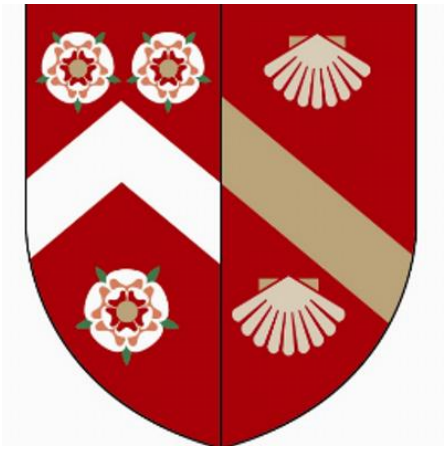
New Strategies for Isoquinoline Functionalisation with Applications in Total Synthesis

Timothy Charles Jenkins



A thesis submitted to the Board of the Faculty of Mathematical, Physical and Life Sciences in partial fulfilment of the requirement for the degree of

Doctor of Philosophy

at the

University of Oxford

Trinity term 2025

Supervisor: Prof. Timothy J. Donohoe

Declaration

The work described herein was carried out in the Chemistry Research Laboratory, University of Oxford, from October 2021 until June 2025. All of the work is entirely my own unless otherwise explicitly stated and has not been submitted previously for any other degree at this or any other university.

Timothy C. Jenkins

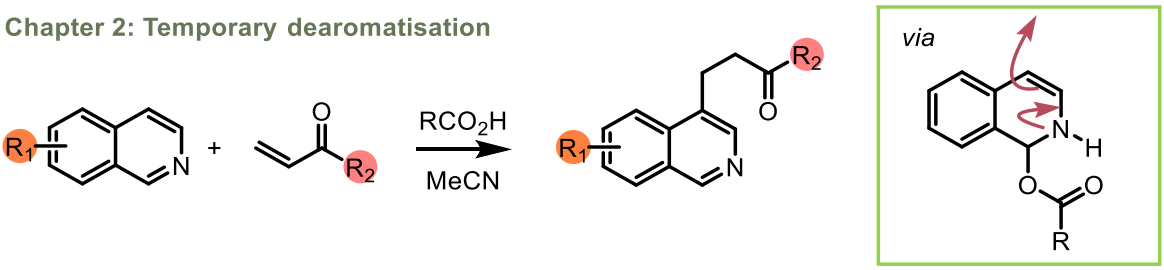
September 2025

Abstract

This thesis describes three techniques for the *β*-functionalisation of isoquinolines, with applications to the total synthesis of Crinane family natural products.

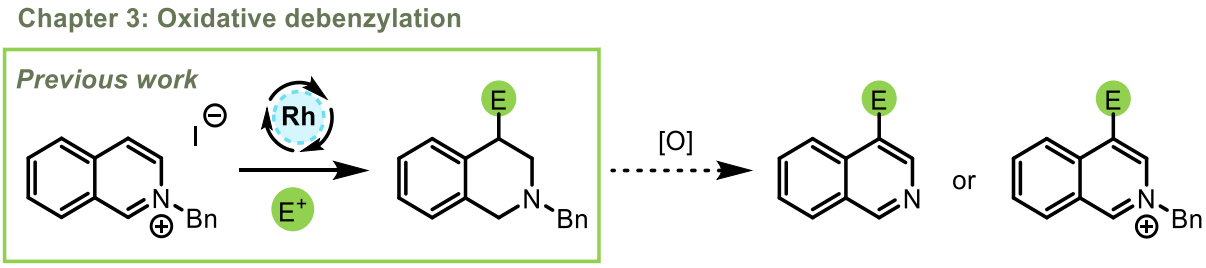
Chapter 1 is a general introduction to the chemistry of isoquinolines, covering background, synthesis and selected reactivity of this class of molecule.

Chapter 2 will detail a temporary dearomatisation strategy towards the direct *β*-functionalisation of isoquinolines, making use of nucleophilic activation by carboxylic acids. This reveals enamine functionality, which is then free to add into a conjugate acceptor. The scope of the reaction is explored, and a small scope of vinyl ketones is described.



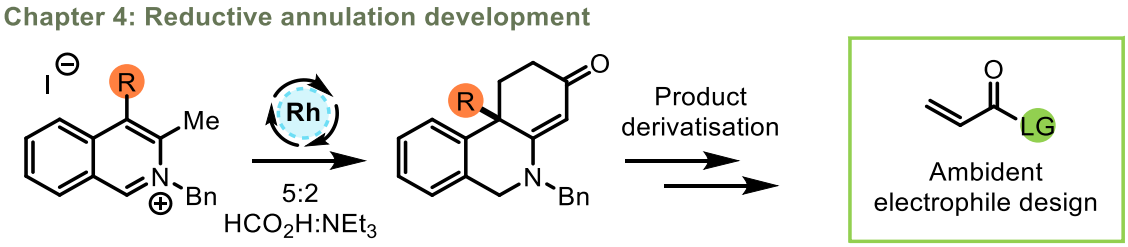
Scheme I: Temporary dearomatisation strategy towards *β*-functionalised isoquinolines.

Chapter 3 explores a different approach for achieving *β*-functionalised isoquinolines, building upon reductive functionalisation chemistry developed previously within the group to afford *β*-functionalised THIQs. An oxidative approach is used to synthesise isoquinolines from THIQs, which furnishes a two-step sequence to *β*-functionalised isoquinolines from isoquinolinium salts. A scope is described, including both simple mono-functionalised THIQs and more complex systems including a quinoline example. The mechanism is investigated, and results indicate that a debenzylative retro-ene reaction is part of the oxidative sequence.



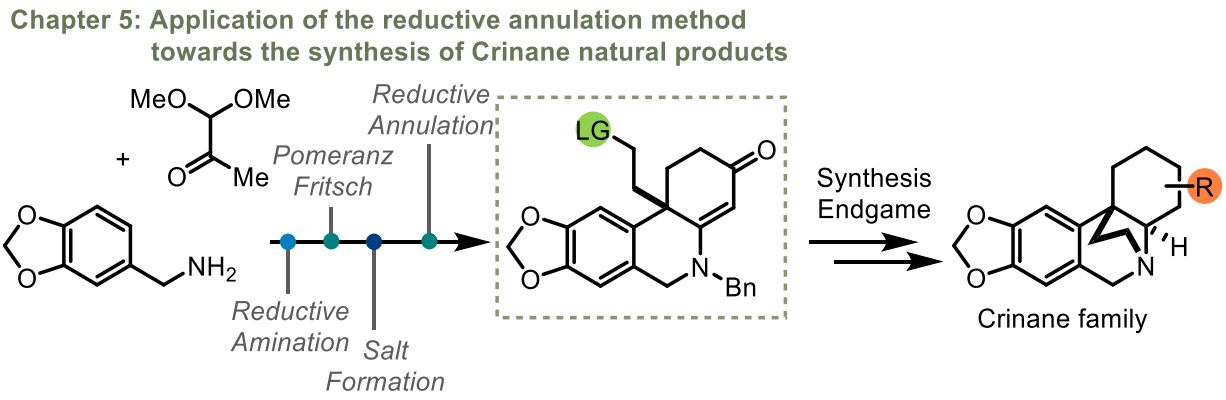
Scheme II: Oxidative debenzylation strategy to synthesise *β*-functionalised isoquinolines from THIQs.

Expanding upon existing group methods focussing on reductive functionalisation, Chapter 4 describes the development and optimisation of a reductive annulation reaction. The design of an ambident electrophile is investigated to achieve a one-pot annulation reaction. Downstream-derivatisation of the tricyclic vinylogous amide product is subsequently investigated.



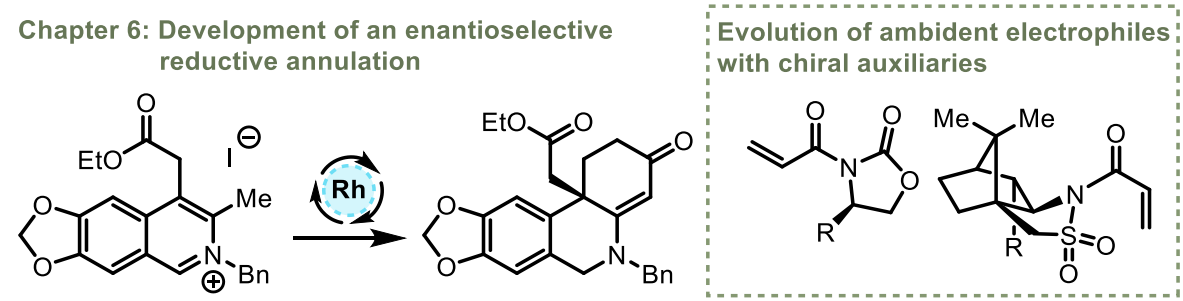
Scheme III: Development of a reductive annulation reaction to produce a tricyclic THIQ skeleton.

The methodology developed in Chapter 4 is then applied to an electron-rich isoquinoline system in Chapter 5, towards the synthesis of the Crinane family of natural products. The family's parent compound Crinane is synthesised in 8 steps, with optimisation of several steps. A brief investigation towards route diversification strategies is attempted in order to synthesise further members of the natural product family.



Scheme IV: Application of the reductive annulation reaction to the total synthesis of the Crinane family.

Finally, Chapter 6 will explore the evolution of the reductive annulation reaction developed in Chapter 4 to render it enantioselective. A chiral auxiliary approach is adopted and explored through the development of further ambident chiral electrophiles incorporating auxiliaries as leaving groups. The reaction is then optimised and the mechanism briefly investigated through an alternative substrate that allows intermediate isolation.



Scheme V: Evolution of the reductive annulation to be enantioselective, making use of chiral auxiliaries.

Acknowledgements

I would like to begin by thanking Prof Tim Donohoe, who let me continue working with him despite what can only be described as a ‘unique’ part II project. Tim’s suggestions, advice and support have been instrumental in shaping the course of the last four years and are always gratefully heeded.

I would also like to thank my industrial supervisor Dr Darren Poole, who welcomed me into his team at GSK and went out of his way to support me during a challenging time in my project. His efforts with my many, but ultimately fruitless, high-throughput screens were greatly appreciated, as was Gemma’s entirely altruistic help when Darren wasn’t around. Thanks, should also go to Blandine, Andrew, Callum, Julie and Heather from the MMC team and also Cyrille and the other PhD students for being so welcoming. I would also like to thank Chloe for being a wonderful friend and always having some great gossip over a hot chocolate.

I am extremely grateful to the X-ray and NMR teams for providing me with sanctuary from synthetic chemistry whenever I wanted it and teaching me lots about your fields. Many thanks to Amber, Kirsten, Aggy, Coral, James, Caitlin, Ed, Nick and of course Harold for being such good colleagues; I will severely miss Amber’s baking and the NMR team daily crossword. It brings me such joy to know that I have seen three NMR service managers and yet the ‘new’ submission portal is still not ready. I would also like to acknowledge the facilities team for all their tireless work keeping our workplace patched together, they have saved me on several occasions, mainly involving my vacuum pump.

A huge thank you to everyone who has had a hand in proofreading this thesis, this document would not be half as good as it is without your combined efforts and dedication to meticulously finding all the mistakes and omissions. Thank you to Andrew B, Andrew T, Teddy, Oskar, Tim Davidson, Jess, Lydia, Bruno, Disha, Nik, and Tansy, I couldn’t have done it without you.

The group I joined was a very different creature to the group I am leaving. I have had the pleasure of working with several different generations of TJDs, numbering some of the best synthetic chemists I have known. To Nik, thank you for all of your Reddit jokes, both the work appropriate ones and the others, and for propagating such a strong meme culture in the lab. Thanks to Bruno for his larger-than-life personality, amusing pronunciation of acronyms and for introducing me to humorous alliterative three-word summations. To Lydia, for teaching me how to run a lab with an iron fist, and for my wings, which I kept until the very end. To Jess, for introducing me to Foundry Sterling Medium and her amazing eye for writing mistakes and aesthetic choices, my schemes would be a lot drabber without your influence. I never thought I needed to know that much about horse trials, but I do now. To Francisco for being the best comedian in F8, I have never considered such work inappropriate 'would you rather?' questions, but now I can hardly stop myself. To Comrade Ford, a true man of the people. Thank you for all your late-night fumehood chats and selfless attempts to make the lab a better place. To George Blake and Dylan O'Reilly for being such excellent part II students, both of you were fantastic pupils, but also it was truly a privilege to get to know you both. I wish you both the best of luck in your respective next steps. To Zac and Mia for a year of hilarity in F8, I am so pleased to know you both. I am thankful to Zac, the poshest man I know, for insisting on a daily crossword and for putting on University Challenge in the lab. I am also thankful for Mia, who has introduced me to new octaves I didn't know my auditory range could reach to, and for new pronunciations of the word 'heard'. Thanks, should also go to Matheus and Louis for their excellent companionship this year, especially Matheus' optical spectroscopy and Louis' readiness to choose violence at any time. No thanks should go to Matheus' music tastes, I have never wanted to feel glorpy or gelatinous and the sentiment hasn't changed. Thank you to Akvile for teaching me that scaling up is always the answer and thank you to Medium Tim for insistence on Friday pub and for continuing my work without protest.

The largest thanks have to go to my two greatest lab friends and partners in crime, Teddy and Andrew. To Señor Teduardo for his impeccable Spanish heritage, his excellent anecdotes of sunny Seville and for all the laughs, advice, assistance, late night meetings of the Brains Trust and for introducing me to the analytical technique of 'vibes-based assessment'. To Andrew Tonkler, the posh man with many nicknames, your influence on this project is vast and I cannot thank you enough for all the ideas and advice you have come up with over the last 4 years. I am also supremely grateful for all of the evenings in the pub, at choir or around a dinner table where you are always excellent company, irrespective of whether you are the correct one-and-a-half drinks in. Any future work environment will never quite be as strong as when the two of you were around to laugh with me and at me in equal measure.

Thank you also to all of the other members of the Donohoe group past and present that have really helped define the last four years, to (in no particular order) Anna, Andrew B, Mo, Aron, Dani, Lirong, Lukas, Matt, Josh, Karan, Clement, Megan, Dana, Jane, Sam, Hannah, Jinfang, Ciaran, and Elliot.

Thank you also to my Oxford and Oxfordshire friends who have kept me sane over the last 4 years. To Disha for her helpful talks over a drink or a walk, to Emma for always making me smile and to Craig for his incredibly accommodating cooking. To Jack, Dillon, Cynthia, Maria, Adam, Jo, Kristina, Polina and Grace for all the excellent times we have had with choir over the last few years, your laughs, quotes, facial expressions and dinner-and-cards evening were treasured for all the joy they brought. Thanks, should also go to my steam-engine friends, Steven, Andrew, Leigh, Ed, Zep, Mark, Harry, Ali, Nick, Alex, Thomas, Laura and Fraser for some wonderful times on and off the footplate.

Finally, I would like to thank my parents, who have always supported me no matter how often I forgot to ring them. Their tireless efforts to help me move house, sort my finances remotely or just be there when I need someone to talk to with advice and kind words are so valued.

Table of Contents

Glossary of Abbreviations

δ	Chemical shift	DMDO	Dimethyldioxirane
Å	Angstrom	DMF	Dimethyl formamide
Ac	Acyl	DMS	Dimethyl sulfoxide
aq.	Aqueous	DMA	Dimethyl acetamide
Ar	Aryl	DMAD	Dimethyl acetylenedicarboxylate
BAr^F_4	Tetrakis(3,5-bis(triflurorомethyl)phenyl)borate	DMAP	Dimethylaminopyridine
BHT	Butylated hydroxytoluene	DMDO	Dimethyldioxirane
Bn	Benzyl	DMF	Dimethyl formamide
Boc	*Tert*-Butyloxycarbonyl	DMSO	Dimethyl sulfoxide
br.	Broad	DNBA	3,5-Dinitrobenzoic acid
Bu	Butyl	dppb	1,4-Bis(diphenylphosphino) butane
Bz	Benzoyl	d.r.	Diastereomeric ratio
°C	Degree(s) Celsius	DTBP	Di-*tert*-butyl peroxide
cat.	Catalytic	DMSO	Dimethyl sulfoxide
$CDCl_3$	Deuterated Chloroform	DNBA	3,5-Dinitrobenzoic acid
cm^{-1}	Wavenumbers	E	Generic electrophile
conc.	concentrated	e.e.	Enantiomeric excess
Cp*	Pentamethylcyclopentadiene	equiv.	Equivalent(s)
CSA	Camphor sulfonic acid	e.r.	Enantiomeric ratio
dba	Dibenzylidene acetone	ESI	Electrospray ionisation
DBB	4,4'-Di-*tert*-butylbiphenyl	Et	Ethyl
DBDMH	1,3-Dibromo-5,5-dimethylhydantoin	g	Gram(s)
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene	h	Hour(s)
DMA	Dimethyl acetamide	HOMO	Highest occupied molecular orbital
DMAD	Dimethyl acetylenedicarboxylate	HPLC	High Performance Liquid Chromatography
DMAP	Dimethylaminopyridine	HRMS	High Resolution Mass Spectrometry

Hz	Hertz	m.p.	Melting point
IR	Infra-red Spectroscopy	MS	Molecular sieves
IPA	Isopropyl alcohol	MVK	Methyl vinyl ketone
^{i}Pr	Isopropyl	m/z	Mass to charge ratio
J	Coupling constant	^{n}Bu	*n*-Butyl
k	Reaction rate constant	NFSI	*N*-Fluoro benzenesulfonamide
K	Kelvin	NIS	*N*-Iodo succinimide
L	Litre	NMO	*N*-Methyl morpholine-*N*-oxide
LED	Light Emitting Diode	NMR	Nuclear Magnetic Resonance
Oxone	The triple salt $2KHSO_5$ $KHSO_4$ K_2SO_4	NOESY	Nuclear Overhauser effect spectroscopy
LG	Leaving group	Nu	Generic Nucleophile
LRMS	Low Resolution Mass Spectrometry	[O]	Generic oxidant
LUMO	Lowest unoccupied molecular orbital	PC	Photo Catalyst
M	Molar (mol dm^{-3})	Ph	Phenyl
*m*CPBA	*meta*-Chloro peroxybenzoic acid	Ph*	Pentamethyl phenyl
Me	Methyl	Pin	Pinacol
mg	Milligram(s)	ppm	Parts per million
MHz	MegaHertz	PTFE	Polytetrafluroethylene
min	Minute(s)	PyBroP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
mL	Millilitre(s)	R	Generic aliphatic or aromatic group
mm	Millimetre(s)	rac	Racemic mixture
mmol	Millimole(s)	r.t.	Room temperature
mol	Mole(s)	s	Seconds
mol%	Molar percentage	sat.	Saturated
MOM	Methoxymethylene	S_EAr	Electrophilic aromatic substitution
MOF	Metal Organic Framework		
MP	Methylpyruvate		

Selectfluor	1-(Chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diium ditetrafluoroborate	Ts	Tosyl
SFC	Supercritical Fluid Chromatography	UV	Ultra Violet
S_N2	Nucleophilic substitution bimolecular	μL	Microlitre(s)
T	Temperature or Tesla	μm	Micrometre(s)
TBCA	Tribromoisocyanuric acid	μmol	Micromole(s)
TBA	Tetrabutylammonium	Vaska's complex	$IrCl(CO)(PPh_3)_2$
TBE	*Tert*-Butyl ethylene	wt%	Weight percentage
^{t}Bu	*t*-Butyl	X	Generic halogen or halide
TCCA	Trichloroisocyanuric acid	XPhos	Dicyclohexyl[2',4',6'-tris(propan-2-yl)[1,1'-biphenyl]-2-yl]phosphane
TEMPO	2,2,6,6-Tetramethyl piperindine-1-oxyl free radical	ZIF	Zeolitic Imidazolate Framework
Tf	Trifluoromethane sulfonyl		
TFA	Trifluoroacetic acid		
TFAA	Trifluoroacetic anhydride		
THF	Tetrahydrofuran		
THIQ	Tetrahydroisoquinoline		
THQ	Tetrahydroquinoline		
TLC	Thin layer chromatography		
TMAO	Tetramethyl amine-*N*-oxide		
TMS	Trimethylsilyl		
TMDS	Tetramethyldisiloxane		
TMEDA	Tetramethylethylenediamine		
TMP	2,2,6,6-Tetramethyl piperidine		
Tol	Tolyl – *para*-methylphenyl		

Chapter 1 – Introduction to isoquinoline chemistry

1.1 Isoquinoline

This thesis contains varied content, themed around the reactivity of isoquinoline and its derivatives. Each chapter is introduced throughout, detailing the specific fields referenced where pertinent. Here follows a short general introduction to the core motif and its reactivity.

