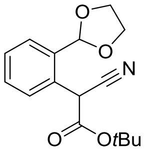
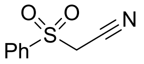
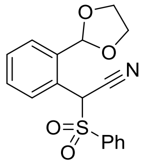
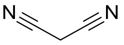
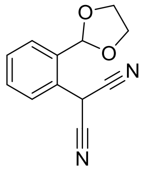
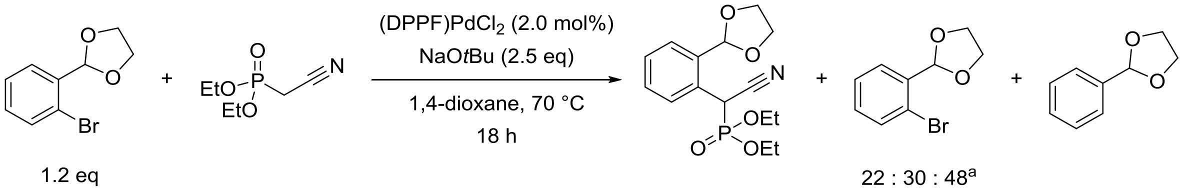
Entry	Nitrile		pK_a in DMSO	Time / h	Product		Yield / %
1		**70**	13.1[74]	4		**444**	92
2		**448**	–	4		**451**	92
3		**449**	12.0[235]	18		**452**	94
4		**450**	11.1[48]	4		**453**	92

Table 11. α-Arylation of stabilised nitrile enolates

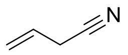
Less successful nitriles included phosphonate **454** (pK_a = 16.4 in DMSO),[236] which was completely consumed, but the crude reaction mixture contained only a small amount of product **455** along with starting material **217** and protodebrominated compound **456** in a 22:30:48 ratio (**Scheme 122**). Mass recovery was poor and nitrile **455** was isolated in only 21% yield as phosphonate **454** had largely decomposed under the reaction conditions.



217 **454** **455 21%** **217** **456**

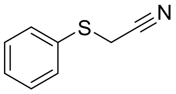
Scheme 122. Attempted α-arylation of phosphonate **454**. ^{a} Ratio based on ^{1}H NMR; ^{b} Isolated yield

Allyl cyanide **457** did not react, and (phenylthio)acetonitrile **439** once again gave only aryl bromide starting material and the product of the corresponding Thorpe reaction (**Figure 28**).



457

no reaction



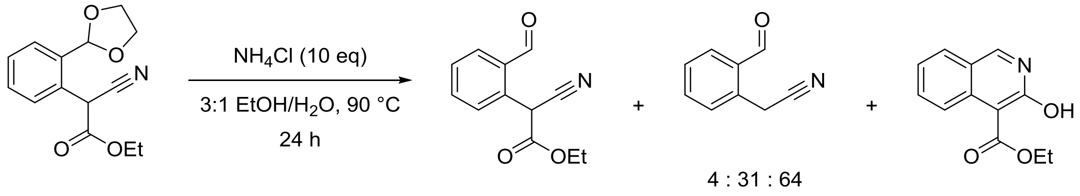
439

Thorpe reaction

Figure 28. Failed nitrile substrates

2.3.2 Cyclisation of α-aryl nitriles

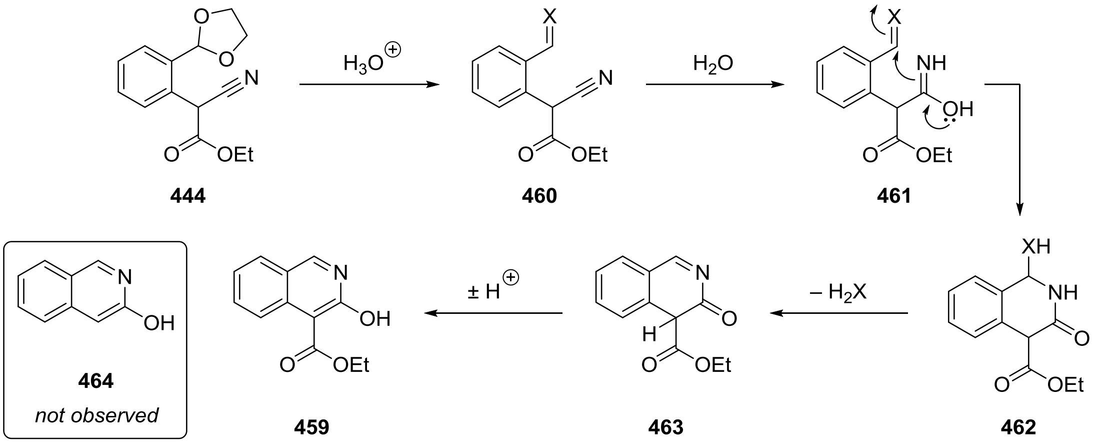
Attention then turned to the conversion of arylated ethyl cyanoacetate **444** to a 3-aminoisoquinoline. It was difficult to predict whether compound **444** would possess sufficient stability under the standard cyclisation conditions since the ethyl ester could hydrolyse or, as found by Suzuki,[75] it could be lost completely *via* decarboxylation. As an initial experiment, α-aryl cyanoacetate **444** was treated with 1 M ammonium chloride solution in 3:1 EtOH/H_2O at 90 °C for 24 hours (**Scheme 123**). No starting material remained, and a mixture of products was obtained, comprising deprotected aldehyde **457**, deprotected and decarboxylated compound **458**, and 3-hydroxyisoquinoline **459**. In agreement with previous observations, nitriles **457** and **458** had not cyclised to 3-aminoisoquinolines under the acidic conditions.



444 **457** **458** **459**

Scheme 123. Reaction of arylcyanoacetate **444** with ammonium chloride. Ratio based on ^{1}H NMR

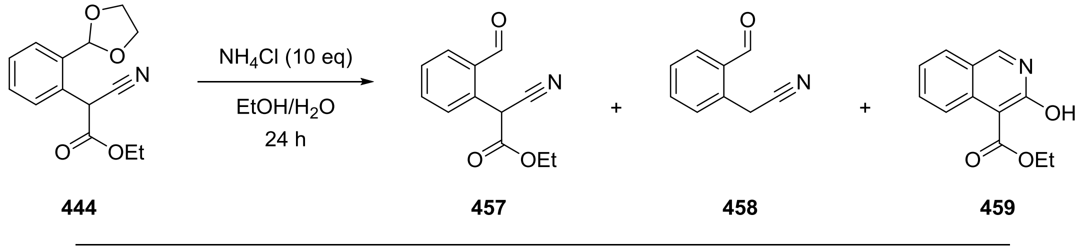
It was propsed that 3-hydroxyisoquinoline **459** was formed *via* the addition of water to the nitrile in **460**, in which the electron withdrawing ester moiety enhanced the electrophilicity of the nitrile carbon atom thereby enabling attack by water (**Scheme 124**). The resulting imidic acid **461** then cyclised through the nitrogen atom to give isoquinolone **463** after elimination of H_2X. Subsequent tautomerisation furnished 3-hydroxyisoquinoline **459**. The fact that the decarboxylated analogue **464** was not formed (*via* aldehyde **458**), was indicative of the crucial role of the ester moiety in activating the nitrile towards the addition of water.



Scheme 124. Proposed mechanism for the formation of 3-hydroxyisoquinoline **459**. X = O, NH

The bright yellow 3-hydroxyisoquinoline **459** could only be isolated in impure form, but confirmation that it was not the isoquinolone tautomer **463** was provided by the presence of nine aromatic carbon signals in the ^{13}C NMR spectrum.

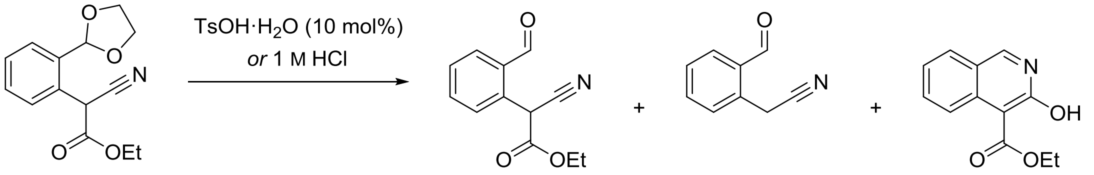
The dependence of the product distribution on temperature and the amount of water in the solvent mixture was then assessed (**Table 12**). Reducing the temperature to 70 °C appeared to decelerate both decarboxylation, which could theoretically occur from **444** or **457**, and the conversion of **457** to **459** (Entry 2 vs Entry 1), but decreasing the ratio of water in the solvent mixture had little effect (Entries 3 and 4).



Entry	EtOH/H_2O ratio	Temperature / °C	457 : 458 : 459[a]
1	3:1	90	4 : 31 : 64
2	3:1	70	50 : 15 : 35
3	6:1	90	0 : 26 : 74
4	10:1	90	0 : 29 : 71

Table 12. Effect of temperature and water content on product distribution
[a] Ratio based on ^{1}H NMR

It was then decided to explore different acids in an attempt to effect sole cleavage of the acetal of compound **444**, forming aldehyde **457**, which might later undergo cyclisation to the corresponding 3-aminoisoquinoline when treated with a basic source of ammonia (**Table 13**). When ammonium chloride was replaced with a catalytic amount of *para*-toluenesulfonic acid ($TsOH{\cdot}H_2O$), starting material **444** was consumed and the three products **457**–**459** were observed once again. Hence, no external nitrogen source was required for the formation of **459**, which further supported the mechanism proposed in **Scheme 124**.



444 **457** **458** **459**

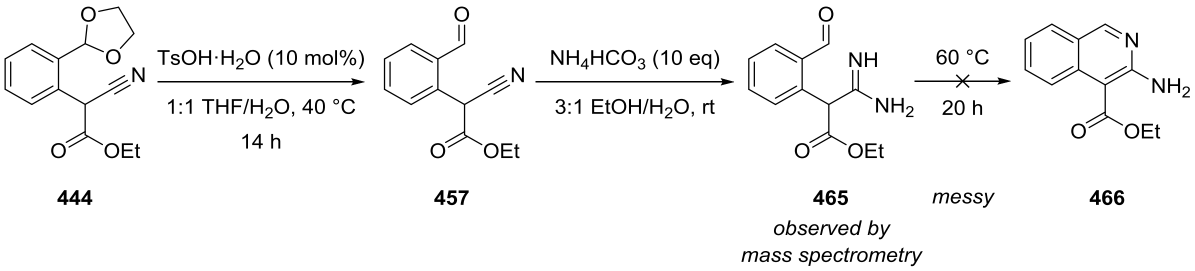
Entry	Acid	Solvent	Temperature / °C	Time / h	444 : 457 : 458 : 459[a]
1	$TsOH{\cdot}H_2O$	3:1 $EtOH/H_2O$	90	24	0 : 45 : 14 : 41
2	$TsOH{\cdot}H_2O$	3:1 $EtOH/H_2O$	rt	24	56 : 44 : 0 : 0
3	$TsOH{\cdot}H_2O$	EtOH	rt	24	63 : 37 : 0 : 0
4	$TsOH{\cdot}H_2O$	EtOH	90	24	66 : 34 : 0 : 0
5	$TsOH{\cdot}H_2O$	1:1 THF/H_2O	rt	24	33 : 67 : 0 : 0
6	HCl	1:1 THF/H_2O	rt	72	35 : 65 : 0 : 0
7	$TsOH{\cdot}H_2O$	1:1 THF/H_2O	40	15	0 : 100 : 0 : 0

Table 13. Effect of temperature and ratio of water in the solvent mixture on product distribution
[a] Ratio based on ^1H NMR

Reducing the reaction temperature from 90 °C to room temperature prevented decarboxylation and cyclisation, but reduced the consumption of starting material **444** significantly (Entry 2). Avoiding water as a co-solvent (and therefore relying on the water content of EtOH for acetal hydrolysis) produced a similar result (Entry 3 vs Entry 2). Increasing the reaction temperature to 90 °C, again without water as co-solvent, had negligible effect on conversion (Entry 4). Therefore it was clear that an elevated temperature and a significant amount of water were necessary for full consumption of starting material **444**, but this also resulted in both decarboxylation and cyclisation to 3-hydroxyisoquinoline **459** when using EtOH as the solvent.

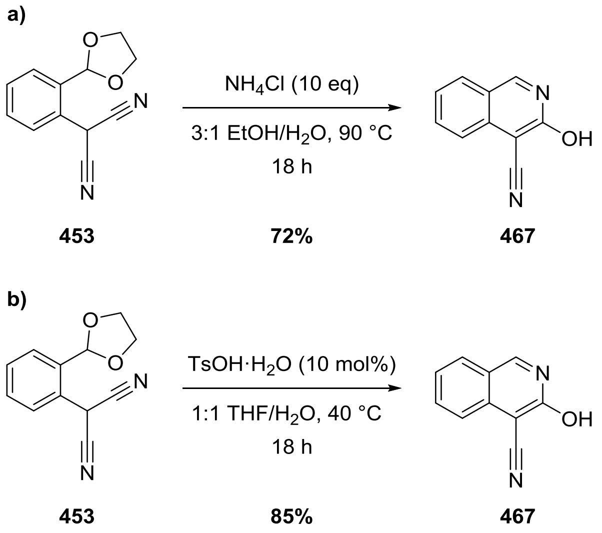
Changing the solvent to THF/H_2O increased the conversion of **444** to **457** at room temperature, giving **457** as the major product after 24 hours (Entry 5). When using HCl rather than TsOH·H_2O, 72 hours were required to achieve similar conversion (Entry 6). Employing TsOH·H_2O and elevating the temperature slightly, to 40 °C, resulted in complete hydrolysis of acetal **444**, with no side product formation, after 15 hours.

Having developed conditions for the smooth hydrolysis of acetal **444**, the reaction was repeated and, following workup, the crude product was treated with ten equivalents of NH_4HCO_3 in 3:1 EtOH/H_2O (**Scheme 125**). Upon addition of the ammonia source at room temperature, the solution became orange, and mass spectrometric analysis indicated the formation of amidine **465**. The reaction was then stirred at 60 °C for 20 hours, and a bright yellow oil was obtained after workup. TLC revealed a complex mixture of products, of which no structural information could be obtained by NMR spectroscopy.



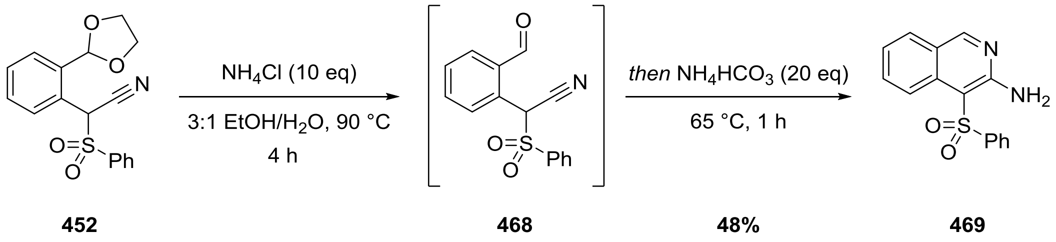
Scheme 125. Unsuccessful attempt to form 3-aminoisoquinoline **466**

The other successfully arylated nitriles were next treated with ammonium chloride. Compound **453** had been synthesised by the arylation of malononitrile, which was the most acidic of the series (pK_a = 11.1 in DMSO)[48] due to the strong electron withdrawing ability of both nitrile groups (**Table 11**). Accordingly, it was found that reaction with ammonium chloride produced 3-hydroxyisoquinoline **467** exclusively, with none of the uncyclised aldehyde observed (**Scheme 126a**). The product **467** necessitated isolation by reverse phase flash column chromatography, which was achieved in 72% yield. Furthermore, 3-hydroxyisoquinoline **467** could be obtained in 85% yield when subjected to the mild acetal hydrolysis conditions developed previously, underlining the enhanced reactivity of dinitrile **453** towards hydration (**Scheme 126b**). The second nitrile group, which became the C4 substitutent in isoquinoline **467**, was not hydrated as the electron rich heteroaromatic ring reduced the electrophilicity of the nitrile carbon atom compared to dinitrile **453**.



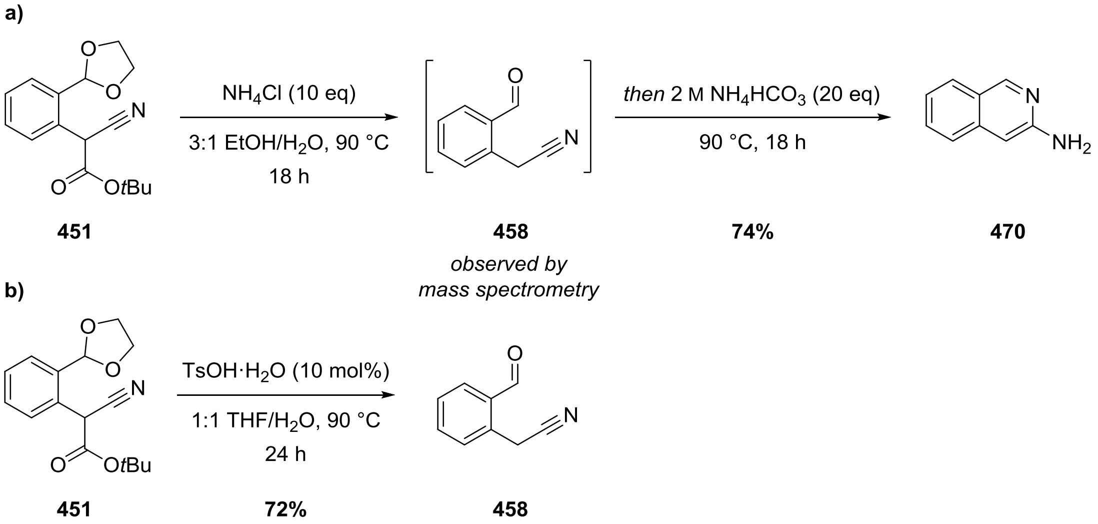
Scheme 126. Synthesis of 3-hydroxyisoquinoline **467** from dinitrile **453**

Nitrile **452**, synthesised by arylation of the next most acidic nitrile in this study, (phenylsulfonyl)acetonitrile **449** (pK_a = 12.0 in DMSO),[235] was then subjected to our standard nitrile cyclisation conditions (**Scheme 127**). On this occasion, some of the deprotected aldehyde **468** survived treatment with ammonium chloride and could be converted into 3-aminoisoquinoline **469** upon basification with ammonium bicarbonate. It is likely that the remainder of the material contained the analogous 3-hydroxyisoquinoline, but this compound was not isolated due to the impracticality of reverse phase flash column chromatography.



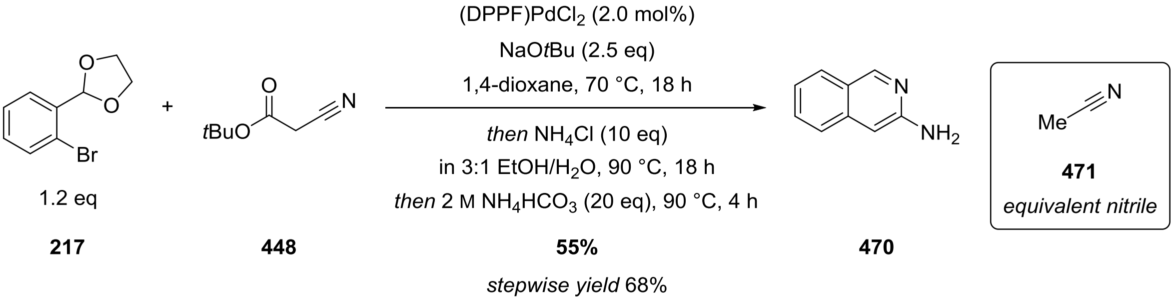
Scheme 127. Synthesis of 3-amino-4-sulfonylisoquinoline **469**

Finally, when the product of the α-arylation of *tert*-butyl cyanoacetate, **451**, was treated with ammonium chloride solution (**Scheme 128a**), almost complete decarboxylation occurred to give intermediate **458**, which could also be obtained by treatment with TsOH·H_2O (**Scheme 128b**). The addition of ammonium bicarbonate, according to our nitrile cyclisation protocol (Chapter 2.3.1), provided 3-aminoisoquinoline **470** in 74% yield (**Scheme 128a**).



Scheme 128. Acid-mediated decarboxylation of **451** and cyclisation to 3-aminoisoquinoline **470**

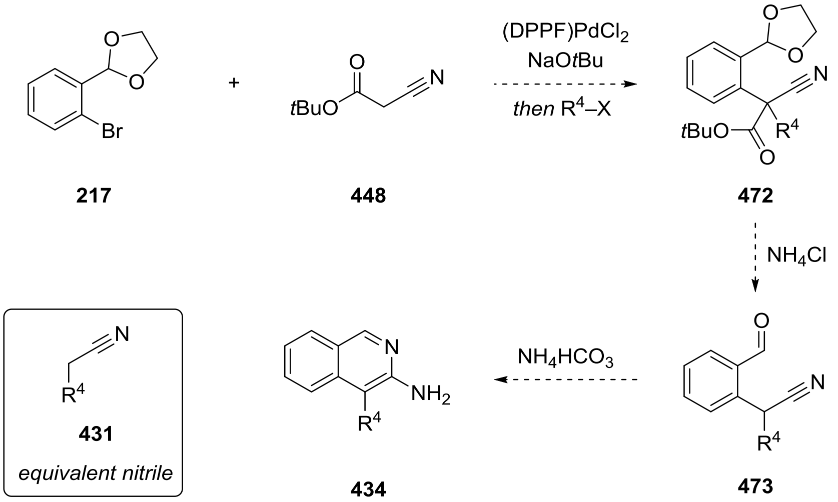
Having finally accessed a targeted 3-aminoisoquinoline in good yield, the α-arylation and cyclisation reactions of *tert*-butyl cyanoacetate **448** were combined in a one-pot process, affording product **470** in 55% yield (**Scheme 129**). It should be emphasised that this route was equivalent to arylating acetonitrile **471**, which is an incredibly challenging arylation substrate.



Scheme 129. One-pot synthesis of 3-aminoisoquinoline **470**

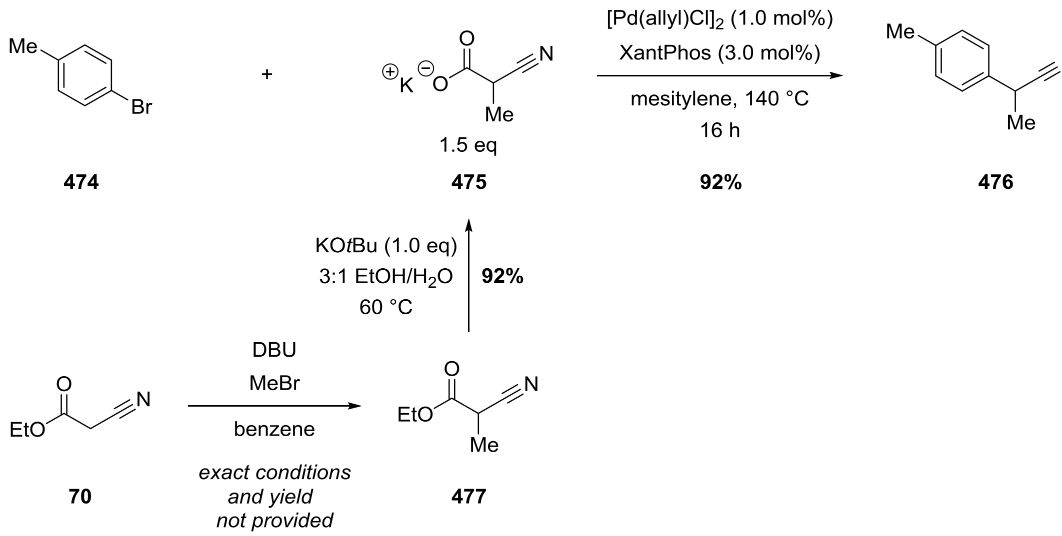
2.3.3 C4-Functionalised 3-aminoisoquinolines from *tert*-butyl cyanoacetate

It was decided that *tert*-butyl cyanoacetate **448**, with its clean decarboxylation and smooth conversion to the desired 3-aminoisoquinoline, would be a suitable alternative to troublesome alkyl nitriles in our α-arylation-based route to isoquinolines. It was envisaged that the coupling of *tert*-butyl cyanoacetate **448** with aryl bromide **217** could be followed by *in situ* functionalisation, in a manner similar to that of Wang,[234] and to our previous work with ketones, to give an α,α-difunctionalised *tert*-butyl cyanoacetate **472** (**Scheme 130**). Decarboxylation would generate the equivalent product that could theoretically be synthesised by the arylation of primary nitrile **431**. Subsequent cyclisation would furnish C4-functionalised, 3-aminoisoquinoline **434**.



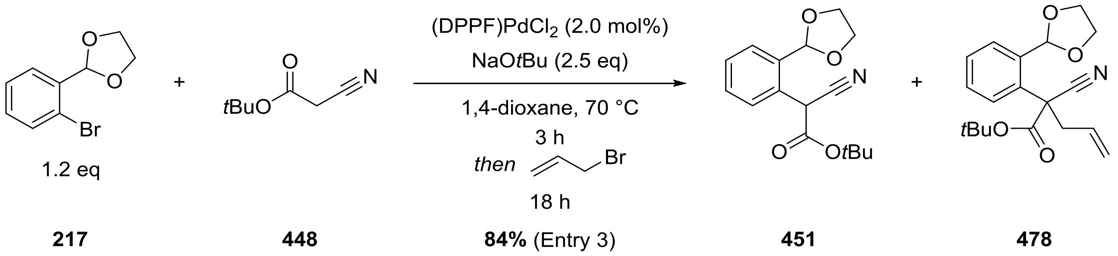
Scheme 130. Proposed synthesis of C4-functionalised 3-aminoisoquinolines **434**

It was noted that while the decarboxylative coupling developed by Liu and coworkers also allows access to compounds similar to **473**, these reactions require the prior alkylation of ethyl cyanoacetate **70** followed by conversion to the potassium cyanoacetate salt **475** (**Scheme 131**).[237] In addition, high temperatures (140 °C) are required for the coupling and the capability to functionalise *ortho* substituted aryl bromides has not been demonstrated by Liu and coworkers.



Scheme 131. Liu's decarboxylative coupling of cyanoacetate salts with aryl halides

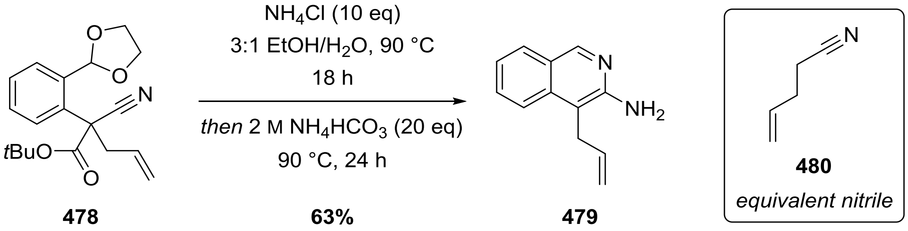
The sequence was first attempted using allyl bromide to trap the product of the α-arylation of *tert*-butyl cyanoacetate **448** (**Table 14**). At room temperature, allylation did not occur when one equivalent of allyl bromide was added, and therefore only arylation product **451** was observed (Entry 1). Increasing the temperature to 70 °C gave some functionalised product **478** (Entry 2), but to achieve complete conversion, 1.2 instead of 1.0 equivalents of allyl bromide were required (Entry 3). The difunctionalised product **478** was subsequently isolated in 84% yield.



Entry	Allyl bromide / eq	Temperature / °C	451 : 478[a]	Isolated yield / %
1	1.0	rt	100 : 0	–
2	1.0	70	36 : 64	–
3	1.2	70	0 : 100	84

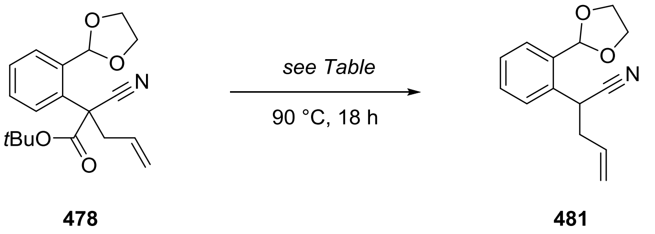
Table 14. One-pot arylation-allylation of *tert*-butyl cyanoacetate. [a] Ratio based on ^{1}H NMR

Nitrile **478** was then cyclised to 3-aminoisoquinoline **479** by sequential treatment with ammonium chloride and ammonium bicarbonate, though the yield of 63% was only moderate compared to the outcome of the similar reaction performed earlier (**Scheme 132**).



Scheme 132. Synthesis of 3-aminoisoquinoline **479**

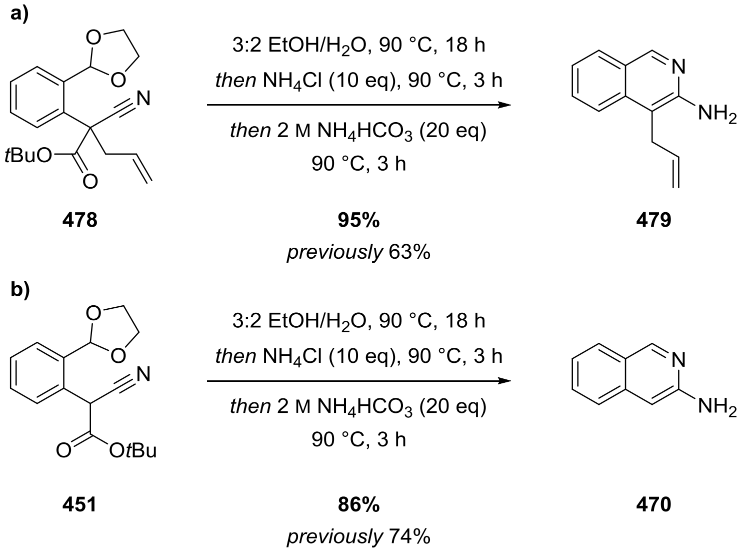
Upon workup, the bright yellow colour of the aqueous phase suggested the presence of a 3-hydroxyisoquinoline side product. In order to prevent its formation *via* protonation and hydration of the nitrile, the decarboxylation of **478** was attempted under basic ammonium bicarbonate conditions, with complete decarboxylation observed by ^{1}H NMR spectroscopy (**Table 15**, Entry 1). It was discovered that the ester could also be removed under neutral conditions, when merely heated in aqueous ethanol (Entry 2). The employment of water as co-solvent was found to be essential to the success of the reaction (Entry 3).



Entry	Solvent	Additive	478 : 481[a]
1	3:1 EtOH/H_2O	NH_4HCO_3 (10 eq)	0 : 100
2	3:1 EtOH/H_2O	–	0 : 100
3	EtOH	–	100 : 0

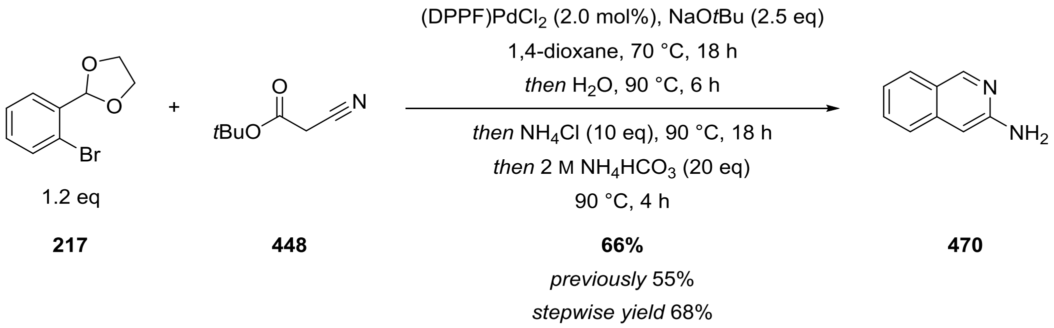
Table 15. Decarboxylation of difunctionalised *tert*-butyl cyanoacetate **478**. [a] Ratio based on ^{1}H NMR

An improved set of cyclisation conditions was therefore developed, whereby cyanoacetate **478** was first heated in a mixture of ethanol and water to effect decarboxylation, then ammonium chloride was added to cleave the acetal (with no competing hydration of the nitrile due to the preceding removal of the ester moiety), and finally, basification with ammonium bicarbonate to cyclise the nitrile (**Scheme 133a**). Thus, the yield of 3-aminoisoquinoline **479** was increased from 63% to 95%.



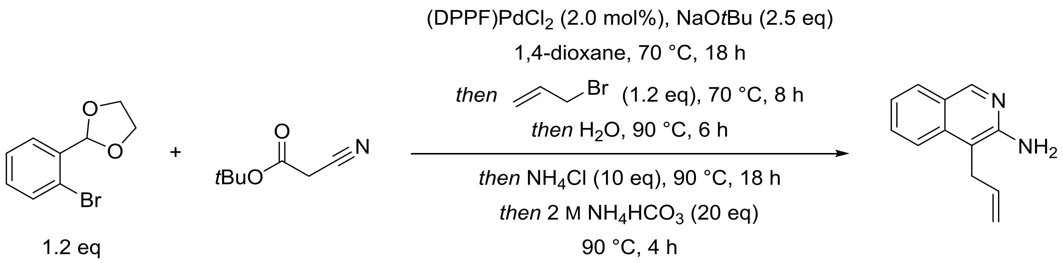
Scheme 133. Improved conditions for the synthesis of 3-aminoisoquinolines

Returning to the parent isoquinoline **470**, an improved yield of 86% was attained (**Scheme 133b**). When the modified conditions were employed in the one-pot protocol, the overall yield of isoquinoline **470** was also significantly enhanced (**Scheme 134**).



Scheme 134. One-pot synthesis of 3-aminoisoquinoline **470**

The one-pot, four component coupling between aryl bromide **217**, *tert*-butyl cyanoacetate **448**, allyl bromide, and ammonia was also possible, providing 3-aminoisoquinoline **479** in 34% yield (**Scheme 135**). The modest yield may be a result of the amino group in **479** reacting with the excess allyl bromide present, and/or the aldehyde formed by deprotection of the slight excess of acetal **217**.

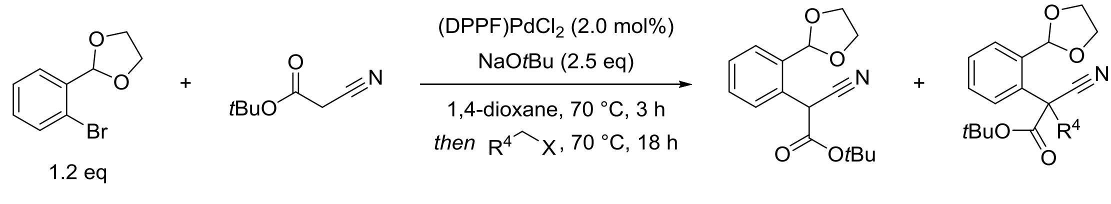


217 **448** **34%** **479**

stepwise yield 80%

Scheme 135. One-pot synthesis of C4-allyl 3-aminoisoquinoline **479**

Given the reduced efficiency of the one-pot procedure, it was decided to focus on a stepwise approach when exploring other electrophiles in the four component coupling (**Table 16**). When the α-arylation reaction was quenched with iodomethane, an excess amount was once again required for complete conversion (Entry 3 vs Entries 1 and 2), and difunctionalised cyanoacetate **482** could be isolated in 85% yield. Similarly, 3.0 equivalents of benzyl bromide were needed to produce **483** in 91% yield (Entry 6), and quenching with 5.0 equivalents of methyl bromoacetate afforded **484** in 87% yield (Entry 7).



217 **448** **451** **472**

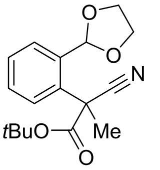
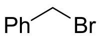
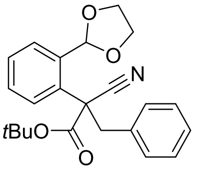
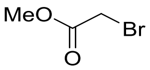
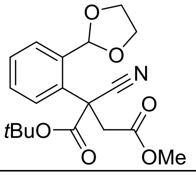
Entry	R^4 X	Eq	451 : 472[a]	Product		Isolated yield / %
1	Me–I	1.0[b]	100 : 0		**482**	–
2		1.0	52 : 48			–
3		1.5	0 : 100			**85**
4		1.5	43 : 57		**483**	–
5		2.0	8 : 92			–
6		3.0	0 : 100			**91**
7		5.0	0 : 100		**484**	**87**

Table 16. Arylation-alkylation of *tert*-butyl cyanoacetate. [a] Ratio based on ^{1}H NMR; [b] rt instead of 70 °C

A number of additional electrophiles, shown in **Figure 29**, were found to be incompatible with the procedure due to either decomposition at 70 °C, or lack of reactivity.

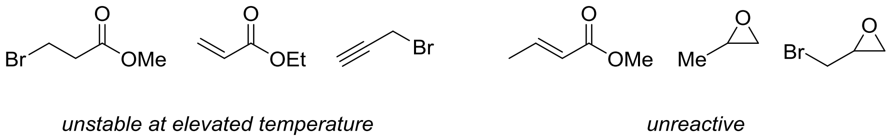
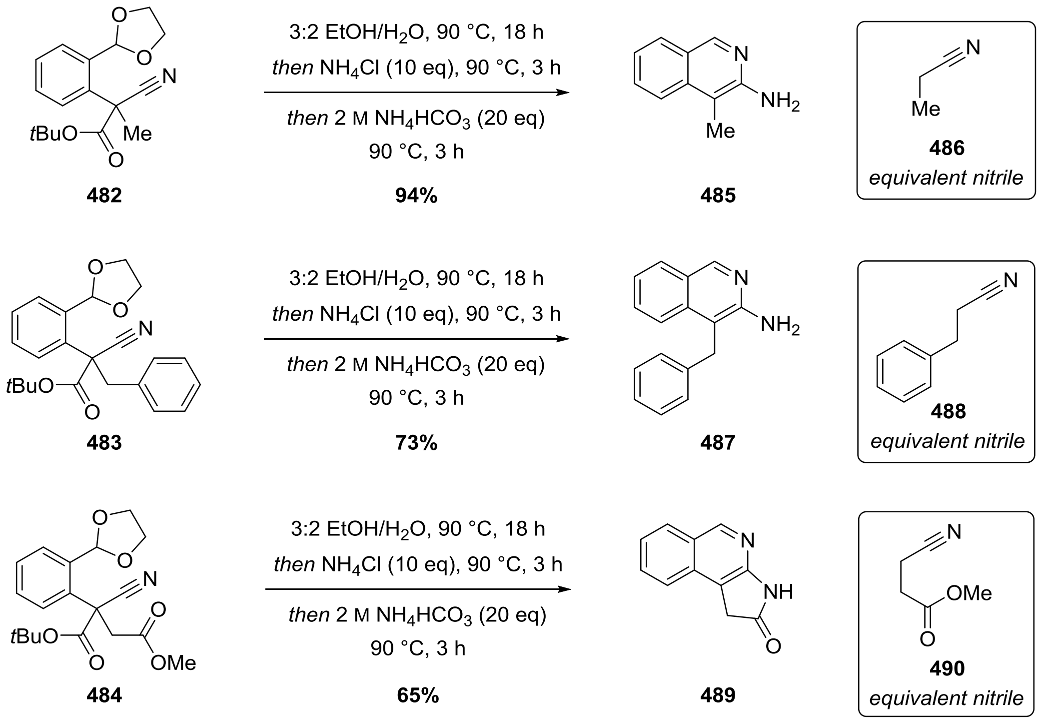


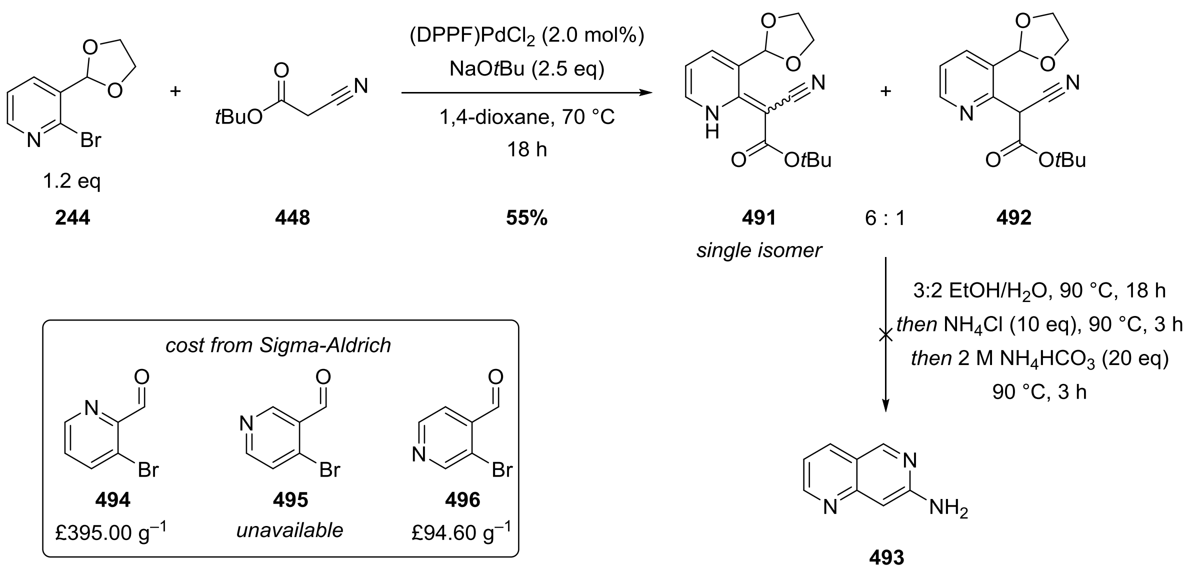
Figure 29. Incompatible electrophiles

Intermediates **482**–**484** were then cyclised to the corresponding 3-aminoisoquinolines using the optimised conditions (**Scheme 136**). The nitriles were first heated in aqueous ethanol to effect decarboxylation, then ammonium chloride was added to hydrolyse the acetal before ammonium bicarbonate facilitated cyclisation of the nitrile onto the aldehyde. C4-Methyl isoquinoline **485** was obtained in 94% yield, benzylated isoquinoline **487** in 73% yield, and lactam-fused isoquinoline **489**, where the amino group had cyclised onto the pendant ester, was furnished in 65% yield.



Scheme 36. Synthesis of C4-functionalised 3-aminoisoquinolines

In their publication describing the arylation-alkylation of ethyl cyanoacetate using a $Pd(OAc)_2$/DPPF catalyst system, Wang and coworkers were able to use 2-bromopyridine, 3-bromopyridine and 5-bromopyrimidine as aryl coupling partners, giving the desired products in very good yields,[234] after finding that cyanoacetates failed to couple with such heterocycles using Hartwig's Pd(dba)$_2$/P*t*Bu$_3$ system.[78] 3-Bromopyridine was a poor second coupling partner in our ketone α,α-heterodiarylation methodology using (D*t*BPF)PdCl$_2$, and earlier investigations in the Donohoe group had found that pyridyl bromide **244** (**Scheme 137**) failed to couple with acetophenone. Since DPPF appeared to be a more active ligand for the coupling of heteroaryl bromides, the arylation of *tert*-butyl cyanoacetate **448**, with pyridyl bromide **244**, was therefore attempted using (DPPF)PdCl$_2$. The relative positions of the acetal, bromide, and nitrogen atoms in **244** makes it a challenging substrate due to its ability to chelate and deactivate palladium, however alternative starting materials **494**–**496** were either commercially unavailable or prohibitively expensive. Despite this, the arylation product was obtained in 55% yield as a mixture of tautomers **491** and **492**, with the fully conjugated isomer **491** predominating. The identity of **491** was supported by a broad NH singlet at 15.3 ppm in the ^{1}H NMR spectrum, and a peak at 62.2 ppm in the ^{13}C NMR spectrum corresponding to the nitrile- and ester-substituted double bond carbon atom. In pyridine **492**, the proton at this position gave a singlet at 5.42 ppm in the ^{1}H NMR spectrum.



Scheme 137. Arylation of *tert*-butyl cyanoacetate using pyridyl bromide **244**

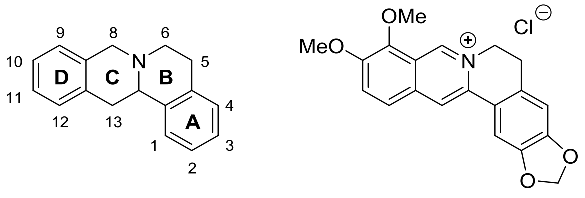
Upon heating the mixture of **491** and **492** in EtOH/H_2O, mass spectrometry indicated that decarboxylation had occurred. However when treated with ammonium chloride and ammonium bicarbonate, a complex mixture of different unidentified products was generated and naphthyridine **493** could not be isolated.

Despite this limitation, which was in agreement with previous difficulties encountered when employing pyridine substrates in α-arylation reactions, it had been demonstrated that *tert*-butyl cyanoacetate could be used as a convenient alternative to unsubstituted alkyl nitriles for the oxidation-free synthesis of 3-aminoisoquinolines *via* enolate arylation. The combination of α-arylation, *in situ* functionalisation, and decarboxylative cyclisation afforded the higher oxidation-level heterocycles directly, with a variety of substituents introduced at the C4 position.

2.4 Total synthesis of quaternary protoberberine alkaloids

2.4.1 Berberine

Having established a versatile α-arylation route to isoquinolines, it was decided to test the synthetic utility of the methodology by applying it to the total synthesis of quaternary protoberberine alkaloids (QPAs).[238] Members of the protoberberine family are biogenetically derived from tyrosine and share a common tetracyclic skeleton, with variation occurring predominantly in the oxidation level of the B and C rings and the position of the alkoxy or hydroxy substituents on the A and D rings (**Figure 30**). In plant tissues, the isoquinolinium QPAs are paired with chloride ions or the anions of organic acids, such as succinic acid, and are often isolated as the chlorides or iodides. These secondary metabolites are highly fluorescent and possess significant biological activities largely as a result of their ability to bind or intercalate nucleic acids.[239]



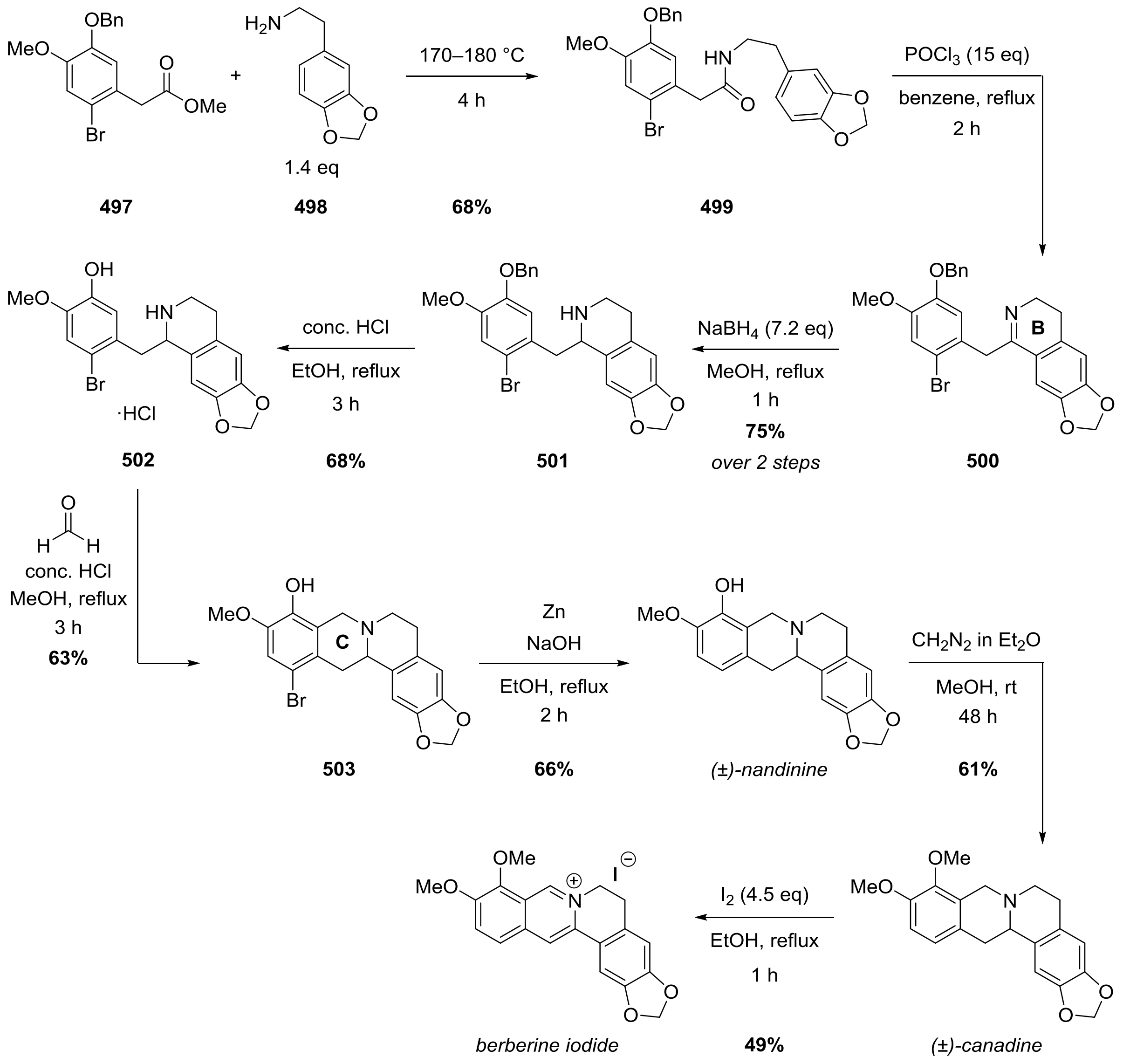
protoberberine skeleton *berberine chloride*

Figure 30. The protoberberine alkaloids

The parent compound, berberine, was chosen as a suitable synthetic target for the exemplification of our methodology. As one of the most widely distributed alkaloids, isolated from plants of the Berberidaceae family, its bright yellow colour has seen *Berberis* extracts employed in the dying of wood, leather and wool. Having long been used as a traditional medicine and dietary supplement in East Asia, more recent pharmacological studies have unveiled a wide range of potentially beneficial biological properties, including antifungal,[240] antibacterial,[241] anti-inflammatory,[242] antimalarial,[243] antidiabetic,[244] and anticancer activity.[245,246]

2.4.2 Previous synthetic efforts

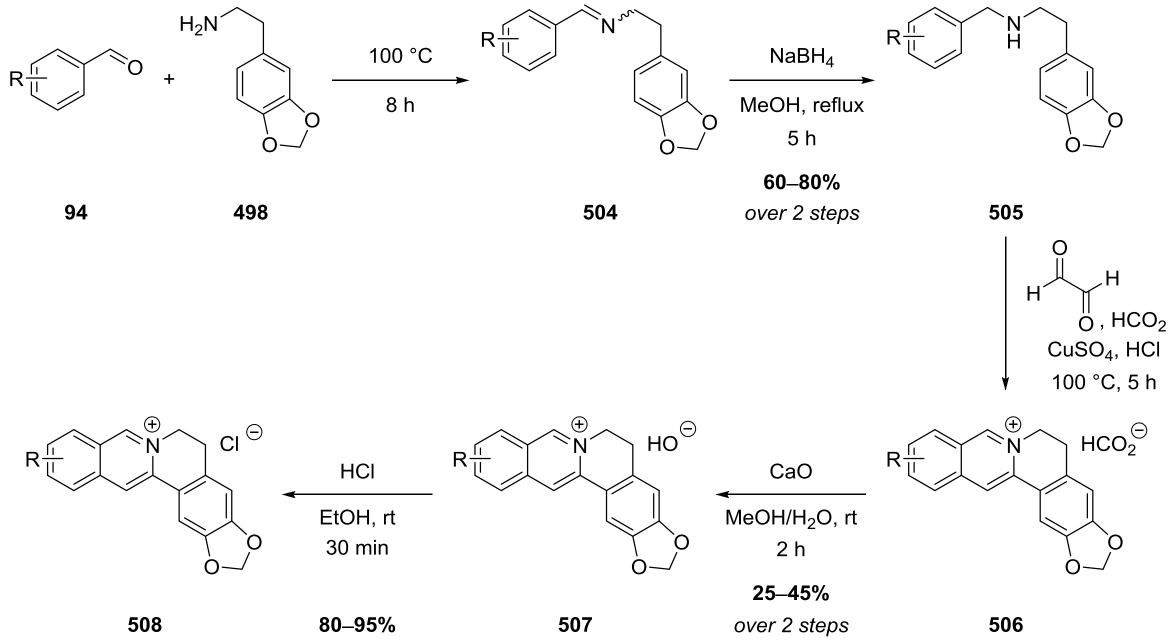
Whilst several methods are reported for the synthesis of at least partially saturated protoberberine species, only one total synthesis of berberine itself has been published, by Kametani and coworkers in 1969 (**Scheme 138**).[247] The reported synthesis began from commercially unavailable ester **497**, but no details were provided for its preparation.



Scheme 138. Kametani’s 1969 synthesis of berberine iodide

The condensation of amine **498** with methyl ester **497** afforded amide **499**, which was subjected to a Bischler-Napieralski reaction with $POCl_3$ to close the B ring. Reduction of dihydroisoquinoline **500** with sodium borohydride afforded tetrahydroisoquinoline **501**, which was debenzylated by refluxing in concentrated HCl. The hydrochloride salt **502** was then subjected to a Pictet-Spengler reaction with formaldehyde to furnish tetrahydroprotoberberine derivative **503**, which was reductively debrominated with zinc powder to afford the alkaloid (±)-nandinine. Methylation of the phenol gave (±)-canadine, which was oxidised with iodine to provide berberine iodide in 4.3% yield over eight steps.

More recently, synthetic efforts have focused on accessing analogues of berberine in order to probe their biological activity. For example, He and coworkers used glyoxal as a two-carbon fragment in the synthesis of berberine derivatives for evaluation of their antihyperglycemic activity.[248] A similar route was employed by Song when investigating cholesterol-lowering properties (**Scheme 139**).[249,250]



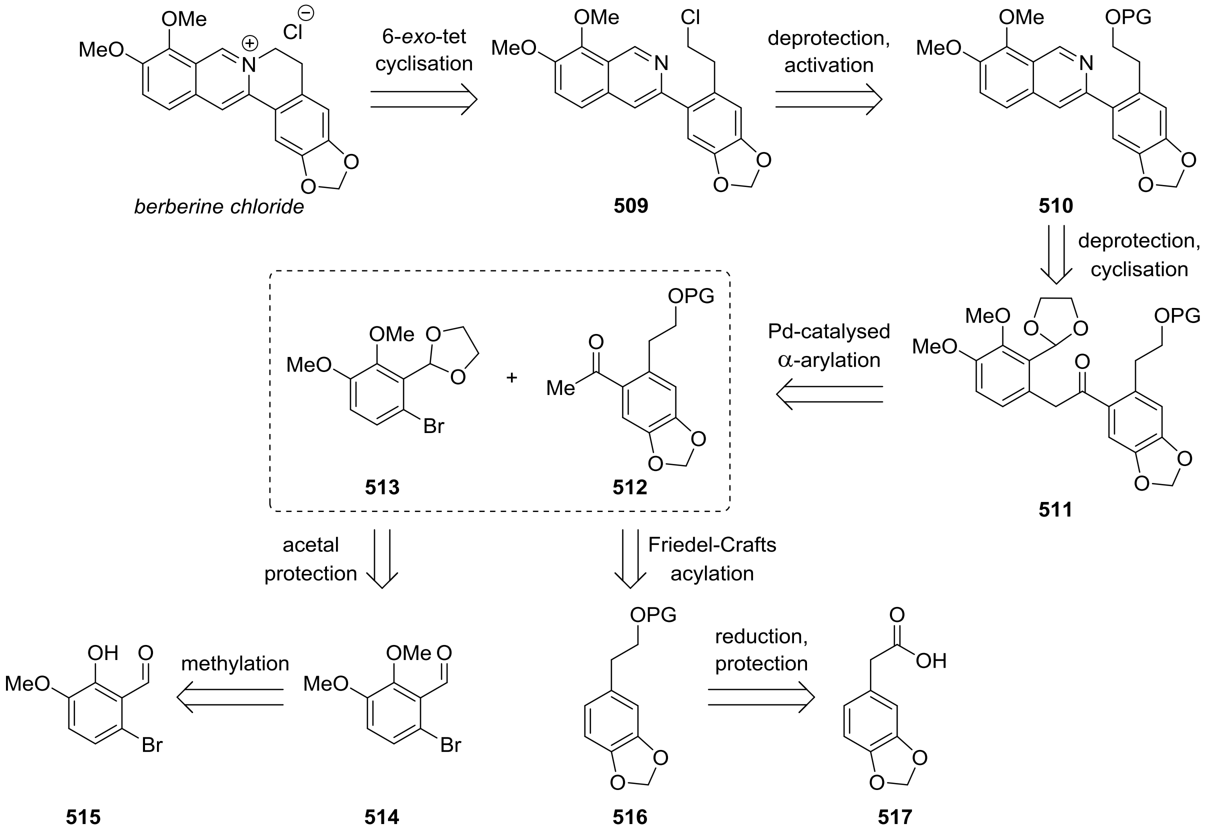
Scheme 139. Song’s route to berberine analogues

Amine **498** was condensed with a number of commercially available benzaldehydes (**94**) to form imine **504** which was directly reduced to amine **505** using sodium borohydride. A Pictet-Spengler reaction formed the B ring and a subsequent intramolecular Friedel-Crafts reaction closed the C ring, affording formate salt **506**. Anion exchange was performed *via* basification then treatment with HCl to give berberine derivative **508** in five steps.

Since, in both synthetic routes, the B and C rings were formed *via* electrophilic aromatic substitution reactions, only compounds containing electron rich A and D rings could be synthesised. It was envisaged that the application of our versatile α-arylation approach to isoquinolines would not only give a short, convergent, synthesis of berberine, but would also allow rapid access to a range of analogues, including electron deficient congeners.

2.4.3 Retrosynthetic strategy

It was anticipated that the formation of the B ring of berberine chloride could be achieved *via* intramolecular nucleophilic attack of the isoquinoline nitrogen atom on to the primary chloride of isoquinoline **509**, which would be introduced by deprotection and activation of the corresponding protected alcohol **510** (**Scheme 140**). Isoquinoline **510** would be generated by the cyclisation of ketone **511**, which is the product of the palladium-catalysed α-arylation of ketone **512** with aryl bromide **513**.

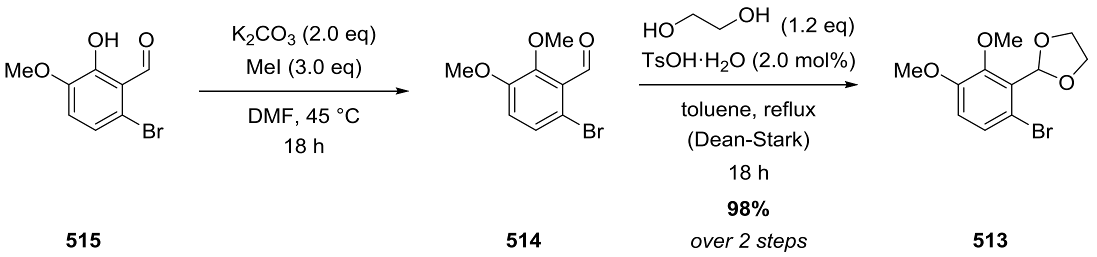


Scheme 140. Retrosynthetic analysis of berberine chloride. PG = protecting group

Aryl bromide **513** could be obtained by acetal formation from aldehyde **514**, which is not commercially available, but could easily be accessed by the methylation of commercially available phenol **515**. The ketone coupling partner **512** would be the product of a regioselective Friedel-Crafts acylation of compound **516**, which contains a protected pendant alcohol originating from the reduction of 3,4-(methylenedioxy)phenylacetic acid **517**.

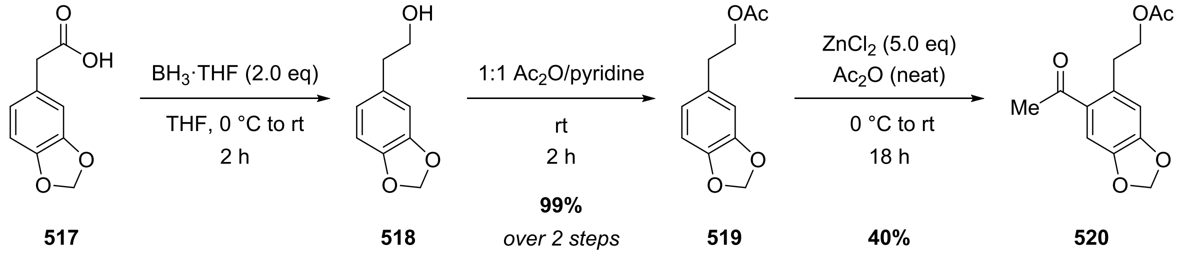
2.4.4 Preliminary studies

Initial investigations into the synthesis of berberine were conducted by a coworker, who had independently proposed an identical retrosynthetic approach to berberine.[176] The aryl bromide coupling partner **513** was synthesised *via* the methylation of commercially available 6-bromo-2-hydroxy-3-methoxybenzaldehyde **515** by treatment with K_2CO_3 and iodomethane (**Scheme 141**). The crude aldehyde **514** was then protected under the standard acetal-formation conditions, affording acetal **513** in 98% yield over two steps.



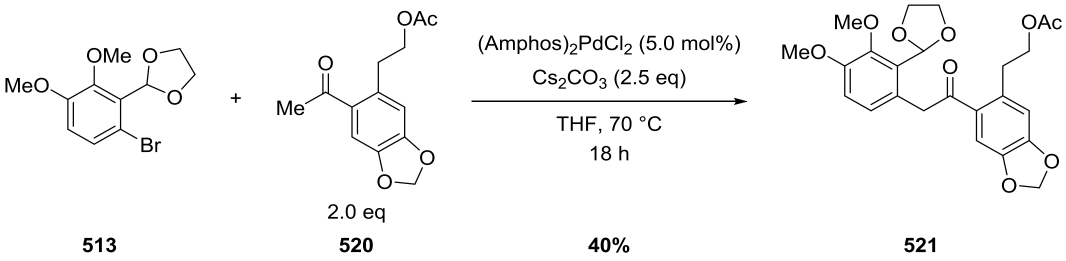
Scheme 141. Synthesis of aryl bromide coupling partner **513**

The synthesis of the ketone coupling partner began with the borane reduction of 3,4-(methylenedioxy)phenylacetic acid **517** to give alcohol **518** (**Scheme 142**). In this preliminary work, the primary hydroxyl was protected as an acetate group by treating alcohol **518** with acetic anhydride and pyridine, furnishing acetate **519** in 99% yield over two steps. Lewis acids, including $SnCl_4$, $AlCl_3$, $TiCl_4$, P_2O_5, ZnO and $ZnCl_2$, were then screened in the Friedel-Crafts acylation of intermediate **519** using AcCl or Ac_2O either neat or in CH_2Cl_2. The use of $ZnCl_2$ in Ac_2O gave the best result, though ketone **520** was isolated in only 40% yield. The presence of two singlets at 7.22 and 6.74 ppm in the ^{1}H NMR spectrum supported the regiochemistry shown in **Scheme 142**, but it was acknowledged that a similar spectrum would arise if the ketone were *ortho* to the methylenedioxy group rather than the alkyl side chain. It was anticipated that the structure of **520** would later be proven by the ability to synthesise berberine *via* 6-*exo*-tet closure of the B ring.



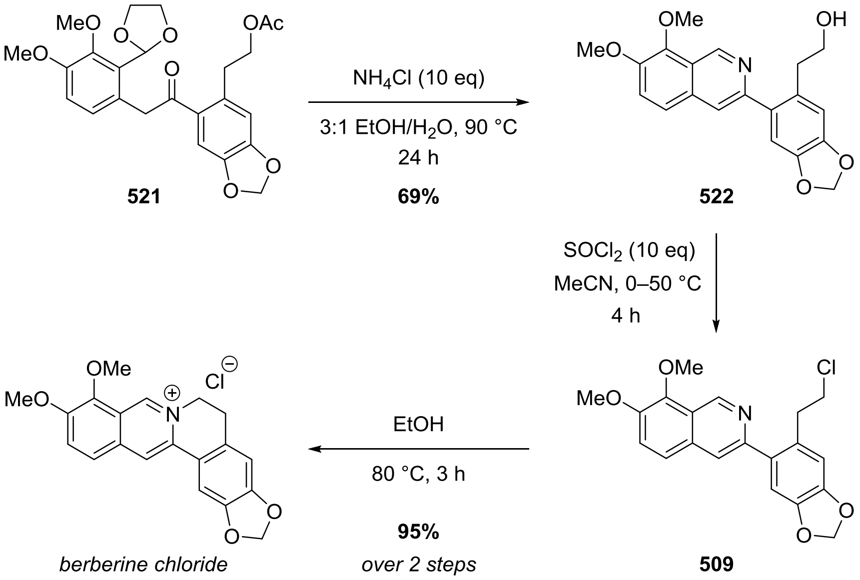
Scheme 142. Synthesis of ketone coupling partner **520**

With the two coupling partners in hand, the α-arylation reaction was attempted using 5.0 mol% of $(Amphos)_2PdCl_2$, Cs_2CO_3, and two equivalents of ketone **520** (**Scheme 143**). The α-aryl ketone **521** was afforded in 40% yield.



Scheme 143. Coupling reaction of aryl bromide **513** with ketone **520**

The isoquinoline precursor **521** was then subjected to the standard cyclisation conditions. Upon treatment with ammonium chloride, isoquinoline formation was accompanied by acetate hydrolysis to afford alcohol **522** in 69% yield (**Scheme 144**). This was followed by treatment with thionyl chloride to generate chloride **509**. The reaction mixture was then concentrated *in vacuo* to remove the excess thionyl chloride, and the residue was redissolved in EtOH since it was thought that a more polar solvent would stabilise the charge separation during the formation of the isoquinolinium salt. Upon heating to 80 °C, closure of the B ring proceeded to afford berberine chloride in 95% yield, which was isolated simply by the removal of solvent *in vacuo*.[176]

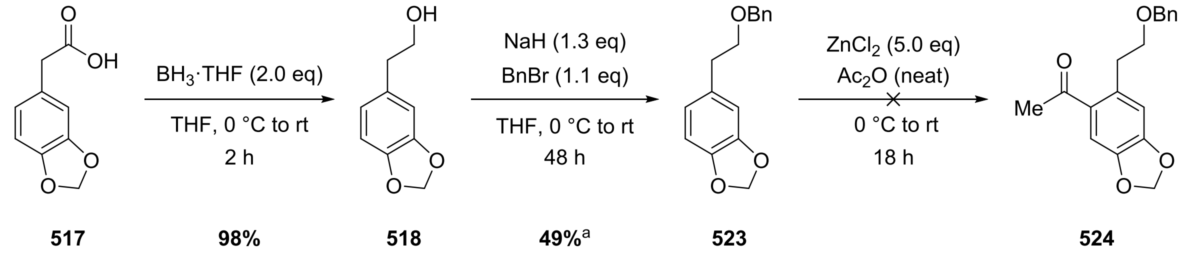


Scheme 144. Formation of the B and C rings in the synthesis of berberine

Thus, it was demonstrated that berberine could be synthesised *via* palladium-catalysed enolate arylation. In this initial study, berberine chloride was obtained in 26% yield from the limiting starting material, aryl bromide **513**. However, the yield over the longest linear sequence of seven steps, which began from the precursor to ketone **520**, was only 10% due to the two low yielding Friedel-Crafts and α-arylation reactions. More detailed studies were subsequently conducted by the author of this thesis towards an improved synthesis of berberine.

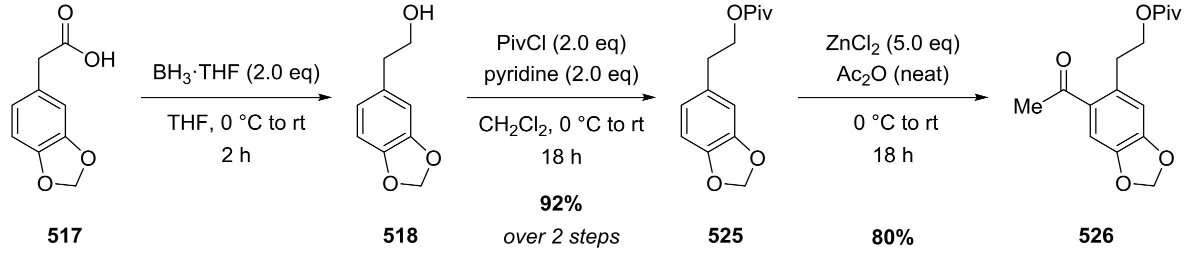
2.4.5 Optimisation of the synthesis of berberine

The most important challenge to be addressed in the synthetic route was the poorly yielding α-arylation reaction between aryl bromide **513** and acetate-containing ketone **520**. It was postulated that the low yield for this reaction (40%) was a result of the incompatibility of the acetate moiety with the basic arylation conditions. It was possible that the ketone enolate of **520** might undergo an intramolecular Claisen reaction with the pendant acetate, or that acetic acid could be eliminated *via* deprotonation at the benzylic position of the side chain. The poor yield of the Friedel-Crafts acylation for the synthesis of ketone **520** may have been an additional consequence of its relative instability. It was therefore decided to investigate alternative alcohol protecting groups, beginning with a benzyl ether which would be expected to demonstrate high stability under Friedel-Crafts acylation, α-arylation and cyclisation conditions. Phenylacetic acid starting material **517** was reduced in 98% yield by the addition of $BH_3 \cdot THF$ complex solution to give alcohol **518**, from which the benzyl ether **523** was obtained using sodium hydride and benzyl bromide (**Scheme 145**).[251] When subjected to the Friedel-Crafts acylation reaction, rapid debenzylation of **523** occurred, returning alcohol **518**. No trace of the debenzylated, but acylated, derivative of **523** was observed.



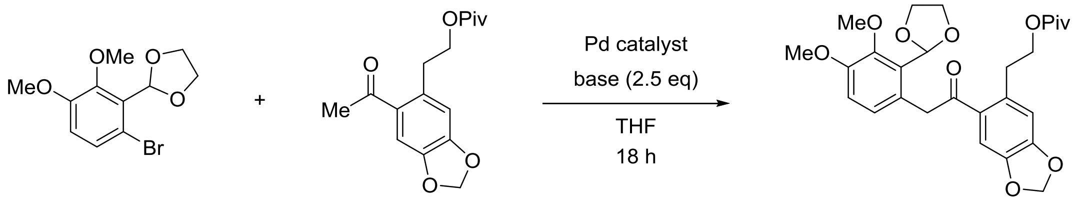
Scheme 145. Synthesis of benzyl ether **523** and unsuccessful Friedel-Crafts acylation attempt
[a] The low conversion for the benzylation reaction was attributed to the use of impure sodium hydride

Next, it was decided to employ the pivaloyl ester protecting group, whose steric bulk and lack of enolisable protons was expected to confer greater stability than the corresponding acetate. The borane reduction of acid **517** and treatment of the crude alcohol **518** with pivaloyl chloride and pyridine furnished pivaloate **525** in 92% yield over two steps (**Scheme 146**). When subjected to Friedel-Crafts acylation conditions using Ac_2O and $ZnCl_2$, substrate **525** was consumed and ketone **526** was isolated in 80% yield. The two singlets at 7.22 and 6.74 ppm in the ^1H NMR spectrum were consistent with the regiochemistry shown.



Scheme 146. Successful synthesis of ketone coupling partner **526**

Having obtained ketone **526** in high yield, the optimisation of the α-arylation reaction commenced. The combination of (D*t*BPF)PdCl$_2$ and NaO*t*Bu failed to deliver any of α-aryl ketone **527** due to the decomposition of ketone **526**, a finding which further supported the hypothesised instability of such ketones under basic conditions (**Table 17**, Entry 1). It was anticipated, however, that the bulky pivaloate moiety would be tolerated by milder arylation conditions, so Cs$_2$CO$_3$ was employed with (Amphos)$_2$PdCl$_2$, which had consistently outperformed (D*t*BPF)PdCl$_2$ alongside milder bases. The α-aryl ketone **527** was furnished in 52% yield, which was an improvement on the 40% yield of acetate **520** (**Scheme 143**) under identical conditions.



513 **526** **527**

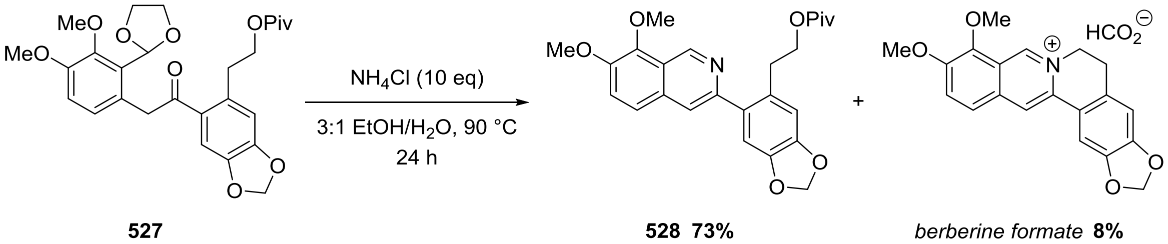
Entry	Pd catalyst (mol%)	Base	Ketone / eq	Temperature / °C	Yield / %
1	(D*t*BPF)PdCl$_2$ (5.0)	NaO*t*Bu	2.0	70	0[a]
2	(Amphos)$_2$PdCl$_2$ (5.0)	Cs$_2$CO$_3$	2.0	70	52
3	(Amphos)$_2$PdCl$_2$ (5.0)	Cs$_2$CO$_3$	2.0[b]	90	84
4	(Amphos)$_2$PdCl$_2$ (5.0)	Cs$_2$CO$_3$	1.2	90	74
5	(Amphos)$_2$PdCl$_2$ (2.0)	Cs$_2$CO$_3$	2.0	90	45

Table 17. Optimisation of the α-arylation of ketone **526** with aryl bromide **513**
[a] Ketone **526** decomposed; [b] 99% of the excess ketone was recovered

It was found that raising the temperature to 90 °C led to greater conversion of the starting material **513**, affording ketone **527** in 84% yield, and suggesting that the rate of the α-arylation of ketone **526** was slower than for simpler substrates (Entry 3). It was possible to recover 99% of the excess quantity of ketone **526** for recycling, which confirmed its stability under the mild reaction conditions. When the reaction was attempted under microwave irradiation, only 11% conversion was achieved in one hour, so this approach was not pursued further. Reducing the amount of ketone **526** to 1.2 equivalents still provided the product **527** in a respectable yield of 74% (Entry 4). The lower yield when using 1.2 equivalents of ketone

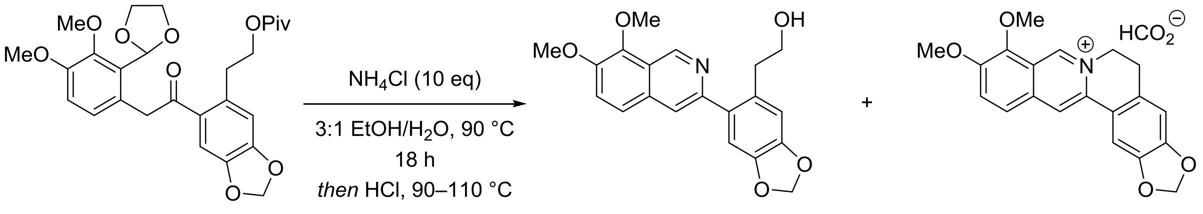
526, combined with the fact that 99% of the excess ketone could be recovered untouched when 2.0 equivalents were used, suggested that the concentration of enolate was crucial for ensuring complete reaction before the catalyst became inactive. Reducing the catalyst loading to 2.0 mol% resulted in a significant decrease in yield to 45% (Entry 5).

With α-aryl ketone **527** in hand, it was subjected to the standard isoquinoline-forming conditions (**Scheme 147**). As anticipated, treatment with ammonium chloride in 3:1 EtOH/H_2O at 90 °C provided the desired isoquinoline **528** in 73% yield. However, upon workup, the characteristic bright yellow colour of berberine was observed in the aqueous phase, and subsequent concentration of the aqueous washes *in vacuo,* followed by purification by MDAP (reverse phase mass-directed autopreparative HPLC), buffered with formic acid, afforded berberine formate in 8% yield.



Scheme 147. Synthesis of isoquinoline **528** and formation of berberine formate

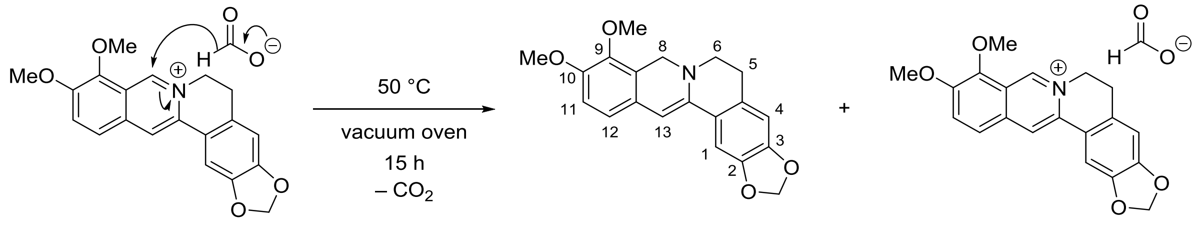
Hence, it was apparent that some intramolecular displacement of the pivaloate group had occurred from isoquinoline **528**. Rather than deprotecting the pivaloate **528** and then transforming the primary alcohol into the chloride before cyclising, it was decided to attempt to exploit this unexpected reactivity and convert isoquinoline **528** to berberine directly by the 6-*exo*-tet displacement of pivaloate. In an initial experiment, α-aryl ketone **527** was subjected to the ammonium chloride cyclisation conditions to form isoquinoline **528**, then HCl was added portionwise and the temperature was increased to 110 °C in an attempt to promote the displacement of pivaloate. Monitoring the reaction by LCMS revealed that pivaloate species **528** was slowly consumed over 2.5 days, producing a mixture of deprotected alcohol **522** and berberine (**Scheme 148**). A further 2.5 days at 110 °C were required for the conversion of alcohol **522** into berberine, which was subsequently separated from ammonium chloride by MDAP. Berberine formate was obtained in 78% yield.