Isoquinoline (**1**) is a benzo-fused 6,6-heterocyclic molecule, one of the single nitrogen analogues of naphthalene (Figure 1.1). Its behaviour and reactivity are distinct from its sister *N*-heterocycle, quinoline (**2**), due to the methine unit separating the nitrogen atom from the rest of the aromatic system. This has consequences in the molecule's reactivity, with the sites of highest electron density residing at C4 and C5 of the isoquinoline molecule. Quinoline shows similar preference for reactivity at C5 on the benzenoid ring, but also shows some reactivity at C8, unlike isoquinoline.

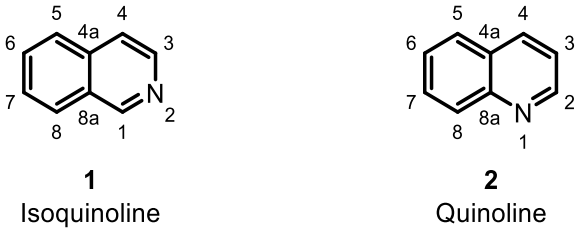
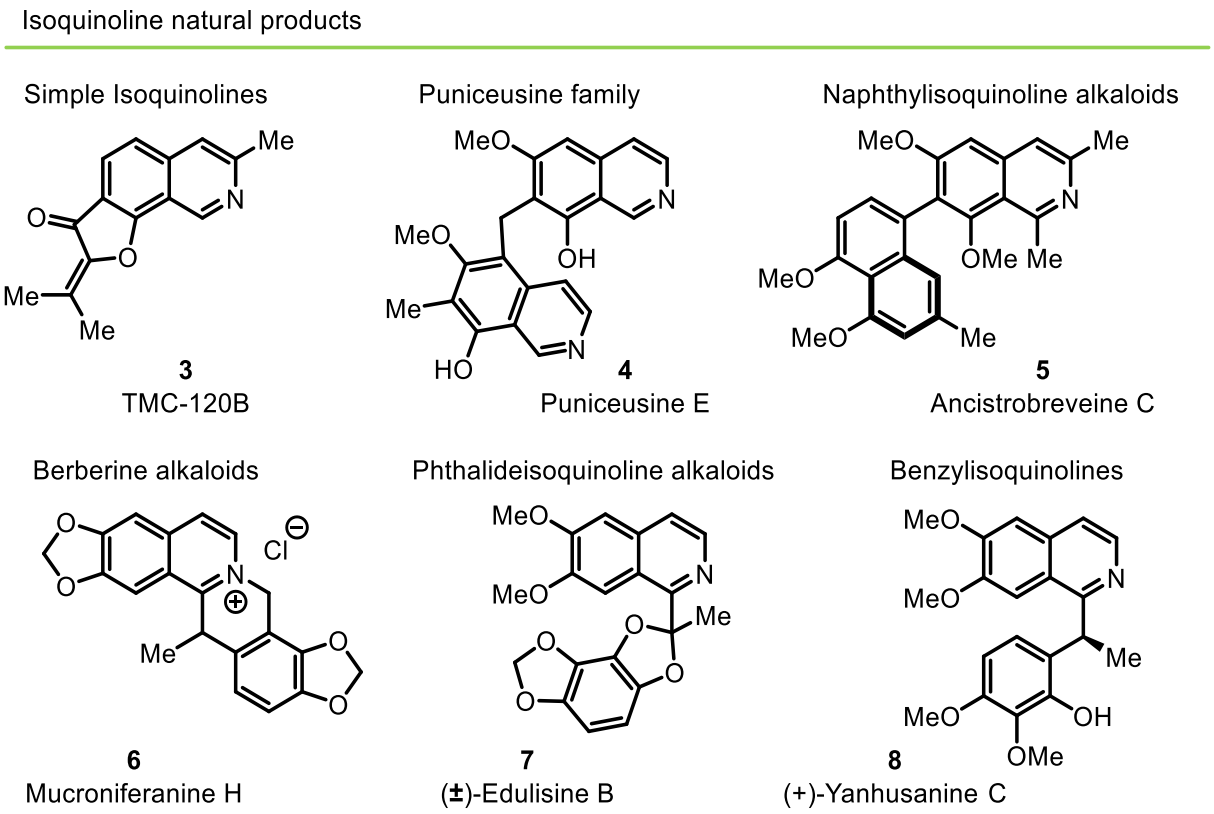


Figure 1.1: Isoquinoline **1** and quinoline **2**, the two simplest benzo-fused *N*-heterocycles.

Isoquinoline was first isolated in 1885 from coal tar, a waste product of the gas extraction industry.[1] Fractional recrystallisation was exploited to separate isoquinoline from quinoline as the acid sulfate salt, as isoquinoline is more basic, with a pKa_H (H_2O) of 5.46 compared with 4.85 for quinoline.[2]

The isoquinoline moiety is present in a wide variety of naturally occurring compounds, ranging from simple substituted isoquinolines to more complex natural product scaffolds (Scheme 1.1).[3] Several classes of natural products are entirely or almost entirely composed of

isoquinoline-containing compounds, such as the Puniceusine and Berberine families. Other classes contain some members at the isoquinoline oxidation state but also partly reduced or dearomatised compounds, at the tetrahydroisoquinoline (THIQ) oxidation state, such as the papaverine family and the phthalideisoquinoline alkaloids.

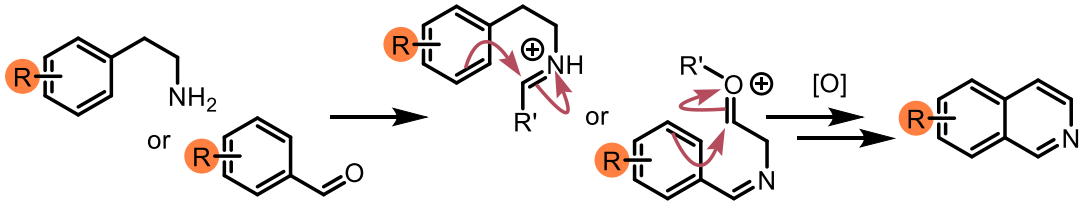


Scheme 1.1: A selective overview of isoquinoline natural product families.

Apart from these closely related compounds, there are other classes of natural products that are derived from isoquinoline, or incorporate the polycyclic ring structure derived from a 6,6-*N*-heterocyclic framework, such as the morphine, pavine, aporphine and protopine families. In total, isoquinoline or isoquinoline derived natural products number around 3000 compounds, with more discovered each year.[4]

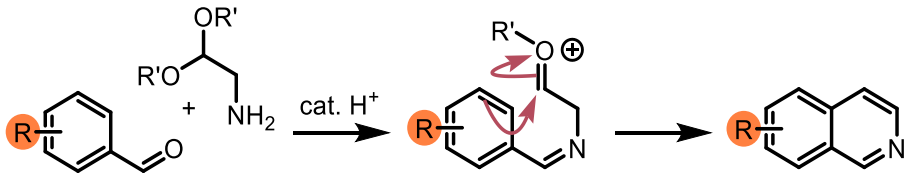
1.2 Isoquinoline synthesis

Isoquinoline has been synthesised in a wide variety of ways, traditionally by performing S_EAr from a benzenoid ring onto an electrophile (Scheme 1.2). This is usually generated *in situ* through condensation to create an iminium or an oxonium which is then intercepted in the S_EAr chemistry.



Scheme 1.2: General strategies for isoquinoline synthesis.

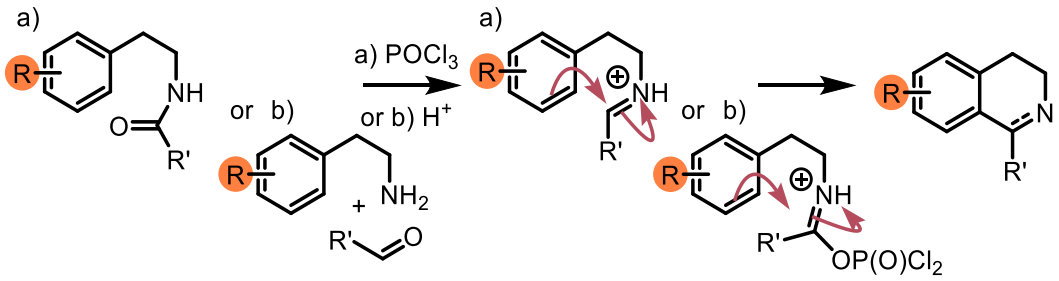
The Pomeranz-Fritsch reaction is a good example of this principle, with S_EAr intercepting an oxonium intermediate created from an acid catalysed collapse of an acetal (Scheme 1.3).[5] The Pomeranz-Fritsch reaction is one of the few methods of synthesising isoquinolines without substitution on the heterocyclic ring. The strategy makes use of the existing carbonyl oxidation state in the starting material; the imine formed through condensation of the two reactants together is retained in the product, with elimination of an alcohol responsible for the remaining olefin.



Scheme 1.3: Pomeranz-Fritsch reaction to furnish C1, C3 and C4-unsubstituted isoquinolines.

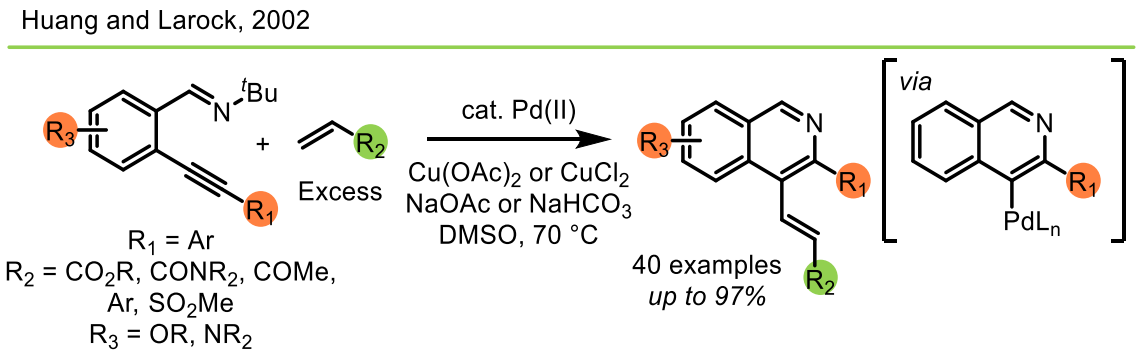
Taking a more controlled and step-wise approach, both the Bischler-Napieralski and the Pictet-Spengler processes generate a THIQ or DHIQ intermediate which can then be oxidised to an isoquinoline (Scheme 1.4).[6-7] Both processes generate C1 substitution through subtly different

techniques, although they share the same strategy of generating a C1-N iminium which is attacked through a S_EAr mechanism to give a THIQ or DHIQ intermediate. The intermediate is then often oxidised to form the isoquinoline, commonly using a stoichiometric oxidant such as DDQ. The Pictet-Spengler reaction produces a THIQ product due to the use of the aldehyde oxidation state, as opposed to the amide equivalent generated by the Bischler-Napieralski. Whilst many methods have been developed for the oxidation of THIQs to isoquinolines (*vide infra*), this process is most commonly stopped at the THIQ oxidation state and the product isolated.



Scheme 1.4: a) Bischler-Napieralski or b) Pictet-Spengler techniques for the synthesis of DHIQs from iminium intermediates generated *in situ*.

Using more modern techniques, isoquinolines have been synthesised using palladium cross-coupling methods, making use of benzylic amine nucleophiles with alkyne and alkene coupling partners to achieve cyclisation *via* a Heck-type process. Huang and Larock made use of this strategy in 2002, intramolecularly coupling an activated imine to an alkyne to generate an isoquinoline *in situ* making use of palladium-π co-ordination (Scheme 1.5).[8] The aryl-palladacycle produced participates in an intermolecular Heck coupling with a range of olefins to give C3-aryl C4-alkenyl isoquinolines. The method was shown to be applicable to a wide range of isoquinoline and alkene substituents, with products afforded in good yields of up to 97%.

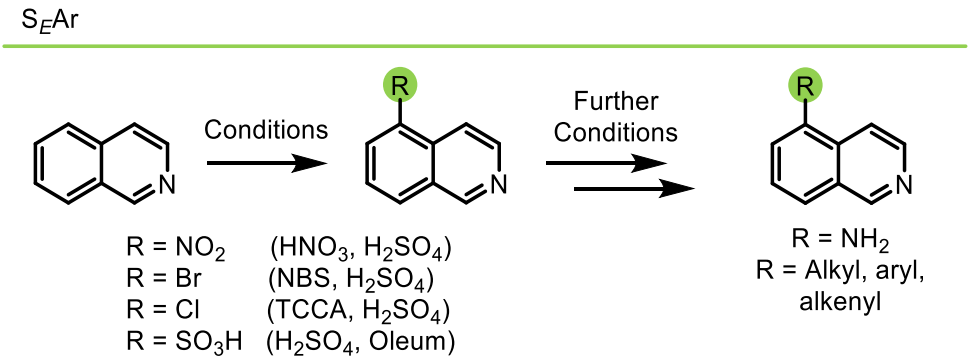


Scheme 1.5: Palladium catalysed Heck method for isoquinoline synthesis.

1.3 Isoquinoline reactivity

1.3.1 S_EAr at C5

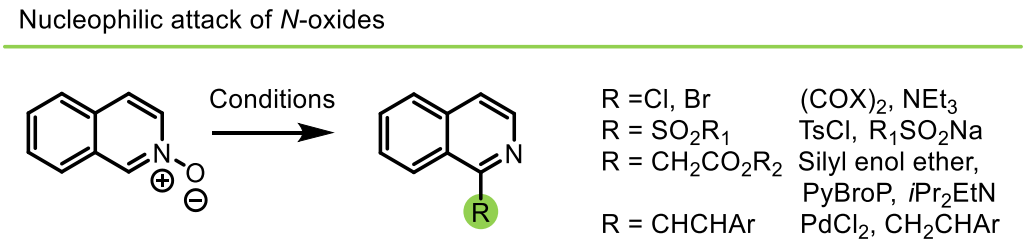
Isoquinoline can undergo direct electrophilic aromatic substitution like its benzenoid analogues, showing regiochemical preference for the C5-position, due to inductive withdrawing effects of the more electronegative nitrogen in the heterocyclic ring (Scheme 1.6).[9-12] This technique can be used to give a range of functionality by changing the reagents applied, with nitration, sulfonation and halogenation achievable within one synthetic step. Further functionality such as amines or alkyl groups can then be accessed by modifying these common substituents using techniques such as reduction and transition metal-catalysed cross coupling respectively.



Scheme 1.6: Standard conditions for S_EAr functionalisation of isoquinoline.