527 **522** 2.5 days: 38 : 62[a] *berberine formate*
5 days: 9 : 91[a] **78%**

Scheme 148. Direct synthesis of berberine from pivaloate **527**. [a] Ratio based on LCMS

Prior to its full characterisation, berberine formate was dried overnight in a vacuum oven at 50 °C. After this treatment, it was discovered that a new product had formed, as the major component of an 8:1 mixture with berberine formate. In the ^{1}H NMR spectrum of the mixture, the integration of the formate signal was equal to that of individual berberine protons, therefore the formate ion was only associated with berberine, and not the new product. In addition, the characteristic isoquinolinium C8 and C13 proton signals at 9.86 and 8.90 ppm originated from berberine only. LCMS, ^{1}H NMR, ^{13}C NMR, COSY and HSQC analyses of the mixture in DMSO-d$_6$ were consistent with the reduction of berberine to dihydroberberine **529**, *via* hydride transfer from the formate counterion, which is entropically driven by the release of CO$_2$ (**Scheme 149**).

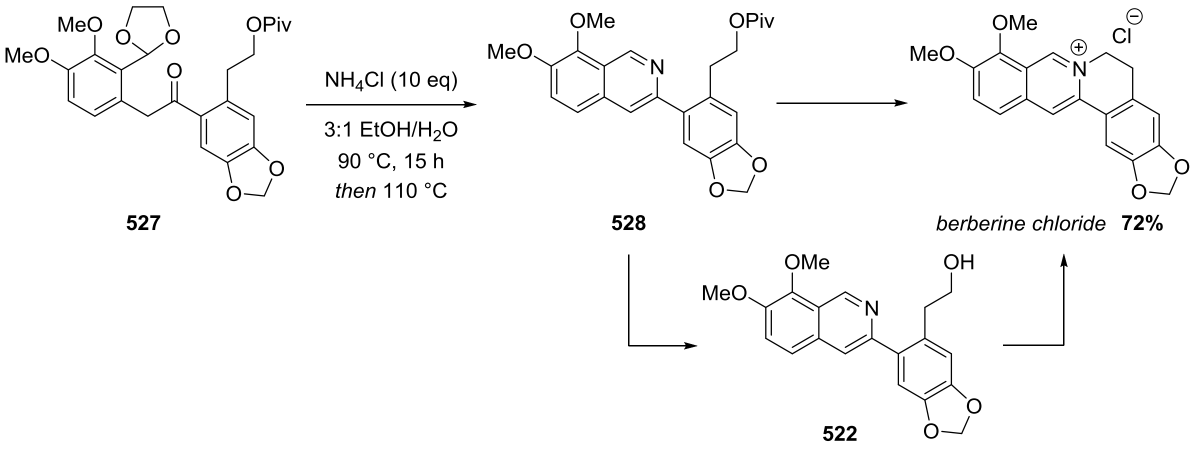


berberine formate **529** 8 : 1 *berberine formate*

Scheme 149. Reduction of berberine *via* hydride transfer from formate counterion

In the ^{1}H NMR spectrum, a two-proton singlet appeared at 5.99 ppm, corresponding to the C8 CH$_2$ protons, and a one-proton signal was observed at 6.03 ppm, originating from the C13 alkenyl proton. Published data for dihydroberberine **529**, which was synthesised in the literature by the reduction of berberine with $LiAlH_4$, were recorded in $CDCl_3$,[252] but since our sample was dissolved in DMSO-d_6, direct comparison with this data was not possible. Instead, the mixture was subjected to MDAP purification in an attempt to separate **529** from berberine. This was unsuccessful, however, as **529** was reoxidised to berberine during the attempted isolation.

At this point, attention returned to the berberine-forming reaction shown in **Scheme 148** as, at five days in length, the procedure was deemed somewhat inconvenient. It is likely that the addition of HCl following the formation of isoquinoline **528**, which was intended to protonate the pivaloate and enhance its leaving group ability, also accelerated the hydrolysis of the pivaloyl ester, furnishing primary alcohol **522**. Since the hydroxyl (when protonated) would be an inferior leaving group to pivaloate, this would decelerate berberine formation. In addition, partial protonation of the mildly basic isoquinoline nitrogen atom would prevent nucleophilic attack on the pendant primary pivaloate. In light of this, ketone **527** was subjected once again to the reaction with ammonium chloride to form isoquinoline **528**, and the temperature was then raised to 110 °C but no additional acid was added (**Table 18**). The reaction was monitored closely by LCMS, and once again, the intermediate isoquinoline **528** was formed and consumed within 2.5 days, but the ratio of alcohol **522** to berberine lay much more in favour of the natural product (Entry 4). After a further 24 hours, alcohol **522** was almost entrirely converted into berberine, some of which precipitated as a yellow solid (Entry 6). The reaction was therefore complete after 3.5 days, compared to 5 days previously.



Entry	Temperature	Time of analysis / h	528 : 522 : berberine[a]
1	90 °C	15	76 : 11 : 6
2	110 °C	24	56 : 21 : 23
3	110 °C	36	22 : 21 : 57
4	110 °C	60	1 : 12 : 85
5	110 °C	68	0 : 13 : 86
6	110 °C	84	0 : 8 : 92

Table 18. Progress of the berberine-forming reaction with time
[a] Ratio based on LCMS

Given the previous reliance on sophisticated MDAP instrumentation for the isolation of berberine, it was desirable to develop a more convenient, widely applicable, procedure for the removal of ammonium chloride. To this end, the reaction mixture was diluted with Et_2O and the precipitate was filtered and washed with Et_2O to remove organic impurities. The solid was then washed with a minimum volume of cold H_2O in order to dissolve and remove ammonium chloride, whilst dissolving as little berberine as possible. The resulting bright yellow solid was dissolved in methanol and the solution concentrated *in vacuo* to provide berberine chloride in 72% yield. The NMR spectra were consistent with those previously reported,[253,254] and the absence of a singlet at around 1 ppm confirmed that the pivaloate salt had not been obtained. Comparison of the IR spectrum of the synthetic berberine chloride with that of ammonium chloride and an authentic sample of berberine chloride provided evidence for the complete removal of ammonium chloride (**Figure 31**).

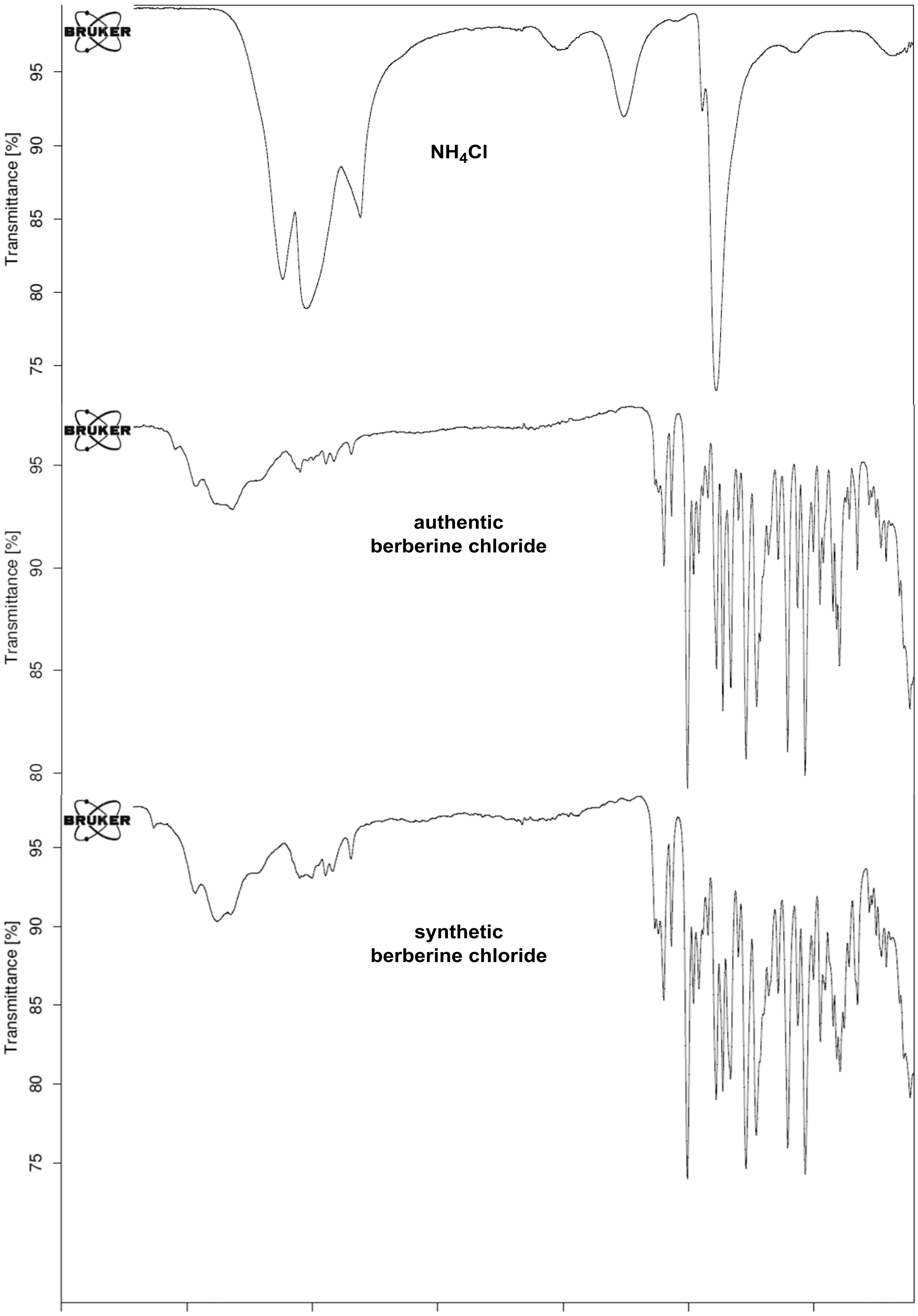
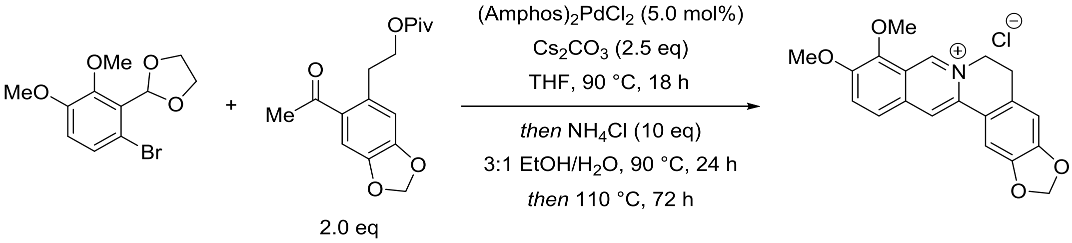


Figure 31. IR spectra of ammonium chloride, authentic berberine chloride, and synthetic berberine chloride

The possibility of executing both the α-arylation reaction and the subsequent formation of berberine in one pot was then investigated, since this would reduce the total synthesis to just four distinct steps, involving only two chromatographic separations. Indeed, this was possible, and berberine chloride was provided in 40% yield from aryl bromide **513** by adding ammonium chloride solution to the completed α-arylation reaction and heating at 90 °C, then at 110 °C (**Scheme 150**). The yield of berberine was lower than in the stepwise case, due to the need for more extensive washing of the product with H_2O for the removal of Cs_2CO_3 as well as ammonium chloride.

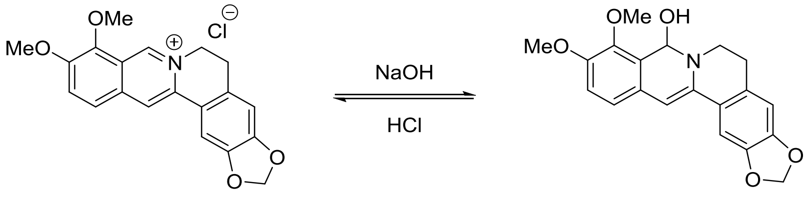


513 **526** **40%** *berberine chloride*

stepwise yield 60%

Scheme 150. One-pot synthesis of berberine from α-arylation coupling partners **513** and **526**

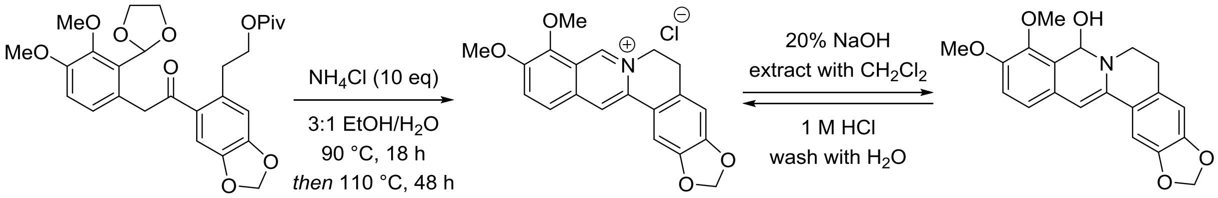
The loss of some berberine chloride during the washing process was evidenced by the yellow colour of the filtrate. Thus, an improved, but still chromatography-free, purification procedure was sought. For this, inspiration was taken from the typical process for isolation of protoberberines from their plant sources, which is based on the interconversion between the protoberberine salt (soluble in water and stable in acidic and neutral media) and the base **530** (soluble in organic solvents) (**Scheme 151**).[238]



berberine chloride **530**

Scheme 151. Interconversion of berberine chloride and berberine base **530**

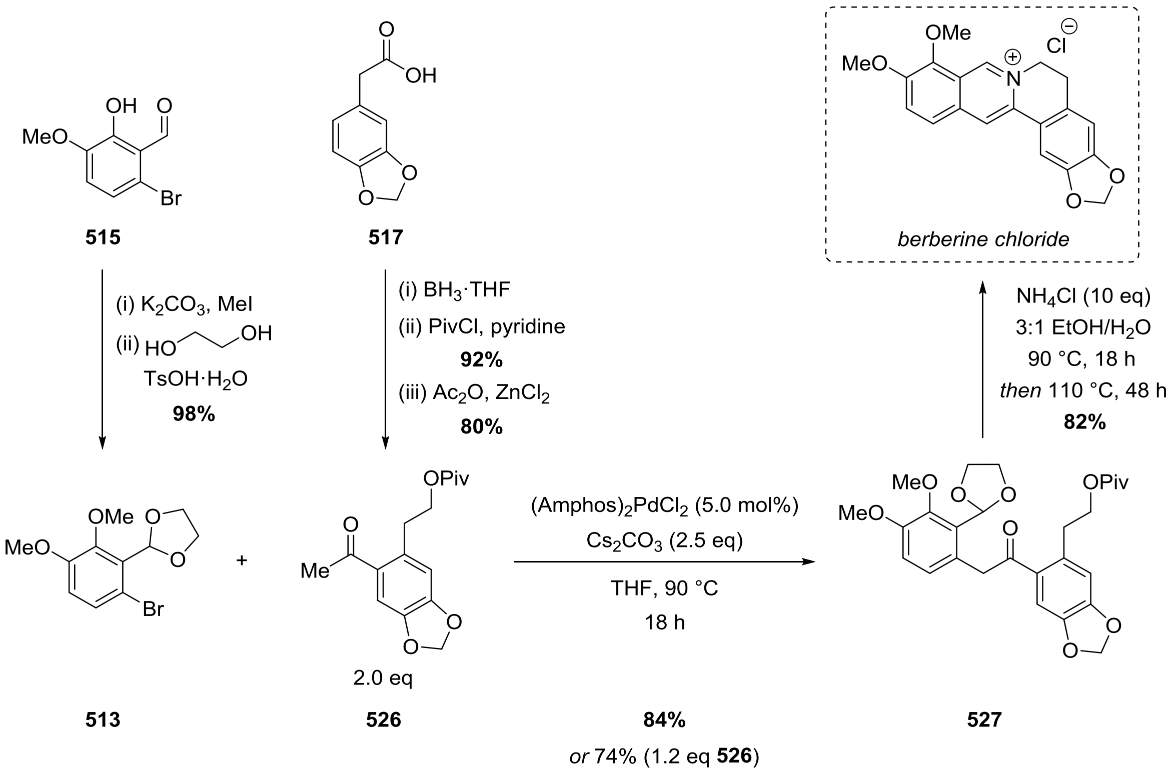
The α-arylation product **527** was cyclised to berberine using the previously developed procedure (**Scheme 152**). Once complete, the reaction mixture was concentrated *in vacuo* to afford a solid residue containing berberine and ammonium chloride. This material was dissolved in H_2O before aqueous NaOH was added to convert berberine to the hydroxide adduct **530**, upon which the bright yellow solution immediately turned dark red. It is likely that the ammonium chloride was also neutralised during this process. The red berberine base **530** was extracted with CH_2Cl_2 before the organic solution was treated with HCl to regenerate berberine chloride, which was washed out with H_2O, leaving organic impurities in the CH_2Cl_2 phase. Concentration of the aqueous washes *in vacuo* afforded pure berberine chloride in an improved yield of 82%, completing the optimised synthesis. When this workup was applied to the one-pot protocol, it was clear that berberine had been formed in a greater yield than the 40% achieved previously (**Scheme 150**), but an impurity present in the sample could not be removed, despite extensive efforts.



527 **82%** *previously* 72% *berberine chloride* **530**

Scheme 152. Improved workup in the cyclisation of **527** to berberine chloride

To summarise, the total synthesis of berberine chloride was achieved *via* the route depicted in **Scheme 153**. The overall yield, with respect to the limiting aryl bromide starting material **515**, was 68%, though the longest linear sequence of five steps began from acid **517**. Berberine was provided in 50% overall yield from this starting material when 2.0 equivalents of ketone **526** were employed in the α-arylation reaction, or in 45% yield using 1.2 equivalents. Only three instances of column chromatography were required.[255]

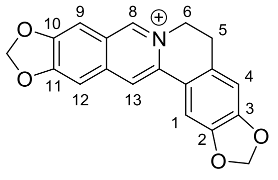


Scheme 153. The convergent total synthesis of berberine chloride *via* enolate arylation

A key, advantageous, feature of this modular route was the potential to access structurally diverse alkaloids simply by varying the aryl bromide and/or ketone coupling partners. It was decided to exemplify this versatility with the synthesis of additional quaternary protoberberine alkaloids.

2.4.6 Pseudocoptisine

Pseudocoptisine was chosen as the next synthetic target, since it possesses a different substitution pattern to berberine due to the replacement of the D ring methoxy substituents with a methylenedioxy group, which occupies the C10 and C11 positions rather than the C9 and C10 positions (**Figure 32**).

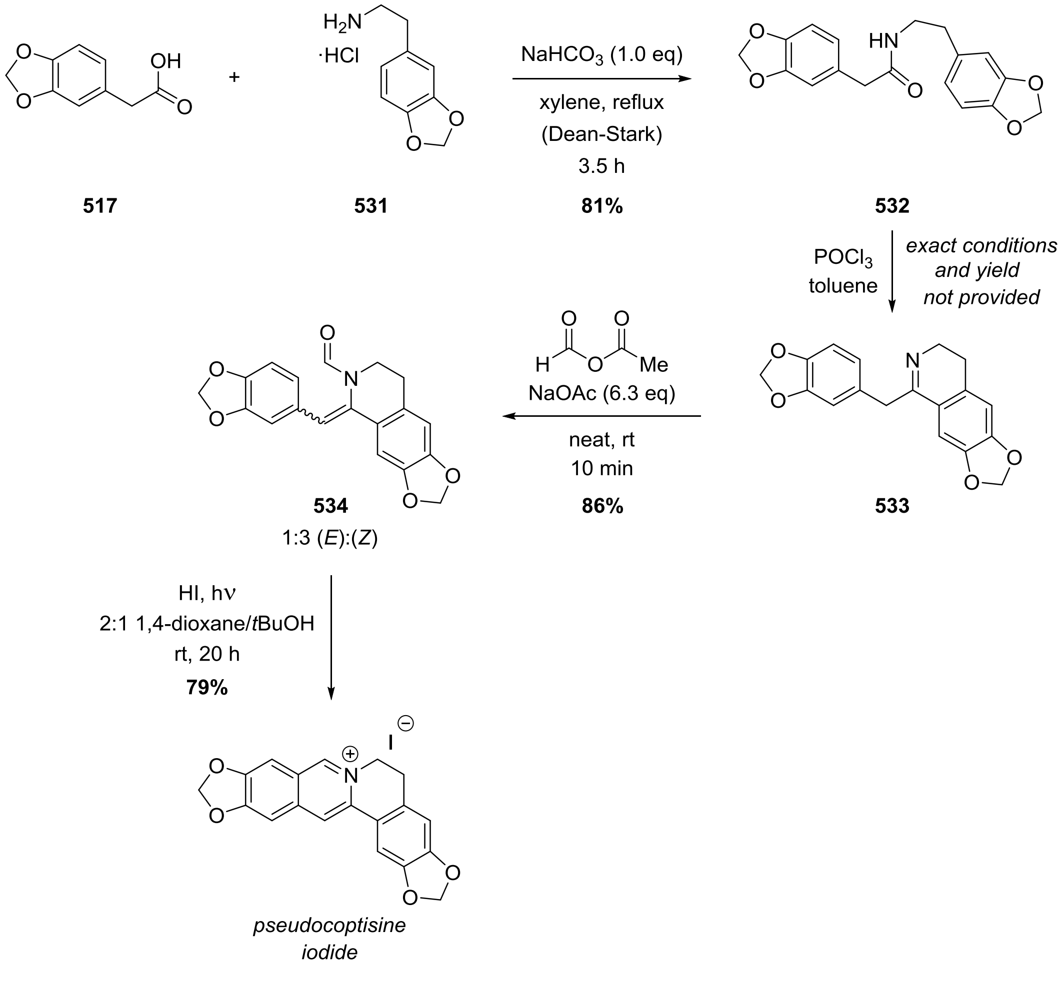


pseudocoptisine

Figure 32. Pseudocoptisine

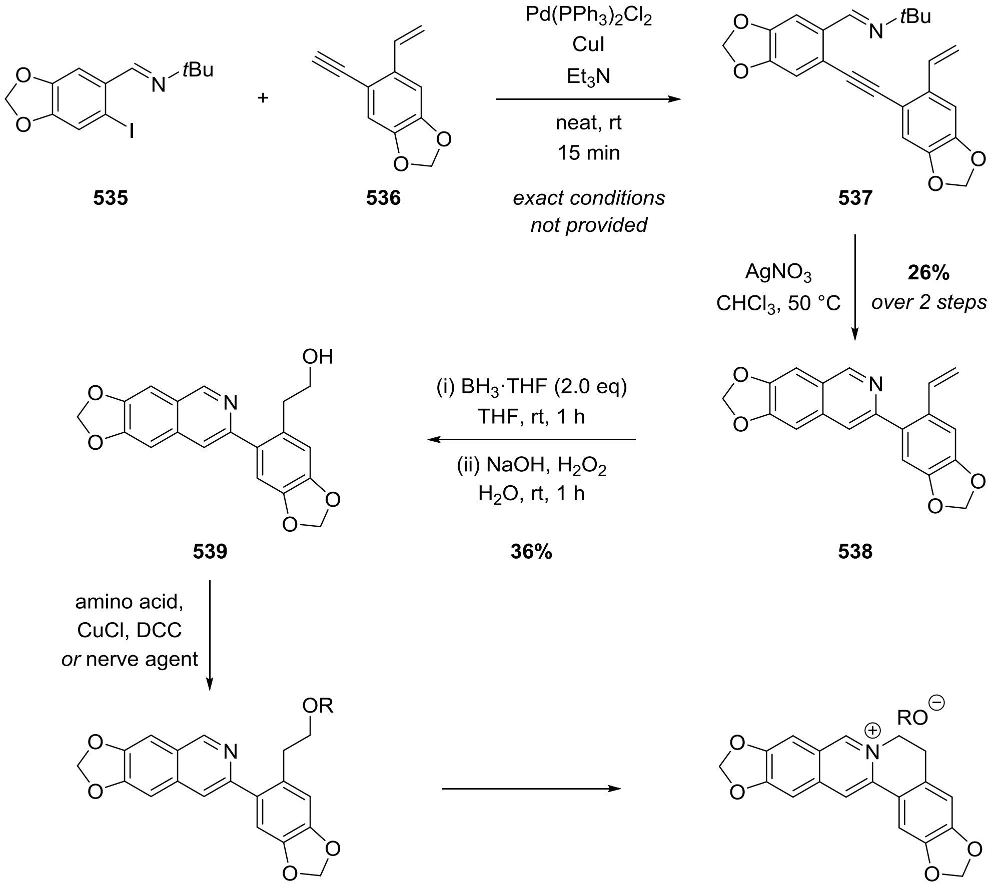
The biological properties of pseudocopitisine are diverse, and include anti-inflammatory activity,[256] and cognitive-enhancing activity stemming from the inhibition of acetylcholinesterase, which may be useful for the treatment of Alzheimer's disease.[257]

A concise synthetic route to pseudocoptisine iodide was reported by Lenz in 1976 (**Scheme 154**).[258] The synthesis commenced with the condensation of phenylacetic acid **517** with amine **531** to afford amide **532**. In a similar manner to Kametani's synthesis of berberine, the Bischler-Napieralski reaction of amide **532**, using $POCl_3$, produced 3,4-dihydroisoquinoline **533**. The reaction of the imine moiety in **533** with preformed mixed acetic formic anhydride in the presence of NaOAc yielded enamide **534** as a mixture of (*E*) and (*Z*) isomers. The mixture was then irradiated in the presence of HI to close the C ring and produce pseudocoptisine iodide in 79% yield.



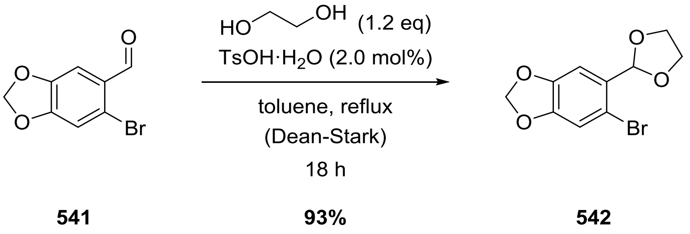
Scheme 154. Lenz's synthesis of pseudocoptisine iodide

In the patent literature, a synthesis of pseudocoptisine was implied by McElhanon and Shepodd, who demonstrated the use of pseudocoptisine precursor **539** as a sensor for chemical and biological warfare agents (**Scheme 155**).[259] The authors coupled aryl iodide **535** and alkyne **536**, whose syntheses were not described, *via* a Sonogashira reaction. The product **537** was then cyclised in the presence of a Lewis acid to form isoquinoline **538** in a low yield over two steps. Hydroboration of the pendant alkene in **538**, followed by oxidation of the intermediate borane, furnished alcohol **539**, which resembles the isoquinoline intermediate in the α-arylation-based route to berberine. The alcohol moiety in **539** was then derivatised either by treatment with a nerve agent, or by coupling with an amino acid, to afford general compound **540**. Measurement of the fluorescence response with time revealed that **540** rapidly cyclised to a pseudocoptisine salt, which exhibited strong fluorescence.



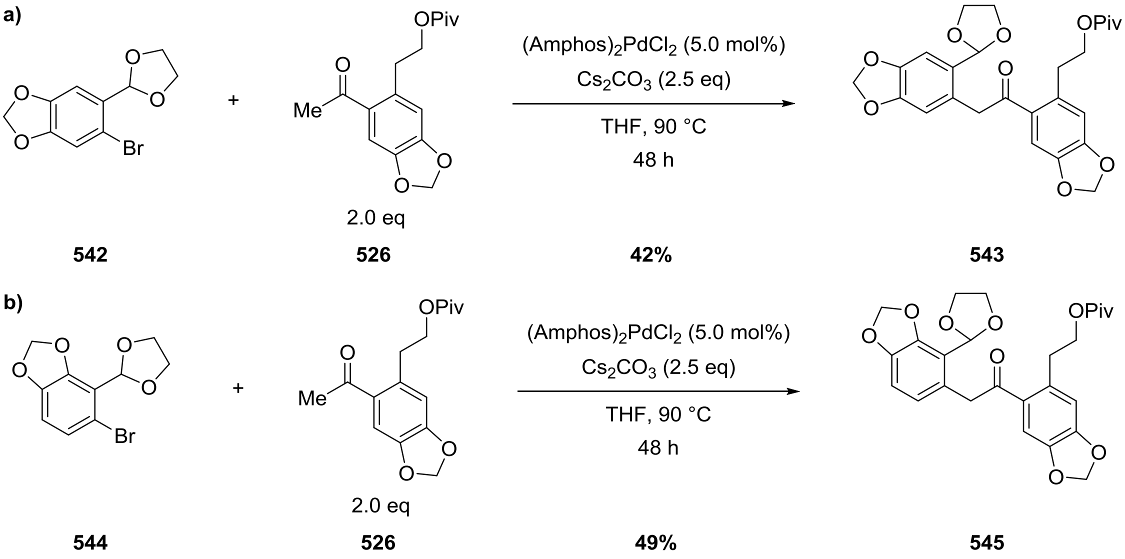
Scheme 155. Pseudocoptisine synthesis for the detection of chemical and biological warfare agents

The requisite ketone coupling partner for the α-arylation-based synthesis of pseudocoptisine was identical to that used in the synthesis of berberine. Therefore, it only remained to synthesise aryl bromide **542** by the acetal protection of commercially available 6-bromo-1,3-benzodioxole-5-carboxaldehyde **541**, which was achieved in 93% yield (**Scheme 156**).



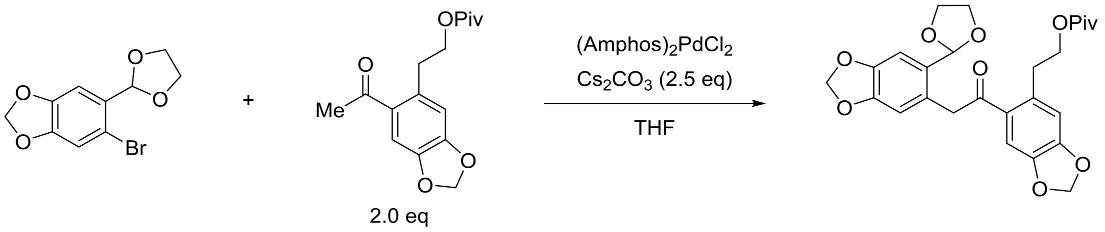
Scheme 156. Synthesis of aryl bromide **542**

When aryl bromide **542** and ketone **526** were subjected to the α-arylation conditions that were employed in the synthesis of berberine, TLC showed a significant amount of unreacted aryl bromide **542** after 24 hours. The reaction was continued for a further 24 hours, after which ketone **543** was obtained in only 42% yield (**Scheme 157a**). To determine the reason for this poor result, aryl bromide **544**, in which the D ring substituents were located at the identical positions to the corresponding berberine precursor, was also employed, and a similar result was obtained (**Scheme 157b**). This suggested that methylenedioxy-containing aryl bromides were less reactive than their methoxy-substituted counterparts.



Scheme 157. Low-yielding α-arylation reactions of aryl bromides **542** and **544**

A control experiment was then performed, in which aryl bromide **542** was subjected to the α-arylation conditions but ketone **526** was absent. After 48 hours at 90 °C, the starting material **542** was recovered in just 78% yield, indicating a degree of decomposition under these conditions, possibly *via* deprotonation of the methylenedioxy moiety. The α-arylation reaction between aryl bromide **542** and ketone **526** was therefore repeated at 70 °C, with no detrimental effect on the yield (**Table 19**, Entry 2). Furthermore, it was discovered that performing the α-arylation reaction for just 24 hours at 90 °C afforded α-aryl ketone **543** in a virtually identical yield to the 48 hour reaction, so it was concluded that the catalyst had become inactive over 24 hours (Entry 3). With these observations in mind, the reaction was conducted at 70 °C to minimise the decomposition of aryl bromide **542**, and a second portion of 5.0 mol% $(Amphos)_2PdCl_2$ was added after 24 hours. Following an additional 24 hours, the product **543** was furnished in 62% yield (Entry 4).



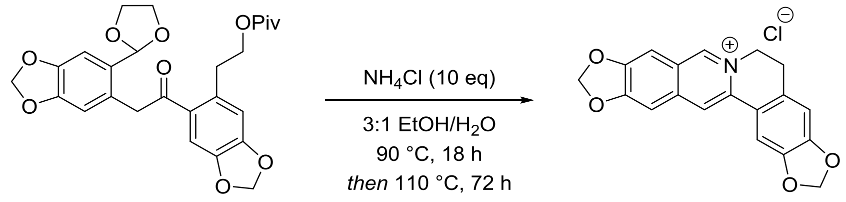
542 **526** **543**

Entry	Catalyst / mol%	Temperature / °C	Time / h	Yield / %
1	5.0	90	48	42
2	5.0	70	48	42
3	5.0	90	24	41
4	2 × 5.0[a]	70	2 × 24	62

Table 19. Optimisation of the α-arylation reaction of ketone **526** with aryl bromide **542**

[a] A second portion of 5.0 mol% $(Amphos)_2PdCl_2$ was added after 24 hours

The α-aryl ketone **543** was then treated with ammonium chloride in 3:1 $EtOH/H_2O$ at 90 °C to effect acetal hydrolysis and isoquinoline formation (**Scheme 158**). After 18 hours, the temperature was elevated to 110 °C to promote the direct displacement of the pivaloate group by the nitrogen atom of the isoquinoline, furnishing pseudocoptisine chloride. The effectiveness of the optimised isolation procedure was demonstrated once again, since the natural product could be obtained as a yellow solid in 79% yield by sequential treatment of the crude residue with NaOH and HCl, whereas trituration with Et_2O and cold H_2O provided pseudocoptisine in only 66% yield.



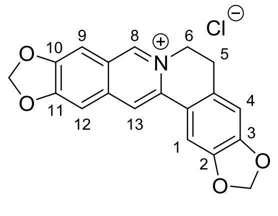
543 **79%** *trituration* 66% *pseudocoptisine chloride*

Scheme 158. Completed synthesis of pseusocoptisine chloride

Thus, pseudocoptisine chloride was synthesised *via* an analogous route to berberine simply by altering the aryl bromide coupling partner. From the limiting starting material, aldehyde **542**, pseudocoptisine was furnished in 46% yield.[255]

Unfortunately, a direct match with literature NMR data could not be made. When pseudocoptisine chloride was isolated from *Corydalis* tuber by Bae and coworkers, a brown powder was obtained, and ^1H and ^{13}C NMR data were recorded in $CDCl_3$.[257] No reference to previously reported data was made by the authors. The material synthesised in this laboratory was yellow in colour, similar to the berberine chloride obtained previously, and was found to be insoluble in $CDCl_3$. In 1977, Moulis and coworkers also commented on the poor solubility of pseudocoptisine in $CHCl_3$, but did not report any alternative characterisation data.[260] When Lee and coworkers isolated pseudocoptisine, it was stated that the alkaloid was identified by comparison with the data reported by Bae, but no spectral data of their own were published.[256] Baek and coworkers claimed to make the same comparison, however the authors measured their own ^1H and ^{13}C NMR spectra in CD_3OD, not $CDCl_3$.[261] Our sample was subsequently characterised in CD_3OD, but the chemical shifts did not match those reported by Baek. This was attributed to a difference in counterion, whose identity was not commented upon by Baek, and which could not be elucidated by examination of the isolation procedure. The authors treated *Corydalis* extract with NaOH to convert the quaternary protoberberine alkaloids to their corresponding hydroxide adducts, which were then chromatographed on SiO_2, with pseudocoptisine eluted using a 3:1 $CHCl_3$/MeOH solvent mixture. Hence, it is unclear when the isoquinolinium salt was regenerated, and what the counterion may be. Lenz and coworkers provided ^{1}H NMR data recorded in deuterated trifluoroacetic acid for their synthetic pseudocoptisine iodide, but did not make reference to previous literature data.[258] The spectra of our synthetic pseudocoptisine chloride were duly measured in deuterated trifluoroacetic acid, somewhat reluctantly due to the solvent's corrisive nature, but the ^{1}H NMR data were found not to match, which was once again attributed to the difference in counterion.

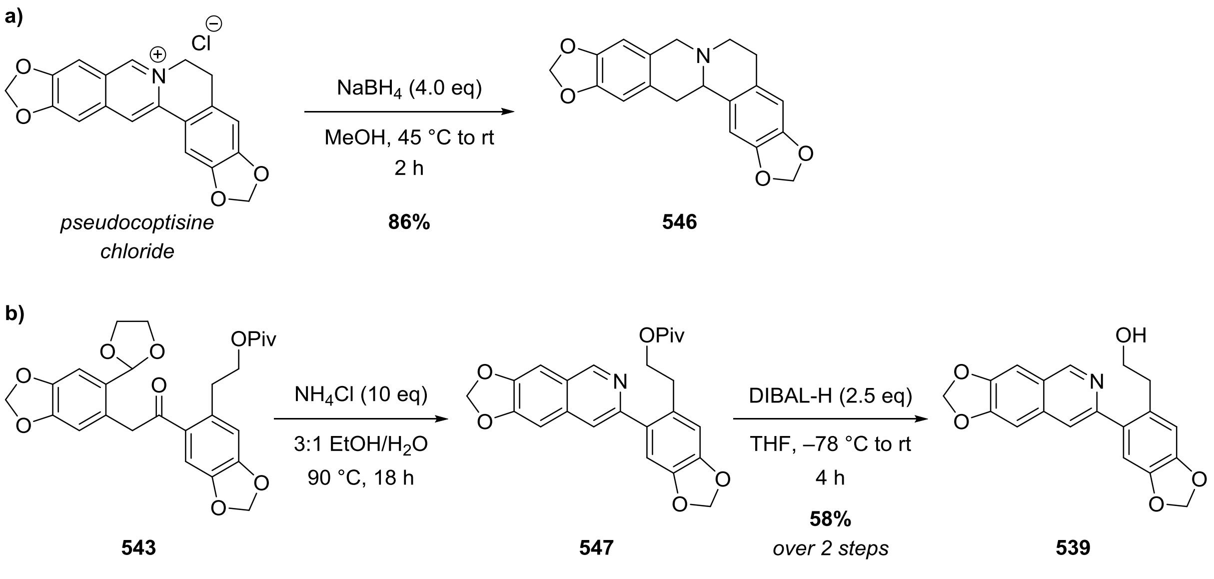
Thus, the pseudocoptisine chloride synthesised herein was characterised independently. ESI$^+$ accurate mass spectrometry gave a mass of 320.0914 for the isoquinolinium cation $[M]^+$, which was in agreement with the calculated monoiostopic mass of 320.0917. In the ^{1}H NMR spectrum measured in DMSO-d_6, the characteristic signal of the C8 proton, adjacent to nitrogen in the isoquinolinium scaffold, was observed at 9.58 ppm. Four singlets at 7.75, 7.72, 7.54 and 7.10 ppm confirmed the substitution pattern of the A and D rings, and the two singlets at 6.42 and 6.17 ppm, which had double the integration, were indicative of the two methylene dioxy CH_2 groups (**Figure 33**). HMBC NMR spectroscopy was used to aid assignment of the spectra.



pseudocoptisine chloride

Figure 33. Structure of pseudocoptisine chloride

Additional proof was obtained by taking inspiration from Moulis, who reduced pseudocoptisine to its tetrahydro derivative.[260,262] Accordingly, the synthetic pseudocoptisine was treated with sodium borohydride in MeOH, furnishing tetrahydropseudocoptisine **546** in 86% yield (**Scheme 159a**). Spectroscopic data for this compound were consistent with those previously reported.[263,262] Furthermore, it was decided to synthesise alcohol **539**, which was a pseudocoptisine presursor in the chemical sensor work of McElhanon and Shepodd (**Scheme 159b**).[259] The α-aryl ketone **543** was cyclised to isoquinoline **547** under standard ammonium chloride conditions and the pivaloate group was reduced by the addition of DIBAL-H solution, affording the corresponding alcohol **539** in 58% yield. ^{1}H and ^{13}C NMR data for isoquinoline **539** were consistent with those previously reported, except for the benzylic CH_2 signal observed at 2.82 ppm in the ^{1}H NMR spectrum.[259] In the published data, the authors erroneously reported a chemical shift of 5.08 ppm for these protons.



Scheme 159. Synthesis of tetrahydropseudocoptisine **546** and pseudocoptisine precursor **539**

Thus, it was concluded that sufficient evidence had been obtained to confirm that the product of the α-arylation-based synthesis possessed the structure shown in **Figure 33**, and was indeed the alkaloid pseudocoptisine chloride.

2.4.7 Palmatine and dehydrocorydaline

Attention then turned to the total synthesis of dehydrocorydaline, which contains the same protoberberine skeleton as the alkaloid palmatine with the addition of a methyl group at C13 (**Figure 34**). Both palmatine and dehydrocorydaline differ from berberine and pseudocoptisine by the replacement of the C2–C3 methylenedioxy group with two methoxy substituents.

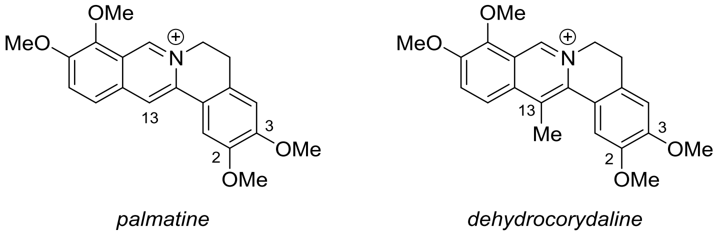
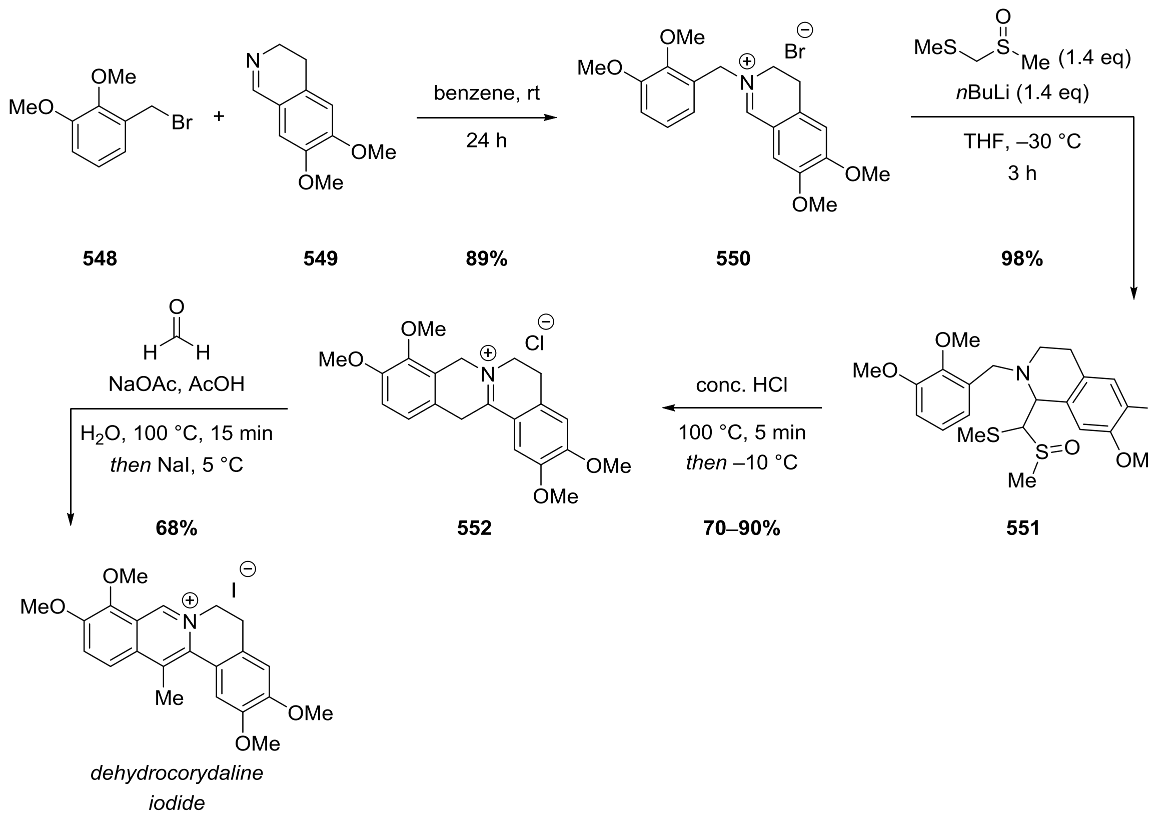


Figure 34. Related alkaloids palmatine and dehydrocorydaline

Like pseudocoptisine, dehydrocorydaline possesses acetylcholinesterase inhibitory activity,[264] as well as insecticidal properties.[265] It has also been shown to suppress the formation of inflammatory cytokines, which may be useful for the treatment of sepsis, autoimmune disorders and inflammatory bowel disease.[266,267]

Several semisyntheses of dehydrocorydaline have been reported, whereby palmatine is methylated,[268,269] along with one total synthesis, which was published by MacLean and coworkers in 1980 (**Scheme 160**).[270] In their work, dihydroisoquinoline **549**, which the authors imply was synthesised *via* a Bischler-Napieralski reaction, was alkylated with benzyl bromide **548** to provide isoquinolinium salt **550**. The anion of methyl methylthiomethylsulfoxide (MMTS) was employed as a one-carbon nucleophile to add to the iminium moiety, affording sulfoxide **551** as a mixture of diastereoisomers. When sulfoxide **551** was treated with concentrated HCl, and then cooled in an ice-salt bath, iminium salt **552** was formed as crystals. The product was heated with formaldehyde and NaOAc in aqueous acetic acid, then treated with NaI, to afford dehydrocorydaline iodide.

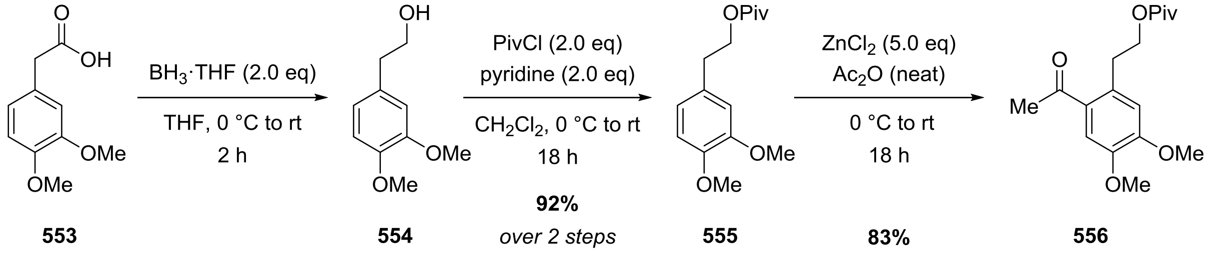


Scheme 160. MacLean's total synthesis of dehydrocorydaline iodide

Despite this relatively short and high yielding synthesis, it was thought that the α-arylation-based route to dehydrocorydaline would be advantageous since MacLean's synthesis relied on two electrophilic aromatic substitution reactions to form the B and C rings, and access to analogues would therefore be restricted to substrates containing electron rich A and D rings. Furthermore, it was anticipated that the application of the α-arylation/*in situ* functionalisation methodology (Chapter 2.2), using iodomethane as the electrophile, would allow the facile introduction of the methyl group at C13. It would also be possible to generate a number of derivatives at this position simply by varying the electrophile quench. The length of the alkyl chain at the C13 position has been shown to influence both antibacterial and fungicidal activities.[271,272]

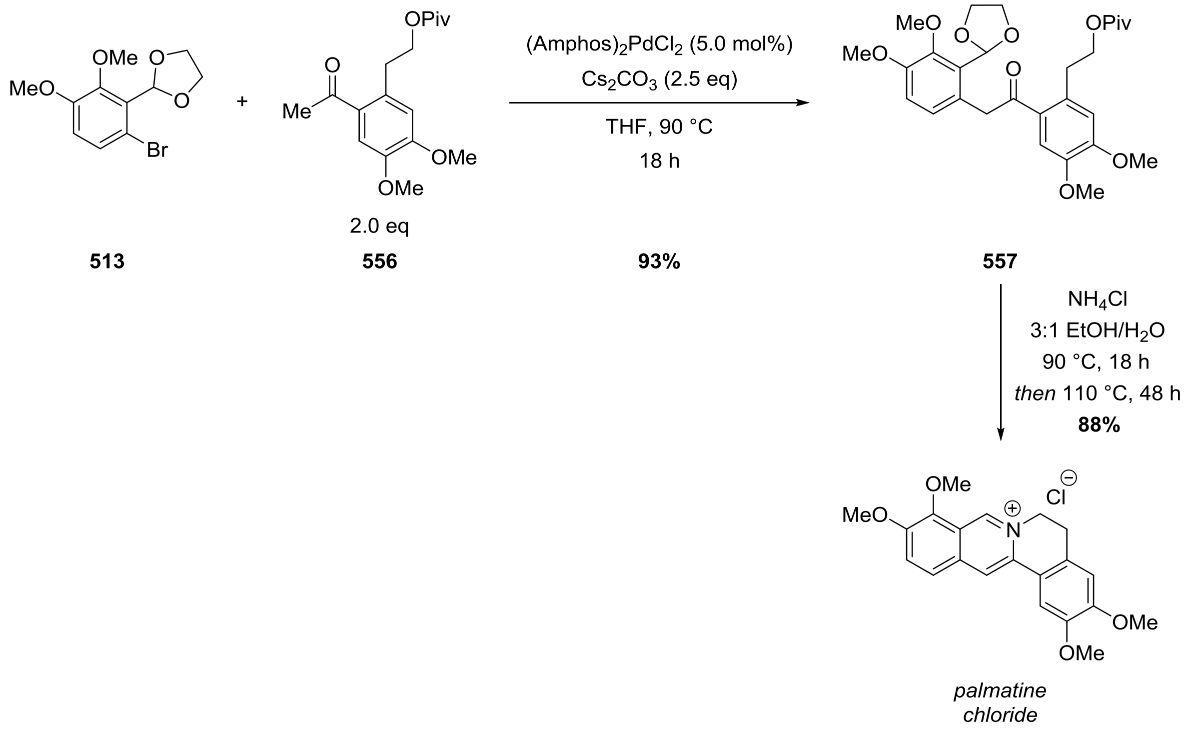
As before, the requisite ketone coupling partner for the α-arylation reaction was synthesised *via* the borane reduction of the corresponding phenylacetic acid **553** to alcohol **554**, followed by treatment with pivaloyl chloride and pyridine to furnish pivaloate **555** in 92% yield

(**Scheme 161**). Friedel-Crafts acylation of **555** using $ZnCl_2$ in neat Ac_2O provided ketone **556** in 83% yield. The regiochemistry of **556** was supported by the presence of two singlets at 7.24 and 6.73 ppm in the ^1H NMR spectrum.



Scheme 161. Synthesis of ketone coupling partner **556**

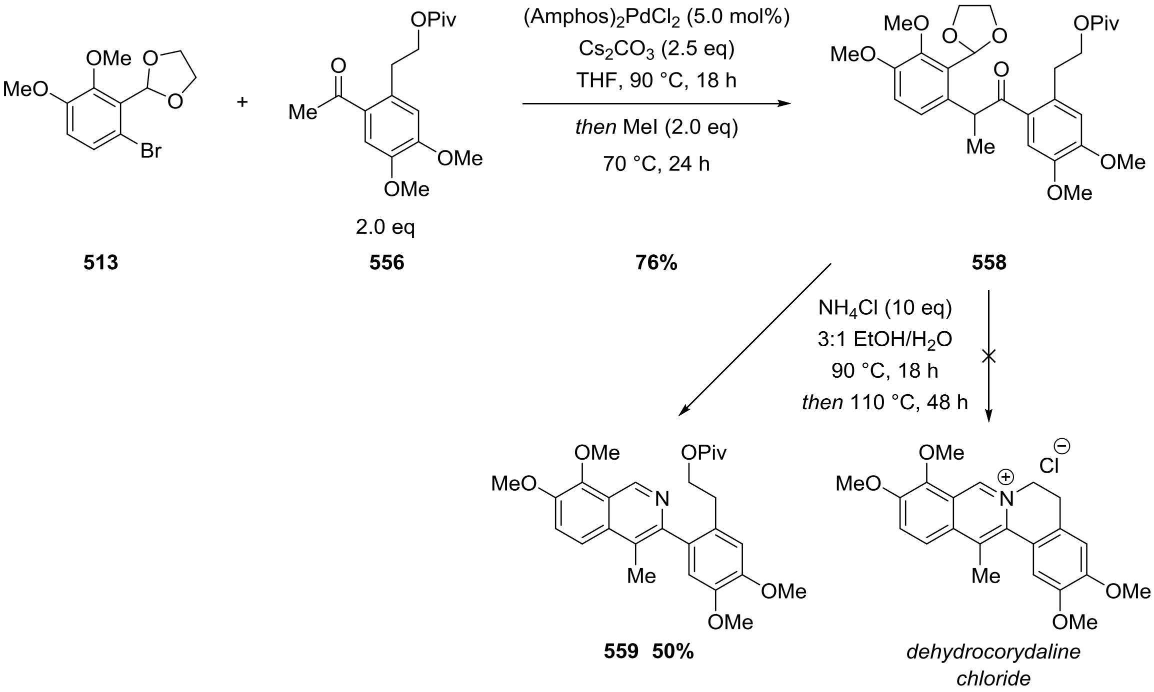
The α-arylation reaction between ketone **556** and aryl bromide **513** was tested prior to its use in the one-pot α-arylation-alkylation protocol (**Scheme 162**). No optimisation was required as the reaction was successful under identical conditions to those used in the synthesis of berberine. α-Aryl ketone **557** was obtained in an excellent yield of 93% and could be efficiently converted into the alkaloid palmatine in 88% yield. ^1H and ^{13}C NMR data for palmatine were consistent with those previously reported.[273]



Scheme 162. Synthesis of palmatine *via* palladium-catalysed α-arylation

Thus, palmatine chloride was synthesised in 73% overall yield from the precursor to aryl bromide **513**, which was the most valuable starting material. Over the longest linear sequence of five steps from carboxylic acid **553**, palmatine was obtained in 62% yield.

Having demonstrated the compatibility of ketone **556** with the α-arylation reaction, the one-pot arylation-alkylation protocol was then implemented (**Scheme 163**). Adding two equivalents of iodomethane after the α-arylation reaction, and heating to 70 °C for a further 24 hours, provided α-methylketone **558** in 76% yield. However, subjecting ketone **558** to the ammonium chloride cyclisation conditions did not facilitate its one-pot conversion to dehydrocorydaline. Instead, isoquinoline **559** was isolated in 50% yield.



Scheme 163. Arylation-methylation of ketone **556** and attempts towards the synthesis of dehydrocorydaline

It was proposed that the presence of the methyl group at C4 in isoquinoline **559**, which would become C13 in dehydrocorydaline, introduced sufficient steric hindrance to restrict rotation about the isoquinoline C3–arene bond and disfavour the near-planar conformation required for closure of the C ring. Indeed, inspection of the ^{1}H NMR spectrum of isoquinoline **559** revealed that the benzylic CH_2 protons adjacent to the A ring were diastereotopic, indicating the presence of chiral rotamers. High temperature ^{1}H NMR spectroscopy was conducted at 90 °C in DMSO-d_6, and it was found that the two CH_2 peaks coalesced at this temperature, confirming that rotation about the C4–aryl bond was indeed hindered (**Figure 35**).

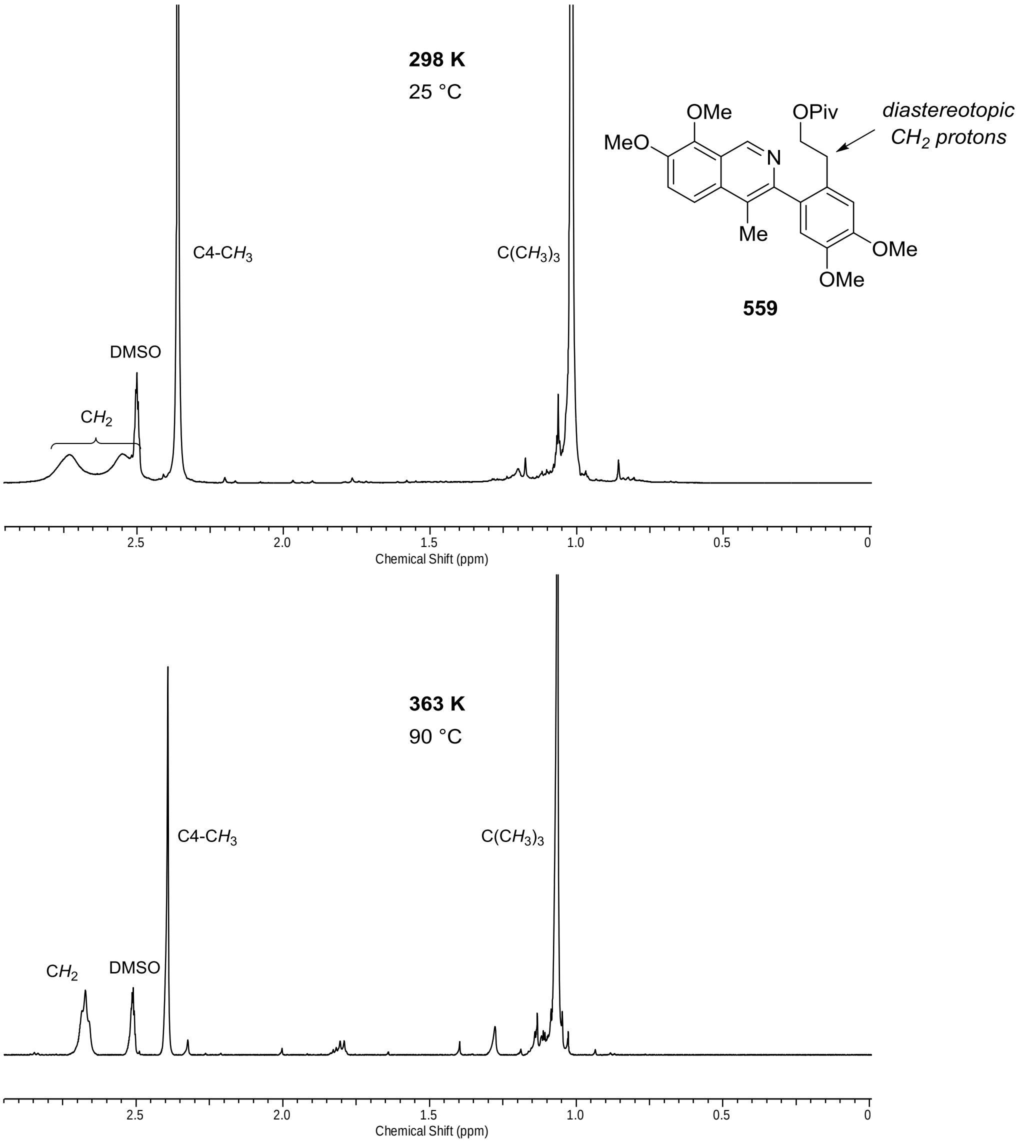
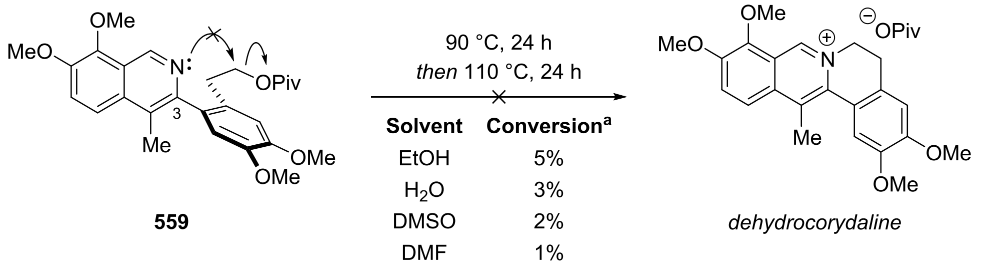


Figure 35. Variable temperature ^{1}H NMR experiments on isoquinoline **559**

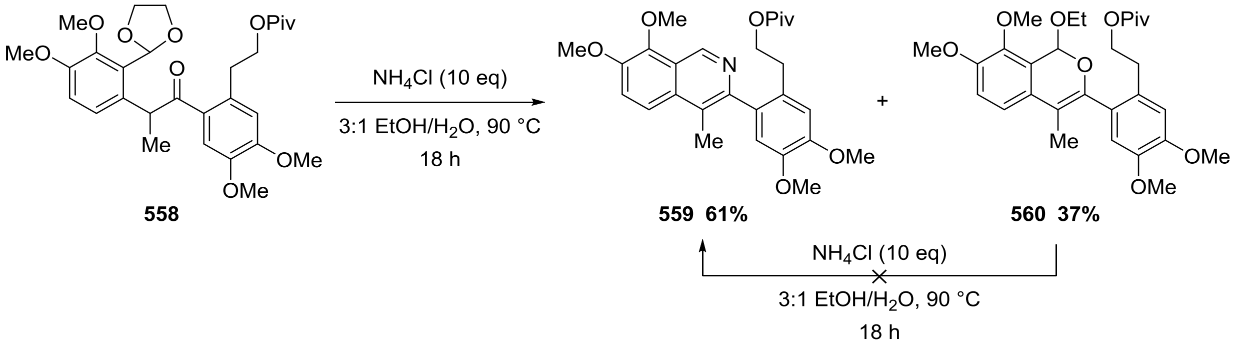
Hence, it was hypothesised that the restricted rotation about the C3–aryl bond, combined with the relatively poor leaving group ability of pivaloate, rendered isoquinoline **559** unreactive towards attempted cyclisation, even at 110 °C. Isoquinoline **559** was subsequently heated in a number of polar solvents, without ammonium chloride to avoid the protonation of nitrogen, but in each case conversions were negligable (**Scheme 164**). Elevating the temperature further was undesirable as isoquinoline **559** began to decompose above 110 °C.



Solvent	Conversion[a]
EtOH	5%
H_2O	3%
DMSO	2%
DMF	1%

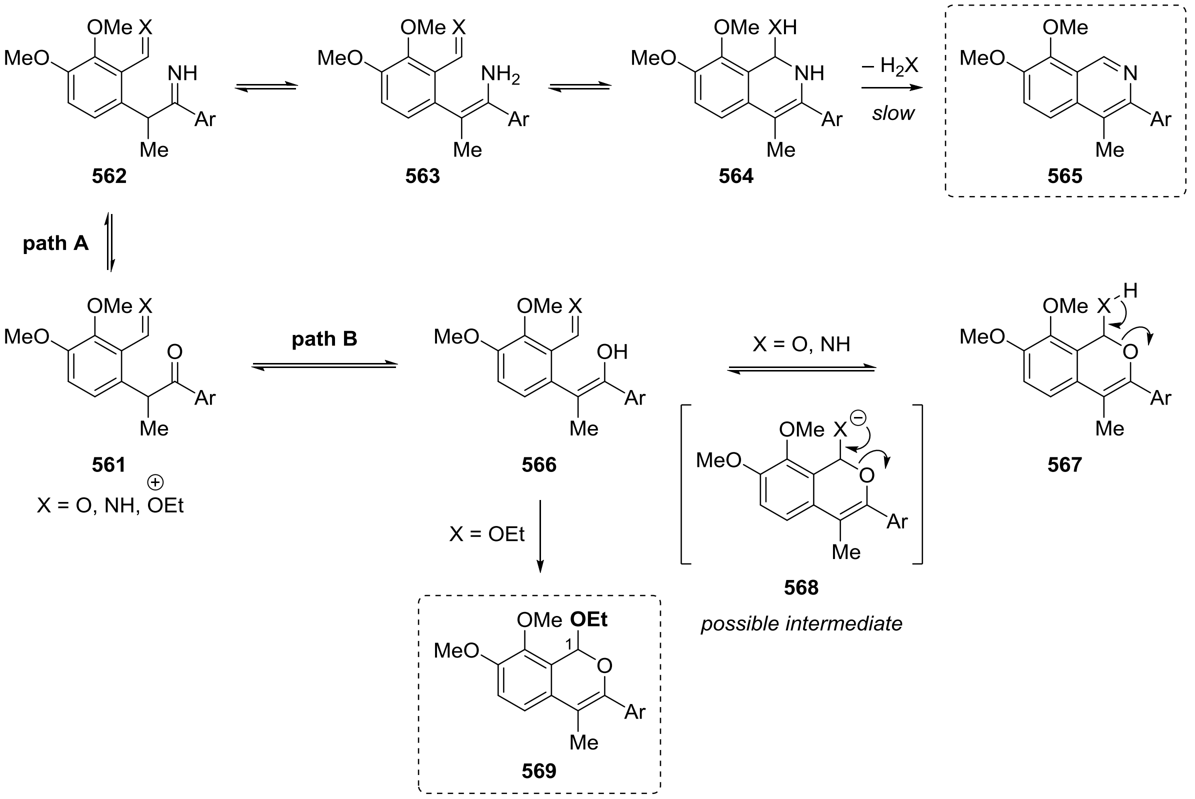
Scheme 164. Torsional strain preventing the cyclisation of isoquinoline **559**
[a] Conversion based on ^{1}H NMR

It was anticipated that replacing the pivaloate moiety with a more effective chloride leaving group would facilitate the closure of the C ring at a lower temperature. With this in mind, ketone **558** was treated with ammonium chloride at 90 °C to obtain isoquinoline **559** (**Scheme 165**). Although the desired isoquinoline **559** could be isolated in 61% yield, an isochromene side product **560** was also obtained in 37% yield. When isochromene **560** was resubjected to the reaction conditions, it was not converted into isoquinoline **559**.



Scheme 165. Formation of isochromene **560** during isoquinoline synthesis

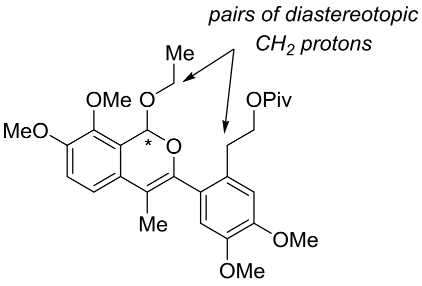
It was proposed that, in the mechanism of formation of isoquinoline **559** from acetal hydrolysis product **561**, the final, irreversible, elimination from species **564** was slower than usual due to the reduced conformational flexibility available in isoquinoline **565**, whose planarity incurs torsional strain about the C3–aryl bond courtesy of the C4 methyl group (**Scheme 166**, path A). Path B depicts a possible mechanism for the formation of isochromene **560**. The cyclisation of enol **566**, rather than enamine **563**, onto the carbonyl derivative C=X gives the analogous acetal **567** or **569**. The inertness of isochromene **569** when resubjected to reaction with ammonium chloride indicates that if X = OEt, hydrolysis of the isochromene does not occur, and its formation is essentially irreversible. Conversely, the analogous oxacycles **567**, where X = OH or NH_2, which were not observed, are formed reversibly. This would suggest that ring opening in the reverse process is promoted by deprotonation of the heteroatom in **567** to give **568**, which is clearly not accessible from **569**. It is therefore hypothesised that the only irreversible steps under these conditions are the isoquinoline-forming elimination from **564**, and the formation of the O–Et isochromene **569** which, although non-aromatic, is less strained than **565** due to the tetrahedral centre at C1. In summary, it appeared that the final isoquinoline-forming elimination from **564** was sufficiently slow to allow the observation of isochromene **569**, whose formation would otherwise be minimised by the rapid consumption of isoquinoline precursor **564** and the resulting shift of the equilibria in favour of **565**.



Scheme 166. Proposed mechanisms for isoquinoline formation (path A) and isochromene formation (path B)

It is acknowledged that alternative mechanisms for the formation of species **567** and **569** may also be in operation. For example, the oxygen atom of either the aldehyde or ketone group in **561** may cyclise onto the other carbonyl derivative without prior enolisation.

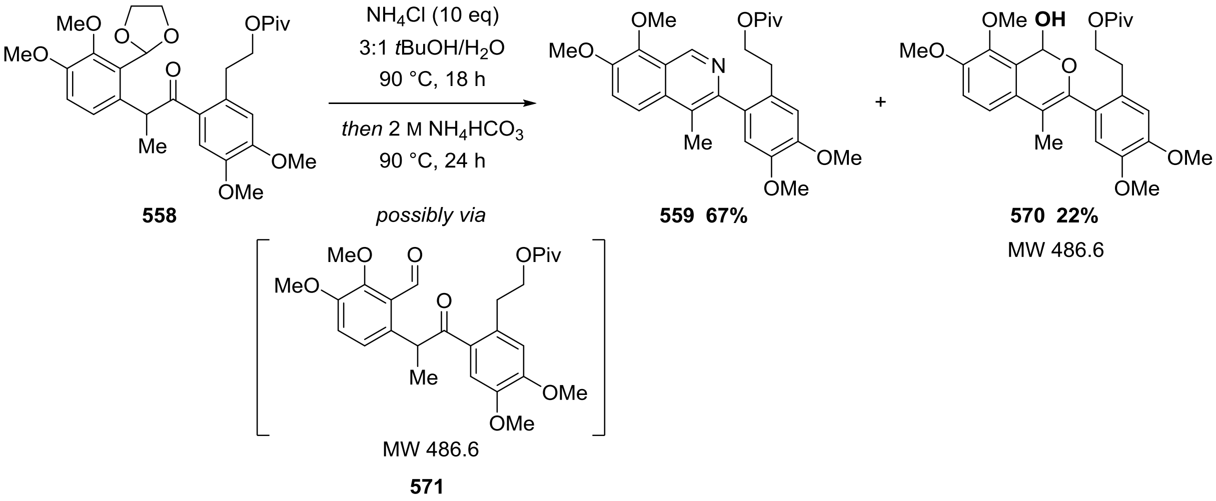
The OCH_2 protons in isochromene **560** are diastereotopic by virtue of the stereogenic centre (*) and gave two distinct signals in the ^1H NMR spectrum (**Figure 36**). In addition, the signal corresponding to the benzylic CH_2 protons on the side chain of the A ring was not a triplet, but a broad multiplet. In order to evaluate whether these NMR features were connected solely by the stereogenic centre (*), or whether **560** also possessed a chiral axis, ^1H NMR spectroscopy was conducted at 90 °C in DMSO-d_6. The broad benzylic CH_2 signal sharpened at higher temperature, suggesting a move from intermediate exchange to fast exchange on the NMR timescale (see Appendix 2). Hence, rotation about the isochromene-arene bond was relatively restricted but, since coalescence had already occurred at room temperature, the barrier to rotation was not as high as in **559**.



560

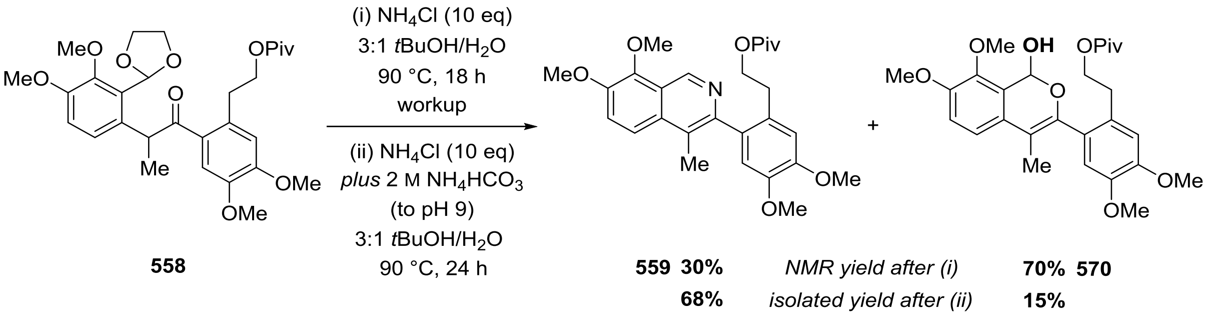
Figure 36. Isochromene **560**

In order to prevent the formation of side product **560**, the isoquinoline synthesis was conducted in aqueous *t*BuOH instead of EtOH, since it was thought that the more hindered alcohol would be less nucleophilic than EtOH (**Scheme 167**). Upon treatment with ammonium chloride, a major spot was observed by TLC which did not display the characteristic isoquinoline fluoresence under UV irradiation. The $[M + Na]^+$ peak at $m/z = 510.3$ in the ESI^+ mass spectrum was consistent with the presence of dicarbonyl compound **571**. Since the reluctance of some unmasked dicarbonyls to cyclise to isoquinolines was known (for example in the synthesis of C1 methyl isoquinolines, Chapter 1.4.3), the reaction mixture was basified to pH 9 by the addition of 2 M ammonium bicarbonate according to the previously successful protocol. After an additional 24 hours at 90 °C, isoquinoline **559** was isolated in 67% yield along with 22% of the previously unobserved O–H isochromene **570**.



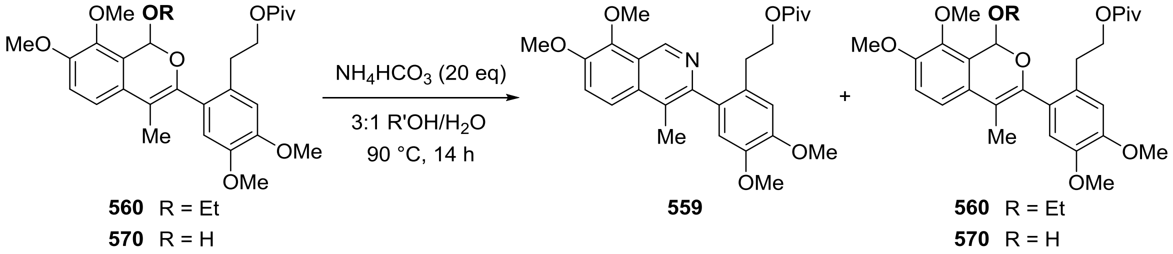
Scheme 167. Isoquinoline formation in *t*BuOH/H_2O instead of EtOH/H_2O

Since 1,5-dicarbonyl **571** and isochromene **570** are isomers, it was recognised that the species formed after treatment with ammonium chloride may have in fact been isochromene **571**. Consequently, the reaction with ammonium chloride was repeated, worked up, and analysed by ^{1}H NMR spectroscopy, and isochromene **570** was indeed the major product of this step (**Scheme 168**). The crude residue was subsequently treated with ammonium bicarbonate as before, affording isoquinoline **559** in 68% yield, and isochromene **570** in 15% yield.



Scheme 168. Formation of isochromene **570** and its conversion to isoquinoline **559**

Hence, it was evident that isochromene **570** was converted into isoquinoline **559** under basic conditions, which supported the hypothesis that ring opening was promoted by deprotonation of the hydroxyl group in **570** (**Scheme 166**). Attention therefore turned to the optimisation of conditions for this transformation. To this end, pure isochromenes **560** and **570** were treated with ammonium bicarbonate in EtOH/H_2O or *t*BuOH/H_2O solvent mixtures at 90 °C for 14 hours (**Table 20**). The O–Et isochromene **560** gave only 24% conversion to isoquinoline **559** in aqueous EtOH (Entry 1), and virtually no isoquinoline was formed in aqueous *t*BuOH (Entry 2). In the latter case, however, O–Et isochromene **560** was partially converted into O–H isochromene **570**. Since base-catalysed acetal hydrolysis is unusual, it is possible that cleavage of the O–Et isochromene **560** occurred *via* an S_N2 reaction at the ethyl CH_2 centre, generating anion **568** (**Scheme 166**) which could undergo ring opening as previously suggested. The analogous O–H isochromene **570** gave 42% conversion to isoquinoline **559** in EtOH, and was also partially converted to the O–Et isochromene **560** in this solvent (Entry 3). Once again, very little starting material was consumed in *t*BuOH/H_2O (Entry 4).

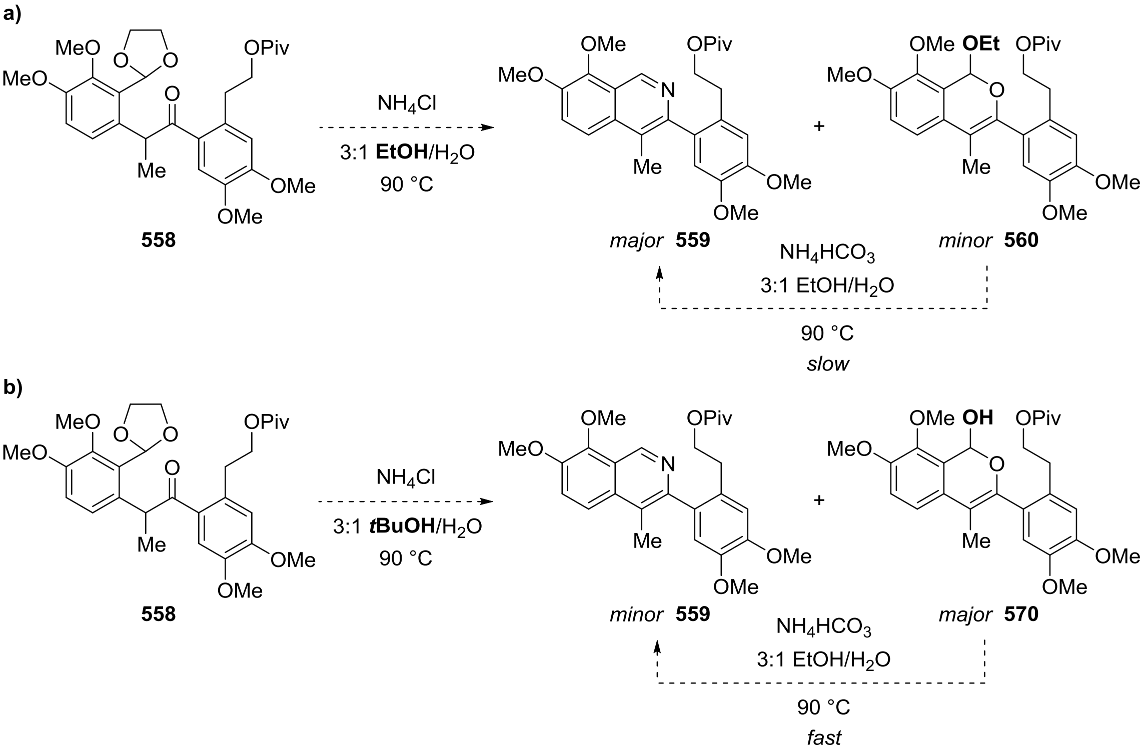


Entry	Starting material, R	Solvent R'OH	560 : 570: 559[a]
1	**560**, Et	EtOH	76 : 0 : 24
2	**560**, Et	*t*BuOH	71 : 27 : 2
3	**570**, H	EtOH	44 : 14 : 42
4	**570**, H	*t*BuOH	0 : 92 : 8

Table 20. Interconversion of isochromenes **560** and **570** and isoquinoline **559**
[a] Ratio based on ^1H NMR

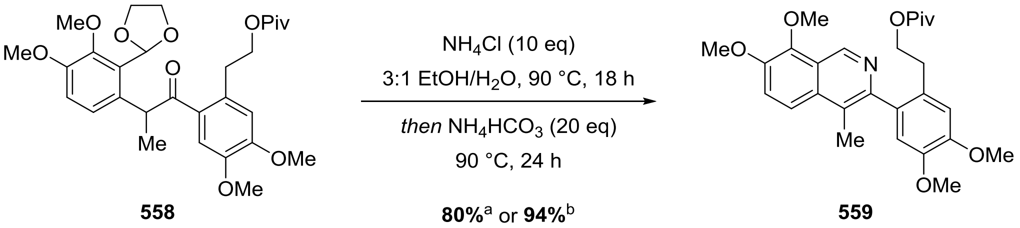
It was therefore concluded that EtOH was a better co-solvent than *t*BuOH for the ammonium bicarbonate-mediated transformation of the isochromenes into isoquinoline **559**. In addition, O–H isochromene **570** underwent faster conversion than the corresponding O–Et species **560**.

Therefore, two possible sets of conditions emerged for the efficient synthesis of isoquinoline **559** from α-aryl ketone **558**. The initial ammonium chloride-mediated reaction could be conducted in aqueous EtOH, giving a mixture of **559** and **560**, of which isoquinoline **559** would be the major component (**Scheme 169a**). The reaction could then be basified with ammonium bicarbonate to convert the O–Et isochromene **560** into isoquinoline **559**. Alternatively, ketone **558** could be treated with ammonium chloride in aqueous *t*BuOH rather than EtOH, giving mostly O–H isochromene **570**, which was known to undergo faster conversion to isoquinoline **559** compared to the O–Et analogue **560** (**Scheme 169b**). In this case, solvent exchange to EtOH/H_2O would be required prior to basification.



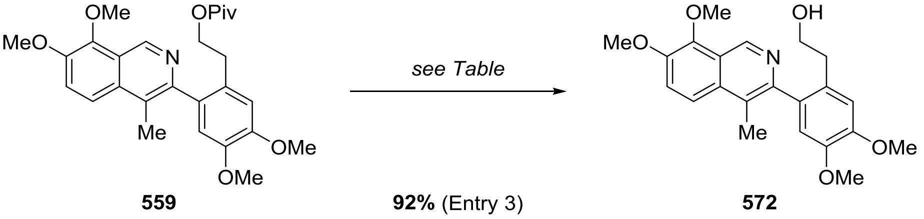
Scheme 169. Proposed conditions for the synthesis of isoquinoline **559** from ketone **558**

The former approach was implemented by treating ketone **558** with ammonium chloride in 3:1 EtOH/H_2O for 18 hours at 90 °C, then cooling to room temperature before the addition of solid ammonium bicarbonate (**Scheme 170**). After a further 24 hours at 90 °C, the reaction was worked up and ^{1}H NMR analysis of the crude residue showed complete conversion of **558** to isoquinoline **559**. Isoquinoline **559** was subsequently isolated in 80% yield, which increased to 94% yield when conducted on a larger scale. In light of this excellent result, it was deemed unnecessary to attempt the procedure described in **Scheme 169b**.



Scheme 170. Cyclisation of α-aryl ketone **558** to C4-methyl isoquinoline **559**
[a] 53 mg **558**; [b] 108 mg **558**

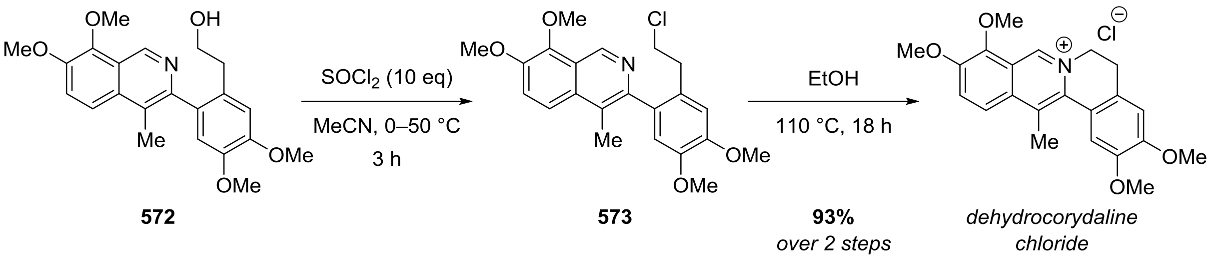
With isoquinoline **559** afforded in good yield, the synthesis continued with the cleavage of the pivaloyl ester. Refluxing pivaloate **559** with KOH in 1:1 THF/H_2O resulted in only 59% conversion after three days (**Table 21**, Entry 1). Alcohol **572** was isolated in 63% yield by treating **559** with TsOH·H_2O for 24 hours (Entry 2), but the reductive removal of the ester with DIBAL-H furnished alcohol **572** in 92% yield after four hours at −78 °C (Entry 3).



Entry	Reagent		Solvent	Temperature / °C	Time	Yield / %
1	KOH	(3.0 eq)	1:1 THF/H_2O	110	3 d	59[a]
2	TsOH·H_2O	(2.0 eq)	1:1 THF/H_2O	110	24 h	63
3	DIBAL-H	(2.5 eq)	THF	−78	4 h	92

Table 21. Deprotection of pivaloate **559**
[a] Conversion based on ^{1}H NMR

With alcohol **572** in hand, its transformation to a more effective leaving group was required prior to the closure of the B ring. A solution of alcohol **572** and thionyl chloride in acetonitrile was heated at 50 °C for three hours, after which TLC analysis indicated complete conversion to a less polar compound, i.e. the chloride (**Scheme 171**).[176] The solvent and excess thionyl chloride were removed *in vacuo* before the product was heated at 110 °C in EtOH for 18 hours to afford dehydrocorydaline chloride in 93% yield.



Scheme 171. Final cyclisation step in the synthesis of dehydrocorydaline chloride

Single crystal X-ray diffraction confirmed the structure of dehydrocorydaline (**Figure 37**).

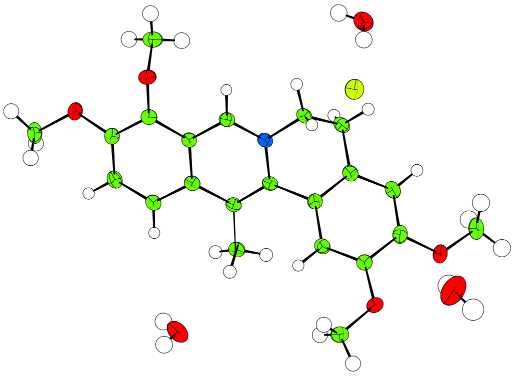


Figure 37. Representation of crystal structure of dehydrocorydaline chloride

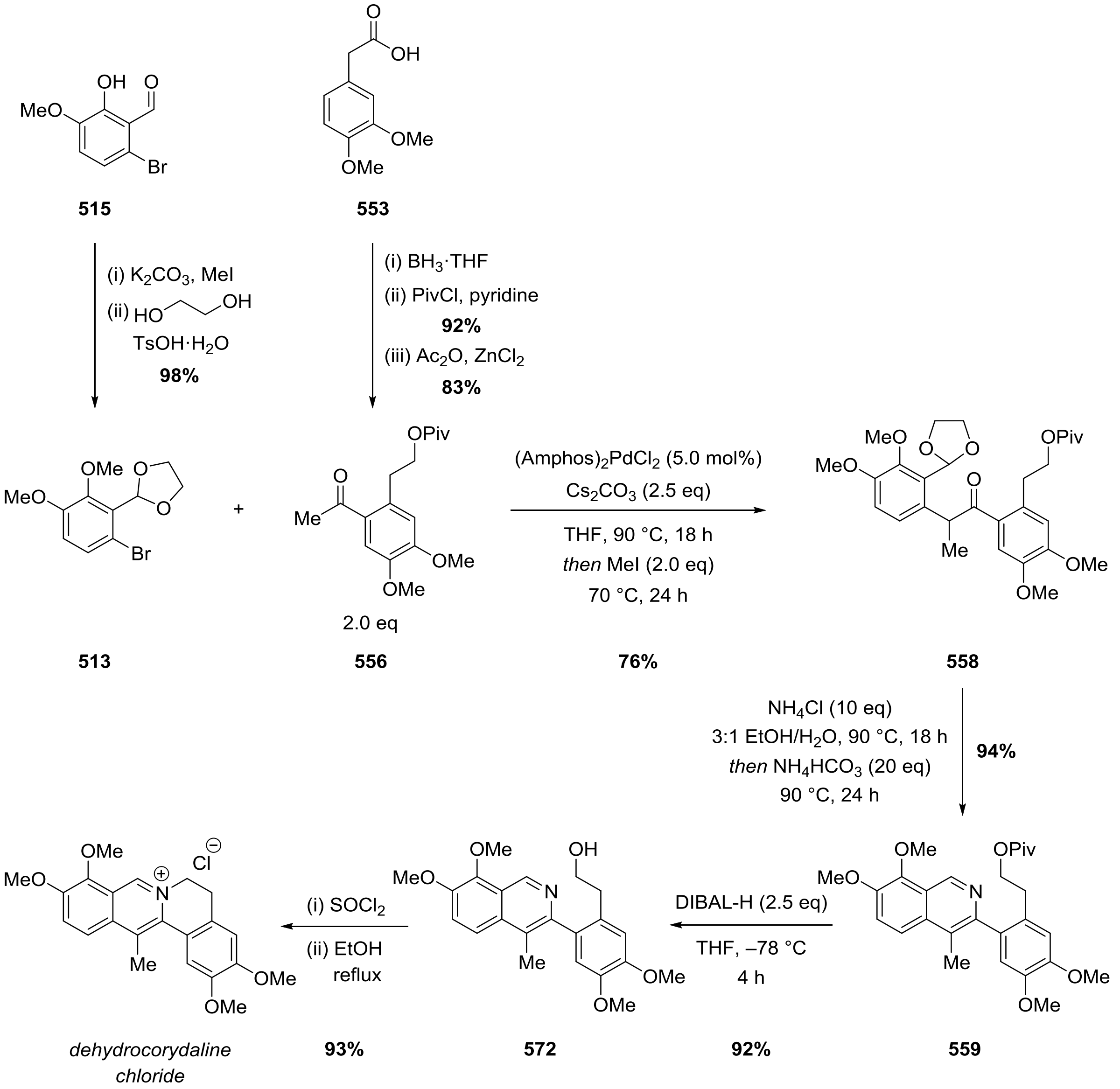
In addition, the ^{1}H and ^{13}C NMR data for dehydrocorydaline chloride were consistent with those previously reported.[274,275] It was noted that the literature ^{1}H NMR data, recorded in DMSO-d$_6$, differed between the chloride and iodide salts, which supported the hypothesis that a difference in counterion was responsible for the inability to match the spectral data of pseudocoptisine chloride in Chapter 2.4.6 (**Table 22**).

δ_H (DMSO-d$_6$) / ppm

Atom	Observed (Cl$^-$)	Δ	Lit. (Cl$^-$)[274]	Δ	Lit. (I$^-$)[265]
1	7.39	0.00	7.39	0.17	7.56
4	7.18	0.00	7.18	−0.12	7.06
5	3.14	0.02	3.16	0.04	3.20
6	4.85	0.03	4.88	0.06	4.94
8	9.91	0.02	9.93	−0.11	9.82
11	8.22	−0.02	8.20	−0.15	8.05
12	8.19	0.01	8.20	−0.03	8.17
2-OCH$_3$	3.85	0.01	3.86	0.05	3.91
3-OCH$_3$	3.89	0.01	3.90	0.17	4.07
9-OCH$_3$	4.10	0.01	4.11	0.01	4.12
10-OCH$_3$	4.09	0.01	4.10	0.02	4.12
13-CH$_3$	2.98	0.01	2.99	−0.49	2.50

Table 22. Comparison of ^{1}H NMR chemical shifts of dehydrocorydaline chloride and iodide salts

Hence, the total synthesis of dehydrocorydaline chloride was achieved *via* the route depicted in **Scheme 172**, in an overall yield of 60% with respect to the limiting aryl bromide starting material **515**, or 47% over the longest linear sequence from acid **553**.[255]

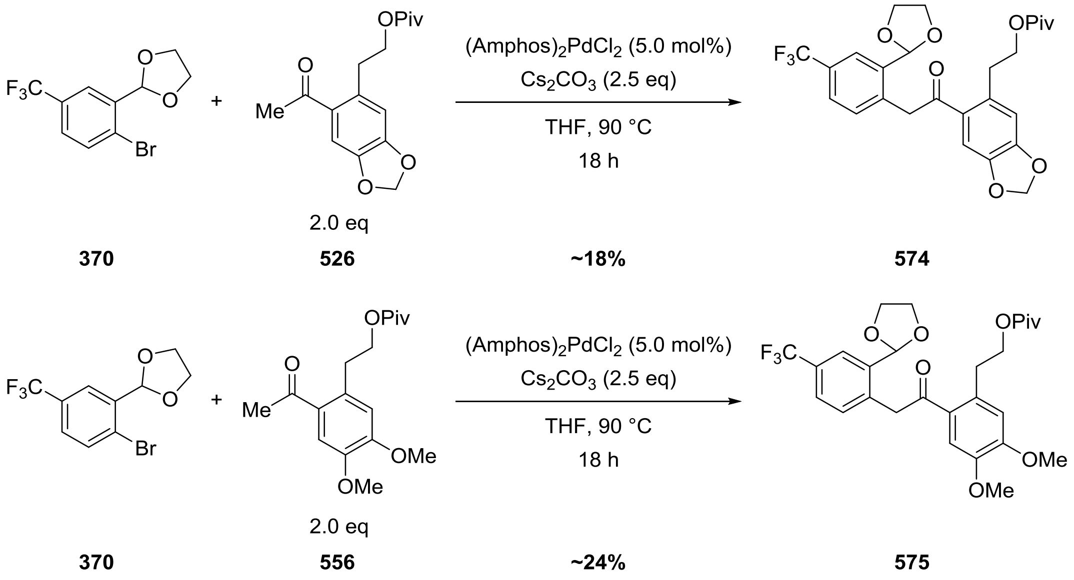


Scheme 172. Total synthesis of dehydrocorydaline chloride *via* α-arylation

The synthesis compares favourably with MacLean's route, which provided the natural product in 53% yield from a commercially unavailable dihydroisoquinoline.[270] Furthermore, the application of the *in situ* α-arylation-alkylation methodology presents the opportunity to rapidly introduce varied functionality at the C13 position, although this strategy was not explored further in the current study.

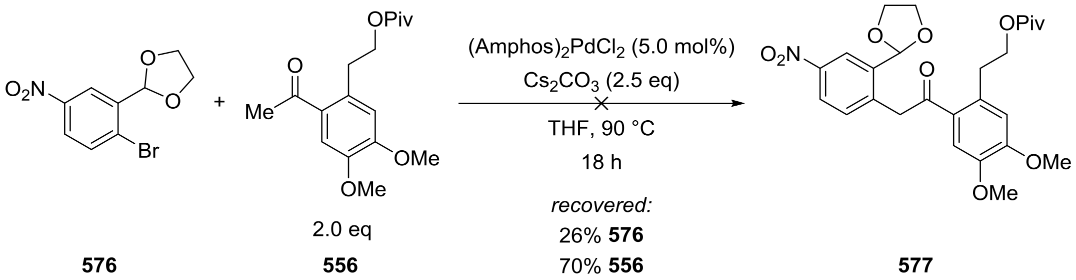
2.4.8 The synthesis of unnatural protoberberine analogues

Finally, the scope of the synthetic route was tested by the attempted preparation of unnatural protoberberine analogues. The ability to access such derivatives, with tunable electronic and steric properties, particularly those that do not contain solely electron rich aromatic rings, is potentially important from a medicinal chemistry perspective. As such, trifluoromethyl-containing aryl bromide **370** was subjected to the α-arylation reaction with ketones **526** and **556** (**Scheme 173**). In both cases, around half of the aryl bromide starting material did not react, and the products **574** and **575** were formed in approximately 20% yield. Isolation of the pure α-aryl ketones was not possible as they decomposed upon repeated chromatography.



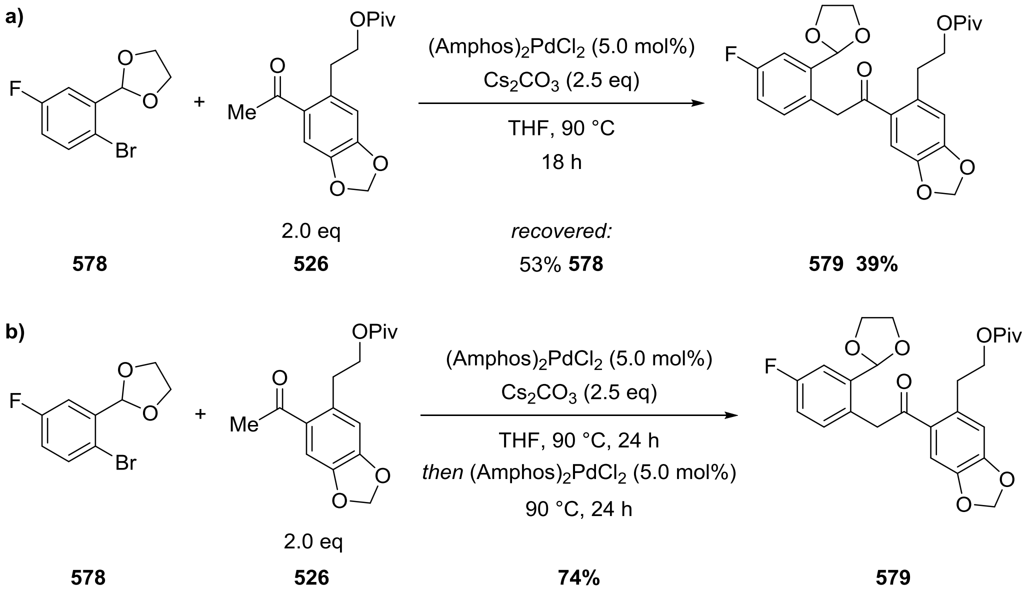
Scheme 173. Attempted couplings of trifluoromethyl aryl bromide **370**

The nitro-containing aryl bromide **576** was employed next, as it had previously been found to survive the first generation isoquinoline synthesis (Chapter 1.4.4)[175] (**Scheme 174**). Unusually, the reaction mixture took on a deep purple colour, and it was discovered that in this more complex α-arylation system, both the starting material **576** and product **577**, if formed, decomposed under the reaction conditions. The aryl bromide **576** was recovered in only 26% yield, and 1.4 equivalents, or 70%, of ketone **556** was returned.



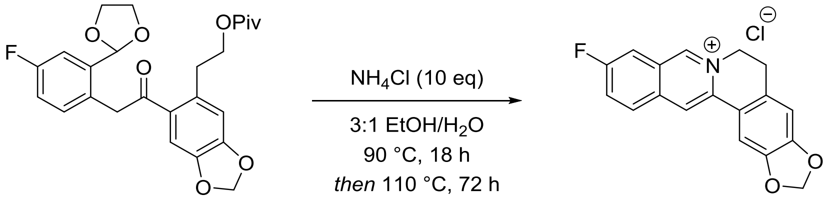
Scheme 174. Attempted coupling of nitro-containing aryl bromide **576**

It was concluded that highly electron deficient aryl bromides were unsuited to this procedure, possibly due to the susceptibility of electron deficient species to nucleophilic attack at the elevated temperature of 90 °C, and/or in the presence of the electron rich ketone enolate **526**. Consequently, it was decided to employ aryl bromide **578**, which is considered electron neutral, but contains a medicinally significant fluorine atom (**Scheme 175a**). When **578** and ketone **526** were coupled using 5.0 mol% (Amphos)$_2$PdCl$_2$ and 2.5 equivalents of Cs$_2$CO$_3$ at 90 °C, the product **579** was obtained in 39% yield.



Scheme 175. α-Arylation of fluorine-containing aryl bromide **578**

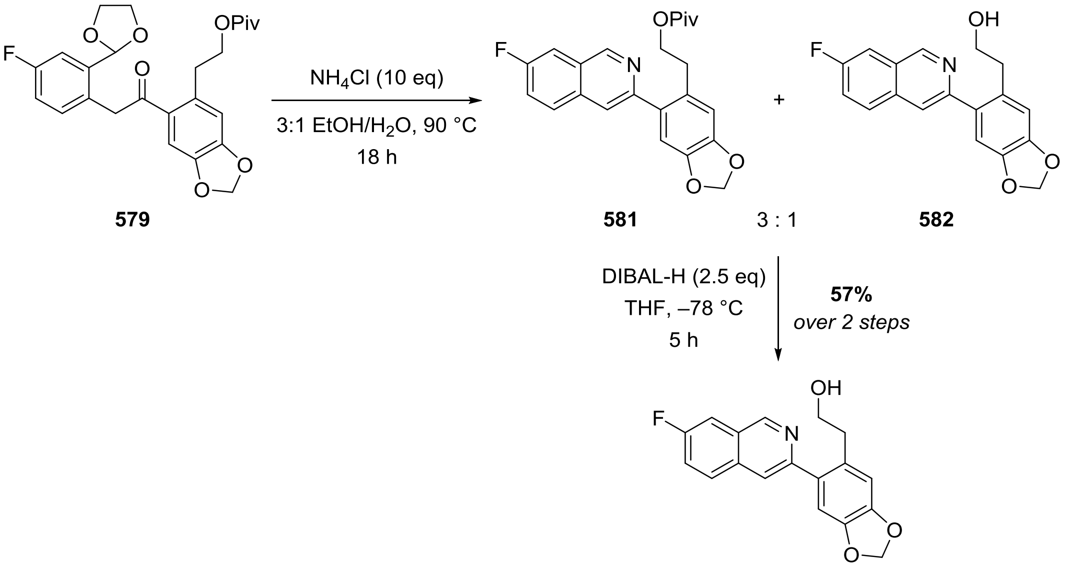
Unreacted aryl bromide **578** was recovered from the reaction mixture in 53% yield. The reaction was therefore repeated, and a second portion of 5.0 mol% catalyst was added before the mixture was heated at 90 °C for a further 24 hours, in a similar manner to the synthesis of pseudocoptisine (**Scheme 175b**). Greater conversion was achieved under these conditions, and the α-aryl ketone **579** was furnished in 74% yield. The product **579** was then treated with ammonium chloride according to the protoberberine-forming protocol, providing an impure yellow-green precipitate that contained the isoquinolinium salt **580** (**Scheme 176**).



579 *impure* **580**

Scheme 176. Observed formation of protoberberine analogue **580** under standard cyclisation conditions

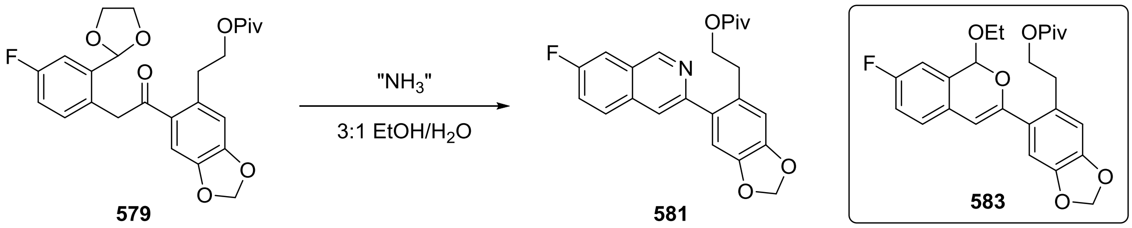
Due to the difficulty of isolating **580** from the impurities, it was decided to separate the two steps *en route* to the protoberberine derivative **580** from ketone **579**. When ketone **579** was heated with ammonium chloride at 90 °C for 18 hours, a 3:1 mixture of isoquinoline **581** and the deprotected equivalent **582** was generated (**Scheme 177**). The mixture was then treated with DIBAL-H to reduce the remaining pivaloate to alcohol **582**, which was isolated in 57% yield.



582

Scheme 177. Synthesis of isoquinoline **582** from α-aryl ketone **579**

Since the DIBAL-H mediated reduction of pivaloyl esters was very high yielding in previous examples, it was believed that the initial isoquinoline-forming reaction was responsible for the moderate overall yield, which may have been a result of the partial decomposition of **579** or **581**, presumably *via* nucleophilic aromatic substitution. Therefore, the reaction with ammonium chloride was repeated at 70 °C instead of 90 °C (**Table 23**, Entry 1). It was anticipated that acetal hydrolysis would still occur at this temperature as the D ring was not strongly electron donating. Indeed, ketone **579** was completely consumed and isoquinoline **581** was formed after 24 h, but several additional products were visible by TLC. The desired product **581** was isolated in 62% yield.

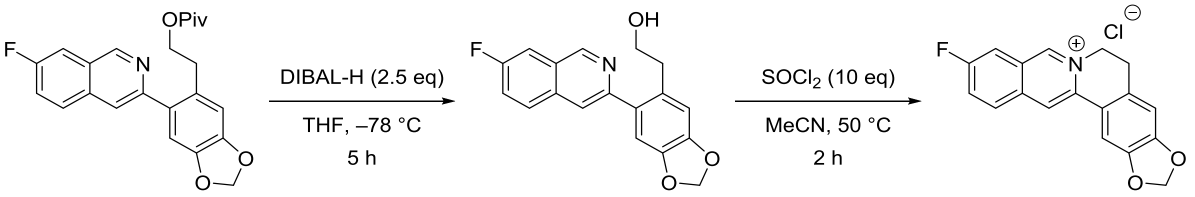


Entry		"NH$_3$"		Conditions	Yield / %	
1		NH_4Cl	(10 eq)	70 °C, 24 h	62	
2	a	NH_4Cl	(10 eq)	60 °C, 24 h		
	b	*then* NH_4HCO_3	(20 eq)	60 °C, 24 h	54	+ 27% **583**
3	a	NH_4Cl	(10 eq)	60 °C, 24 h		
	b	*then* NH_4HCO_3	(20 eq)	90 °C, 24 h	64	+ trace **583**

Table 23. Cyclisation of ketone **579** to isoquinoline **581**

When ketone **579** was heated with ammonium chloride at 60 °C, a cleaner reaction occurred, and isoquinoline **581** was formed along with another major product, postulated to be the diketone formed by acetal cleavage (Entry 2a). Ammonium bicarbonate was added to promote the cyclisation at the reduced temperature of 60 °C, affording isoquinoline in 54% yield (Entry 2b). Owing to the cleaner reaction, a major side product, isochromene **583**, could be isolated in 27% yield. This isochromene could be partially converted into isoquinoline **581**, which was furnished in 64% yield, by increasing the reaction temperature to 90 °C upon the addition of ammonium bicarbonate (Entry 3b). Hence, it appeared that the success of the isoquinoline-forming reaction was limited by the temperature that could be employed, which controlled the balance between the conversion of isochromene **583** into isoquinoline **581**, and the occurrence of undesired side reactions.

With pivaloate-containing isoquinoline **581** in hand, the primary alcohol **582** could be obtained by deprotection with DIBAL-H in 95% yield (**Scheme 178**), and in 61% yield over two steps from **579**. This result was only a marginal improvement on the previous yield of 57% (**Scheme 177**). Upon reaction with thionyl chloride in acetonitrile at 50 °C, alcohol **582** was converted into the corresponding chloride, which cyclised to the isoquinolinium salt *in situ* without the need for solvent exchange and elevation of temperature, providing the fluorine-containing protoberberine analogue **580** in 82% yield (**Scheme 178**).



581 **95%** **582** **82%** **580**

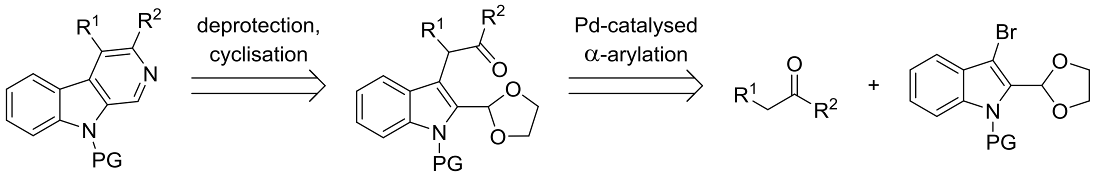
Scheme 178. Completion of the synthesis of analogue **580**

The synthesis of analogue **580** concluded the study into the application of the palladium-catalysed enolate arylation reaction in the synthesis of isoquinoline-containing alkaloids. Berberine chloride had been synthesised *via* a five step route (the longest linear sequence) in 68% yield from the limiting aryl bromide starting material **513**. By substitution of the aryl bromide and ketone coupling partners, analogous syntheses of pseudocoptisine and palmatine (in 46% and 73% yield, respectively) and of the unnatural fluorine-containing analogue **580** (in 38% yield) were achieved. Enolate arylation was combined with *in situ* methylation to derivatise the alkaloid C13 position, resulting in the total synthesis of dehydrocorydaline in 60% yield.[255]

2.5 Palladium-catalysed α-arylation in the synthesis of β-carbolines

2.5.1 Synthetic routes to β-carbolines

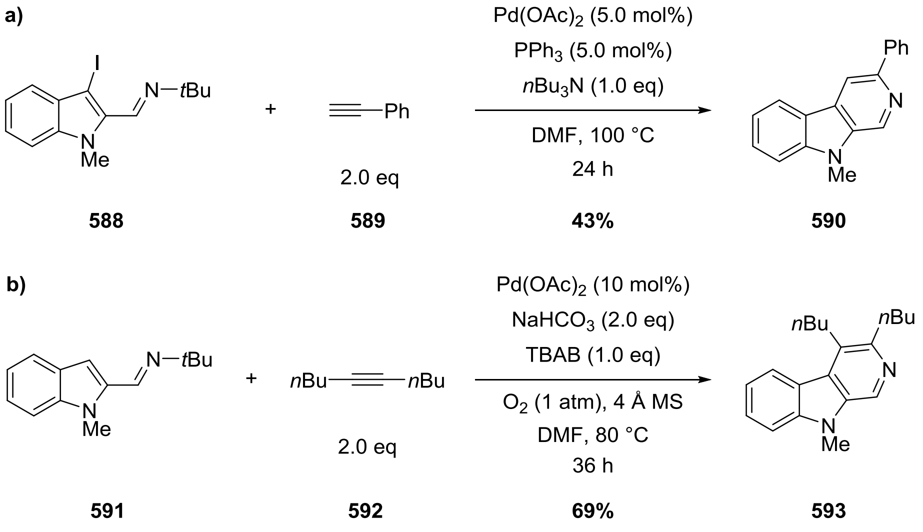
With the isoquinoline synthesis methodology well developed, it was considered how else the relatively under-exploited enolate arylation reaction might find use in the synthesis of aromatic heterocycles. It was realised that if the benzenoid aryl bromide was replaced with a 3-bromoindole **587**, the palladium-catalysed α-arylation of ketone **586** would eventually lead to the formation of β-carboline **584** (**Scheme 179**). Compounds containing the β-carboline skeleton have been found to exhibit a wide range of biological properties, including antitumour activity.[276–279]



584 **585** **586** **587**

Scheme 179. Proposed α-arylation-based route to β-carbolines

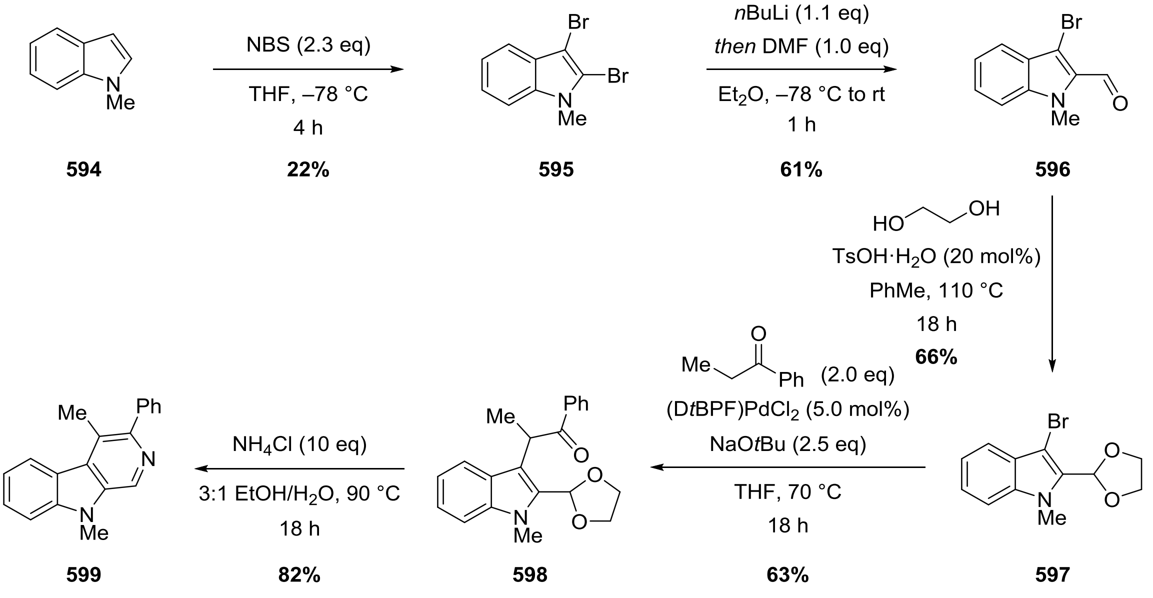
Modern palladium-catalysed syntheses of this class of compounds include Sakamoto's amination-arylation of aryl halides with pyridyl amines to close the five-membered ring,[280] and several reports of the stepwise alkynylation of *ortho* oxime or imine derivatives of 3-haloindoles, followed by palladium-catalysed annulation.[281–287] In a similar manner to their approach towards isoquinolines,[128–131] Larock employed a one-pot iminoannulation of alkynes to access β-carbolines in modest yields (**Scheme 180a**),[288] which was later converted into a C–H activation-based route by Jiao and coworkers (**Scheme 180b**).[289] Both these approaches suffered from significant regioselectivity issues.



Scheme 180. Larock and Jiao's immunoannulation routes to β-carbolines

2.5.2 Preliminary studies

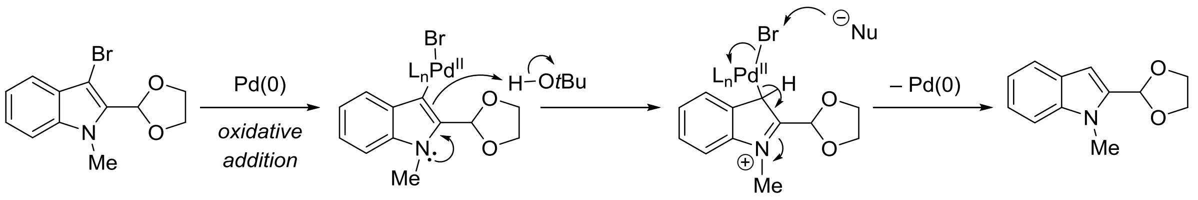
Investigation into an α-arylation-based route to β-carbolines began with the synthesis of bromoindole coupling partner **597**. Commercially available *N*-methylindole **594** was dibrominated with NBS according to a literature procedure to afford compound **595** in 22% yield (**Scheme 181**).[290] This yield was considerably lower than the published 90% yield, but it was assumed that the future use of recrystallised NBS and careful control of its rate of addition would result in a significant improvement.



Scheme 181. The synthesis of β-carboline **599** *via* palladium-catalysed α-arylation

Since a sufficient quantity of dibromoindole **595** had been obtained, the remaining steps of the synthesis were approached prior to optimisation. The formylation of **595** *via* halogen-metal exchange and reaction with DMF afforded **596** in 61% yield.[291] The incorporation of the aldehyde in **596** was confirmed by the presence of a singlet at 10.09 ppm in the ^{1}H NMR spectrum. Aldehyde **596** was then protected as a cyclic acetal by treatment with ethylene glycol and $TsOH{\cdot}H_2O$. Due to the small scale of the reaction, a Dean-Stark apparatus could not be used. Therefore, a large excess of ethylene glycol was employed instead. Although the reaction did not go to completion, acetal **597** could still be isolated in a reasonable yield of 66%. Bromoindole **597** was employed in the crucial α-arylation reaction with propiophenone, furnishing ketone **598** in 63% yield with the use of 5.0 mol% (D*t*BPF)$PdCl_2$ and 2.5 equivalents of NaO*t*Bu. Ketone **598** was cyclised to β-carboline **599** in 82% yield when subjected to the standard cyclisation conditions.

Thus, it was demonstrated that the palladium-catalysed enolate arylation reaction was a viable strategy *en route* to β-carbolines, though an improved synthesis of the bromoindole starting material **597** would be required. Furthermore, in the coupling of **598** and propiophenone, approximately 25% of protodebrominated indole **602** was formed along with the desired product **599**, possibly due to the electron rich indole undergoing *ipso* protonation by *t*BuOH once bound to palladium (**Scheme 182**). This might be avoided by preforming the enolate using a strong lithium amide base, thereby removing the proton source from the α-arylation reaction. These modifications are currently being investigated by another member of the Donohoe group.



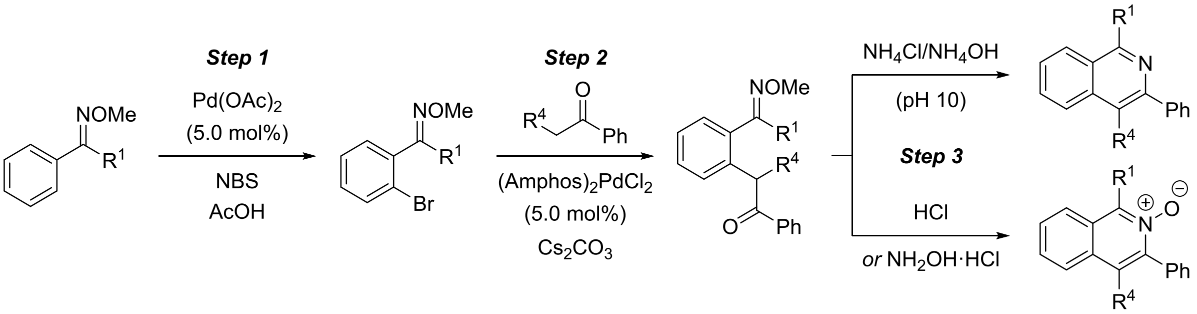
598 **600** **601** **602** **~25%**

Scheme 182. Proposed mechanism for protodebromination of indole **598**

2.6 Conclusion

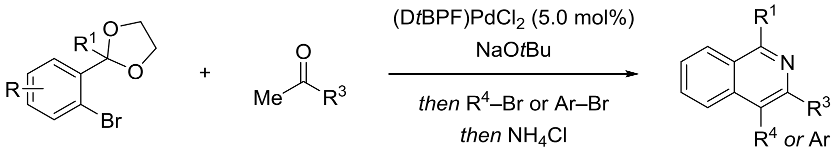
2.6.1 Summary of results

It is concluded from the work described herein that whilst the direct palladium-catalysed α-arylation reaction of ketone enolates with arenes *via* directing group-assisted C–H activation remains a challenge, the equivalent overall transformation can be conducted in a stepwise fashion using two palladium-catalysed processes (**Scheme 183**). Aryl *O*-methyl oximes have been shown to undergo a Pd(II)-catalysed *ortho* bromination in yields of up to 90%, and the resulting aryl bromides can be coupled with propiophenone in a Pd(0)-catalysed α-arylation reaction. The enolate of propiophenone is formed in the presence of Cs_2CO_3, and is coupled with oxime-containing aryl bromides by the commercially available precatalyst $(Amphos)_2PdCl_2$. The oxime can subsequently be hydrolysed to unmask the 1,5-dicarbonyl moiety, which cyclises in the presence of an ammonia source to provide isoquinolines. Alkyl and phenyl groups can be installed at C1 through the use of the appropriate ketone-derived oxime. It is also possible to retain the nitrogen and oxygen atoms of the oxime directing group and synthesise isoquinoline *N*-oxides by treating the α-arylation product with HCl.



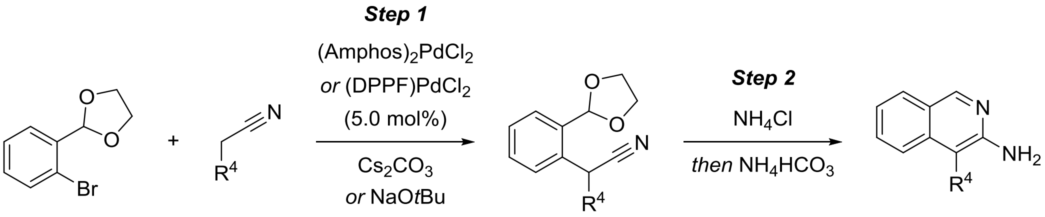
Scheme 183. Stepwise C–H activation/bromination and α-arylation reactions in the synthesis of isoquinolines

It has also been shown that the α-arylation reactions of methyl ketones with acetal-protected *ortho*-bromobenzaldehyes or ketones can be succeeded by an additional α-functionalisation *in situ* upon the addition of an electrophile such as an alkyl halide (**Scheme 184**). An unprecedented α,α-heterodiarylation, which is sterically controlled, has been developed, with the resulting diarylated ketones undergoing acetal hydrolysis and cyclisation in the presence of an acidic source of ammonia to give C4-aryl isoquinolines. Furthermore, the three steps can be combined in a one-pot, four component coupling to afford C4-aryl isoquinolines in an operationally simple procedure in yields of up to 80%. Electron rich, electron neutral and electron poor aryl bromides are compatible, as are a number of aryl and alkyl methyl ketones.[219]



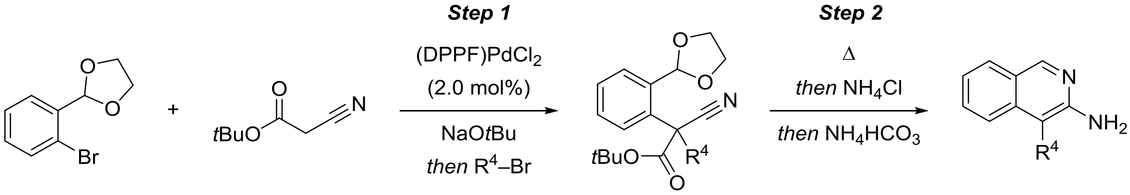
Scheme 184. One-pot synthesis of C4-functionalised isoquinolines

A slight modification of conditions allows for the α-arylation of nitrile derivatives in yields of up to 94%. The products can be smoothly converted into isoquinolines at a higher oxidation level, i.e. those bearing an amino group at the C3 position, by acetal hydrolysis and treatment with ammonium bicarbonate (**Scheme 185**). When strongly electron withdrawing groups are present at the nitrile α-position, the competing formation of 3-hydroxyisoquinolines can occur *via* hydration of the nitrile.



Scheme 185. Synthesis of 3-aminoisoquinolines *via* palladium-catalysed nitrile arylation

It was shown that *tert*-butyl cyanoacetate is a highly proficient substitute for primary alkyl nitriles, which are an extremely challenging class of α-arylation substrate. Palladium-catalysed arylation can be followed by *in situ* functionalisation, decarboxylation, acetal hydrolysis, and ammonium bicarbonate-mediated cyclisation to afford C4-functionalised 3-aminoisoquinolines (**Scheme 186**).[219]

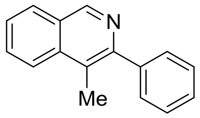


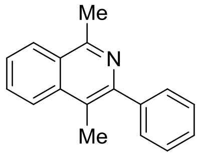
Scheme 186. Synthesis of C4-functionalised 3-aminoisoquinolines from *tert*-butyl cyanoacetate

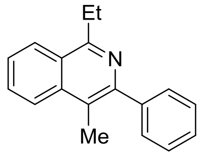
The α-arylation-based isoquinoline synthesis methodology has been applied to the short and efficient total synthesis of berberine chloride in an overall yield of 68% from the corresponding aryl bromide starting material. A total of seven synthetic steps were required, involving only three chromatographic separations. The longest linear sequence of five steps began with the preparation of the ketone α-arylation substrate. By employing different aryl bromide and ketone coupling partners, analogous syntheses of pseudocoptisine and palmatine (in 46% and 73% yield, respectively) and of an unnatural fluorine-containing analogue (in 38% yield) were also achieved. Enolate arylation was combined with *in situ* methylation to derivatise the alkaloid C13 position, resulting in the total synthesis of dehydrocorydaline in 60% yield.

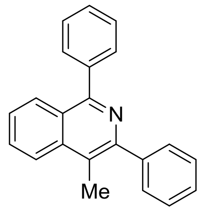
Finally, preliminary studies have revealed that the palladium-catalysed enolate arylation reaction can be employed in the regioselective synthesis of β-carbolines, *via* a route that begins with a 3-bromoindole rather than a bromobenzene derivative. This approach is being explored further by another member of the Donohoe group.

2.6.2 Collated heterocycle syntheses

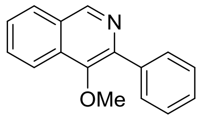


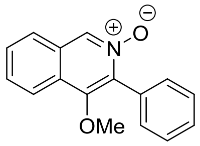


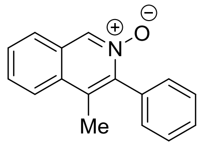


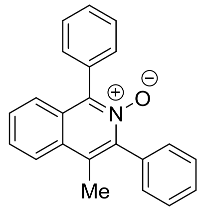


	190	**222**	**324**	**332**
Step 1	**51%**	**55%**	**70%**	**90%**
Step 2	**91%**	**29%**	**52%**	**93%**
Step 3	**88%**	**84%**	**86%**	**84%**
One-pot 2 & 3	**83%**	**25%**	**46%**	**69%**



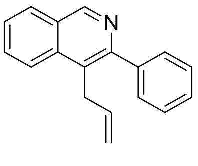


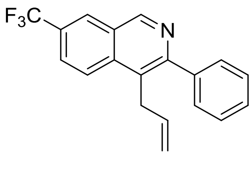


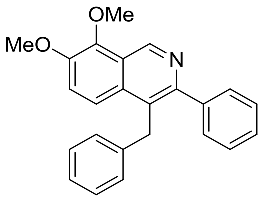


	236	**343**	**247**	**344**
Step 1	**51%**	**51%**	**51%**	**90%**
Step 2	**85%**	**85%**	**91%**	**93%**
Step 3	**56%**	**74%**	**99%**	**85%**
One-pot 2 & 3	**80%**	–	**64%**	–

Figure 38. Isoquinoline derivatives synthesised *via* C–H activation/bromination and α-arylation
Step 1: bromination; Step 2: α-arylation; Step 3: cyclisation (**Scheme 183**)

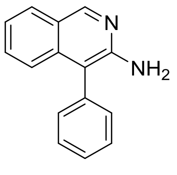


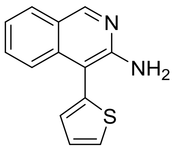


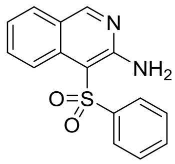


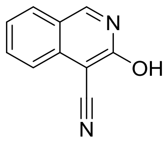
367	**371**	**373**
71%	**60%**	**40%**

Figure 39. Isoquinolines synthesised *via* one-pot α-arylation/*in situ* functionalisation of ketones (**Scheme 184**)



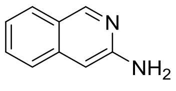


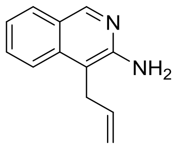


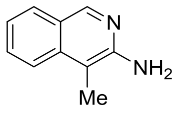


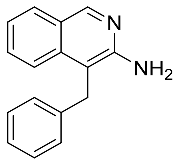
	442	**443**	**469**	**467**
Step 1	**50%**	**38%**	**94%**	**92%**
Step 2	**72%**	**75%**	**48%**	**85%**[a]

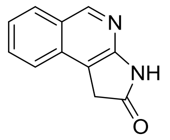
Figure 40. 3-Amino- and -hydroxyisoquinolines synthesised by the stepwise α-arylation/cyclisation of nitriles
Step 1: α-arylation; Step 2: cyclisation (**Scheme 185**); [a] Treated with $TsOH \cdot H_2O$ instead of NH_4Cl/NH_4HCO_3





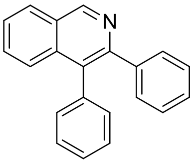






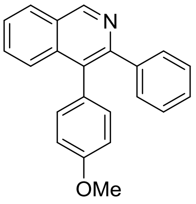
	470	**479**	**485**	**487**	**489**
Step 1	**92%**	**84%**	**85%**	**91%**	**87%**
Step 2	**86%**	**95%**	**94%**	**73%**	**65%**
One-pot	**66%**	**34%**	**–**	**–**	**–**

Figure 41. C4-functionalised 3-aminoisoquinolines from the arylation-alkylation of *tert*-butyl cyanoacetate *Step 1: α-arylation; Step 2: cyclisation* (**Scheme 186**)



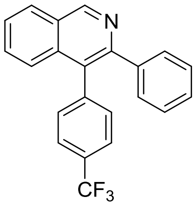
121

77%



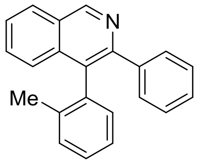
404

80%



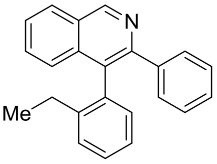
406

73%



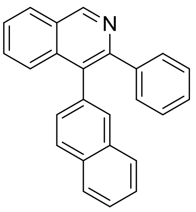
408

65%



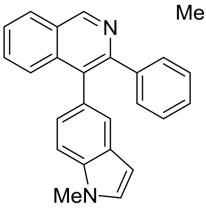
410

67%



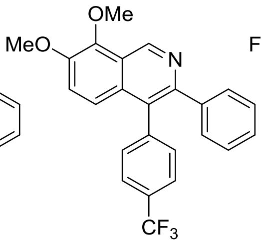
414

66%



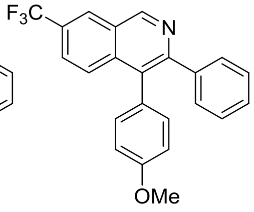
417

69%



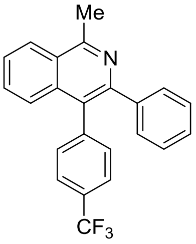
419

68%



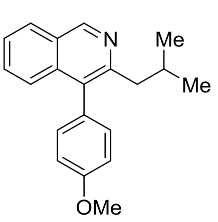
420

67%



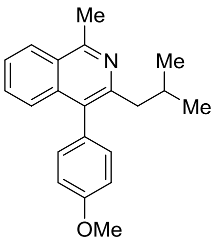
421

57%



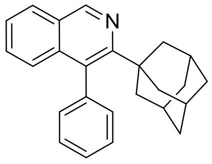
423

53%



425

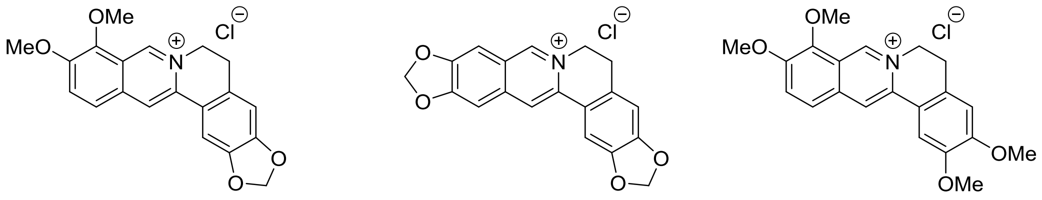
65%



427

54%

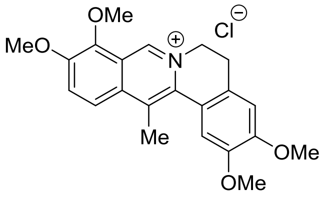
Figure 42. C4-Aryl isoquinolines synthesised *via* the one-pot α,α-heterodiarylation/cyclisation protocol (**Scheme 184**)

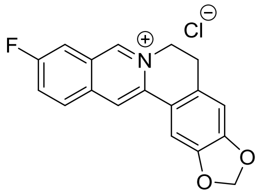


berberine chloride
68%

pseudocoptisine chloride
46%

palmatine chloride
73%

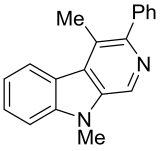




dehydrocorydaline chloride
60%

580
38%

Figure 43. Protoberberine alkaloids and analogues synthesised



599
52%

Figure 44. β-Carboline **599** synthesised by α-arylation with an *ortho*-acetal substituted 3-bromoindole

Chapter 3. Experimental

3.1 General Methods

^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at room temperature on a 200 MHz, 300 MHz, 400 MHz or 500 MHz Bruker spectrometer (DPX200, DPX300, AVII400, AVIII400 or AVII500) in $CDCl_3$, CD_3OD, DMSO-d_6 or pyridine-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 for ^{1}H NMR and 0.1 ppm for ^{13}C and ^{19}F NMR. Signal splittings are reported 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. Assignments are made based on DEPT, COSY, HSQC and HMBC experiments and by comparison of the spectral data with that of known compounds.

Infrared spectra were recorded neat as thin films or powders on a Bruker Tensor 27 FT-IR spectrometer equipped with attenuated total reflectance sampling accessories. Absorption maxima are quoted in wavenumbers (cm^{-1}) in the range 3500–1000 cm^{-1}.

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

Melting points (m.p.) were obtained from amorphous samples using a Lecia VMTG heated-stage microscope and are uncorrected.

Flash column chromatography was performed using silica gel (60 Å, 0.033–0.070 mm, BDH) or basic alumina (pH 9.5, 58 Å, 150 mesh, Sigma-Aldrich). TLC analyses were performed on Merck Kieselgel 60 F_{254} 0.25 mm precoated silica plates or Macherey-Nagel Alugram Alox N/UV_{254} 0.20 mm precoated alumina plates. Product spots were visualized under UV light (λ_{max} = 254 nm or 365 nm) and/or by staining with vanillin, potassium permanganate or phosphomolybdic acid solution. LCMS analysis was carried out using a Waters Acquity UPLC/Waters Micromass Q-Tof 2 system. Reverse phase mass-directed autopreparative

HPLC (MDAP) was carried out with the Waters AutoPurification system. Automated flash column chromatography was conducted on Argonaut or Jones Chromatography FlashMaster II instruments with a Gilson 204 fraction collector.

Reagents obtained from Sigma-Aldrich, Alfa Aesar, Acros, Fluorochem, Strem and TCI were used directly as supplied except for *N*-bromosuccinimide which was recrystallised.[292] Palladium catalysts were obtained from Johnson Matthey and stored in a desiccator. NaO*t*Bu, Cs_2CO_3, and acetals of benzaldehydes were also stored in a desiccator. An authentic sample of berberine chloride was obtained from Sigma-Aldrich.

All anhydrous reactions were carried out in flame-dried glassware under an inert atmosphere of argon. THF, toluene, CH_2Cl_2, MeOH and MeCN were dried by purification through an activated alumina purification column.[293] Dry 1,4-dioxane and pyridine were used directly from Sure/Seal® bottles from Sigma-Aldrich. Brine refers to a saturated aqueous solution of NaCl.

3.2 General Procedures

General Procedure 1: Synthesis of *O*-methyl oximes [294]

To a solution of the aldehyde (1.0 eq) in 3:1 H_2O/THF (2.0 mL mmol^{-1}) was added methoxylamine hydrochloride (1.7 eq) and sodium acetate trihydrate (1.5 eq). The reaction mixture was stirred at room temperature for 4 h then diluted with Et_2O (5 mL mmol^{-1}), washed with brine (10 mL mmol^{-1}), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified as specified.

General Procedure 2: Alternative synthesis of *O*-methyl oximes [295]

To a solution of the aldehyde or ketone (1.0 eq) in EtOH (10 mL mmol^{-1}) was added methoxylamine hydrochloride (1.6 eq) and pyridine (1.2 mL mmol^{-1}) and the reaction was stirred as specified. The mixture was concentrated *in vacuo* and the residue redissolved in EtOAc (10 mL mmol^{-1}), washed with H_2O (10 mL mmol^{-1}), and brine (10 mL mmol^{-1}), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified as specified.

General Procedure 3: Palladium-catalysed C–H halogenation [209]

To a screw-cap tube containing a solution of the *O*-alkyl oxime (1.0 eq) in acetic acid (8.0 mL mmol^{-1}) was added $Pd(OAc)_2$ (5.0 mol%) and either *N*-bromosuccinimide or *N*-iodosuccinimide (1.1 eq). The resulting mixture was stirred at 100 °C for the specified time then allowed to cool to room temperature and concentrated *in vacuo*. The crude residue was purified as specified.

General Procedure 4: Palladium-catalysed α-arylation of ketones

To a screw-cap tube fitted with a rubber septum was added $(Amphos)_2PdCl_2$ (5.0 mol%) and Cs_2CO_3 (2.5 eq) before the vessel was evacuated and backfilled with argon. A solution of the aryl bromide (1.0 eq) in anhydrous THF (5.0 mL mmol^{-1}) was added, followed by the ketone (2.0 eq). The septum was replaced with a screw cap under a flow of argon and the reaction mixture was heated at 70 °C for 18 h. After cooling to room temperature, the reaction was quenched with H_2O (5 mL mmol^{-1}) and the resulting mixture was extracted with Et_2O (3 × 10 mL mmol^{-1}). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide a crude residue which was purified as specified.

General Procedure 5: Synthesis of isoquinolines from *O*-alkyl oximes

To a screw-cap tube containing the α-aryl ketone (1.0 eq) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (10 eq), which had been basified to ~pH 9 by the dropwise addition of 25% aqueous NH_4OH. The resulting mixture was stirred at 110 °C for 24 h then cooled to room temperature and quenched with saturated aqueous NH_4Cl (10 mL mmol^{-1}). The mixture was extracted with Et_2O (3 × 20 mL mmol^{-1}) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified as specified.

General Procedure 6: One-pot synthesis of isoquinolines from *O*-alkyl oximes

To a screw-cap tube fitted with a rubber septum was added $(Amphos)_2PdCl_2$ (5.0 mol%) and Cs_2CO_3 (2.5 eq) before the vessel was evacuated and backfilled with argon. A solution of the aryl bromide (1.0 eq) in anhydrous THF (5.0 mL mmol^{-1}) was added, followed by the ketone (2.0 eq). The septum was replaced with a screw cap under a flow of argon and the reaction mixture was heated at 70 °C for 18 h. After cooling to room temperature, a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (20 eq), which had been basified to ~pH 9 by the dropwise addition of 25% aqueous NH_4OH, was added and the resulting mixture was stirred at 110 °C for 24 h. After cooling to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (10 mL mmol^{-1}) and the mixture was extracted with Et_2O (3 × 15 mL mmol^{-1}). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide a crude residue which was purified as specified.

General Procedure 7: Synthesis of isoquinoline *N*-oxides[175]

To a screw-cap tube containing the α-aryl ketone (1.0 eq) was added a 1 M solution of hydroxylamine hydrochloride in 9:1 EtOH/H_2O (10 eq) and the resulting solution was stirred at 110 °C for 4 h. The mixture was then concentrated *in vacuo*, and H_2O removed by azeotropic distillation with toluene, to provide a crude residue which was purified as specified.

General Procedure 8: Cyclic acetal protection of aldehydes and ketones[175]

To a solution of the aldehyde or ketone (1.0 eq) in toluene (10 mL mmol^{-1}) was added ethylene glycol (1.2 eq) and *para*-toluenesulfonic acid monohydrate (2.0 mol%). The resulting mixture was stirred at reflux for 18 h using a Dean-Stark apparatus then cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (10 mL mmol^{-1}). The mixture was extracted with Et_2O (3 × 25 mL mmol^{-1}) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified as specified.

General Procedure 9: Synthesis of isoquinolines from cyclic acetals

To a screw-cap tube containing the α-aryl ketone (1.0 eq) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (10 eq). The reaction was stirred at 90 °C for 18 h then cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (10 mL mmol^{-1}). The resulting mixture was extracted with EtOAc (3 × 20 mL mmol^{-1}) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified as specified.

General Procedure 10: One-pot synthesis of C4-aryl isoquinolines (R^1 = H)

To a microwave vial fitted with a rubber septum was added (D*t*BPF)$PdCl_2$ (5.0 mol%) and NaO*t*Bu (2.5 eq). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of the aryl bromide (1.0 eq) in anhydrous THF (4.0 mL $mmol^{-1}$) was added *via* syringe, followed by the addition of the ketone (1.2 eq) and the reaction mixture was heated at 70 °C for 6 h. After cooling to room temperature, the second aryl bromide (2.5 eq) was added *via* syringe and the reaction mixture was stirred at 100 °C for a further 18 h. After cooling to room temperature, a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (10 eq) was added and the resulting mixture was stirred at 90 °C for 24 h. The reaction was then cooled to room temperature and quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL $mmol^{-1}$) and the resulting mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide a crude residue which was purified as specified.

General Procedure 11: One-pot synthesis of C4-aryl isoquinolines (R^1 = Me)

To a microwave vial fitted with a rubber septum was added (D*t*BPF)$PdCl_2$ (5.0 mol%) and NaO*t*Bu (2.5 eq). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of the aryl bromide (1.0 eq) in anhydrous THF (4 mL $mmol^{-1}$) was added *via* syringe, followed by the addition of the ketone (1.2 eq). The reaction mixture was heated at 70 °C for 6 h. After cooling to room temperature, the second aryl bromide (2.5 eq) was added *via* syringe and the reaction mixture was stirred at 100 °C for a further 18 h. After cooling to room temperature, the pH of the mixture was adjusted to pH 5 by the dropwise addition of a 1 M aqueous solution of HCl before a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (10 eq) was added. The resulting mixture was stirred at 120 °C for 48 h then cooled to room temperature. 2 M aqueous NH_4HCO_3 (20 eq) was then added and the solution was stirred at 90 °C for 6 h. After cooling to room temperature, the reaction was diluted with H_2O and the resulting mixture extracted with EtOAc (3 × 15 mL).

The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide a crude residue which was purified as specified.

General Procedure 12: Synthesis of 3-aminoisoquinolines

A solution of the arylated *tert*-butyl cyanoacetate (1.0 eq) in 3:2 EtOH/H_2O (10 mL $mmol^{-1}$) in a screw-cap tube was stirred at 90 °C for 18 h. After cooling to room temperature, NH_4Cl (10 eq) was added and the reaction was reheated to 90 °C and stirred for 3 h. The mixture was then cooled to room temperature and basified by the addition of 2 M aqueous NH_4HCO_3 (20 eq). The reaction mixture was stirred at 90 °C for a further 3 h then cooled to room temperature and extracted with 4:1 EtOAc/*n*BuOH (3 × 10 mL $mmol^{-1}$). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide a crude residue which was purified as specified.

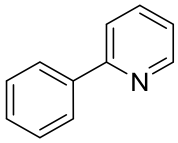
General Procedure 13: Arylation-alkylation of *tert*-butyl cyanoacetate

To a microwave vial fitted with a rubber septum was added (DPPF)$PdCl_2$ (2.0 mol%) and NaO*t*Bu (2.5 eq). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (1.2 eq) in anhydrous 1,4-dioxane (4.0 mL $mmol^{-1}$) was added *via* syringe, followed by the addition of *tert*-butyl cyanoacetate (1.0 eq) and the reaction was heated at 70 °C for 4 h. After cooling to room temperature, the specified quantity of electrophilic reagent was added *via* syringe and the reaction was stirred at 70 °C for a further 8 h. The reaction was cooled to room temperature and quenched with saturated aqueous NH_4Cl (5 mL $mmol^{-1}$). The resulting mixture was extracted with EtOAc (3 × 10 mL $mmol^{-1}$) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified as specified.

3.3 Experimental Details

3.3.1 Chapter 2.1 compounds

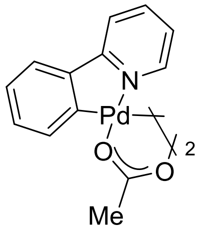
2-Phenylpyridine 257 [202]



A solution of 2-bromopyridine (0.489 g, 3.09 mmol), phenylboronic acid (565 mg, 4.63 mmol), Pd(OAc)$_2$ (34.6 mg, 0.154 mmol) and K$_3$PO$_4$ (1.31g, 6.17 mmol) in ethylene glycol (12 mL) was stirred at 80 °C in a sealed tube for 18 h. The reaction mixture was allowed to cool to room temperature then poured into a separating funnel containing brine (15 mL) and the resulting mixture was extracted with Et$_2$O (3 × 15 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, 9:1 petrol/EtOAc) afforded 2-phenylpyridine **257** as a pale yellow oil (301 mg, 1.94 mmol, 63%).

^{1}H NMR (400 MHz, CDCl$_3$) δ_H 8.71 (1 H, m, *H*C(6)$_{Py}$), 8.05–7.98 (2 H, m, 2 × *o-H*C$_{Ph}$), 7.77–7.70 (2 H, m, *H*C(3)$_{Py}$ and *H*C(4)$_{Py}$), 7.53–7.46 (2 H, m, 2 × *m-H*C$_{Ph}$), 7.46–7.40 (1 H, m, *p-H*C$_{Ph}$), 7.19–7.26 (1 H, m, *H*C(5)$_{Py}$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 157.5 (*C*(2)$_{Py}$), 149.6 (H*C*(6)$_{Py}$), 139.4 (*C*$_{Ph}$), 136.8 (H*C*(4)$_{Py}$), 129.0 (*p*-H*C*$_{Ph}$), 128.7 (*m*-H*C*$_{Ph}$), 126.9 (*o*-H*C*$_{Ph}$), 122.1 (H*C*(5)$_{Py}$), 120.6 (H*C*(3)$_{Py}$). Spectroscopic data were consistent with those previously reported.[296]

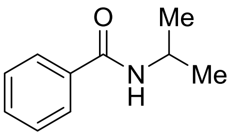
2-Phenylpyridyl palladium acetate dimer 275 [203]



To a solution of 2-phenylpyridine **257** (112 mg, 0.722 mmol) in CH$_2$Cl$_2$ (7.2 mL) was added Pd(OAc)$_2$ (162 mg, 0.722 mmol) and the reaction mixture was stirred at 40 °C for 3 h. The solution was then concentrated *in vacuo* and the crude product was triturated with Et$_2$O (10 mL). The suspension was filtered and the solid washed with Et$_2$O (3 × 5 mL) to afford palladacycle **275** as a yellow solid (219 mg, 0.343 mmol, 95%).

M.p. decomposed at 263 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.92–7.83 (1 H, m, $HC(6)_{Py}$), 7.37 (1 H, td, J = 7.8, 1.5, $HC(4)_{Py}$), 7.09 (1 H, d, J = 8.1, $HC(3)_{Py}$), 6.96–6.77 (4 H, m, 4 × HC_{Ph}), 6.45 (1 H, td, J = 6.6, 1.0, $HC(5)_{Py}$), 2.28 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 181.6 (C=O), 164.1 ($C(2)_{Py}$), 151.8 (C_{Ph}), 150.0 ($HC(6)_{Py}$), 144.4 ($C_{Ph}Pd$), 137.4 ($HC(4)_{Py}$), 131.7, 128.4, 123.8, 122.3 (4 × HC_{Ph}), 121.0 ($HC(5)_{Py}$), 117.1 ($HC(3)_{Py}$), 24.8 (CH_3); **IR** ν_{max} (powder)/cm^{-1} 1585, 1563, 1484, 1411, 102. Spectroscopic data were consistent with those previously reported.[203] See Appendix 3 for single crystal X-ray diffraction report.

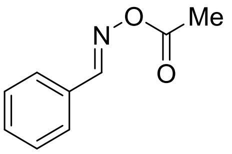
N-isopropylbenzamide 278



To a solution of isopropylamine (0.909 mL, 10.7 mmol) in CH_2Cl_2 (8.0 mL) at 0 °C was added benzoyl chloride (0.413 mL, 3.26 mmol) dropwise and the reaction was stirred at 0 °C for 3 h. After warming to room temperature, the reaction mixture was washed with saturated aqueous NH_4Cl (3 × 10 mL) and the organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford amide **278** as a colourless solid (567 mg, 3.47 mmol, 98%).

M.p. 103–105 °C (lit. 100–102 °C);[297] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.77–7.74 (2 H, m, 2 × HC_{Ar}), 7.47–7.42 (1 H, m, HC_{Ar}), 7.39–7.35 (2 H, m, 2 × HC_{Ar}), 6.28 (1 H, br. s, NH), 4.32–4.20 (1 H, sept., J = 6.6, $HC(CH_3)_2$), 1.23 (6 H, d, J = 6.6, $(CH_3)_2$; **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 166.7 (C=O), 134.9 (C_{Ar}), 131.1 (HC_{Ar}), 128.3 (C_{Ar}), 126.8 (HC_{Ar}), 41.8 ($HC(CH_3)_2$), 22.7 ($(CH_3)_2$). Spectroscopic data were consistent with those previously reported.[297]

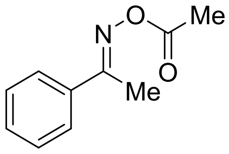
(*E*)-Benzaldehyde *O*-acetyloxime 279



A solution of oxime **281** (620 mg, 5.12 mmol) in 1:1 $AcOH/Ac_2O$ (20 mL) was stirred at room temperature for 2 h. The reaction was then diluted with H_2O (25 mL) and the resulting mixture was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford *O*-acetyloxime **279** as a colurless oil (804 mg, 4.93 mmol, 96%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.35 (1 H, s, *H*C=N), 7.74–7.71 (2 H, m, 2 × HC_{Ar}), 7.49–7.39 (3 H, m, 3 × HC_{Ar}), 2.22 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 168.6 (*C*=O), 155.8 (H*C*=N), 131.6 (HC_{Ar}), 130.0 (C_{Ar}), 128.8 (HC_{Ar}), 128.3 (HC_{Ar}), 19.5 (CH_3). Spectroscopic data were consistent with those previously reported.[298]

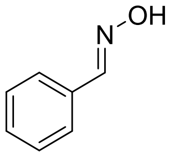
(*E*)-Acetophenone *O*-acetyloxime 280



A solution of oxime **282** (500 mg, 0.3.51 mmol) in 1:1 AcOH/Ac_2O (14 mL) was stirred at room temperature for 2 h. The reaction was then diluted with H_2O (20 mL) and the resulting mixture was extracted with Et_2O (3 × 25 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford *O*-acetyloxime **280** as a colurless oil (638 mg, 2.30 mmol, 79%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76–7.74 (2 H, m, 2 × HC_{Ar}), 7.46–7.39 (3 H, m, 3 × HC_{Ar}), 2.95 (3 H, s, CH_3C=N), 2.28 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.0 (*C*=O), 162.4 (*C*=N), 134.8 (C_{Ar}), 130.5 (HC_{Ar}), 128.6 (C_{Ar}), 127.0 (HC_{Ar}), 19.8 (CH_3), 14.4 (CH_3C=N). Spectroscopic data were consistent with those previously reported.[153]

(*E*)-Benzaldehyde oxime 281 [299]

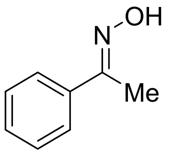


A solution of benzaldehyde (0.191 mL, 1.89 mmol), hydroxylamine hydrochloride (223 mg, 3.21 mmol), and sodium acetate trihydrate (387 mg, 2.84 mmol) in H_2O (3.8 mL) was stirred at room temperature for

4 h. The solution was then extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed with H_2O (25 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford oxime **281** as a colourless oil (218 mg, 1.80 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.21 (1 H, s, *H*C=N), 7.63–7.59 (2 H, m, 2 × HC_{Ar}), 7.43–7.41 (3 H, m, 3 × HC_{Ar}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 150.3 (H*C*=N), 131.8 (C_{Ar}), 130.1, 128.8, 127.0 (3 × HC_{Ar}). Spectroscopic data were consistent with those previously reported.[300]

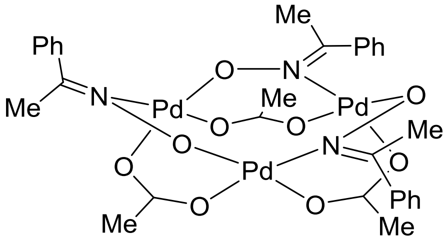
(*E*)-Acetophenone oxime 282



A solution of acetophenone (220 mg, 1.83 mmol), hydroxylamine hydrochloride (203 mg, 2.93 mmol), and sodium acetate trihydrate (500 mg, 3.66 mmol) in 1:1 MeOH/H_2O (7.0 mL) was stirred at 90 °C for 4 h. After cooling to room temperature, the reaction mixture was extracted with Et_2O (3 × 15 mL) and the combined organic extracts were washed with H_2O (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford oxime **282** as a colourless solid (247 mg, 1.83 mmol, 100%).

M.p. 54–56 °C (lit. 56–58 °C);[301] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.70–7.60 (2 H, m, 2 × *o*-HC_{Ar}), 7.45–7.39 (3 H, m, 3 × HC_{Ar}), 2.33 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.1 (*C*=N), 136.5 (C_{Ar}), 129.3 (*p*-HC_{Ar}), 128.5 (*o*-HC_{Ar}), 126.1 (*m*-HC_{Ar}), 12.4 (CH_3). Spectroscopic data were consistent with those previously reported.[301]

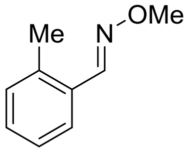
$[Pd(\mu\text{-}(E)\text{-}ON{=}C(CH_3)Ph)(\mu\text{-}OAc)]_3$ 286



A solution of *O*-methyl oxime **282** (49.2 mg, 0.364 mmol) and $Pd(OAc)_2$ (81.7 mg, 0.364 mmol) in CH_2Cl_2 (3.6 mL) was stirred at 40 °C for 18 h then cooled to room temperature. The reaction mixture was concentrated *in vacuo* and the crude product was triturated with Et_2O (10 mL). The resulting solid was washed with Et_2O (3 × 10 mL) to afford palladium complex **286** as an orange solid (86.4 mg, 0.288 mmol, 79%).

M.p. decomposed at at 320 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.13 (6 H, d, $J = 7.2$, 6 × HC$_{Ar}$), 7.63 (6 H, t, $J = 7.4$, 6 × HC$_{Ar}$), 7.54 (3 H, t, $J = 7.5$, 3 × HC$_{Ar}$), 2.07 (9 H, s, 3 × CO_2CH_3), 2.05 (9 H, s, 3 × $CH_3C{=}N$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 184.0 (CO_2Me), 158.6 ($C{=}N$), 137.5 (C_{Ar}), 129.7, 128.6, 127.3 (3 × HC_{Ar}), 23.1 (CO_2CH_3), 18.1 ($CH_3C{=}N$); **IR** ν_{max} (powder)/cm^{-1} 3056, 2918, 2850, 1559, 1427, 1261, 1101, 1049, 1022; **HRMS** (ESI$^+$) $C_{30}H_{33}N_3NaO_9{}^{106}Pd$ requires 919.9214, found $[M+Na]^+$ 919.9230 (Δ +1.8 ppm). NMR data were consistent with those previously reported.[207]

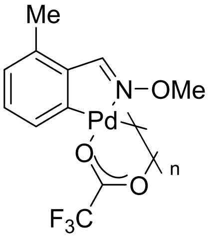
(*E*)-2-Methylbenzaldehyde *O*-methyl oxime 287



2-Methylbenzaldehyde (0.990 mL, 8.30 mmol) was subjected to **General Procedure 1**. Purification by flash column chromatography (SiO_2, petrol) afforded (*E*)-*O*-methyl oxime **287** as a pale yellow oil (1.23 g, 8.24 mmol, 99%).

^{1}H NMR (200 MHz, $CDCl_3$) δ_H 8.36 (1 H, s, HC=N), 7.79–7.68 (1 H, m, HC(6)), 7.36–7.13 (3 H, m, 3 × HC$_{Ar}$), 4.01 (3 H, s, OCH_3), 2.43 (3 H, s, CH_3); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_C 147.9 (HC=N), 137.2 (C_{Ar}), 131.2 (HC(6)), 130.8 (C_{Ar}), 130.0, 127.1, 126.6 (3 × HC_{Ar}), 62.4 (OCH_3), 20.2 (CH_3). Spectroscopic data were consistent with those previously reported.[210]

(*E*)-2-Methylbenzaldehyde *O*-methyl oxime palladium trifluoroacetate 288

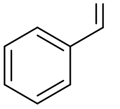


To a screw-cap tube containing a solution of *O*-methyl oxime **287** (49.4 mg, 0.331 mmol) in 1,2-dichloroethane (3.3 mL) was added $Pd(OCOCF_3)_2$ (110 mg, 0.331 mmol) and the resulting mixture was stirred at 50 °C for 16 h. The solution was then concentrated *in vacuo* to afford a 4:1 mixture of oligomers of palladacyle **288** as a viscous oil (121 mg, 0.329 mmol, 100%).