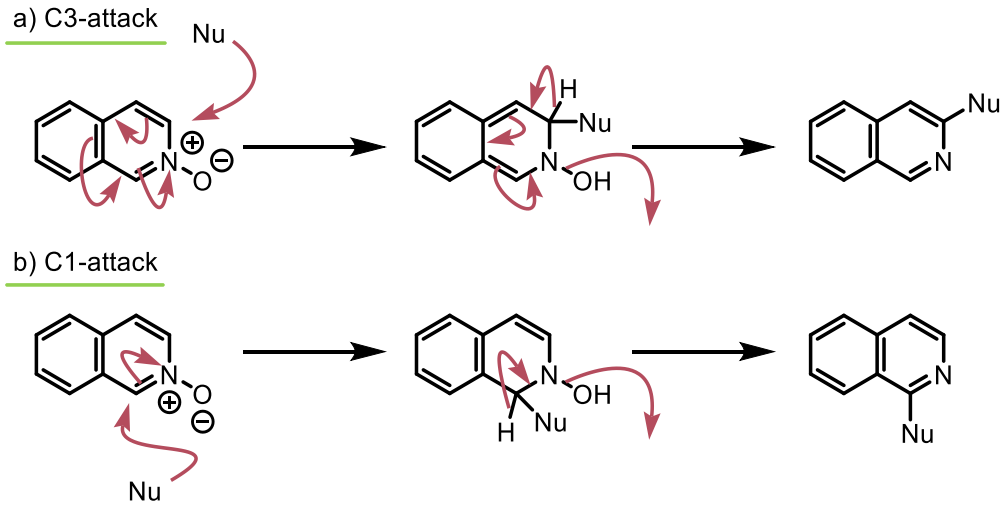
1.3.2 C1-substituents *via N*-oxides

The formation of isoquinoline-*N*-oxides can be used to access C1-substituents; activation of the heterocycle nitrogen enhances the electrophilicity of C1 which can be attacked by a variety of nucleophiles (Scheme 1.7).[13-15] Elimination of the activating group to form water rearomatizes the molecule, affording a C1-functionalised isoquinoline. Through this technique C1-halogenation, sulfonylated and alkylated isoquinolines can be synthesised in good yields and with a reasonable range of functionality. Utilising a slightly different technique, Liu and co-workers made use of palladium catalysis to access C1-alkenyl isoquinolines, taking advantage of the increased acidity of the C1-proton in isoquinoline-*N*-oxides as compared to their isoquinoline analogues.[16] The *N*-oxide also acts as an *in-situ* oxidant, reforming the active palladium species.



Scheme 1.7: Standard conditions for the formation of C1-substituted isoquinolines from isoquinoline-*N*-oxides.

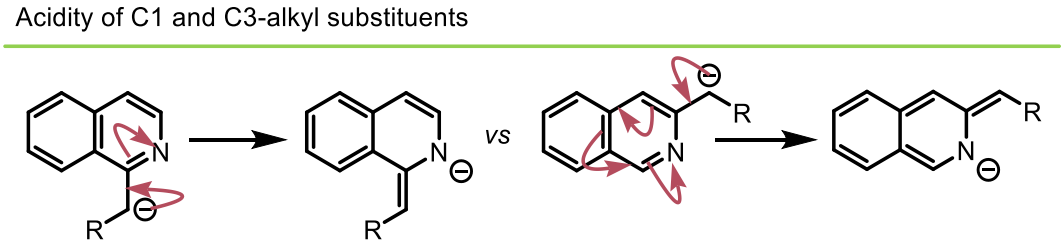
The reactions detailed above are regioselective for C1-substitution due to the electronics of isoquinoline. This can be rationalised by noting that attack at the alternative C3-position would dearomatise the entire π-system (Scheme 1.8). This has a much higher energy barrier and therefore it is not the major reaction pathway.



Scheme 1.8: Nucleophilic attack at a) C3 and b) C1 positions of isoquinoline with the associated electronic consequences.

1.3.3 Relative acidity of C1 and C3-alkyl substituents

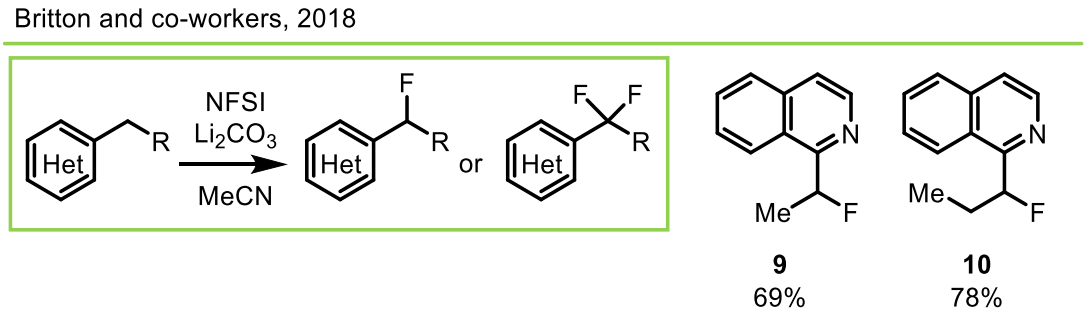
C1 and C3-alkyl substituents are more acidic than at other positions on the isoquinoline scaffold due to the inductive and mesomeric withdrawing effects of the heterocyclic nitrogen (Scheme 1.9). Delocalisation into the heterocyclic ring of isoquinoline is possible from a C1-α-anion and does not lead to the total loss of aromaticity. C3-substituents do not share this advantage, with delocalisation into the isoquinoline π-system leading to complete aromaticity loss.



Scheme 1.9: Increased acidity of C1 and C3-substituents due to charge delocalisation into the heterocycle.

This effect can be exploited to achieve late-stage functionalisation on C1-isoquinoline alkyl groups. Britton and co-workers have developed mono and di-fluorination protocols for alkyl substituents of *N*-heterocycles using NFSI as the fluorinating reagent (Scheme 1.10).[17] The

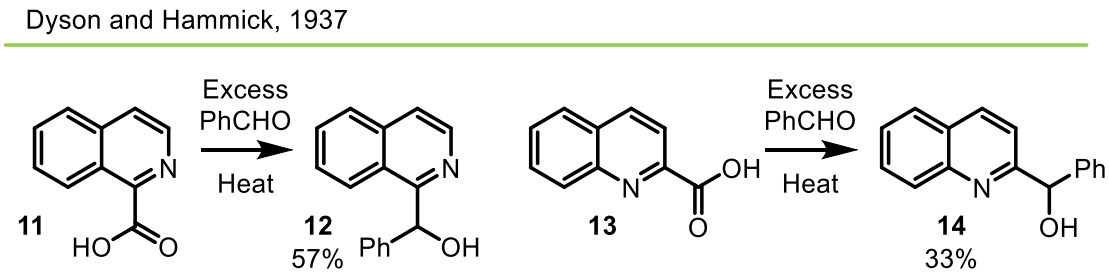
reaction used Li_2CO_3 as a base to deprotonate the alkyl substituent. The anion is then quenched by the fluorinating agent. When applied to two C1-alkyl isoquinolines, reasonable yields of products **9** and **10** were afforded (69% and 78% respectively).



Scheme 1.10: Mono and di-fluorination protocol for heteroaromatic alkyl substituents making use of acidic alkyl positions.

1.3.4 C1-Decarboxylation

Quinaldinic acid and isoquinaldinic acids can be heated in the presence of aldehyde electrophiles to achieve a decarboxylation-functionalisation sequence (Scheme 1.11).[18] The inductive effects of an α-nitrogen stabilise the anion sufficiently for decarboxylation to be favourable. The excess electrophile is then attacked by the anion generated from decarboxylation to give an alternatively C1-substituted isoquinoline. Although transient, the presence of a C1-anion (as part of a zwitterionic molecular form) is a testament to the inductive power of the heterocyclic nitrogen in supporting and stabilising charge within the aromatic system.



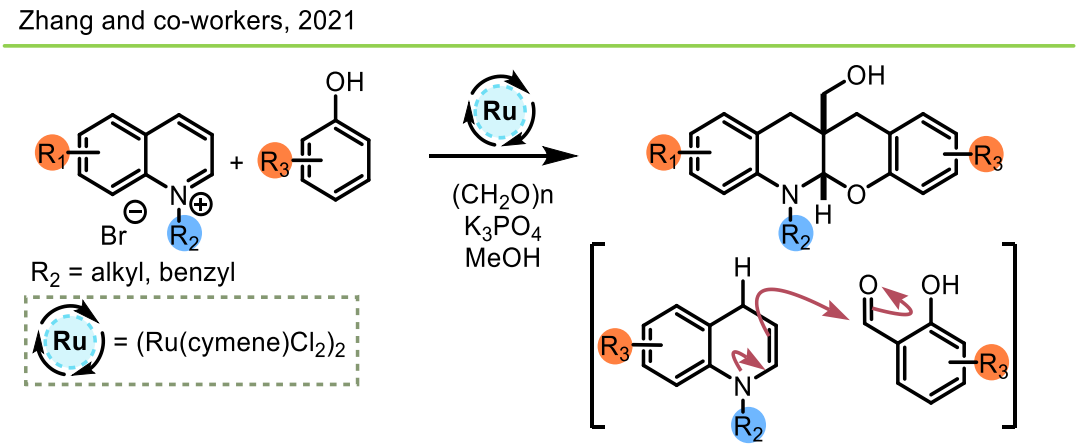
Scheme 1.11: C1-Decarboxylation and functionalisation sequence of quinaldinic and isoquinaldinic acids.

1.3.5 Reductive functionalisation of *N*-heterocycles including isoquinolines

A growing field in more recent years has been the reductive functionalisation of *N*-heterocycles. Reduction of *N*-heterocycles has been achieved many times over the last century by a multitude of techniques, mainly involving transition metal-catalysed hydrogenation. Harnessing the intermediates of this transformation to render a functionalisation as part of the process is less common, but more examples are emerging in the last decade.[19]

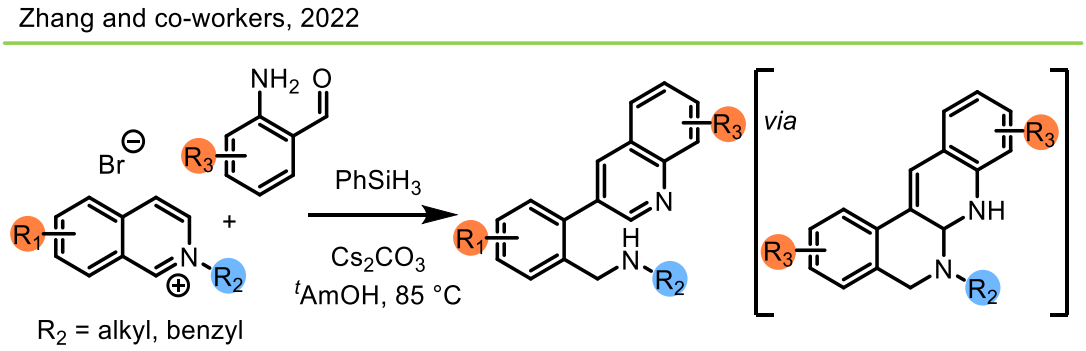
Partial reduction of a *N*-heterocycle can reveal an enamine, which can be used as a nucleophile capable of conjugate addition to an electrophile. The iminium formed by this addition is most commonly reduced further, to afford a reduced and functionalised *N*-heterocycle. The simplest form of dearomatising nucleophile, a hydride, can be metal catalysed or metal-free. Both the Zhang and Donohoe groups have published extensively in this area, exploring both metal catalysed and metal-free methods to achieve reductive functionalisations with a range of nucleophiles and electrophiles.

The Zhang group have taken a basic metal-catalysed approach to quinoline reductive functionalisation, using formaldehyde as the terminal reductant, but incorporating other molecular fragments by performing an intramolecular trapping cascade (Scheme 1.12).[20] Their initial work uses phenols which form salicylaldehydes *in situ*. These then act as electrophiles for the *in situ* generated enamine, which creates an iminium that can be attacked by the pendant phenol to create a tetra-cyclic product. The reaction is therefore formally a reductive annulation with two side chains added and a polycyclic structure created. Once again, activation of the *N*-heterocycle is necessary for the reaction and the products afforded are therefore protected partially saturated *N*-heterocycles.



Scheme 1.12: Intramolecular trapping cascade using formaldehyde as both a reductant and part of the electrophile.

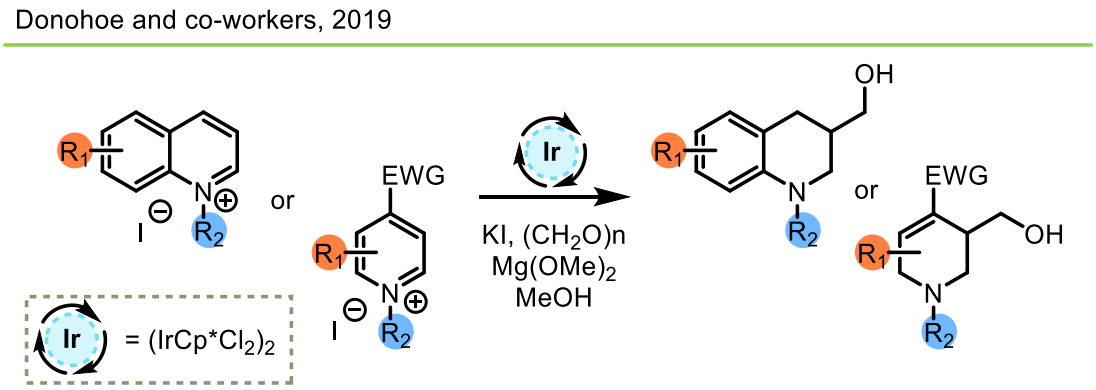
Developing the reactivity further to not require any metal catalyst, the Zhang group used phenyl silane as a reductant to functionalise activated isoquinolinium salts directly (Scheme 1.13).[21] The movement away from formaldehyde has allowed for a greater range of electrophiles to be used, in this case an aniline aldehyde. The reaction generated a quinoline through formation of an aminal after trapping of the aldehyde by the *in situ* generated enamine.



Scheme 1.13: Development of a metal-free reductive annulation using aniline substrates to create a quinoline core.

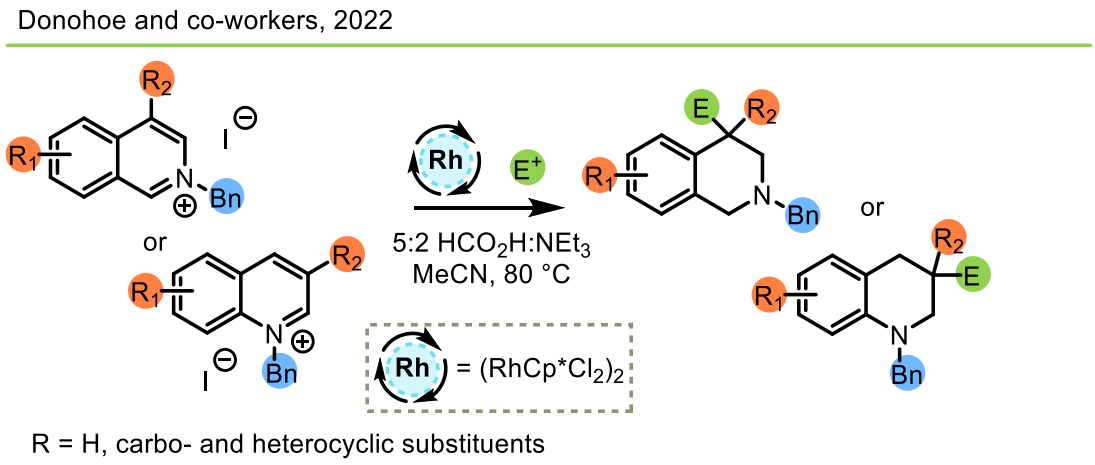
Donohoe and co-workers took a different approach, and reported a metal-catalysed transformation in 2019 that used formaldehyde as both the reductant and electrophile (Scheme 1.14).[22] Although the *N*-heterocycle scope was wide, the use of the highly electrophilic formaldehyde as the terminal reductant limited the transformation to

hydroxymethylation of the *N*-heterocycles. The reaction was iridium catalysed, with the iridium hydride generated *in situ* by oxidation of the formaldehyde to the methyl ester. Activation of the *N*-heterocycles was required, resulting in salt formation and deprotection steps to achieve the transformation between aromatic *N*-heterocycle to the *N*-unsubstituted partially reduced heterocycle.



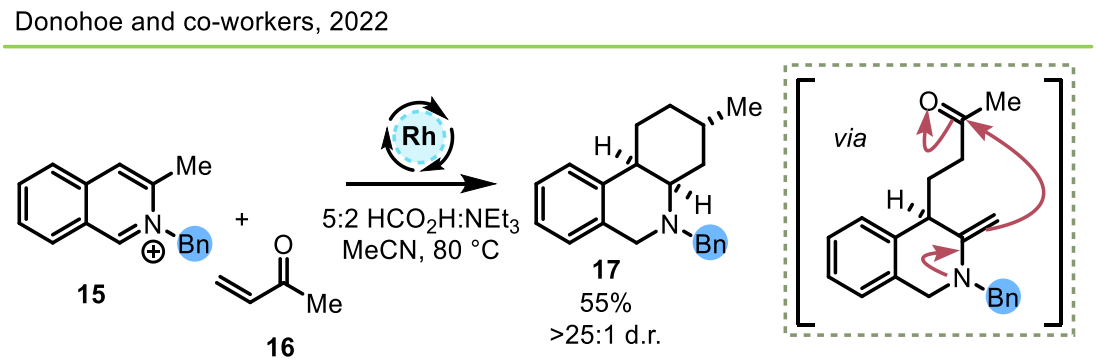
Scheme 1.14: Reduction functionalisation of *N*-heterocycles using formaldehyde as both the electrophile and the reductant.

This transformation was then expanded further by Donohoe and co-workers to a wider array of electrophiles and *N*-heterocycles by way of an acidic terminal reductant (Scheme 1.15).[23] Switching to rhodium catalysis and an azeotrope of formic acid and triethylamine as an acidic (and non-electrophilic) reductant, the transformation allows a multitude of electrophiles to be used to generate mono and di-*β*-functionalised *N*-heterocycles, including isoquinolines. The authors show that the transformation can occur *via* a metal-free pathway, but the reaction rate is increased by the presence of a metal-hydride species.



Scheme 1.15: Expanding the scope of reductive functionalisation using an acidic terminal reductant.

The authors further demonstrated that, in the case of 3-Me isoquinolinium salts, use of an ambident electrophile can lead to a reductive annulation reaction (Scheme 1.16).[23] The mechanism proceeds *via* an external enamine, generated as part of the possible enamine forming tautomerisation steps of the mechanism. Use of an ambident electrophile, such as MVK **16**, allows for 1,2-direct carbonyl attack following the initial conjugate addition into the electrophile. The products observed result from total reduction of the heterocyclic ring, where any iminium formed as part of the cyclisation process is reduced. As before, the authors show that the reaction functions under metal-catalysed or metal-free conditions. For further mechanistic details, see Chapter 4, Scheme 4.4.



Scheme 1.16: Reductive annulation *via* an external enamine in the case of 3-Me isoquinolinium salts.

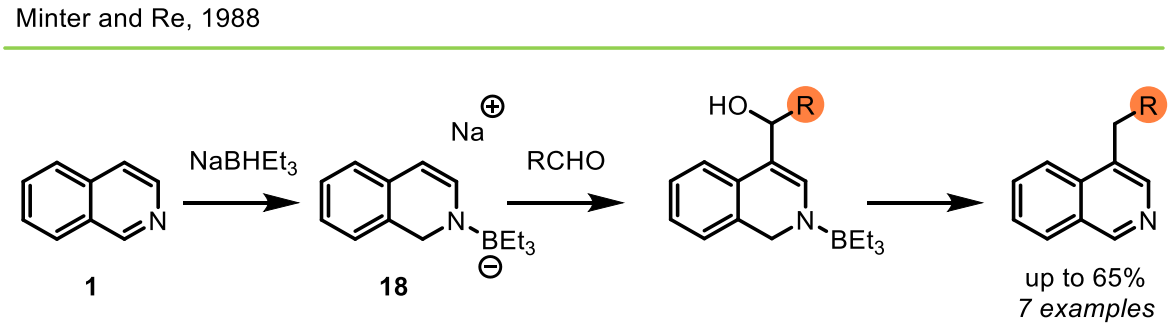
Chapter 2 – Acid promoted C4 functionalisation of isoquinolines

2.1 Temporary dearomatisation techniques to functionalise *N*-heterocycles

2.1.1 Isoquinoline temporary dearomatisation

Temporary dearomatisation is a mild technique to facilitate direct *β*-functionalisation of heterocyclic molecules. By dearomatising a heterocycle *in situ*, the activation energy required for an aromatic molecule to attack an electrophile is reduced, allowing a previously impossible functionalisation to occur directly. The group responsible for dearomatising the heterocycle can then be removed, revealing the masked aromaticity in a one-pot process.

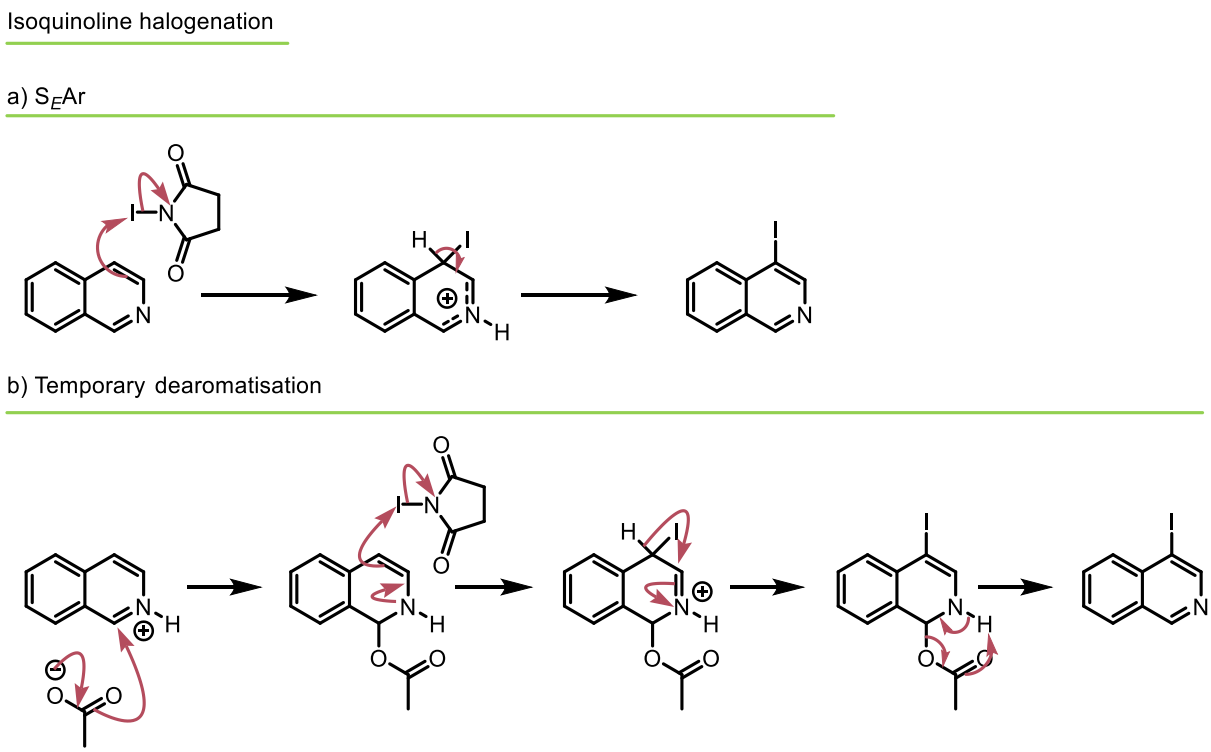
The field of temporary dearomatisation is small, but a number of reactions have been developed to achieve this feat. Minter and Re, for example, used sodium triethyl borohydride to temporarily dearomatise isoquinoline, activating on nitrogen and reducing at C1 simultaneously (Scheme 2.1).[24] The enamine produced, **18**, whilst not stable to isolation, could be functionalised by the addition of aldehydes. After elimination of water and some proton transfers followed by loss of triethyl borane, the *β*-functionalised isoquinoline was revealed; it is worth noting that a final elimination of water is required to achieve the desired aromatic oxidation state, any other electrophile would stop the reaction at the dihydroisoquinoline state.



Scheme 2.1: Temporary dearomatisation of isoquinolines using $NaBHEt_3$.

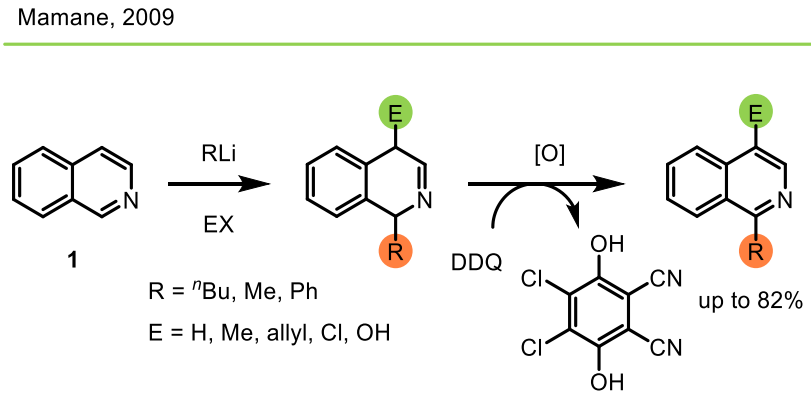
Minter and Re go on to describe a small scope composed of aliphatic and aromatic aldehydes, affording a reasonably mild method to functionalise isoquinoline at C4 with a few carbon groups. The dearomatising reagent, however, is not regenerated as part of the reaction, producing stoichiometric triethyl borane.

Traditionally, the *β*-functionalisation of *N*-heterocycles could be achieved by halogenating the heterocycle using either acetic acid or peroxide-based conditions, then cross coupling the halogenated heterocycle with a carbon fragment using palladium chemistry. The halogenation itself, however, could be considered as a temporary dearomatisation reaction, due to the proposed mechanism (Scheme 2.2).[25] Taking the acetic acid-based conditions as an example, S_EAr is a possible, albeit highly unlikely mechanism, with the heterocycle attacking an electrophile to generate a Wheland intermediate, which will then collapse with loss of a proton to reveal the substituted heterocycle (Scheme 2.2a). A second possibility is that the solvent, acetic acid, activates the heterocycle through protonation, then adds in to the *α*-position to temporarily dearomatise the heterocyclic ring (Scheme 2.2b). The revealed enamine then attacks the electrophile, and then after tautomerisation the acetic acid can eliminate, either in a step-wise or concerted manner, to reveal the substituted heterocycle.



Scheme 2.2: Possible mechanisms for acid promoted *N*-heterocycle halogenation, including a) S_EAr and b) Temporary dearomatisation.

Mamane and co-workers attempted a related strategy with alkyl lithium reagents in 2009, whereby attack at C1 reveals a lithiated enamine as before, which can then attack a halogen electrophile (Scheme 2.3).[26] The product of the first step was an imine, which the authors then oxidised using DDQ to afford the isoquinoline product.

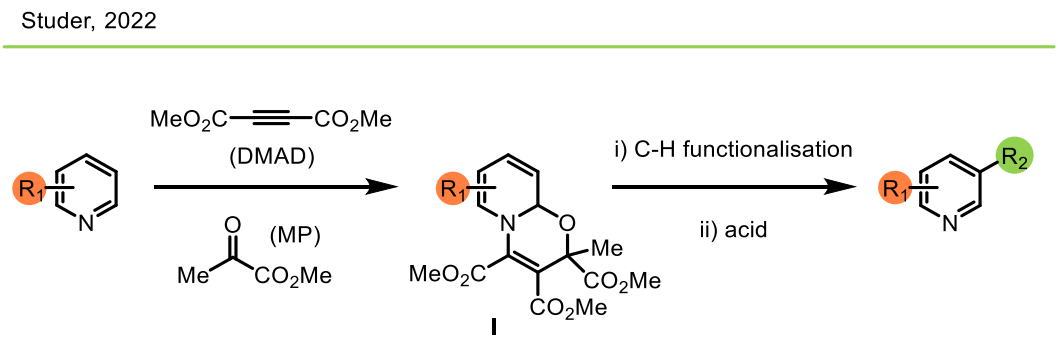


Scheme 2.3: A two-stage dearomatisation strategy towards C4 functionalisation of isoquinolines.

A small scope of the method was described, allowing access to a variety of C1-C4 difunctionalised isoquinolines. The harsh nature of the alkyl lithium nucleophilic reagent, however, makes the transformation unsuitable for late-stage functionalisation, limiting the generality of the reaction. The requirement of a second oxidation step also renders the reaction not truly a temporary dearomatisation, as aromaticity is not broken and returned in the same process.

2.1.2 Pyridine temporary dearomatisation

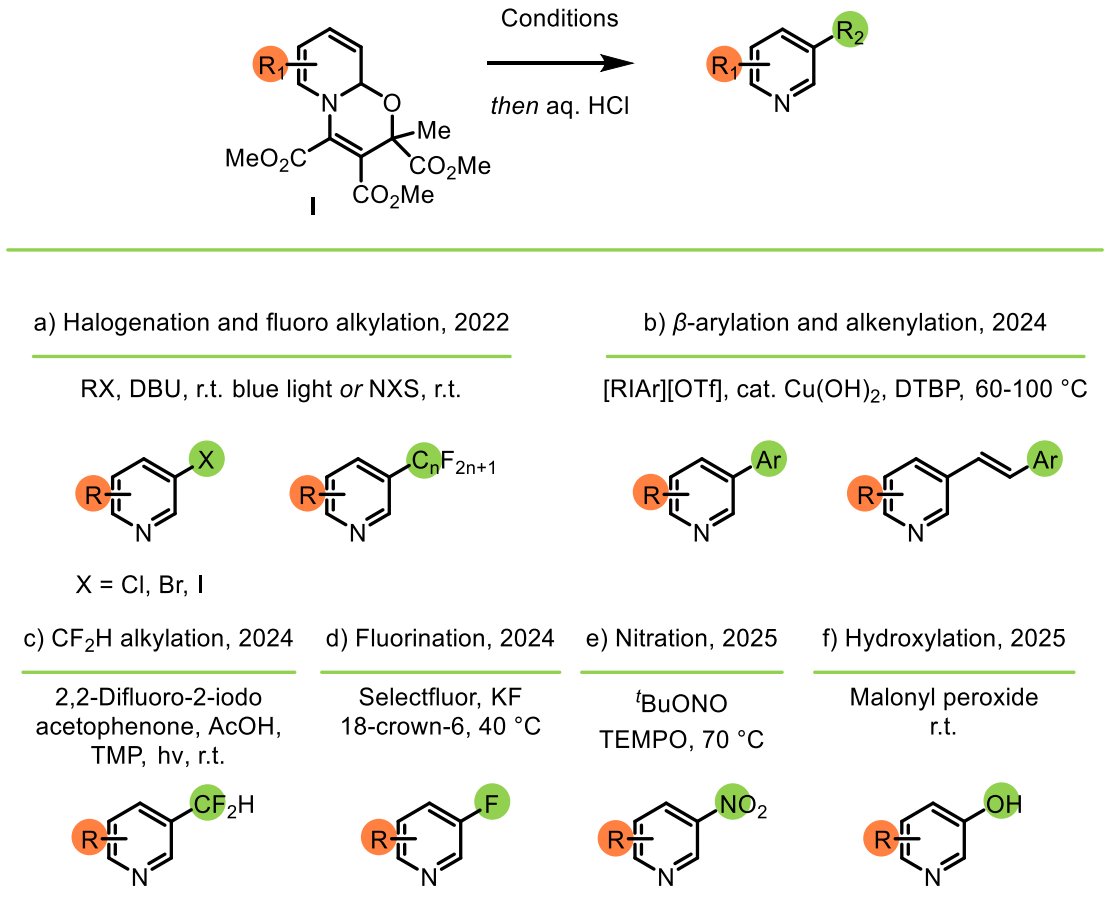
Studer and co-workers published a novel temporary dearomatisation strategy of pyridines in 2022, making use of a multi-step strategy.[27] A temporary scaffold is constructed, using the nucleophilic nature of pyridine to attack a stabilised alkyne, which then in turn couples to a carbonyl, which completes the ring at the C2 position of the pyridine (Scheme 2.4). This dearomatised cyclic structure is bench stable and can be isolated on the multi-gram scale.



Scheme 2.4: Two-stage dearomatisation strategy for *β*-functionalisation of pyridines.

Intermediate **I** can then be functionalised with a wide range of reagents, both ionic and radical, before the dearomatising scaffold is removed with acid. Studer's article begins with alkyl halide electrophiles used to install CF_3 and C_4F_9 groups in a photochemically initiated radical process, but also describes halogen installation using NXS electrophiles in an ionic process.

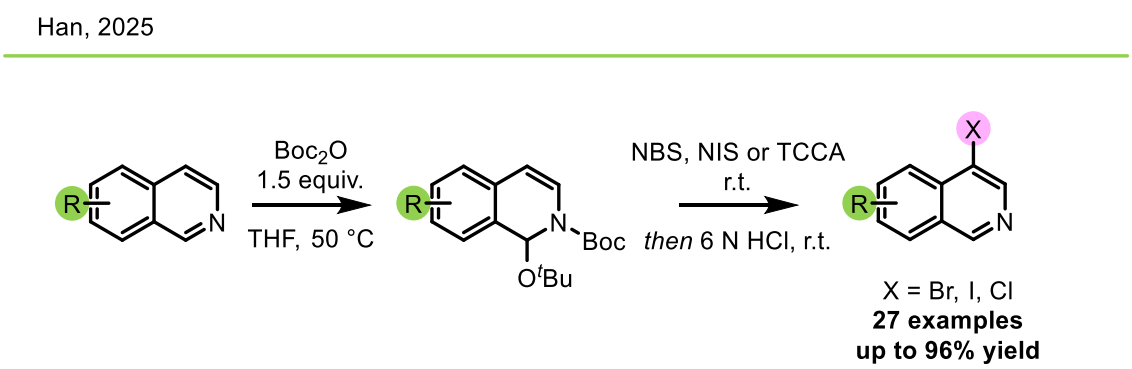
Studer then went on to publish further *β*-functionalisation reactions using the isolable dearomatised intermediate **I**, including copper catalysed arylation and alkenylation, peroxide radical induced CF_2H alkylations, fluorination, TEMPO mediated nitration, and peroxide mediated hydroxylation (Scheme 2.5).[28-33] The broad applicability of the bench stable dearomatised intermediate **I** makes this method a powerful technique to synthesise any *β*-functionalised pyridine, especially for late-stage transformations such as library building, due to the mild nature of the various reaction conditions. It is worth noting, however, that the atom economy of the process is low, due to the need to install the dearomatisation scaffold, only to hydrolyse it after the transformation has occurred, with the two components not isolated for re-use.



Scheme 2.5: *β*-functionalisation of pyridines *via* a temporary dearomatisation technique.[28-33]

2.1.3 Three-step one-pot isoquinoline C4-halogenation

Since the conclusion of our studies into temporary dearomatisation reactions, Han and co-workers have shown that isoquinolines can be halogenated at C4 in a three-step one-pot process, using a related strategy to Studer (Scheme 2.6).[34] Instead of isolating the exposed enamine intermediate, the halogen electrophile was added immediately following dearomatisation, then aqueous acid was added to hydrolyse the dearomatising Boc group. The method is broad and tolerant of a wide range of functional groups, but still suffers from most of the same drawbacks as Studer's work, albeit with a cheaper, more readily available activating group.



Scheme 2.6: Temporary dearomatisation strategy for C4 isoquinoline halogenation in a three-step one-pot process.

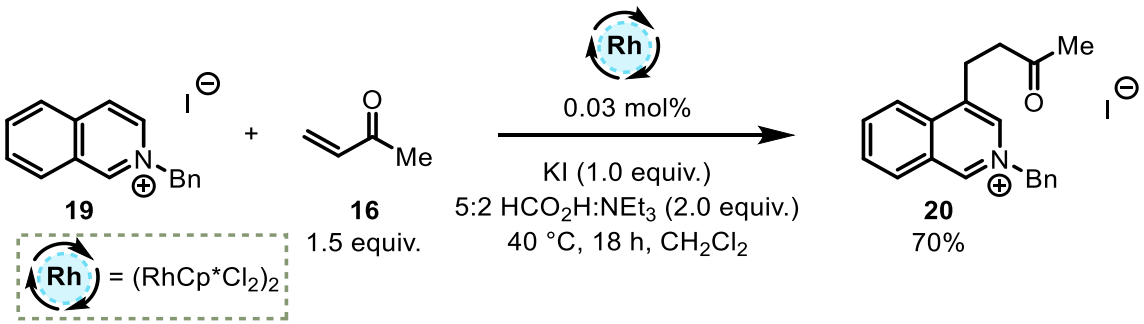
2.2 Previous work in the Donohoe group on temporary dearomatisation

All data presented herein was collected by Timothy Jenkins unless explicitly specified otherwise.