Major oligomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.38 (1 H, s, *H*C=N), 6.94–6.77 (3 H, m, 3 × HC_{Ar}), 3.77–3.71 (3 H, s, OCH_3), 2.16 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 165.9 (q, ^{2}J = 38.9, CO_2CF_3), 161.9 (H*C*=N), 151.9, 137.3, 135.5 (3 × C_{Ar}), 129.5, 129.4, 126.8 (3 × HC_{Ar}), 115.5 (q, ^{1}J = 287.4, CO_2CF_3), 62.5 (OCH_3), 19.3 (CH_3); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −74.4 (CF_3).

Minor oligomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.04 (1 H, s, *H*C=N), 6.59–6.42 (2 H, m, 2 × HC_{Ar}), 6.30 (1 H, d, *J* = 7.8, HC_{Ar}), 3.92 (3 H, s, OCH_3), 2.19 (3 H, s, CH_3); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 166.8 (q, ^{2}J = 39.4, CO_2CF_3), 162.8 (H*C*=N), 152.1, 137.3, 134.9 (3 × C_{Ar}), 129.3, 129.0, 126.5 (3 × HC_{Ar}), 62.9 (OCH_3), 19.2 (CH_3). The CF_3 signal could not be resolved. **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −73.8 (CF_3); **IR** ν_{max} (neat)/cm^{-1} 1658, 1569, 1451, 1195, 1149, 1036.

(*E*)-Benzaldehyde *O*-methyl oxime 294

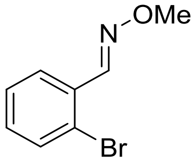


Benzaldehyde (0.960 mL, 9.43 mmol) was subjected to **General Procedure 1** to afford (*E*)-*O*-methyl oxime **295** as a colourless oil (1.23 g, 9.41 mmol, 100%). Purification was not required.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.10 (1 H, s, *H*C=N), 7.67–7.55 (2 H, m, 2 × *o*-HC_{Ar}), 7.43–7.35 (3 H, m, 3 × HC_{Ar}), 4.01 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 148.6

(H*C*=N), 132.2 (C_{Ar}), 129.8 (*p*-HC_{Ar}), 128.7 (*o*-HC_{Ar}), 127.0 (*m*-HC_{Ar}), 62.0 (OCH_3). Spectroscopic data were consistent with those previously reported.[210]

(*E*)-2-Bromobenzaldehyde *O*-methyl oxime 295



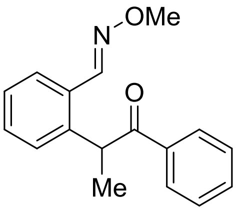
Method A: 2-Bromobenzaldehyde (1.26 mL, 10.8 mmol) was subjected to **General Procedure 1** to afford aryl bromide **295** as a colourless oil (2.29 g, 10.7 mmol, 99%). Purification was not required.

Method B:[210] To a screw-cap tube containing a solution of *O*-methyl oxime **294** (51.1 mg, 0.378 mmol) in 1,2-dichloroethene (1.2 mL) was added $Pd(OAc)_2$ (8.5 mg, 0.038 mmol), *N*-bromosuccinimide (67.3 mg, 0.378 mmol), $Ag(OCOCF_3)$ (8.4 mg, 0.038 mmol), and acetic acid (21.6 µL, 0.378 mmol). The resulting mixture was stirred at 120 °C for 5 h then allowed to cool to room temperature and quenched with saturated aqueous $NaHCO_3$ (2 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 petrol/CH_2Cl_2) afforded aryl bromide **295** as a colourless oil (29.2 mg, 0.136 mmol, 36%).

Method C: *O*-Methyl oxime **294** (55.0 mg, 0.407 mmol) was subjected to **General Procedure 3**, using 0.9 eq of *N*-bromosuccinimide, and stirred for 18 h. Purification by flash column chromatography (SiO_2, 8:2 petrol/CH_2Cl_2) afforded (*E*)-aryl bromide **295** as a colourless oil (44.4 mg, 0.208 mmol, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.46 (1 H, s, *H*C=N), 7.88 (1 H, d, *J* = 7.8, HC_{Ar}), 7.57 (1 H, d, *J* = 8.1, HC_{Ar}), 7.35–7.18 (2 H, m, 2 × HC_{Ar}), 4.01 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 147.9 (H*C*=N), 133.1 (HC_{Ar}), 131.5 (C_{Ar}), 131.0 (HC_{Ar}), 127.5, 127.5 (2 × HC_{Ar}), 123.8 (C_{Ar}Br), 62.3 (OCH_3). Spectroscopic data were consistent with those previously reported.[210]

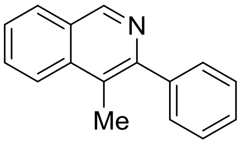
(*E*)-2-(1-Oxo-1-phenylpropan-2-yl)benzaldehyde *O*-methyl oxime 306



Propiophenone (0.248 mL, 1.868 mmol) and aryl bromide **295** (200 mg, 0.934 mmol) were subjected to **General Procedure 4**. Purification by flash column chromatography (SiO_2, 99:1 petrol/EtOAc) afforded ketone **306** as a viscous oil (227 mg, 0.850 mmol, 91%). Oxime geometry was assigned as (*E*) by analogy to oxime **295**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.45 (1 H, s, *H*C=N), 7.93–7.86 (2 H, m, 2 × *o*-*H*C_{Ph}), 7.62–7.55 (1 H, m, *H*C(6)), 7.50–7.43 (1 H, m, *p*-*H*C_{Ph}), 7.40–7.32 (2 H, m, 2 × *m*-*H*C_{Ph}), 7.30–7.20 (2 H, m, *H*C(4) and *H*C(5)), 7.18–7.11 (1 H, m, *H*C(3)), 5.34 (1 H, q, *J* = 6.8, C*H*CH_3), 3.96 (3 H, s, OCH_3), 1.52 (3 H, d, *J* = 6.8, CHCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 200.5 (*C*=O), 148.1 (H*C*=N), 140.3, 136.3 (2 × C_{Ar}), 132.8 (*p*-HC_{Ph}), 130.2 (H*C*(5)), 129.7 (H*C*(6)), 129.1 (C_{Ar}), 128.7 (*o*-HC_{Ph}), 128.5 (*m*-HC_{Ph}), 128.1 (H*C*(3)), 127.1 (H*C*(4)), 62.1 (OCH_3), 44.2 (*C*HCH_3), 18.6 (CHCH_3); **IR** ν_{max} (neat)/cm^{-1} 2953, 1684, 1597, 1448, 1222, 1048; **HRMS** (ESI$^+$) $C_{17}H_{17}NNaO_2$ requires 290.1151, found [M+Na]$^+$ 290.1151 (Δ +0.1 ppm).

4-Methyl-3-phenylisoquinoline 190

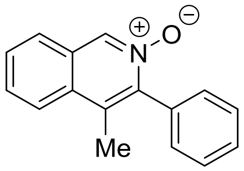


Method A: Ketone **306** (63.9 mg, 0.239 mmol) was subjected to **General Procedure 5**. Purification by flash column chromatography (SiO_2, 85:15 petrol/EtOAc) afforded isoquinoline **190** as a pale yellow solid (46.3 mg, 0.211 mmol, 88%).

Method B: Propiophenone (81.9 µL, 0.616 mmol) and aryl bromide **295** (67.0 mg, 0.313 mmol) were subjected to **General Procedure 6**. Purification by flash column chromatography (SiO_2, 85:15 petrol/EtOAc) afforded isoquinoline **190** as a pale yellow solid (56.7 mg, 0.258 mmol, 83%).

M.p. 97–99 °C (lit. 96–98 °C);[175] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.22 (1 H, s, *H*C(1)), 8.07 (1 H, d, *J* = 8.3, *H*C$_{Ar}$), 8.01 (1 H, d, *J* = 8.1, *H*C$_{Ar}$), 7.77 (1 H, ddd, *J* = 8.4, 7.0, 1.3, *H*C$_{Ar}$), 7.66–7.58 (3 H, m, *H*C$_{Ar}$ and 2 × *o*-*H*C$_{Ph}$), 7.54–7.46 (2 H, m, 2 × *m*-*H*C$_{Ph}$), 7.46–7.38 (1 H, m, *p*-*H*C$_{Ph}$), 2.67 (3 H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 151.8 (*C*(3)), 150.2 (H*C*(1)), 141.3 (*C*$_{Ph}$), 136.2 (*C*$_{Ar}$), 130.4 (H*C*$_{Ar}$), 129.9 (*o*-H*C*$_{Ph}$), 128.1 (H*C*$_{Ar}$ and *m*-H*C*$_{Ph}$), 127.6 (*p*-H*C*$_{Ph}$), 127.3 (*C*$_{Ar}$), 126.6 (H*C*$_{Ar}$), 124.0 (*C*(4)), 123.6 (H*C*$_{Ar}$), 15.5 (*C*H$_3$). Spectroscopic data were consistent with those previously reported.[175]

4-Methyl-3-phenylisoquinoline 2-oxide 247



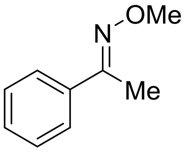
Method A: To a screw-cap tube containing ketone **306** (25.6 mg, 0.0958 mmol) was added a 1 M solution of HCl in 3:1 EtOH/H_2O (0.96 mL, 0.96 mmol) and the resulting solution was stirred at 110 °C for 24 h. The mixture was concentrated *in vacuo* using a toluene azeotrope and the crude residue dissolved in 8:2 EtOAc/MeOH, filtered through a short plug of basic Al_2O_3, and concentrated *in vacuo* to afford isoquinoline *N*-oxide **247** as an off-white solid (22.2 mg, 0.0943 mmol, 99%).

Method B: Ketone **306** (29.9 mg, 0.112 mmol) was subjected to **General Procedure 7**. The crude product was dissolved in 8:2 EtOAc/MeOH, filtered through a short plug of basic Al_2O_3, and concentrated *in vacuo* to afford isoquinoline *N*-oxide **247** as an off-white solid (25.6 mg, 0.110 mmol, 99%).

Method C: To a screw-cap tube fitted with a rubber septum was added $(Amphos)_2PdCl_2$ (22.8 mg, 0.0322 mmol) and Cs_2CO_3 (525 mg, 1.61 mmol) before the vessel was evacuated and backfilled with argon. A solution of aryl bromide **295** (138 mg, 0.645 mmol) in anhydrous THF (3.2 mL) was added, followed by propiophenone (0.172 mL, 1.29 mmol). The septum was replaced with a screw cap under a flow of argon and the reaction mixture was heated at 70 °C for 18 h. After cooling to room temperature, a solution of 1 M HCl in 3:1 EtOH/H_2O (12.9 mL, 12.9 mmol) was added and the tube was resealed and stirred at 110 °C for 24 h. The resulting solution was concentrated onto basic Al_2O_3 and purified by flash column chromatography (basic Al_2O_3, 95:5 EtOAc/MeOH) to afford isoquinoline *N*-oxide **247** as an off-white solid (97.4 mg, 0.413 mmol, 64%).

M.p. 180–181 °C (lit. 181–184 °C);[175] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.87 (1 H, s, *H*C(1)), 8.02–7.89 (1 H, m, *H*C_{Ar}), 7.79–7.70 (1 H, m, *H*C_{Ar}), 7.69–7.58 (2 H, m, *H*C(6) and *H*C(7)), 7.57–7.45 (3 H, m, 3 × *H*C_{Ph}), 7.44–7.36 (2 H, m, 2 × *H*C_{Ph}), 2.42 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 146.1 (C_{Ar}), 135.1 (H*C*(1)), 132.9, 130.9 (2 × C_{Ar}), 130.0 (HC_{Ph}), 129.5 (C_{Ar}), 128.9, 128.9 (H*C*(6) and H*C*(7)), 128.6 (2 × HC_{Ph}), 128.5 (C_{Ar}), 125.4, 124.0 (H*C*(5) and H*C*(8)), 16.1 (*C*H_3). Spectroscopic data were consistent with those previously reported.[175]

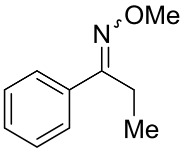
(*E*)-Acetophenone *O*-methyl oxime 310



Acetophenone (1.55 g, 12.9 mmol) was subjected to **General Procedure 2**, stirring at room temperature for 3 h, to afford (*E*)-*O*-methyl oxime **310** as a colourless oil (1.56 g, 10.4 mmol, 81%). Purification was not required.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72–7.62 (2 H, m, *H*C(2) and *H*C(6)), 7.47–7.33 (3 H, m, *H*C(3), *H*C(4) and *H*C(5)), 4.03 (3 H, s, OCH_3), 2.26 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 154.6 (*C*=N), 136.7 (C_{Ar}), 129.0, 128.4, 126.0 (3 × HC_{Ar}), 61.9 (O*C*H_3), 12.6 (*C*H_3). Spectroscopic data were consistent with those previously reported.[302]

Propiophenone *O*-methyl oxime 311



Method A: Propiophenone (1.29 g, 9.58 mmol) was subjected to **General Procedure 2**, stirring at room temperature for 4 h, to afford an

11:1 mixture of (*E*)- and (*Z*)-*O*-methyl oxime **311** as a colourless oil (1.42 g, 8.70 mmol, 91%). Purification was not required.

Method B: [303] To a solution of benzonitrile (0.100 mL, 0.977 mmol) in anhydrous THF (2.4 mL) at 0 °C was added a 1 M solution of ethylmagnesium bromide in THF (1.17 mL, 1.17 mmol) dropwise. The resulting mixture was allowed to warm to room temperature and stirred under argon for 5 days. After cooling to 0 °C, a cold solution of methoxylamine hydrochloride (134 mg, 1.60 mmol) in EtOH (10 mL) was added, followed by pyridine (1.3 mL), and the reaction was stirred at room temperature for a further 18 h. The solution was then concentrated *in vacuo* and the residue redissolved in EtOAc (10 mL), washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 99:1 petrol/Et_2O) afforded an 11:1 mixture of (*E*)- and (*Z*)-*O*-methyl oxime **311** as a colourless oil (104 mg, 0.637 mmol, 65%).

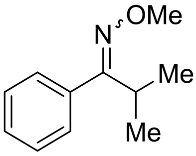
Method C: [214] To a solution of benzonitrile (0.199 mL, 1.94 mmol) in anhydrous THF (2.7 mL) at 0 °C was added a 1 M solution of ethylmagnesium bromide in THF (2.33 mL, 2.33 mmol) dropwise, followed by CuBr (5.6 mg, 0.039 mmol). The reaction vessel was purged with argon for 5 min before the mixture was allowed to warm to room temperature and stirred under argon for 24 h. After cooling to 0 °C, a cold solution of methoxylamine hydrochloride (259 mg, 3.10 mmol) in EtOH (19 mL) was added, followed by pyridine (2.4 mL), and the reaction was stirred at room temperature for 90 min. The solution was then concentrated *in vacuo*, the residue dissolved in Et_2O (15 mL), washed with H_2O (15 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford an 11:1 mixture of (*E*)- and (*Z*)-*O*-methyl oxime **311** as a colourless oil (279 mg, 1.71 mmol, 88%).

(*E*)-311: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.72–7.62 (2 H, m, 2 × *o*-HC_{Ar}), 7.46–7.33 (3 H, m, 3 × HC_{Ar}), 4.01 (3 H, s, OCH_3), 2.78 (2 H, q, *J* = 7.6, CH_2CH_3), 1.16 (3 H, t, *J* = 7.6, CH_2CH_3); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 159.8 (*C*=N), 135.6 (C_{Ar}), 129.0, 128.5, 126.3

(3 × H*C*$_{Ar}$), 61.9 (O*C*H$_3$), 20.1 (*C*H$_2$CH$_3$), 11.2 (CH$_2$*C*H$_3$). Spectroscopic data were consistent with those previously reported.[304]

(*Z*)-311: ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$ 7.74–7.61 (2 H, m, 2 × *o*-*H*C$_{Ar}$), 7.46–7.32 (3 H, m, 3 × *H*C$_{Ar}$), 3.86 (3 H, s, OC*H*$_3$), 2.58 (2 H, q, *J* = 7.6, C*H*$_2$CH$_3$), 1.09 (3 H, t, *J* = 7.5, CH$_2$C*H*$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ$_C$ 159.0 (*C*=N), 133.9 (*C*$_{Ar}$), 128.6, 128.1, 127.8 (3 × H*C*$_{Ar}$), 61.6 (O*C*H$_3$), 28.9 (*C*H$_2$), 11.6 (*C*H$_3$). See Appendix 1 for nOe enhancements.

2-Methyl-1-phenylpropan-1-one *O*-methyl oxime 312

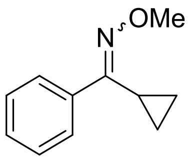


Isobutyrophenone (614 mg, 4.14 mmol) was subjected to **General Procedure 2**, stirring at room temperature for 16 h, to afford a 1:1 mixture of (*E*)- and (*Z*)-*O*-methyl oxime **312** as a pale yellow oil (653 mg, 3.69 mmol, 89%). Purification was not required.

(*E*)-312: ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$ 7.44–7.34 (5 H, m, 5 × *H*C$_{Ar}$), 3.97 (3 H, s, OC*H*$_3$), 3.54 (1 H, sept., *J* = 7.1, *H*C(CH$_3$)$_2$), 1.21 (6 H, d, *J* = 7.1, (C*H*$_3$)$_2$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ$_C$ 164.5 (*C*=N), 134.2 (*C*$_{Ar}$), 128.4, 128.1, 127.8 (3 × H*C*$_{Ar}$), 61.7 (O*C*H$_3$), 28.2 (H*C*(CH$_3$)$_2$), 19.5 ((*C*H$_3$)$_2$).

(*Z*)-312: ^{1}H NMR (400 MHz, CDCl$_3$) δ$_H$ 7.40–7.34 (3 H, m, 3 × *H*C$_{Ar}$), 7.24–7.22 (2 H, m, 2 × *H*C$_{Ar}$), 3.82 (3 H, s, OC*H*$_3$), 2.83 (1 H, sept., *J* = 6.9, *H*C(CH$_3$)$_2$), 1.14 (6 H, d, *J* = 6.9, (C*H*$_3$)$_2$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ$_C$ 162.6 (*C*=N), 135.8 (*C*$_{Ar}$), 128.1, 128.0, 127.5 (3 × H*C*$_{Ar}$), 61.5 (O*C*H$_3$), 34.4 (H*C*(CH$_3$)$_2$, 20.2 ((*C*H$_3$)$_2$); **IR** ν$_{max}$ (neat)/cm^{-1} 2966, 1465, 1443, 1052, 1033, 1010; **HRMS** (ESI$^+$) $C_{11}H_{15}NNaO$ requires 200.1046, found [M+Na]$^+$ 200.1050 (Δ −1.7 ppm). See Appendix 1 for nOe enhancements.

Cyclopropyl(phenyl)methanone *O*-methyl oxime 313

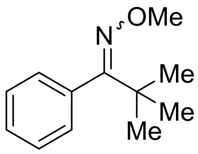


Cyclopropyl phenyl ketone (1.00 g, 6.66 mmol) was subjected to **General Procedure 2**, stirring at 60 °C for 16 h, to afford a 2:1 mixture of (*E*)- and (*Z*)-*O*-methyl oxime **313** as a colourless oil (1.16 g, 6.62 mmol, 99%). Purification was not required.

(*E*)-313: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47–7.31 (5 H, m, 5 × HC_{Ar}), 4.01 (3 H, s, OCH_3), 2.35–2.24 (1 H, m, $HC(CH_2)_2$), 0.98–0.90 (2 H, m, $CH_aH_bCH_aH_b$), 0.67–0.61 (2 H, m, $CH_aH_bCH_aH_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 161.1 (*C*=N), 134.1 (C_{Ar}), 128.6, 128.5, 128.1 (3 × HC_{Ar}), 61.9 (OCH_3), 9.5 ($HC(CH_2)_2$), 5.6 (CH_2CH_2).

(*Z*)-313: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.47–7.32 (4 H, m, 4 × HC_{Ar}), 7.29–7.19 (1 H, m, HC_{Ar}), 3.82 (3 H, s, OCH_3), 1.76 (1 H, quin., *J* = 6.6, $HC(CH_2)_2$), 0.83 (4 H, d, *J* = 6.6, CH_2CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 158.6 (*C*=N), 133.8 (C_{Ar}), 128.6, 128.0, 127.9 (3 × HC_{Ar}), 61.7 (OCH_3), 21.5 ($HC(CH_2)_2$), 5.7 (CH_2CH_2); **IR** ν_{max} (neat)/cm^{-1} 2937, 1494, 1444, 1330, 1053, 1034; **HRMS** (ESI$^+$) $C_{11}H_{14}NO$ requires 176.1070, found $[M+H]^+$ 176.1067 (Δ +1.5 ppm). See Appendix 1 for nOe enhancements.

2,2-Dimethyl-1-phenylpropan-1-one *O*-methyl oxime 314

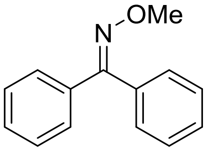


2,2-Dimethylpropiophenone (552 mg, 3.40 mmol) was subjected to **General Procedure 2**, stirring at 90 °C for 5 h, to afford a 13:1 mixture of (*Z*)- and (*E*)-*O*-methyl oxime **314** as a colourless solid (573 mg, 3.00 mmol, 88%). Purification was not required.

(*Z*)-314: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.42–7.32 (3 H, m, 3 × HC_{Ar}), 7.08–7.05 (2 H, m, 2 × HC_{Ar}), 3.77 (3 H, s, OCH_3), 1.18 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 165.6 (*C*=N), 134.5 (C_{Ar}), 127.8 (HC_{Ar}), 127.5, 127.5 (2 × HC_{Ar}), 61.6 (OCH_3), 37.1 ($C(CH_3)_3$), 28.3 ($(CH_3)_3$). Spectroscopic data were consistent with those previously reported.[305]

(*E*)-314: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36–7.32 (3 H, m, 3 × HC_{Ar}), 7.20–7.18 (2 H, m, 2 × HC_{Ar}), 3.91 (3 H, s, OCH_3), 1.26 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 165.6 (*C*=N), 61.7 (OCH_3), 37.1 ($C(CH_3)_3$), 28.8 ($(CH_3)_3$). Aromatic carbon signals could not be resolved. ^{1}H NMR data were consistent with those previously reported.[306]

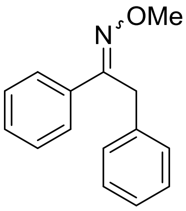
Benzophenone *O*-methyl oxime 315



Benzophenone (1.30 g, 7.14 mmol) was subjected to **General Procedure 2**, stirring at 50 °C for 24 h, to afford *O*-methyl oxime **315** as a colourless solid (1.43 g, 6.77 mmol, 95%). Purification was not required.

M.p. 58–60 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.58–7.31 (10 H, m, 10 × HC_{Ar}), 4.02 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.7 (*C*=N), 136.4, 133.3 (2 × C_{Ar}), 129.3, 129.2, 128.9, 128.3, 128.1, 127.9 (6 × HC_{Ar}), 62.4 (OCH_3); **IR** ν_{max} (powder)/cm^{-1} 2935, 1494, 1444, 1326, 1164, 1051, 1030; **HRMS** (ESI$^+$) $C_{14}H_{14}NO$ requires 212.1070, found $[M+H]^+$ 212.1079 (Δ −4.4 ppm).

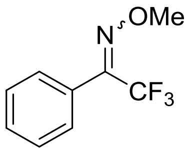
1,2-Diphenylethanone *O*-methyl oxime 316



Deoxybenzoin (1.55 g, 7.66 mmol) was subjected to **General Procedure 2**, stirring at room temperature for 48 h. Purification by flash column chromatography (SiO_2, 95:5 petrol/Et_2O) afforded a single isomer of *O*-methyl oxime **316** as a colourless solid (548 mg, 2.43 mmol, 32%).

M.p. 46–49 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.75 (2 H, td, J = 3.9, 1.9, 2 × HC_{Ar}), 7.43–7.22 (8 H, m, 8 × HC_{Ar}), 4.25 (2 H, s, CH_2), 4.13 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.1 (*C*=N), 136.8, 135.8 (2 × C_{Ar}), 129.2, 128.7 (2 × HC_{Ar}), 128.5 (2 × HC_{Ar}), 126.6, 126.3 (2 × HC_{Ar}), 62.1 (OCH_3), 32.7 (CH_2); **IR** ν_{max} (powder)/cm^{-1} 2937, 1720, 1493, 1445, 1270, 1045; **HRMS** (ESI$^+$) $C_{15}H_{15}NNaO$ requires 248.1046, found [M+Na]$^+$ 248.1049 (Δ −1.3 ppm).

2,2,2-Trifluoro-1-phenylethanone *O*-methyl oxime 317

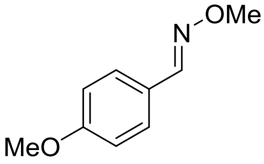


2,2,2-Trifluoroacetophenone (572 mg, 3.29 mmol) was subjected to **General Procedure 1**, stirring at 110 °C for 12 h, to afford a 1.2:1.0 mixture of geometric isomers of *O*-methyl oxime **317** as a colourless oil (549 mg, 2.70 mmol, 82%). Purification was not required.

Major isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.62–7.40 (5 H, m, 5 × HC_{Ar}), 4.13 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 146.2 (q, ^2J = 32.9, *C*=N), 130.3, 128.6, 128.4 (3 × HC_{Ar}), 126.9 (C_{Ar}), 120.6 (q, ^1J = 275.2, CF_3), 63.6 (OCH_3); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −66.3 (CF_3).

Minor isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.62–7.40 (5 H, m, 5 × HC_{Ar}), 4.03 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 146.2 (q, ^2J = 30.0, *C*=N), 130.1 (HC_{Ar}), 128.4, 128.4 (2 × HC_{Ar}), 126.9 (C_{Ar}), 118.3 (q, ^1J = 282.5, CF_3), 64.0 (OCH_3); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −66.3 (CF_3); **IR** ν_{max} (neat)/cm^{-1} 2937, 1446, 1350, 1218, 1136, 1052, 1001; **HRMS** (FI$^+$) $C_9H_8F_3NO$ requires 203.0558, found [M]$^+$ 203.0555 (Δ −1.5 ppm).

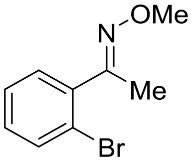
(*E*)-4-Methoxybenzaldehyde *O*-methyl oxime 318



p-Anisaldehyde (1.10 g, 8.09 mmol) was subjected to **General Procedure 2**, stirring at room temperature for 16 h, to afford a single geometric isomer of *O*-methyl oxime **318** as a colourless oil (1.25 g, 7.57 mmol, 93%). Purification was not required. Oxime geometry was assigned as (*E*) by analogy to oxime **294**.

M.p. 38–40 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.02 (1 H, s, *H*C=N), 7.53 (2 H, d, *J* = 8.3, *H*C(2) and *H*C(6)), 6.90 (2 H, d, *J* = 8.6, *H*C(3) and *H*C(5)), 3.96 (3 H, s, NOC*H*$_3$), 3.82 (3 H, m, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 160.9 (C_{Ar}OMe), 148.2 (H*C*=N), 128.5 (HC_{Ar}), 124.8 (C_{Ar}), 114.1 (HC_{Ar}), 61.8 (NO*C*H$_3$), 55.3 (O*C*H$_3$); **IR** ν_{max} (powder)/cm^{-1} 2966, 1607, 1512, 1247, 1168, 1042, 1025; **HRMS** (ESI$^+$) $C_9H_{12}NO$ requires 166.0863, found [M+H]$^+$ 166.0859 (Δ +2.9ppm).

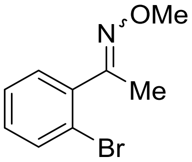
(*E*)-1-(2-Bromophenyl)ethanone *O*-methyl oxime 320



O-Methyl oxime **310** (800 mg, 5.36 mmol) was subjected to **General Procedure 3**, using *N*-bromosuccinimide, and stirred for 18 h. Purification by flash column chromatography (SiO_2, 8:2 petrol/CH_2Cl_2) afforded aryl bromide **320** as a colourless oil (669 mg, 2.93 mmol, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.64–7.53 (1 H, m, *H*C(6)), 7.37–7.17 (3 H, m, 3 × *H*C_{Ar}), 4.00 (3 H, s, OC*H*$_3$), 2.22 (3 H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 157.0 (*C*=N), 138.9 (C_{Ar}), 133.1 (H*C*(6)), 130.3, 130.0, 127.4 (3 × HC_{Ar}), 121.8 (*C*(2)Br), 61.9 (O*C*H$_3$), 16.5 (*C*H$_3$); **IR** ν_{max} (neat)/cm^{-1} 2937, 1471, 1427, 1100, 1048; **HRMS** (ESI$^+$) $C_9H_{11}{}^{79}BrNO$ requires 228.0019, found [M+H]$^+$ 228.0023 (Δ −1.4 ppm).

1-(2-Bromophenyl)ethanone *O*-methyl oxime (S1)

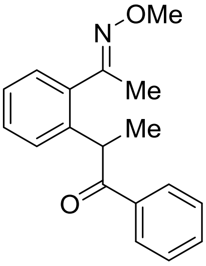


2’-Bromoacetophenone (1.29 mg, 10.4 mmol) was subjected to **General Procedure 2**, and stirred at room temperature for 4 h, to afford a 3:1 mixture of (*E*) and (*Z*) oxime isomers of aryl bromide **S1** as a colourless oil (1.35 g, 5.92 mmol, 91%). Purification was not required.

(*E*)-S1: **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.61–7.56 (1 H, m, *H*C(6)), 7.34–7.19 (3 H, m, 3 × *H*C_{Ar}), 4.00 (3 H, s, OC*H*$_3$), 2.23 (3 H, s, C*H*$_3$).

(*Z*)-S1: **^{1}H NMR** (200 MHz, $CDCl_3$) δ_H 7.62–7.57 (1 H, m, *H*C(6)), 7.39–7.06 (3 H, m, 3 × HC_{Ar}), 3.83 (3 H, s, OCH_3), 2.19 (3 H, s, CH_3). See Appendix 1 for nOe enhancements.

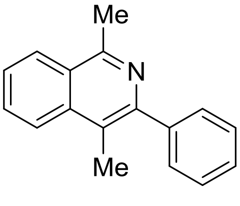
(*E*)-2-(2-(1-(Methoxyimino)ethyl)phenyl)-1-phenylpropan-1-one 321



Propiophenone (0.226 mL, 1.70 mmol) and aryl bromide **320** (194 mg, 0.851 mmol) were subjected to **General Procedure 4**. Purification by flash column chromatography (SiO_2, 99:1 petrol/EtOAc) afforded ketone **321** as a viscous oil (69.5 mg, 0.247 mmol, 29%). Oxime geometry was assigned as (*E*) by analogy to oxime **320**.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.06–7.98 (2 H, m, 2 × *o*-HC_{Ph}), 7.51–7.43 (1 H, m, *p*-HC_{Ph}), 7.42–7.34 (2 H, m, 2 × *m*-HC_{Ph}), 7.32–7.18 (4 H, m, 4 × HC_{Ar}), 5.17 (1 H, q, *J* = 6.8, $CHCH_3$), 3.94 (3 H, s, OCH_3), 2.27 (3 H, s, $CH_3C{=}N$), 1.53 (3 H, d, *J* = 6.8, $CHCH_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 200.9 (*C*=O), 155.8 (*C*=N), 139.2, 136.3 (2 × C_{Ar}), 132.7 (*p*-HC_{Ph}), 129.0 (HC_{Ar}), 128.9 (*o*-HC_{Ph}), 128.8 (HC_{Ar}), 128.4 (*m*-HC_{Ph}), 127.9, 126.9 (2 × HC_{Ar}), 61.8 (OCH_3), 44.1 ($CHCH_3$), 19.4 ($CHCH_3$), 16.6 ($CH_3C{=}N$). One C_{Ar} missing due to overlap; **IR** ν_{max} (neat)/cm^{-1} 2935, 1684, 1448, 1220, 1048; **HRMS** (ESI$^+$) $C_{18}H_{19}NNaO_2$ requires 304.1308, found $[M+Na]^+$ 304.1300 (Δ +2.1 ppm).

1,4-Dimethyl-3-phenylisoquinoline 222

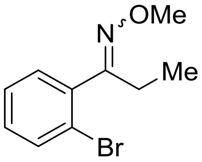


Method A: Ketone **321** (57.2 mg, 0.203 mmol) was subjected to **General Procedure 5**. Purification by flash column chromatography (SiO_2, 97:3 petrol/EtOAc) afforded isoquinoline **222** as an off-white solid (39.8 mg, 0.171 mmol, 84%).

Method B: Propiophenone (0.279 mL, 2.10 mmol) and aryl bromide **320** (240 mg, 1.05 mmol) were subjected to **General Procedure 6**. Purification by flash column chromatography (SiO_2, CH_2Cl_2) afforded isoquinoline **222** as an off-white solid (61.2 mg, 0.263 mmol, 25%).

M.p. 96–98 °C (lit. 95–97 °C);[175] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.18 (1 H, d, *J* = 8.3, *H*C_{Ar}), 8.07 (1 H, d, *J* = 8.3, *H*C_{Ar}), 7.76 (1 H, t, *J* = 7.7, *H*C_{Ar}), 7.67–7.55 (3 H, m, *H*C_{Ar} and 2 × *o*-*H*C_{Ph}), 7.49 (2 H, t, *J* = 7.5, 2 × *m*-*H*C_{Ph}), 7.44–7.36 (1 H, m, *p*-*H*C_{Ph}), 3.01 (3 H, s, C(1)C*H*$_3$), 2.62 (3 H, s, C(4)C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 155.9 (*C*(3)), 150.6 (*C*(1)), 141.5 (*C*$_{Ph}$), 136.3 (*C*$_{Ar}$), 129.9, 129.9 (H*C*$_{Ar}$ and *o*-H*C*$_{Ph}$), 128.1 (*m*-H*C*$_{Ph}$), 127.5 (*p*-H*C*$_{Ph}$), 126.3 (H*C*$_{Ar}$), 126.2 (*C*$_{Ar}$), 126.1, 124.2 (2 × H*C*$_{Ar}$), 122.3 (*C*(4)), 22.5 (C(1)*C*H$_3$), 15.4 (C(4)*C*H$_3$). Spectroscopic data were consistent with those previously reported.[175]

1-(2-Bromophenyl)propan-1-one *O*-methyl oxime 322

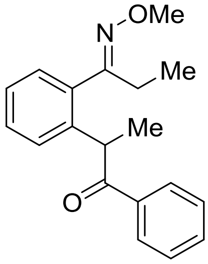


O-Methyl oxime **311** (497 mg, 3.05 mmol) was subjected to **General Procedure 3**, using *N*-bromosuccinimide, and stirred for 18 h. Purification by flash column chromatography (SiO_2, 8:2 petrol/CH_2Cl_2) afforded a 1.2:1.0 mixture of oxime geometric isomers of aryl bromide **322** as a colourless oil (517 mg, 2.14 mmol, 70%).

Major isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.65–7.54 (1 H, m, *H*C(6)), 7.39–7.30 (1 H, m, *H*C_{Ar}), 7.29–7.16 (2 H, m, 2 × *H*C_{Ar}), 3.97 (3 H, s, OC*H*$_3$), 2.75 (2 H, q, *J* = 7.7, OC*H*$_2$CH$_3$), 1.00 (3 H, t, *J* = 7.6, CH$_2$C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 161.9 (*C*=N), 137.5 (*C*$_{Ar}$), 132.9 (H*C*(6)), 130.8, 129.9, 127.3 (3 × H*C*$_{Ar}$), 122.3 (*C*(2)Br), 61.9 (O*C*H$_3$), 22.7 (O*C*H$_2$CH$_3$), 10.0 (CH$_2$*C*H$_3$).

Minor isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.64–7.54 (1 H, m, *H*C(6)), 7.39–7.29 (1 H, m, *H*C_{Ar}), 7.29–7.17 (1 H, m, *H*C_{Ar}), 7.07 (1 H, dd, *J* = 7.6, 1.3, *H*C_{Ar}), 3.83 (3 H, s, OC*H*$_3$), 2.54 (2 H, q, *J* = 7.4, C*H*$_2$CH$_3$), 1.12 (3 H, t, *J* = 7.5, CH$_2$C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 158.4 (*C*=N), 136.9 (*C*$_{Ar}$), 132.6 (H*C*(6)), 129.5, 128.5, 127.1 (3 × H*C*$_{Ar}$), 120.5 (*C*(2)Br), 61.8 (O*C*H$_3$), 28.4 (*C*H$_2$CH$_3$), 10.8 (CH$_2$*C*H$_3$); **IR** ν_{max} (neat)/cm^{-1} 2972, 2937, 1463, 1432, 1048, 1026; **HRMS** (ESI$^+$) $C_{10}H_{13}{}^{79}BrNO$ requires 242.0175, found $[M+H]^+$ 242.0176 (Δ −1.0 ppm).

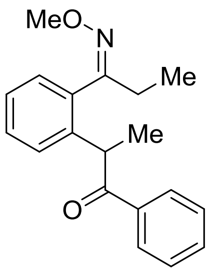
(*E*)-2-(2-(1-(Methoxyimino)propyl)phenyl)-1-phenylpropan-1-one (*E*)-323



Propiophenone (0.156 mL, 1.17 mmol) and aryl bromide **322** (142 mg, 0.587 mmol) were subjected to **General Procedure 4**. Purification by flash column chromatography (SiO_2, 99:1 petrol/EtOAc) afforded **(*E*)-323** as a viscous oil (54.9 mg, 0.186 mmol, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.11–8.00 (2 H, m, 2 × *o*-HC_{Ph}), 7.51–7.43 (1 H, m, *p*-HC_{Ph}), 7.42–7.33 (2 H, m, 2 × *m*-HC_{Ph}), 7.31–7.18 (4 H, m, 4 × HC_{Ar}) 5.13 (1 H, q, *J* = 6.8, C*H*CH_3), 3.91 (3 H, s, OCH_3), 2.87–2.66 (2 H, m, CH_2CH_3), 1.52 (3 H, d, *J* = 7.1, $CHCH_3$), 1.13 (3 H, t, *J* = 7.6, CH_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 201.0 (*C*=O), 160.8 (*C*=N), 139.6, 136.4, 135.1 (3 × C_{Ar}), 132.7 (*p*-HC_{Ph}), 129.0 (*o*-HC_{Ph}), 128.9 (2 × HC_{Ar}), 128.3 (HC_{Ar}), 128.0 (*m*-HC_{Ph}), 126.7 (HC_{Ar}), 61.7 (OCH_3), 44.0 ($CHCH_3$), 23.4 (CH_2CH_3), 19.6 ($CHCH_3$), 10.6 (CH_2CH_3); **IR** ν_{max} (neat)/cm^{-1} 2965, 1683, 1449, 1260, 1221, 1046; **HRMS** (ESI$^+$) $C_{19}H_{21}NNaO_2$ requires 318.1465, found $[M+Na]^+$ 318.1460 (Δ +1.2 ppm). See Appendix 1 for nOe enhancements.

(*Z*)-2-(2-(1-(Methoxyimino)propyl)phenyl)-1-phenylpropan-1-one (*Z*)-323

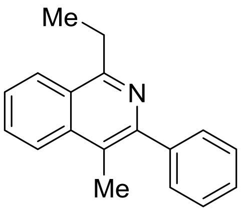


Propiophenone (0.156 mL, 1.17 mmol) and aryl bromide **322** (142 mg, 0.587 mmol) were subjected to **General Procedure 4**. Purification by flash column chromatography (SiO_2, 97:3 petrol/EtOAc) afforded **(*Z*)-323** as a viscous oil (34.7 mg, 0.115 mmol, 20%).

Major rotamer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.01 (2 H, d, *J* = 7.6, 2 × *o*-HC_{Ph}), 7.59–7.23 (6 H, m, 6 × HC_{Ar}), 7.11–6.96 (1 H, m, HC_{Ar}), 4.74–4.59 (1 H, m, $CHCH_3$), 3.44 (3 H, s, OCH_3), 2.70–2.51 (2 H, m, CH_2CH_3), 1.51 (3 H, d, *J* = 7.1, $CHCH_3$), 1.18 (3 H, t, *J* = 7.5, CH_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 200.5 (*C*=O), 159.4 (*C*=N), 138.0, 136.3, 134.6 (3 × C_{Ar}), 132.7 (HC_{Ar}), 128.8 (*o*-HC_{Ph}), 128.6 (2 × HC_{Ar}), 128.5, 126.9, 126.7 (3 × HC_{Ar}), 61.2 (OCH_3), 43.7 ($CHCH_3$), 29.8 (CH_2CH_3), 20.1 ($CHCH_3$), 11.4 (CH_2CH_3).

Minor rotamer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.90 (2 H, d, *J* = 7.6, 2 × *o*-HC_{Ph}), 7.58–7.23 (6 H, m, 6 × HC_{Ar}), 7.11–6.96 (1 H, m, HC_{Ar}), 4.75–4.57 (1 H, m, $CHCH_3$), 3.90 (3 H, s, OCH_3), 2.46–2.21 (2 H, m, CH_2CH_3), 1.57 (3 H, d, *J* = 6.8, $CHCH_3$), 1.01 (3 H, t, *J* = 7.5, CH_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 201.8 (*C*=O), 159.2 (*C*=N), 137.2, 137.1, 135.1 (3 × C_{Ar}), 132.9, 128.7, 128.5 (3 × HC_{Ar}), 128.4, 128.4 (2 × HC_{Ar}), 128.2, 126.3 (2 × HC_{Ar}), 61.6 (OCH_3), 43.7 ($CHCH_3$), 29.7 (CH_2CH_3), 19.2 ($CHCH_3$), 10.6 (CH_2CH_3); **IR** ν_{max} (neat)/cm^{-1} 2935, 1684, 1449, 1252, 1221, 1057, 1030; **HRMS** (ESI$^+$) $C_{19}H_{21}NNaO_2$ requires 318.1465, found $[M+Na]^+$ 318.1458 (Δ +1.9 ppm). See Appendix 2 for VT ^{1}H NMR spectra.

1-Ethyl-4-methyl-3-phenylisoquinoline 324



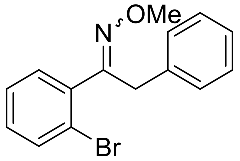
Method A: **(*E*)-323** (49.9 mg, 0.169 mmol) was subjected to **General Procedure 5**. Purification by flash column chromatography (SiO_2, 98:2 petrol/EtOAc) afforded isoquinoline **324** as an orange solid (37.2 mg, 0.150 mmol, 89%).

Method B: **(*Z*)-323** (45.0 mg, 0.152 mmol) was subjected to **General Procedure 5**. Purification by flash column chromatography (SiO_2, 98:2 petrol/EtOAc) afforded isoquinoline **324** as an orange solid (30.8 mg, 0.125 mmol, 82%).

Method C: Propiophenone (80.3 µL, 0.604 mmol) and aryl bromide **322** (73.1 mg, 0.302 mmol) were subjected to **General Procedure 6**. Purification by flash column chromatography (SiO_2, 98:2 petrol/EtOAc) afforded isoquinoline **324** as an orange solid (34.7 mg, 0.140 mmol, 46%).

M.p. 58–61 °C (lit. 64–65 °C);[166] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.23 (1 H, d, *J* = 8.3, HC_{Ar}), 8.08 (1 H, d, *J* = 8.6, HC_{Ar}), 7.75 (1 H, td, *J* = 7.6, 1.1, HC_{Ar}), 7.67–7.57 (3 H, m, HC_{Ar} and 2 × *o*-HC_{Ph}), 7.50 (2 H, t, *J* = 7.5, 2 × *m*-HC_{Ph}), 7.45–7.36 (1 H, m, *p*-HC_{Ph}), 3.39 (2 H, q, *J* = 7.6, CH_2CH_3), 2.63 (3 H, s, CH_3), 1.48 (3 H, t, *J* = 7.6, CH_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 160.7 (*C*(3)), 150.6 (*C*(1)), 141.7 (C_{Ph}), 136.6 (C_{Ar}), 130.0 (*o*-HC_{Ph}), 129.7 (HC_{Ar}), 128.1 (*m*-HC_{Ph}), 127.4 (*p*-HC_{Ph}), 126.2, 125.8 (2 × HC_{Ar}), 125.3 (C_{Ar}), 124.3 (HC_{Ar}), 122.1 (*C*(4)), 28.7 (CH_2CH_3), 15.5 (CH_3), 14.3 (CH_2CH_3). Spectroscopic data were consistent with those previously reported.[166]

1-(2-Bromophenyl)-2-phenylethanone *O*-methyl oxime 328

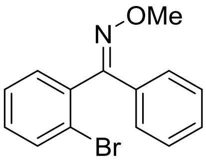


O-Methyl oxime **316** (304 mg, 1.35 mmol) was subjected to **General Procedure 3**, using *N*-bromosuccinimide, and stirred for 18 h. Purification by flash column chromatography (SiO_2, 8:2 petrol/CH_2Cl_2) afforded a 2:1 mixture of (*E*) and (*Z*) oxime isomers of aryl bromide **328** as a colourless oil (287 mg, 0.943 mmol, 70%).

(*E*)-328: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.64–7.53 (1 H, m, HC_{Ar}), 7.31–7.09 (7 H, m, 7 × HC_{Ar}), 7.00 (1H, dd, *J* = 6.7, 2.1, HC_{Ar}), 4.14 (2 H, s, CH_2), 4.06 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 158.5 (*C*=N), 137.2, 135.8 (2 × C_{Ar}), 132.9, 131.3, 130.0, 129.4, 128.4, 127.1, 126.4 (7 × HC_{Ar}), 122.2 ($C_{Ar}Br$), 62.0 (OCH_3), 35.6 (CH_2).

(*Z*)-328: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.64–7.53 (1 H, m, HC_{Ar}), 7.30–7.09 (7 H, m, 7 × HC_{Ar}), 6.69–6.58 (1 H, m, HC_{Ar}), 3.90 (3 H, s, OCH_3), 3.84 (2 H, br. s, CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 156.3 (*C*=N), 136.0, 135.8 (2 × C_{Ar}), 132.5, 129.6, 129.2, 128.4, 126.8, 126.8 (6 × HC_{Ar}), 120.4 ($C_{Ar}Br$), 62.0 (OCH_3), 41.3 (CH_2). One HC_{Ar} missing due to overlap. Spectroscopic data were consistent with those previously reported.[307]

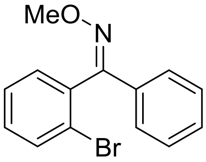
(*E*)-(2-Bromophenyl)(phenyl)methanone *O*-methyl oxime (*E*)-330



O-Methyl oxime **315** (1.00 g, 4.74 mmol) was subjected to **General Procedure 3**, using *N*-bromosuccinimide, and stirred for 2 h. Purification by flash column chromatography (SiO_2, 8:2 petrol/CH_2Cl_2) afforded **(*E*)-330** as a colourless oil (1.24 g, 4.27 mmol, 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65–7.53 (3 H, m, 3 × HC_{Ar}), 7.49 (1 H, dd, J = 7.6, 1.8, HC_{Ar}), 7.44–7.34 (4 H, m, 4 × HC_{Ar}), 7.32–7.23 (1 H, m, HC_{Ar}), 4.07 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 155.8 (C=N), 138.0 (C_{Ar}), 133.4 (HC_{Ar}), 132.4 (C_{Ar}), 131.9, 130.3, 130.1, 129.5, 128.0, 127.4 (6 × HC_{Ar}), 123.5 (C_{Ar}Br), 62.6 (OCH_3); **IR** ν_{max} (neat)/cm^{-1} 2936, 1468, 1445, 1328, 1059, 1036; **HRMS** (ESI$^+$) $C_{14}H_{13}{}^{79}BrNO$ requires 290.0175, found [M+H]$^+$ 290.0176 (Δ −0.5 ppm).

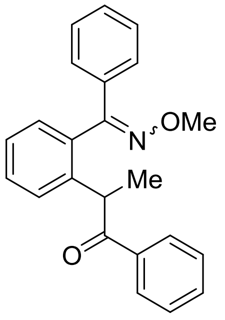
(*Z*)-(2-Bromophenyl)(phenyl)methanone *O*-methyl oxime (*Z*)-330



2-Bromobenzophenone (429 mg, 1.56 mmol) was subjected to **General Procedure 2**, stirring at 90 °C for 16 h. Purification by flash column chromatography afforded **(*Z*)-330** as a colourless solid (371 mg, 1.28 mmol, 82%).

M.p. 102–105 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.69 (1 H, d, J = 8.1, HC_{Ar}), 7.55–7.46 (2 H, m, 2 × HC_{Ar}), 7.45–7.25 (5 H, m, 5 × HC_{Ar}), 7.19 (1 H, dd, J = 7.6, 1.5, HC_{Ar}), 4.01 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 155.3 (C=N), 135.7, 134.6 (2 × C_{Ar}), 132.8, 130.0, 129.8, 129.5, 128.4, 127.3, 126.9 (7 × HC_{Ar}), 121.8 (C_{Ar}Br), 62.7 (OCH_3); **IR** ν_{max} (powder)/cm^{-1} 2931, 1464, 1328, 1051, 1027; **HRMS** (ESI$^+$) $C_{14}H_{13}{}^{79}BrNO$ requires 290.0175, found [M+H]$^+$ 290.0168 (Δ +1.6 ppm). See Appendix 3 for single crystal X-ray diffraction report.

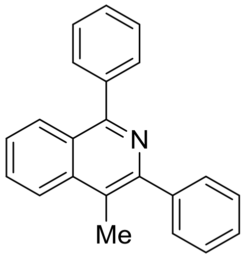
2-(2-(Methoxyimino)(phenyl)methyl)phenyl)-1-phenylpropan-1-one 331



Propiophenone (91.6 µL, 0.689 mmol) and aryl bromide **(*E*)-330** (100 mg, 0.345 mmol) were subjected to **General Procedure 4**. Purification by flash column chromatography (SiO_2, 97:3 petrol/EtOAc) afforded a single oxime isomer of ketone **331** as a colourless solid (110 mg, 0.320 mmol, 93%).

M.p. 84–86 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.88 (2 H, d, J = 7.3, 2 × o-HC_{Ph}), 7.65–7.55 (2 H, m, 2 × o-HC_{Ph}), 7.49–7.37 (4 H, m, 4 × HC_{Ar}), 7.36–7.20 (6 H, m, 6 × HC_{Ar}), 5.02 (1 H, q, J = 6.7, CHCH$_3$), 4.04 (3 H, s, OCH_3), 1.35 (3 H, d, J = 6.8, CHCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 200.8 (C=O), 155.8 (C=N), 140.4, 136.3, 135.7, 133.4 (4 × C_{Ar}), 132.7, 131.1 (2 × HC_{Ar}), 130.1 (HC_{Ph}), 129.7, 129.5 (2 × HC_{Ar}), 128.8 (HC_{Ph}), 128.4, 128.2, 128.0, 126.8 (4 × HC_{Ar}), 62.5 (OCH$_3$), 44.3 (CHCH$_3$), 18.9 (CHCH$_3$); **IR** ν_{max} (powder)/cm^{-1} 2934, 1683, 1447, 1220, 1042; **HRMS** (ESI$^+$) $C_{23}H_{21}NNaO_2$ requires 366.1465, found [M+Na]$^+$ 366.1453 (Δ +3.3 ppm).

4-Methyl-1,3-diphenylisoquinoline 332

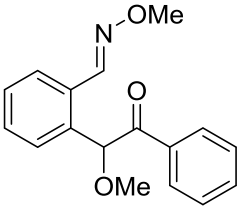


Method A: Ketone **331** (50.3 mg, 0.146 mmol) was subjected to **General Procedure 5**. Purification by flash column chromatography (SiO_2, 99:1 petrol/EtOAc) afforded isoquinoline **332** as a pale yellow solid (36.4 mg, 0.123 mmol, 84%).

Method B: Propiophenone (96.3 µL, 0.724 mmol) and aryl bromide **330** (105 mg, 0.362 mmol) were subjected to **General Procedure 6**. Purification by flash column chromatography (SiO_2, 99:1 petrol/EtOAc) afforded isoquinoline **332** as a pale yellow solid (74.0 mg, 0.251 mmol, 69%).

M.p. 78–83 °C (lit. 77–78 °C);[142] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.15 (2 H, dd, J = 8.5, 3.9, 2 × HC_{Ar}), 7.84–7.71 (3 H, m, 3 × HC_{Ar}), 7.67 (2 H, d, J = 7.3, 2 × HC_{Ar}), 7.62–7.38 (7 H, m, 7 × *H*C$_{Ar}$), 2.73 (3 H, s, C*H*$_3$); ^{13}**C NMR** (100 MHz, CDCl$_3$) δ_C 158.3, 151.0, 141.4, 139.8, 137.1 (5 × *C*$_{Ar}$), 130.2, 130.1 (2 × *o*-HC$_{Ph}$), 130.0, 128.3 (2 × HC$_{Ar}$), 128.2 (*m*-HC$_{Ph}$), 128.1 (HC$_{Ar}$), 128.1 (*m*-HC$_{Ph}$), 127.5, 126.4 (2 × HC$_{Ar}$), 125.4 (*C*$_{Ar}$), 123.9 (HC$_{Ar}$), 123.2 (*C*$_{Ar}$), 15.7 (*C*H$_3$). Spectroscopic data were consistent with those previously reported.[142]

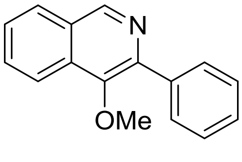
(*E*)-2-(1-Methoxy-2-oxo-2-phenylethyl)benzaldehyde *O*-methyl oxime 341



2-Methoxyacetophenone (0.150 mL, 0.981 mmol) and aryl bromide **295** (105 mg, 0.490 mmol) were subjected to **General Procedure 4**. Purification by flash column chromatography (SiO$_2$, 98:2 petrol/EtOAc) afforded a single oxime isomer of ketone **341** as a viscous oil (118 mg, 0.417 mmol, 85%). Oxime geometry was assigned as (*E*) by analogy to oxime **295**.

^{1}**H NMR** (400 MHz, CDCl$_3$) δ_H 8.36 (1 H, s, *H*C=N), 7.99 (2 H, d, *J* = 7.3, 2 × *o*-*H*C$_{Ph}$), 7.59 (1 H, d, *J* = 7.1, *H*C(6)), 7.55–7.48 (2 H, m, 2 × *H*C$_{Ar}$), 7.47–7.31 (4 H, m, 4 × *H*C$_{Ar}$), 6.23 (1 H, s, *H*COMe), 3.76 (3 H, s, NOC*H*$_3$), 3.51 (3 H, s, HCOC*H*$_3$); ^{13}**C NMR** (100 MHz, CDCl$_3$) δ_C 195.8 (*C*=O), 148.3 (H*C*=N), 135.6, 134.8 (2 × *C*$_{Ar}$), 133.2 (H*C*(6)), 130.7 (*C*$_{Ar}$), 129.8 (2 × H*C*$_{Ar}$), 128.8 (H*C*$_{Ar}$ and *o*-H*C*$_{Ph}$), 128.6 (H*C*$_{Ar}$), 128.5 (*m*-H*C*$_{Ph}$), 82.5 (H*C*OMe), 61.9 (NO*C*H$_3$), 58.0 (HCO*C*H$_3$); **IR** ν_{max} (neat)/cm^{-1} 2936, 1693, 1597, 1448, 1210, 1088, 1043, 1003; **HRMS** (ESI$^+$) $C_{17}H_{17}NNaO_3$ requires 306.1101, found [M+Na]$^+$ 306.1097 (Δ +0.9 ppm).

4-Methoxy-3-phenylisoquinoline 236

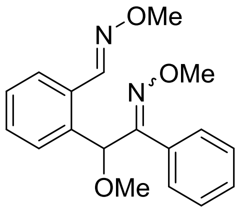


Method A: Ketone **341** (54.0 mg, 0.191 mmol) was subjected to **General Procedure 5**. Purification by flash column chromatography (SiO$_2$, 98:2 petrol/EtOAc) afforded isoquinoline **236** as a viscous oil (25.3 mg, 0.108 mmol, 56%).

Method B: 2-Methoxyacetophenone (0.131 mL, 0.953 mmol) and aryl bromide **295** (102 mg, 0.477 mmol) were subjected to **General Procedure 6**. Purification by flash column chromatography (SiO_2, 97:3 petrol/EtOAc) afforded isoquinoline **236** as a viscous oil (89.6 mg, 0.381 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.16 (1 H, s, *H*C(1)), 8.23 (1 H, d, *J* = 8.3, *H*C(5)), 8.10 (2 H, d, *J* = 7.6, 2 × *o*-*H*C_{Ph}), 8.02 (1 H, d, *J* = 8.3, *H*C(8)), 7.76 (1 H, t, *J* = 7.6, *H*C(6)), 7.63 (1 H, t, *J* = 7.8, *H*C(7)), 7.52 (2 H, t, *J* = 7.7, 2 × *m*-*H*C_{Ph}), 7.42 (1 H, t, *J* = 7.3, *p*-*H*C_{Ph}), 3.70 (3 H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 149.0 (*C*$_{Ar}$), 147.8 (H*C*(1)), 143.1, 138.0, 132.0 (3 × *C*$_{Ar}$), 130.4 (H*C*(6)), 129.3 (*C*$_{Ar}$), 129.2 (*o*-H*C*$_{Ph}$), 128.4 (*m*-H*C*$_{Ph}$), 128.1 (*p*-H*C*$_{Ph}$), 127.4 (H*C*(8)), 127.3 (H*C*(7)), 121.6 (H*C*(5)), 61.2 (O*C*H$_3$). Spectroscopic data were consistent with those previously reported.[175]

(1*E*)-2-(1-Methoxy-2-(methoxyimino)-2-phenylethyl)benzaldehyde *O*-methyl oxime 342



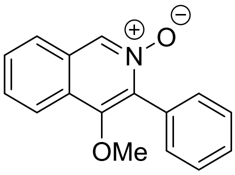
Side product of the synthesis of isoquinoline **236** by **General Procedure 5**. Isolation by flash column chromatography (SiO_2, 99:1 petrol/EtOAc) afforded a 1:1 mixture of diastereoisomers of bis-*O*-methyl oxime **342** as a colourless oil (23.9 mg, 0.0763 mmol, 40%). Aldoxime geometry was assigned as (*E*) by analogy to oxime **295**.

Isomer A: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.42 (1 H, s, *H*C=N), 7.82–7.70 (1 H, m, *H*C$_{Ar}$), 7.53 (2 H, d, *J* = 7.1, 2 × *H*C$_{Ar}$), 7.41–7.35 (1 H, m, *H*C$_{Ar}$), 7.32–7.20 (5 H, m, 5 × *H*C$_{Ar}$), 6.23 (1 H, s, *H*COMe), 4.03 (3 H, s, NOC*H*$_3$), 4.01 (3 H, s, NOC*H*$_3$), 3.40 (3 H, s, HCOC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 157.1 (*C*=N), 147.0 (H*C*=N), 136.5, 133.1, 130.4 (3 × *C*$_{Ar}$), 129.5, 129.0, 128.3, 128.0, 127.9, 127.2, 126.5 (7 × H*C*$_{Ar}$), 74.4 (H*C*OMe), 62.3 (NO*C*H$_3$), 62.0 (NO*C*H$_3$), 57.2 (HCO*C*H$_3$).

Isomer B: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.54 (1 H, s, *H*C=N), 7.83–7.70 (1 H, m, *H*C$_{Ar}$), 7.33–7.20 (6 H, m, 6 × *H*C$_{Ar}$), 7.06–6.97 (2 H, m, 2 × *H*C$_{Ar}$), 5.41 (1 H, s, *H*COMe), 3.97

(3 H, s, NOC*H*$_3$), 3.88 (3 H, s, NOC*H*$_3$), 3.50 (3 H, s, HCOC*H*$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 156.0 (*C*=N), 147.1 (H*C*=N), 136.1, 131.3, 130.0 (3 × *C*$_{Ar}$), 129.4, 128.6, 128.1, 128.0, 127.8, 127.7, 126.8 (7 × H*C*$_{Ar}$), 82.3 (H*C*OMe), 62.3 (NO*C*H$_3$), 61.9 (NO*C*H$_3$), 57.0 (HCO*C*H$_3$). **IR** ν_{max} (neat)/cm^{-1} 2936, 1444, 1262, 1188, 1082, 1054, 1020; **HRMS** (ESI$^+$) $C_{18}H_{20}N_2NaO_3$ requires 335.1366, found [M+Na]$^+$ 335.1357 (Δ +2.5 ppm).

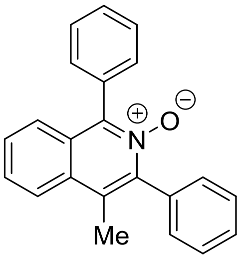
4-Methoxy-3-phenylisoquinoline 2-oxide 343



Ketone **341** (104 mg, 0.367 mmol) was subjected to **General Procedure 7**. Purification by flash column chromatography (basic Al$_2$O$_3$, EtOAc) afforded isoquinoline *N*-oxide **343** as an off-white solid (67.9 mg, 0.270 mmol, 74%).

M.p. 175–178 °C; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 8.81 (1 H, s, *H*C(1)), 8.10–8.01 (1 H, m, *H*C(5)), 7.78–7.69 (1 H, m, *H*C(8)), 7.67–7.58 (4 H, m, *H*C(6), *H*C(7) and 2 × *H*C$_{Ph}$), 7.57–7.45 (3 H, m, 3 × *H*C$_{Ph}$), 3.55 (3 H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 152.1, 140.3 (2 × *C*$_{Ar}$), 133.4 (H*C*(1)), 130.6 (H*C*$_{Ph}$), 129.5, 129.2 (H*C*(6) and H*C*(7)), 128.7 (H*C*$_{Ph}$), 128.5 (*C*$_{Ar}$), 128.3 (H*C*$_{Ph}$), 125.8 (*C*$_{Ar}$), 124.7 (H*C*(8)), 122.0 (H*C*(5)), 61.6 (O*C*H$_3$). One *C*$_{Ar}$ missing due to overlap; **IR** ν_{max} (powder)/cm^{-1} 3062, 2918, 2850, 1588, 1465, 1428, 1366, 1312, 1179, 1128, 1099; **HRMS** (ESI$^+$) $C_{16}H_{14}NO_2$ requires 252.1019, found [M+H]$^+$ 252.1024 (Δ −2.3 ppm).

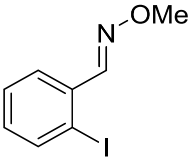
4-Methyl-1,3-diphenylisoquinoline 2-oxide 344



Ketone **331** (23.5 mg, 0.0684 mmol) was subjected to **General Procedure 7**. Purification by flash column chromatography (basic Al$_2$O$_3$, 8:2 EtOAc/MeOH) afforded isoquinoline *N*-oxide **344** as an off-white solid (18.1 mg, 0.0581 mmol, 85%).

M.p. 148–152 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.01 (1 H, d, *J* = 8.3, *H*C$_{Ar}$), 7.67–7.59 (1 H, m, *H*C$_{Ar}$), 7.59–7.39 (12 H, m, 12 × *H*C$_{Ar}$), 2.51 (3 H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 146.4, 144.8, 133.4 131.5 (4 × *C*$_{Ar}$), 130.6, 130.2 (2 × H*C*$_{Ar}$), 129.6, 129.5 (2 × *C*$_{Ar}$), 128.9 (H*C*$_{Ar}$), 128.6 (*C*$_{Ar}$), 128.5 (H*C*$_{Ar}$), 128.4, 128.4 (2 × H*C*$_{Ar}$), 128.2, 126.2, 124.0 (3 × H*C*$_{Ar}$), 16.3 (*C*H$_3$). One *H*C$_{Ar}$ missing due to overlap; **IR** ν_{max} (powder)/cm^{-1} 3059, 2919, 1443, 1350, 1301, 1214, 1132, 1023; **HRMS** (ESI$^+$) $C_{22}H_{18}NO$ requires 312.1383, found [M+H]$^+$ 312.1375 (Δ +2.2 ppm).

(*E*)-2-Iodobenzaldehyde *O*-methyl oxime 345

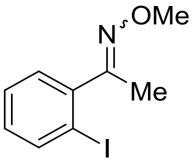


Method A: *O*-Methyl oxime **294** (52.3 mg, 0.387 mmol) was subjected to **General Procedure 3**, using 1.0 eq *N*-iodosuccinimide, and stirred for 18 h. Purification by flash column chromatography (SiO_2, 95:5 petrol/CH_2Cl_2) afforded aryl iodide **345** as a colourless oil (60.6 mg, 0.232 mmol, 60%). Oxime geometry was assigned as (*E*) by analogy to oxime **295**.

Method B: 2-Iodobenzaldehyde (276 mg, 1.15 mmol) was subjected to **General Procedure 1**. Filtration through a short plug of SiO_2, eluting with toluene, afforded aryl iodide **345** as a colourless oil (279 mg, 1.07 mmol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.35 (1 H, s, *H*C=N), 7.86–7.83 (2 H, m, 2 × *H*C$_{Ar}$), 7.34 (1 H, t, *J* = 7.6, *H*C$_{Ar}$), 7.05 (1 H, td, *J* = 7.7, 1.7, *H*C$_{Ar}$), 4.02 (3 H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 152.0 (H*C*=N), 139.6 (H*C*$_{Ar}$), 134.3 (*C*$_{Ar}$), 131.1, 128.2, 127.3 (3 × H*C*$_{Ar}$), 98.9 (*C*$_{Ar}$I), 62.2 (O*C*H$_3$); **IR** ν_{max} (neat)/cm^{-1} 2935, 1698, 1583, 1463, 1434, 1341, 1208, 1057, 1040, 1012; **HRMS** (FI$^+$) C_8H_8INO requires 260.9651, found [M]$^+$ 260.9657 (Δ +2.4 ppm).

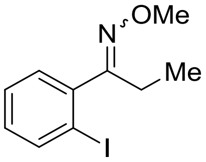
1-(2-iodophenyl)ethan-1-one *O*-methyl oxime 346



O-Methyl oxime **310** (100 mg, 0.670 mmol) was subjected to **General Procedure 3**, using *N*-iodosuccinimide, and stirred for 30 min. Purification by flash column chromatography (SiO$_2$, 9:1 petrol/CH$_2$Cl$_2$) afforded a single oxime isomer of aryl iodide **346** as a colourless oil (144 mg, 0.523 mmol, 78%).

^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.87 (1 H, dd, *J* = 8.0, 1.1, *H*C(6)), 7.36 (1 H, td, *J* = 7.5, 1.1, *H*C(4)), 7.26 (1 H, dd, *J* = 7.6, 1.7, *H*C(3)), 7.05 (1 H, td, *J* = 7.7, 1.7, *H*C(5)), 4.00 (3 H, s, OC*H*$_3$), 2.20 (3 H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 158.5 (*C*=N), 142.6 (*C*$_{Ar}$), 139.5 (H*C*(6)), 129.9 (H*C*(5)), 129.4 (H*C*(3)), 128.1 (H*C*(4)), 95.9 (*C*(2)I), 61.9 (O*C*H$_3$), 16.6 (*C*H$_3$); **IR** ν_{max} (neat)/cm^{-1} 2938, 1585, 1469, 1428, 1364, 1319, 1253, 1187, 1096, 1043, 1010; **HRMS** (ESI$^+$) C$_9$H$_{11}$INO requires 275.9880, found [M+H]$^+$ 275.9881 (–0.4 ppm).

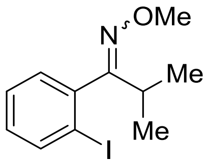
1-(2-Iodophenyl)propan-1-one *O*-methyl oxime 347



O-Methyl oxime **311** (217 mg, 1.31 mmol) was subjected to **General Procedure 3**, using *N*-iodosuccinimide, and stirred for 3 h. Purification by flash column chromatography (SiO$_2$, 9:1 petrol/CH$_2$Cl$_2$) afforded a single oxime isomer of aryl iodide **347** as a yellow oil (296 mg, 1.02 mmol, 78%).

^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.87 (1 H, dd, *J* = 8.0, 0.9, *H*C(6)), 7.37 (1 H, td, *J* = 7.5, 1.2, *H*C(4)), 7.21 (1 H, dd, *J* = 7.5, 1.6, *H*C(3)), 7.05 (1 H, td, *J* = 7.6, 1.7, *H*C(5)) 3.98 (3 H, s, OC*H*$_3$), 2.73 (2 H, q, *J* = 7.6, C*H*$_2$), 1.00 (3 H, t, *J* = 7.6, C*H*$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 163.3 (*C*=N), 141.3 (C(1)), 139.3 (H*C*(6)), 129.9 (H*C*(3)), 129.8 (H*C*(5)), 127.9 (H*C*(4)), 96.9 (*C*(2)I), 61.8 (O*C*H$_3$), 22.9 (*C*H$_2$), 10.0 (*C*H3); **IR** ν_{max} (neat)/cm^{-1} 2962, 2936, 1743, 1569, 1547, 1461, 1429, 1368, 1338, 1044, 1014; **HRMS** (ESI$^+$) C$_{10}$H$_{13}$INO requires 290.0036, found [M+H]$^+$ 290.0043 (–2.3 ppm).

1-(2-Iodophenyl)-2-methylpropan-1-one *O*-methyl oxime 348

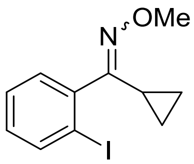


O-Methyl oxime **312** (217 mg, 1.23 mmol) was subjected to **General Procedure 3**, using *N*-iodosuccinimide, and stirred for 2.5 h. Purification by flash column chromatography (SiO_2, 9:1 petrol/CH_2Cl_2) afforded a 12:1 mixture of oxime geometric isomers of aryl iodide **348** as a yellow oil (232 mg, 0.765 mmol, 62%).

Major isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.89 (1 H, dd, *J* = 8.0, 1.0, *H*C(6)), 7.35 (1 H, td, *J* = 7.5, 1.1, *H*C(4)), 7.19 (1 H, dd, *J* = 7.6, 1.6, *H*C(3)), 7.04 (1 H, td, *J* = 7.7, 1.7, *H*C(5)), 3.98 (3 H, s, OC*H*$_3$), 3.44 (1 H, sept., *J* = 7.0, *H*C(CH_3)$_2$), 1.13 (6 H, d, *J* = 7.0, (C*H*$_3$)$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 165.8 (*C*=N), 140.4 (*C*(1)), 139.5 (H*C*(6)), 129.6 (H*C*(5)), 129.3 (H*C*(3)), 127.6 (H*C*(4)), 98.6 (*C*(2)I), 61.8 (O*C*H$_3$), 28.8 (*C*H(CH_3)$_2$), 19.5 ((*C*H$_3$)$_2$).

Minor isomer: Carbon and aromatic proton NMR signals could not be resolved. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.80 (3 H, s, OC*H*$_3$), 3.55 (1 H, sept., *J* = 7.2, *H*C(CH_3)$_2$), 1.19 (6 H, d, *J* = 7.1, (C*H*$_3$)$_2$); **IR** ν_{max} (neat)/cm^{-1} 2965, 2935, 1466, 1428, 1362, 1056, 1042, 1014; **HRMS** (ESI$^+$) $C_{11}H_{15}INO$ requires 304.0193, found [M+H]$^+$ 304.0185 (Δ +2.6 ppm).

Cyclopropyl(2-iodophenyl)methanone *O*-methyl oxime 359



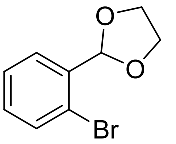
O-Methyl oxime **313** (253 mg, 1.44 mmol) was subjected to **General Procedure 3**, using *N*-iodosuccinimide, and stirred for 30 min. Purification by flash column chromatography (SiO_2, 8:2 petrol/CH_2Cl_2) afforded a single oxime isomer of aryl iodide **359** as a yellow oil (196 mg, 0.651 mmol, 45%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.83 (1 H, dt, *J* = 8.0, 0.6, *H*C(6)), 7.32 (1 H, td, *J* = 7.5, 1.2, *H*C(4)), 7.11 (1 H, dd, *J* = 7.6, 1.7, *H*C(3)), 7.03 (1 H, td, *J* = 7.4, 1.7, *H*C(5)), 4.00 (3 H, s, OC*H*$_3$), 2.55–2.48 (1 H, m, *H*C(CH_2)$_2$), 0.95–0.90 (2 H, m, C*H*$_a$H$_b$C*H*$_a$H$_b$), 0.48–0.44 (2 H,

$CH_aCH_bCH_aH_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 163.2 (*C*=N), 139.0 (H*C*(6)), 137.4 (C_{Ar}), 130.4 (H*C*(3)), 129.9 (H*C*(5)), 127.6 (H*C*(4)), 99.4 (C_{Ar}I), 61.9 (OCH_3), 9.47 ($HC(CH_2)_2$), 6.04 (CH_2CH_2); **IR** ν_{max} (neat)/cm^{-1} 2936, 1601, 1467, 1427, 1328, 1055, 1041, 1017; **HRMS** (ESI$^+$) $C_{11}H_{13}INO$ requires 302.0036, found [M+H]$^+$ 302.0036 (Δ +0.2 ppm).

3.3.2 Chapter 2.2 compounds

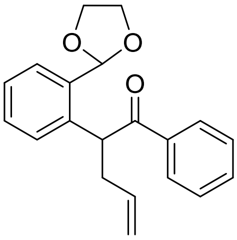
2-(2-Bromophenyl)-1,3-dioxolane 217



2-Bromobenzaldehyde (5.15 g, 27.8 mmol) was subjected to **General Procedure 8**. Purification by flash column chromatographgy (SiO_2, 95:5 petrol/EtOAc) afforded acetal **217** as a colourless oil (5.96 g, 26.0 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.52 (1 H, dd, *J* = 7.7, 1.6, HC_{Ar}), 7.48 (1 H, dd, *J* = 7.8, 0.7, HC_{Ar}), 7.26 (1 H, t, *J* = 7.2, HC_{Ar}), 7.14 (1 H, td, *J* = 7.7, 1.6, HC_{Ar}), 6.02 (1 H, s, $HC(OR)_2$), 4.12–3.94 (4 H, m, OCH_2CH_2O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 136.6 (C_{Ar}), 132.9, 130.6, 127.7, 127.4 (4 × HC_{Ar}), 122.9 (C_{Ar}), 102.6 ($HC(OR)_2$), 65.4 (OCH_2CH_2O). Spectroscopic data were consistent with those previously reported.[175]

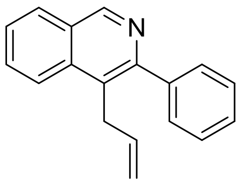
2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-phenylpent-4-en-1-one 366



To a microwave vial fitted with a rubber septum was added (D*t*BPF)$PdCl_2$ (6.9 mg, 0.011 mmol) and NaO*t*Bu (105 mg, 1.06 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (97.1 mg, 0.423 mmol) in anhydrous THF (2.1 mL) was added *via* syringe, followed by acetophenone (98.8 μL, 0.847 mmol). The reaction mixture was heated at 70 °C for 6 h. After cooling to 0 °C, allyl bromide (36.8 μL, 0.423 mmol) was added *via* syringe and the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 petrol/CH_2Cl_2) afforded ketone **366** as a colourless solid (102 mg, 0.331 mmol, 78%).

M.p. 71–73 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.11–8.04 (2 H, m, 2 × *o*-HC_{Ph}), 7.63–7.57 (1 H, m, HC_{Ar}), 7.49–7.43 (1 H, m, *p*-HC_{Ar}), 7.40–7.33 (2 H, m, 2 × *m*-HC_{Ar}), 7.28–7.22 (2 H, m, 2 × HC_{Ar}), 7.18–7.14 (1 H, m, HC_{Ar}), 6.13 (1 H, s, $HC(OR)_2$), 5.87 (1 H, ddt, J = 17.0, 10.2, 6.8, $HC{=}CH_2$), 5.15 (1 H, dd, J = 9.2, 4.7, $CHC{=}O$), 5.08 (1 H, dq, J = 17.1, 1.6, $HC{=}CH_aH_b$), 4.99 (1 H, m, $HC{=}CH_aH_b$), 4.26–4.18 (2 H, m, $OCH_aH_bCH_aH_bO$), 4.17–4.09 (2 H, m, $OCH_aH_bCH_aH_bO$), 3.04–2.93 (1 H, m, $CH_aH_bCH{=}CH_2$), 2.60–2.48 (1 H, m, $CH_aH_bCH{=}CH_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 199.6 ($C{=}O$), 138.4, 136.8 (2 × C_{Ar}), 136.6 ($HC{=}CH_2$), 133.9 (C_{Ar}), 132.7 (*p*-HC_{Ph}), 129.7 (HC_{Ar}), 128.9 (*o*-HC_{Ph}), 128.4 (*m*-HC_{Ar}), 127.8, 127.7, 127.0 (3 × HC_{Ar}), 116.2 ($HC{=}CH_2$), 102.9 ($HC(OR)_2$), 65.2 (OCH_2CH_2O), 65.1 (OCH_2CH_2O), 48.9 ($CHC{=}O$), 38.3 (CH_2CH); **IR** ν_{max} (powder)/cm^{-1} 3070, 2888, 1680, 1597, 1448, 1410, 1343, 1242, 1207, 1103, 1068, 1045; **HRMS** (ESI$^+$) $C_{20}H_{20}NaO_3$ requires 331.1305, found $[M+Na]^+$ 331.1301 (Δ +0.2 ppm).

4-Allyl-3-phenylisoquinoline 367

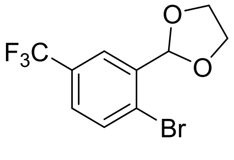


Method A: Ketone **366** (40.3 mg, 0.131 mmol) was subjected to **General Procedure 9**. Purification by flash column chromatography (SiO_2, 85:15 petrol/EtOAc) afforded isoquinoline **367** as a yellow oil (30.7 mg, 0.126 mmol, 96%).