2.2.1 Initial hit from hydrogen borrowing conditions

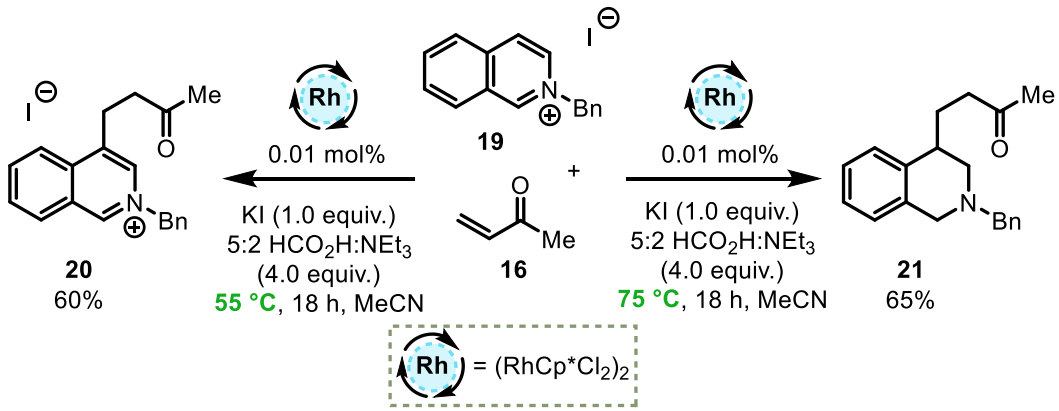
An initial hit from Dr M. Kishkewitz showed that a rhodium hydride reductant system, generated *in situ* from a Rh (III) source and the mildly acidic reductant 5:2 HCO_2H:NEt_3, could be used to functionalise isoquinolinium salts in a redox neutral process (Scheme 2.7). *N*-benzyl

isoquinolinium **19** could be reacted with methyl vinyl ketone (MVK) **16** to afford a good yield of the C4 functionalised *N*-benzyl isoquinolinium **20**. As opposed to the group's previous work on reductive functionalisation, this reaction functionalised the heterocycle at the same oxidation state, rather than reducing the heterocycle ring.



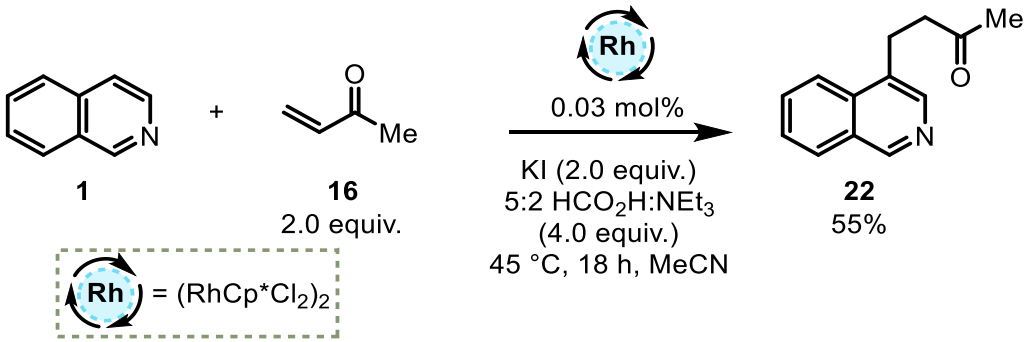
Scheme 2.7: Redox neutral functionalisation of isoquinolinium salts with a Rhodium hydride. Data collected by Dr M. Kischkewitz.

It was noted that temperature played a significant role in the reaction outcome, with a higher temperature favouring the fully reduced tetrahydroisoquinoline (THIQ) product **21** whereas a lower temperature favoured the redox neutral functionalised isoquinolinium salt **20** (Scheme 2.8).



Scheme 2.8: Redox neutral and reductive functionalisation of isoquinolinium salt **19** showing dependence of reaction pathway on temperature. Data collected by Dr M. Kischkewitz.

In an attempt to simplify the procedure, Dr. M. Kischkewitz attempted the transformation with unactivated isoquinoline, which pleasingly produced a 55% yield of C4-functionalised isoquinoline **22** (Scheme 2.9). Gratifyingly, this removed the need for a benzylation step and rendered an isoquinoline product which is significantly more versatile than producing an isoquinolinium salt.



Scheme 2.9: Application of redox neutral functionalisation conditions to unactivated isoquinoline **1**. Data collected by Dr M. Kischkewitz.

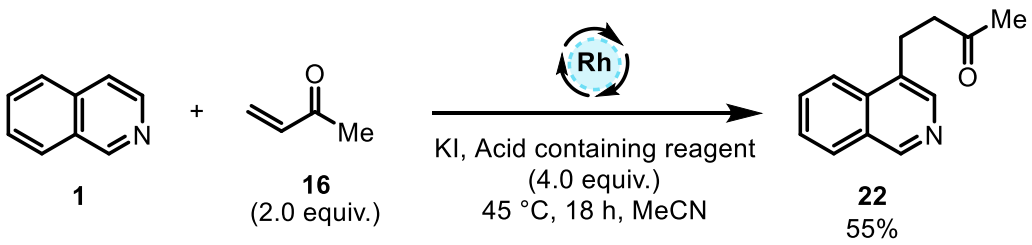
2.2.2 Control experiments leading to new conditions

A series of control experiments were conducted to evaluate the role of any rhodium species in the reaction (Table 2.1). A reaction performed without any rhodium catalyst still produced 32% yield, which is a decrease from the optimised conditions but still showing activity (Table 2.1, Entries 1-2). Similarly, removal of KI produces a reduction in yield but does not shut down reactivity completely (Table 2.1, Entries 1, 3).

Use of an alternative buffer system, 5:2 AcOH:NEt_3, still gave 36% yield, despite the lack of formic acid (Table 2.1, Entry 4). It had been thought that the active reductant species was a rhodium hydride, generated through reaction of the Rh(III) catalyst with formate, releasing CO_2 as a by-product. Since the reaction can still occur with another acid lacking a hydride generation route implies that the mechanism of the reaction with this reagent does not proceed *via* a metal hydride reduction event, but by a different mechanism. We hypothesise that the

reaction proceeds *via* a metal hydride reduction when hydride generation is possible, but switches to a nucleophilic model of reactivity when metal hydride generation is not feasible. A further reaction with 5:2 AcOH:NEt_3 and also in the absence of any Rh(III) catalyst confirmed this suspicion and afforded a 25% yield (Table 2.1, Entry 5).

Performing the reaction with only 4.0 equiv. of AcOH produced a 43% yield of product, which added further evidence to the hypothesis that the reaction occurring was not doing so by the involvement of a metal hydride (Table 2.1, Entry 6). Finally, removal of all reagents apart from MVK **16** afforded no yield, which confirmed a lack of background reaction without activation (Table 2.1, Entry 7).

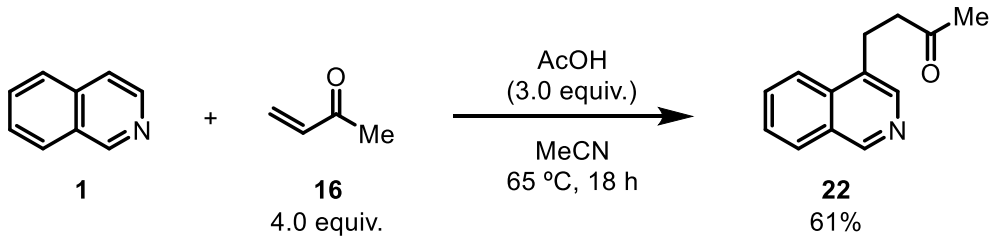


Entry	Acid Buffer	Rh Catalyst (mol%)	KI (equiv.)	Product Yield (%)
1	5:2 HCO_2H:NEt_3	0.03	2.0	55
2	5:2 HCO_2H:NEt_3	0.00	2.0	32
3	5:2 HCO_2H:NEt_3	0.03	0.0	20
4	5:2 AcOH:NEt_3	0.03	2.0	36
5	5:2 AcOH:NEt_3	0.00	0.0	25
6	AcOH	0.00	0.0	43
7	-	0.00	0.0	0

Table 2.1: Control experiments for redox neutral functionalisation of isoquinoline **1**. Yields reported are determined by quantitative ^{1}H NMR. Data collected by Dr M. Kischkewitz. Rhodium catalyst used is $(RhCp^*Cl_2)_2$.

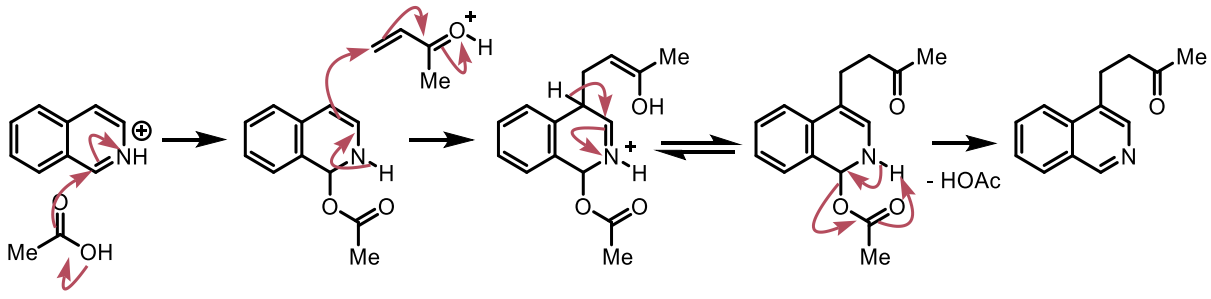
2.3 Optimisation of conditions

The reaction detailed above was further studied and optimised to produce a maximum yield of 61% (Scheme 2.10). The reaction is, therefore, a metal free redox neutral activation of an *N*-heterocycle using a mild reagent and non-forcing conditions.



Scheme 2.10: Newly optimised reaction conditions. Data collected by Dr M. Kischkewitz.

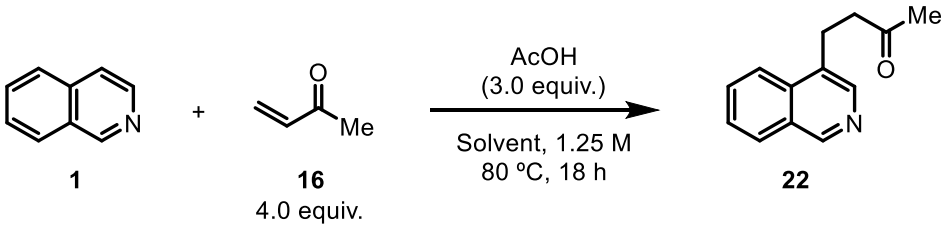
A mechanism for this reaction was proposed (Scheme 2.11). Acetic acid, acting as a nucleophile, attacks protonated isoquinoline at C1 to reveal an enamine, which can react with methyl vinyl ketone *via* a 1,4-addition. The isoquinoline product **22** is subsequently unmasked by elimination of AcOH.



Scheme 2.11: Proposed mechanism by Dr M. Kischkewitz.

This work was continued by screening several solvents, beginning with common polar solvents (Table 2.2). All solvents that were screened produced very similar yields, with polar aprotic solvents acetone, MeCN and DCE performing as well as the polar protic solvent MeOH (Table 2.2, Entries 1-4). Conducting the reaction in the absence of solvent produced an excellent yield of 70%, outperforming the four solvents screened, however it was decided to

continue using solvent at a starting material concentration of 1.25 M (Table 2.2, Entry 5). Any lack of solvent would make it challenging to screen solid electrophiles, and there was some concern that the reaction might generate repeatability problems as a result.



Entry	Solvent	Yield of 22 (%)
1	Acetone	62
2	MeCN	63
3	DCE	62
4	MeOH	60
5	Solvent free	70

Table 2.2: Short solvent screen of polar solvents. Yields quoted are isolated. Data collected by Dr A. Day. Reactions performed on 0.125 mmol scale.

Based on this proposed mechanism (*vide supra*), carboxylic acids and other suitable nucleophiles were screened in an attempt to find other nucleophilic species that would also effect the transformation (Figure 2.1). The pKa of the carboxylic acid seemed to have very little bearing on reaction yield as *p*-nitro benzoic acid (67%) gave a very similar yield to benzoic acid (73%), with TFA (0%) performing less well than acetic acid (63%). Stronger Brönsted acids such as TsOH (0%), sulphuric acid (0%) and oxalic acid (43%) were all outperformed by benzoic acid (73%) which gave the highest yield of the acids screened. Interestingly using NaI as a nucleophile afforded a small amount of product, although this wasn't repeated for other non-acidic nucleophiles such as CuCN and EtSH. (Figure 2.1). It was

decided to proceed with BzOH as the reagent of choice, as not only did it afford the highest product yield, it is a bench stable solid, much easier to handle and not as corrosive as AcOH.

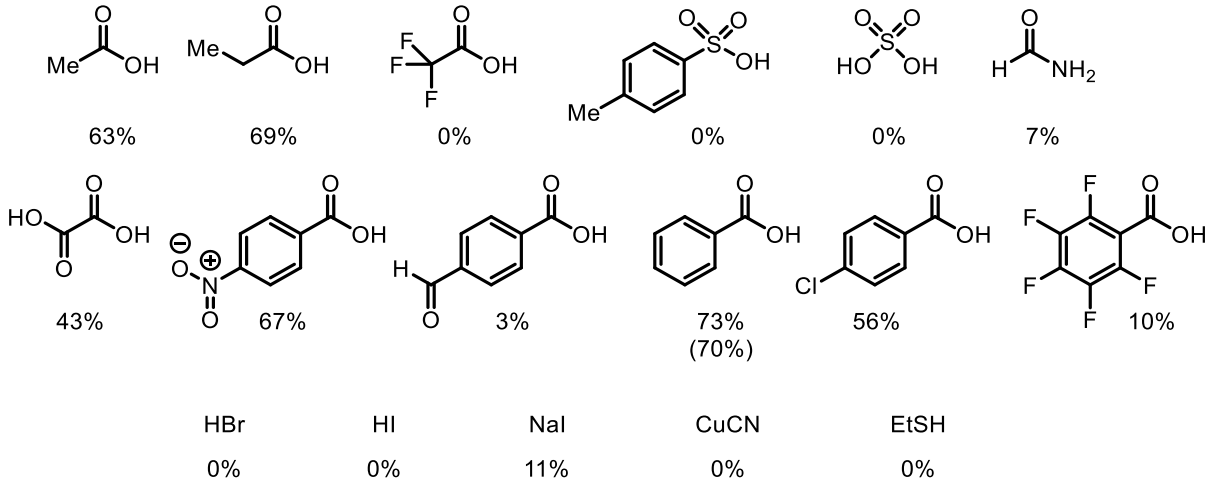
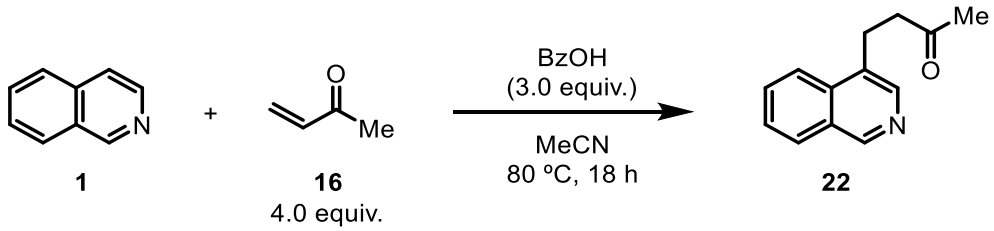


Figure 2.1: Acid and nucleophile screening. Yields reported are determined by quantitative ^{1}H NMR. Brackets indicate isolated yields. Data collected by Dr A. Day. Reactions performed on 0.125 mmol scale.

It was postulated that over oxidation of the starting material or product could be responsible for the poor mass recovery we had observed with this reaction, and so a study of gaseous headspace conditions was performed (Table 2.3). Unexpectedly, both an oxygen free environment, in the form of an argon atmosphere, and an oxygen enriched environment produced reduced yields of 51% and 27% respectively (Table 2.3, Entries 1-2). A reduced yield when using an oxygen enriched atmosphere adds weight to our theory that atmospheric oxygen was causing product degradation, however it is unclear why a rigorously oxygen-free atmosphere also generates less product.

A balloon of air afforded a reasonable isolated yield of 66%, comparable to our optimised yield, which was an expected result, being similar in environment to a sealed reaction, however a reaction pierced with a needle, a reaction set up also exposed to air, only produced a 45% yield (Table 2.3, Entries 3-4). This unexpected yield reduction could be explained by solvent loss,

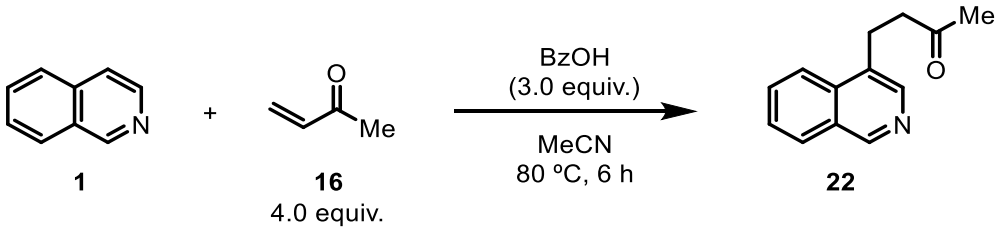
leading to insufficient stirring during the reaction progress and potentially leading to product degradation.