Method B: To a microwave vial fitted with a rubber septum was added (D*t*BPF)$PdCl_2$ (6.0 mg, 0.0092 mmol) and NaO*t*Bu (91.4 mg, 0.923 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (84.6 mg, 0.369 mmol) in anhydrous THF (1.8 mL) was added *via* syringe, followed by the addition of acetophenone (86.1 µL, 0.738 mmol) and the reaction mixture was heated at 70 °C for 6 h. After cooling to 0 °C, allyl bromide (31.9 µL, 0.369 mmol) was added *via* syringe. The reaction mixture was then allowed to warm to room temperature and stirred for 18 h. The pH was then adjusted to pH 5 by the dropwise addition of 1 M aqueous HCl before a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (3.7 mL) was added. The resulting mixture was stirred at 90 °C for 24 h then cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (5 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 85:15 petrol/CH_2Cl_2 then 9:1 petrol/Et_2O) afforded isoquinoline **367** as a yellow oil (64.3 mg, 0.262 mmol, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.26 (1 H, s, *H*C(1)), 8.06–8.01 (2 H, m, *H*C(5) and *H*C(8)), 7.75 (1 H, t, *J* = 6.8, *H*C(7)), 7.65–7.60 (3 H, m, *H*C(6) and 2 × HC_{Ph}), 7.50–7.40 (3 H, m, 3 × HC_{Ph}), 6.16 (1 H, ddt, *J* = 17.3, 10.9, 5.4, *H*C=CH_2), 5.17 (1 H, app. d, *J* = 10.9, HC=CH_aH_b), 4.90 (1 H, app. d, *J* = 17.3, HC=CH_aH_b), 3.84–3.81 (2 H, m, CH_2CH=CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 152.6 (*C*(3)), 150.9 (H*C*(1)), 141.0 (C_{Ar}), 136.9 (H*C*=CH_2), 135.8 (C_{Ar}), 130.4 (H*C*(7)), 129.2 (HC_{Ph}), 128.1 (H*C*(5)), 128.0, 127.7 (2 × HC_{Ph}), 127.6 (C_{Ar}), 126.6 (H*C*(6)), 125.5 (C_{Ar}), 124.3 (H*C*(8)), 116.7 (HC=CH_2), 33.1 (CH_2CH=CH_2). Spectroscopic data were consistent with those previously reported.[132]

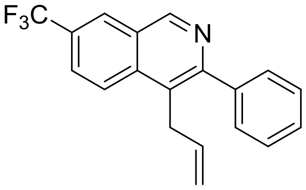
2-(2-Bromo-5-(trifluoromethyl)phenyl)-1,3-dioxolane 370



2-Bromo-5-(trifluromethyl)benzaldehyde (1.46 g, 5.77 mmol) was subjected to **General Procedure 8**. Purification by flash column chromatography (SiO_2, 95:5 petrol/EtOAc) afforded acetal **370** as a colourless oil (1.58 g, 5.32 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.87 (1 H, s, HC_{Ar}), 7.70 (1 H, d, J = 8.3, HC_{Ar}), 7.48 (1 H, d, J = 8.3, HC_{Ar}), 6.10 (1 H, s, $HC(OR)_2$), 4.24–4.03 (4 H, m, OCH_2CH_2O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 137.9 (C_{Ar}), 133.6 (HC_{Ar}), 130.0 (q, ^{2}J = 33.4, $C_{Ar}CF_3$), 127.1 (HC_{Ar}), 126.8 (C_{Ar}), 124.9 (HC_{Ar}), 123.7 (q, ^{1}J = 273.2, CF_3), 101.8 ($HC(OR)_2$), 65.6 (OCH_2CH_2O); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −62.7 (CF_3). Spectroscopic data were consistent with those previously reported.[175]

4-Allyl-3-phenyl-7-(trifluoromethyl)isoquinoline 371

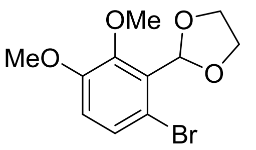


To a microwave vial fitted with a rubber septum was added (D*t*BPF)$PdCl_2$ (5.5 mg, 0.0084 mmol) and NaO*t*Bu (83.4 mg, 0.842 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (100 mg, 0.337 mmol) in anhydrous THF (1.4 mL) was added *via* syringe, followed by the addition of acetophenone (47.1 μL, 0.404 mmol) and the reaction mixture was heated at 70 °C for 6 h. After cooling to 0 °C, allyl bromide (29.3 μL, 0.337 mmol) was added *via* syringe and the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The pH was then adjusted to pH 5 by the dropwise addition of 1 M aqueous HCl before a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (3.4 mL) was added. The resulting mixture was stirred at 90 °C for 5 days then cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (10 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Repeated purification by flash column chromatography (SiO_2, 3:7 petrol/CH_2Cl_2 then 9:1 petrol/Et_2O) afforded isoquinoline **371** as a cream solid (63.4 mg, 0.202 mmol, 60%).

M.p. 91–93 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.35 (1 H, s, $HC(1)$), 8.34 (1 H, s, $HC(8)$), 8.16 (1 H, dd, J = 8.9, 0.6, $HC(5)$), 7.90 (1 H, dd, J = 8.9, 1.7, $HC(6)$), 7.66–7.60 (2 H, m, 2 × HC_{Ph}), 7.54–7.42 (3 H, m, 3 × HC_{Ph}), 6.24–6.09 (1 H, m, $HC{=}CH_2$), 5.20 (1 H, dq,

J = 10.3, 1.7, HC=CH_aH_b), 4.87 (1 H, dq, J = 17.3, 1.8, HC=CH_aH_b), 3.84 (2 H, dt, J = 5.0, 2.0, CH_2CH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 154.7 (*C*(3)), 151.5 (H*C*(1)), 140.4, 137.3 (2 × C_{Ar}), 136.5 (H*C*=CH_2), 129.2 (HC_{Ph}), 128.5 (q, ^2J = 33.4, *C*(7)CF_3), 128.2 (HC_{Ph}), 126.4 (C_{Ar}), 126.0, 125.9, 125.8, 125.6 (4 × HC_{Ar}), 123.9 (q, ^1J = 271.8, *C*F_3), 117.18 (HC=*C*H_2), 33.1 (*C*H_2CH). One C_{Ar} missing due to overlap; **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −62.6 (CF_3); **IR** ν_{max} (powder)/cm^{-1} 1632, 1582, 1438, 1347, 1314, 1273, 1222, 1149, 1122, 1074; **HRMS** (ESI$^+$) $C_{19}H_{15}F_3N$ requires 314.1151, found [M+H]$^+$ 314.1151 (Δ −0.5 ppm).

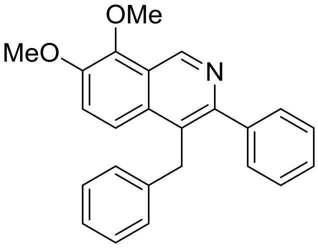
2-(6-Bromo-2,3-dimethoxyphenyl)-1,3-dioxolane 372



To a suspension of K_2CO_3 (558 mg, 4.04 mmol) in DMF (5.0 mL) were added 6-bromo-2-hydroxy-3-methoxybenzaldehyde (467 mg, 2.02 mmol) and iodomethane (0.379 mL, 6.06 mmol) and the resulting mixture was stirred at 45 °C for 18 h. After cooling to room temperature, the reaction was diluted with H_2O (20 mL) and quenched with 1 M aqueous HCl (20 mL). The resulting mixture was extracted with EtOAc (3 × 25 mL) and the combined organic extracts were washed with brine (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was then subjected to **General Procedure 8**. Purification by flash column chromatography (SiO_2, 9:1 petrol/EtOAc) afforded acetal **372** as a colourless solid (572 mg, 1.98 mmol, 98%).

M.p. 76–79 °C (lit. 79 °C);[308] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.29 (1 H, d, J = 8.8, *H*C(5)), 6.81 (1 H, d, J = 8.8, *H*C(4)), 6.35 (1 H, s, *H*C(OR)$_2$), 4.30–4.27 (2 H, m, OCH_aH_bCH_aH_bO), 4.06–4.03 (2 H, m, OCH_aH_bCH_aH_bO), 3.86 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 152.8, 150.2 (2 × C_{Ar}OMe), 129.4 (C_{Ar}), 129.1, 114.4 (2 × HC_{Ar}), 113.3 (*C*(6)Br), 101.7 (H*C*(OR)$_2$), 65.9 (O*C*H_2*C*H_2O), 61.6, 56.1 (2 × O*C*H_3). Spectroscopic data were consistent with those previously reported.[308]

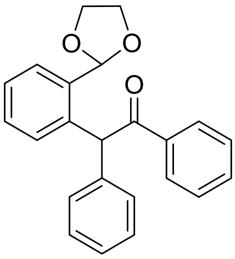
4-Benzyl-7,8-dimethoxy-3-phenylisoquinoline 373



To a microwave vial fitted with a rubber septum was added (D*t*BPF)$PdCl_2$ (5.9 mg, 0.0091 mmol), NaO*t*Bu (90.0 mg, 0.908 mmol), and aryl bromide **217** (105 mg, 0.363 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. The solids were dissolved in anhydrous THF (1.8 mL) then acetophenone (84.7 µL, 0.726 mmol) was added *via* syringe and the reaction was heated at 70 °C for 6 h. After cooling to 0 °C, benzyl bromide (86.3 µL, 0.726 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 18 h. A 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (4 mL) was then added and the resulting mixture was stirred at 90 °C for 48 h. After cooling to room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 petrol/CH_2Cl_2) afforded isoquinoline **373** as a cream solid (51.9 mg, 0.146 mmol, 40%).

M.p. 167–168 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.52 (1 H, d, *J* = 0.7, *H*C(1)), 7.49 (1 H, dd, *J* = 9.3, 0.8, HC_{Ar}), 7.46–7.42 (2 H, m, 2 × HC_{Ar}), 7.33–7.26 (4 H, m, 4 × HC_{Ar}), 7.19–7.12 (2 H, m, 2 × HC_{Ar}), 7.10 (1 H, d, *J* = 7.3, HC_{Ar}), 6.99–6.93 (2 H, m, HC_{Ar}), 4.37 (2 H, s, CH_2), 4.01 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 151.4 (*C*(3)), 148.3 (C_{Ar}OMe), 146.1 (H*C*(1)), 143.9 (C_{Ar}OMe), 141.0, 141.0, 131.6 (3 × C_{Ar}), 129.2, 128.5, 128.1, 128.1, 127.6, 125.9 (6 × HC_{Ar}), 125.1, 123.4 (2 × C_{Ar}), 121.0, 119.7 (2 × HC_{Ar}), 61.7, 56.8 (2 × OCH_3), 35.0 (CH_2); **IR** ν_{max} (powder)/cm^{-1} 1570, 1503, 1448, 1372, 1272, 1243, 1140, 1082, 1015; **HRMS** (ESI$^+$) $C_{24}H_{22}NO_2$ requires 356.1645, found $[M+H]^+$ 356.1643 (Δ +0.3 ppm).

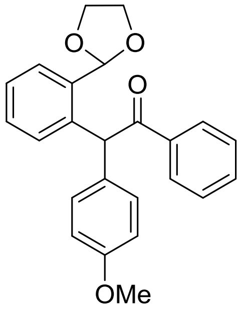
2-(2-(1,3-Dioxolan-2-yl)phenyl)-1,2-diphenylethanone 394



To a microwave vial fitted with a rubber septum was added (D*t*BPF)PdCl$_2$ (3.6 mg, 0.0055 mmol) and NaO*t*Bu (52.5 mg, 0.546 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (50.0 mg, 0.218 mmol) in anhydrous THF (1.0 mL) was added *via* syringe, followed by the addition of acetophenone (31.5 mg, 0.262 mmol) and the reaction was heated at 70 °C for 6 h. After cooling to room temperature, bromobenzene (58.2 µL, 0.546 mmol) was added *via* syringe and the reaction mixture was stirred at 70 °C for a further 18 h. After cooling to room temperature, the reaction was quenched with saturated aqueous NH$_4$Cl (2 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo.* Purification by flash column chromatography (SiO$_2$, 1:1 petrol/CH$_2$Cl$_2$) afforded ketone **394** as a cream solid (66.1 mg, 0.192 mmol, 88%).

M.p. 136–139 °C; **^{1}H NMR** (500 MHz, CDCl$_3$) δ_H 8.14–8.07 (2 H, m, 2 × HC_{Ar}), 7.66–7.61 (1 H, m, HC_{Ar}), 7.55–7.48 (1 H, m, HC_{Ar}), 7.46–7.40 (2 H, m, 2 × HC_{Ar}), 7.39–7.24 (7 H, m, 7 × HC_{Ar}), 7.21–7.17 (1 H, m, HC_{Ar}), 6.73 (1 H, s, *H*CPh), 5.92 (1 H, s, *H*C(OR)$_2$), 4.14–4.07 (1 H, m, $OCH_aH_bCH_aH_bO$), 4.04–3.98 (1 H, m, $OCH_aH_bCH_aH_bO$), 3.98–3.92 (2 H, m, $OCH_aH_bCH_aH_bO$); **^{13}C NMR** (126 MHz, CDCl$_3$) δ_C 198.2 (*C*=O), 138.4, 137.6, 136.7, 134.4 (4 × C_{Ar}), 132.7, 130.1, 129.4, 129.2, 128.9, 128.6, 128.4, 127.1, 127.0, 127.0 (10 × HC_{Ar}), 102.7 (H*C*(OR)$_2$), 64.9 (OCH$_2$*C*H$_2$O), 64.8 (O*C*H$_2$CH$_2$O), 55.0 (H*C*Ph)); **IR** ν_{max} (powder)/cm^{-1} 2883, 2763, 1690, 1595, 1578, 1494, 1447, 1404, 1206, 1076, 1041; **HRMS** (ESI$^+$) $C_{23}H_{20}NaO_3$ requires 367.1305, found [M+Na]$^+$ 367.1305 (Δ −0.5 ppm).

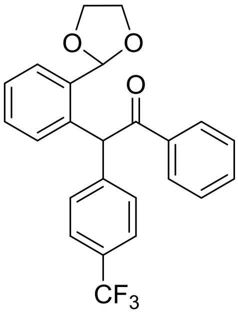
2-(2-(1,3-Dioxolan-2-yl)phenyl)-2-(4-methoxyphenyl)-1-phenylethanone 397



To a microwave vial fitted with a rubber septum was added (D*t*BPF)PdCl$_2$ (7.1 mg, 0.011 mmol) and NaO*t*Bu (54.0 mg, 0.546 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (50.0 mg, 0.218 mmol) in anhydrous THF (1.0 mL) was added *via* syringe, followed by the addition of acetophenone (30.6 µL, 0.262 mmol) and the reaction was heated at 70 °C for 6 h. After cooling to room temperature, 4-bromoanisole (68.4 µL, 0.546 mmol) was added *via* syringe and the reaction mixture was stirred at 100 °C for a further 18 h. After cooling to room temperature the reaction was quenched by the addition of saturated aqueous NH$_4$Cl (4 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo.* Purification by flash column chromatography (SiO$_2$, 4:6 petrol/CH$_2$Cl$_2$) afforded ketone **397** as a viscous oil (79.0 mg, 0.211 mmol, 97%).

^{1}H NMR (400 MHz, CDCl$_3$) δ_H 8.08–8.02 (2 H, m, 2 × HC$_{Ph}$), 7.61–7.56 (1 H, m, HC$_{Ar}$), 7.52–7.46 (1 H, m, HC$_{Ar}$), 7.43–7.37 (2 H, m, 2 × HC$_{Ph}$), 7.31–7.25 (2 H, m, 2 × HC$_{Ar}$), 7.17–7.11 (3 H, m, HC$_{Ar}$ and 2 × *m*-OMe HC$_{Ar}$), 6.90–6.84 (2 H, m, 2 × *o*-OMe HC$_{Ar}$), 6.61 (1 H, s, CHC=O), 5.88 (1 H, s, HC(OR)$_2$), 4.12–4.05 (1 H, m, OCH_aH$_b$CH$_a$H$_b$), .04–3.91 (3 H, m, OCH$_a$$H_bCH_a$$H_b$), 3.79 (3 H, s, OC$H_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 198.6 (C=O), 158.6, 138.0, 136.8, 134.4 (4 × C_{Ar}), 132.7 (HC_{Ar}), 130.5 (*m*-OMe HC_{Ar}), 130.4 (C_{Ar}), 130.1, 129.3 (2 × HC_{Ar}), 129.0, 128.5 (2 × HC_{Ph}), 127.1, 127.0 (2 × HC_{Ar}), 114.1 (*o*-OMe HC_{Ar}), 102.8 (HC(OR)$_2$), 65.0 (OCH$_2$$CH_2$O), 64.9 (O$CH_2CH_2$O), 55.2 (O$CH_3$), 54.3 ($C$HC=O); **IR** ν_{max} (neat)/cm^{-1} 2892, 1688, 1610, 1511, 1447, 1277, 1252, 1207, 1179, 1072; **HRMS** (ESI$^+$) C$_{24}$H$_{22}$NaO$_4$ requires 397.1410, found [M+Na]$^+$ 397.1394 (Δ +3.6 ppm).

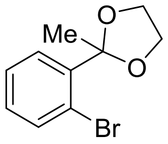
2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-phenyl-2-(4-(trifluoromethyl)phenyl)ethanone 398



To a microwave vial fitted with a rubber septum was added (D*t*BPF)PdCl$_2$ (7.1 mg, 0.011 mmol) and NaO*t*Bu (54.0 mg, 0.546 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (50.0 mg, 0.218 mmol) in anhydrous THF (1.0 mL) was added *via* syringe, followed by the addition of acetophenone (30.5 μL 0.262 mmol) and the reaction was heated at 70 °C for 6 h. After cooling to room temperature, 4-bromobenzotrifluoride (75.4 μL, 0.546 mmol) was added *via* syringe and the reaction mixture was stirred at 100 °C for a further 18 h. After cooling to room temperature the reaction was quenched with saturated aqueous NH$_4$Cl (4 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo.* Purification by flash column chromatography (SiO$_2$, 6:4 petrol/CH$_2$Cl$_2$) afforded ketone **398** as a viscous oil (77.3 mg, 0.187 mmol, 86%).

^{1}H NMR (400 MHz, CDCl$_3$) δ_H 8.09–8.02 (2 H, m, 2 × *H*C$_{Ar}$), 7.66–7.60 (1 H, m, *H*C$_{Ar}$), 7.58 (2 H, d, *J* = 8.1, 2 × *H*C$_{Ar}$), 7.55–7.48 (1 H, m, *H*C$_{Ar}$), 7.45–7.38 (2 H, m, 2 × *H*C$_{Ar}$), 7.36–7.29 (4 H, m, 4 × *H*C$_{Ar}$), 7.17–7.11 (1 H, m, *H*C$_{Ar}$), 6.73 (1 H, s, C*H*C=O), 5.84 (1 H, s, *H*C(OR)$_2$), 4.15–4.08 (1 H, m, OCH_aH$_b$CH$_a$H$_b$O), 4.07–3.93 (3 H, m, OCH$_a$$H_bCH_a$$H_b$O); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 197.8 (*C*=O), 142.7, 136.6, 136.3, 134.6 (4 × *C*$_{Ar}$), 133.1, 129.9, 129.8, 129.8, 129.5, 129.1, 128.6, 127.5 (8 × H*C*$_{Ar}$), 125.5 (q, ^3J = 4.8, H*C*$_{Ar}$), 102.7 (H*C*(OR)$_2$), 65.1 (OCH$_2$*C*H$_2$O), 65.0 (O*C*H$_2$CH$_2$O), 54.8 (*C*HC=O). *C*F$_3$ and *C*$_{Ar}$CF$_3$ missing due to overlap; **^{19}F{^{1}H} NMR** (377 MHz, CDCl$_3$) δ_F −62.4 (C*F*$_3$); **IR** ν_{max} (neat)/cm^{-1} 2892, 1688, 1325, 1278, 1210, 1163, 1111, 1068; **HRMS** (ESI$^+$) C$_{24}$H$_{19}$F$_3$NaO$_3$ requires 435.1179, found [M+Na]$^+$ 435.1187 (Δ −1.9 ppm).

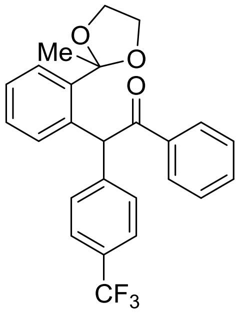
2-(2-Bromophenyl)-2-methyl-1,3-dioxolane 399 [175]



Aryl bromide **399** was donated by a coworker, by whom it was synthesised by subjecting 2'-bromoacetophenone (1.98 g, 9.92 mmol) to **General Procedure 8**. Purification by flash column chromatographgy (SiO_2, 95:5 petrol/EtOAc) afforded aryl bromide **399** as a colourless oil (2.26 g, 9.31 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.67 (1 H, dd, J = 7.9, 1.8, HC_{Ar}), 7.59 (1 H, dd, J = 8.1, 1.3, HC_{Ar}), 7.28 (1 H, td, J = 7.6, 1.1, HC_{Ar}), 7.13 (1 H, td, J = 7.7, 1.6, HC_{Ar}), 4.10–4.01 (2 H, m, $OCH_aH_bCH_aH_bO$), 3.80–3.71 (2 H, m, $OCH_aH_bCH_aH_bO$), 1.81 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 141.1 (C_{Ar}), 134.9, 129.5, 127.9, 127.1 (4 × HC_{Ar}), 120.5 (C_{Ar}), 108.7 ($C(OR)_2$), 64.2 (OCH_2CH_2O), 25.3 (CH_3). Spectroscopic data were consistent with those previously reported.[147]

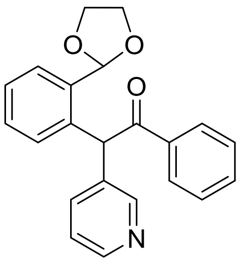
2-(2-(2-Methyl-1,3-dioxolan-2-yl)phenyl)-1-phenyl-2-(4-(trifluoromethyl)phenyl)-ethanone 400



To a microwave vial fitted with a rubber septum was added (D*t*BPF)PdCl$_2$ (17.7 mg, 0.0271 mmol) and NaO*t*Bu (135 mg, 1.36 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **399** (132 mg, 0.543 mmol) in anhydrous THF (2.2 mL) was added *via* syringe, followed by the addition of acetophenone (76.0 µL, 0.652 mmol) and the reaction was heated at 70 °C for 6 h. After cooling to room temperature, 4-bromobenzotrifluoride (0.188 mL, 1.36 mmol) was added *via* syringe and the reaction mixture was stirred at 100 °C for a further 18 h. After cooling to room temperature the reaction was quenched with saturated aqueous NH_4Cl (4 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Purification by flash column chromatography (SiO_2, 1:1 petrol/CH_2Cl_2) afforded ketone **400** as an off-white solid (169 mg, 0.465 mmol, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.93–7.91 (2 H, m, 2 × HC_{Ar}), 7.58–7.56 (1 H, m, HC_{Ar}), 7.48 (2 H, d, J = 8.1, 2 × HC_{Ar}), 7.44–7.39 (1 H, m, HC_{Ar}), 7.31 (2 H, m, 2 × HC_{Ar}), 7.26 (2 H, d, J = 8.1, 2 × HC_{Ar}), 7.18–7.15 (2 H, m, 2 × HC_{Ar}), 6.99–6.96 (1 H, m, HC_{Ar}), 6.88 (1 H, s, CHC=O), 3.87 (1 H, td, J = 7.2, 6.1, $OCH_aH_bCH_aH_bO$), 3.73–3.68 (1 H, m, $OCH_aH_bCH_aH_bO$), 3.61–3.56 (1 H, m, $OCH_aH_bCH_aH_bO$), 3.45–3.40 (1 H, m, $OCH_aH_bCH_aH_bO$), 1.63 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 198.1 (C=O), 143.8, 140.5, 136.7, 135.3 (4 × C_{Ar}), 132.9, 131.8, 129.7, 128.8, 128.6, 128.2, 127.2, 126.5 (8 × HC_{Ar}), 125.7 (q, ^{3}J = 3.2, HC_{Ar}), 109.1 ($C(OR)_2$), 64.4 (OCH_2CH_2O), 63.9 (OCH_2CH_2O), 55.1 (CHC=O), 28.3 (CH_3). CF_3 and $C_{Ar}CF_3$ missing due to overlap; **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −62.4 (CF_3); **IR** ν_{max} (neat)/cm^{-1} 2970, 1739, 1676, 1376, 1326, 1213, 1161, 1122, 1068, 1036, 1021, 1002; **HRMS** (ESI$^+$) $C_{25}H_{22}F_3O_3$ requires 427.1516, found $[M+H]^+$ 427.1521 (Δ −0.9 ppm).

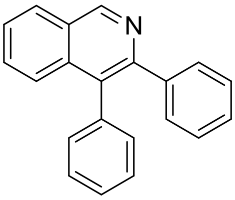
2-(2-(1,3-Dioxolan-2-yl)phenyl)-1-phenyl-2-(pyridin-3-yl)ethanone 401



To a microwave vial fitted with a rubber septum was added (D*t*BPF)$PdCl_2$ (12.3 mg, 0.0188 mmol) and NaO*t*Bu (93.0 mg, 0.939 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (85.9 mg, 0.375 mmol) in anhydrous THF (1.5 mL) was added *via* syringe, followed by the addition of acetophenone (52.6 µL 0.451 mmol) and the reaction was heated at 70 °C for 6 h. After cooling to room temperature, 3-bromopyridine (90.5 µL, 0.939 mmol) was added *via* syringe and the reaction mixture was stirred at 100 °C for a further 18 h. After cooling to room temperature the reaction was quenched with saturated aqueous NH_4Cl (4 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 85:15 CH_2Cl_2/Et_2O) afforded ketone **401** as a viscous oil (42.0 mg, 0.122 mmol, 32%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.51–8.49 (2 H, m, 2 × HC_{Ar}), 8.09–8.06 (2 H, m, 2 × HC_{Ar}), 7.63 (1 H, dd, J = 5.6, 3.6, HC_{Ar}), 7.53–7.49 (2 H, m, 2 × HC_{Ar}), 7.43–7.38 (2 H, m, 2 × HC_{Ar}), 7.33–7.29 (2 H, m, 2 × HC_{Ar}), 7.25 (1 H, ddd, J = 7.9, 4.8, 0.6, HC_{Ar}), 7.17–7.15 (1 H, m, HC_{Ar}), 6.67 (1 H, s, C*H*C=O), 5.87 (1 H, s, *H*C(OR)$_2$), 4.15–3.97 (4 H, m, OC*H*$_2$C*H*$_2$O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 197.5 (*C*=O), 150.4, 148.3, 137.0 (3 × HC_{Ar}), 136.3, 136.1, 134.6, 134.3 (4 × C_{Ar}), 133.1 (HC_{Ar}), 129.5 (2 × HC_{Ar}), 129.1, 128.6 (2 × HC_{Ar}), 127.6 (2 × HC_{Ar}), 123.4 (HC_{Ar}), 102.5 (H*C*(OR)$_2$), 65.1 (O*C*H$_2$CH$_2$O), 65.0 (OCH$_2$*C*H$_2$O), 52.6 (*C*HC=O); **IR** $\nu_{max\ (neat)}$/cm^{-1} 2891, 1684, 1579, 1479, 1449, 1424, 1282, 1211, 1109, 1070, 1046, 1027, 1003; **HRMS** (ESI$^+$) $C_{22}H_{19}NNaO_3$ requires 368.1257, found [M+Na]$^+$ 368.1251 (Δ +1.9 ppm).

3,4-Diphenylisoquinoline 121



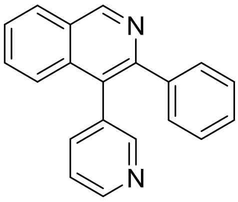
Method A: Ketone **394** (102 mg, 0.296 mmol) was subjected to **General Procedure 9**. Purification by flash column chromatography (SiO_2, 85:15 petrol/EtOAc) afforded isoquinoline **121** as a colourless solid (76.5 mg, 0.272 mmol, 92%).

Method B: Aryl bromide **217** (122 mg, 0.533 mmol) was subjected to **General Procedure 10** using acetophenone (74.6 μL, 0.640 mmol) and bromobenzene (0.142 mL, 1.33 mmol), stirring at 70 °C. Purification by flash column chromatography (SiO_2, CH_2Cl_2) afforded isoquinoline **121** as a colourless solid (115 mg, 0.409 mmol, 77%).

M.p. 156–160 °C (lit. 170 °C);[309] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.38 (1 H, s, *H*C(1)), 8.09–7.97 (1 H, m, *H*C(8)), 7.71–7.64 (1 H, m, *H*C(5)), 7.63–7.54 (2 H, m, *H*C(6) and *H*C(7)), 7.42–7.30 (5 H, m, 5 × HC_{Ph}), 7.28–7.12 (5 H, m, 5 × HC_{Ph}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 151.7 (H*C*(1)), 150.5 (*C*(3)), 140.7, 137.1, 135.9 (3 × C_{Ar}), 131.1 (HC_{Ph}), 130.6

(C_{Ar}), 130.4 (HC(6)), 130.2, 128.2, 127.6 (3 × HC_{Ph}), 127.5 (HC(8)), 127.3, 127.0 (2 × HC_{Ph}), 126.8 (HC(7)), 125.5 (HC(5)). One C_{Ar} missing due to overlap. Spectroscopic data were consistent with those previously reported.[309]

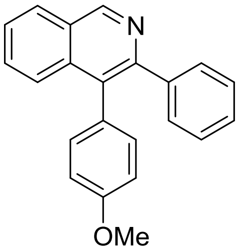
3-Phenyl-4-(pyridin-3-yl)isoquinoline 403



Ketone **401** (41.1 mg, 0.119 mmol) was subjected to **General Procedure 9**. Purification by flash column chromatography (SiO_2, 95:5 CH_2Cl_2/Et_2O) afforded isoquinoline **403** as an off-white solid (12.2 mg, 0.0432 mmol, 36%).

M.p. 158–162 °C (lit. 149–150 °C);[133] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.43 (1 H, d, J = 0.6, HC(1)), 8.61 (1 H, dd, J = 4.9, 1.6, HC$_{Ar}$), 8.55 (1 H, d, J = 1.5, HC$_{Ar}$), 8.12–8.09 (1 H, m, HC$_{Ar}$), 7.69–7.66 (2 H, m, 2 × HC$_{Ar}$), 7.65–7.62 (1 H, m, HC$_{Ar}$), 7.58 (1 H, dt, J = 7.8, 1.9, HC$_{Ar}$), 7.34–7.31 (3 H, m, 3 × HC$_{Ar}$), 7.26–7.21 (3 H, m, 3 × HC$_{Ar}$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 152.5, 151.6 (2 × HC_{Ar}), 151.5 (C_{Ar}), 148.5 (HC_{Ar}), 140.0 (C_{Ar}), 138.6 (HC_{Ar}), 135.7, 133.3 (2 × C_{Ar}), 131.1, 130.3, 127.9, 127.9, 127.5 (5 × HC_{Ar}), 127.3 (C_{Ar}), 127.2 (HC_{Ar}), 126.9 (C_{Ar}), 124.8, 123.2 (2 × HC_{Ar}). Spectroscopic data were consistent with those previously reported.[133]

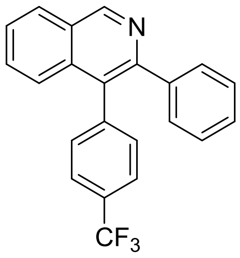
4-(4-Methoxyphenyl)-3-phenylisoquinoline 404



Aryl bromide **217** (120 mg, 0.524 mmol) was subjected to **General Procedure 10** using acetophenone (73.4 µL, 0.629 mmol) and 4-bromoanisole (0.164 mL, 1.31 mmol). Purification by flash column chromatography (SiO_2, CH_2Cl_2) afforded isoquinoline **404** as a colourless solid (131 mg, 0.421 mmol, 80%).

M.p. 135–139 °C (lit. 141–142 °C);[310] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.25 (1 H, d, J = 0.6, HC(1)), 8.05–8.00 (1 H, m, HC(8)), 7.75–7.69 (1 H, m, HC(5)), 7.64–7.54 (2 H, m, HC(6) and *H*C(7)), 7.42–7.35 (2 H, m, 2 × HC_{Ph}), 7.28–7.18 (3 H, m, 3 × HC_{Ph}), 7.18–7.11 (2 H, m, 2 × *m*-OMe HC_{Ar}), 6.94–6.87 (2 H, m, 2 × *o*-OMe HC_{Ar}), 3.72 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 158.7 (C_{Ar}OMe), 151.5 (H*C*(1)), 150.7 (*C*(3)), 140.9, 136.2 (2 × C_{Ar}), 132.2 (*m*-OMe HC_{Ar}), 130.3 (H*C*(6)), 130.2 (HC_{Ph}), 129.2 (C_{Ar}), 127.6 (HC_{Ph}), 127.4 (H*C*(8)), 127.4 (C_{Ar}), 126.9 (HC_{Ph}), 126.7 (H*C*(7)), 125.6 (H*C*(5)), 113.7 (*o*-OMe HC_{Ar}), 55.1 (OCH_3). One C_{Ar} missing due to overlap. Spectroscopic data were consistent with those previously reported.[310]

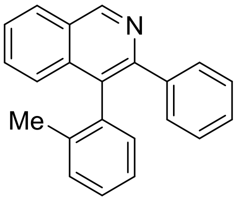
3-Phenyl-4-(4-(trifluoromethyl)phenyl)isoquinoline 406



Aryl bromide **217** (120 mg, 0.524 mmol) was subjected to **General Procedure 10** using acetophenone (73.4 µL, 0.629 mmol) and 4-bromobenzotrifluoride (0.181 mL, 1.31 mmol). Purification by flash column chromatography (SiO_2, 3:6 petrol/CH_2Cl_2) afforded isoquinoline **406** as a cream solid (133 mg, 0.381 mmol, 73%).

M.p. 157–162 °C (lit. 128–129 °C, yellow solid);[133] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.42 (1 H, s, *H*C(1)), 8.12–8.07 (1 H, m, HC_{Ar}), 7.70–7.63 (4 H, m, 4 × HC_{Ar}), 7.62–7.57 (1 H, m, HC_{Ar}), 7.41 (2 H, d, *J* = 7.9, 2 × HC_{Ar}), 7.37–7.31 (2 H, m, 2 × HC_{Ar}), 7.26–7.21 (3 H, m, 3 × HC_{Ar}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 152.3 (H*C*(1)), 150.7 (*C*(3)), 141.2, 140.1, 135.5 (3 × C_{Ar}), 131.6, 131.0, 130.2 (3 × HC_{Ar}), 129.2 (C_{Ar}), 127.9, 127.8, 127.4 (3 × HC_{Ar}), 127.3 (C_{Ar}), 127.2 (HC_{Ar}), 125.3 (q, ^3J = 3.2, HC_{Ar}), 125.0 (HC_{Ar}). CF_3 and $C_{Ar}CF_3$ missing due to overlap; **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −62.4 (CF_3). Spectroscopic data were consistent with those previously reported.[133]

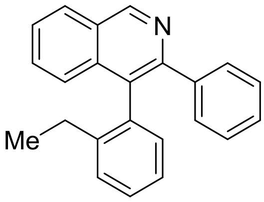
3-Phenyl-4-(*o*-tolyl)isoquinoline 408



Aryl bromide **217** (120 mg, 0.524 mmol) was subjected to **General Procedure 10** using acetophenone (73.4 µL, 0.629 mmol) and 2-bromotoluene (0.158 mL, 1.31 mmol). Purification by flash column chromatography (SiO_2, CH_2Cl_2) afforded isoquinoline **408** as a cream solid (100 mg, 0.339 mmol, 65%).

M.p. 125–130 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.42 (1 H, d, J = 0.7, *H*C(1)), 8.10–8.04 (1 H, m, HC_{Ar}), 7.64–7.58 (2 H, m, 2 × HC_{Ar}), 7.47–7.39 (3 H, m, 3 × HC_{Ar}), 7.33–7.28 (1 H, m, HC_{Ar}), 7.26–7.16 (6 H, m, 6 × HC_{Ar}), 1.90 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 151.8 (H*C*(1)), 150.3, 140.6, 137.0, 136.5, 135.8 (5 × C_{Ar}), 131.3, 130.5, 130.1, 129.7 (4 × HC_{Ar}), 129.8 (C_{Ar}), 129.7, 127.8, 127.6 (3 × HC_{Ar}), 127.2 (C_{Ar}), 127.2, 126.8, 125.7, 125.5 (4 × HC_{Ar}), 19.9 (CH_3); **IR** ν_{max} (powder)/cm^{-1} 3058, 1617, 1558, 1498, 1449, 1370, 1247, 1029; **HRMS** (ESI$^+$) $C_{22}H_{18}N$ requires 296.1434, found $[M+H]^+$ 296.1434 (Δ +0.1 ppm).

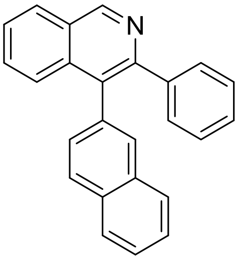
4-(2-Ethylphenyl)-3-phenylisoquinoline 410



Aryl bromide **217** (117 mg, 0.511 mmol) was subjected to **General Procedure 10** using acetophenone (71.6 µL, 0.613 mmol) and 1-bromo-2-ethylbenzene (0.177 mL, 1.28 mmol). Purification by flash column chromatography (SiO_2, 4:6 petrol/CH_2Cl_2 then 9:1 petrol/Et_2O) afforded isoquinoline **410** as a colourless solid (106 mg, 0.343 mmol, 67%).

M.p. 80–83 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.42 (1 H, s, *H*C(1)), 8.09–8.03 (1 H, m, *H*C(8)), 7.64–7.57 (2 H, m, *H*C(7) and HC_{Ar}), 7.49–7.42 (3 H, m, 3 × HC_{Ar}), 7.40–7.35 (1 H, m, HC_{Ar}), 7.33–7.27 (1 H, m, HC_{Ar}), 7.27–7.19 (5 H, m, 5 × HC_{Ar}), 2.29–2.10 (2 H, m, $CH_aH_bCH_3$), 0.85 (3 H, t, J = 7.6, CH_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 151.8 (H*C*(1)), 150.2 (*C*(3)), 142.6, 140.6, 136.3, 135.9 (4 × C_{Ar}), 131.6, 130.4 (2 × HC_{Ar}), 129.8 (HC_{Ph}), 129.8 (C_{Ar}), 128.3, 128.1 (2 × HC_{Ar}), 127.5 (HC_{Ph}), 127.5 (HC_{Ar}), 127.2 (C_{Ar}), 127.2, 126.8 (2 × HC_{Ar}), 125.7 (H*C*(7)), 125.5 (HC_{Ar}), 25.7 (CH_2CH_3), 14.1 (CH_2CH_3); **IR** ν_{max} (powder)/cm^{-1} 2969, 1616, 1559, 1497, 1447, 1370, 1331, 1248, 1027; **HRMS** (ESI$^+$) $C_{23}H_{20}N$ requires 310.1590, found [M+H]$^+$ 310.1582 (Δ +2.4 ppm). See Appendix 2 for VT ^{1}H NMR spectra.

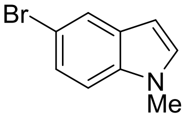
4-(Naphthalen-2-yl)-3-phenylisoquinoline 414



Aryl bromide **217** (110 mg, 0.480 mmol) was subjected to **General Procedure 10** using acetophenone (67.2 µL, 0.576 mmol) and a solution of 2-bromonaphthalene (248 mg, 1.20 mmol) in THF (1.0 mL). Repeated purification by flash column chromatography (SiO_2, 2:8 petrol/CH_2Cl_2 then 7:3 petrol/Et_2O) afforded isoquinoline **414** as a colourless solid (105 mg, 0.317 mmol, 66%).

M.p. 148–149 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.45 (1 H, d, *J* = 0.5, *H*C(1)), 8.12–8.06 (1 H, m, HC_{Ar}), 7.93–7.77 (4 H, m, 4 × HC_{Ar}), 7.73–7.67 (1 H, m, HC_{Ar}), 7.65–7.57 (2 H, m, 2 × HC_{Ar}), 7.59–7.48 (2 H, m, 2 × HC_{Ar}), 7.48–7.42 (2 H, m, 2 × HC_{Ar}), 7.37 (1 H, dd, *J* = 8.4, 1.7, HC_{Ar}), 7.21–7.13 (3 H, m, 3 × HC_{Ar}); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 151.9 (H*C*(1)), 150.9 (*C*(3)), 140.7, 136.2, 134.8, 133.2, 132.5 (5 × C_{Ar}), 130.7 (HC_{Ar}), 130.5 (C_{Ar}), 130.3, 130.3 (2 × HC_{Ar}), 129.3, 128.1, 128.0, 127.8, 127.8, 127.7 (6 × HC_{Ar}), 127.4 (C_{Ar}), 127.2, 127.0, 126.3, 126.3, 125.7 (5 × HC_{Ar}); **IR** ν_{max} (powder)/cm^{-1} 1617, 1556, 1496, 1335, 1246; **HRMS** (ESI$^+$) $C_{25}H_{18}N$ requires 332.1434, found [M+H]$^+$ 332.1425 (Δ +2.3 ppm).

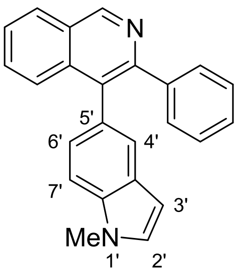
5-Bromo-1-methyl-1*H*-indole 416 [311]



A mixture of NaOH (67.2 mg, 1.68 mmol) in DMSO (3.4 mL) was stirred at 85 °C for 18 h to dissolve the solid. After cooling to room temperature, 5-bromoindole (221 mg, 1.13 mmol) was added and the reaction mixture was stirred at room temperature for 1 h before the addition of iodomethane (0.104 mL, 1.68 mmol). After stirring for 5 h, the solution was diluted with H_2O and the resulting mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with H_2O (2 × 20 mL) and brine (2 × 20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purifcation by flash column chromatography (SiO_2, petrol) afforded 5-bromo-*N*-methylindole **416** as a colourless oil (170 mg, 0.809 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.78 (1 H, d, *J* = 1.8, *H*C(4)), 7.32 (1 H, dd, *J* = 8.7, 1.9, *H*C(6)), 7.20 (1 H, d, *J* = 8.7, *H*C(7)), 7.06 (1 H, d, *J* = 3.1, *H*C(3)), 6.45 (1 H, dd, *J* = 3.1, 0.8, *H*C(2)), 3.78 (3 H, s, NC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 135.3, 130.0 (2 × *C*$_{\text{Ar}}$), 130.0 (H*C*(3)), 124.2 (H*C*(6)), 123.2 (H*C*(4)), 112.6 (*C*(5)Br), 110.6 (H*C*(7)), 100.4 (H*C*(2)), 32.9 (N*C*H$_3$). Spectroscopic data were consistent with those previously reported.[312]

4-(1-Methyl-1*H*-indol-5-yl)-3-phenylisoquinoline 417

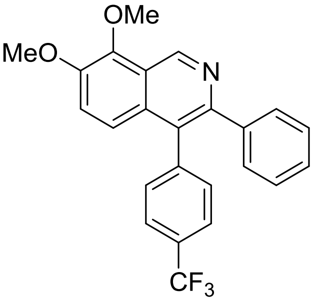


Aryl bromide **217** (79.0 mg, 0.345 mmol) was subjected to **General Procedure 10** using acetophenone (48.3 µL, 0.414 mmol) and a solution of 5-bromo-*N*-methylindole **416** (145 mg, 0.690 mmol) in THF (1.0 mL). Purification by flash column chromatography (SiO_2, CH_2Cl_2) afforded isoquinoline **417** as a pale yellow solid (79.2 mg, 0.237 mmol, 69%).

M.p. 197–201 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.41 (1 H, d, *J* = 0.7, *H*C(1)), 8.09–8.03 (1 H, m, *H*C(8)), 7.78–7.72 (1 H, m, *H*C$_{\text{Ar}}$), 7.62–7.55 (3 H, m, 3 × *H*C$_{\text{Ar}}$), 7.50–7.45 (2 H, m, 2 × *H*C$_{\text{Ar}}$), 7.31 (1 H, d, *J* = 8.4, *H*C$_{\text{Ar}}$), 7.23–7.15 (3 H, m, 3 × *H*C$_{\text{Ar}}$), 7.11–7.06 (2 H, m, *H*C$_{\text{Ar}}$ and *H*C(2’)), 6.49 (1 H, dd, *J* = 3.1, 0.8, *H*C(3’)), 3.82 (3 H, s, NC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 151.2 (H*C*(1)), 150.7 (*C*(3)), 141.2, 136.7, 135.9, 131.7 (4 × *C*$_{\text{Ar}}$), 130.2, 130.1, 129.2 (3 × H*C*$_{\text{Ar}}$), 128.3, 127.9 (2 × *C*$_{\text{Ar}}$), 127.5 (H*C*$_{\text{Ar}}$), 127.4 (*C*$_{\text{Ar}}$), 127.3, 126.7, 126.6, 126.1, 124.9, 123.5 (6 × H*C*$_{\text{Ar}}$), 109.1 (H*C*(2’)), 101.1 (H*C*(3’)), 32.8

(N*C*H$_3$); **IR** ν$_{\mathrm{max}}$ (powder)/cm^{-1} 1618, 1497, 1441, 1376, 1327, 1246; **HRMS** (ESI$^+$) $C_{24}H_{19}N_2$ requires 335.1543, found [M+H]$^+$ 335.1537 (Δ +2.1 ppm).

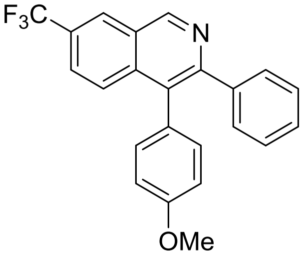
7,8-Dimethoxy-3-phenyl-4-(4-(trifluoromethyl)phenyl)isoquinoline 419



Aryl bromide **372** (119 mg, 0.412 mmol) was subjected to **General Procedure 10** using acetophenone (57.7 μL, 0.494 mmol) and 4-bromobenzotrifluoride (0.142 mL, 1.03 mmol). Purification by flash column chromatography (SiO_2, 98:2 CH_2Cl_2/Et_2O) afforded isoquinoline **419** as an orange solid (115 mg, 0.281 mmol, 68%).

M.p. 175–178 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ$_{\mathrm{H}}$ 9.71 (1 H, d, *J* = 0.9, *H*C(1)), 7.63 (2 H, d, *J* = 7.9, 2 × *o*-CF$_{3\ \mathrm{H}}$C$_{\mathrm{Ar}}$), 7.43 (2 H, d, *J* = 9.3, 2 × *H*C$_{\mathrm{Ar}}$), 7.38 (2 H, d, *J* = 7.9, 2 × *m*-CF$_{3\ \mathrm{H}}$C$_{\mathrm{Ar}}$), 7.35–7.31 (2 H, m, 2 × *H*C$_{\mathrm{Ar}}$), 7.25–7.19 (3 H, m, 3 × *H*C$_{\mathrm{Ar}}$), 4.14 (3 H, s, OC*H*$_3$), 4.01 (3 H, s, OC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ$_{\mathrm{C}}$ 149.0, 148.7 (2 × *C*$_{\mathrm{Ar}}$), 147.2 (H*C*(1)), 143.7, 141.5, 140.2 (3 × *C*$_{\mathrm{Ar}}$), 131.6 (H*C*$_{\mathrm{Ar}}$), 131.2 (*C*$_{\mathrm{Ar}}$), 130.1 (H*C*$_{\mathrm{Ar}}$), 129.5 (q, ^{2}J = 33.3, *C*$_{\mathrm{Ar}}$CF$_3$), 128.6 (*C*$_{\mathrm{Ar}}$), 127.8, 127.2 (2 × H*C*$_{\mathrm{Ar}}$), 125.2 (q, ^{3}J = 3.2, H*C*$_{\mathrm{Ar}}$), 124.1 (q, ^{1}J = 271.6, *C*F$_3$), 122.9 (*C*$_{\mathrm{Ar}}$), 121.4, 119.9 (2 × H*C*$_{\mathrm{Ar}}$), 61.8, 56.9 (2 × O*C*H$_3$); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ$_{\mathrm{F}}$ −62.4 (C*F*$_3$); **IR** ν$_{\mathrm{max}}$ (powder)/cm^{-1} 1563, 1500, 1445, 1378, 1322, 1278, 1252, 1166, 1110, 1090, 1068, 1040; **HRMS** (ESI$^+$) $C_{24}H_{19}F_3NO_2$ requires 410.1362, found [M+H]$^+$ 410.1370 (Δ −1.7 ppm).

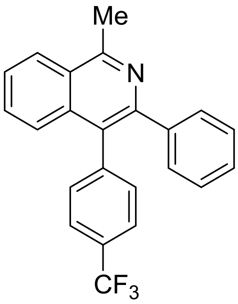
4-(4-Methoxyphenyl)-3-phenyl-7-(trifluoromethyl)isoquinoline 420



Aryl bromide **370** (123 mg, 0.414 mmol) was subjected to **General Procedure 10** using acetophenone (58.0 μL, 0.497 mmol) and 4-bromoanisole (0.142 mL, 1.03 mmol). ^{1}H NMR analysis of the crude product indicated incomplete acetal hydrolysis so the crude residue was dissolved in a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (4.1 mL) and stirred at 90 °C for 48 h. The reaction mixture was then worked up according to **General Procedure 10**. Purification by flash column chromatography afforded isoquinoline **420** as a cream solid (105 mg, 0.277 mmol, 67%).

M.p. 145–147 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.36 (1 H, s, *H*C(1)), 8.27 (1 H, s, *H*C(8)), 7.77 (1 H, d, *J* = 9.2, *H*C(5)), 7.68 (1 H, dd, *J* = 9.0, 1.8, *H*C(6)), 7.33–7.29 (2 H, m, 2 × HC_{Ph}), 7.20–7.13 (3 H, m, 3 × HC_{Ph}), 7.09–7.04 (2 H, m, 2 × *m*-OMe HC_{Ar}), 6.87–6.82 (2 H, m, 2 × *o*-OMe HC_{Ar}), 3.77 (3 H, s, OCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.1 (C_{Ar}OMe), 152.8 (*C*(3)), 152.1 (H*C*(1)), 140.3, 137.7 (2 × C_{Ar}), 132.2 (*m*-OMe HC_{Ar}) , 130.3 (C_{Ar}), 130.2 (HC_{Ar}), 128.4 (C_{Ar}), 127.8, 127.4 (2 × HC_{Ar}), 127.1 (H*C*(5)), 126.2 (C_{Ar}), 125.8 (q, ^3J = 3.2, H*C*(6)), 125.4 (q, ^3J = 4.8, H*C*(8)), 123.9 (q, ^1J = 273.5, CF_3), 114.0 (*o*-OMe HC_{Ar}), 55.2 (OCH_3). One C_{Ar} missing due to overlap; **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −62.6 (CF_3); **IR** ν_{max} (powder)/cm^{-1}1632, 1610, 1515, 1432, 1351, 1311, 1244, 1159, 1119, 1072, 1033; **HRMS** (ESI$^+$) $C_{23}H_{17}F_3NO$ requires 380.1257, found $[M+H]^+$ 380.1239 (Δ +4.4 ppm).

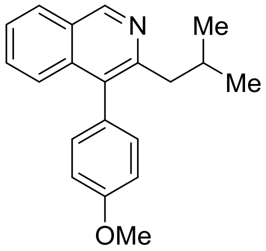
1-Methyl-3-phenyl-4-(4-(trifluoromethyl)phenyl)isoquinoline 421



Aryl bromide **399** (115 mg, 0.473 mmol) was subjected to **General Procedure 11** using acetophenone (66.2 μL, 0.568 mmol) and 4-bromobenzotrifluoride (0.163 mL, 1.18 mmol). Repeated purification by flash column chromatography (SiO_2, 3:7 petrol/CH_2Cl_2 then 9:1 petrol/Et_2O) afforded isoquinoline **421** as a pale yellow solid (98.6 mg, 0.270 mmol, 57%).

M.p. 139–140 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.27–8.21 (1 H, m, *H*C(8)), 7.68–7.61 (4 H, m, *H*C(7) and 3 × HC_{Ar}), 7.61–7.55 (1 H, m, HC_{Ar}), 7.38 (2 H, dd, *J* = 8.6, 0.7, 2 × HC_{Ar}), 7.36–7.31 (2 H, m, 2 × HC_{Ar}), 7.26–7.19 (3 H, m, 3 × HC_{Ar}), 3.11 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 158.5 (*C*(3)), 149.6 (*C*(1)), 141.7, 140.5, 135.5 (3 × C_{Ar}), 131.8, 130.3, 130.2 (3 × HC_{Ar}), 129.3 (q, ^2J = 32.3, C_{Ar}CF$_3$), 127.8 (HC_{Ar}), 127.7 (C_{Ar}), 127.3, 126.8 (2 × HC_{Ar}), 126.1 (C_{Ar}), 125.7 (H*C*(8)), 125.6 (HC_{Ar}), 125.2 (q, ^3J = 3.1, HC_{Ar}), 124.2 (q, ^1J = 271.5, *C*F$_3$), 22.8 (*C*H$_3$); **^{19}F{^{1}H} NMR** (377 MHz, CDCl$_3$) δ_F −62.4 (CF_3); **IR** ν_{max} (powder)/cm^{-1} 1615, 1570, 1553, 1502, 1391, 1322, 1167, 1109, 1064, 1018; **HRMS** (ESI$^+$) $C_{23}H_{17}F_3N$ requires 364.1308, found [M+H]$^+$ 364.1314 (Δ −1.5 ppm).

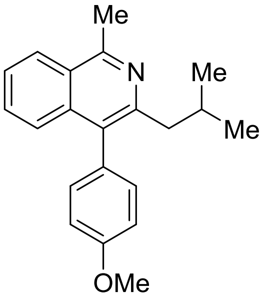
3-Isobutyl-4-(4-methoxyphenyl)isoquinoline 423



Aryl bromide **217** (115 mg, 0.502 mmol) was subjected to **General Procedure 10** using 4-methyl-2-pentanone (75.3 µL, 0.602 mmol) and 4-bromoanisole (0.157 mL, 1.26 mmol). Purification by flash column chromatography (SiO$_2$, CH$_2$Cl$_2$) afforded isoquinoline **423** as a cream solid (76.8 mg, 0.264 mmol, 53%).

M.p. 77–78 °C; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 9.25 (1 H, d, *J* = 0.6, *H*C(1)), 7.99–7.93 (1 H, m, *H*C(8)), 7.56–7.48 (2 H, m, *H*C(6) and *H*C(7)), 7.43–7.37 (1 H, m, *H*C(5)), 7.22–7.16 (2 H, m, 2 × *m*-OMe *H*C_{Ar}), 7.07–7.01 (2 H, m, 2 × *o*-OMe *H*C_{Ar}), 3.92 (3 H, s, OCH_3), 2.65 (2 H, d, *J* = 7.3, CH_2), 2.29–2.16 (1 H, m, C*H*(CH$_3$)$_2$), 0.82 (6 H, d, *J* = 6.7, (CH_3)$_2$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 158.8 (C_{Ar}OMe), 152.4 (*C*(3)), 151.2 (H*C*(1)), 136.2 (C_{Ar}), 131.5 (*m*-OMe HC_{Ar}), 130.8 (C_{Ar}), 130.0 (H*C*(6)), 129.6 (C_{Ar}), 127.3 (H*C*(8)), 126.6 (C_{Ar}), 125.9 (H*C*(7)), 125.3 (H*C*(5)), 113.7 (*o*-OMe HC_{Ar}), 55.2 (O*C*H$_3$), 44.0 (*C*H$_2$), 29.0 (*C*H(CH$_3$)$_2$), 22.5 ((*C*H$_3$)$_2$); **IR** ν_{max} (powder)/cm^{-1} 2960, 2865, 1610, 1571, 1513, 1464, 1381, 1285, 1242, 1179, 1108, 1034; **HRMS** (ESI$^+$) $C_{20}H_{22}NO$ requires 292.1696, found [M+H]$^+$ 292.1689 (Δ +2.7 ppm).

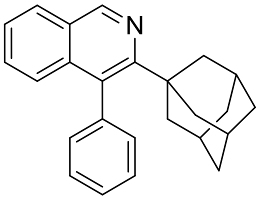
3-Isobutyl-4-(4-methoxyphenyl)-1-methylisoquinoline 425



Aryl bromide **399** (115 mg, 0.473 mmol) was subjected to **General Procedure 11** using 4-methyl-2-pentanone (71.0 µL, 0.568 mmol) and 4-bromoanisole (0.148 mL, 1.18 mmol). Repeated purification by flash column chromatography (SiO_2, CH_2Cl_2 then 85:15 petrol/Et_2O) afforded isoquinoline **425** as an oil (93.3 mg, 0.305 mmol, 65%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.15–8.09 (1 H, m, *H*C(8)), 7.55–7.48 (2 H, m, *H*C(6) and *H*C(7)), 7.43–7.37 (1 H, m, *H*C(5)), 7.21–7.15 (2 H, m, 2 × *m*-OMe HC_{Ar}), 7.06–7.01 (2 H, m, 2 × *o*-OMe HC_{Ar}), 3.92 (3 H, s, OCH_3), 3.01 (3 H, s, CH_3), 2.60 (2 H, d, *J* = 7.3, CH_2), 2.30–2.18 (1 H, m, $CH(CH_3)_2$), 0.81 (6 H, d, *J* = 6.7, $(CH_3)_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 158.7, 157.0, 151.0, 136.4 (4 × C_{Ar}), 131.8 (*m*-OMe HC_{Ar}), 130.0 (C_{Ar}), 129.5 (HC_{Ar}), 129.3 (C_{Ar}), 126.0 (H*C*(5)), 125.6 (HC_{Ar}), 125.3 (H*C*(8)), 113.7 (*o*-OMe HC_{Ar}), 55.3 (OCH_3), 43.9 (CH_2), 28.9 ($CH(CH_3)_2$), 22.5 (CH_3), 22.5 ($(CH_3)_2$). One C_{Ar} missing due to overlap; **IR** ν_{max} (neat)/cm^{-1} 2954, 1611, 1563, 1514, 1463, 1391, 1286, 1244, 1175, 1036; **HRMS** (ESI$^+$) $C_{21}H_{24}NO$ requires 306.1852, found $[M+H]^+$ 306.1859 (Δ −1.6 ppm).

3-(Adamantan-1-yl)-4-phenylisoquinoline 427

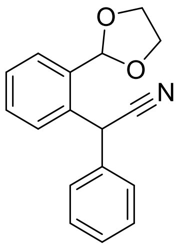


Aryl bromide **217** (123 mg, 0.537 mmol) was subjected to **General Procedure 10** using 1-adamantyl methyl ketone (115 mg, 0.644 mmol) and bromobenzene (0.143 mL, 1.34 mmol). Repeated purification by flash column chromatography (SiO_2, 1:1 petrol/CH_2Cl_2 then 97:3 petrol/Et_2O) afforded isoquinoline **427** as a colourless solid (99.0 mg, 0.292 mmol, 54%).

M.p. 178–181 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.30 (1 H, d, *J* = 0.6, *H*C(1)), 7.94 (1 H, dd, *J* = 7.9, 0.8, *H*C(8)), 7.53–7.40 (5 H, m, *H*C(7) and 4 × HC_{Ar}), 7.33–7.27 (2 H, m, 2 × *H*C$_{Ar}$), 7.09 (1 H, d, *J* = 8.6, *H*C$_{Ar}$), 2.00 (6 H, d, *J* = 2.8, 3 × C(C*H*$_2$R)), 1.95 (3 H, br. s, 3 × C*H*R$_3$), 1.68–1.61 (6 H, m, 3 × C*H*$_2$R$_2$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 157.5 (*C*(3)), 150.5 (H*C*(1)), 139.1, 137.7 (2 × *C*$_{Ar}$), 131.2 (*H*C$_{Ar}$), 129.7, (*C*$_{Ar}$), 129.5, 127.5, 127.3 (3 × H*C*$_{Ar}$), 126.7 (H*C*(8)), 126.1 (*C*$_{Ar}$), 126.0 (H*C*(7)), 125.6 (H*C*$_{Ar}$), 42.7 (C(*C*H$_2$R)), 42.2 (*C*R$_3$), 36.7 (*C*H$_2$R$_2$), 29.1 (*C*HR$_3$); **IR** ν_{max} (powder)/cm^{-1} 2900, 2847, 1618, 1557, 1497, 1451, 1371, 1308; **HRMS** (ESI$^+$) $C_{25}H_{26}N$ requires 340.2060, found [M+H]$^+$ 340.2057 (Δ +1.3 ppm).

3.3.3 Chapter 2.3 compounds

2-(2-(1,3-Dioxolan-2-yl)phenyl)-2-phenylacetonitrile 436

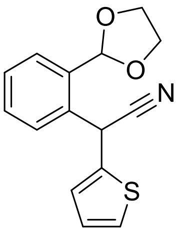


To a screw-cap tube fitted with a rubber septum was added (Amphos)$_2$PdCl$_2$ (15.6 mg, 0.0220 mmol) and Cs_2CO_3 (358 mg, 1.10 mmol) and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (101 mg, 0.441 mmol) in anhydrous THF (2.2 mL) was added *via* syringe, followed by the addition of phenylacetonitrile (61.1 µL, 0.529 mmol). The septum was replaced with a screw cap and the reaction mixture was heated at 70 °C for 18 h. After cooling to room temperature, the reaction was quenched with H_2O (5 mL) and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Purification by flash column chromatography (SiO_2, 9:1 petrol/EtOAc) afforded α-aryl nitrile **436** as a yellow oil (58.5 mg, 0.221 mmol, 50%).

^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.61–7.59 (1 H, m, *H*C$_{Ar}$), 7.44–7.29 (8 H, m, 8 × *H*C$_{Ar}$), 5.91 (1 H, s, C*H*CN), 5.88 (1 H, s, *H*C(OR)$_2$), 4.19–4.05 (4 H, m, OC*H*$_2$C*H*$_2$O); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 135.7, 134.8, 134.6 (3 × *C*$_{Ar}$), 130.0, 129.7, 129.0, 128.3, 128.0, 127.8, 127.4 (7 × H*C*$_{Ar}$), 119.9 (*C*≡N), 102.2 (H*C*(OR)$_2$), 65.1, 65.0 (O*C*H$_2$*C*H$_2$O), 37.8 (*C*HCN);

IR ν_{max} (neat)/cm^{-1} 2892, 1494, 1452, 1406, 1217, 1112, 1075, 1043; **HRMS** (ESI$^+$) $C_{17}H_{15}NNaO_2$ requires 288.0995, found [M+Na]$^+$ 288.0992 (Δ +1.0 ppm).

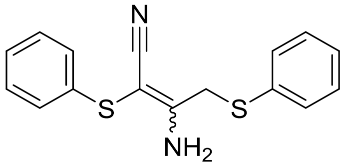
2-(2-(1,3-Dioxolan-2-yl)phenyl)-2-(thiophen-2-yl)acetonitrile 437



To a screw-cap tube fitted with a rubber septum was added $(Amphos)_2PdCl_2$ (16.6 mg, 0.0234 mmol) and Cs_2CO_3 (381 mg, 1.17 mmol) and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (107 mg, 0.467 mmol) in anhydrous THF (2.3 mL) was added *via* syringe, followed by the addition of 2-thiopheneacetonitrile (103 μL, 0.934 mmol). The septum was replaced with a screw cap and the reaction mixture was heated at 70 °C for 18 h. After cooling to room temperature, the reaction was quenched with H_2O (5 mL) and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Repeated purification by flash column chromatography (SiO_2, 9:1 petrol/EtOAc then 1:1 petrol/CH_2Cl_2) afforded α-aryl nitrile **438** as a yellow oil (48.1 mg, 0.177 mmol, 38%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.59 (2 H, m, 2 × HC_{Ar}), 7.45 (1 H, td, J = 7.5, 1.6, HC_{Ar}), 7.39 (1 H, td, J = 7.5, 1.3, HC_{Ar}), 7.27 (1 H, dd, J = 5.2, 1.2, HC_{Ar}), 7.11 (1 H, dt, J = 3.5, 1.1, HC_{Ar}), 6.97 (1 H, dd, J = 5.1, 3.6, HC_{Ar}), 6.09 (1 H, s, C*H*CN), 5.90 (1 H, s, *H*C(OR)$_2$), 4.20–4.05 (4 H, m, OCH_2CH_2O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 138.5, 134.5, 134.2 (3 × C_{Ar}), 130.0, 129.2, 128.6, 127.6, 126.9, 126.8, 126.4 (7 × HC_{Ar}), 119.3 (*C*≡N), 102.2 (H*C*(OR)$_2$), 65.1, 65.0 (O*C*H$_2$*C*H$_2$O), 33.6 (*C*HCN); **IR** ν_{max} (neat)/cm^{-1} 2959, 2925, 2891, 2855, 1738, 1601, 1470, 1389, 1259, 1216, 1074, 1043, 1023; **HRMS** (ESI$^+$) $C_{15}H_{13}NNaO_2S$ requires 294.0559, found [M+Na]$^+$ 294.0554 (Δ +1.8 ppm).

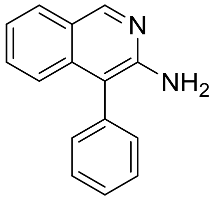
3-Amino-2,4-bis(phenylthio)but-2-enenitrile 441



To a microwave vial fitted with a rubber septum was added (Amphos)$_2$PdCl$_2$ (15.6 mg, 0.0220 mmol) and NaO*t*Bu (109 mg, 1.10 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (101 mg, 0.441 mmol) in anhydrous THF (2.2 mL) was added *via* syringe, followed by the addition of (phenylthio)acetonitrile (115 µL, 0.882 mmol) and the reaction mixture was heated at 70 °C for 18 h. After cooling to room temperature, the reaction was diluted with H_2O (5 mL) and the resulting mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 8:2 petrol/EtOAc) afforded dimer **441** as a viscous yellow oil (123 mg, 0.413 mmol, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.37–7.31 (2 H, m, 2 × *H*C$_{Ar}$), 7.30–7.23 (3 H, m, 3 × *H*C$_{Ar}$), 7.14–7.06 (3 H, m, 3 × *H*C$_{Ar}$), 6.91–6.83 (2 H, m, 2 × *H*C$_{Ar}$), 5.76 (2 H, br. s, N*H*$_2$), 3.98 (2 H, s, C*H*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 163.1 (C=*C*NH$_2$), 134.3, 132.4 (2 × *C*$_{Ar}$), 130.7, 129.4, 129.1, 127.9, 126.1, 126.1 (6 × H*C*$_{Ar}$), 119.9 (*C*≡N), 68.2 (*C*=CNH$_2$), 36.1 (*C*H$_2$); **IR** ν_{max} (neat)/cm^{-1} 3438, 3315, 2182, 1606, 1581, 1547, 1477, 1439, 1069, 1024; **HRMS** (ESI$^+$) $C_{16}H_{14}N_2NaS_2$ requires 321.0491, found [M+Na]$^+$ 321.0489 (Δ +0.2 ppm).

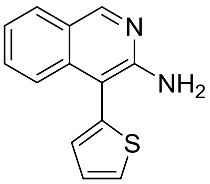
4-Phenylisoquinolin-3-amine 442



To a screw-cap tube containing α-aryl nitrile **436** (50.0 mg, 0.188 mmol) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (1.9 mL) and the resulting mixture was stirred at 90 °C for 24 h. After cooling to room temperature, 2 M aqueous NH_4HCO_3 was added until the reaction mixture reached pH 9, and the solution was stirred at 90 °C for a further 24 h. The reaction was then cooled to room temperature, quenched with H_2O (5 mL) and the mixture extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 8:2 petrol/EtOAc) afforded 3-aminoisoquinoline **442** as a yellow solid (29.8 mg, 0.135 mmol, 72%).

M.p. 131–133 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.91 (1 H, d, *J* = 0.5, *H*C(1)), 7.83 (1 H, d, *J* = 8.2, *H*C(8)), 7.58–7.54 (2 H, m, 2 × *H*C_{Ar}), 7.49–7.39 (4 H, m, 4 × *H*C_{Ar}), 7.29–7.25 (2 H, m, 2 × *H*C_{Ar}), 4.41 (2 H, br. s, N*H*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 151.7 (*C*(3)), 151.1 (H*C*(1)), 137.2, 135.6 (2 × *C*$_{Ar}$), 130.6, 130.4, 129.4 (3 × H*C*$_{Ar}$), 127.9 (H*C*(8)), 127.8 (H*C*$_{Ar}$), 123.8 (*C*$_{Ar}$), 123.0, 122.7 (2 × H*C*$_{Ar}$), 111.5 (*C*$_{Ar}$). Spectroscopic data were consistent with those previously reported.[233]

4-(Thiophen-2-yl)isoquinolin-3-amine 443

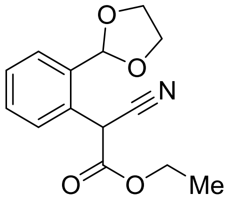


To a screw-cap tube containing α-aryl nitrile **438** (51.6 mg, 0.190 mmol) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (1.9 mL) and the resulting mixture was stirred at 90 °C for 18 h. After cooling to room temperature, 2 M aqueous NH_4HCO_3 was added until the reaction mixture reached pH 9, and the solution was stirred at 90 °C for a further 24 h. The reaction was then cooled to room temperature, diluted with H_2O (5 mL) and the mixture extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 99:1 EtOAc/MeOH) afforded 3-amino isoquinoline **443** as a pale yellow oil (43.1 mg, 0.143 mmol, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.82 (1 H, s, *H*C(1)), 7.72 (1 H, dd, *J* = 8.1, 0.7, *H*C_{Ar}), 7.45 (1 H, dt, *J* = 5.2, 0.9, *H*C_{Ar}), 7.38 (2 H, app. d, *J* = 3.6, 2 × *H*C_{Ar}), 7.22–7.14 (2 H, m, 2 × *H*C_{Ar}), 7.03 (1 H, dd, *J* = 3.4, 0.9, *H*C_{Ar}), 4.55 (2 H, br. s, N*H*$_2$); **^{13}C NMR** (75 MHz,

$CDCl_3$) δ_C 153.2 (*C*(3)), 152.3 (H*C*(1)), 138.5, 136.0 (2 × C_{Ar}), 130.9, 128.8, 127.9, 127.8, 127.2 (5 × HC_{Ar}), 123.6 (C_{Ar}), 122.9, 122.9 (2 × HC_{Ar}), 103.4 (C_{Ar}S); **IR** ν_{max} (neat)/cm^{-1} 3301, 3170, 1620, 1578, 1455, 1426, 1373, 1217, 1147; **HRMS** (ESI$^+$) $C_{13}H_{11}N_2S$ requires 227.0638, found [M+H]$^+$ 227.0633 (Δ +2.2 ppm).

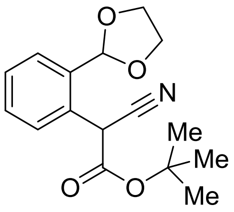
Ethyl 2-(2-(1,3-dioxolan-2-yl)phenyl)-2-cyanoacetate 444



To a microwave vial fitted with a rubber septum was added (DPPF)$PdCl_2$ (5.3 mg, 0.0073 mmol) and NaO*t*Bu (90.2 mg, 0.910 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (100 mg, 0.437 mmol) in anhydrous 1,4-dioxane (1.5 mL) was added *via* syringe, followed by the addition of ethyl cyanoacetate (38.7 µL, 0.364 mmol) and the reaction was heated at 70 °C for 18 h. After cooling to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Purification by flash column chromatography (SiO_2, 9:1 petrol/EtOAc) afforded α-aryl nitrile **444** as a pale yellow oil (87.1 mg, 0.333 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 (1 H, dd, *J* = 7.7, 1.3, *H*C_{Ar}), 7.56 (1 H, dd, *J* = 7.5, 1.6, *H*C_{Ar}), 7.49–7.37 (2 H, m, 2 × *H*C_{Ar}), 5.93 (1 H, s, *H*C(OR)$_2$), 5.47 (1 H, s, C*H*CN), 4.25 (2 H, q, *J* = 7.2, OCH_2CH_3), 4.19–3.96 (4 H, m, OCH_2CH_2O), 1.28 (3 H, t, *J* = 7.2, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 158.4 (*C*=O), 135.3 (C_{Ar}), 130.2, 129.9, 129.3 (3 × HC_{Ar}), 129.3 (C_{Ar}), 128.3 (HC_{Ar}), 116.4 (*C*≡N), 102.9 (H*C*(OR)$_2$), 65.3 (O*C*H$_2$CH$_2$O), 65.1 (OCH$_2$*C*H$_2$O), 63.3 (O*C*H$_2$CH$_3$), 40.2 (*C*HCN), 14.1 (*C*H$_3$); **IR** ν_{max} (neat)/cm^{-1} 2895, 1743, 1454, 1405, 1222, 1160, 1111, 1076, 1025; **HRMS** (ESI$^+$) $C_{14}H_{15}NNaO_4$ requires 284.0893, found [M+Na]$^+$ 284.0899 (Δ −2.1 ppm).

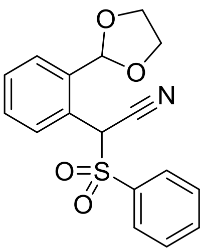
***tert*-Butyl 2-(2-(1,3-dioxolan-2-yl)phenyl)-2-cyanoacetate 451**



To a microwave vial fitted with a rubber septum were added (DPPF)PdCl$_2$ (7.7 mg, 0.011 mmol) and NaO*t*Bu (131 mg, 1.32 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (145 mg, 0.633 mmol) in anhydrous 1,4-dioxane (2.1 mL) was added *via* syringe, followed by the addition of *tert*-butyl cyanoacetate (75.3 µL, 0.527 mmol) and the reaction mixture was heated at 70 °C for 4 h. After cooling to room temperature, the reaction was quenched with saturated aqueous NH$_4$Cl (2 mL) and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, 85:15 petrol/EtOAc) afforded α-aryl nitrile **451** as a colourless oil (140 mg, 0.484 mmol, 92%).

^{1}H NMR (400 MHz, CDCl$_3$) δ_H 7.61 (1 H, dd, *J* = 7.6, 1.3, *H*C$_{Ar}$), 7.55 (1 H, dd, *J* = 7.5, 1.5, *H*C$_{Ar}$), 7.50–7.36 (2 H, m, 2 × *H*C$_{Ar}$), 5.93 (1 H, s, C*H*CN), 5.34 (1 H, s, *H*C(OR)$_2$), 4.17–4.00 (4 H, m, OC*H*$_2$C*H*$_2$O), 1.46 (9 H, s, ((C*H*$_3$)$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 164.0 (*C*=O), 135.0 (*C*$_{Ar}$), 129.9, 129.7 (2 × H*C*$_{Ar}$), 129.5 (*C*$_{Ar}$), 128.9, 128.0 (2 × H*C*$_{Ar}$), 116.6 (*C*≡N), 102.7 (H*C*(OR)$_2$), 84.2 (*C*(CH$_3$)$_3$), 65.1 (O*C*H$_2$CH$_2$O), 64.9 (OCH$_2$*C*H$_2$O), 41.0 (*C*HCN), 27.7 ((*C*H$_3$)$_3$); **IR** ν_{max} (neat)/cm^{-1} 2980, 1739, 1456, 1395, 1370, 1259, 1145, 1109, 1076, 1045; **HRMS** (ESI$^+$) $C_{16}H_{19}NNaO_4$ requires 312.1206, found [M+Na]$^+$ 312.1193 (Δ +3.3 ppm).

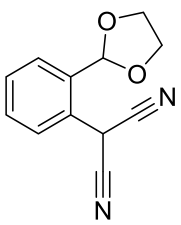
2-(2-(1,3-Dioxolan-2-yl)phenyl)-2-(phenylsulfonyl)acetonitrile 452



To a microwave vial fitted with a rubber septum was added (DPPF)PdCl$_2$ (7.5 mg, 0.010 mmol), NaO*t*Bu (126 mg, 1.27 mmol), and (phenylsulfonyl)acetonitrile **449** (92.2 mg, 0.509 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon before a solution of aryl bromide **217** (140 mg, 0.611 mmol) in anhydrous 1,4-dioxane (2.0 mL) was added *via* syringe. The reaction was heated at 70 °C for 18 h. After cooling to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Purification by flash column chromatography (SiO_2, 7:3 petrol/EtOAc) afforded α-aryl nitrile **452** as a colourless solid (158 mg, 0.480 mmol, 94%).

M.p. 99–101 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.83 (2 H, dd, *J* = 8.3, 1.2, 2 × HC_{Ph}), 7.75 (1 H, td, *J* = 7.5, 1.1, HC_{Ph}), 7.68 (1 H, d, *J* = 7.6, HC_{Ar}), 7.60–7.56 (2 H, m, 2 × HC_{Ph}), 7.47 (1 H, ddd, *J* = 7.9, 6.3, 2.5, HC_{Ar}), 7.37–7.31 (2 H, m, 2 × HC_{Ar}), 6.38 (1 H, s, C*H*CN), 6.18 (1 H, s, *H*C(OR)$_2$), 4.10–3.94 (4 H, m, OCH_2CH_2O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 138.1 (C_{Ar}), 135.2 (HC_{Ph}), 135.0 (C_{Ar}), 130.6, 130.4 (2 × HC_{Ar}), 129.9, 129.2 (2 × HC_{Ph}), 129.1, 127.0 (2 × HC_{Ar}), 123.7 (C_{Ar}), 114.1 (*C*≡N), 101.4 (H*C*(OR)$_2$), 64.9 (OCH_2CH_2O), 58.9 (*C*HCN); **IR** ν_{max} (powder)/cm^{-1} 2936, 2891, 1691, 1582, 1447, 1391, 1327, 1310, 1154, 1104, 1064, 1027; **HRMS** (ESI$^+$) $C_{17}H_{15}NNaO_4S$ requires 352.0614, found $[M+Na]^+$ 352.0605 (Δ +2.4 ppm).

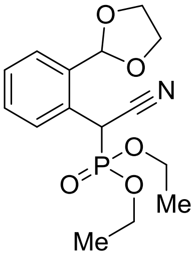
2-(2-(1,3-Dioxolan-2-yl)phenyl)malononitrile 453



To a microwave vial fitted with a rubber septum was added (DPPF)$PdCl_2$ (5.9 mg, 0.0080 mmol), NaO*t*Bu (100 mg, 1.00 mmol), and malononitrile (26.4 mg, 0.400 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon before a solution of aryl bromide **217** (110 mg, 0.480 mmol) in anhydrous 1,4-dioxane (1.6 mL) was added *via* syringe and the reaction was heated at 70 °C for 4 h. After cooling to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (2 mL) and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Purification by flash column chromatography (SiO_2, 25:75 petrol/CH_2Cl_2) afforded dinitrile **453** as a colourless oil (72.5 mg, 0.338 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (1 H, dd, J = 7.5, 1.3, HC_{Ar}), 7.60–7.48 (3 H, m, 3 × HC_{Ar}), 5.89 (1 H, s, $HC(OR)_2$), 5.87 (1 H, s, $HC(CN)_2$), 4.21–4.14 (2 H, m, $OCH_aH_bCH_aH_bO$), 4.14–4.07 (2 H, m, $OCH_aH_bCH_aH_bO$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 134.6 (C_{Ar}), 130.7, 130.3, 129.3, 129.2 (4 × HC_{Ar}), 125.5 (C_{Ar}), 112.3 ($C\equiv N$), 102.8 ($HC(OR)_2$), 65.0 (OCH_2CH_2O), 24.9 ($HC(CN)_2$); **IR** ν_{max} (neat)/cm^{-1} 2899, 2257, 1459, 1405, 1289, 1228, 1114, 1075, 1043; **HRMS** (ESI$^-$) $C_{12}H_9N_2O_2$ requires 213.0670, found $[M-H]^-$ 213.0662 (Δ +3.5 ppm).

Diethyl ((2-(1,3-dioxolan-2-yl)phenyl)(cyano)methyl)phosphonate 455

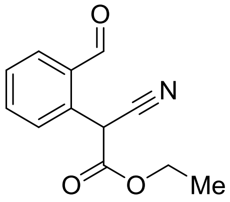


To a microwave vial fitted with a rubber septum was added (DPPF)$PdCl_2$ (7.2 mg, 0.0098 mmol) and NaO*t*Bu (122 mg, 1.23 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon before a solution of aryl bromide **217** (135 mg, 0.589 mmol) in anhydrous 1,4-dioxane (2.0 mL) was added *via* syringe, followed by the addition of diethyl cyanomethylphosphonate (79.4 μL, 0.491 mmol). The reaction was heated at 70 °C for 18 h. After cooling to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Purification by flash column chromatography (SiO_2, 1:1 petrol/EtOAc) afforded α-aryl nitrile **455** as a colourless solid (40.3 mg, 0.124 mmol, 21%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74–7.71 (1 H, m, HC_{Ar}), 7.63–7.61 (1 H, m, HC_{Ar}), 7.46–7.36 (2 H, m, 2 × HC_{Ar}), 6.12 (1 H, s, $HC(OR)_2$), 5.21 (1 H, d, J = 25.6, $CHCN$), 4.19–3.99 (8 H, m, OCH_2CH_2O and 2 × OCH_2CH_3), 1.30 (3 H, t, J = 6.9, OCH_2CH_3), 1.27

(3 H, t, $J = 6.9$, OCH_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 136.3 (d, $^3J = 4.8$, $C(2)$), 129.9 (d, $J = 3.2$, HC_{Ar}), 129.5 (d, $J = 3.2$, HC_{Ar}), 128.8, 126.8 (2 × HC_{Ar}), 126.7 (d, $^2J = 7.9$, $C(1)$), 116.1 (d, $^2J = 9.5$, $C\equiv N$), 101.4 ($HC(OR)_2$), 65.1 (OCH_2CH_2O), 64.9 (OCH_2CH_2O), 64.6 (d, $^2J = 6.4$, OCH_2CH_3), 64.3 (d, $^2J = 6.4$, OCH_2CH_3), 32.6 (d, $^1J = 138.4$, $CHCN$), 16.2 (d, $^3J = 6.4$, OCH_2CH_3), 16.2 (d, $^3J = 6.4$, OCH_2CH_3); **^{31}P{^{1}H,^{13}C} NMR** (162 MHz, $CDCl_3$) δ_P 15.1 (P=O); **IR** ν_{max} (neat)/cm^{-1} 2985, 2930, 1711, 1447, 1393, 1370, 1295, 1264, 1164, 1138, 1043, 1018; **HRMS** (ESI$^+$) $C_{15}H_{20}NNaO_5P$ requires 348.0971, found $[M+Na]^+$ 348.0957 (Δ +4.0 ppm).

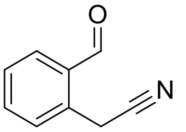
Ethyl 2-cyano-2-(2-formylphenyl)acetate 457



To a screw-cap tube containing a solution of α-aryl nitrile **444** (50.0 mg, 0.191 mmol) in EtOH (2 mL) was added *para*-toluenesulfonic acid monohydrate (3.6 mg, 0.019 mmol) and the resulting mixture was stirred at room temperature for 24 h. The reaction was diluted with H_2O (2 mL) and the resulting solution was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 95:5 petrol/EtOAc) afforded aldehyde **457** as a colourless oil (7.1 mg, 0.033 mmol, 17%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.04 (1 H, s, HC=O), 7.90 (1 H, dt, $J = 7.0$, 1.2, HC_{Ar}), 7.74–7.67 (3 H, m, 3 × HC_{Ar}), 6.02 (1 H, s, $CHCN$), 4.29 (2 H, q, $J = 7.2$, OCH_2CH_3), 1.34 (3 H, t, $J = 7.2$, OCH_2CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 193.2 (HC=O), 164.4 (ROC=O), 136.4, 134.5 (2 × HC_{Ar}), 132.9 (C_{Ar}), 130.5 (HC_{Ar}), 130.3 (C_{Ar}), 129.8 (HC_{Ar}), 115.5 ($C\equiv N$), 63.3 (OCH_2CH_3), 40.0 ($CHCN$), 13.9 (OCH_2CH_3); **IR** ν_{max} (neat)/cm^{-1} 2982, 2917, 2850, 1745, 1698, 1602, 1581, 1454, 1396, 1369, 1250, 1162, 1027; **HRMS** (ESI$^+$) $C_{12}H_{11}NNaO_3$ requires 240.0631, found $[M+Na]^+$ 240.0638 (Δ −2.6 ppm).

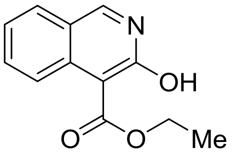
2-(2-Formylphenyl)acetonitrile 458



To a screw-cap tube containing a solution of α-aryl nitrile **444** (55.3 mg, 0.191 mmol) in 1:1 THF/H_2O (1.0 mL) was added *para*-toluenesulfonic acid monohydrate (3.6 mg, 0.019 mmol) and the resulting mixture was stirred at 90 °C for 18 h. After cooling to room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (1 mL) and the resulting mixture was extracted with EtOAc (5 × 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 petrol/EtOAc) afforded aldehyde **458** as a colourless oil (19.9 mg, 0.137 mmol, 72%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 10.09 (1 H, s, *H*C=O), 7.87–7.85 (1 H, m, *H*C_{Ar}), 7.70–7.59 (3 H, m, 3 × *H*C_{Ar}), 4.28 (2 H, s, CH_2CN); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 193.2 (H*C*=O), 136.1, 134.3 (2 × HC_{Ar}), 133.0, 131.1 (2 × C_{Ar}), 130.1, 128.8 (2 × HC_{Ar}), 117.3 (*C*≡N), 22.1 (*C*H_2CN). Spectroscopic data were consistent with those previously reported.[313]

Ethyl 3-hydroxyisoquinoline-4-carboxylate 459

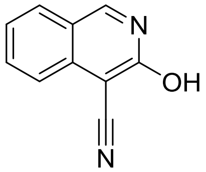


To a screw-cap tube containing α-aryl nitrile **444** (97.9 mg, 0.375 mmol) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (3.8 mL) and the reaction mixture was stirred at 90 °C for 24 h. After cooling to room temperature, the reaction was diluted with H_2O (4 mL) and the resulting mixture was extracted with EtOAc (5 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 6:4 petrol/EtOAc) afforded impure 3-hydroxyisoquinoline **459** as a yellow oily solid (38.3 mg, <0.176 mmol, <47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.11 (1 H, s, *H*C(1)), 8.74 (1 H, dd, *J* = 8.9, 0.7, *H*C(5)), 7.92 (1 H, dd, *J* = 8.1, 0.6, *H*C(8)), 7.75 (1 H, ddd, *J* = 8.7, 7.0, 1.5, *H*C(6)), 7.46 (1 H, ddd, *J* = 8.0, 7.0, 1.0, *H*C(7)), 4.62 (2 H, q, *J* = 7.2, OCH_2CH$_3$), 1.56 (3 H, t, *J* = 7.2, OCH$_2$CH_3);

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 171.9 (*C*(3)), 166.4 (*C*=O), 159.0 (H*C*(1)), 136.0 (C_{Ar}), 133.0 (H*C*(6)), 129.7 (C_{Ar}), 129.3 (H*C*(8)), 124.9 (C_{Ar}), 124.5 (H*C*(5)), 124.5 (H*C*(7)), 62.6 (O*C*H_2CH_3), 14.3 (OCH_2*C*H_3); **HRMS** (ESI$^+$) $C_{12}H_{11}NNaO_3$ requires 240.0631, found [M+Na]$^+$ 240.0636 (Δ −1.7 ppm).

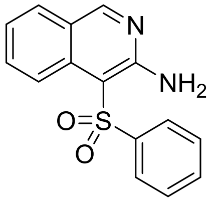
3-Hydroxyisoquinoline-4-carbonitrile 467



To a screw-cap tube containing a solution of dinitrile **453** (97.1 mg, 0.453 mmol) in 1:1 THF/H_2O (2.5 mL) was added *para*-toluenesulfonic acid monohydrate (9.5 mg, 0.050 mmol) and the reaction was stirred at 50 °C for 18 h. After cooling to room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the resulting mixture was extracted with 4:1 EtOAc/*n*BuOH (5 × 5 mL). The combined organic extracts were concentrated *in vacuo*. Purification by flash column chromatography (C18 reversed phase SiO_2, H_2O) afforded 3-hydroxyisoquinoline **467** as a bright yellow solid (65.4 mg, 0.384 mmol, 85%).

M.p. >320 °C; **^{1}H NMR** (400 MHz, CD_3OD) δ_H 8.83 (1 H, s, *H*C(1)), 7.75 (1 H, d, *J* = 8.1, *H*C(8)), 7.59–7.52 (2 H, m, 2 × *H*C_{Ar}), 7.12 (1 H, ddd, *J* = 8.1, 6.4, 1.5, *H*C(7)); **^{13}C NMR** (100 MHz, CD_3OD) δ_C 173.0 (*C*(3)), 158.1 (H*C*(1)), 141.9 (C_{Ar}), 133.0 (H*C*(6)), 130.0 (H*C*(8)), 122.4 (H*C*(7)), 121.8 (H*C*(5)), 121.7 (C_{Ar}), 120.7 (*C*≡N), 83.2 (*C*(4)); **IR** ν_{max} (powder)/cm^{-1} 3263, 2581, 2214, 1622, 1580, 1555, 1467, 1438, 1221, 1179, 1047, 1014; **HRMS** (ESI$^+$) $C_{10}H_6N_2NaO$ requires 193.0372, found [M+Na]$^+$ 193.0369 (Δ +1.6 ppm).

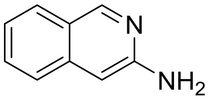
4-(Phenylsulfonyl)isoquinolin-3-amine 469



To a microwave vial containing nitrile **452** (53.8 mg, 0.163 mmol) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (1.6 mL). The reaction was stirred at 90 °C for 4 h, then cooled to room temperature before NH_4HCO_3 (258 mg, 3.26 mmol) was added. The reaction mixture was stirred at 65 °C for a further 1 h, then cooled to room temperature and diluted with H_2O (5 mL). The mixture was extracted with 4:1 EtOAc/*n*BuOH (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 8:2 petrol/EtOAc) afforded 3-aminoisoquinoline **469** as an off-white solid (22.2 mg, 0.0781 mmol, 48%).

M.p. 191–193 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.91 (1 H, s, *H*C(1)), 8.44 (1 H, dd, J = 8.8, 0.7, HC_{Ar}), 8.01–7.98 (2 H, m, 2 × HC_{Ar}), 7.74 (1 H, dd, J = 8.1, 0.8, HC_{Ar}), 7.62–7.51 (2 H, m, 2 × HC_{Ar}), 7.49–7.45 (2 H, m, 2 × HC_{Ar}), 7.28 (1 H, dd, J = 7.0, 0.9, HC_{Ar}), 6.66 (2 H, br. s, NH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 159.1 (H*C*(1)), 155.3 (*C*(3)), 143.0, 134.6 (2 × C_{Ar}), 133.1, 133.0, 129.2, 129.0, 126.0 (5 × HC_{Ar}), 123.6 (C_{Ar}), 123.5, 122.0 (2 × HC_{Ar}). One C_{Ar} missing due to overlap; **IR** ν_{max} (powder)/cm^{-1} 3441, 3293, 3170, 1633, 1557, 1478, 1437, 1291, 1136, 1083; **HRMS** (ESI$^+$) $C_{15}H_{12}N_2NaO_2S$ requires 307.0512, found [M+Na]$^+$ 307.0503 (Δ +2.5 ppm).

Isoquinolin-3-amine 470

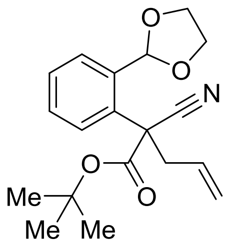


Method A: Arylated cyanoacetate **451** (53.6 mg, 0.185 mmol) was subjected to **General Procedure 12**. Purification by flash column chromatography (SiO_2, 8:2 petrol/EtOAc) afforded 3-aminoisoquinoline **470** as a yellow solid (22.8 mg, 0.158 mmol, 86%).

Method B: To a microwave vial fitted with a rubber septum was added (DPPF)$PdCl_2$ (8.5 mg, 0.012 mmol) and NaO*t*Bu (144 mg, 1.46 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (160 mg, 0.698 mmol) in anhydrous 1,4-dioxane (2.3 mL) was added *via* syringe, followed by the addition of *tert*-butyl cyanoacetate (83.2 µL, 0.582 mmol) and the reaction mixture was heated at 70 °C for 4 h. After cooling to room temperature, H_2O (1.5 mL) was added and the reaction was reheated to 90 °C and stirred for 6 h. The reaction was then cooled to room temperature before NH_4Cl (311 mg, 5.82 mmol) was added and the reaction was stirred at 90 °C. After 18 h, the solution was cooled to room temperature and 2 M aqueous NH_4HCO_3 (0.58 mL, 1.2 mmol) was added. The reaction was heated at 90 °C for a final 4 h before it was cooled to room temperature and extracted with 4:1 EtOAc/*n*BuOH (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 petrol/EtOAc) afforded 3-aminoisoquinoline **470** as a yellow solid (55.5 mg, 0.385 mmol, 66%).

M.p. 175–180 °C (lit. 177–178 °C);[314] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.87 (1 H, s, *H*C(1)), 7.78 (1 H, dd, *J* = 8.2, 0.5, *H*C(8)), 7.58–7.46 (2 H, m, *H*C(5) and *H*C(6)), 7.28–7.21 (1 H, m, *H*C(7)), 6.74 (1 H, s, *H*C(4)), 4.19 (2 H, br. s, N*H*$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 154.5 (*C*(3)), 151.6 (H*C*(1)), 138.9 (*C*$_{Ar}$), 130.4 (H*C*(6)), 127.8 (H*C*(8)), 124.6 (H*C*(5), 123.8 (*C*$_{Ar}$), 123.0 (H*C*(7)), 99.4 (H*C*(4)). Spectroscopic data were consistent with those previously reported.[314]

***tert*-Butyl 2-(2-(1,3-dioxolan-2-yl)phenyl)-2-cyanopent-4-enoate 478**

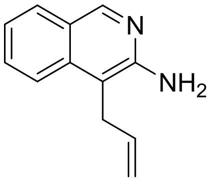


Aryl bromide **217** (127 mg, 0.554 mmol) was subjected to **General Procedure 13** using allyl bromide (47.9 µL, 0.554 mmol). Purification by flash column chromatography (SiO_2, 9:1 petrol/EtOAc) afforded nitrile **478** as a colourless solid (128 mg, 0.389 mmol, 84%).

M.p. 43–46 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.73 (1 H, d, *J* = 9.4, *H*C$_{Ar}$), 7.49 (1 H, s, *H*C$_{Ar}$), 7.46–7.38 (2 H, m, 2 × *H*C$_{Ar}$), 6.21 (1 H, s, *H*C(OR)$_2$), 5.88–5.74 (1 H, m, *H*C=CH$_2$), 5.28 (1 H, dd, *J* = 17.0, 1.5, HC=C*H*$_a$H$_b$), 5.24–5.20 (1 H, m, HC=CH$_a$*H*$_b$), 4.23–3.96 (4 H, m, OC*H*$_2$C*H*$_2$O), 3.22–3.12 (1 H, m, C*H*$_a$H$_b$CH=CH$_2$), 3.12–3.02 (1 H, m, CH$_a$*H*$_b$CH=CH$_2$), 1.46 (9 H, s, (C*H*$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 166.5 (*C*=O), 135.9, 132.7 (2 × *C*$_{Ar}$), 130.9 (H*C*=CH$_2$), 129.5, 128.9, 128.6, 127.5 (4 × H*C*$_{Ar}$), 120.8 (HC=*C*H$_2$), 118.6 (*C*≡N),

99.5 (H*C*(OR)$_2$), 84.6 (*C*(CH$_3$)$_3$), 65.3 (O*C*H$_2$CH$_2$O), 65.1 (OCH$_2$*C*H$_2$O), 53.1 (*C*(CN)), 41.6 (*C*H$_2$CH=CH$_2$), 27.5 ((*C*H$_3$)$_3$); **IR** ν_{max} (powder)/cm^{-1} 2982, 2890, 1736, 1453, 1370, 1250, 1146, 1121, 1068; **HRMS** (ESI$^+$) $C_{19}H_{23}N_2NaO_4$ requires 352.1519, found [M+Na]$^+$ 352.1506 (Δ +3.6 ppm).

4-Allylisoquinolin-3-amine 479

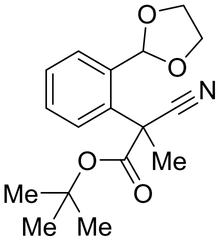


Method A: Nitrile **478** (49.0 mg, 0.149 mmol) was subjected to **General Procedure 12**. Purification by flash column chromatography (SiO$_2$, 85:15 petrol/EtOAc) afforded 3-aminoisoquinoline **479** as an orange solid (25.9 mg, 0.141 mmol, 95%).

Method B: To a microwave vial fitted with a rubber septum was added (DPPF)PdCl$_2$ (9.0 mg, 0.012 mmol) and NaO*t*Bu (153 mg, 1.54 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of aryl bromide **217** (169 mg, 0.738 mmol) in anhydrous 1,4-dioxane (2.5 mL) was added *via* syringe, followed by the addition of *tert*-butyl cyanoacetate (87.9 µL, 0.615 mmol) and the reaction mixture was heated at 70 °C for 24 h. After cooling to room temperature, allyl bromide (64.2 µL, 0.738 mmol) was added *via* syringe and the reaction mixture was stirred at 70 °C for 8 h. After cooling to room temperature, H$_2$O (1.5 mL) was added and the reaction was reheated to 90 °C and stirred for 15 h. It was then cooled to room temperature before NH$_4$Cl (329 mg, 6.15 mmol) was added and the reaction stirred at 90 °C. After 18 h, the solution was cooled to room temperature and 2 M aqueous NH$_4$HCO$_3$ (0.615 mL, 1.23 mmol) was added. The reaction was heated at 90 °C for a final 5 h before it was cooled to room temperature and extracted with 4:1 EtOAc/*n*BuOH (3 × 10 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, 9:1 petrol/EtOAc) afforded 3-aminoisoquinoline **479** as an orange solid (38.5 mg, 0.209 mmol, 34%).

M.p. 59–61 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.83 (1 H, s, *H*C(1)), 7.81 (1 H, d, *J* = 8.1, *H*C(8)), 7.76 (1 H, d, *J* = 8.7, *H*C(5)), 7.59–7.55 (1 H, m, *H*C(6)), 7.34–7.22 (1 H, m, *H*C(7)), 6.04–5.89 (1 H, m, *H*C=CH_2), 5.12 (1 H, dd, *J* = 10.1, 1.6, HC=CH_aH_b), 5.04 (1 H, dd, *J* = 17.1, 1.7, HC=CH_aH_b), 4.50 (2 H, br. s, NH_2), 3.66–3.54 (2 H, m, CH_2CH=CH_2); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 152.7 (*C*(3)), 150.2 (H*C*(1)), 137.0 (C_{Ar}), 134.1 (H*C*=CH_2), 130.4 (H*C*(6)), 128.4 (H*C*(8)), 124.3 (C_{Ar}), 122.6 (H*C*(7)), 121.2 (H*C*(5)), 116.1 (HC=CH_2), 106.4 (*C*(4)), 30.2 (CH_2CH=CH_2); **IR** ν_{max} (powder)/cm^{-1} 3449, 3360, 3192, 2918, 1620, 1582, 1499, 1455, 1378, 1257, 1139; **HRMS** (ESI$^+$) $C_{12}H_{13}N_2$ requires 185.1073, found [M+H]$^+$ 185.1074 (Δ −0.7 ppm).

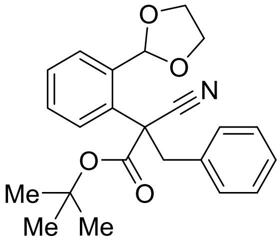
tert-Butyl 2-(2-(1,3-dioxolan-2-yl)phenyl)-2-cyanopropanoate 482



Aryl bromide **217** (137 mg, 0.598 mmol) was subjected to **General Procedure 13** using iodomethane (46.6 µL, 0.748 mmol). Purification by flash column chromatography (SiO_2, 85:15 petrol/EtOAc) afforded nitrile **482** as a colourless solid (129 mg, 0.425 mmol, 85%).

M.p. 111–113 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.76–7.68 (1 H, m, HC_{Ar}), 7.52–7.38 (3 H, m, 3 × HC_{Ar}), 6.21 (1 H, s, *H*C(OR)$_2$), 4.21–4.12 (1 H, m, $OCH_aH_bCH_aH_bO$), 4.10–3.97 (3 H, m, $OCH_aH_bCH_aH_bO$), 2.06 (3 H, s, CH_3), 1.48 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 167.6 (*C*=O), 135.9, 133.9 (2 × C_{Ar}), 129.6, 128.9, 128.5, 126.8 (4 × HC_{Ar}), 120.0 (*C*≡N), 100.1 (H*C*(OR)$_2$), 84.1 (*C*$(CH_3)_3$), 65.1 (OCH_2CH_2O), 65.0 (OCH_2CH_2O), 47.6 (*C*(CN)), 27.5 ($(CH_3)_3$), 25.3 (CH_3); **IR** ν_{max} (powder)/cm^{-1} 2980, 2889, 1737, 1458, 1370, 1252, 1142, 1075; **HRMS** (ESI$^+$) $C_{17}H_{21}NNaO_4$ requires 326.1363, found [M+Na]$^+$ 326.1358 (Δ +1.3 ppm).

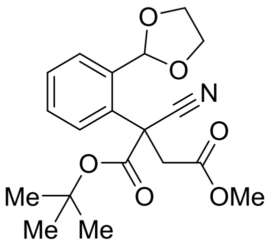
tert-Butyl 2-(2-(1,3-dioxolan-2-yl)phenyl)-2-cyano-3-phenylpropanoate 483



Aryl bromide **217** (163 mg, 0.712 mmol) was subjected to **General Procedure 13** using benzyl bromide (0.212 mL, 1.78 mmol). Purification by flash column chromatography (SiO_2, 9:1 petrol/EtOAc) afforded nitrile **483** as a viscous oil (205 mg, 0.540 mmol, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70–7.63 (1 H, m, HC_{Ar}), 7.32 (1 H, s, HC_{Ar}), 7.21–7.04 (5 H, m, 2 × HC_{Ar} and 3 × HC_{Ph}), 6.97 (2 H, dd, J = 7.8, 1.7, 2 × HC_{Ph}), 5.98 (1 H, s, $HC(OR)_2$), 4.22–4.11 (2 H, m, $OCH_aH_bCH_aH_bO$), 4.02–3.87 (2 H, m, $OCH_aH_bCH_aH_bO$), 3.63 (1 H, d, J = 13.6, CH_aH_bPh), 3.47 (1 H, d, J = 13.6, CH_aH_bPh), 1.35 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 168.6 (C=O), 135.1, 134.0, 133.0 (3 × C_{Ar}), 130.5 (HC_{Ph}), 129.5, 128.8, 128.7, 128.4 (4 × HC_{Ar}), 128.0, 127.4 (2 × HC_{Ph}), 118.5 (C≡N), 99.3 ($HC(OR)_2$), 84.9 ($C(CH_3)_3$, 65.4 (OCH_2CH_2O), 65.3 (OCH_2CH_2O), 55.7 (C(CN)), 43.0 (CH_2Ph), 27.3 ($(CH_3)_3$); **IR** ν_{max} (neat)/cm^{-1} 2981, 1736, 1455, 1370, 1251, 1149, 1123, 1068; **HRMS** (ESI$^+$) $C_{23}H_{25}NNaO_4$ requires 402.1676, found $[M+Na]^+$ 402.1671 (Δ +0.3 ppm).

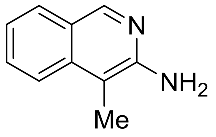
1-*tert*-Butyl 4-methyl 2-(2-(1,3-dioxolan-2-yl)phenyl)-2-cyanosuccinate 484



Aryl bromide **217** (256 mg, 1.12 mmol) was subjected to **General Procedure 13** using methyl bromoacetate (0.441 mL, 4.66 mmol). Purification by flash column chromatography (SiO_2, 85:15 petrol/EtOAc) afforded nitrile **484** as a viscous oil (293 mg, 0.811 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74–7.66 (1 H, m, HC_{Ar}), 7.41–7.25 (3 H, m, 3 × HC_{Ar}), 6.32 (1 H, s, $HC(OR)_2$), 4.12–4.04 (2 H, m, $OCH_aH_bCH_aH_bO$), 4.01–3.93 (2 H, m, $OCH_aH_bCH_aH_bO$), 3.64 (3 H, s, OCH_3), 3.42–3.25 (2 H, m, CH_2C=O), 1.44 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 169.1, 165.8 (2 × C=O), 135.8, 132.3 (2 × C_{Ar}), 129.7, 129.1, 128.7, 127.3 ($4 \times \mathrm{H}C_{\mathrm{Ar}}$), 118.5 ($C{\equiv}\mathrm{N}$), 99.2 ($\mathrm{H}C(\mathrm{OR})_2$), 85.2 ($C(\mathrm{CH_3})_3$), 65.2 ($\mathrm{O}C\mathrm{H_2CH_2O}$), 65.2 ($\mathrm{OCH_2}C\mathrm{H_2O}$), 52.1 ($\mathrm{O}C\mathrm{H_3}$), 50.3 ($C(\mathrm{CN})$), 42.1 ($C\mathrm{H_2C{=}O}$), 27.4 ($(C\mathrm{H_3})_3$); **IR** ν_{max} (neat)/cm^{-1} 2981, 1738, 1438, 1370, 1255, 1207, 1149, 1125, 1071; **HRMS** (ESI$^+$) $\mathrm{C_{19}H_{23}NNaO_6}$ requires 384.1418, found $[\mathrm{M{+}Na}]^+$ 384.1010 (Δ +2.0 ppm).

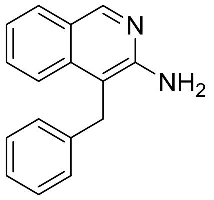
4-Methylisoquinolin-3-amine 485



Nitrile **482** (50.9 mg, 0.168 mmol) was subjected to **General Procedure 12**. Purification by flash column chromatography ($\mathrm{SiO_2}$, 8:2 petrol/EtOAc) afforded 3-aminoisoquinoline **485** as a pale yellow solid (25.8 mg, 0.158 mmol, 94%).

M.p. 110–113 °C (lit. 118–119 °C);[315] **^{1}H NMR** (400 MHz, $\mathrm{CDCl_3}$) δ_{H} 8.69 (1 H, s, *H*C(1)), 7.74–7.65 (2 H, m, *H*C(5) and *H*C(8)), 7.47 (1 H, m, *H*C(6)), 7.24–7.13 (1 H, m, *H*C(7)), 4.37 (2 H, br. s, $\mathrm{N}H_2$), 2.28 (3 H, s, $\mathrm{C}H_3$); **^{13}C NMR** (100 MHz, $\mathrm{CDCl_3}$) δ_{C} 152.3 (*C*(3)), 149.3 (H*C*(1)), 137.1 (C_{Ar}), 130.1 (H*C*(6)), 128.3 (H*C*(8)), 124.1 (C_{Ar}), 122.4 (H*C*(7)), 121.4 (H*C*(5)), 104.9 (*C*(4)), 11.4 ($C\mathrm{H_3}$)). Spectroscopic data were consistent with those previously reported.[315]

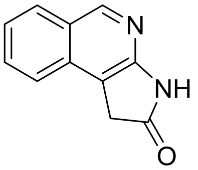
4-Benzylisoquinolin-3-amine 487



Nitrile **483** (50.8 mg, 0.134 mmol) was subjected to **General Procedure 12**. Purification by flash column chromatography ($\mathrm{SiO_2}$, 85:15 petrol/EtOAc) afforded 3-aminoisoquinoline **487** as a cream solid (22.7 mg, 0.0982 mmol, 73%).

M.p. 125–127 °C (lit. 112–120 °C, orange solid);[316] **^{1}H NMR** (400 MHz, $\mathrm{CDCl_3}$) δ_{H} 8.78 (1 H, s, *H*C(1)), 7.76 (1 H, d, *J* = 8.1, *H*C(8)), 7.72 (1 H, d, *J* = 8.7, *H*C(5)), 7.47 (1 H, ddd, *J* = 8.5, 6.9, 1.3, *H*C(6)), 7.25–7.00 (6 H, m, *H*C(7) and $5 \times H\mathrm{C_{Ph}}$), 4.31 (2 H, br. s, $\mathrm{N}H_2$), 4.17 (2 H, s, $\mathrm{C}H_2$); **^{13}C NMR** (100 MHz, $\mathrm{CDCl_3}$) δ_{C} 152.9 (*C*(3)), 150.6 (H*C*(1)), 138.5, 137.5 (2 × C_{Ar}), 130.7 (H*C*(6)), 128.8 (HC_{Ph}), 128.5 (H*C*(8)), 128.0, 126.5 (2 × HC_{Ph}), 124.3 (C_{Ar}), 122.6 (H*C*(7)), 121.4 (H*C*(5)), 107.6 (*C*(4)), 31.6 (CH_2). Spectroscopic data were consistent with those previously reported.[316]

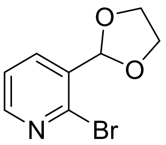
1,3-Dihydro-2*H*-pyrrolo[2,3-*c*]isoquinolin-2-one 489



Nitrile **484** (88.2 mg, 0.244 mmol) was subjected to **General Procedure 12**. Purification by flash column chromatography (SiO_2, EtOAc) afforded isoquinoline **489** as a cream solid (28.8 mg, 0.157 mmol, 65%).

M.p. 235–240 °C; **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 8.98 (1 H, s, *H*C(1)), 8.89 (1 H, br. s, N*H*), 7.95 (1 H, d, *J* = 8.4, *H*C(8)), 7.73–7.66 (1 H, m, *H*C(6)), 7.64 (1 H, d, *J* = 8.1, *H*C(5)), 7.45 (1 H, ddd, *J* = 8.2, 6.8, 1.1, *H*C(7)), 3.85 (2 H, s, CH_2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 175.5 (*C*=O), 152.2 (*C*(3)), 151.1 (H*C*(1)), 133.5 (C_{Ar}), 131.7 (H*C*(6)), 129.0 (H*C*(8)), 126.0 (C_{Ar}), 124.8 (H*C*(7)), 121.7 (H*C*(5)), 110.5 (*C*(4)), 34.8 (CH_2); **IR** ν_{max} (powder)/cm^{-1} 2970, 1751, 1722, 1630, 1566, 1524, 1442, 1367, 1260, 1229, 1143, 1089; **HRMS** (FI$^+$) $C_{11}H_8N_2O$ requires 184.0637, found $[M]^+$ 184.0638 (Δ +0.7 ppm).

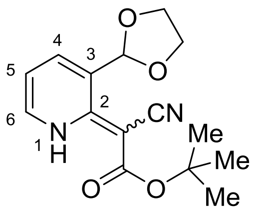
2-Bromo-3-(1,3-dioxolan-2-yl)pyridine 244



2-Bromo-3-pyridine-carboxaldehyde (1.04 g, 5.17 mmol) was subjected to **General Procedure 8**. Purification by flash column chromatography (SiO_2, 85:15 petrol/EtOAc) afforded acetal **244** as a colourless solid (1.16 g, 5.04 mmol, 98%).

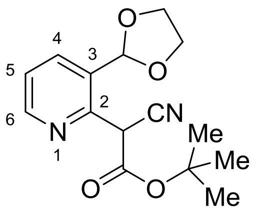
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.40–8.37 (1 H, m, *H*C(6)), 7.92–7.88 (1 H, m, *H*C(4)), 7.34–7.29 (1 H, m, *H*C(5)), 6.06 (1 H, s, *H*C(OR)$_2$), 4.21–4.06 (4 H, m, OCH_2CH_2O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 150.5 (H*C*(6)), 142.4 (C_{Ar}), 136.4 (H*C*(4)), 134.2 (C_{Ar}), 122.8 (H*C*(5)), 101.7 (H*C*(OR)$_2$), 65.6 (OCH_2CH_2O). Spectroscopic data were consistent with those previously reported.[317]

tert-Butyl 2-(3-(1,3-dioxolan-2-yl)pyridin-2(1*H*)-ylidene)-2-cyanoacetate, 491, and *tert*-butyl 2-(3-(1,3-dioxolan-2-yl)pyridin-2-yl)-2-cyanoacetate 492



491

+



492

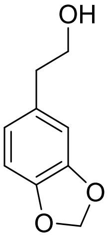
To a microwave vial fitted with a rubber septum was added (DPPF)$PdCl_2$ (7.7 mg, 0.011 mmol) and NaO*t*Bu (131 mg, 1.32 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of pyridyl bromide **244** (145 mg, 0.633 mmol) in anhydrous 1,4-dioxane (2.1 mL) was added *via* syringe, followed by the addition of *tert*-butyl cyanoacetate (75.3 µL, 0.527 mmol) and the reaction mixture was heated at 70 °C for 18 h. After cooling to room temperature, the reaction was quenched with saturated aqueous NH_4Cl (2 mL) and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo.* Purification by flash column chromatography (SiO_2, 7:3 petrol/EtOAc) afforded a 6:1 mixture of tautomeric nitriles **491** and **492** as a colourless oil (83.7 mg, 0.288 mmol, 55%).

491: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 15.3 (1 H, br. s, N*H*), 7.98 (1 H, dd, *J* = 7.5, 1.5, *H*C(6)), 7.62 (1 H, td, *J* = 6.1, 1.6, *H*C(4)), 6.65 (1 H, m, *H*C(5)), 6.52 (1 H, s, *H*C(OR)$_2$), 4.09–3.99 (4 H, m, OC*H*$_2$C*H*$_2$O), 1.49 (9 H, s, (C*H*$_3$)$_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 171.8 (*C*=O), 153.4 (*C*(2)), 137.5 (H*C*(6)), 134.6 (H*C*(4)), 127.9 (*C*(3)), 120.5 (*C*≡N), 112.0 (H*C*(5)), 97.7 (H*C*(OR)$_2$), 81.1 (*C*(CH$_3$)$_3$), 64.5 (O*C*H$_2$*C*H$_2$O), 62.2 (*C*(CN)), 28.3 ((*C*H$_3$)$_3$).

492: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 8.60 (1 H, dd, *J* = 4.8, 1.7, *H*C(6)), 7.86 (1 H, dd, *J* = 7.9, 1.7, H*C*(4)), 7.31 (1 H, dd, *J* = 7.8, 4.8, *H*C(5)), 5.94 (1 H, s, *H*C(OR)$_2$), 5.41 (1 H, s, C*H*CN), 4.09–3.99 (4 H, m, OC*H*$_2$C*H*$_2$O), 1.43 (9 H, s, (C*H*$_3$)$_3$); ^{13}**C NMR** (100 MHz, $CDCl_3$) δ_C 163.0 (*C*=O), 149.8 (*C*(6)), 149.0 (*C*(2)), 135.6 (H*C*(4)), 131.8 (*C*(3)), 123.4 (H*C*(5)), 115.2 (*C*≡N), 100.8 (H*C*(OR)$_2$), 84.3 (*C*(CH$_3$)$_3$), 64.5 (O*C*H$_2$*C*H$_2$O), 44.3 (*C*HCN), 27.2 ((*C*H$_3$)$_3$); **IR** ν_{max} (neat)/cm^{-1} 2977, 2886, 2189, 1746, 1628, 1583, 1525, 1475, 1447, 1391, 1366, 1347, 1312, 1275, 1249, 1227, 1161, 1142, 1100, 1075, 1053, 1012; **HRMS** (ESI$^+$) $C_{15}H_{18}N_2NaO_4$ requires 313.1159, found $[M+Na]^+$ 313.1148 (Δ −3.4 ppm).

3.3.4 Chapter 2.4 compounds

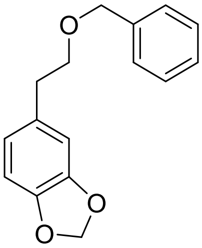
2-(Benzo[*d*][1,3]dioxol-5-yl)ethan-1-ol 518



Borane-THF complex solution (1 M, 27.8 mL, 27.8 mmol) was added dropwise to a solution of 3,4-(methylenedioxy)phenylacetic acid **517** (2.50 g, 13.9 mmol) in anhydrous THF (70 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 2 h then quenched with 1 M aqueous NaOH (50 mL) and diluted with H_2O (50 mL). The resulting mixture was extracted with Et_2O (3 × 100 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by automated flash column chromatography (100 g SiO_2 cartridge, 0–25% EtOAc in cyclohexane) afforded alcohol **518** as a colourless oil (2.25 g,13.5 mmol, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.76 (1 H, d, $J = 7.7$, HC_{Ar}), 6.73 (1 H, d, $J = 1.5$, HC_{Ar}), 6.68 (1 H, dd, $J = 7.9, 1.6$, HC_{Ar}), 5.93 (2 H, s, OCH_2O), 3.81 (2 H, t, $J = 6.5$, CH_2OH), 2.78 (2 H, t, $J = 6.5$, CH_2CH_2OH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 147.7, 146.1 (2 × $C_{Ar}OR$), 132.2 (C_{Ar}), 121.8, 109.3, 108.3 (3 × HC_{Ar}), 100.8 (OCH_2O), 63.7 (CH_2OH), 38.8 (CH_2CH_2OH). Spectroscopic data were consistent with those previously reported.[318]

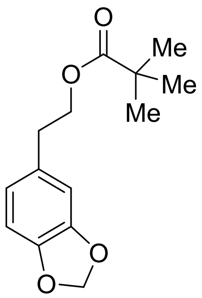
5-(2-(Benzyloxy)ethyl)benzo[*d*][1,3]dioxole 523 [251]



Sodium hydride (60% dispersion in mineral oil, 441 mg, 11.0 mmol) was added to a solution of alcohol **518** (1.41 g, 8.47 mmol) in anhydrous THF (11 mL) at 0 °C and the resulting suspension was stirred at 0 °C for 30 min. A solution of benzyl bromide (1.11 mL, 9.32 mmol) in anhydrous THF (9.0 mL) was added dropwise before the reaction was allowed to warm to room temperature and stirred for 48 h. The reaction was then quenched with H_2O (20 mL) and the resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by automated flash column chromatography (100 g SiO_2 cartridge, 0–25% EtOAc in cyclohexane) afforded benzyl ether **523** as a colourless oil (1.06 g, 4.14 mmol, 49%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.38–7.32 (5 H, m, 5 × HC_{Ph}), 6.79–6.76 (2 H, m, 2 × HC_{Ar}), 6.73–6.71 (1 H, m, HC_{Ar}), 5.94 (2 H, s, OCH_2O), 4.57 (2 H, s, OCH_2Ph), 3.69 (2 H, t, J = 7.0, CH_2OBn), 2.89 (2 H, t, J = 7.0, CH_2CH_2OBn); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 147.5, 145.9 (2 × $C_{Ar}OR$), 138.4, 132.8 (2 × C_{Ar}), 128.3, 127.6 (2 × HC_{Ph}), 127.5, 121.7, 109.3, 108.1 (4 × HC_{Ar}), 100.7 (OCH_2O), 72.9 (OCH_2Ph), 71.3 (CH_2OBn), 36.0 (CH_2CH_2OBn); **IR** ν_{max} (neat)/cm^{-1} 2860, 1488, 1442, 1359, 1244, 1188, 1097, 1037; **HRMS** (ESI$^+$) $C_{16}H_{16}NaO_3$ requires 279.0992, found $[M+Na]^+$ 279.0990 (Δ +0.7 ppm).

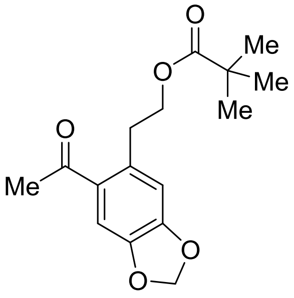
2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl pivaloate 525



Borane-THF complex solution (1 M, 11.7 mL, 11.7 mmol) was added slowly to a solution of 3,4-(methylenedioxy)phenylacetic acid **517** (1.05 g, 5.83 mmol) in THF (30 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 2 h then quenched by the dropwise addition of 1 M aqueous NaOH (10 mL). The organic phase was washed with H_2O (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was then dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C before pyridine (0.944 mL, 11.7 mmol) and pivaloyl chloride (1.44 mL, 11.7 mmol) were added sequentially. The reaction mixture was allowed to warm to room temperature and stirred for 18 h then diluted with H_2O (25 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 96:4 petrol/Et_2O) afforded pivaloate **525** as a colourless oil (1.34 g, 5.35 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.74–6.71 (2 H, m, 2 × HC_{Ar}), 6.65 (1 H, dd, J = 7.8, 1.5, HC_{Ar}), 5.92 (2 H, s, OCH_2O), 4.22 (2 H, t, J = 6.9, CH_2OPiv), 2.85 (2 H, t, J = 6.9, CH_2CH_2OPiv), 1.18 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 178.3 (C=O), 147.6, 146.1 (2 × $C_{Ar}OR$), 131.7 (C_{Ar}), 121.8, 109.3, 108.1 (3 × HC_{Ar}), 100.8 (OCH_2O), 64.9 (CH_2OPiv), 38.6 ($C(CH_3)_3$), 34.8 (CH_2CH_2OPiv), 27.1 ($(CH_3)_3$); **IR** ν_{max} (neat)/cm^{-1} 2972, 1725, 1504, 1489, 1443, 1398, 1365, 1282, 1246, 1150, 1037; **HRMS** (ESI$^+$) $C_{14}H_{18}NaO_4$ requires 273.1097, found $[M+Na]^+$ 273.1099 (Δ −0.8 ppm).

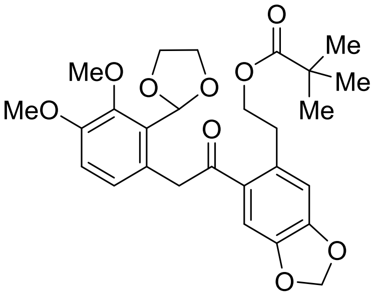
2-(6-Acetylbenzo[*d*][1,3]dioxol-5-yl)ethyl pivaloate 526



Zinc chloride (11.0 g, 80.5 mmol) was added to a solution of pivaloate **525** (4.02 g, 16.1 mmol) in acetic anhydride (40 mL) at 0 °C and the resulting suspension was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was then concentrated *in vacuo* and the residue redissolved in EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), H_2O (100 mL) and brine (100 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 92.5:7.5 petrol/EtOAc) afforded ketone **526** as a colourless solid (3.76 g, 12.9 mmol, 80%).

M.p. 51–53 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.22 (1 H, s, HC_{Ar}), 6.74 (1 H, s, HC_{Ar}), 6.01 (2 H, s, OCH_2O), 4.26 (2 H, t, J = 6.7, CH_2OPiv), 3.17 (2 H, t, J = 6.7, CH_2CH_2OPiv), 2.53 (3 H, s, CH_3C=O), 1.16, (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 199.0 (C=O), 178.4 (ROC=O), 150.0, 146.1, 135.1, 130.8 (4 × C_{Ar}), 112.3, 109.9 (2 × HC_{Ar}), 101.8 (OCH_2O), 64.9 (CH_2OPiv), 38.7 ($C(CH_3)_3$), 33.8 (CH_2CH_2OPiv), 29.4 (CH_3C=O), 27.2 ($(CH_3)_3$); **IR** ν_{max} (powder)/cm^{-1} 2972, 1715, 1681, 1611, 1504, 1479, 1372, 1270, 1247, 1157, 1109, 1036; **HRMS** (ESI$^+$) $C_{16}H_{20}NaO_5$ requires 315.1203, found $[M+Na]^+$ 315.1202 (Δ −0.2 ppm).

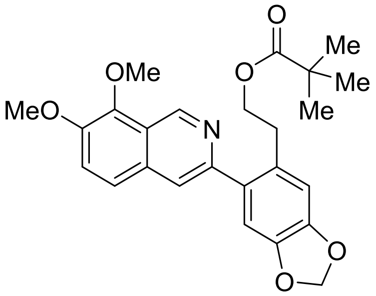
2-(6-(2-(2-(1,3-Dioxolan-2-yl)-3,4-dimethoxyphenyl)acetyl)benzo[*d*][1,3]dioxol-5-yl)ethyl pivaloate 527



To a microwave vial fitted with a rubber septum were added aryl bromide **513** (308 mg, 1.07 mmol), ketone **526** (623 mg, 2.13 mmol), Cs_2CO_3 (868 mg, 2.66 mmol), and $(Amphos)_2PdCl_2$ (37.9 mg, 0.0535 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with nitrogen before the solids were dissolved in anhydrous THF (5.4 mL). The reaction mixture was stirred at 90 ºC for 18 h then cooled to room temperature and quenched with H_2O (5 mL). The resulting mixture was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by automated flash column chromatography (70 g SiO_2 cartridge, 0–50% EtOAc in cyclohexane) afforded ketone **527** as an off-white solid (447 mg, 0.893 mmol, 84%).

M.p. 124–127 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.32 (1 H, s, HC_{Ar}), 6.95–6.89 (2 H, m, 2 × HC_{Ar}), 6.77 (1 H, s, HC_{Ar}), 6.12 (1 H, s, $HC(OR)_2$), 6.02 (2 H, s, OCH_2O), 4.29 (2 H, t, J = 6.6, CH_2OPiv), 4.26 (2 H, s, CH_2C=O), 3.86–3.75 (10 H, m, 2 × OCH_3 and OCH_2CH_2O), 3.13 (2 H, t, J = 6.6, CH_2CH_2OPiv), 1.16 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 198.8 (*C*=O), 178.4 (RO*C*=O), 151.5, 149.6, 149.3, 145.9, 135.2, 131.1 (6 × C_{Ar}), 128.3 (HC_{Ar}), 127.5, 127.0 (2 × C_{Ar}), 113.1, 112.3, 108.8 (3 × HC_{Ar}), 101.7 (OCH_2O), 99.3 ($HC(OR)_2$), 65.2 (CH_2OPiv), 64.6 (OCH_2CH_2O), 61.7, 55.7 (2 × OCH_3), 44.5 (CH_2C=O), 38.6 ($C(CH_3)_3$), 33.6 (CH_2CH_2OPiv), 27.2 ($(CH_3)_3$); **IR** ν_{max} (powder)/cm^{-1} 2965, 1717, 1687, 1493, 1379, 1271, 1241, 1149, 1083, 1062, 1043; **HRMS** (ESI$^+$) $C_{27}H_{32}NaO_9$ requires 523.1939, found $[M+Na]^+$ 523.1917 (Δ +4.0 ppm).

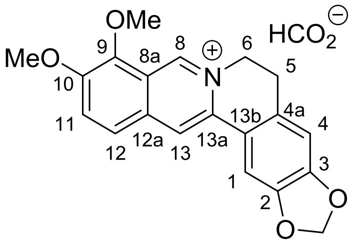
2-(6-(7,8-Dimethoxyisoquinolin-3-yl)benzo[*d*][1,3]dioxol-5-yl)ethyl pivaloate 528



To a microwave vial containing ketone **527** (83.1 mg, 0.166 mmol) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (1.7 mL) and the reaction was stirred at 90 °C for 18 h. After cooling to room temperature, the reaction was diluted with H_2O (5 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo.* Purification by automated flash column chromatography (10 g SiO_2 cartridge, 0–50% EtOAc in cyclohexane) afforded isoquinoline **528** as a pale yellow oil (53.1 mg, 0.121 mmol, 73%).

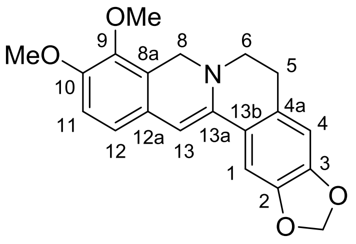
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.58 (1 H, s, *H*C(1)), 7.63 (1 H, d, *J* = 0.8, *H*C(4)), 7.59 (1 H, d, *J* = 8.9, *H*C(6)), 7.51 (1 H, d, *J* = 8.9, *H*C(5)), 6.95 (1 H, s, HC_{Ar}), 6.86 (1 H, s, HC_{Ar}), 5.98 (2 H, s, OCH_2O), 4.18 (2 H, t, *J* = 6.9, CH_2OPiv), 4.11 (3 H, s, OCH_3), 4.02 (3 H, s, OCH_3), 3.01 (2 H, t, *J* = 6.9, CH_2CH$_2$OPiv), 1.14 (9 H, s, (CH_3)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 178.4 (*C*=O), 151.4 (*C*(3)), 148.8, 147.3 (2 × C_{Ar}), 146.7 (H*C*(1)), 146.2, 144.0, 134.4, 132.2, 130.2 (5 × C_{Ar}), 122.8 (H*C*(6)), 122.7 (C_{Ar}), 120.5 (H*C*(5)), 119.4 (H*C*(4)), 110.5 (2 × HC_{Ar}), 101.1 (O*C*H$_2$O), 65.0 (*C*H$_2$OPiv), 61.6, 57.1 (2 × O*C*H$_3$), 38.6 (*C*(CH$_3$)$_3$), 32.3 (*C*H$_2$CH$_2$OPiv), 27.1 ((*C*H$_3$)$_3$); **IR** ν_{max} (neat)/cm^{-1} 2969, 1721, 1585, 1567, 1494, 1371, 1281, 1260, 1223, 1151, 1115, 1093, 1036; **HRMS** (ESI$^+$) $C_{25}H_{28}NO_6$ requires 438.1911, found [M+H]$^+$ 438.1918 (Δ −1.3 ppm).

Berberine formate and dihydroberberine 529



berberine formate

+



529

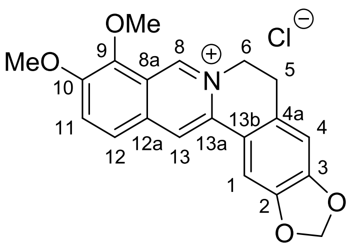
To a microwave vial containing ketone **527** (103 mg, 0.206 mmol) was added a 1 M solution of

NH_4Cl in 3:1 EtOH/H_2O (2.1 mL) and the resulting mixture was stirred at 90 °C for 18 h. After cooling to room temperature, the pH was adjusted to ~pH 1 by the dropwise addition of 2 M aqueous HCl. The reaction mixture was stirred at 90 °C for a further 7 h then cooled to room temperature and additional 2 M aqueous HCl (0.7 mL) was added. After stirring at 90 °C for 18 h, this process was repeated and the reaction mixture was heated at 110 °C for 24 h. After cooling to room temperature, a fourth portion of 2 M aqueous HCl (0.7 mL) was added and the resulting mixture was stirred at 110 °C for 2.5 days. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the crude residue was dissolved in 1:1 DMSO/MeOH and purified by MDAP (formic acid modifier) in 5 × 1 mL portions to afford berberine formate as a yellow solid (61.3 mg, 0.161 mmol, 78%). The solid was dried at 50 °C under vacuum for 18 h, after which an 8:1 mixture of dihydroberberine **529** and berberine formate was obtained.

Berberine formate: ^{1}H NMR (400 MHz, CD_3OD) δ_H 9.76 (1 H, s, *H*C(8)), 8.67 (1 H, s, *H*C(13)), 8.34 (1 H, s, HCO_2^-), 8.11 (1 H, d, *J* = 9.2, *H*C(11)), 7.99 (1 H, d, *J* = 9.2, *H*C(12)), 7.63 (1 H, s, *H*C(1)), 6.96 (1 H, s, *H*C(4)), 6.11 (2 H, s, OCH_2O), 4.94 (2 H, t, *J* = 6.3, C(6)H_2), 4.22 (3 H, s, OCH_3), 4.11 (3 H, s, OCH_3), 3.27 (2 H, t, *J* = 6.3, C(5)H_2).

529: ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 7.28 (1 H, s, *H*C(1)), 6.82 (1 H, d, *J* = 8.3, *H*C(11)), 6.74 (1 H, s, *H*C(4)), 6.69 (1 H, d, *J* = 8.3, *H*C(12)), 6.03 (1 H, s, *H*C(13)), 6.00 (2 H, s, C(8)H_2), 4.21 (2 H, s, OCH_2O), 3.77 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), 3.05 (2 H, t, *J* = 5.9, C(6)H_2), 2.80 (2 H, t, *J* = 5.9, C(5)H_2); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C 150.4, 147.4, 146.9, 144.5, 141.5, 129.1, 128.8, 124.4, 122.0 (9 × C_{Ar}), 118.9 (H*C*(12)), 112.2 (H*C*(11)), 108.3 (H*C*(4)), 104.0 (H*C*(1)), 101.4 (*C*(8)H_2), 96.4 (H*C*(13)), 60.6 (O*C*H_3), 56.2 (O*C*H_3), 49.3 (O*C*H_2O), 48.8 (*C*(6)H_2), 29.4 (*C*(5)H_2).

Berberine chloride

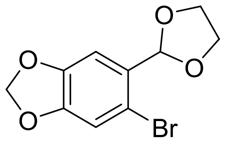


Method A: To a microwave vial containing ketone **527** (72.5 mg, 0.145 mmol) was added a 1 M solution of NH_4Cl in 3:1 $EtOH/H_2O$ (1.5 mL) and the resulting mixture was stirred at 90 °C for 18 h. The temperature was then increased to 110 °C and the reaction was stirred for a further 48 h before it was cooled to room temperature and concentrated *in vacuo*. The residue was redissolved in H_2O (10 mL), 20% w/w aqueous NaOH (10 mL) was added and the solution was stirred for 5 min then extracted with CH_2Cl_2 (5 × 15 mL). The combined organic extracts were poured into a separating funnel containing H_2O (20 mL) before 1 M aqueous HCl (20 mL) was added to regenerate berberine chloride. The resulting mixture was washed with H_2O (5 × 20 mL) and the aqueous washes were combined and concentrated *in vacuo*. The solid residue was triturated with CH_2Cl_2 (2 × 5 mL) to afford berberine chloride as a bright yellow solid (44.2 mg, 0.119 mmol, 82%).

Method B: To a microwave vial fitted with a rubber septum were added aryl bromide **513** (200 mg, 0.692 mmol), ketone **526** (403 mg, 1.38 mmol), Cs_2CO_3 (564 mg, 1.73 mmol), and $(Amphos)_2PdCl_2$ (24.5 mg, 0.0346 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with nitrogen before the solids were dissolved in anhydrous THF (3.5 mL). The reaction mixture was stirred at 90 ºC for 18 h then cooled to room temperature. A 1 M solution of NH_4Cl in 3:1 $EtOH/H_2O$ (10.4 mL, 10.4 mmol) was then added and the reaction was stirred at 90 °C for a further 24 h, then stirred at 110 °C for 72 h. After cooling to room temperature, the suspension was diluted with Et_2O (10 mL) and filtered. The solid was washed with cold H_2O (5 × 5 mL) then dissolved in MeOH (15 mL). The MeOH solution was concentrated *in vacuo* and the resulting solid was triturated with Et_2O (2 × 5 mL), EtOAc (2 × 5 mL) and ice cold H_2O (2 × 2 mL) then redissolved in MeOH (15 mL). Concentration *in vacuo* afforded berberine chloride as a bright yellow solid (103 mg, 0.277 mmol, 40%).

M.p. decomposed at 207 °C (lit. 203–205 °C);[253] **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ_H 9.90 (1 H, s, *H*C(8)), 8.97 (1 H, s, *H*C(13)), 8.19 (1 H, d, *J* = 9.1, *H*C(11)), 8.01 (1 H, d, *J* = 9.1, *H*C(12)), 7.79 (1 H, s, *H*C(1)), 7.08 (1 H, s, *H*C(4)), 6.17 (2 H, s, OCH_2O), 4.95 (2 H, t, *J* = 6.3, C(6)H_2), 4.10 (3 H, s, C(9)OCH_3), 4.07 (3 H, s, C(10)OCH_3), 3.21 (2 H, t, *J* = 6.3, C(5)H_2); **^{13}C NMR** (100 MHz, DMSO-d$_6$) δ_C 150.3 (*C*(10)), 149.8 (*C*(3)), 147.6 (*C*(2)), 145.4 (H*C*(8)), 143.6 (*C*(9)), 137.4 (*C*(13a)), 133.0 (*C*(12a)), 130.6 (*C*(4a)), 126.7 (H*C*(11)), 123.5 (H*C*(12)), 121.4 (*C*(8a)), 120.4 (*C*(13b)), 120.2 (H*C*(13)), 108.4 (H*C*(4)), 105.4 (H*C*(1)), 102.0 (O*C*H$_2$O), 61.9 (C(9)O*C*H$_3$), 57.1 (C(10)O*C*H$_3$), 55.1 (*C*(6)H$_2$), 26.3 (*C*(5)H$_2$). Spectroscopic data were consistent with those previously reported.[253,254]

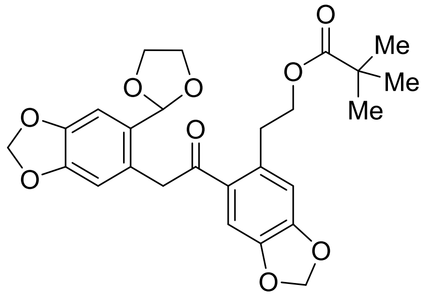
5-Bromo-6-(1,3-dioxolan-2-yl)benzo[*d*][1,3]dioxole 542



6-Bromo-1,3-benzodioxole-5-carboxaldehyde (2.05 g, 8.68 mmol) was subjected to **General Procedure 8**. Purification by automated flash column chromatography (100 g SiO$_2$ cartridge, 0–25% TBME in cyclohexane) afforded acetal **542** as a colourless solid (2.20 g, 8.06 mmol, 93%).

M.p. 64–68 °C (lit. 68–69 °C);[319] **^{1}H NMR** (CDCl$_3$, 400 MHz) δ_H 7.08 (1 H, s, *H*C$_{Ar}$), 7.00 (1 H, s, *H*C$_{Ar}$), 6.02 (1 H, s, *H*C(OR)$_2$), 5.99 (2 H, s, OCH_2O), 4.18–4.10 (2 H, m, OCH_aH$_b$CH_aH$_b$O), 4.09–4.01 (2 H, m, OCH$_a$$H_bCH_a$$H_b$O); **^{13}C NMR** (CDCl$_3$, 100 MHz) δ_C 149.0, 147.5 (2 × *C*$_{Ar}$OR), 130.0 (*C*$_{Ar}$), 113.9 (*C*$_{Ar}$Br), 112.8, 107.7 (2 × H*C*$_{Ar}$), 102.6 (H*C*(OR)$_2$), 101.9 (O*C*H$_2$O), 65.4 (O*C*H$_2$*C*H$_2$O). Spectroscopic data were consistent with those previously reported.[319]

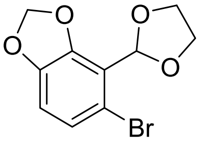
2-(6-(2-(6-(1,3-Dioxolan-2-yl)benzo[*d*][1,3]dioxol-5-yl)acetyl)benzo[*d*][1,3]dioxol-5-yl)ethyl pivaloate 543



To a microwave vial fitted with a rubber septum were added aryl bromide **542** (119 mg, 0.436 mmol), ketone **526** (255 mg, 0.872 mmol), Cs_2CO_3 (355 mg, 1.08 mmol), and $(Amphos)_2PdCl_2$ (15.4 mg, 0.0218 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon before the solids were dissolved in anhydrous THF (2.2 mL) and the reaction was stirred at 70 ºC for 24 h. After cooling to room temperature, the crimped cap was removed and replaced with a rubber septum and the flask was purged with argon whilst additional $(Amphos)_2PdCl_2$ (15.4 mg, 0.0218 mmol) was added. A new microwave cap was fitted and the vessel purged with argon for 5 mins before stirring at 70 °C for a further 24 h. After cooling to room temperature, the reaction was quenched with H_2O (5 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 8:2 petrol/EtOAc) afforded ketone **543** as an off-white solid (130 mg, 0.268 mmol, 62%).

M.p. 119–121 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.34 (1 H, s, HC_{Ar}), 7.07 (1 H, s, HC_{Ar}), 6.77 (1 H, s, HC_{Ar}), 6.65 (1 H, s, HC_{Ar}), 6.03 (2 H, s, OCH_2O), 5.95 (2 H, s, OCH_2O), 5.75 (1 H, s, $HC(OR)_2$), 4.25 (2 H, s, $CH_2C{=}O$), 4.25 (2 H, t, J = 6.6, CH_2OPiv), 4.00–3.90 (4 H, m, OCH_2CH_2O), 3.10 (2 H, t, J = 6.6, CH_2CH_2OPiv), 1.16 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 198.5 ($C{=}O$), 178.3 ($ROC{=}O$), 149.9, 148.0, 146.6, 146.1 (4 × $C_{Ar}OR$), 135.3, 130.6, 129.3, 127.4 (4 × C_{Ar}), 112.4, 111.5, 109.1, 107.3 (4 × HC_{Ar}), 102.1 ($HC(OR)_2$), 101.8, 101.2 (2 × OCH_2O), 65.0 (CH_2OPiv), 64.9 (OCH_2CH_2O), 44.6 ($CH_2C{=}O$), 38.6 ($C(CH_3)_3$), 33.7 (CH_2CH_2OPiv), 27.2 ($(CH_3)_3$); **IR** ν_{max} (powder)/cm^{-1} 2923, 1722, 1681, 1610, 1502, 1487, 1371, 1263, 1241, 1155, 1100, 1078, 1031; **HRMS** (ESI$^+$) $C_{26}H_{28}NaO_9$ requires 507.1626, found $[M+Na]^+$ 507.1618 (Δ +1.1 ppm).

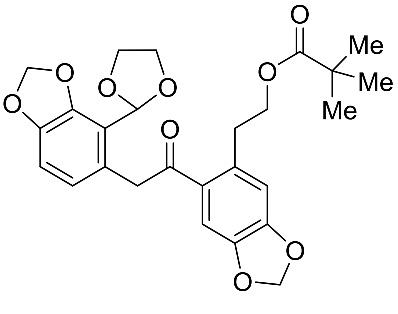
5-Bromo-4-(1,3-Dioxolan-2-yl)benzo[*d*][1,3]dioxole 544



5-Bromo-1,3-benzodioxole-4-carboxaldehyde (750 mg, 3.14 mmol) was subjected to **General Procedure 8**. Purification by flash column chromatography (SiO_2, 9:1 petrol/EtOAc) afforded acetal **544** as a colourless oil (857 mg, 3.14 mmol, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.03–7.00 (1 H, m, HC_{Ar}), 6.69–6.86 (1 H, m, HC_{Ar}), 6.21 (1 H, s, $HC(OR)_2$), 6.02 (2 H, s, OCH_2O), 4.22–4.16 (2 H, m, $OCH_aH_bCH_aH_bO$), 4.05–4.01 (2 H, m, $OCH_aH_bCH_aH_bO$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 147.8, 147.0 (2 × C_{Ar}OR), 125.7 (HC_{Ar}), 119.3 (C_{Ar}), 113.7 (C_{Ar}Br), 110.0 (HC_{Ar}), 102.3 ($HC(OR)_2$), 101.9 (OCH_2O), 65.7 (OCH_2CH_2O); **IR** ν_{max} (neat)/cm^{-1} 2961, 2893, 1457, 1386, 1335, 1239, 1212, 1097, 1046, 1019; **HRMS** (FI$^+$) $C_{10}H_9{}^{79}BrO_4$ requires 271.9684, found $[M]^+$ 271.9678 (Δ −2.3 ppm).

2-(6-(2-(4-(1,3-Dioxolan-2-yl)benzo[*d*][1,3]dioxol-5-yl)acetyl)benzo[*d*][1,3]dioxol-5-yl)ethyl pivaloate 545

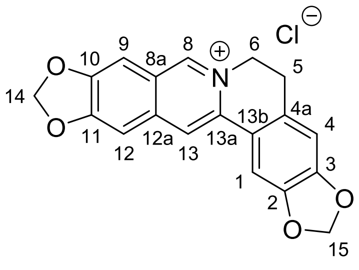


To a microwave vial fitted with a rubber septum were added ketone **526** (209 mg, 0.716 mmol), Cs_2CO_3 (292 mg, 0.895 mmol), and $(Amphos)_2PdCl_2$ (12.7 mg, 0.0179 mmol). The septum was replaced with a microwave cap and the vessel was purged with argon before a solution of aryl bromide **544** (97.8 mg, 0.358 mmol) in anhydrous THF (1.8 mL) was added *via* syringe. The reaction mixture was stirred at 90 °C for 48 h then cooled to room temperature and quenched with H_2O (2 mL).

The resulting mixture was extracted with $\mathrm{Et_2O}$ (3 × 10 mL) and the combined organic extracts were dried over $\mathrm{MgSO_4}$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography ($\mathrm{SiO_2}$, 6:4 petrol/EtOAc) afforded ketone **545** as an off-white solid (84.8 mg, 0.175 mmol, 49%).

M.p. 145–146 °C; **^{1}H NMR** (400 MHz, $\mathrm{CDCl_3}$) δ_H 7.32 (1 H, s, $H\mathrm{C_{Ar}}$), 6.79 (1 H, d, J = 7.9, $H\mathrm{C_{Ar}}$), 6.77 (1 H, s, $H\mathrm{C_{Ar}}$), 6.64 (1 H, d, J = 7.9, $H\mathrm{C_{Ar}}$), 6.02 (2 H, s, $\mathrm{OC}H_2\mathrm{O}$), 5.97 (2 H, s, $\mathrm{OC}H_2\mathrm{O}$), 5.91 (1 H, s, $H\mathrm{C(OR)_2}$), 4.27 (2 H, t, J = 6.6, $\mathrm{C}H_2\mathrm{OPiv}$), 4.25 (2 H, s, $\mathrm{C}H_2\mathrm{C{=}O}$), 3.86 (4 H, s, $\mathrm{OC}H_2\mathrm{C}H_2\mathrm{O}$), 3.12 (2 H, t, J = 6.6, $\mathrm{C}H_2\mathrm{CH_2OPiv}$), 1.16 (9 H, s, $(\mathrm{C}H_3)_3$); **^{13}C NMR** (100 MHz, $\mathrm{CDCl_3}$) δ_C 198.5 (C=O), 178.3 (ROC=O), 149.7, 147.3, 146.7, 146.0 (4 × C_ArOR), 135.3, 130.6, 127.5 (3 × C_Ar), 125.2 (HC_Ar), 116.3 (C_Ar), 112.3 (HC_Ar), 108.9 (2 × HC_Ar), 101.7, 101.3 (2 × O$C\mathrm{H_2O}$), 99.4 (H$C\mathrm{(OR)_2}$), 65.1 ($C\mathrm{H_2OPiv}$), 64.8 (O$C\mathrm{H_2}C\mathrm{H_2O}$), 44.7 ($C\mathrm{H_2C{=}O}$), 38.6 ($C\mathrm{(CH_3)_3}$), 33.6 ($C\mathrm{H_2CH_2OPiv}$), 27.2 (($C\mathrm{H_3})_3$); **IR** ν_max (powder)/cm^{-1} 2973, 2899, 1721, 1688, 1611, 1505, 1487, 1459, 1374, 1250, 1154, 1098, 1079, 1047; **HRMS** (ESI$^+$) $\mathrm{C_{26}H_{28}NaO_9}$ requires 507.1626, found [M+Na]$^+$ 507.1633 (Δ −1.2 ppm).

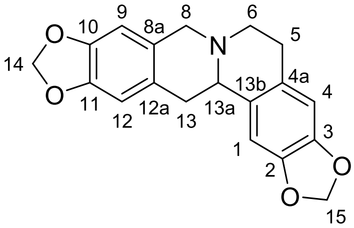
Pseudocoptisine chloride



To a screw-cap tube containing ketone **543** (59.1 mg, 0.122 mmol) was added a 1 M solution of $\mathrm{NH_4Cl}$ in 3:1 EtOH/$\mathrm{H_2O}$ (1.2 mL) and the resulting mixture was stirred at 90 °C for 18 h. The temperature was then increased to 110 °C and the reaction was stirred for a further 72 h. The reaction mixture was concentrated *in vacuo* and the residue redissolved in $\mathrm{H_2O}$ (5 mL), 20% w/w aqueous NaOH (10 mL) was added and the solution was stirred for 5 min then extracted with $\mathrm{CH_2Cl_2}$ (3 × 15 mL). The combined organic extracts were poured into a separating funnel containing 1 M aqueous HCl (20 mL) and the resulting mixture was washed with 1 M HCl (3 × 20 mL). The combined aqueous washes were concentrated *in vacuo* and the solid residue was triturated with Et_2O (5 × 10 mL) to afford pseudocoptisine chloride as a pale yellow solid (34.4 mg, 0.0967 mmol, 79%).

M.p. decomposed at 318 °C (lit. decomposed at 300 °C);[260] **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H 9.58 (1 H, s, *H*C(8)), 8.78 (1 H, s, *H*C(13)), 7.75 (1 H, s, *H*C(1)), 7.72 (1 H, s, *H*C(9)), 7.54 (1 H, s, *H*C(12)), 7.10 (1 H, s, *H*C(4)), 6.42 (2 H, s, C(15)H_2), 6.17 (2 H, s, C(14)H_2), 4.76 (2 H, t, J = 6.3, C(6)H_2), 3.19 (2 H, t, J = 6.3, C(5)H_2); **^{1}H NMR** (500 MHz, CD_3OD) δ_H 9.31 (1 H, s, *H*C(8)), 8.55 (1 H, s, *H*C(13)), 7.64 (1 H, s, *H*C(1)), 7.55 (1 H, s, *H*C(9)), 7.51 (1 H, s, *H*C(12)), 6.96 (1 H, s, *H*C(4)), 6.35 (2 H, s, C(15)H_2), 6.11 (2 H, s, C(14)H_2), 4.78 (2 H, t, J = 6.5, C(6)H_2), 3.23 (2 H, t, J = 6.5, C(5)H_2); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C 156.4 (*C*(10)), 151.3 (*C*(11)), 150.5 (*C*(2)), 148.1 (*C*(3)), 146.3 (H*C*(8)), 139.3 (*C*(8a)), 139.1 (*C*(13a)), 131.3 (*C*(4a)), 124.0 (*C*(12a)), 120.8 (*C*(13b)), 119.4 (H*C*(13)), 109.0 (H*C*(4)), 105.9 (H*C*(1)), 104.4 (*C*(15)H_2), 104.2 (H*C*(9)), 103.1 (H*C*(12)), 102.6 (*C*(14)H_2), 54.9 (*C*(6)H_2), 26.8 (*C*(5)H_2); **^{13}C NMR** (126 MHz, CD_3OD) δ_C 158.5 (*C*(10)), 153.3 (*C*(11)), 152.5 (*C*(2)), 150.1 (*C*(3)), 146.7 (H*C*(8)), 141.3 (*C*(8a)), 141.0 (*C*(13a)), 132.2 (*C*(13b)), 125.8 (*C*(12a)), 121.9 (*C*(4a)), 120.4 (H*C*(13)), 109.6 (H*C*(4)), 106.7 (H*C*(1)), 105.6 (*C*(15)H_2), 104.9 (H*C*(9)), 104.2 (H*C*(12)), 103.9 (*C*(14)H_2), 56.4 (*C*(6)H_2), 28.3 (*C*(5)H_2); **IR** ν_{max} (powder)/cm^{-1} 3385, 1613, 1495, 1458, 1369, 1270, 1233, 1207, 1189, 1098, 1033; **HRMS** (ESI$^+$) $C_{19}H_{14}NO_4$ requires 320.0917, found $[M]^+$ 320.0914 (Δ +0.6 ppm).

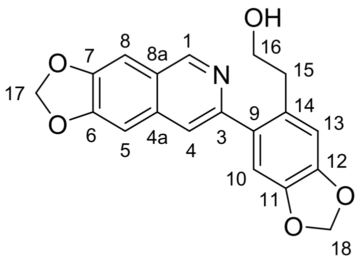
Tetrahydropseudocoptisine 546



To a solution of pseudocoptisine chloride (17.5 mg, 0.0492 mmol) in MeOH (2.0 mL) at 45 °C was added $NaBH_4$ (7.5 mg, 0.12 mmol) portionwise. The reaction mixture was allowed to cool to room temperature and stirred for 2 h then concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (5 mL) and poured into a separating funnel containing H_2O (5 mL). The resulting mixture was extracted with $CHCl_3$ (4 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, $CHCl_3$) afforded tetrahydropseudocoptisine **546** as a colourless solid (13.7 mg, 0.0424 mmol, 86%).

M.p. 214–217 °C (lit. 212–214 °C);[258] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.73 (1 H, s, *H*C(1)), 6.62 (1 H, s, *H*C(12)), 6.59 (1 H, s, *H*C(4)), 6.55 (1 H, s, *H*C(9)), 5.92 (2 H, s, C(15)H_2), 5.91 (2 H, s, C(14)H_2), 3.91 (1 H, d, *J* = 14.6, C(8)H_aH$_b$), 3.64 (1 H, d, *J* = 14.6, C(8)H$_a$$H_b$), 3.54 (1 H, dd, *J* = 11.2, 3.8, *H*C(13a)), 3.17 (1 H, dd, *J* = 15.9, 3.8, C(13)H_aH$_b$), 3.14–3.07 (2 H, m, C(5)H_aH$_b$ and C(6)H_aH$_b$), 2.80 (1 H, dd, *J* = 15.9, 11.4, C(13)H$_a$$H_b$), 2.71–2.54 (2 H, m, C(5)H$_a$$H_b$ and C(6)H$_a$$H_b$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 146.1, 146.1, 145.9, 145.8 (*C*(2), *C*(3), *C*(10) and *C*(11)), 130.7 (*C*(4a)), 127.7 (*C*(13b)), 127.0 (*C*(8a) and *C*(12a)), 108.4 (H*C*(12)), 108.4 (H*C*(4)), 106.0 (H*C*(9)), 105.4 (H*C*(1)), 100.8 (*C*(15)H_2), 100.6 (*C*(14)H_2), 59.8 (H*C*(13a)), 58.5 (*C*(8)H_2), 51.2 (*C*(6)H_2), 36.9 (*C*(13)H_2), 29.5 (*C*(5)H_2); **IR** ν_{max} (powder)/cm^{-1} 2903, 2795, 2746, 1483, 1389, 1345, 1248, 1228, 1162, 1127, 1034; **HRMS** (ESI$^+$) $C_{19}H_{18}NO_4$ requires 324.1230, found [M+H]$^+$ 324.1228 (Δ −0.8 ppm). NMR data were consistent with those previously reported.[262,263]

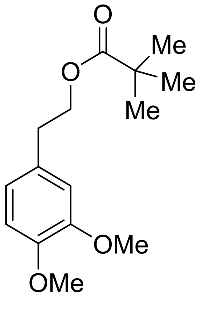
2-(6-([1,3]Dioxolo[4,5-*g*]isoquinolin-7-yl)benzo[*d*][1,3]dioxol-5-yl)ethan-1-ol 539



To a screw-cap tube containing ketone **543** (83.8 mg, 0.173 mmol) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (1.7 mL) and the reaction was stirred at 90 °C for 18 h. After cooling to room temperature, the reaction was diluted with H_2O (5 mL) and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting residue was redissolved in anhydrous THF (1.7 mL) and cooled to −78 °C before a 1 M solution of DIBAL-H in hexanes (0.433 mL, 0.433 mmol) was added slowly *via* syringe. The reaction mixture was warmed to room temperature and stirred for 4 h then quenched with H_2O (2 mL). The resulting mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 1:1 petrol/Et_2O) afforded alcohol **539** as a colourless solid (33.7 mg, 0.0999 mmol, 58%).