Entry	Conditions	Yield of 22 (%)
1	Degassed solvent, Ar balloon	(51)
2	Oxygenated solvent, O_2 balloon	27
3	Air balloon	(66)
4	Needle	45

Table 2.3: Gaseous headspace investigations. Yields reported are determined by quantitative ^{1}H NMR. Brackets indicate isolated yields. Reactions performed on 0.125 mmol scale.

It was decided to examine the effect of concentration on the reaction as a final optimisation parameter with results showing a general trend of yield decreasing as dilution increases (Table 2.4, Entries 1-4). Our current concentration, 1.25 M, produced a reasonable yield of 47%, although this is lower than previous yields recorded due to the shorter reaction time of 6 h (Table 2.4, Entry 1). Halving the molarity produced a similar yield of 49% but the yield decreased sharply once molarity decreased below 0.625 M (Table 2.4, Entries 2-4). We decided to maintain a 1.25 M concentration as our optimised conditions, as doubling the solvent volume produced a similar yield within experimental error.



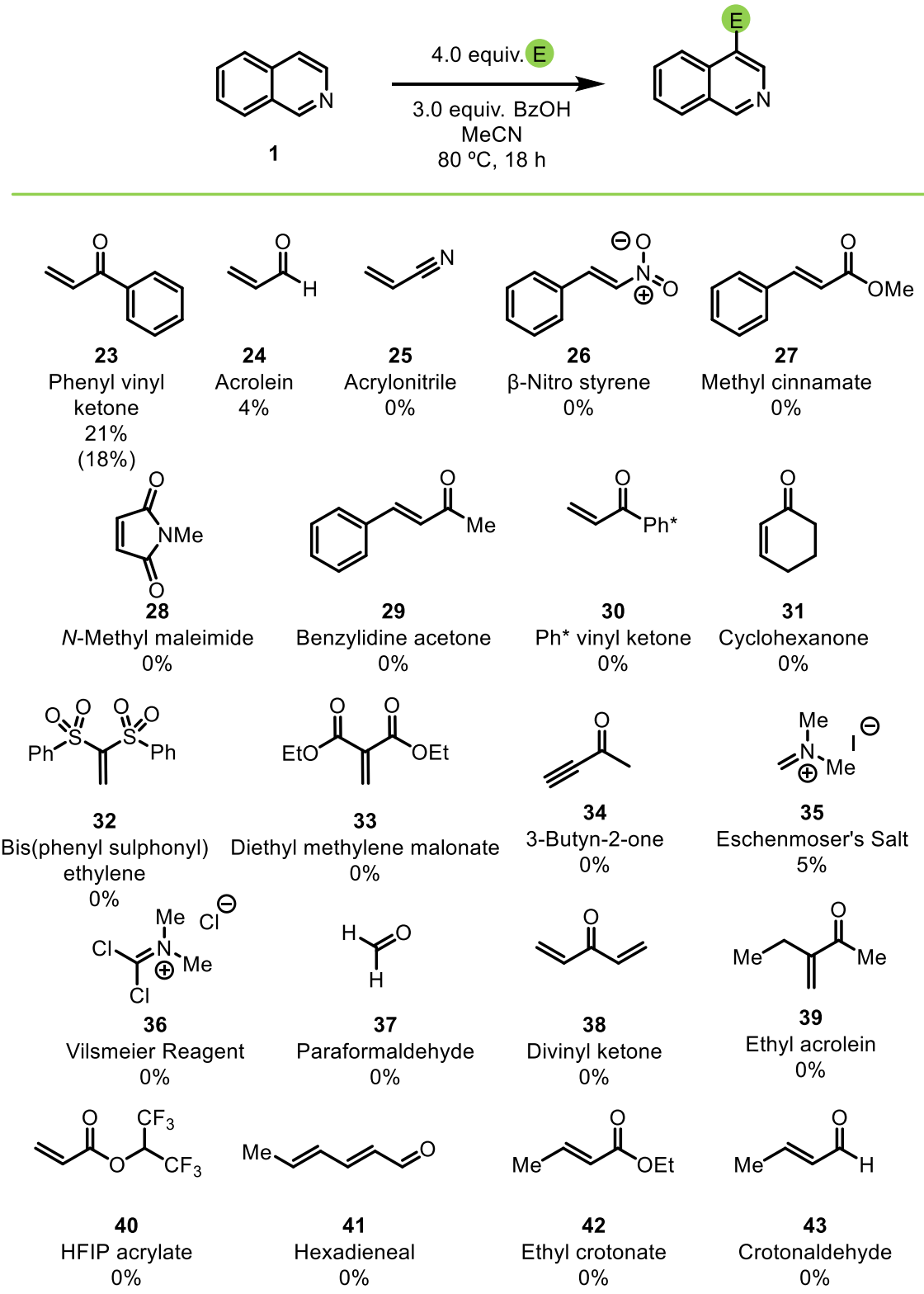
Entry	Concentration (M)	Yield of 22 (%)
1	1.25	47
2	0.625	49
3	0.313	27
4	0.156	14

Table 2.4: Concentration studies. Yields reported are determined by quantitative ^{1}H NMR. Brackets indicate isolated yields. Reactions performed on 0.125 mmol scale.

2.4 Scope of electrophiles

2.4.1 First attempt at electrophile screening

An initial attempt at electrophile screening began with disappointing results (Scheme 2.12). Whilst MVK **16** had previously demonstrated a good isolated yield of 70%, this could not be replicated with other, even structurally or electronically similar electrophiles. The three most notable examples trialled were that phenyl vinyl ketone **23** produced a promising isolated yield of 18%, then acrolein **24** and Eschenmoser's salt **35** both a trace amount (4% and 5% respectively). All other electrophiles screened afforded no product, showing predominantly starting material in their crude ^{1}H NMR spectra.

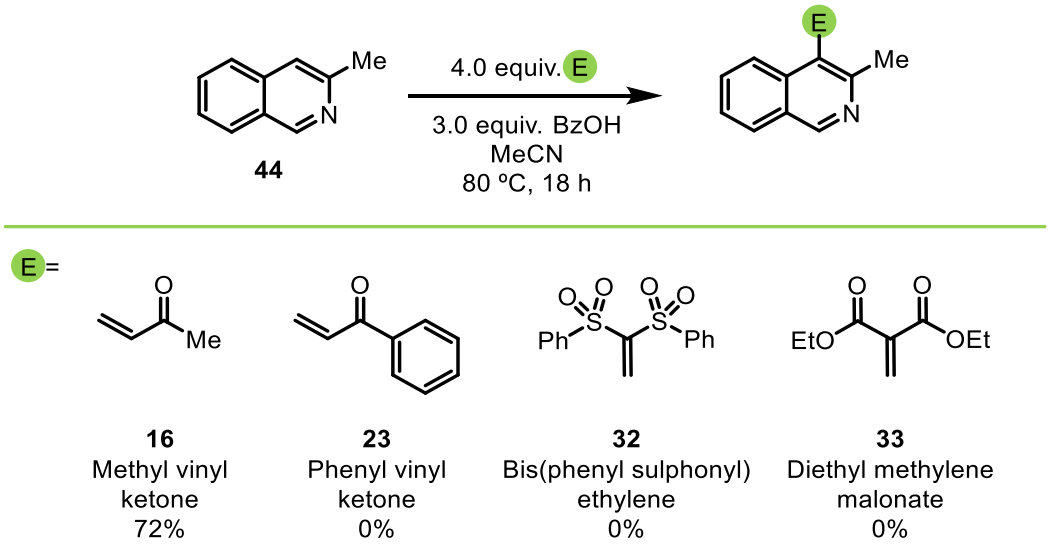


Scheme 2.12: First attempt at electrophile screening. Yields reported are determined by quantitative ^{1}H NMR.

Brackets indicate isolated yields. Reactions performed on 0.125 mmol scale.

2.4.2 3-Me isoquinoline 44 as a sterically encumbered alternative

It was postulated that some electrophiles were failing as isoquinoline itself was too nucleophilic, therefore multiple side reactions could be occurring. In an attempt to prevent this, four electrophiles were trialled with 3-methyl isoquinoline **44** in place of isoquinoline **1** (Scheme 2.13). Methyl vinyl ketone produced a slightly increased yield of 72%, but disappointingly bis(phenyl sulphonyl) ethylene **32** and diethyl methylene malonate **33** did not afford any product when subjected to the reaction conditions. When phenyl vinyl ketone **23** was used as the electrophile, no product was afforded, in contrast to 18% produced with isoquinoline **1**. This may be due to the increased steric bulk around the nucleophilic carbon, C4, therefore it is possible that using 3-methyl isoquinoline **44** has decreased reaction rates irrespective of any advantageous side pathway supressing properties.

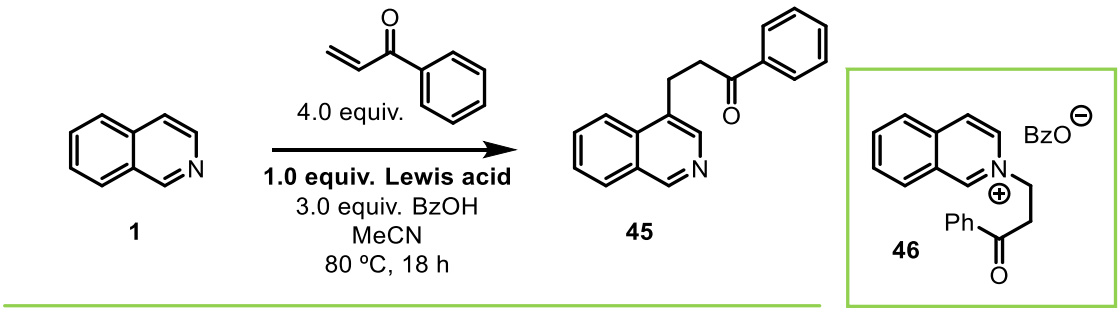


Scheme 2.13: Electrophile screening with 3-Me isoquinoline. Reactions performed on 0.125 mmol scale. Isolated yields are reported.

2.4.3 Further optimisation with Phenyl Vinyl Ketone – Lewis acid screening

Phenyl vinyl ketone was the only electrophile previously screened to produce any promising yield; it was decided to attempt a short optimisation with phenyl vinyl ketone **23** in an attempt to boost the yield further.

It was suggested that Lewis acid additives may increase the reaction yield, and so a selection of Lewis acids were screened, using phenyl vinyl ketone as the electrophile. Disappointingly, all Lewis acid screened apart from basic Al_2O_3 performed worse than with no additive, with Al_2O_3 producing 24%, a comparable yield of **45** to the control reaction (Table 2.5). It was thought that perhaps these low yields might be due to the presence of Lewis acids promoting an alternative reaction pathway, reacting with the Lewis acids on N. An observation later made by Dr A. Day (*vide infra*) showed that isoquinoline **1** is highly liable to form an adduct with any vinyl ketone electrophile, in this case salt **46**. Although Dr A. Day later showed that this occurs normally during the reaction progress, we do not believe it is the reactive species (*vide infra*). The presence of Lewis acid may therefore bias the equilibrium towards the salt, thereby reducing the amount of reactive isoquinoline species present in the reaction mixture and decreasing the reaction rate.



Entry	Lewis Acid	Yield of 45 (%)
1	None	21
2	$ZnBr_2$	3
3	MgI_2	0
4	$Sc(OTf)_3$	0
5	SiO_2	13
6	Basic Al_2O_3	24
7	TMSCl	0
8	$CeCl_3$	10

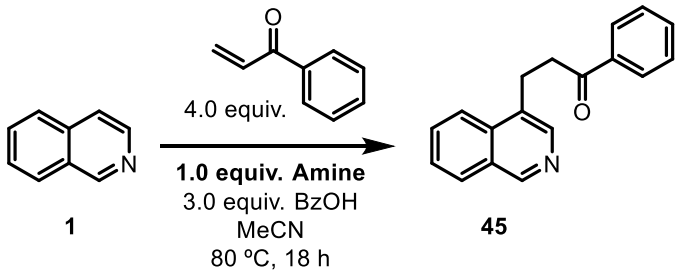
Table 2.5: Lewis acid screening. Yields reported are determined by quantitative ^{1}H NMR. Reactions performed on 0.125 mmol scale.

2.4.4 Further optimisation with Phenyl Vinyl Ketone – Primary and Secondary amine screening

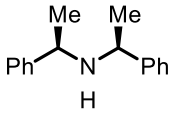
In another attempt to manipulate carbonyl electrophilicity, it was posited that adding 1.0 equivalents of a primary or secondary amine could react with phenyl vinyl ketone **23** to form an imine or iminium *in-situ*. The mildly acidic conditions would catalyse such a condensation, and it could lower the HOMO-LUMO gap, making attack by the enamine generated *in situ* more electronically favoured.

Subsequently, a selection of both primary and secondary amines were screened with phenyl vinyl ketone **23** as the electrophile, but results were again disappointing, showing only a

reduction in yield as compared to the control experiment (Table 2.6, Entry 1). The addition of secondary amine **47** drastically reduced the yield, with the reaction affording only 3% product (Table 2.6, Entry 2). Similarly, addition of **48** shut down reactivity completely (Table 2.6, Entry 3). Of the secondary amines screened, only morpholine **49** did not affect yield, affording 24%, a comparable quantity to the control experiment (Table 2.6, Entry 4). Overall, the three primary amines screened performed worse, with two amines generating no yield at all (Table 2.6, Entries 6-7). Only isopinocampheylamine **50** produced any yield, affording 13%, a reduction on the control experiment (Table 2.6, Entries 1, 5). These disappointing yields may be due to the amines acting as competing nucleophiles, adding to phenyl vinyl ketone quicker than isoquinoline and thereby competitively inhibiting the reaction, although this possibility was not investigated.



1 45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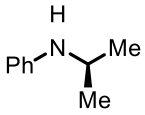
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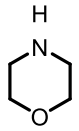
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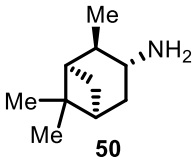
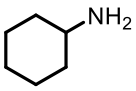

50


51


52

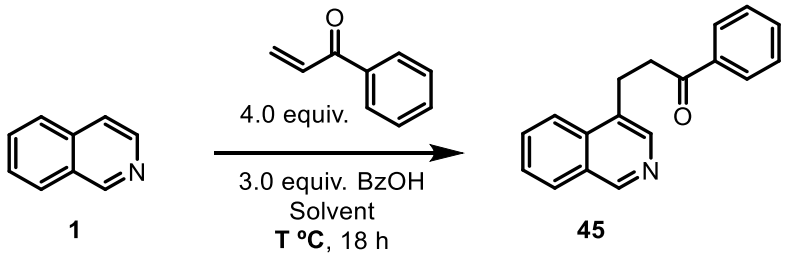
Entry	Amine	Yield of 45 (%)
1	None	21
2	**47**	3
3	**48**	0
4	**49**	24
5	**50**	13
6	**51**	0
7	**52**	0

Table 2.6: Amine additive screening. Yields reported are determined by quantitative ^{1}H NMR. Reactions performed on 0.125 mmol scale.

2.4.5 Further optimisation with Phenyl Vinyl Ketone 23 – Solvent and temperature investigations

We then looked to investigate solvent and temperature (Table 2.7) with the hope that increasing the reaction temperature might still further increase yield.

Decreasing the reaction temperature predictably decreased the yield, with a 4% observed, however increasing the reaction temperature to 100 °C did show a good increase in yield to 34% (Table 2.7, Entries 1-3). Altering the solvent choice showed some interesting insight into the reaction, with PhMe affording no product, but H_2O producing a comparable yield to MeCN at 35% (Table 2.7, Entries 4-5). Conducting the reaction in the absence of solvent produced an increase in yield to 44%, presumably due to the higher concentration, an effect noted before with this system (*vide supra*) (Table 2.7, Entry 6).



1 **45**

Entry	Temperature (°C)	Solvent	Yield of 45 (%)
1	65	MeCN	4
2	80	MeCN	(15)
3	100	MeCN	32 (34)
4	100	PhMe	0
5	100	H_2O	35
6	100	Solvent Free	44

Table 2.7: Phenyl vinyl ketone initial optimisation. Yields reported are determined by quantitative ^{1}H NMR. Brackets indicate isolated yields. Reactions performed on 0.125 mmol scale.

The experiments performed above show that an increased temperature of 100 °C is required for optimum yields when using aryl vinyl ketones, and so was carried forwards into the aryl vinyl ketone scope. Although it is possible that higher temperatures could afford higher yields, the hazards encountered when heating solvents above their boiling points were deemed

sufficient to not explore this possibility. Similarly, although conducting the reaction under solvent free conditions led to an increase in yield, concerns were raised about solid aryl vinyl ketone electrophiles and the lack of reproducibility that the inhomogeneity of the reaction might generate. Phenyl vinyl ketone is a liquid at r.t. and therefore does not suffer these issues. As such, it was decided to continue the scope using MeCN as the solvent.

2.4.6 Vinyl ketone scope

Next, we fixed our attention to expanding the substrate scope of electron rich and electron poor aryl vinyl ketones. The success of MVK **16** as an electrophile in the reaction, and the partial success of phenyl vinyl ketone **23** indicates that the reaction is well suited to vinyl ketone type electrophiles. As a result, it was decided that a scope of aryl vinyl ketone electrophiles should be explored, to investigate how the electrophilicity of the ketone affects reactivity. It was hoped that a trend might emerge which could give an insight into the reaction and its limitations.