M.p. 184–186 °C; **^{1}H NMR** (400 MHz, ($CDCl_3$) δ_H 8.95 (1 H, s, *H*C(1)), 7.63 (1 H, s, *H*C(4)), 7.22 (1 H, s, *H*C(8)), 7.10 (1 H, s, *H*C(5)), 6.91 (1 H, s, *H*C(10)), 6.87 (1 H, s, *H*C(13)), 6.13 (2 H, s, C(17)H_2), 6.00 (2 H, s, C(18)H_2), 3.98 (2 H, t, $J = 5.6$, C(16)H_2), 2.82 (2 H, t, $J = 5.6$, C(15)H_2); **^{13}C NMR** (100 MHz, ($CDCl_3$) δ_C 151.6 (*C*(7)), 151.4 (*C*(3)), 148.6 (*C*(6)), 148.1 (*C*(12)), 147.9 (H*C*(1)), 146.1 (*C*(11)), 135.5 (*C*(8a)), 133.5 (*C*(9)), 132.7 (*C*(14)), 124.4 (*C*(4a)), 120.3 (H*C*(4)), 110.0 (H*C*(13)), 109.9 (H*C*(10)), 103.0 (H*C*(8)), 102.5 (H*C*(5)), 101.8 (*C*(17)H_2), 101.2 (*C*(18)H_2), 63.8 (*C*(16)H_2), 35.2 (*C*(15)H_2); **IR** ν_{max} (neat)/cm^{-1} 3174, 2907, 2850, 1600, 1503, 1482, 1453, 1234, 1039; **HRMS** (ESI$^+$) $C_{19}H_{16}NO_5$ requires 338.1023, found $[M+H]^+$ 338.1014 (Δ −2.5 ppm). NMR data were consistent with those previously reported.[259]

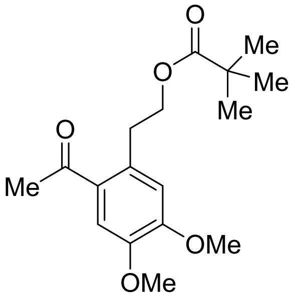
3,4-Dimethoxyphenethyl pivaloate 555



Borane-THF complex solution (1 M, 11.3 mL, 11.3 mmol) was added slowly to a solution of 3,4-dimethoxyphenylacetic acid (1.11 g, 5.66 mmol) in THF (30 mL) at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 2 h then quenched by the dropwise addition of 1 M aqueous NaOH (10 mL). The organic phase was washed with H_2O (2 × 25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was then dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C before pyridine (0.912 mL, 11.3 mmol) and pivaloyl chloride (1.39 mL, 11.3 mmol) were added. The reaction mixture was allowed to warm to room temperature and stirred for 18 h then diluted with H_2O (25 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 8:2 petrol/Et_2O) afforded pivaloate **555** as a colourless solid (1.40 g, 5.23 mmol, 92%).

M.p. 46–50 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 6.82–6.80 (1 H, m, HC_{Ar}), 6.77–6.75 (2 H, m, 2 × HC_{Ar}), 4.25 (2 H, t, J = 6.9, CH_2OPiv), 3.87 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 2.88 (2 H, t, J = 6.9, CH_2CH_2OPiv), 1.14 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 178.4 (C=O), 148.8, 147.6 (2 × C_{Ar}OMe), 130.5 (C_{Ar}), 120.9, 112.1, 111.2 (3 × HC_{Ar}), 65.0 (CH_2OPiv), 55.8, 55.7 (2 × OCH_3), 38.6 ($C(CH_3)$), 34.7 (CH_2CH_2OPiv), 27.1 ($(CH_3)_3$); **IR** ν_{max} (powder)/cm^{-1} 2961, 1721, 1589, 1515, 1467, 1284, 1258, 1234, 1151, 1029; **HRMS** (ESI$^+$) $C_{15}H_{22}NaO_4$ requires 289.1410, found $[M+Na]^+$ 289.1416 (Δ −1.6 ppm).

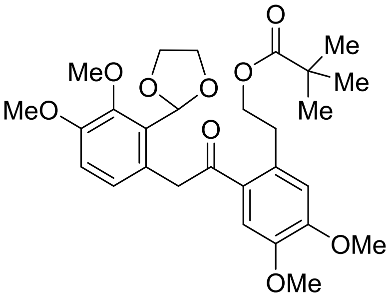
2-Acetyl-4,5-dimethoxyphenethyl pivaloate 556



Zinc chloride (9.40 g, 69.0 mmol) was added to a solution of pivaloate **555** (3.67 g, 13.8 mmol) in acetic anhydride (35 mL) at 0 °C. The resulting suspension was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was then concentrated *in vacuo* and the residue redissolved in EtOAc (100 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), H_2O (100 mL) and brine (100 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 8:2 petrol/Et_2O) afforded ketone **556** as a colourless oil (3.53 g, 11.4 mmol, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.24 (1 H, s, $HC(3)$), 6.73 (1 H, s, $HC(6)$), 4.25 (2 H, t, J = 6.7, CH_2OPiv), 3.89 (6 H, s, 2 × OCH_3), 3.18 (2 H, t, J = 6.7, CH_2CH_2OPiv), 2.55 (3 H, s, CH_3C=O), 1.12 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 199.1 (C=O), 178.3 (ROC=O), 151.4, 146.7 (2 × C_{Ar}OMe), 133.3, 129.2 (2 × C_{Ar}), 114.8 ($HC(6)$), 113.4 ($HC(3)$), 64.8 (CH_2OPiv), 56.0, 55.8 (2 × OCH_3), 38.5 ($C(CH_3)_3$), 33.6 (CH_2CH_2OPiv), 29.2 (CH_3C=O), 27.1 ($(CH_3)_3$); **IR** ν_{max} (neat)/cm^{-1} 2969, 1722, 1673, 1604, 1568, 1518, 1462, 1360, 1266, 1206, 1148, 1058; **HRMS** (ESI$^+$) $C_{17}H_{24}NaO_5$ requires 331.1516, found $[M+Na]^+$ 331.1526 (Δ −3.8 ppm).

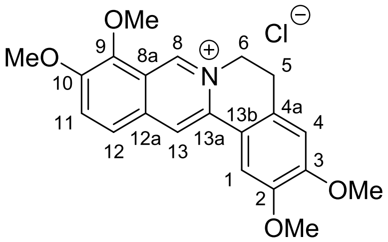
2-(2-(2-(1,3-Dioxolan-2-yl)-3,4-dimethoxyphenyl)acetyl)-4,5-dimethoxyphenethyl pivaloate 557



To a microwave vial fitted with a rubber septum were added aryl bromide **513** (196 mg, 0.679 mmol), Cs_2CO_3 (553 mg, 1.70 mmol), and $(Amphos)_2PdCl_2$ (24.1 mg, 0.0340 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon before a solution of ketone **556** (419 mg, 1.36 mmol) in anhydrous THF (3.4 mL) was added *via* syringe. The reaction mixture was stirred at 90 ºC for 18 h then cooled to room temperature and quenched with H_2O (5 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 petrol/EtOAc) afforded ketone **557** as an off-white solid (325 mg, 0.629 mmol, 93%).

M.p. 130–134 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.34 (1 H, s, HC_{Ar}), 6.91–6.86 (2 H, m, 2 × HC_{Ar}), 6.76 (1 H, s, HC_{Ar}), 6.14 (1 H, s, $HC(OR)_2$), 4.31 (2 H, s, $CH_2C=O$), 4.31 (2 H, t, J = 6.7, CH_2OPiv), 3.91 (3 H, s, OCH_3), 3.87–3.75 (4 H, m, OCH_2CH_2O), 3.85 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 3.19 (2 H, t, J = 6.7, CH_2CH_2OPiv), 1.15 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 199.2 (C=O), 178.4 (ROC=O), 151.3, 150.9, 149.1, 146.6 (4 × $C_{Ar}OMe$), 133.7, 129.1, 127.8 (3 × C_{Ar}), 127.8 (HC_{Ar}), 126.6 (C_{Ar}), 114.9, 113.1, 112.7 (3 × HC_{Ar}), 99.2 ($HC(OR)_2$), 65.1 (CH_2OPiv), 64.6 (OCH_2CH_2O), 61.7, 56.1, 55.7, 55.6 (4 × OCH_3), 44.5 ($CH_2C=O$), 38.6 ($C(CH_3)_3$), 33.5 (CH_2CH_2OPiv), 27.2 ($(CH_3)_3$); **IR** ν_{max} (powder)/cm^{-1} 2965, 1721, 1684, 1570, 1518, 1494, 1456, 1391, 1349, 1266, 1199, 1157, 1125, 1061, 1043; **HRMS** (ESI$^+$) $C_{28}H_{36}NaO_9$ requires 539.2252, found $[M+Na]^+$ 539.2250 (Δ +0.1 ppm).

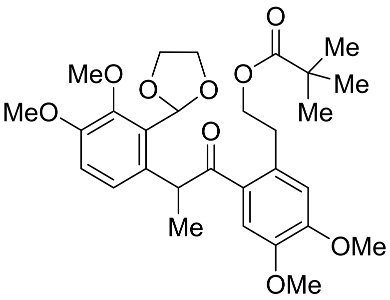
Palmatine chloride



To a microwave vial containing ketone **557** (163 mg, 0.316 mmol) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (3.2 mL) and the resulting mixture was stirred at 90 °C for 18 h. The temperature was then increased to 110 °C and the reaction was stirred for a further 48 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and the residue redissolved in H_2O (10 mL). A 20% w/w aqueous solution of NaOH (10 mL) was added and the solution was stirred for 5 min then extracted with CH_2Cl_2 (5 × 15 mL). The combined organic extracts were poured into a separating funnel containing H_2O (20 mL) before 1 M aqueous HCl (20 mL) was added to regenerate palmatine chloride. The resulting mixture was washed with H_2O (3 × 20 mL) and the aqueous washes were combined and concentrated *in vacuo*. The solid residue was triturated with EtOAc (5 × 10 mL) to afford palmatine chloride as an orange-yellow solid (108 mg, 0.278 mmol, 88%).

M.p. 203–206 °C (lit. 206–208 °C);[273] **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H 9.91 (1 H, s, *H*C(8)), 9.10 (1 H, s, *H*C(13)), 8.21 (1 H, d, *J* = 9.2, *H*C(11)), 8.04 (1 H, d, *J* = 9.2, *H*C(12)), 7.73 (1 H, s, *H*C(1)), 7.09 (1 H, s, *H*C(4)), 4.96 (2 H, t, *J* = 6.1, C(6)H_2), 4.10 (3 H, s, C(9)OCH_3), 4.07 (3 H, s, C(10)OCH_3), 3.94 (3 H, s, C(2)OCH_3), 3.87 (3 H, s, C(3)OCH_3), 3.23 (2 H, t, *J* = 6.1, C(5)H_2); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C 151.5 (*C*(3)), 150.2 (*C*(10)), 148.7 (*C*(2)), 145.5 (H*C*(8)), 143.6 (*C*(9)), 137.7 (*C*(13a)), 133.1 (*C*(12a)), 128.6 (*C*(4a)), 126.7 (H*C*(11)), 123.4 (H*C*(12)), 121.3 (*C*(8a)), 119.9 (H*C*(13)), 118.9 (*C*(13b)), 111.3 (H*C*(4)), 108.8 (H*C*(1)), 61.9 (C(9)O*C*H_3), 57.0 (C(10)O*C*H_3), 56.2 (C(2)O*C*H_3), 55.9 (C(3)O*C*H_3), 55.3 (*C*(6)H_2), 26.0 (*C*(5)H_2). Spectroscopic data were consistent with those previously reported.[273]

2-(2-(2-(1,3-Dioxolan-2-yl)-3,4-dimethoxyphenyl)propanoyl)-4,5-dimethoxyphenethyl pivaloate 558

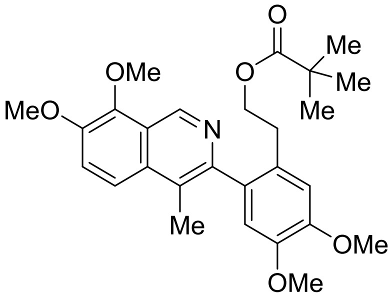


To a microwave vial fitted with a rubber septum were added aryl bromide **513** (203 mg, 0.702 mmol), Cs_2CO_3 (572 mg, 1.76 mmol), and $(Amphos)_2PdCl_2$ (24.9 mg, 0.0351 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon before a solution of ketone **556** (433 mg, 1.40 mmol) in anhydrous THF (3.5 mL) was added *via* syringe. The reaction mixture was stirred at 90 ºC for 18 h then cooled to room temperature. Iodomethane (87.4 μL, 1.40 mmol) was added *via* syringe and the reaction was stirred at 70 °C for 24 h, after which it was cooled to room temperature and quenched with H_2O (5.0 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 petrol/EtOAc) afforded ketone **558** as an off-white solid (284 mg, 0.535 mmol, 76%).

M.p. 136–138 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.48 (1 H, s, *H*C_{Ar}), 6.79 (1 H, d, *J* = 8.7, *H*C_{Ar}), 6.70 (1 H, d, *J* = 8.7, *H*C_{Ar}), 6.70 (1 H, s, *H*C_{Ar}), 6.34 (1 H, s, *H*C(OR)$_2$), 5.02 (1 H, q, *J* = 6.7 C*H*(CH$_3$)), 4.38 (2 H, t, *J* = 6.7, C*H*$_2$OPiv), 4.19–4.14 (2 H, m, OC$H_a$$H_bCH_a$$H_b$O), 4.08–4.03 (2 H, m, OCH$_a$$H_bCH_a$$H_b$O), 3.87 (3 H, s, OC*H*$_3$), 3.81 (3 H, s, OC*H*$_3$), 3.80 (3 H, s, OC*H*$_3$), 3.74 (3 H, s, OC*H*$_3$), 3.31–3.17 (2 H, m, C$H_a$$H_bCH_2$OPiv), 1.49 (3 H, d, *J* = 6.7, CH(C*H*$_3$)), 1.18 (9 H, s, (C*H*$_3$)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 202.7 (*C*=O), 178.6 (RO*C*=O), 151.0, 150.7, 149.4, 146.7 (4 × C_{Ar}OMe), 135.7, 134.0, 128.6, 125.7 (4 × C_{Ar}), 124.0, 114.7, 114.2, 113.6 (4 × HC_{Ar}), 99.7 (H*C*(OR)$_2$), 65.2 (*C*H$_2$OPiv), 64.9, 64.5

(OCH$_2$$CH_2$O), 61.8, 56.4, 55.7, 55.6 (4 × OCH$_3$), 45.0 (CH(CH$_3$)), 38.7 (C(CH$_3$)$_3$), 34.2 (CH$_2$CH$_2$OPiv), 27.3 ((CH$_3$)$_3$), 19.8 (CH(CH$_3$)); **IR** ν_{max} (powder)/cm^{-1} 2970, 1722, 1671, 1568, 1492, 1456, 1391, 1349, 1267, 1205, 1156, 1137, 1056, 1030; **HRMS** (ESI$^+$) $C_{29}H_{38}NaO_9$ requires 553.2408, found [M+Na]$^+$ 553.2403 (Δ +0.6 ppm).

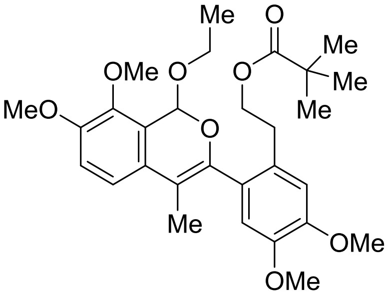
2-(7,8-Dimethoxy-4-methylisoquinolin-3-yl)-4,5-dimethoxyphenethyl pivaloate 559



To a microwave vial containing ketone **558** (108 mg, 0.204 mmol) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (2.0 mL) and the resulting mixture was stirred at 90 °C for 24 h. After cooling to room temperature, NH_4HCO_3 (323 mg, 4.08 mmol) was added and the reaction was stirred at 90 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 petrol/EtOAc) afforded isoquinoline **559** as a yellow oil (89.3 mg, 0.191 mmol, 94%).

^{1}H NMR (400 MHz, CDCl$_3$) δ_H 9.47 (1 H, s, HC(1)), 7.77 (1 H, d, J = 9.2, HC(5)), 7.56 (1 H, d, J = 9.2, HC(6)), 6.90 (1 H, s, HC$_{Ar}$), 6.76 (1 H, s, HC$_{Ar}$), 4.10 (3 H, s, OCH_3), 4.06–4.04 (2 H, m, CH_2OPiv), 4.04 (3 H, s, OCH_3), 3.93 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 2.88–2.77 (1 H, m, CH_aH$_b$CH$_2$OPiv), 2.68–2.59 (1 H, m, CH$_a$$H_bCH_2$OPiv), 2.42 (3 H, s, C$H_3$), 1.11 (9 H, s, (C$H_3$)$_3$); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 178.4 (C=O), 149.7, 148.5, 148.3, 147.3 (4 × C_{Ar}OMe), 144.8 (HC(1)), 144.1 (C(3)), 133.3, 131.6, 128.6, 124.5, 123.0 (5 × C_{Ar}), 119.8 (HC(5)), 119.6 (HC(6)), 113.0 (2 × HC_{Ar}), 64.4 (CH$_2$OPiv), 61.7, 56.9, 55.9, 55.9 (4 × OCH$_3$), 38.5 (C(CH$_3$)$_3$), 32.0 (CH$_2$CH$_2$OPiv), 27.1 ((CH$_3$)$_3$), 15.1 (CH$_3$); **IR** ν_{max} (neat)/cm^{-1} 2959, 1723, 1569, 1517, 1462, 1374, 1263, 1207, 1158, 1079, 1024; **HRMS** (ESI$^+$) $C_{27}H_{34}NO_6$ requires 468.2381, found [M+H]$^+$ 468.2385 (Δ −0.4 ppm). See Appendix 2 for VT ^{1}H NMR spectra.

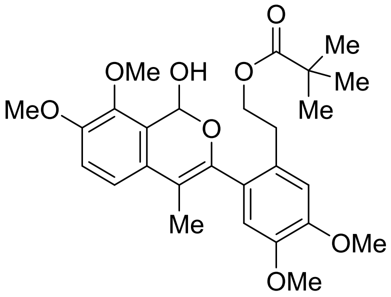
2-(1-Ethoxy-7,8-dimethoxy-4-methyl-1*H*-isochromen-3-yl)-4,5-dimethoxyphenethyl pivaloate 560



To a screw-cap tube containing ketone **558** (326 mg, 0.614 mmol) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (6.1 mL) and the reaction was stirred at 90 °C for 18 h. After cooling to room temperature, the reaction was diluted with H_2O (5 mL) and the resulting mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 8:2 petrol/EtOAc) afforded isochromene **560** as an off-white solid (113 mg, 0.220 mmol, 36%).

M.p. 33–35 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.05 (1 H, d, J = 8.6, HC_{Ar}), 7.00 (1 H, d, J = 8.6, HC_{Ar}), 6.85 (1 H, s, HC_{Ar}), 6.77 (1 H, s, HC_{Ar}), 6.34 (1 H, s, $HC(OR)_2$), 4.22 (2 H, t, J = 6.7, CH_2OPiv), 4.05–4.00 (1 H, m, $OCH_aH_bCH_3$), 3.93 (3 H, s, OCH_3), 3.91 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 3.85–3.83 (1 H, m, $OCH_aH_bCH_3$), 3.06–2.87 (2 H, m, $CH_aH_bCH_2$OPiv), 1.86 (3 H, s, CH_3), 1.28 (3 H, t, J = 7.1, OCH_2CH_3), 1.16 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 178.4 (C=O), 151.3, 148.8, 147.2, 145.1 (4 × C_{Ar}OMe), 144.7 (C=COR), 129.8, 127.8, 125.1, 122.2 (4 × C_{Ar}), 117.5, 113.2, 113.1, 112.4 (4 × HC_{Ar}), 107.2 (C=COR), 93.6 ($HC(OR)_2$), 64.6 (CH_2OPiv), 63.8 (OCH_2CH_3), 60.9, 55.9, 55.8, 55.8 (4 × OCH_3), 38.6 ($C(CH_3)_3$), 31.5 (CH_2CH_2OPiv), 27.1 ($(CH_3)_3$), 15.1 (OCH_2CH_3), 13.2 (CH_3); **IR** ν_{max} (powder)/cm^{-1} 2972, 1725, 1514, 1498, 1462, 1354, 1278, 1248, 1228, 1155, 1058, 1026; **HRMS** (ESI$^+$) $C_{29}H_{38}NaO_8$ requires 537.2459, found [M+Na]$^+$ 537.2460 (Δ −0.3 ppm). See Appendix 2 for VT ^{1}H NMR spectra.

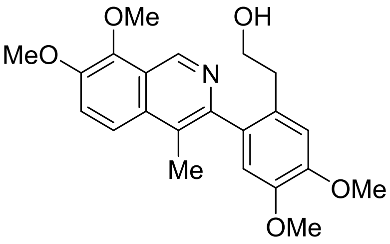
2-(1-Hydroxy-7,8-dimethoxy-4-methyl-1*H*-isochromen-3-yl)-4,5-dimethoxyphenethyl pivaloate 570



To a screw-cap tube containing a solution of ketone **558** (132 mg, 0.249 mmol) in 3:1 *t*BuOH/H_2O (2.5 mL) was added NH_4Cl (133 mg, 2.49 mmol) and the reaction mixture was stirred at 90 °C for 18 h. After cooling to room temperature, NH_4HCO_3 (394 mg, 4.98 mmol) was added and the reaction was stirred at 90 °C for 18 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and redissolved in EtOAc (5 mL). H_2O (5 mL) was added and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 6:4 petrol/EtOAc) afforded isochromene **570** as a colourless oil (26.7 mg, 0.0549 mmol, 22%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.07 (1 H, d, J = 8.6, HC_{Ar}), 7.02 (1 H, d, J = 8.6, HC_{Ar}), 6.83 (1 H, s, HC_{Ar}), 6.78 (1 H, s, HC_{Ar}), 6.76 (1 H, d, J = 5.6, $HC(OR)_2$), 4.58–4.52 (1 H, m, CH_aH_bOPiv), 4.19–4.12 (1 H, m, CH_aH_bOPiv), 3.96 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 3.91 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 3.17–3.07 (1 H, m, $CH_aH_bCH_2OPiv$), 2.92–2.85 (1 H, m, $CH_aH_bCH_2OPiv$), 1.93 (3 H, s, CH_3), 1.18 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 179.5 (C=O), 151.3, 149.2, 147.1, 145.0, 144.9 (C=COR and 4 × C_{Ar}OMe), 130.1, 127.5, 125.2, 122.9 (4 × C_{Ar}), 117.5, 113.9, 113.3, 113.1 (4 × HC_{Ar}), 106.7 (C=COR), 88.2 (HC(OR)$_2$), 65.4 (CH_2OPiv), 61.4, 56.1, 56.0, 55.9 (4 × OCH_3), 38.8 ($C(CH_3)_3$), 32.4 (CH_2CH_2OPiv), 27.1 (($CH_3)_3$), 13.6 (CH_3); **IR** ν_{max} (neat)/cm^{-1} 3467, 2962, 1723, 1514, 1497, 1462, 1278, 1247, 1227, 1205, 1155, 1133, 1098, 1026; **HRMS** (ESI$^+$) $C_{27}H_{34}NaO_8$ requires 509.2146, found [M+Na]$^+$ 509.2121 (Δ −4.8 ppm).

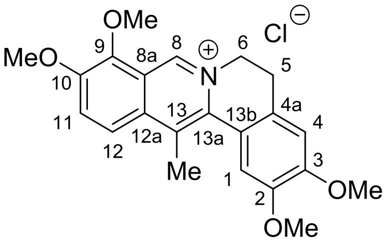
2-(2-(7,8-Dimethoxy-4-methylisoquinolin-3-yl)-4,5-dimethoxyphenyl)ethan-1-ol 572



To a solution of isoquinoline **559** (53.0 mg, 0.113 mmol) in THF (1.1 mL) at −78 °C was added a 1 M solution of DIBAL-H in hexanes (0.283 mL, 0.283 mmol) dropwise. The reaction mixture was stirred at −78 °C for 4 h then warmed to room temperature and quenched by the dropwise addition of H_2O (5 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 3:7 petrol/EtOAc) afforded alcohol **572** as a colourless oil (40.0 mg, 0.104 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.44 (1 H, s, *H*C(1)), 7.77 (1 H, dd, *J* = 9.3, 0.8, *H*C(5)), 7.57 (1 H, d, *J* = 9.3, *H*C(6)), 6.91 (1 H, s, HC_{Ar}), 6.74 (1 H, s, HC_{Ar}), 4.08 (3 H, s, OCH_3), 4.03 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 3.93–3.89 (1 H, m, CH_aH_bOH), 3.83 (3 H, s, OCH_3), 3.81–3.76 (1 H, m, CH_aH_bOH), 2.69–2.66 (2 H, m, CH_2CH_2OH), 2.51 (3 H, s, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 149.0, 148.8, 148.6, 146.7, 144.1 (5 × C_{Ar}), 143.9 (H*C*(1)), 132.4, 132.1, 131.0, 125.1, 122.8 (5 × C_{Ar}), 120.0 (H*C*(6)), 119.7 (H*C*(5)), 113.6, 112.5 (2 × HC_{Ar}), 63.6 (CH_2OH), 61.7, 56.9, 56.0, 55.9 (4 × OCH_3), 35.2 (CH_2CH_2OH), 15.6 (CH_3); **IR** ν_{max} (neat)/cm^{-1} 3232, 2936, 2845, 1570, 1515, 1451, 1374, 1261, 1213, 1158, 1079, 1021; **HRMS** (ESI$^+$) $C_{22}H_{26}NO_5$ requires 384.1806, found $[M+H]^+$ 384.1796 (Δ −2.6 ppm).

Dehydrocorydaline chloride

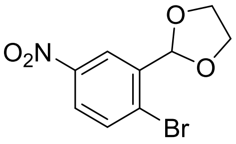


To a solution of alcohol **572** (49.1 mg, 0.128 mmol) in anhydrous MeCN (5.0 mL) at 0 °C was added thionyl chloride (92.9 µL, 1.28 mmol) and the reaction was warmed to room temperature then stirred at 50 °C for 3 h.

The reaction mixture was then concentrated *in vacuo* and the solid residue was redissolved in EtOH (5.0 mL) and stirred at 110 °C for 18 h. Concentration *in vacuo* afforded dehydrocorydaline as an orange-yellow solid (47.9 mg, 0.119 mmol, 93%).

M.p. 173–175 °C (lit. 162–163 °C);[274] **^{1}H NMR** (500 MHz, DMSO-d$_6$) δ_H 9.91 (1 H, s, *H*C(8)), 8.22 (1 H, d, *J* = 9.3, *H*C(11)), 8.19 (1 H, d, *J* = 9.3, *H*C(12)), 7.39 (1 H, s, *H*C(1)), 7.18 (1 H, s, *H*C(4)), 4.85 (2 H, br. t, *J* = 5.6, C(6)H_2), 4.10 (3 H, s, C(9)OCH_3), 4.09 (3 H, s, C(10)OCH_3), 3.89 (3 H, s, C(3)OCH_3), 3.85 (3 H, s, C(2)OCH_3), 3.14 (2 H, br. t, *J* = 5.6, C(5)H_2), 2.98 (3 H, s, CH_3); **^{13}C NMR** (126 MHz, DMSO-d$_6$) δ_C 150.6 (*C*(3)), 150.2 (*C*(10)), 147.2 (*C*(2)), 144.0 (*C*(9)), 144.0 (H*C*(8)), 136.0 (*C*(13a)), 133.1 (*C*(12a)), 131.8 (*C*(4a)), 129.7 (*C*(13)), 125.9 (H*C*(11)), 121.3 (H*C*(12)), 120.7 (*C*(8a)), 119.1 (*C*(13b)), 114.3 (H*C*(1)), 110.9 (H*C*(4)), 62.0 (C(9)O*C*H$_3$), 57.0 (C(10)O*C*H$_3$), 56.8 (*C*(6)H$_2$), 56.2 (C(2)O*C*H$_3$), 55.9 (C(3)O*C*H$_3$), 26.8 (*C*(5)H$_2$), 17.7 (*C*H$_3$); **^{13}C NMR** (176 MHz, CDCl$_3$, for comparison with lit.) δ_C 151.3, 150.6, 147.7, 146.3 (*C*(2), *C*(3), *C*(9), *C*(10)), 146.3 (H*C*(8)), 136.5, 133.8, 132.2 (3 × C_{Ar}), 128.8 (*C*(13)), 125.6 (H*C*(12)), 121.8 (C_{Ar}), 120.1 (H*C*(11)), 119.3 (C_{Ar}), 114.0 (H*C*(4)), 110.8 (H*C*(1)), 63.8 (*C*(6)H$_2$), 57.8 (C(3)O*C*H$_3$), 57.2 (C(9)O*C*H$_3$), 56.8 (C(10)O*C*H$_3$), 56.3 (C(2)O*C*H$_3$), 28.6 (*C*(5)H$_2$), 18.4 (C(13)*C*H$_3$). Spectroscopic data were consistent with those previously reported.[274,275]

2-(2-Bromo-5-nitrophenyl)-1,3-dioxolane 576

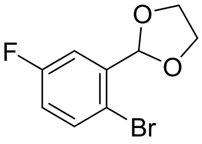


2-Bromo-5-nitrobenzaldehyde (72.7 mg, 0.316 mmol) was subjected to **General Procedure 8**. Purification by flash column chromatography (SiO$_2$, 1:1 petrol/CH$_2$Cl$_2$) afforded acetal **576** as an off-white solid (66.2 mg, 0.242 mmol, 76%).

M.p. 96–98 °C (lit. 98–99 °C);[317] **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 8.45 (1 H, d, *J* = 2.8, HC_{Ar}), 8.08 (1 H, dd, *J* = 8.7, 2.8, HC_{Ar}), 7.76 (1 H, d, *J* = 8.7, HC_{Ar}), 6.10 (1 H, s, *H*C(OR)$_2$), 4.23–4.19 (2 H, m, OCH_aH$_b$CH_aH$_b$O), 4.14–4.10 (2 H, m, OCH$_a$$H_bCH_a$$H_b$O);

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 147.2, 139.0 (2 × C_{Ar}), 134.1 (HC_{Ar}), 130.0 (C_{Ar}), 124.9, 123.0 (2 × HC_{Ar}), 101.5 ($HC(OR)_2$), 65.7 (OCH_2CH_2O). Spectroscopic data were consistent with those previously reported.[317]

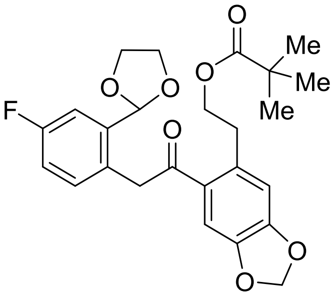
2-(2-Bromo-5-fluorophenyl)-1,3-dioxolane 578



2-Bromo-5-fluorobenzaldehyde (2.07 g, 10.2 mmol) was subjected to **General Procedure 8**. Purification by flash column chromatography (SiO_2, 9:1 petrol/EtOAc) afforded acetal **578** as a colourless oil (2.49 g, 10.1 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.51 (1 H, dd, J = 8.7, 5.1, HC_{Ar}), 7.33 (1 H, dd, J = 9.2, 3.1, HC_{Ar}), 6.95 (1 H, m, HC_{Ar}), 6.04 (1 H, d, ^5J = 1.3, $HC(OR)_2$), 4.17–4.02 (4 H, m, OCH_2CH_2O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 161.9 (d, ^1J = 247.8, $C_{Ar}F$), 138.8 (d, ^3J = 6.3, C_{Ar}), 134.2 (d, ^3J = 8.0, HC_{Ar}), 117.6 (d, ^2J = 22.4, HC_{Ar}), 116.7 (d, ^4J = 3.2, $C_{Ar}Br$), 115.0 (d, ^2J = 24.9, HC_{Ar}), 101.9 ($HC(OR)_2$), 65.4 (OCH_2CH_2O); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −113.9 ($C_{Ar}F$); **IR** ν_{max} (neat)/cm^{-1} 2890, 1583, 1468, 1415, 1391, 1264, 1159, 1118, 1082, 1030; **HRMS** (FI$^+$) $C_9H_8{}^{79}BrFO_2$ requires 245.9692, found $[M]^+$ 245.9693 (Δ +0.5 ppm).

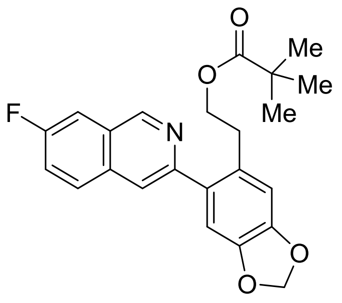
2-(6-(2-(2-(1,3-Dioxolan-2-yl)-4-fluorophenyl)acetyl)benzo[*d*][1,3]dioxol-5-yl)ethyl pivaloate 579



To a microwave vial fitted with a rubber septum were added aryl bromide **578** (330 mg, 1.34 mmol), ketone **526** (781 mg, 2.67 mmol), Cs_2CO_3 (1.09 g, 3.34 mmol), and $(Amphos)_2PdCl_2$ (47.3 mg, 0.0668 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon before the solids were dissolved in anhydrous THF (6.7 mL). The reaction mixture was stirred at 90 ºC for 24 h then cooled to room temperature. The crimped cap was removed and replaced with a rubber septum and the flask was purged with argon whilst additional (Amphos)$_2$PdCl$_2$ (47.3 mg, 0.0668 mmol) was added. A new microwave cap was fitted and the vessel purged with argon for 5 min before stirring at 90 °C for a further 24 h. After cooling to room temperature, the reaction was quenched with H_2O (5 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 75:25 petrol/Et_2O) afforded ketone **579** as an off-white solid (456 mg, 0.995 mmol, 74%).

M.p. 78–82 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.36 (1 H, s, HC_{Ar}), 7.32 (1 H, dd, J = 9.7, 2.8, HC_{Ar}), 7.16–7.13 (1 H, m, HC_{Ar}), 7.04 (1 H, td, J = 8.2, 2.8, HC_{Ar}), 6.78 (1 H, s, HC_{Ar}), 6.04 (2 H, s, OCH_2O), 5.84 (1 H, s $HC(OR)_2$), 4.32 (2 H, s, $CH_2C{=}O$), 4.25 (2 H, t, J = 6.6, CH_2OPiv), 4.02–3.99 (2 H, m, $OCH_aH_bCH_aH_bO$), 3.97–3.94 (2 H, m, $OCH_aH_bCH_aH_bO$), 3.11 (2 H, t, J = 6.6, CH_2CH_2OPiv), 1.16 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 198.2 (C=O), 178.4 (ROC=O), 161.8 (d, ^1J = 246.3, C_{Ar}F), 150.0, 146.1 (2 × C_{Ar}OR), 138.3 (d, ^3J = 6.3, C_{Ar}), 135.4 (C_{Ar}), 133.2 (d, ^3J = 7.9, HC_{Ar}), 130.6 (C_{Ar}), 129.1 (d, ^4J = 3.2, C_{Ar}), 115.7 (d, ^2J = 20.7, HC_{Ar}), 113.8 (d, ^2J = 22.3, HC_{Ar}), 112.4, 109.1 (2 × HC_{Ar}), 101.8 (OCH_2O), 101.6 ($HC(OR)_2$), 65.0 (OCH_2CH_2O, CH_2OPiv), 44.3 ($CH_2C{=}O$), 38.7 ($C(CH_3)_3$), 33.7 (CH_2CH_2OPiv), 27.2 ($(CH_3)_3$); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −115.1 ($C_{Ar}F$); **IR** ν_{max} (powder)/cm^{-1} 2976, 2900, 1721, 1686, 1611, 1489, 1375, 1266, 1241, 1156, 1078, 1036; **HRMS** (ESI$^+$) $C_{25}H_{27}FNaO_7$ requires 481.1633, found $[M+Na]^+$ 481.1620 (Δ −2.8 ppm).

2-(6-(7-Fluoroisoquinolin-3-yl)benzo[*d*][1,3]dioxol-5-yl)ethyl pivaloate 581

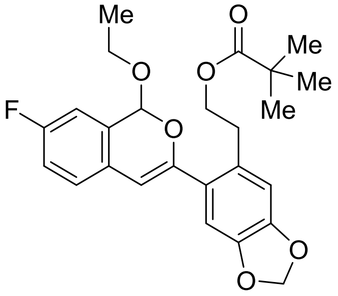


To a microwave vial containing ketone **579** (55.0 mg, 0.120 mmol) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (1.2 mL) and the resulting mixture was stirred at 60 °C for 4 h. After cooling to room temperature, NH_4HCO_3 (190 mg, 2.40 mmol) was added and the reaction was stirred at 90 °C for 18 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 petrol/Et_2O) afforded isoquinoline **581** as a colourless oil (30.4 mg, 0.0769 mmol, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.26 (1 H, s, *H*C(1)), 7.87 (1 H, dd, *J* = 8.9, 5.2, *H*C(5)), 7.74 (1 H, s, *H*C(4)), 7.61 (1 H, dd, *J* = 8.7, 2.5, *H*C(8)), 7.50 (1 H, td, *J* = 8.9, 2.6, *H*C(6)), 6.95 (1 H, s, HC_{Ar}), 6.87 (1 H, s, HC_{Ar}), 6.00 (2 H, s, OCH_2O), 4.19 (2 H, t, *J* = 6.9, CH_2OPiv), 3.01 (2 H, t, *J* = 6.9, CH_2CH_2OPiv), 1.14 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 178.4 (*C*=O), 160.8 (d, ^1J = 249.4, *C*(7)F), 152.8 (d, ^6J = 3.2, *C*(3)), 151.0 (d, ^4J = 5.6, H*C*(1)), 147.5, 146.2 (2 × C_{Ar}OR), 134.0, 133.3 (2 × C_{Ar}), 130.1 (*C*(4a)), 129.4 (d, ^3J = 8.0, H*C*(5)), 127.7 (^3J = 8.4, *C*(8a)), 121.2 (d, ^2J = 25.3, H*C*(6)), 120.0 (H*C*(4)), 110.5 (d, ^2J = 19.8, H*C*(8)), 110.5, 110.5 (2 × HC_{Ar}), 101.2 (OCH_2O), 64.9 (CH_2OPiv), 38.6 ($C(CH_3)_3$), 32.3 (CH_2CH_2OPiv), 27.1 ($(CH_3)_3$); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −111.2 (C(7)*F*); **IR** ν_{max} (neat)/cm^{-1} 2972, 1721, 1619, 1494, 1459, 1373, 1283, 1249, 1230, 1150, 1037; **HRMS** (ESI$^+$) $C_{23}H_{23}FNO_4$ requires 396.1606, found $[M+H]^+$ 396.1597 (Δ −2.1 ppm).

2-(6-(1-Ethoxy-7-fluoro-1*H*-isochromen-3-yl)benzo[*d*][1,3]dioxol-5-yl)ethyl pivaloate

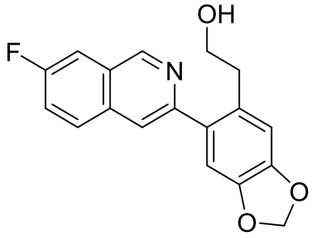
583



To a microwave vial containing ketone **579** (57.7 mg, 0.126 mmol) was added a 1 M solution of NH_4Cl in 3:1 EtOH/H_2O (1.3 mL) and the resulting mixture was stirred at 60 °C for 20 h. After cooling to room temperature, the reaction mixture was diluted with H_2O (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 9:1 petrol/Et_2O) afforded isochromene **583** as a colourless oil (15.1 mg, 0.00341 mmol, 27%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.13 (1 H, dd, J = 8.5, 5.4, HC_{Ar}), 7.06 (1 H, td, J = 8.6, 2.6, HC_{Ar}), 6.99 (1 H, dd, J = 8.6, 2.5, HC_{Ar}), 6.89 (1 H, s, HC_{Ar}), 6.79 (1 H, s, HC_{Ar}), 6.15 (1 H, s, $HC(OR)_2$), 6.05 (1 H, s, HC=COR), 5.98 (2 H, s, OCH_2O), 4.27 (2 H, t, J = 7.0, CH_2OPiv), 4.03–3.95 (1 H, m, $OCH_aH_bCH_3$), 3.83–3.75 (1 H, m, $OCH_aH_bCH_3$), 3.04 (2 H, t, J = 7.0, CH_2CH_2OPiv), 1.26 (3 H, t, J = 7.1, OCH_2CH_3), 1.18 (9 H, s, $(CH_3)_3$); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_C 178.5 (C=O), 161.5 (d, ^1J = 245.0, $C_{Ar}F$), 150.5 (d, ^6J = 2.8, HC=COR), 148.0, 146.1 (2 × C_{Ar}OR), 130.7, 128.9 (2 × C_{Ar}), 128.2 (d, ^3J = 6.6, C_{Ar}), 126.4 (d, ^4J = 2.8, C_{Ar}), 125.9 (d, ^3J = 7.7, HC_{Ar}), 116.4 (d, ^2J = 20.9, HC_{Ar}), 112.7 (d, ^2J = 22.0, HC_{Ar}), 110.3, 109.6 (2 × HC_{Ar}), 103.2 (HC=COR), 101.3 (OCH_2O), 98.4 (d, ^4J = 1.9, H$C(OR)_2$), 65.0 (CH_2OPiv), 64.1 (OCH_2CH_3), 38.7 ($C(CH_3)_3$), 32.4 (CH_2CH_2OPiv), 27.2 ($(CH_3)_3$), 15.2 (OCH_2CH_3); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −114.5 ($C_{Ar}F$); **IR** ν_{max} (neat)/cm^{-1} 2975, 2906, 1724, 1501, 1485, 1283, 1258, 1224, 1150, 1075, 1036; **HRMS** (ESI$^+$) $C_{25}H_{27}NaO_6F$ requires 465.1684, found $[M+Na]^+$ 465.1676 (Δ −1.7 ppm).

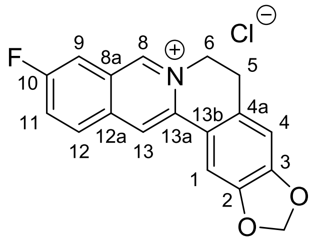
2-(6-(7-Fluoroisoquinolin-3-yl)benzo[*d*][1,3]dioxol-5-yl)ethan-1-ol 582



To a solution of isoquinoline **581** (43.1 mg, 0.109 mmol) in THF (1.1 mL) at −78 °C was added a 1 M solution of DIBAL-H in hexanes (0.272 mL, 0.272 mmol) dropwise. The reaction mixture was stirred at −78 °C for 5 h then warmed to room temperature and quenched by the dropwise addition of H_2O (5 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 7:3 petrol/EtOAc) afforded alcohol **582** as a colourless solid (32.1 mg, 0.103 mmol, 95%).

M.p. 115–118 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 9.20 (1 H, s, *H*C(1)), 7.89 (1 H, dd, *J* = 8.8, 5.2, *H*C(5)), 7.82 (1 H, s, *H*C(4)), 7.63 (1 H, dd, *J* = 8.8 2.5, *H*C(8)), 7.53 (1 H, td, *J* = 8.8, 2.5, *H*C(6)), 6.92 (1 H, s, HC_{Ar}), 6.88 (1 H, s, HC_{Ar}), 6.55 (1 H, br. s, O*H*), 6.00 (2 H, s, OCH_2O), 3.98 (2 H, t, *J* = 5.7, CH_2OH), 2.82 (2 H, t, *J* = 5.7, CH_2CH_2OH); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 160.9 (d, ^1J = 249.4, *C*(7)F), 152.0 (*C*(3)), 149.6 (d, ^4J = 4.8, H*C*(1)), 148.3, 146.2 (2 × $C_{Ar}OR$), 133.9, 133.1, 132.6 (3 × C_{Ar}), 129.4 (d, ^3J = 8.7, H*C*(5)), 127.6 (d, ^3J = 8.6, C_{Ar}), 121.8 (d, ^2J = 25.4, H*C*(6)), 120.5 (H*C*(4)), 110.7 (d, ^2J = 20.7, H*C*(8)), 110.0 (2 × HC_{Ar}), 101.3 (OCH_2O), 63.8 (CH_2OH), 35.2 (CH_2CH_2OH); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −110.4 (C(7)*F*); **IR** ν_{max} (powder)/cm^{-1} 3222, 2853, 1619, 1494, 1461, 1376, 1248, 1232, 1141, 1042; **HRMS** (ESI$^+$) $C_{18}H_{15}FNO_3$ requires 312.1031, found $[M+H]^+$ 312.1022 (Δ −2.6 ppm).

10-Fluoro-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolino[3,2-*a*]isoquinolin-7-ium chloride 580

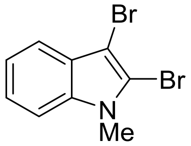


To a solution of alcohol **582** (27.4 mg, 0.0880 mmol) in anhydrous MeCN (3.0 mL) at 0 °C was added thionyl chloride (63.8 µL, 0.880 mmol) and the reaction mixture was warmed to room temperature and stirred at 50 °C for 2 h. The resulting suspension was concentrated *in vacuo* and the solid triturated with Et_2O (5 × 5 mL) to afford protoberberine analogue **580** as a yellow solid (23.7 mg, 0.0719 mmol, 82%).

M.p. decomposed at 299 °C; **^{1}H NMR** (400 MHz, DMSO-d_6) δ_H 10.12 (1 H, s, *H*C(8)), 9.14 (1 H, s, *H*C(13)), 8.36–8.33 (1 H, m, *H*C(12)), 8.28 (1 H, dd, *J* = 8.7, 2.0, *H*C(9)), 8.14 (1 H, td, *J* = 8.8, 2.3, *H*C(11)), 7.82 (1 H, s, *H*C(1)), 7.11 (1 H, s, *H*C(4)), 6.18 (2 H, s, OCH_2O), 4.90 (2 H, t, *J* = 6.0, C(6)H_2), 3.23 (2 H, t, *J* = 6.0, C(5)H_2); **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C 161.5 (d, ^1J = 250.8, *C*(10)F), 150.2 (*C*(2)), 149.6 (d, ^4J = 5.1, H*C*(8)), 147.7 (*C*(3)), 139.5 (*C*(13a)), 136.0 (*C*(12a)), 131.1 (*C*(13b)), 130.9 (d, ^3J = 9.5, H*C*(12)), 127.3 (d, ^2J = 26.8, H*C*(11), 126.5 (d, ^3J = 11.2, *C*(8a)), 120.7 (H*C*(13)), 120.2 (*C*(4a)), 112.85 (d, ^2J = 23.7, H*C*(9)), 108.5 (H*C*(4)), 105.7 (H*C*(1)), 102.2 (O*C*H_2O), 55.4 (*C*(6)H_2), 26.2 (*C*(5)H_2); **^{19}F{^{1}H} NMR** (377 MHz, $CDCl_3$) δ_F −106.5 (C(10)*F*); **IR** ν_{max} (powder)/cm^{-1} 3357, 2999, 2921, 1606, 1497, 1476, 1371, 1253, 1223, 1163, 1094, 1034; **HRMS** (ESI$^+$) $C_{18}H_{13}NO_2F$ requires 294.0925, found $[M]^+$ 294.0918 (Δ −2.2 ppm).

3.3.5 Chapter 2.5 compounds

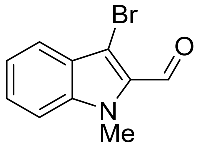
2,3-Dibromo-1-methyl-1*H*-indole 595[290]



To a solution of *N*-methyl indole (0.450 mL, 3.50 mmol) in THF (10 mL) at −78 °C was added *N*-bromosuccinimide (1.46 g, 8.04 mmol) portionwise and the reaction was stirred at −78 °C for 4 h. After warming to room temperature, the reaction was diluted with H_2O (15 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, pentane) afforded dibromoindole **595** as a pale yellow oil (222 mg, 0.768 mmol, 22%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.52–7.50 (1 H, m, *H*C$_{Ar}$), 7.27–7.23 (2 H, m, 2 × *H*C$_{Ar}$), 7.20–7.16 (1 H, m, *H*C$_{Ar}$), 3.79 (3 H, s, NC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 136.3, 126.9 (2 × *C*$_{Ar}$), 122.9, 120.8, 118.8 (3 × H*C*$_{Ar}$), 114.9 (*C*(2)), 109.6 (H*C*$_{Ar}$), 92.6 (*C*(3)), 32.3 (N*C*H$_3$). Spectroscopic data were consistent with those previously reported.[321]

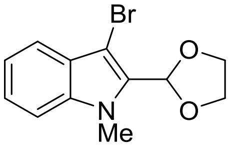
3-Bromo-1-methyl-1*H*-indole-2-carbaldehyde 596[291]



To a suspension of dibromoindole **595** (196 mg, 0.678 mmol) in Et_2O (2.0 mL) at −78 °C was added a 2.5 M solution of *n*-butyllithium in hexanes (0.298 mL, 0.746 mmol) and the reaction mixture was stirred at −78 °C for 1 h. DMF (53.5 µL, 0.692 mmol) was added *via* syringe and the reaction was allowed to warm to room temperature. The reaction was then quenched with saturated aqueous NH_4Cl (2 mL) and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 8:2 pentane/CH_2Cl_2) afforded aldehyde **596** as an off-white solid (97.9 mg, 0.411 mmol, 61%).

M.p. 86–89 °C (lit. 86–89 °C);[322] **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 10.09 (1 H, s, *H*C=O), 7.66 (1 H, dt, *J* = 8.1, 0.9, *H*C_{Ar}), 7.47–7.43 (1 H, m, *H*C_{Ar}), 7.34 (1 H, d, *J* = 8.6, *H*C_{Ar}), 7.23 (1 H, ddd, *J* = 8.1, 7.0, 0.8, *H*C_{Ar}), 4.04 (3 H, s, NCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 182.4 (*C*=O), 139.2, 129.8 (2 × C_{Ar}), 128.0 (HC_{Ar}), 125.9 (C_{Ar}), 121.5, 121.4, 110.4 (3 × HC_{Ar}), 105.8 ($C_{Ar}Br$), 31.7 (NCH_3). Spectroscopic data were consistent with those previously reported.[322]

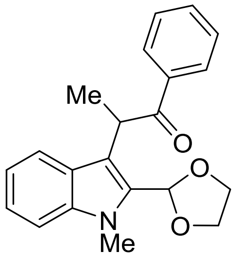
3-Bromo-2-(1,3-dioxolan-2-yl)-1-methyl-1*H*-indole 597



To a screw-cap tube containing a solution of aldehyde **596** (92.9 mg, 0.390 mmol) in toluene (2.0 mL) were added ethylene glycol (1.0 mL, 18 mmol) and *para*-toluenesulfonic acid monohydrate (14.8 mg, 0.0780 mmol). The resulting mixture was stirred at 110 °C for 18 h then cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (5 mL). The resulting mixture was extracted with EtOAc (3 × 15 mL) and the combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, 95:5 petrol/EtOAc) afforded acetal **597** as a colourless oil (73.0 mg, 0.259 mmol, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 (1 H, dt, *J* = 8.0, 0.9, *H*C_{Ar}), 7.35–7.33 (2 H, m, 2 × *H*C_{Ar}), 7.23–7.19 (1 H, m, *H*C_{Ar}), 6.22 (1 H, s, *H*$C(OR)_2$), 4.28–4.22 (2 H, m, $OCH_aH_bCH_aH_bO$), 4.16–4.09 (2 H, m, $OCH_aH_bCH_aH_bO$), 3.85 (3 H, s, NCH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C 137.5, 128.9, 126.2 (3 × C_{Ar}), 123.9, 120.2, 119.8, 109.4 (4 × HC_{Ar}), 98.5 ($HC(OR)_2$), 93.9 ($C_{Ar}Br$), 65.2 (OCH_2CH_2O), 31.1 (NCH_3); **IR** ν_{max} (neat)/cm^{-1} 2950, 2888, 1558, 1468, 1385, 1317, 1238, 1184, 1078, 1022; **HRMS** (ESI$^+$) $C_{12}H_{13}{}^{79}BrNO_2$ requires 282.0124, found $[M+H]^+$ 282.0118 (Δ −2.1 ppm).

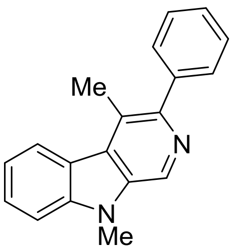
2-(2-(1,3-Dioxolan-2-yl)-1-methyl-1*H*-indol-3-yl)-1-phenylpropan-1-one 598



To a microwave vial fitted with a rubber septum were added (D*t*BPF)PdCl$_2$ (5.9 mg, 0.0090 mmol) and NaO*t*Bu (44.6 mg, 0.450 mmol). The septum was replaced with a microwave cap and the vessel was evacuated and backfilled with argon. A solution of bromoindole bromide **597** (50.8 mg, 0.180 mmol) in anhydrous THF (0.9 mL) was added *via* syringe, followed by the addition of propiophenone (47.9 µL, 0.360 mmol) and the reaction mixture was heated at 70 °C for 18 h. After cooling to room temperature, the reaction was diluted with H$_2$O (2 mL) and the resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (SiO$_2$, 8:2 petrol/EtOAc) afforded ketone **598** as an off-white solid (38.3 mg, 0.114 mmol, 63%).

M.p. 133–136 °C; **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 8.02–8.00 (2 H, m, 2 × HC_{Ph}), 7.67 (1 H, d, $J = 8.1$, HC_{Ar}), 7.41–7.36 (1 H, m, HC_{Ph}), 7.31–7.25 (3 H, m, HC_{Ar} and 2 × HC_{Ph}), 7.24–7.20 (1 H, m, HC_{Ar}), 7.08 (1 H, ddd, $J = 8.0, 6.8, 1.2$, HC_{Ar}), 6.27 (1 H, s, $HC(OR)_2$), 5.09 (1 H, q, $J = 6.9$, CHCH$_3$), 4.28–4.25 (2 H, m, OCH_aH$_b$CH_aH$_b$O), 4.16–4.12 (2 H, m, OCH$_a$$H_bCH_a$$H_b$O), 3.76 (3 H, s, NC$H_3$), 1.64 (3 H, d, $J = 6.9$, CHCH_3); **^{13}C NMR** (100 MHz, CDCl$_3$) δ_C 200.8 (C=O), 137.8, 126.7 (2 × C_{Ar}), 132.4, 128.6, 128.2 (3 × HC_{Ph}), 125.3 (C_{Ar}), 122.7, 119.9, 119.4 (3 × HC_{Ar}), 116.1 (C_{Ar}), 109.2 (HC_{Ar}), 98.3 (HC(OR)$_2$), 65.2, 65.1 (OCH$_2$$CH_2$O), 39.3 ($CHCH_3$), 30.7 (N$CH_3$), 18.2 (CH$CH_3$); **IR** ν_{max} (powder)/cm^{-1} 2974, 2931, 2890, 1679, 1579, 1471, 1448, 1409, 1365, 1306, 1220, 1180, 1077, 1019; **HRMS** (ESI$^+$) $C_{21}H_{21}NaNO_3$ requires 358.1414, found [M+Na]$^+$ 358.1405 (Δ −2.6 ppm).

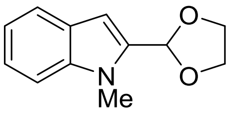
4,9-Dimethyl-3-phenyl-9*H*-pyrido[3,4-*b*]indole 599



Ketone **598** (38.3 mg, 0.114 mmol) was subjected to **General Procedure 9**. Filtration through a short plug of silica, eluting with $CHCl_3$, afforded β-carboline **599** as an off-white solid (25.6 mg, 0.0940 mmol, 82%).

M.p. 163–166 °C (lit. 166–168 °C);[289] **^{1}H NMR** (400 MHz, $CDCl_3$) δ$_{\mathrm{H}}$ 8.82 (1 H, s *H*CN), 8.28 (1 H, d, *J* = 7.9, *H*C$_{\mathrm{Ar}}$), 7.65–7.61 (3 H, m, 3 × *H*C$_{\mathrm{Ar}}$), 7.52–7.48 (3 H, m, 3 × *H*C$_{\mathrm{Ar}}$), 7.43–7.39 (1 H, m, *H*C$_{\mathrm{Ar}}$), 7.33 (1 H, ddd, *J* = 8.0, 7.1, 1.0, *H*C$_{\mathrm{Ar}}$), 3.94 (3 H, s, NC*H*$_3$), 2.87 (3 H, s, C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ$_{\mathrm{C}}$ 148.8, 141.9, 141.2, 135.8 (4 × *C*$_{\mathrm{Ar}}$), 129.9, 128.8, 128.0, 127.5, 127.1 (5 × H*C*$_{\mathrm{Ar}}$), 124.7 (*C*$_{\mathrm{Ar}}$), 124.0 (H*C*$_{\mathrm{Ar}}$), 122.1 (*C*$_{\mathrm{Ar}}$), 119.5 (H*C*$_{\mathrm{Ar}}$), 29.3 (N*C*H$_3$), 17.5 (*C*H$_3$). Spectroscopic data were consistent with those previously reported.[289]

2-(1,3-Dioxolan-2-yl)-1-methyl-1*H*-indole 602

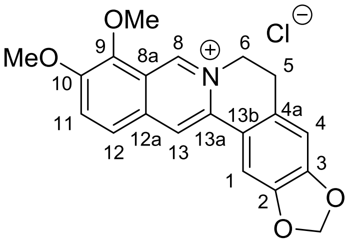


Isolated as an impure oil by flash column chromatography (SiO_2, 95:5 petrol/EtOAc) as a side product in the synthesis of **598** (~9.0 mg, ~0.044 mmol, ~25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ$_{\mathrm{H}}$ 7.62 (1 H, dt, *J* = 7.9, 0.9, *H*C$_{\mathrm{Ar}}$), 7.34 (1 H, dd, *J* = 8.3, 0.8, *H*C$_{\mathrm{Ar}}$), 7.26 (1 H, ddd, *J* = 8.2, 6.9, 1.1, *H*C$_{\mathrm{Ar}}$), 7.12 (1 H, ddd, *J* = 7.9, 6.9, 1.0, *H*C$_{\mathrm{Ar}}$), 6.64 (1 H, s, *H*C(3)), 6.13 (1 H, s, *H*C(OR)$_2$), 4.20–4.14 (2 H, m, OC*H*$_{\mathrm{a}}$H$_{\mathrm{b}}$C*H*$_{\mathrm{a}}$H$_{\mathrm{b}}$O), 4.13–4.07 (2 H, m, OCH$_{\mathrm{a}}$*H*$_{\mathrm{b}}$CH$_{\mathrm{a}}$*H*$_{\mathrm{b}}$O), 3.82 (3 H, s, NC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ$_{\mathrm{C}}$ 138.4, 135.0, 126.8 (3 × *C*$_{\mathrm{Ar}}$), 122.2, 121.1, 119.5, 109.1 (4 × H*C*$_{\mathrm{Ar}}$), 102.3 (H*C*(3)), 99.3 (H*C*(OR)$_2$), 65.0 (O*C*H$_2$*C*H$_2$O), 30.5 (N*C*H$_3$); **HRMS** (ESI$^+$) $C_{12}H_{14}O_2N$ requires 204.1019, found $[M+H]^+$ 204.1016 (Δ −1.3 ppm).

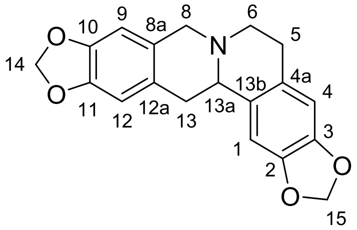
3.4 Protoberberine NMR Comparison Tables

Berberine chloride



	δ_H (multiplicity, *J*)			δ_C		
Atom	Lit.[253] (DMSO-d_6)	Observed (DMSO-d_6)	Δ	Lit.[253] (DMSO-d_6)	Observed (DMSO-d_6)	Δ
1	7.79 (s)	7.79 (s)	0.00	105.4	105.4	0.0
2	-	-	-	147.6	147.6	0.0
3	-	-	-	149.8	149.8	0.0
4	7.09 (s)	7.08 (s)	−0.01	108.4	108.4	0.0
4a	-	-	-	130.6	130.6	0.0
5	3.22 (t, 6.2)	3.21 (t, 6.2)	−0.01	26.4	26.3	−0.1
6	4.95 (t, 6.3)	4.95 (t, 6.3)	0.00	55.2	55.1	−0.1
8	9.91 (s)	9.90 (s)	−0.01	145.4	145.4	0.0
8a	-	-	-	121.4	121.4	0.0
9	-	-	-	143.6	143.6	0.0
10	-	-	-	150.4	150.3	−0.1
11	8.20 (d, 9.1)	8.19 (d, 9.1)	−0.01	126.7	126.7	0.0
12	8.01 (d, 9.1)	8.01 (d, 9.1)	0.00	123.5	123.5	0.0
12a	-	-	-	132.9	133.0	0.1
13	8.96 (s)	8.97 (s)	0.01	120.2	120.2	0.0
13a	-	-	-	137.4	137.4	0.0
13b	-	-	-	120.4	120.4	0.0
OCH_2O	6.17 (s)	6.17 (s)	0.00	102.1	102.0	−0.1
9-OCH_3	4.10 (s)	4.10 (s)	0.00	62.0	61.9	−0.1
10-OCH_3	4.07 (s)	4.07 (s)	0.00	57.1	57.1	0.0

Tetrahydropseudocoptisine 546



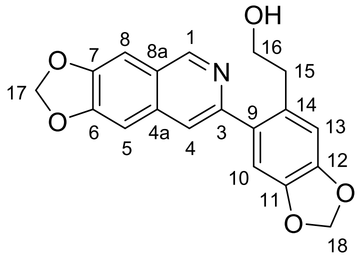
	δ_H (multiplicity, *J*)		
Atom	Lit.[263] (CDCl$_3$)	Observed (CDCl$_3$)	Δ
1	6.72 (s)	6.73 (s)	0.01
2	-	-	-
3	-	-	-
4	6.58 (s)	6.59 (s)	0.01
4a	-	-	-
13(H$_a$)	3.19–3.10 (m)	3.17 (dd, 16.1, 3.9)	−0.03*
5(H$_a$)		3.14–3.07 (m)	
6(H$_a$)			
13(H$_b$)	2.83–2.59 (m)	2.80 (dd, 15.7, 11.4)	−0.04*
5(H$_b$)		2.71–2.54 (m)	
6(H$_b$)			
8(H$_a$)	3.92–3.87 (m)	3.91 (d, 14.6)	0.01
8(H$_b$)	3.65–3.51 (m)	3.64 (d, 14.6)	0.01*
13a		3.54 (dd, 11.2, 3.6)	
8a	-	-	-
9	6.53 (s)	6.55 (s)	0.02
10	-	-	-
11	-	-	-
12	6.60 (s)	6.62 (s)	0.02
12a	-	-	-
13b	-	-	-
14	5.90 (s)	5.91 (s)	0.01
15	5.91 (s)	5.92 (s)	0.01

	δ_C		
Atom	Lit.[262] (CDCl$_3$)	Observed (CDCl$_3$)	Δ
1	105.5	105.4	−0.1
2	146.3#	146.1#	−0.2
3	146.3#	146.1#	−0.2
10	146.2#	145.9#	−0.3
11	146.0#	145.8#	−0.2
4	108.5	108.4	−0.1
4a	130.9#	130.7	−0.2
13b	127.8#	127.7	−0.1
5	29.6	29.5	−0.1
6	51.2	51.2	0.0
8	58.6	58.5	−0.1
8a	127.3	127.2	−0.1
9	106.1	106.0	−0.1
12	108.5	108.4	−0.1
12a	127.3	127.2	−0.1
13	37.0	36.9	−0.1
13a	59.9	59.8	−0.1
14	100.7	100.6	−0.1
15	100.8	100.8	0.0

* Average Δ with respect to midpoint of multiplets.

\# Individual peaks not assigned.

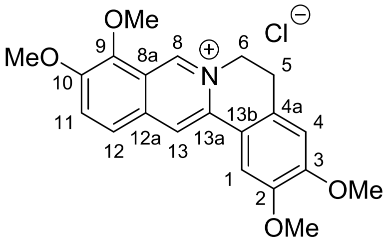
2-(6-([1,3]Dioxolo[4,5-*g*]isoquinolin-7-yl)benzo[*d*][1,3]dioxol-5-yl)ethan-1-ol 539



	δ_H (multiplicity, *J*)			δ_C		
Atom	Lit.[259] ($CDCl_3$)	Observed ($CDCl_3$)	Δ	Lit.[259] ($CDCl_3$)	Observed ($CDCl_3$)	Δ
1	9.00 (s)	8.95 (s)	−0.05	147.7	147.9	0.2
3	-	-	-	151.0	151.4	0.4
4	7.63 (s)	7.63 (s)	0.00	120.5	120.3	−0.2
4a	-	-	-	124.4	124.4	0.0
5	7.10 (s)	7.10 (s)	0.00	102.6	102.5	−0.1
6	-	-	-	148.8	148.6	−0.2
7	-	-	-	151.9	151.6	−0.3
8	7.22 (s)	7.22 (s)	0.00	103.2	103.0	−0.2
8a	-	-	-	135.8	135.5	−0.3
10	not reported	6.91 (s)	-	110.0	109.9	−0.1
11	-	-	-	146.2	146.1	−0.1
12	-	-	-	148.2	148.1	−0.1
13	6.85 (s)	6.87 (s)	−0.02	110.1	110.0	−0.1
15	5.08 (t, 6.0)*	2.82 (t, 5.6)	-	35.3	35.2	−0.1
16	3.97 (t, 6.0)	3.98 (t, 5.6)	0.01	63.8	63.8	0.0
17	6.12 (s)	6.13 (s)	0.01	101.9	101.8	−0.1
18	5.98 (s)	6.00 (s)	0.02	101.3	101.2	−0.1

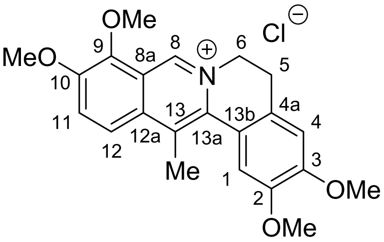
* δ assumed incorrect.

Palmatine chloride



	δ_H (multiplicity, *J*)			**δ_C**		
Atom	Lit.[273] (DMSO-d_6)	Observed (DMSO-d_6)	Δ	Lit.[273] (DMSO-d_6)	Observed (DMSO-d_6)	Δ
1	7.72 (s)	7.73 (s)	0.01	109.2	108.8	−0.4
2	-	-	-	148.9	148.7	−0.2
3	-	-	-	151.7	151.5	−0.2
4	7.08 (s)	7.09 (s)	0.01	111.5	111.3	−0.2
4a	-	-	-	128.8	128.6	−0.2
5	3.22 (t, 6.2)	3.23 (t, 5.8)	0.01	26.1	26.0	−0.1
6	4.95 (t, 6.1)	4.96 (t, 5.8)	0.01	55.5	55.3	−0.2
8	9.88 (s)	9.91 (s)	0.03	145.6	145.5	−0.1
8a	-	-	-	121.5	121.3	−0.2
9	-	-	-	143.8	143.6	−0.2
10	-	-	-	150.4	150.2	−0.2
11	8.20 (d, 9.2)	8.21 (d, 9.0)	0.01	127.0	126.7	−0.3
12	8.03 (d, 9.1)	8.04 (d, 9.0)	0.01	123.6	123.4	−0.2
12a	-	-	-	133.3	133.1	−0.2
13	9.07 (s)	9.10 (s)	0.03	120.1	119.9	−0.2
13a	-	-	-	137.9	137.7	−0.2
13b	-	-	-	119.1	118.9	−0.2
2-OCH_3	3.93 (s)	3.94 (s)	0.01	56.4	56.2	−0.2
3-OCH_3	3.86 (s)	3.87 (s)	0.01	56.0	55.9	−0.1
9-OCH_3	4.09 (s)	4.10 (s)	0.01	62.1	61.9	−0.2
10-OCH_3	4.06 (s)	4.07 (s)	0.01	57.2	57.0	−0.2

Dehydrocorydaline chloride



	δ_H (multiplicity, *J*)			δ_C		
Atom	Lit.[274] (DMSO-d_6)	Observed (DMSO-d_6)	Δ	Lit.[275] ($CDCl_3$)	Observed ($CDCl_3$)	Δ
1	7.39 (s)	7.39 (s)	0.00	110.7	110.8	0.1
2	-	-	-	151.3#	151.3#	0.1
3	-	-	-	150.5#	150.6#	0.1
9	-	-	-	147.7#	147.7#	0.0
10	-	-	-	146.3#	146.3#	0.0
4a	-	-	-	136.3#	136.5#	0.2
8a	-	-	-	133.7#	133.8#	0.1
12a	-	-	-	132.2#	132.2#	0.0
13a	-	-	-	121.7#	121.8#	0.1
13b	-	-	-	119.2#	119.3#	0.1
4	7.18 (s)	7.18 (s)	0.00	113.9	114.0	0.1
5	3.16 (t, 5.4)	3.14 (t, 5.6)	−0.02	28.2	28.6	0.4
6	4.88 (t, 5.4)	4.85 (t, 5.6)	−0.03	63.2	63.8	0.6
8	9.93 (s)	9.91 (s)	−0.02	146.5	146.3	−0.2
11	8.20 (s)	8.22 (d, 9.3)	0.02	119.7	120.1	0.4
12	8.20 (s)	8.19 (d, 9.3)	−0.01	125.4	125.6	0.2
13	-	-	-	128.5	128.8	0.3
2-OCH_3	3.86 (s)	3.85 (s)	−0.01	56.2	56.3	0.1
3-OCH_3	3.90 (s)	3.89 (s)	−0.01	57.1	57.8	0.7
9-OCH_3	4.11 (s)	4.10 (s)	−0.01	56.9	57.2	0.3
10-OCH_3	4.10 (s)	4.09 (s)	−0.01	56.5	56.8	0.3
13-CH_3	2.99 (s)	2.98 (s)	−0.01	17.9	18.4	0.5

Individual peaks not assigned

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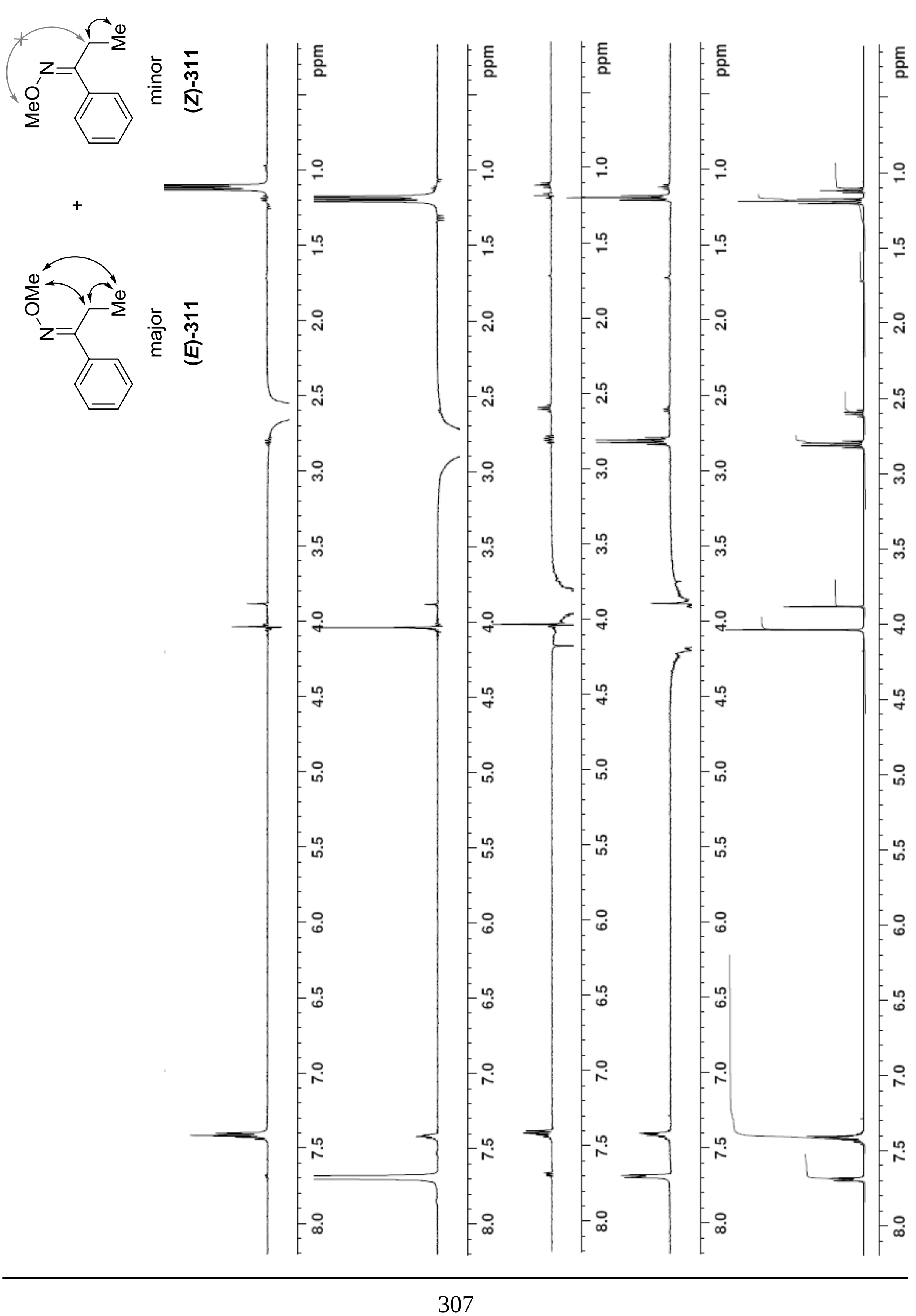
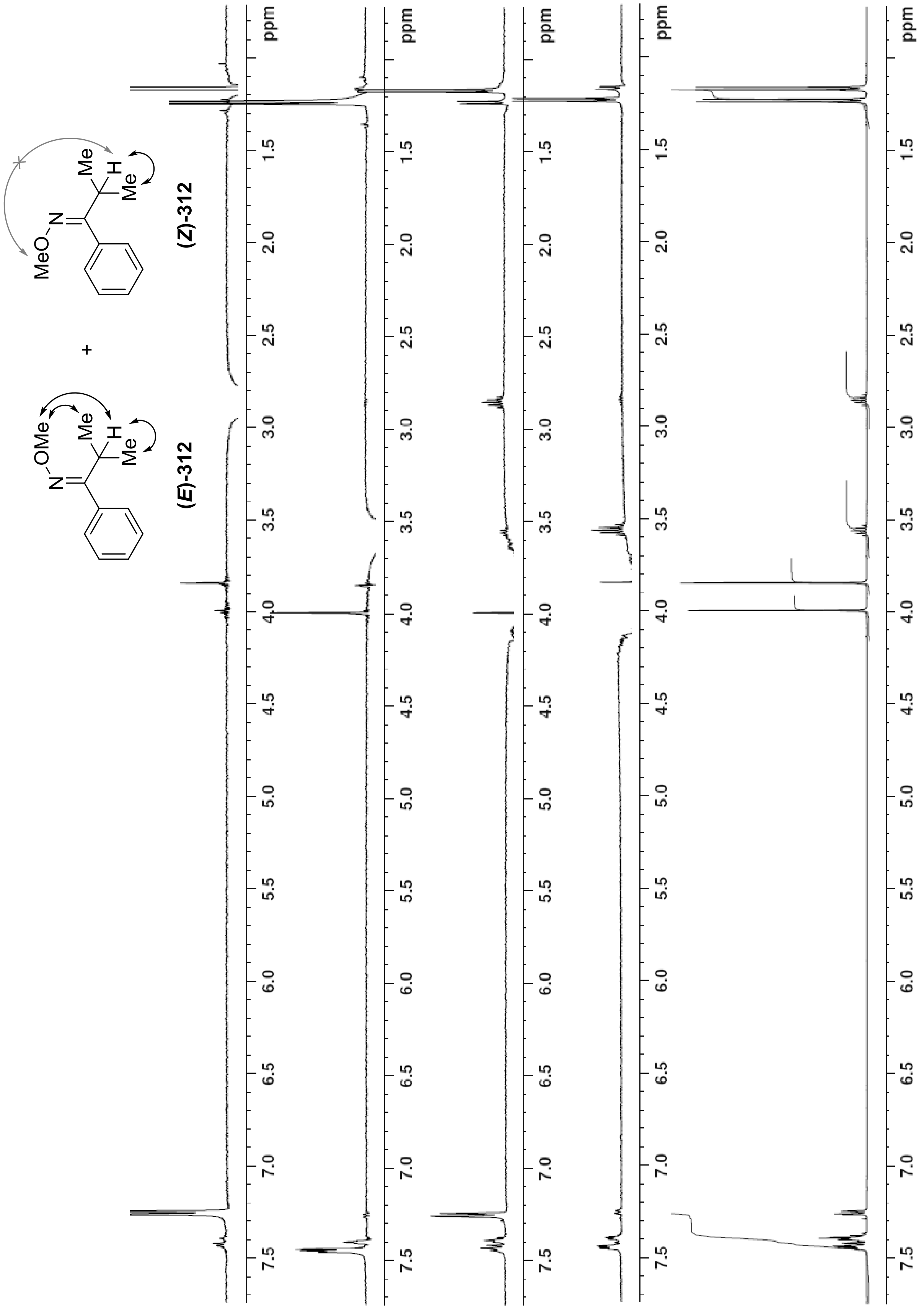
Appendix 1. nOe Enhancements

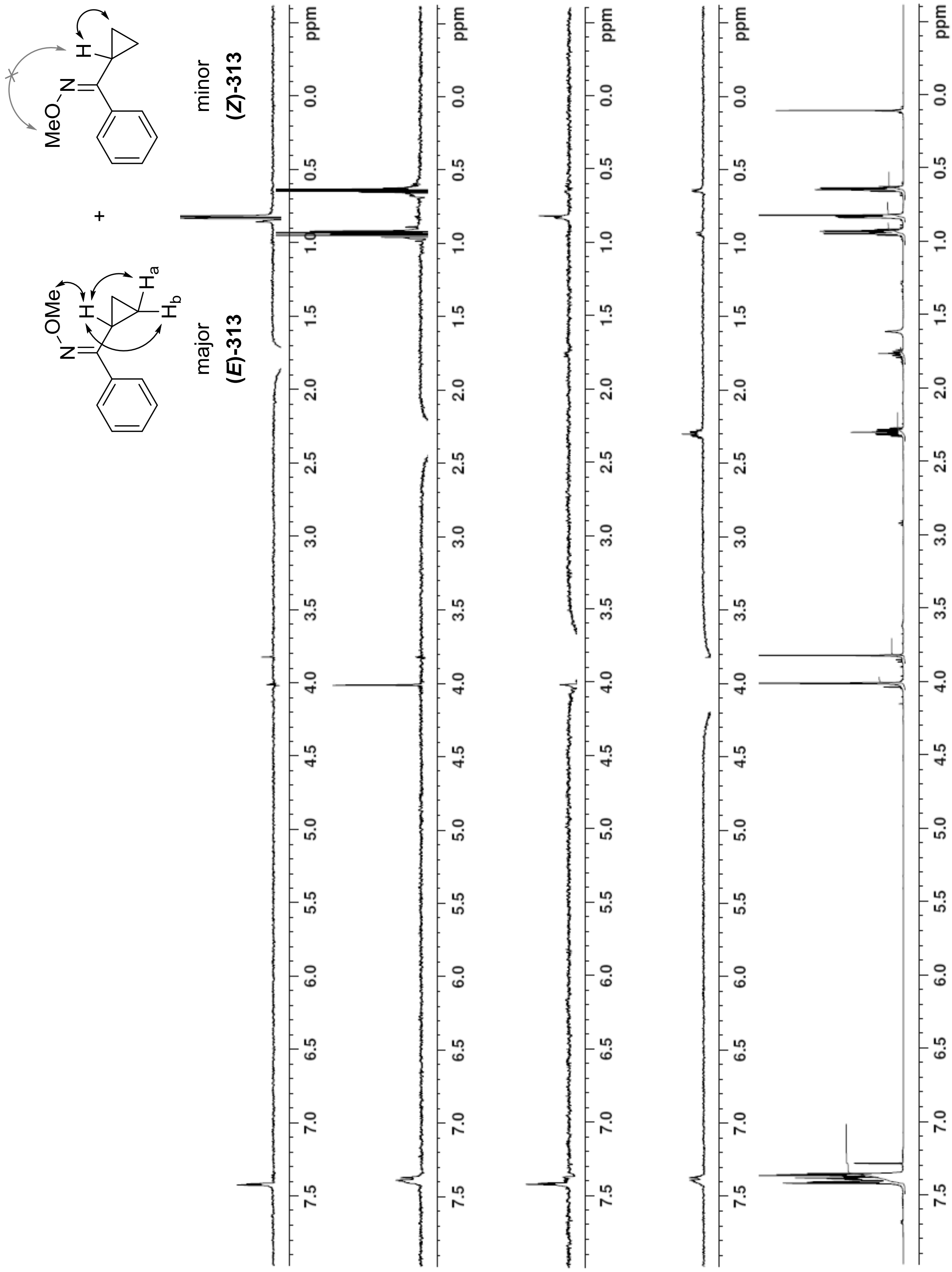
Propiophenone *O*-methyl oxime 311



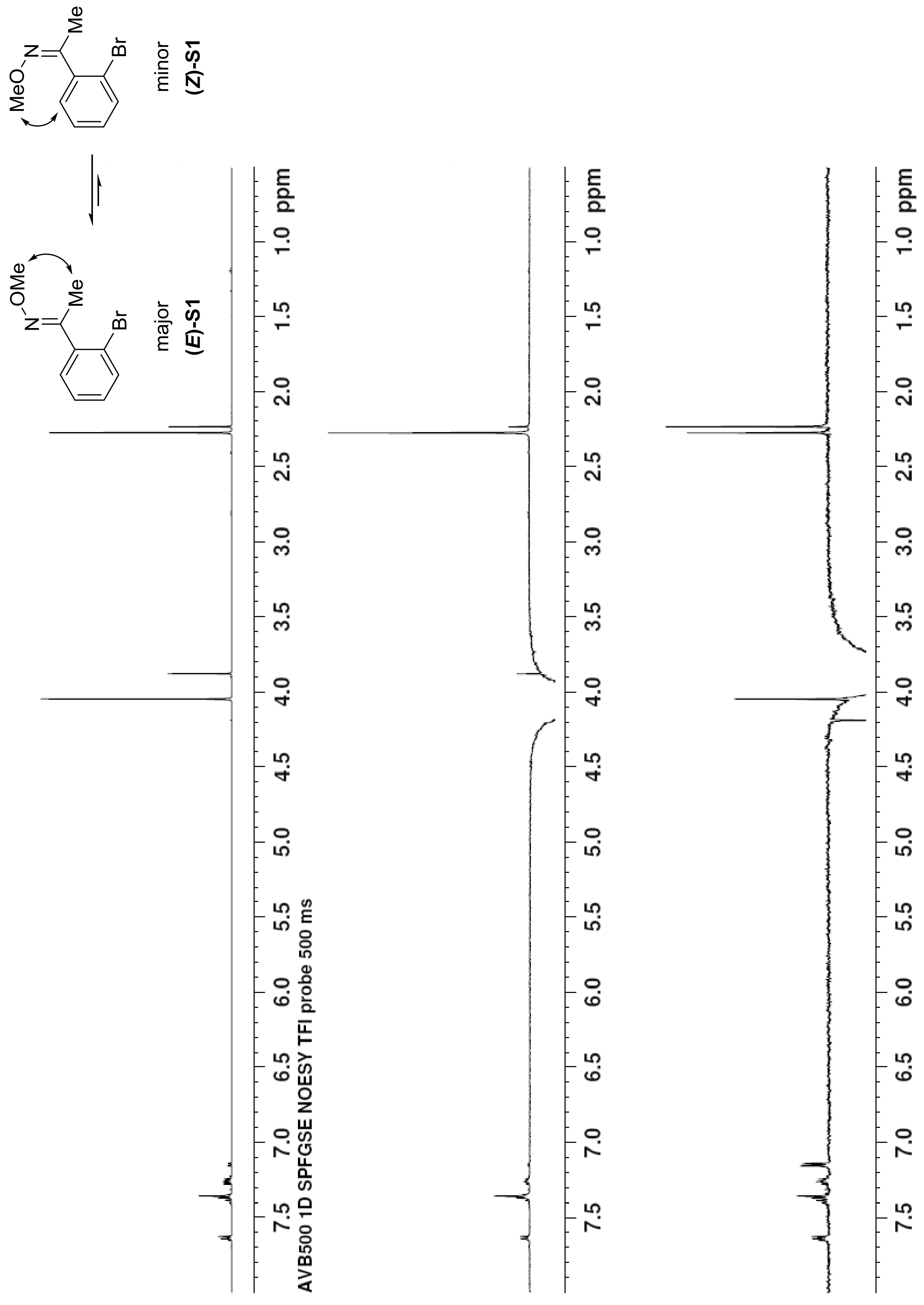
2-Methyl-1-phenylpropan-1-one *O*-methyl oxime 312



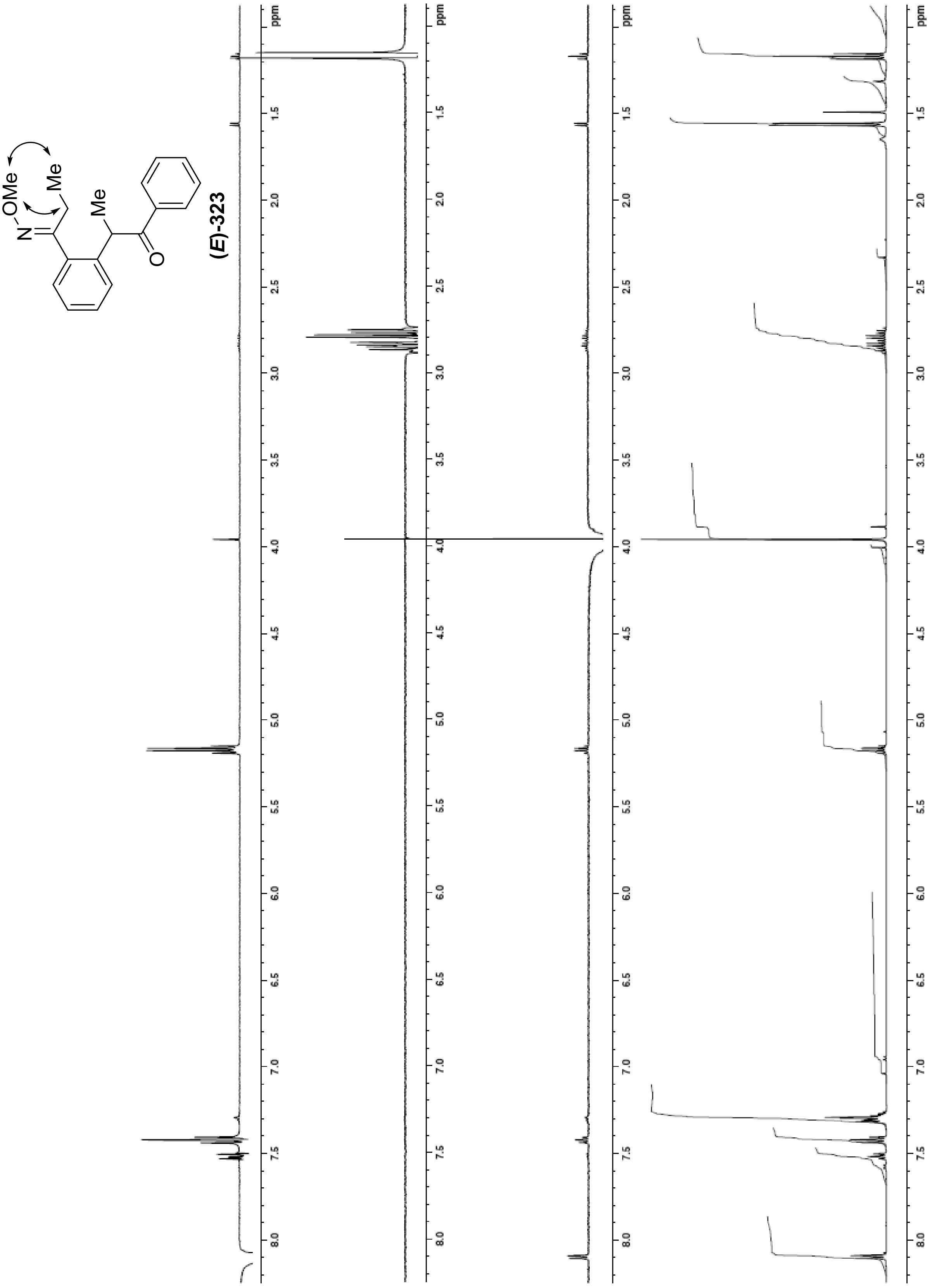
Cyclopropyl(phenyl)methanone *O*-methyl oxime 313



1-(2-Bromophenyl)ethanone *O*-methyl oxime S1

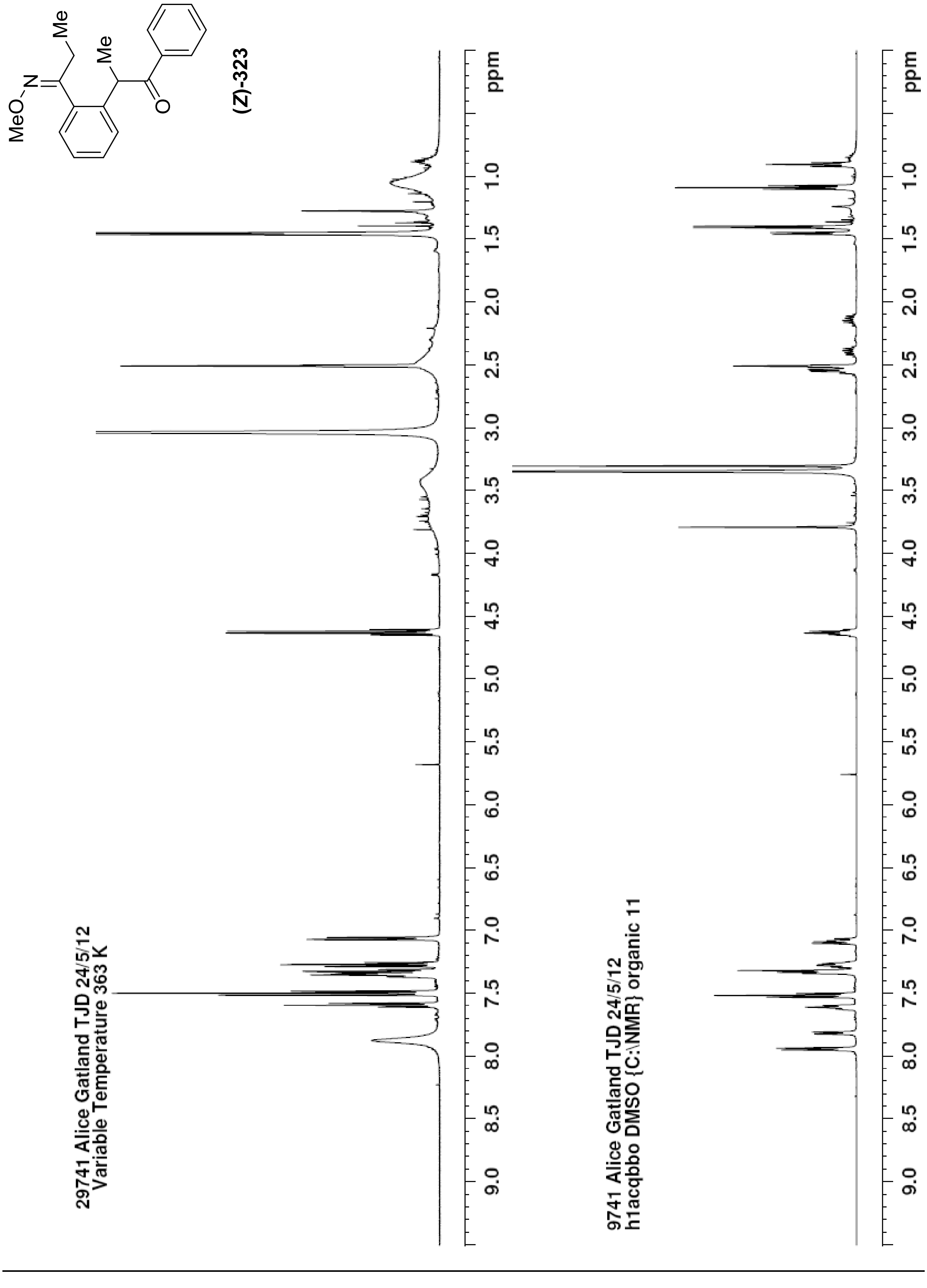


(*E)*-2-(2-(1-(Methoxyimino)propyl)phenyl)-1-phenylpropan-1-one (*E*)-323

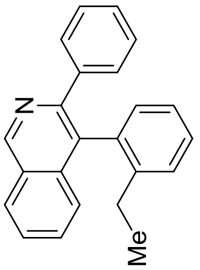


Appendix 2. Variable Temperature NMR

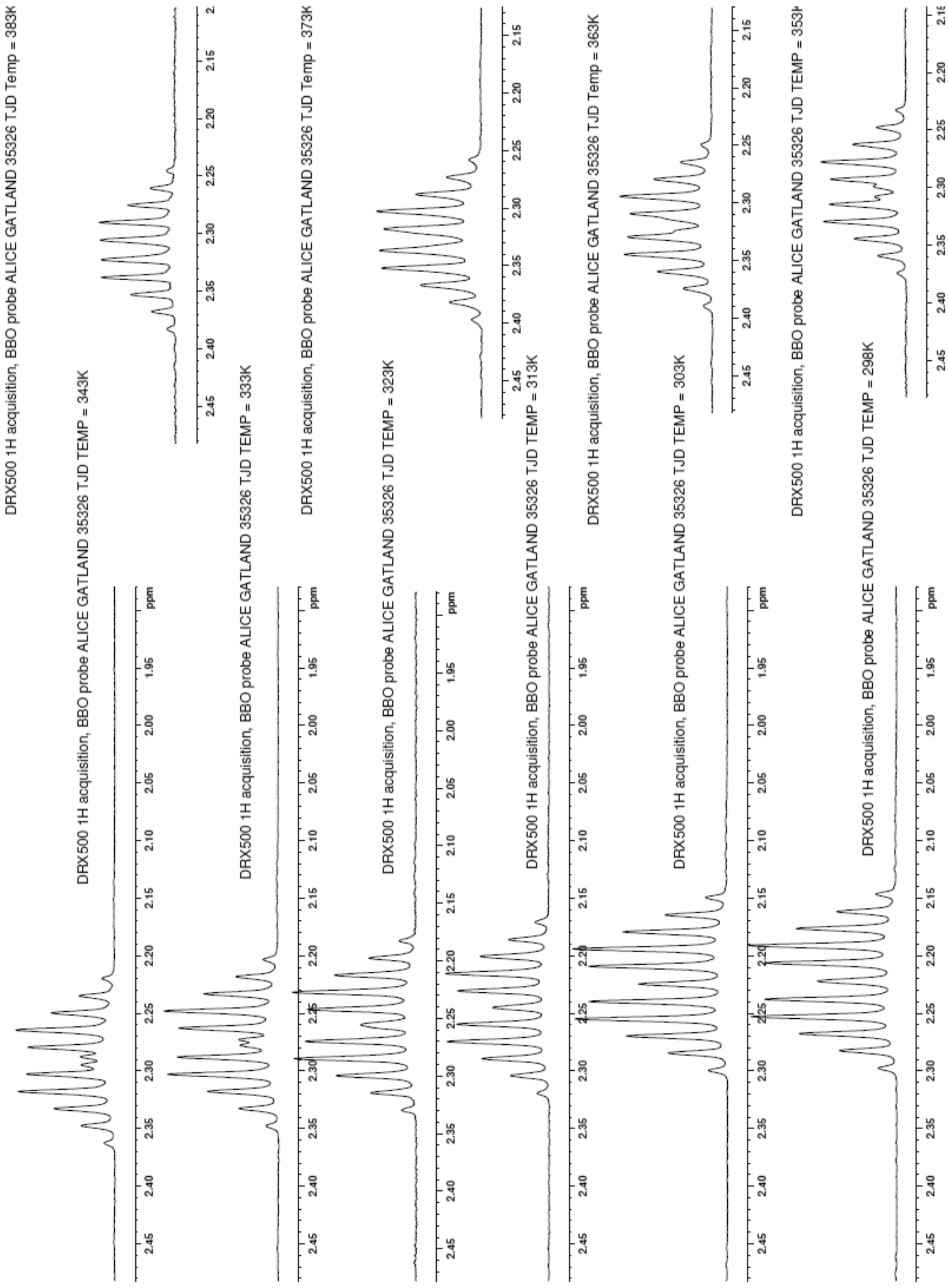
(*Z*)-2-(2-(1-(Methoxyimino)propyl)phenyl)-1-phenylpropan-1-one (*Z*)-323



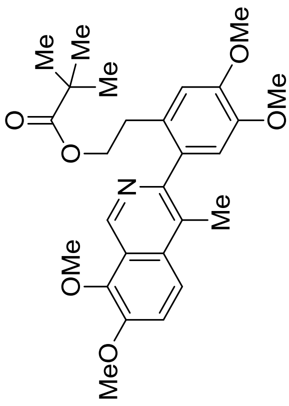
4-(2-Ethylphenyl)-3-phenylisoquinoline 410



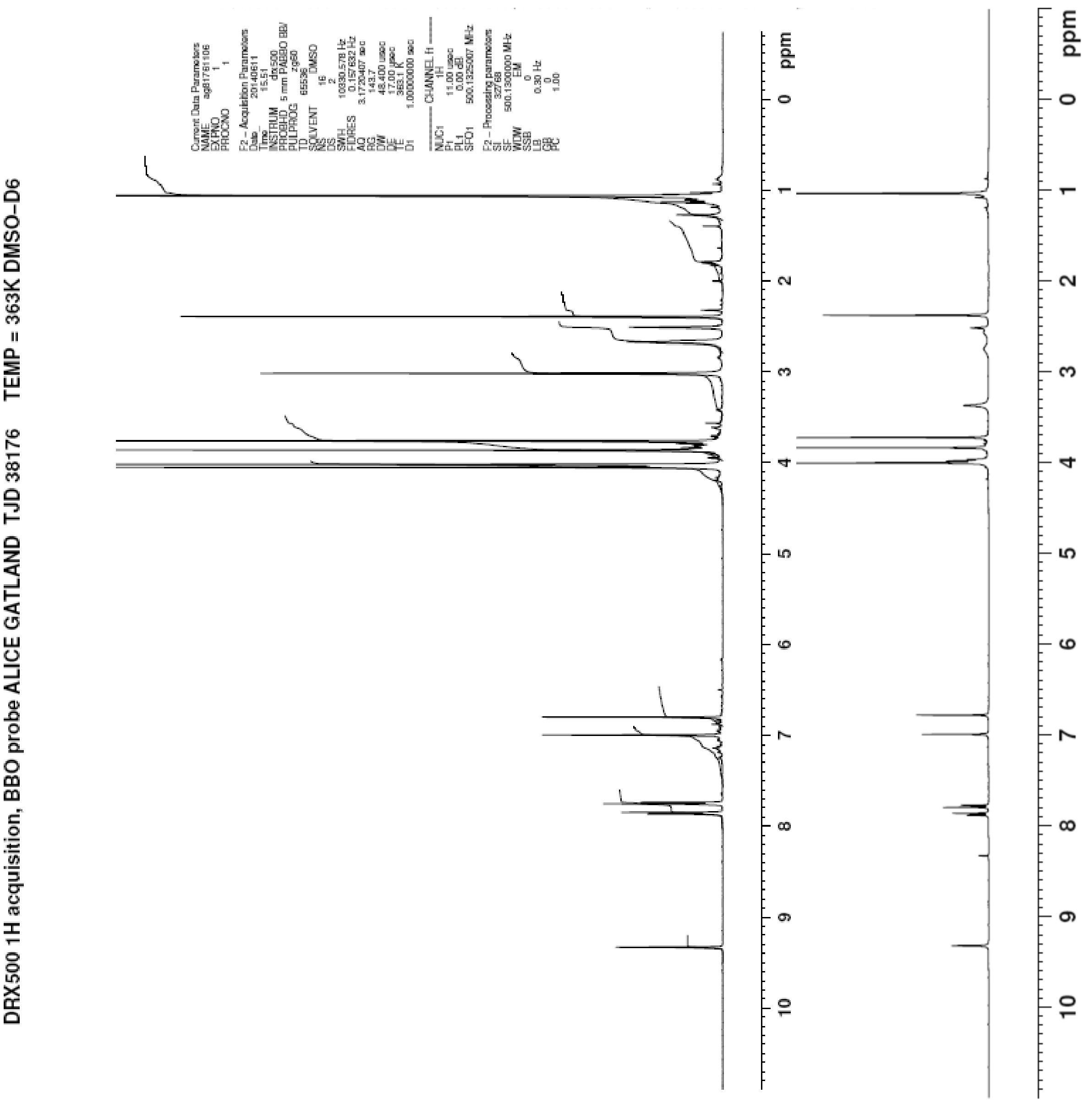
410



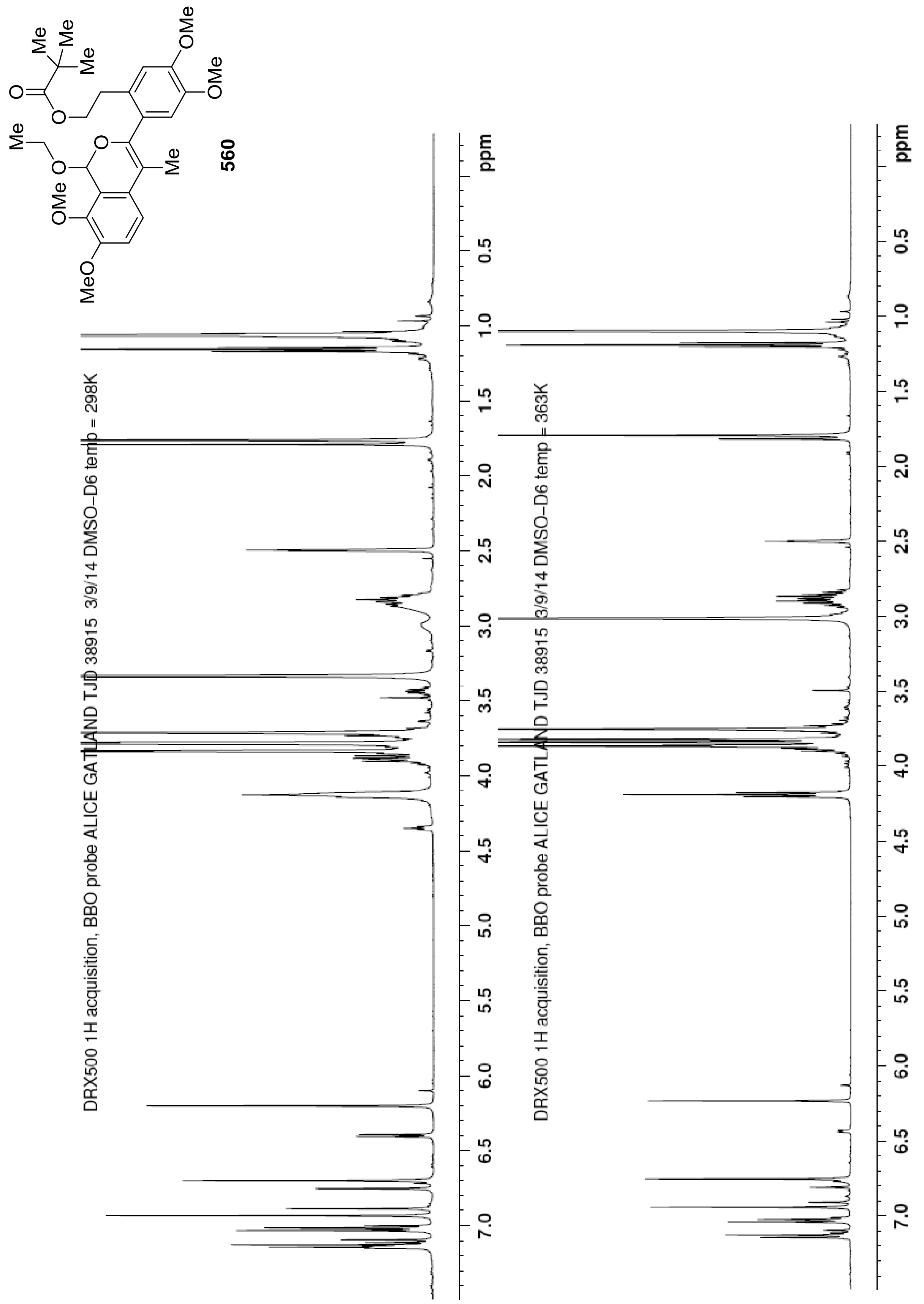
2-(7,8-Dimethoxy-4-methylisoquinolin-3-yl)-4,5-dimethoxyphenethyl pivaloate 559



559

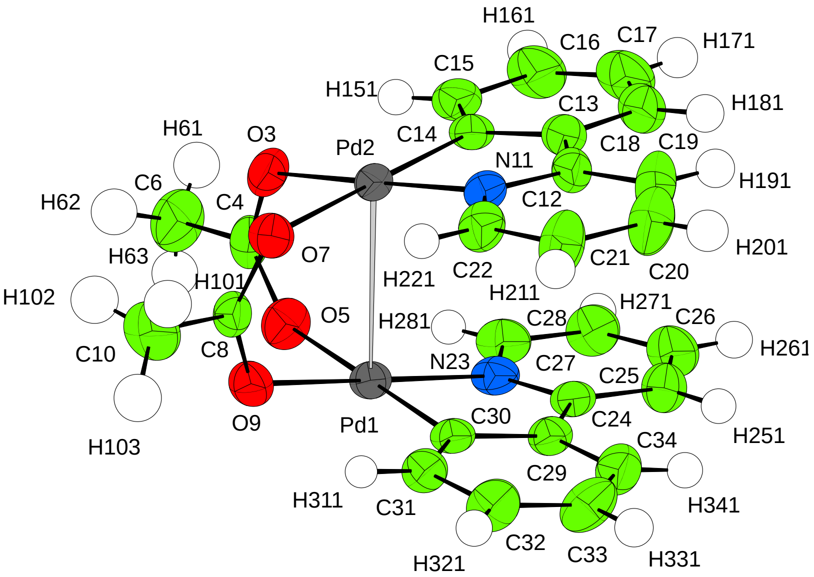


2-(1-Ethoxy-7,8-dimethoxy-4-methyl-1*H*-isochromen-3-yl)-4,5-dimethoxyphenethyl pivaloate 560



Appendix 3.
Single Crystal X-Ray Diffraction Reports

2-Phenylpyridyl palladium acetate dimer 275



Crystals of **275** were grown from pentane/CH_2Cl_2. The single crystal selected for X-ray analysis was representative of the bulk of the sample provided.

Computing details

Data collection: *COLLECT* (Nonius, 2001);[323] cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997);[324] data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997);[324] program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994);[325] program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003);[326] molecular graphics: *CAMERON* (Watkin *et al.*, 1996);[327] software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).[326]

Crystal data

$C_{26}H_{22}N_2O_4Pd_2$
$M_r = 639.27$
Orthorhombic, $P2_12_12_1$
Hall symbol: P 2ac 2ab
$a = 13.0916$ (3) Å
$b = 14.7604$ (3) Å
$c = 14.9405$ (4) Å
$V = 2887.06$ (12) Å^3
$Z = 4$
$F(000) = 1264$

$D_x = 1.471$ Mg m^{-3}
Melting point: decomposition at 536 K
Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
Cell parameters from 3541 reflections
$\theta = 1–27°$
$\mu = 1.27$ mm^{-1}
$T = 150$ K
Block, clear_pale_colourless
0.3 × 0.2 × 0.2 mm

Data collection

Nonius KappaCCD diffractometer
Graphite monochromator
ω scans
Absorption correction: multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)
$T_{\min} = 0.72$, $T_{\max} = 0.77$
17122 measured reflections
6470 independent reflections

6018 reflections with $I > 2.0\sigma(I)$
$R_{\rm int} = 0.028$
$\theta_{\max} = 27.5°$, $\theta_{\min} = 1.9°$
$h = -16 \rightarrow 16$
$k = 0 \rightarrow 19$
$l = 0 \rightarrow 19$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.037$
$wR(F^2) = 0.097$
$S = 0.92$
6453 reflections
307 parameters
0 restraints

Primary atom site location: structure-invariant direct methods
Hydrogen site location: difference Fourier map
H-atom parameters constrained
Method, part 1, Chebychev polynomial, (Watkin, 1994, Prince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (Prince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 64.6 107. 66.6 29.9 7.77
$(\Delta/\sigma)_{\max} = 0.002$
$\Delta\rho_{\max} = 0.47$ e Å^{-3}
$\Delta\rho_{\min} = -0.79$ e Å^{-3}

Special details

Refinement
The difference map indicated the presence of diffuse electron density believed to be disordered solvent. SQUEEZE was used leaving a void from which the electron density was removed.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	$U_{\rm iso}$*/$U_{\rm eq}$
Pd1	0.76558 (2)	0.19137 (2)	0.39233 (2)	0.0347
Pd2	0.64346 (3)	0.08083 (2)	0.27962 (2)	0.0352
O3	0.7590 (3)	0.0952 (2)	0.1887 (2)	0.0474
C4	0.8294 (4)	0.1545 (4)	0.1996 (3)	0.0460
O5	0.8411 (3)	0.2055 (3)	0.2664 (2)	0.0502
C6	0.9031 (6)	0.1657 (6)	0.1212 (5)	0.0705

O7	0.7341 (3)	−0.0168 (2)	0.3510 (2)	0.0439
C8	0.8116 (4)	−0.0014 (3)	0.3953 (3)	0.0392
O9	0.8484 (3)	0.0751 (2)	0.4161 (2)	0.0453
C10	0.8713 (6)	−0.0829 (5)	0.4290 (5)	0.0726
N11	0.5254 (3)	0.0775 (3)	0.3640 (3)	0.0395
C12	0.4493 (4)	0.1385 (3)	0.3472 (4)	0.0448
C13	0.4648 (4)	0.1891 (4)	0.2629 (4)	0.0472
C14	0.5545 (4)	0.1680 (3)	0.2174 (3)	0.0399
C15	0.5759 (5)	0.2117 (4)	0.1372 (4)	0.0512
C16	0.5063 (6)	0.2776 (5)	0.1049 (5)	0.0673
C17	0.4205 (6)	0.2977 (5)	0.1499 (5)	0.0688
C18	0.3980 (5)	0.2558 (4)	0.2295 (5)	0.0591
C19	0.3691 (5)	0.1508 (4)	0.4058 (5)	0.0631
C20	0.3677 (6)	0.1015 (5)	0.4834 (6)	0.0714
C21	0.4468 (5)	0.0383 (4)	0.5022 (5)	0.0639
C22	0.5231 (4)	0.0295 (4)	0.4395 (4)	0.0499
N23	0.6734 (3)	0.2996 (3)	0.3778 (3)	0.0406
C24	0.6033 (4)	0.3112 (3)	0.4430 (3)	0.0392
C25	0.5281 (4)	0.3779 (4)	0.4344 (4)	0.0500
C26	0.5261 (5)	0.4298 (4)	0.3580 (4)	0.0571
C27	0.6003 (5)	0.4201 (4)	0.2926 (4)	0.0545
C28	0.6729 (5)	0.3519 (4)	0.3034 (4)	0.0493
C29	0.6164 (4)	0.2490 (3)	0.5191 (3)	0.0385
C30	0.6959 (3)	0.1862 (3)	0.5084 (3)	0.0363
C31	0.7146 (4)	0.1254 (3)	0.5777 (3)	0.0422
C32	0.6549 (5)	0.1278 (4)	0.6567 (4)	0.0540
C33	0.5780 (5)	0.1917 (5)	0.6642 (4)	0.0614
C34	0.5569 (5)	0.2517 (4)	0.5962 (4)	0.0530
H63	0.9463	0.2170	0.1316	0.1040*
H62	0.9463	0.1125	0.1155	0.1042*
H61	0.8657	0.1759	0.0669	0.1043*
H103	0.9189	−0.0653	0.4752	0.1111*
H102	0.9116	−0.1070	0.3792	0.1114*
H101	0.8254	−0.1298	0.4505	0.1109*
H151	0.6354	0.1989	0.1057	0.0619*
H161	0.5200	0.3070	0.0510	0.0787*
H171	0.3757	0.3419	0.1269	0.0809*
H181	0.3385	0.2717	0.2624	0.0701*
H191	0.3160	0.1924	0.3932	0.0736*
H201	0.3140	0.1084	0.5240	0.0851*
H211	0.4490	0.0027	0.5543	0.0762*
H221	0.5767	−0.0111	0.4498	0.0599*
H251	0.4805	0.3880	0.4803	0.0599*
H261	0.4730	0.4724	0.3499	0.0668*
H271	0.6035	0.4585	0.2435	0.0651*

H281	0.7232	0.3431	0.2599	0.0577*
H311	0.7662	0.0831	0.5732	0.0508*
H321	0.6675	0.0873	0.7021	0.0650*
H331	0.5382	0.1929	0.7167	0.0733*
H341	0.5035	0.2957	0.6032	0.0620*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Pd1	0.03795 (16)	0.03194 (15)	0.03416 (15)	0.00103 (12)	−0.00534 (13)	−0.00286 (12)
Pd2	0.03586 (15)	0.03230 (15)	0.03735 (16)	0.00501 (13)	−0.00517 (14)	−0.00726 (13)
O3	0.051 (2)	0.0504 (19)	0.0409 (16)	0.0119 (16)	0.0058 (15)	−0.0083 (14)
C4	0.041 (2)	0.051 (3)	0.046 (3)	0.013 (2)	0.0078 (19)	0.003 (2)
O5	0.051 (2)	0.053 (2)	0.0468 (19)	−0.0027 (16)	0.0091 (16)	0.0016 (16)
C6	0.066 (4)	0.088 (5)	0.057 (4)	0.003 (3)	0.022 (3)	−0.002 (3)
O7	0.0483 (18)	0.0307 (14)	0.0528 (19)	0.0067 (14)	−0.0108 (16)	0.0004 (13)
C8	0.039 (2)	0.037 (2)	0.041 (2)	0.0090 (17)	0.001 (2)	−0.0002 (19)
O9	0.0433 (17)	0.0418 (17)	0.0509 (18)	0.0062 (15)	−0.0085 (14)	−0.0006 (14)
C10	0.080 (4)	0.052 (3)	0.086 (4)	0.026 (3)	−0.031 (4)	0.010 (3)
N11	0.0394 (18)	0.0309 (16)	0.048 (2)	−0.0022 (16)	−0.0014 (15)	−0.0088 (16)
C12	0.034 (2)	0.038 (2)	0.063 (3)	0.0009 (18)	0.000 (2)	−0.011 (2)
C13	0.047 (2)	0.037 (2)	0.057 (3)	0.009 (2)	−0.016 (2)	−0.010 (2)
C14	0.043 (2)	0.035 (2)	0.042 (2)	0.0018 (17)	−0.013 (2)	−0.0078 (18)
C15	0.061 (3)	0.046 (3)	0.046 (3)	0.012 (2)	−0.018 (2)	−0.007 (2)
C16	0.080 (4)	0.063 (4)	0.059 (3)	0.017 (3)	−0.026 (3)	0.008 (3)
C17	0.072 (4)	0.054 (3)	0.081 (4)	0.013 (3)	−0.033 (3)	0.003 (3)
C18	0.052 (3)	0.043 (3)	0.082 (4)	0.010 (2)	−0.016 (3)	−0.011 (3)
C19	0.049 (3)	0.047 (3)	0.093 (5)	0.006 (2)	0.024 (3)	−0.004 (3)
C20	0.064 (4)	0.062 (4)	0.088 (5)	0.009 (3)	0.027 (4)	−0.003 (3)
C21	0.062 (3)	0.049 (3)	0.081 (4)	0.004 (3)	0.030 (3)	0.003 (3)
C22	0.051 (3)	0.034 (2)	0.065 (3)	−0.001 (2)	0.004 (2)	−0.005 (2)
N23	0.050 (2)	0.0293 (16)	0.042 (2)	−0.0004 (15)	−0.0114 (16)	−0.0021 (15)
C24	0.047 (2)	0.034 (2)	0.037 (2)	0.0036 (19)	−0.0128 (18)	−0.0066 (18)
C25	0.051 (3)	0.040 (2)	0.059 (3)	0.010 (2)	−0.006 (2)	−0.002 (2)
C26	0.065 (3)	0.044 (3)	0.062 (3)	0.016 (3)	−0.021 (3)	0.006 (2)
C27	0.071 (3)	0.044 (3)	0.048 (3)	0.010 (3)	−0.011 (3)	0.009 (2)
C28	0.061 (3)	0.040 (2)	0.046 (3)	−0.002 (2)	−0.011 (2)	0.0055 (19)
C29	0.042 (2)	0.034 (2)	0.039 (2)	−0.0005 (17)	−0.0048 (18)	−0.0051 (18)
C30	0.043 (2)	0.0299 (19)	0.036 (2)	−0.0012 (18)	−0.0096 (17)	−0.0050 (17)
C31	0.050 (3)	0.040 (2)	0.037 (2)	0.006 (2)	−0.0050 (18)	0.0018 (18)
C32	0.073 (4)	0.048 (3)	0.041 (2)	0.009 (3)	−0.002 (3)	0.008 (2)
C33	0.086 (4)	0.057 (3)	0.041 (3)	0.002 (3)	0.012 (3)	−0.003 (3)
C34	0.057 (3)	0.051 (3)	0.051 (3)	0.012 (2)	0.000 (2)	−0.004 (2)

Geometric parameters (Å, º)

Pd1—Pd2	2.8379 (4)	C17—C18	1.373 (11)
Pd1—O5	2.135 (3)	C17—H171	0.942
Pd1—O9	2.061 (3)	C18—H181	0.951
Pd1—N23	2.014 (4)	C19—C20	1.368 (10)
Pd1—C30	1.961 (5)	C19—H191	0.947
Pd2—O3	2.044 (4)	C20—C21	1.422 (10)
Pd2—O7	2.150 (3)	C20—H201	0.935
Pd2—N11	1.995 (4)	C21—C22	1.375 (8)
Pd2—C14	1.968 (5)	C21—H211	0.941
O3—C4	1.282 (7)	C22—H221	0.934
C4—O5	1.260 (6)	N23—C24	1.349 (7)
C4—C6	1.527 (8)	N23—C28	1.353 (6)
C6—H63	0.957	C24—C25	1.398 (7)
C6—H62	0.972	C24—C29	1.472 (7)
C6—H61	0.960	C25—C26	1.375 (8)
O7—C8	1.232 (6)	C25—H251	0.939
C8—O9	1.266 (6)	C26—C27	1.385 (9)
C8—C10	1.519 (7)	C26—H261	0.944
C10—H103	0.966	C27—C28	1.394 (8)
C10—H102	0.979	C27—H271	0.929
C10—H101	0.971	C28—H281	0.934
N11—C12	1.366 (6)	C29—C30	1.403 (7)
N11—C22	1.333 (7)	C29—C34	1.391 (8)
C12—C13	1.479 (8)	C30—C31	1.391 (6)
C12—C19	1.379 (8)	C31—C32	1.415 (8)
C13—C14	1.391 (7)	C31—H311	0.922
C13—C18	1.408 (7)	C32—C33	1.384 (9)
C14—C15	1.390 (8)	C32—H321	0.919
C15—C16	1.418 (8)	C33—C34	1.376 (9)
C15—H151	0.929	C33—H331	0.941
C16—C17	1.342 (11)	C34—H341	0.960
C16—H161	0.932		
Pd2—Pd1—O5	78.14 (10)	C15—C16—C17	121.3 (7)
Pd2—Pd1—O9	85.38 (10)	C15—C16—H161	119.3
O5—Pd1—O9	89.40 (15)	C17—C16—H161	119.3
Pd2—Pd1—N23	93.12 (11)	C16—C17—C18	120.9 (6)
O5—Pd1—N23	96.03 (16)	C16—C17—H171	119.5
O9—Pd1—N23	173.96 (16)	C18—C17—H171	119.6
Pd2—Pd1—C30	103.91 (12)	C13—C18—C17	119.3 (6)
O5—Pd1—C30	176.64 (17)	C13—C18—H181	119.9
O9—Pd1—C30	93.41 (17)	C17—C18—H181	120.8
N23—Pd1—C30	81.25 (18)	C12—C19—C20	118.6 (6)
Pd1—Pd2—O3	85.28 (10)	C12—C19—H191	121.1

Pd1—Pd2—O7	77.29 (9)	C20—C19—H191	120.3
O3—Pd2—O7	89.45 (15)	C19—C20—C21	120.4 (6)
Pd1—Pd2—N11	94.36 (11)	C19—C20—H201	120.2
O3—Pd2—N11	174.73 (16)	C21—C20—H201	119.4
O7—Pd2—N11	95.60 (16)	C20—C21—C22	117.2 (6)
Pd1—Pd2—C14	103.74 (12)	C20—C21—H211	123.5
O3—Pd2—C14	93.26 (19)	C22—C21—H211	119.3
O7—Pd2—C14	177.17 (19)	C21—C22—N11	122.8 (5)
N11—Pd2—C14	81.7 (2)	C21—C22—H221	119.6
Pd2—O3—C4	121.2 (3)	N11—C22—H221	117.6
O3—C4—O5	126.6 (4)	Pd1—N23—C24	115.5 (3)
O3—C4—C6	115.5 (5)	Pd1—N23—C28	123.0 (4)
O5—C4—C6	117.8 (5)	C24—N23—C28	121.2 (4)
Pd1—O5—C4	125.7 (3)	N23—C24—C25	120.1 (5)
C4—C6—H63	109.5	N23—C24—C29	113.6 (4)
C4—C6—H62	110.4	C25—C24—C29	126.3 (5)
H63—C6—H62	108.0	C24—C25—C26	118.8 (5)
C4—C6—H61	110.1	C24—C25—H251	120.8
H63—C6—H61	108.3	C26—C25—H251	120.4
H62—C6—H61	110.5	C25—C26—C27	121.0 (5)
Pd2—O7—C8	126.7 (3)	C25—C26—H261	119.4
O7—C8—O9	127.5 (4)	C27—C26—H261	119.6
O7—C8—C10	117.1 (5)	C26—C27—C28	118.1 (5)
O9—C8—C10	115.4 (5)	C26—C27—H271	121.7
C8—O9—Pd1	120.0 (3)	C28—C27—H271	120.1
C8—C10—H103	110.9	C27—C28—N23	120.7 (5)
C8—C10—H102	108.3	C27—C28—H281	120.0
H103—C10—H102	107.0	N23—C28—H281	119.3
C8—C10—H101	110.8	C24—C29—C30	114.2 (4)
H103—C10—H101	110.7	C24—C29—C34	123.8 (4)
H102—C10—H101	108.9	C30—C29—C34	121.9 (5)
Pd2—N11—C12	115.6 (3)	C29—C30—Pd1	114.8 (3)
Pd2—N11—C22	124.4 (3)	C29—C30—C31	118.1 (4)
C12—N11—C22	119.3 (4)	Pd1—C30—C31	127.0 (4)
N11—C12—C13	112.9 (4)	C30—C31—C32	120.5 (5)
N11—C12—C19	121.6 (5)	C30—C31—H311	120.8
C13—C12—C19	125.4 (5)	C32—C31—H311	118.7
C12—C13—C14	114.7 (4)	C31—C32—C33	119.1 (5)
C12—C13—C18	124.7 (5)	C31—C32—H321	120.0
C14—C13—C18	120.5 (6)	C33—C32—H321	120.9
C13—C14—Pd2	114.6 (4)	C32—C33—C34	121.6 (5)
C13—C14—C15	119.1 (5)	C32—C33—H331	118.9
Pd2—C14—C15	126.2 (4)	C34—C33—H331	119.4
C14—C15—C16	118.8 (6)	C29—C34—C33	118.7 (5)
C14—C15—H151	120.8	C29—C34—H341	121.1

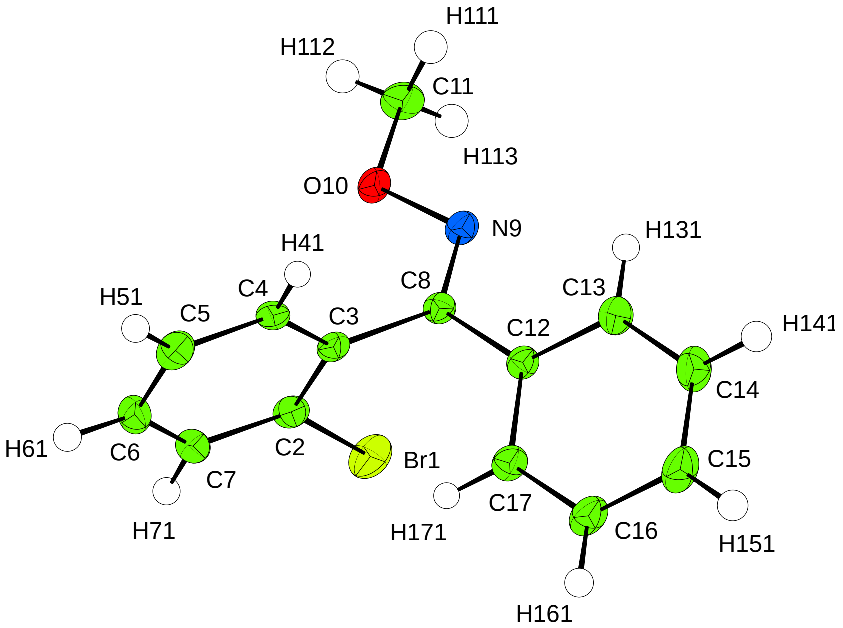
C16—C15—H151	120.4	C33—C34—H341	120.1

Hydrogen bond geometries (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C17—H171···O7^{i}	0.94	2.55	3.405 (8)	150
C22—H221···O7	0.93	2.54	3.138 (8)	122
C25—H251···O9^{ii}	0.94	2.38	3.318 (8)	173
C28—H281···O5	0.93	2.55	3.134 (8)	121

Symmetry codes: (i) –*x*+1, *y*+1/2, –*z*+1/2; (ii) *x*–1/2, –*y*+1/2, –*z*+1.

(*Z*)-(2-bromophenyl)(phenyl)methanone *O*-methyl oxime (*Z*)-330



Crystals of **(*Z*)-330** were grown from petrol/EtOAc. The single crystal selected for X-ray analysis was representative of the bulk of the sample provided.

Computing details

Data collection: *COLLECT* (Nonius, 2001);[323] cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997);[324] data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997);[324] program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007);[328] program(s) used to refine structure: *CRYSTALS* (Betteridge *et al*., 2003);[326] molecular graphics: *CAMERON* (Watkin *et al*., 1996);[327] software used to prepare material for publication: *CRYSTALS* (Betteridge *et al*., 2003).[326]

Crystal data

$C_{14}H_{12}BrNO$	$F(000) = 584$
$M_r = 290.16$	$D_x = 1.552$ Mg m^{-3}
Monoclinic, $P2_1/c$	Melting point = 375–378 K
Hall symbol: -P 2ybc	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 12.5635$ (4) Å	Cell parameters from 2986 reflections
$b = 7.7543$ (3) Å	$\theta = 1–27°$
$c = 12.7743$ (5) Å	$\mu = 3.29$ mm^{-1}
$\beta = 94.0786$ (16)°	$T = 150$ K
$V = 1241.34$ (8) Å^3	Plate, clear_colourless
$Z = 4$	0.6 × 0.4 × 0.1 mm

Data collection

Nonius KappaCCD diffractometer
Graphite monochromator
ω scans
Absorption correction: multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)
T_{min} = 0.59, T_{max} = 0.72
16647 measured reflections
2827 independent reflections

2257 reflections with $I > 2.0\sigma(I)$
R_{int} = 0.033
θ_{max} = 27.5°, θ_{min} = 1.6°
$h = -16 \rightarrow 16$
$k = -10 \rightarrow 9$
$l = -16 \rightarrow 16$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.099
S = 0.93
2820 reflections
154 parameters
0 restraints

Primary atom site location: Other
Hydrogen site location: difference Fourier map
H-atom parameters constrained
Method, part 1, Chebychev polynomial, (Watkin, 1994, Prince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ··· + A_{n-1}]*T_{n-1}(x)]
where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (Prince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 16.0 22.5 10.8 2.60
$(\Delta/\sigma)_{\mathrm{max}}$ = 0.0003
$\Delta\rho_{\mathrm{max}}$ = 0.86 e Å^{-3}
$\Delta\rho_{\mathrm{min}}$ = −0.81 e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
Br1	0.12643 (3)	0.37898 (5)	0.53491 (3)	0.0326
C2	0.1808 (3)	0.5938 (4)	0.4921 (3)	0.0230
C3	0.2274 (2)	0.6055 (4)	0.3968 (2)	0.0196
C4	0.2701 (3)	0.7686 (5)	0.3665 (3)	0.0243
C5	0.2618 (3)	0.9063 (5)	0.4328 (3)	0.0281
C6	0.2145 (3)	0.8921 (5)	0.5271 (3)	0.0288
C7	0.1742 (3)	0.7345 (5)	0.5574 (3)	0.0272
C8	0.2334 (2)	0.4539 (4)	0.3248 (2)	0.0188
N9	0.1584 (2)	0.4152 (4)	0.2552 (2)	0.0213
O10	0.07338 (18)	0.5324 (3)	0.25888 (19)	0.0247
C11	−0.0133 (3)	0.4771 (5)	0.1869 (3)	0.0309
C12	0.3298 (2)	0.3445 (4)	0.3314 (2)	0.0198
C13	0.3534 (3)	0.2356 (5)	0.2489 (3)	0.0266
C14	0.4434 (3)	0.1309 (5)	0.2579 (3)	0.0332

C15	0.5110 (3)	0.1337 (5)	0.3490 (3)	0.0340
C16	0.4890 (3)	0.2417 (5)	0.4302 (3)	0.0297
C17	0.3993 (2)	0.3474 (4)	0.4220 (3)	0.0236
H41	0.3017	0.7815	0.3060	0.0298*
H51	0.2883	1.0135	0.4120	0.0341*
H61	0.2105	0.9893	0.5708	0.0350*
H71	0.1435	0.7226	0.6221	0.0328*
H112	−0.0733	0.5524	0.1948	0.0483*
H111	0.0072	0.4843	0.1153	0.0479*
H113	−0.0327	0.3609	0.2009	0.0482*
H131	0.3075	0.2324	0.1869	0.0323*
H141	0.4583	0.0578	0.2016	0.0410*
H151	0.5715	0.0633	0.3550	0.0415*
H161	0.5347	0.2446	0.4906	0.0366*
H171	0.3848	0.4219	0.4783	0.0294*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Br1	0.03339 (19)	0.02790 (19)	0.0375 (2)	0.00176 (15)	0.00908 (14)	0.01080 (16)
C2	0.0232 (15)	0.0228 (16)	0.0224 (15)	0.0012 (12)	−0.0017 (12)	0.0026 (13)
C3	0.0166 (13)	0.0198 (15)	0.0216 (14)	0.0027 (12)	−0.0038 (11)	0.0006 (12)
C4	0.0194 (14)	0.0298 (17)	0.0220 (15)	0.0090 (13)	−0.0094 (12)	−0.0056 (13)
C5	0.0248 (16)	0.0218 (17)	0.0365 (19)	−0.0010 (13)	−0.0057 (14)	0.0008 (14)
C6	0.0286 (17)	0.0248 (17)	0.0317 (17)	0.0036 (14)	−0.0067 (13)	−0.0086 (15)
C7	0.0314 (17)	0.0286 (18)	0.0211 (15)	0.0071 (14)	−0.0009 (13)	−0.0032 (14)
C8	0.0203 (14)	0.0175 (14)	0.0187 (14)	−0.0010 (12)	0.0013 (11)	0.0019 (11)
N9	0.0191 (12)	0.0210 (13)	0.0236 (13)	0.0024 (10)	0.0002 (10)	0.0007 (11)
O10	0.0185 (10)	0.0227 (12)	0.0316 (12)	0.0048 (9)	−0.0077 (9)	−0.0049 (10)
C11	0.0213 (16)	0.0334 (19)	0.0363 (19)	−0.0023 (14)	−0.0106 (14)	−0.0018 (16)
C12	0.0192 (14)	0.0182 (15)	0.0219 (14)	−0.0003 (11)	0.0008 (11)	0.0006 (12)
C13	0.0256 (16)	0.0272 (17)	0.0272 (16)	0.0056 (13)	0.0027 (13)	−0.0021 (14)
C14	0.0312 (18)	0.0310 (18)	0.0376 (19)	0.0080 (16)	0.0048 (15)	−0.0066 (16)
C15	0.0233 (16)	0.0303 (19)	0.048 (2)	0.0083 (15)	−0.0003 (15)	−0.0038 (17)
C16	0.0234 (16)	0.0245 (17)	0.040 (2)	0.0024 (13)	−0.0077 (14)	0.0002 (15)
C17	0.0192 (14)	0.0218 (16)	0.0291 (16)	−0.0003 (12)	−0.0038 (12)	−0.0006 (13)

Geometric parameters (Å, º)

Br1—C2	1.896 (3)	O10—C11	1.439 (4)
C2—C3	1.391 (4)	C11—H112	0.965
C2—C7	1.379 (5)	C11—H111	0.969
C3—C4	1.437 (5)	C11—H113	0.954

C3—C8	1.498 (4)	C12—C13	1.398 (5)
C4—C5	1.371 (5)	C12—C17	1.398 (4)
C4—H41	0.899	C13—C14	1.391 (5)
C5—C6	1.385 (5)	C13—H131	0.946
C5—H51	0.941	C14—C15	1.391 (5)
C6—C7	1.388 (5)	C14—H141	0.945
C6—H61	0.941	C15—C16	1.377 (5)
C7—H71	0.942	C15—H151	0.934
C8—N9	1.285 (4)	C16—C17	1.392 (5)
C8—C12	1.476 (4)	C16—H161	0.929
N9—O10	1.405 (3)	C17—H171	0.950

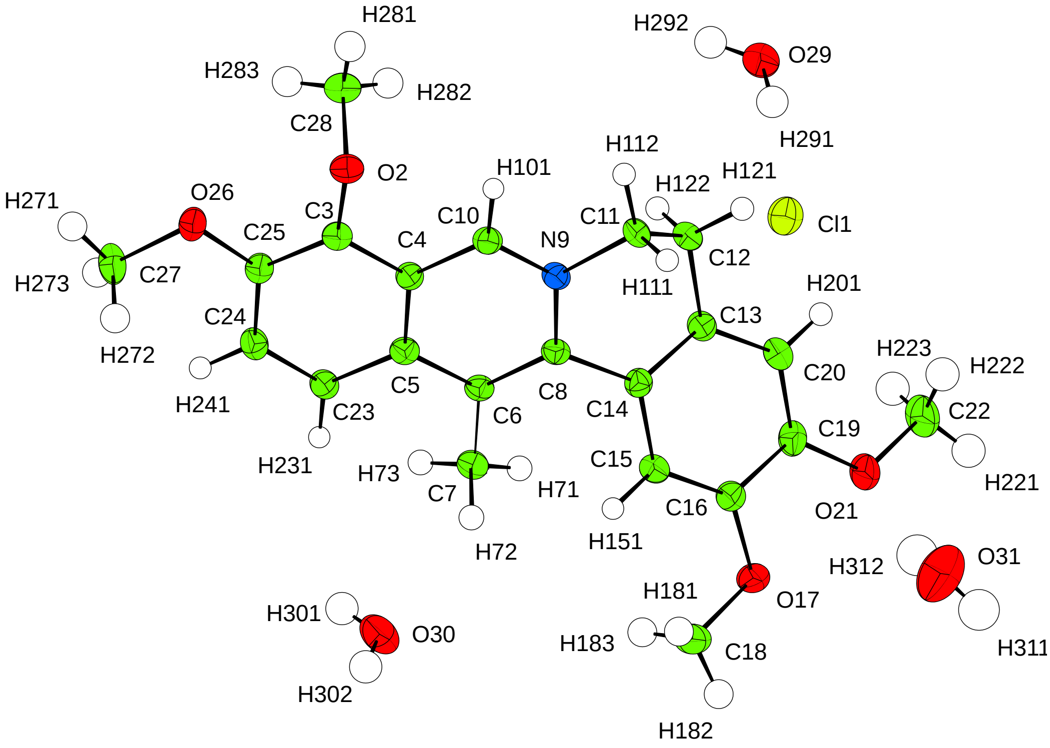
Br1—C2—C3	119.5 (2)	O10—C11—H111	110.2
Br1—C2—C7	118.8 (3)	H112—C11—H111	109.0
C3—C2—C7	121.6 (3)	O10—C11—H113	110.7
C2—C3—C4	118.8 (3)	H112—C11—H113	109.9
C2—C3—C8	121.9 (3)	H111—C11—H113	108.6
C4—C3—C8	119.3 (3)	C8—C12—C13	121.3 (3)
C3—C4—C5	118.2 (3)	C8—C12—C17	120.0 (3)
C3—C4—H41	121.7	C13—C12—C17	118.7 (3)
C5—C4—H41	120.1	C12—C13—C14	120.3 (3)
C4—C5—C6	122.1 (3)	C12—C13—H131	119.9
C4—C5—H51	118.1	C14—C13—H131	119.7
C6—C5—H51	119.8	C13—C14—C15	120.3 (3)
C5—C6—C7	120.0 (3)	C13—C14—H141	119.5
C5—C6—H61	119.8	C15—C14—H141	120.2
C7—C6—H61	120.2	C14—C15—C16	119.8 (3)
C6—C7—C2	119.3 (3)	C14—C15—H151	120.3
C6—C7—H71	120.8	C16—C15—H151	119.9
C2—C7—H71	120.0	C15—C16—C17	120.4 (3)
C3—C8—N9	122.8 (3)	C15—C16—H161	119.7
C3—C8—C12	119.5 (3)	C17—C16—H161	119.9
N9—C8—C12	117.7 (3)	C12—C17—C16	120.5 (3)
C8—N9—O10	110.4 (3)	C12—C17—H171	119.6
N9—O10—C11	109.1 (2)	C16—C17—H171	119.9
O10—C11—H112	108.4		

Hydrogen bond geometries (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C6—H61···N9^{i}	0.94	2.60	3.393 (5)	143 (1)

Symmetry codes: (i) *x*, –*y*+3/2, *z*+1/2.

Dehydrocorydaline chloride



Crystals of **dehydrocorydaline chloride** were grown from pentane/MeOH. The single crystal selected for X-ray analysis was representative of the bulk of the sample provided.

Computing details

Data collection: *COLLECT* (Nonius, 2001);[323] cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997);[324] data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997);[324] program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994);[325] program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003);[326] molecular graphics: *CAMERON* (Watkin *et al.*, 1996);[327] software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).[326]

Crystal data

$C_{22}H_{24}NO_4\cdot Cl\cdot 3(H_2O)$	$F(000) = 968$
$M_r = 455.94$	$D_x = 1.355$ Mg m^{-3}
Monoclinic, $P2_1/n$	Melting point = 446–448 K
Hall symbol: -P 2yn	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 16.5082$ (4) Å	Cell parameters from 5394 reflections
$b = 7.3738$ (2) Å	$\theta = 5$–27°
$c = 18.6316$ (6) Å	$\mu = 0.21$ mm^{-1}
$\beta = 99.7175$ (9)°	$T = 150$ K
$V = 2235.45$ (11) Å^3	Plate, clear_bright_yellow
$Z = 4$	0.24 × 0.15 × 0.04 mm

Data collection

Nonius KappaCCD diffractometer
Graphite monochromator
ω scans
Absorption correction: multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)
$T_{\min} = 0.93$, $T_{\max} = 0.99$
29411 measured reflections
5096 independent reflections

3459 reflections with $I > 2.0\sigma(I)$
$R_{\rm int} = 0.033$
$\theta_{\max} = 27.5°$, $\theta_{\min} = 5.1°$
$h = -21\rightarrow21$
$k = -9\rightarrow8$
$l = -24\rightarrow24$

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)] = 0.045$
$wR(F^2) = 0.135$
$S = 0.97$
5096 reflections
280 parameters
0 restraints

Primary atom site location: structure-invariant direct methods
Hydrogen site location: difference Fourier map
H-atom parameters constrained
Method, part 1, Chebychev polynomial, (Watkin, 1994, Prince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (Prince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 16.9 24.8 12.2 3.19
$(\Delta/\sigma)_{\max} = 0.001$
$\Delta\rho_{\max} = 0.52$ e Å^{-3}
$\Delta\rho_{\min} = -0.48$ e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	$U_{\rm iso}$*/$U_{\rm eq}$
Cl1	0.67983 (4)	0.18688 (9)	0.81582 (4)	0.0352
O2	0.43285 (10)	0.1458 (2)	0.66916 (9)	0.0285
C3	0.42636 (14)	0.2136 (3)	0.59989 (12)	0.0230
C4	0.49644 (13)	0.2055 (3)	0.56520 (12)	0.0211
C5	0.49207 (14)	0.2564 (3)	0.49118 (12)	0.0219
C6	0.56468 (13)	0.2487 (3)	0.45904 (11)	0.0210
C7	0.56011 (14)	0.3128 (3)	0.38176 (12)	0.0254
C8	0.63786 (13)	0.1876 (3)	0.50006 (11)	0.0212
N9	0.63874 (11)	0.1470 (3)	0.57369 (10)	0.0224
C10	0.57197 (14)	0.1525 (3)	0.60456 (12)	0.0230
C11	0.71788 (14)	0.0955 (3)	0.61991 (12)	0.0262
C12	0.78490 (14)	0.2197 (3)	0.60300 (12)	0.0281
C13	0.79037 (14)	0.1997 (3)	0.52371 (12)	0.0248
C14	0.71784 (13)	0.1706 (3)	0.47469 (12)	0.0222
C15	0.72213 (14)	0.1241 (3)	0.40190 (12)	0.0239
C16	0.79711 (14)	0.1170 (3)	0.37874 (12)	0.0253

O17	0.80777 (10)	0.0663 (3)	0.31019 (9)	0.0325
C18	0.73551 (16)	0.0173 (4)	0.25966 (13)	0.0349
C19	0.86970 (14)	0.1603 (3)	0.42686 (13)	0.0281
C20	0.86577 (14)	0.1978 (3)	0.49934 (13)	0.0274
O21	0.94030 (10)	0.1539 (3)	0.39806 (10)	0.0367
C22	1.01275 (16)	0.2318 (5)	0.44043 (17)	0.0464
C23	0.41482 (13)	0.3134 (3)	0.45321 (12)	0.0238
C24	0.34767 (14)	0.3242 (3)	0.48811 (13)	0.0253
C25	0.35269 (13)	0.2783 (3)	0.56222 (12)	0.0234
O26	0.28945 (10)	0.2928 (2)	0.60006 (9)	0.0291
C27	0.20877 (14)	0.3254 (4)	0.55912 (15)	0.0351
C28	0.45040 (17)	0.2749 (4)	0.72771 (14)	0.0370
O29	0.65009 (12)	0.5366 (3)	0.71489 (10)	0.0412
O30	0.43237 (12)	0.1483 (3)	0.24540 (11)	0.0438
O31	0.54038 (17)	0.2469 (4)	0.14665 (16)	0.0710
H71	0.6135	0.3586	0.3737	0.0404*
H73	0.5191	0.4098	0.3720	0.0403*
H72	0.5430	0.2128	0.3479	0.0402*
H101	0.5778	0.1210	0.6555	0.0283*
H112	0.7106	0.1071	0.6716	0.0333*
H111	0.7310	−0.0327	0.6101	0.0335*
H121	0.8380	0.1832	0.6328	0.0353*
H122	0.7715	0.3461	0.6134	0.0351*
H151	0.6731	0.0942	0.3687	0.0305*
H182	0.7541	−0.0131	0.2133	0.0548*
H181	0.7087	−0.0900	0.2788	0.0550*
H183	0.6976	0.1226	0.2531	0.0548*
H201	0.9151	0.2213	0.5333	0.0338*
H221	1.0564	0.2247	0.4102	0.0717*
H222	1.0279	0.1637	0.4866	0.0718*
H223	1.0001	0.3591	0.4502	0.0719*
H231	0.4096	0.3438	0.4015	0.0296*
H241	0.2957	0.3637	0.4610	0.0312*
H271	0.1698	0.3175	0.5938	0.0545*
H273	0.2076	0.4468	0.5371	0.0552*
H272	0.1961	0.2331	0.5205	0.0556*
H281	0.4526	0.2080	0.7734	0.0598*
H282	0.5041	0.3320	0.7262	0.0589*
H283	0.4055	0.3643	0.7226	0.0592*
H302	0.4050	0.0592	0.2259	0.0681*
H301	0.4075	0.2411	0.2577	0.0679*
H292	0.6946	0.5830	0.7044	0.0653*
H291	0.6529	0.4449	0.7419	0.0649*
H311	0.5076	0.2150	0.1756	0.1077*
H312	0.5488	0.3591	0.1432	0.1081*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Cl1	0.0356 (3)	0.0299 (3)	0.0403 (3)	−0.0023 (3)	0.0073 (2)	−0.0006 (3)
O2	0.0314 (9)	0.0331 (9)	0.0211 (8)	0.0005 (7)	0.0053 (6)	0.0028 (7)
C3	0.0255 (11)	0.0211 (11)	0.0224 (10)	−0.0002 (9)	0.0038 (8)	0.0000 (9)
C4	0.0215 (10)	0.0197 (10)	0.0218 (10)	0.0006 (8)	0.0026 (8)	−0.0011 (8)
C5	0.0247 (10)	0.0177 (10)	0.0228 (10)	−0.0005 (8)	0.0025 (8)	−0.0024 (8)
C6	0.0237 (10)	0.0183 (10)	0.0204 (10)	−0.0013 (8)	0.0023 (8)	−0.0028 (8)
C7	0.0269 (11)	0.0271 (11)	0.0217 (11)	0.0007 (9)	0.0024 (8)	0.0019 (9)
C8	0.0233 (10)	0.0204 (10)	0.0192 (10)	−0.0002 (8)	0.0017 (8)	−0.0017 (8)
N9	0.0225 (9)	0.0232 (9)	0.0203 (9)	0.0018 (7)	0.0003 (7)	−0.0006 (7)
C10	0.0245 (10)	0.0239 (11)	0.0203 (10)	0.0010 (9)	0.0027 (8)	−0.0005 (9)
C11	0.0223 (11)	0.0338 (13)	0.0208 (10)	0.0057 (9)	−0.0011 (8)	0.0023 (9)
C12	0.0243 (11)	0.0343 (13)	0.0235 (11)	0.0027 (10)	−0.0020 (9)	−0.0041 (10)
C13	0.0237 (10)	0.0247 (11)	0.0252 (11)	0.0012 (9)	0.0013 (9)	−0.0010 (9)
C14	0.0222 (10)	0.0212 (10)	0.0234 (10)	0.0015 (9)	0.0039 (8)	0.0000 (9)
C15	0.0238 (11)	0.0248 (11)	0.0225 (11)	−0.0020 (9)	0.0018 (8)	0.0001 (9)
C16	0.0241 (11)	0.0275 (12)	0.0244 (11)	0.0001 (9)	0.0045 (9)	0.0007 (9)
O17	0.0279 (9)	0.0475 (11)	0.0232 (8)	−0.0028 (8)	0.0080 (7)	−0.0028 (8)
C18	0.0333 (13)	0.0465 (16)	0.0254 (12)	−0.0065 (12)	0.0062 (10)	−0.0046 (11)
C19	0.0216 (10)	0.0309 (12)	0.0325 (12)	0.0009 (9)	0.0065 (9)	0.0039 (10)
C20	0.0224 (10)	0.0302 (12)	0.0282 (11)	−0.0008 (9)	−0.0001 (9)	0.0003 (10)
O21	0.0209 (8)	0.0564 (12)	0.0336 (9)	−0.0027 (8)	0.0071 (7)	0.0014 (9)
C22	0.0230 (12)	0.070 (2)	0.0466 (16)	−0.0100 (13)	0.0067 (11)	0.0004 (15)
C23	0.0231 (10)	0.0236 (11)	0.0239 (11)	0.0008 (9)	0.0012 (8)	−0.0005 (9)
C24	0.0221 (10)	0.0227 (11)	0.0298 (12)	0.0020 (9)	0.0006 (9)	−0.0012 (9)
C25	0.0220 (10)	0.0212 (11)	0.0271 (11)	−0.0007 (8)	0.0047 (8)	−0.0020 (9)
O26	0.0219 (8)	0.0354 (10)	0.0309 (9)	0.0039 (7)	0.0068 (7)	0.0008 (7)
C27	0.0204 (11)	0.0419 (15)	0.0426 (14)	0.0033 (11)	0.0045 (10)	0.0066 (12)
C28	0.0386 (14)	0.0475 (17)	0.0246 (12)	0.0037 (12)	0.0042 (10)	−0.0033 (11)
O29	0.0361 (10)	0.0475 (12)	0.0380 (10)	−0.0015 (9)	0.0003 (8)	0.0114 (9)
O30	0.0394 (11)	0.0425 (12)	0.0440 (11)	0.0000 (9)	−0.0086 (9)	−0.0041 (9)
O31	0.0698 (17)	0.0653 (17)	0.0867 (19)	−0.0068 (14)	0.0387 (15)	−0.0075 (15)

Geometric parameters (Å, º)

O2—C3	1.371 (3)	C16—C19	1.407 (3)
O2—C28	1.440 (3)	O17—C18	1.435 (3)
C3—C4	1.418 (3)	C18—H182	0.990
C3—C25	1.382 (3)	C18—H181	1.001
C4—C5	1.419 (3)	C18—H183	0.992
C4—C10	1.391 (3)	C19—C20	1.391 (3)
C5—C6	1.429 (3)	C19—O21	1.364 (3)

C5—C23	1.414 (3)	C20—H201	0.959
C6—C7	1.505 (3)	O21—C22	1.437 (3)
C6—C8	1.391 (3)	C22—H221	0.988
C7—H71	0.979	C22—H222	0.990
C7—H73	0.981	C22—H223	0.985
C7—H72	0.980	C23—C24	1.379 (3)
C8—N9	1.402 (3)	C23—H231	0.978
C8—C14	1.481 (3)	C24—C25	1.410 (3)
N9—C10	1.327 (3)	C24—H241	0.965
N9—C11	1.488 (3)	C25—O26	1.359 (3)
C10—H101	0.967	O26—C27	1.439 (3)
C11—C12	1.510 (3)	C27—H271	0.988
C11—H112	0.993	C27—H273	0.983
C11—H111	0.993	C27—H272	0.987
C12—C13	1.502 (3)	C28—H281	0.979
C12—H121	0.993	C28—H282	0.986
C12—H122	0.985	C28—H283	0.985
C13—C14	1.395 (3)	O29—H292	0.862
C13—C20	1.395 (3)	O29—H291	0.839
C14—C15	1.412 (3)	O30—H302	0.844
C15—C16	1.379 (3)	O30—H301	0.849
C15—H151	0.958	O31—H311	0.859
C16—O17	1.370 (3)	O31—H312	0.843
C3—O2—C28	116.49 (19)	C15—C16—O17	124.4 (2)
O2—C3—C4	118.24 (19)	C15—C16—C19	120.3 (2)
O2—C3—C25	121.7 (2)	O17—C16—C19	115.2 (2)
C4—C3—C25	119.9 (2)	C16—O17—C18	117.18 (18)
C3—C4—C5	121.3 (2)	O17—C18—H182	106.4
C3—C4—C10	119.9 (2)	O17—C18—H181	109.5
C5—C4—C10	118.7 (2)	H182—C18—H181	110.7
C4—C5—C6	119.2 (2)	O17—C18—H183	108.7
C4—C5—C23	117.3 (2)	H182—C18—H183	110.6
C6—C5—C23	123.5 (2)	H181—C18—H183	110.8
C5—C6—C7	118.57 (19)	C16—C19—C20	119.3 (2)
C5—C6—C8	119.7 (2)	C16—C19—O21	115.7 (2)
C7—C6—C8	121.7 (2)	C20—C19—O21	124.9 (2)
C6—C7—H71	110.8	C13—C20—C19	120.6 (2)
C6—C7—H73	109.1	C13—C20—H201	119.2
H71—C7—H73	109.3	C19—C20—H201	120.2
C6—C7—H72	110.0	C19—O21—C22	117.2 (2)
H71—C7—H72	109.3	O21—C22—H221	106.5
H73—C7—H72	108.3	O21—C22—H222	109.8
C6—C8—N9	118.13 (19)	H221—C22—H222	111.6
C6—C8—C14	126.2 (2)	O21—C22—H223	107.4
N9—C8—C14	115.58 (18)	H221—C22—H223	110.6

C8—N9—C10	123.05 (19)	H222—C22—H223	110.7
C8—N9—C11	118.96 (18)	C5—C23—C24	120.7 (2)
C10—N9—C11	118.00 (18)	C5—C23—H231	118.9
C4—C10—N9	121.1 (2)	C24—C23—H231	120.4
C4—C10—H101	121.2	C23—C24—C25	121.9 (2)
N9—C10—H101	117.7	C23—C24—H241	119.0
N9—C11—C12	109.09 (19)	C25—C24—H241	119.1
N9—C11—H112	107.5	C24—C25—C3	118.8 (2)
C12—C11—H112	111.3	C24—C25—O26	124.5 (2)
N9—C11—H111	109.5	C3—C25—O26	116.8 (2)
C12—C11—H111	110.4	C25—O26—C27	117.49 (19)
H112—C11—H111	109.0	O26—C27—H271	106.9
C11—C12—C13	108.26 (19)	O26—C27—H273	108.9
C11—C12—H121	109.1	H271—C27—H273	110.9
C13—C12—H121	109.2	O26—C27—H272	109.5
C11—C12—H122	109.6	H271—C27—H272	110.8
C13—C12—H122	109.9	H273—C27—H272	109.7
H121—C12—H122	110.7	O2—C28—H281	107.4
C12—C13—C14	118.1 (2)	O2—C28—H282	109.1
C12—C13—C20	121.7 (2)	H281—C28—H282	109.8
C14—C13—C20	120.0 (2)	O2—C28—H283	108.5
C8—C14—C13	119.4 (2)	H281—C28—H283	109.7
C8—C14—C15	121.27 (19)	H282—C28—H283	112.2
C13—C14—C15	119.3 (2)	H292—O29—H291	119.4
C14—C15—C16	120.2 (2)	H302—O30—H301	119.6
C14—C15—H151	120.2	H311—O31—H312	116.5
C16—C15—H151	119.6		

Hydrogen bond geometries (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C7—H72···O30	0.98	2.46	3.250 (3)	138
C15—H151···O2$^{\mathrm{i}}$	0.96	2.50	3.334 (3)	145
C23—H231···O29$^{\mathrm{ii}}$	0.98	2.39	3.324 (3)	159
C27—H271···O31$^{\mathrm{iii}}$	0.99	2.54	3.493 (3)	161
C28—H281···O21$^{\mathrm{iii}}$	0.98	2.58	3.249 (3)	126
C28—H283···O17$^{\mathrm{iii}}$	0.99	2.53	3.240 (3)	129
O30—H301···O29$^{\mathrm{ii}}$	0.85	2.00	2.852 (3)	179
O31—H311···O30	0.86	2.01	2.863 (3)	178
O31—H312···O21$^{\mathrm{iv}}$	0.84	2.32	3.145 (3)	165

Symmetry codes: (i) –*x*+1, –*y*, –*z*+1; (ii) –*x*+1, –*y*+1, –*z*+1; (iii) *x*–1/2, –*y*+1/2, *z*+1/2; (iv) –*x*+3/2, *y*+1/2, –*z*+1/2.