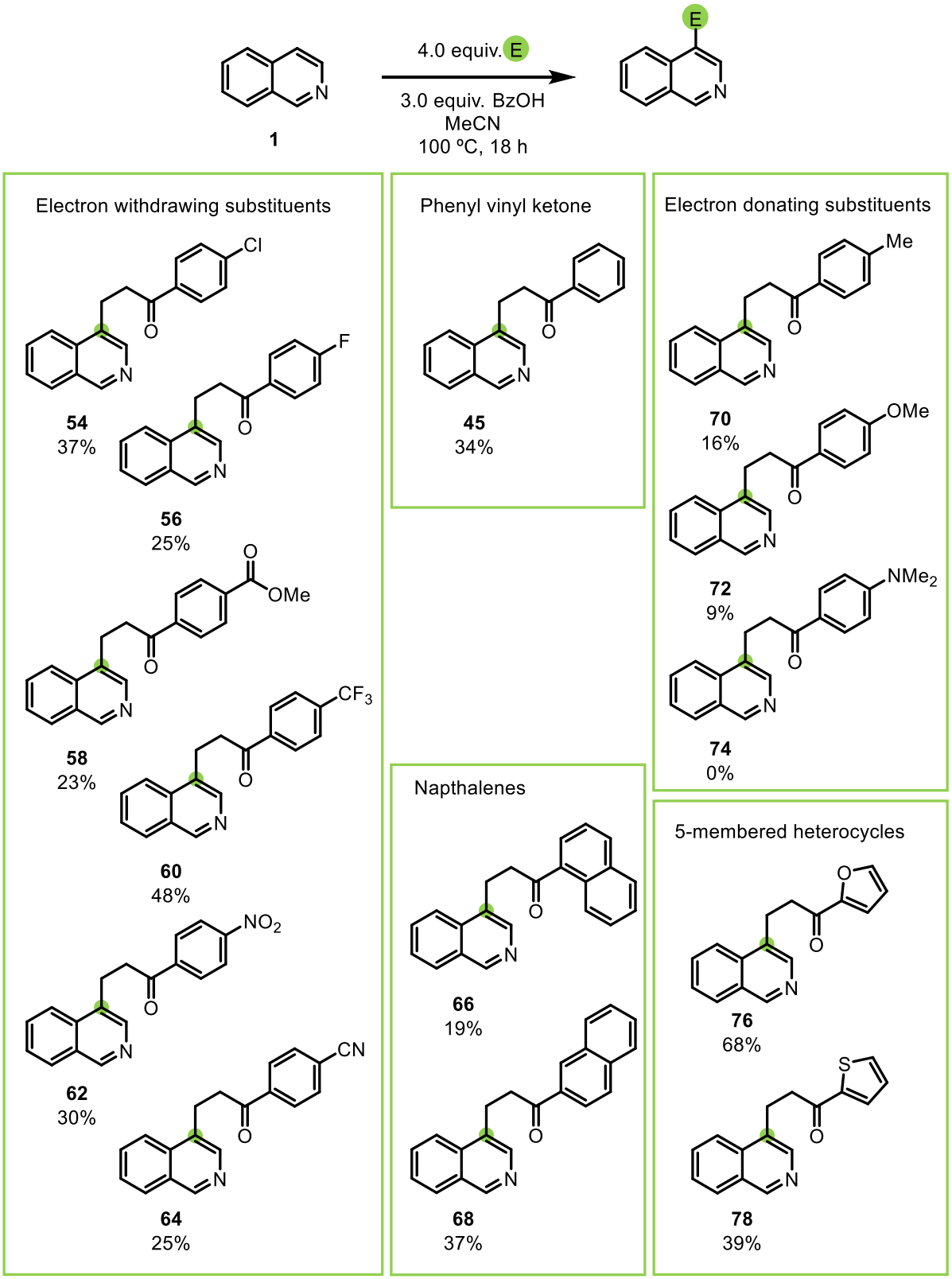
The substrates that were synthesised were subjected to the acid catalysed reaction conditions with varying results (Scheme 2.14). Some general trends emerged, showing that electron rich aryl vinyl ketones performed less well than phenyl vinyl ketone **23**, with tolyl vinyl ketone **69** affording only a 16% yield of isoquinoline **70**, the *para*-MeO analogue only a 9% and the *para*-NMe_2 analogue not producing any product at all.

Our theory was reinforced by the overall good performance of electron poor aryl vinyl ketones, which mostly performed as well as phenyl vinyl ketone if not better. The trend is not nearly as pronounced as with electron rich aryl vinyl ketones, but higher yields were observed. *Para*-fluoro phenyl vinyl ketone **55** afforded a lower yield (25%) of isoquinoline **56** than isoquinoline **45** when phenyl vinyl ketone was used, however its chloro-analogue performed better, affording a 37% yield of isoquinoline **54**, comparable to the use of phenyl vinyl ketone **23** as an electrophile. The *para*-CF_3 analogue (**59**) performed the best of all phenyl vinyl ketone

derivatives trialled, producing a 48% yield of isoquinoline **60**. Unfortunately, adjusting the electrophilicity of the vinyl ketone carbonyl through more electron withdrawing groups did not increase yield as hoped, with the highly electron deficient *para*-CO_2Me, *para*-CN and *para*-NO_2 analogues producing isoquinolines **58**, **64** and **62** in 23%, 25% and 30% yields respectively (Scheme 2.14). We hypothesise that the lack of a clear trend with electron deficient electrophiles is due to a very narrow window of reactivity in the reaction. It is possible that highly electron withdrawing groups merely push their respective electrophiles beyond this window and thus decrease the reactivity of the system. The more electron deficient electrophiles might also be suffering from competitive polymerisation, a process destructive to the desired reaction but one that is challenging to observe and measure.

Other aryl vinyl ketones were then trialled, with 1-naphthyl and 2-naphthyl analogues **65** and **67** producing isoquinolines **66** and **68** in 19% and 37% yield respectively. The lower yield when using 1-naphthyl vinyl ketone is attributed to the increased steric forces experienced around the site of reactivity as compared to the 2-naphthyl analogue.

Vinyl ketones with furyl and thiophenyl substituents were also subjected to the reaction conditions, with much more promising results. Our highest scope yield yet was attributed to furyl vinyl ketone **75**, which afforded isoquinoline **76** in a pleasing yield of 68%. This decreased with the thiophenyl analogue, which only produced a 39% yield of isoquinoline **78**. The reasons for this discrepancy are unclear, since the 5-membered heterocyclic substituent is formally electron donating, yet the yields observed are more comparable with those produced from electron withdrawing aryl substituents.

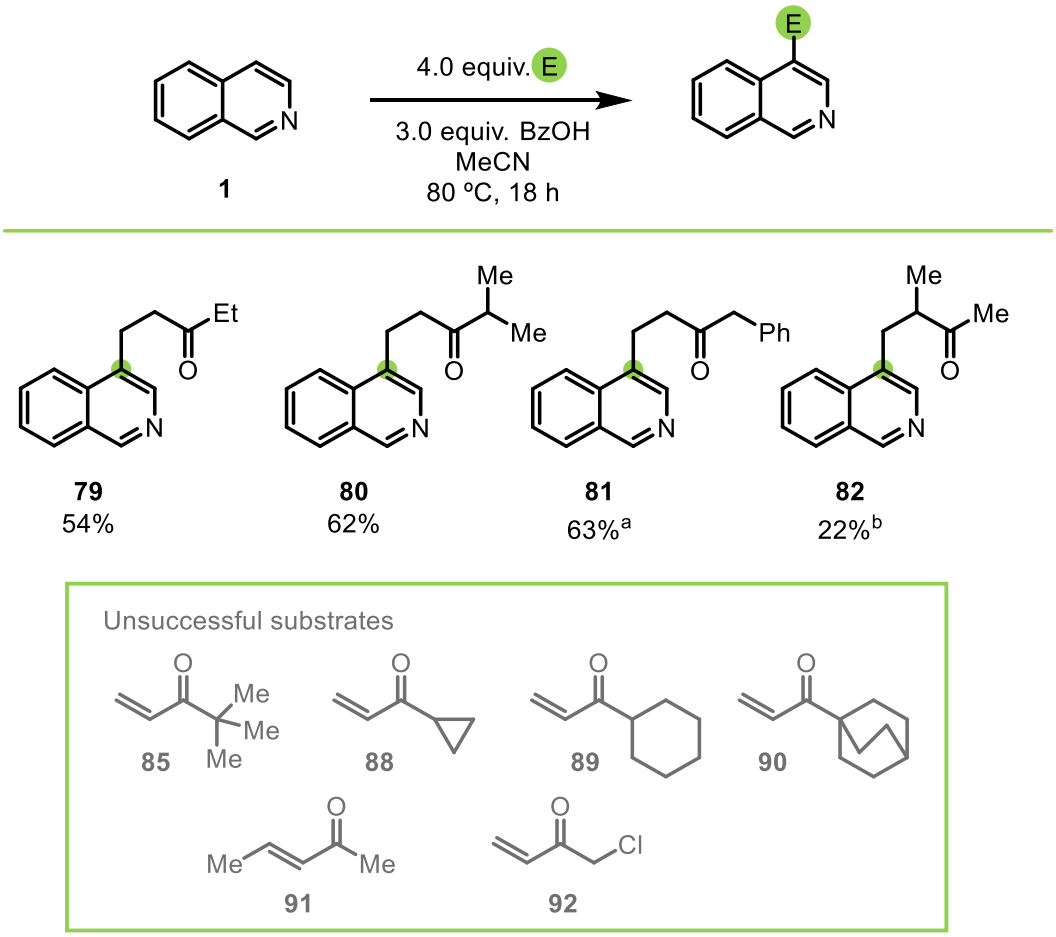


Scheme 2.14: Substrate scope using aryl vinyl ketones as electrophiles. Isolated yields are reported. Reactions performed on 0.25 mmol scale.

2.4.7 Alkyl vinyl ketone scope

We proceeded to explore alkyl vinyl ketones as electrophiles and produced the following short scope (Scheme 2.15). Increasing the length of the side chain adjunct to the vinyl ketone carbonyl did little to change the reaction yield, with both ethyl vinyl ketone **83** and isopropyl vinyl ketone **84** affording very respectable yields of isoquinolines **79** and **80** in 54% and 62% respectively. Additional steric bulk, in the form of *tert*-butyl vinyl ketone **85** did, however, prevent any reactivity, with no product being formed. Benzyl vinyl ketone **86** produced isoquinoline **81** in an excellent yield of 63%, far surpassing the yields observed with phenyl vinyl ketone **23** as the electrophile (*vide supra*). This could well demonstrate that the steric bulk surrounding the vinyl ketone carbonyl is a strongly determining characteristic of the electrophile reactivity.

Finally, increasing steric bulk around the vinyl portion of the electrophile led to a noticeable decrease in reactivity. α-Methyl vinyl ketone **87** required a higher reaction temperature of 100 °C to produce a low yield (22%) of isoquinoline **82**, and 3-pentan-2-one **91** did not react at all. Other unsuccessful electrophiles are also detailed in Scheme 2.15, including the more sterically bulky cyclohexyl vinyl ketone **89** and adamantyl vinyl ketone **90**. Cyclopropyl vinyl ketone **88** was also unsuccessful, despite being not as sterically encumbered as isopropyl vinyl ketone; similarly, α-chloro vinyl ketone **92** was unsuccessful.



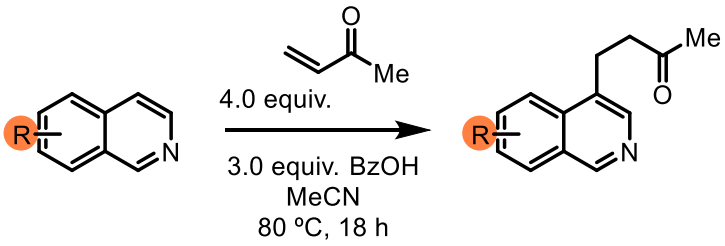
Scheme 2.15: Alkyl vinyl ketone scope encompassing unsuccessful substrates. Isolated yields are reported. Reactions performed on 0.25 mmol scale. [a]Reaction performed on 0.125 mmol scale. [b]Reaction performed at 100 °C. Data obtained by Dr A. Day.

2.4.8 Isoquinoline scope

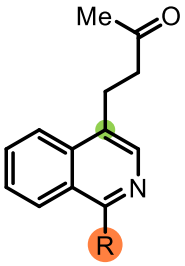
The isoquinoline scope of the reaction was also explored, subjecting a range of C1, C3, C5, C6, C7 and C8 substituted isoquinolines to the reaction conditions (Scheme 2.16).

C1 functionalised isoquinolines performed very poorly, with neither substrate trialled affording any product (R = Me, R = Cl). Since our working mechanistic theory involves attack at C1 by benzoic acid, these results are perhaps unsurprising, as any steric impediment to attack at the electrophilic carbon will drastically decrease reaction rate.

We have already seen how C3 functionalised 3-methyl isoquinoline performed very well under the reaction conditions to afford **93** in a 72% yield (*vide supra*), however other C3 analogues fared less well. The C3 methylene hydroxyl product **94** was generated in a modest 25% yield, however any other substituent trialled (Br, Cl, Ph, CO_2Me, NH_2 and OH) afforded no product.

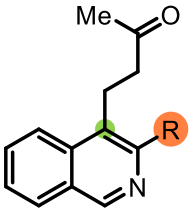


C1



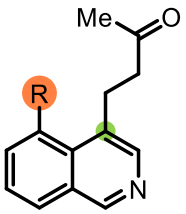
R = Me 0%
R = Cl 0%

C3



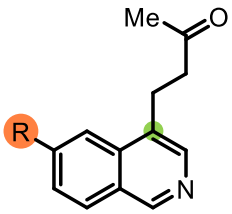
93 R = Me 72%
94 R = CH_2OH 25%
R = Ph 0%
R = Br 0%
R = Cl 0%
R = CO_2Me 0%
R = NH_2 0%
R = OH 0%

C5



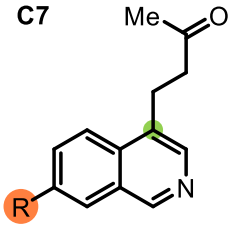
95 R = Me 50%
96 R = Ph 86%
97 R = Br 27%
98 R = Cl 35%
99 R = OMe 49%
R = CHO 0%
R = CO_2 0%
R = SO_3H 0%
R = OH Trace

C6



100 R = Me 59%
101 R = Ph 80%
102 R = Br 56%
103 R = OMe 40%
R = OH 0%

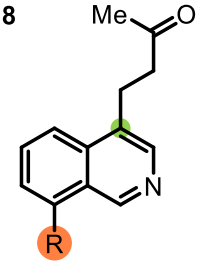
C7



104 R = Me 88%
105 R = Ph 58%
106 R = Br 73%
R = OH 0%
R = NH_2 0%

107 R = Me 81%
108 R = Ph 80%
109 R = Br 92%
110 R = Cl 80%

C8



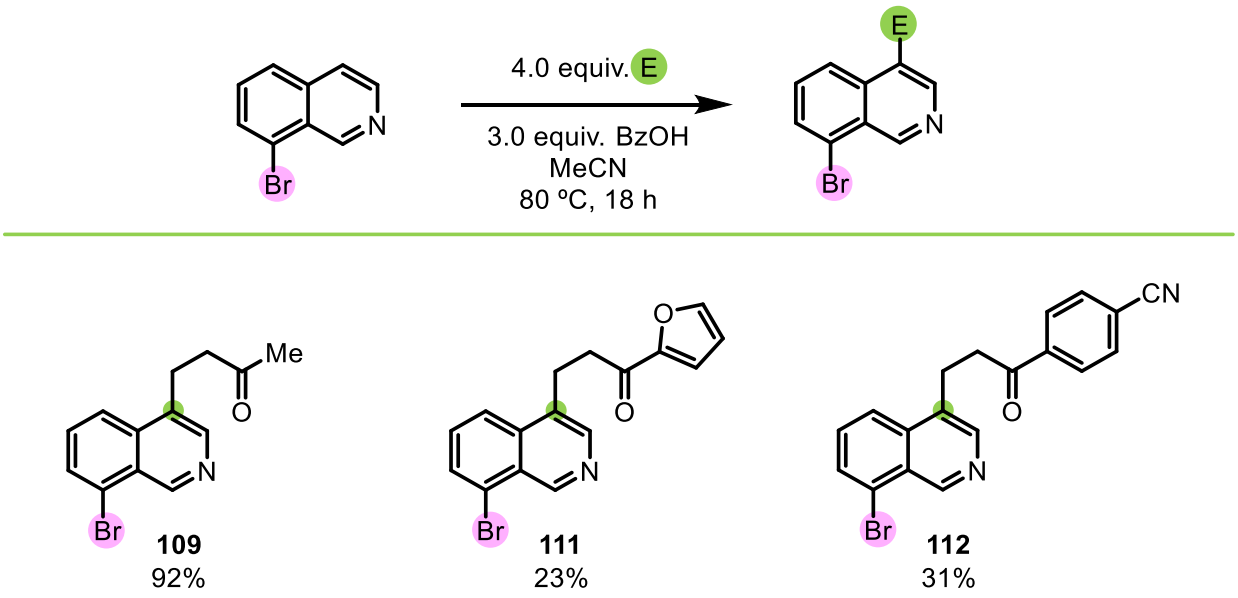
Scheme 2.16: Isoquinoline substrate scope. Isolated yields are reported. Reactions performed on 0.25 mmol scale. Data obtained by Dr A. Day.

On the whole, most other C5, C6, C7 and C8 substituents performed well, affording yields of up to 92% in some cases, with most yields at least 60%. This shows the system is highly tolerant

of a variety of substituents with a range of electronics and steric factors altered and yet respectable yields were still obtained.

2.4.9 Combination of the best isoquinolines and the best aryl vinyl ketones

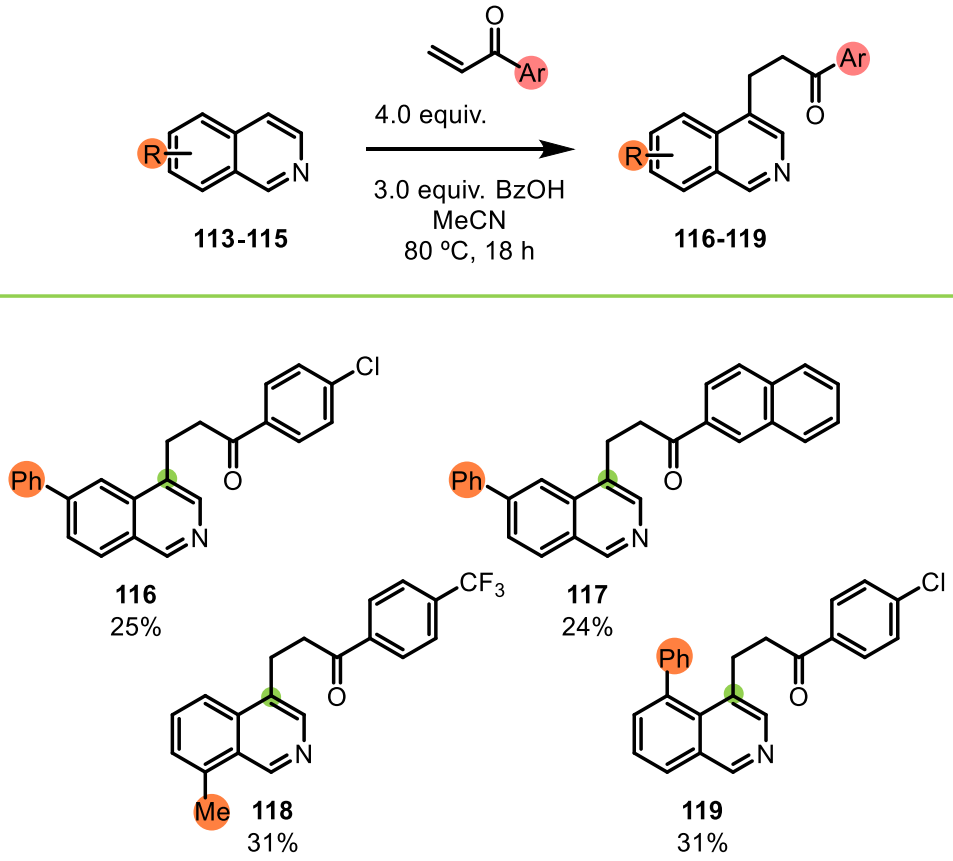
With this hypothesis in mind, several of the previously screened aryl vinyl ketones (*vide supra*, Scheme 2.14) were resubjected to the reaction conditions but with 8-Br isoquinoline as the substrate (Scheme 2.17). Regrettably, all aryl vinyl ketones trialled produced a lower yield than when MVK **16** was used as the electrophile (92%).



Scheme 2.17: Scope of aryl vinyl ketones with 8-Br isoquinoline as the reactant. Isolated yields are reported. Reactions performed on 0.25 mmol scale.

Three further isoquinolines, 8-Me isoquinoline **113**, 5-Ph isoquinoline **114** and 6-Ph isoquinoline **115** were also reacted with other aryl vinyl ketones to see how the substituents affect the yields (Scheme 2.18). As before, all three combinations trialled produced reduced yields compared to when MVK **16** was used as the electrophile (86% and 80% respectively). This is perhaps not surprising, as the aryl vinyl ketone scope had shown reduced yields when compared to MVK **16**, however it was hoped that a combination of the most reactive aryl vinyl

ketone and the highest yielding isoquinolines revealed in the respective scopes might combine to afford some greater yield.



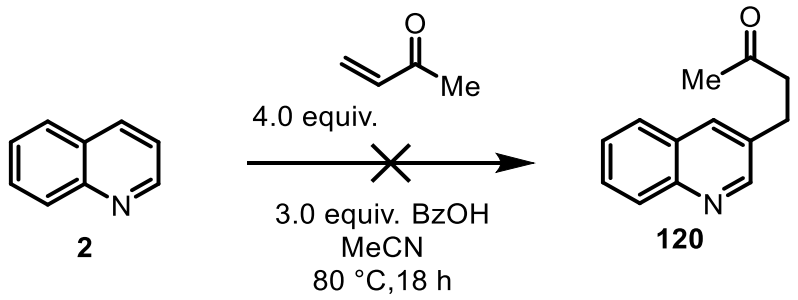
Scheme 2.18: Aryl vinyl ketones trialled with the most successful isoquinolines. Isolated yields are reported. Reactions performed on 0.125 mmol scale.

It is worth noting that these data cannot be directly compared to the aryl vinyl ketone scope (Scheme 2.14) as the experiments were performed at 80 °C, a lower temperature. This was done to allow comparison with the isoquinoline scope.

2.4.10 Expanding the scope to other *N*-heterocycles

We wanted to explore more of the aza-arene family with the reaction, and so a pilot experiment was performed with quinoline **2** using the optimised conditions detailed above (Scheme 2.19). Regrettably, no product was noted, perhaps due to the remote nature of the necessary dearomatisation reaction. As compared to isoquinoline, where any nucleophilic attack to effect

dearomatisation is at C1, here the attack would need to be at C4, further from the nitrogen and therefore possibly not benefitting from any co-ordinating effects.



Scheme 2.19: Quinoline pilot experiments

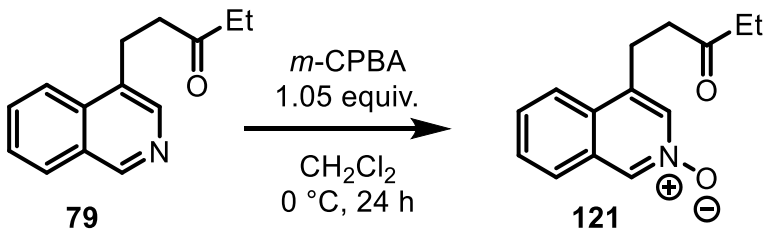
We suggest that these issues would also be present in any pyridine-like system and therefore no further *N*-heterocycles were trialled.

2.5 Derivatisation of products

2.5.1 Rearrangement derivatisations

Our attention then turned to derivatising the products generated in the alkylation reaction, so as to demonstrate its synthetic utility. We wished to functionalise the carbonyl on the C4 side chains, as this would allow a two-step process to a C4 alkyl amine or alkyl alcohol, that the process cannot achieve in one step, being limited to vinyl ketone electrophiles.

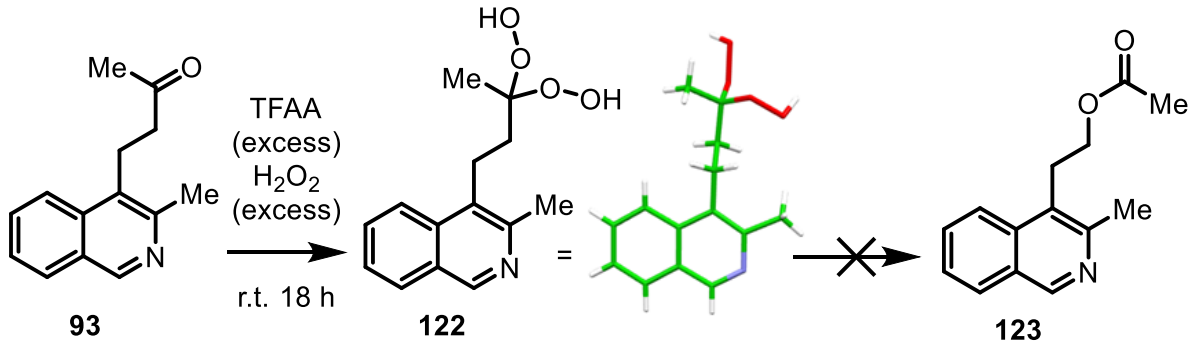
Subsequently, a Baeyer-Villiger oxidation was suggested, to oxidise the ketone in the product into an ester, so that by hydrolysis, an alkyl alcohol could be revealed. Attempts had been previously made by Dr A. Day on a related compound, using *m*-CPBA as the oxidant, however this yielded only the isoquinoline-*N*-oxide (Scheme 2.20).



Scheme 2.20: First generation Baeyer-Villiger conditions. Reaction performed by Dr. A. Day.

Reviewing the literature, a second set of conditions were identified which were developed to tolerate nitrogen.[35] Application of these conditions produced an unusual ^{1}H NMR spectrum and some large crystals in the NMR tube. Characterisation of these crystals by single crystal X-Ray analysis revealed the structure to be the peroxy-diacetal **122**, a rare functional group first reported by Criegee and Metz in 1955 (Scheme 2.21).[36]

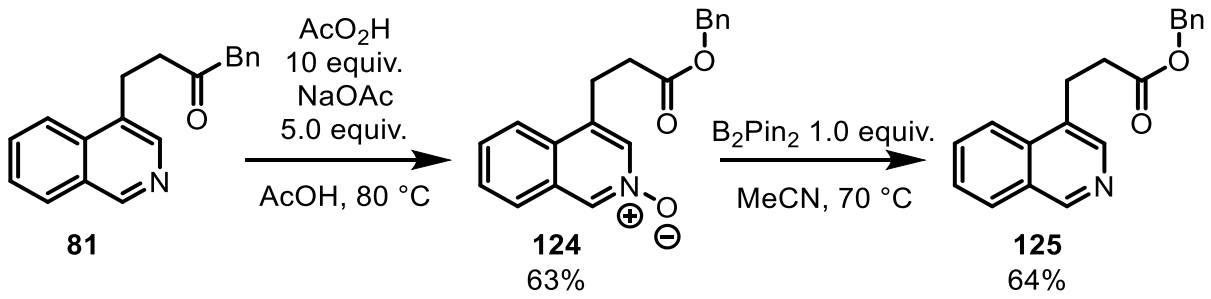
It was posited that the highly acidic conditions will cause isoquinoline to be protonated, thereby inhibiting the isoquinoline fragment from bearing a further partial positive charge and migrating. Methyl groups are not suitable for migration under Baeyer-Villiger conditions therefore the molecule cannot form the desired product.



Scheme 2.21: Second generation Baeyer-Villiger oxidation conditions and single crystal X-Ray structure of the product. Single crystal X-ray analysis conducted by Dr K. E. Christensen.

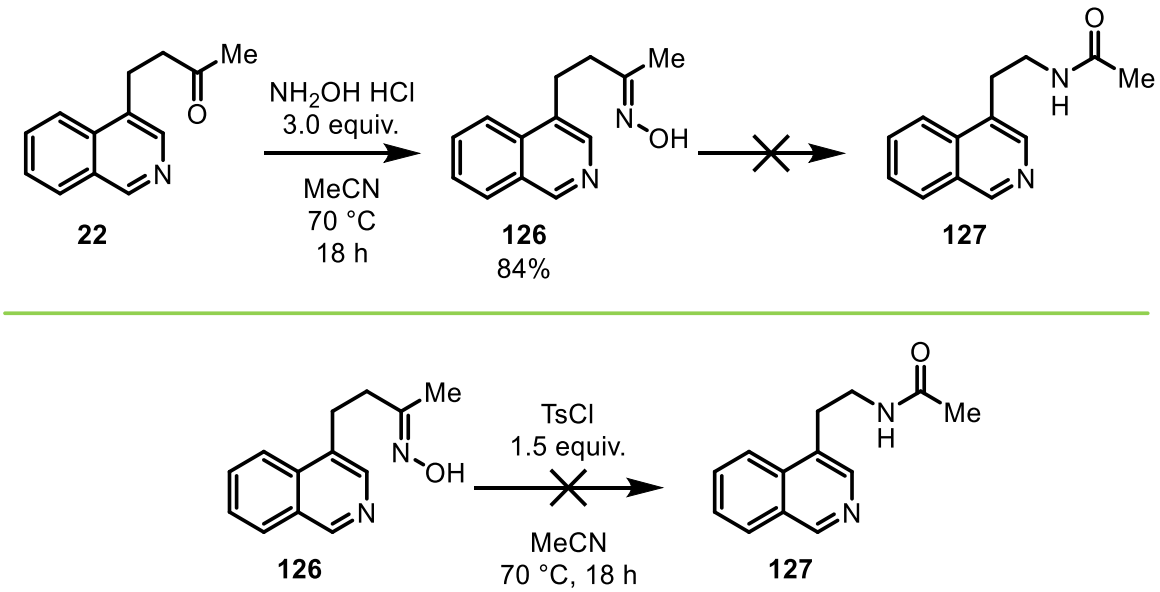
The transformation was eventually performed successfully using benzyl ketone product **81** as the substrate (Scheme 2.22). The presence of the benzyl group allowed the reaction to occur

with the benzyl group migrating, however overoxidation was observed, with a second step required to reduce the isoquinoline-*N*-oxide **124** produced to the desired isoquinoline **125**.



Scheme 2.22: Successful attempts at a Baeyer-Villiger Oxidation. Isolated yields are reported. Reactions performed by Dr A. Day.

An attempt was made to synthesise the analogous amide *via* a Beckmann rearrangement, however only the oxime **126** was observed, which unfortunately did not rearrange to the desired amide **127** when heated to 70 °C and merely decomposed (Scheme 2.23). This further supports our hypothesis that the isoquinoline moiety would be forced to bear a double cationic charge upon rearranging, thereby inhibiting it.

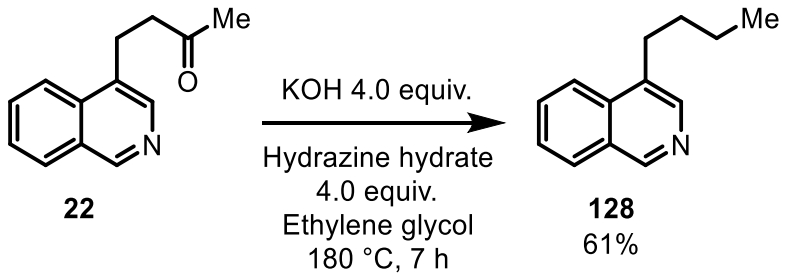


Scheme 2.23: Attempts towards a Beckmann rearrangement. Isolated yield is reported.

A subsequent attempt to force the oxime to rearrange using TsCl was also ultimately unsuccessful, causing starting material degradation (Scheme 2.23).

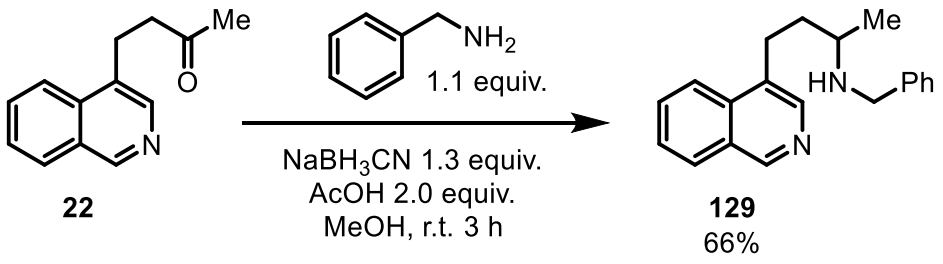
2.5.2 Diverse derivatisations

Focus was next turned to alternative derivatizations of ketones: a Wolff-Kishner reduction using literature conditions afforded product **128** in a respectable yield of 61% (Scheme 2.24).[37]



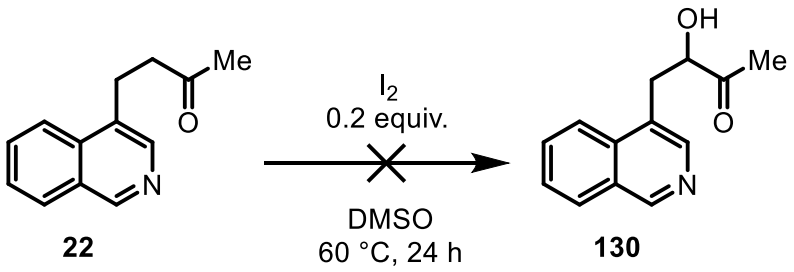
Scheme 2.24: Wolff-Kischner reduction of ketone **22** to form 4-butyl isoquinoline **128**. Isolated yield is reported.

A reductive amination was then performed, using benzylamine, to afford amine **129** in a moderate yield of 66% (Scheme 2.25).



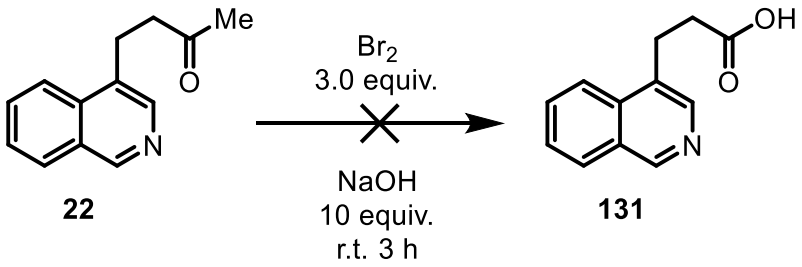
Scheme 2.25: Reductive amination of ketone **22** to form amine **129**. Isolated yield is reported.

Next an attempt at α-hydroxylation using a literature procedure by Jiao and co-workers, whereby molecular iodine and DMSO were used to oxidise the α-carbon.[38] Sadly, these conditions returned only starting material (Scheme 2.26).



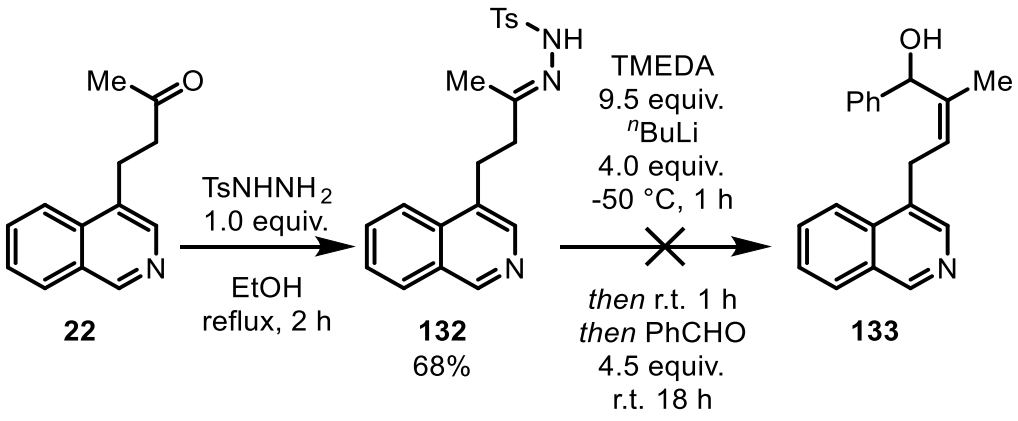
Scheme 2.26: Conditions published by Jiao and co-workers for the α-hydroxylation of ketones.

Several attempts at a haloform reaction were made, however sadly all conditions trialled returned starting material (Scheme 2.27).



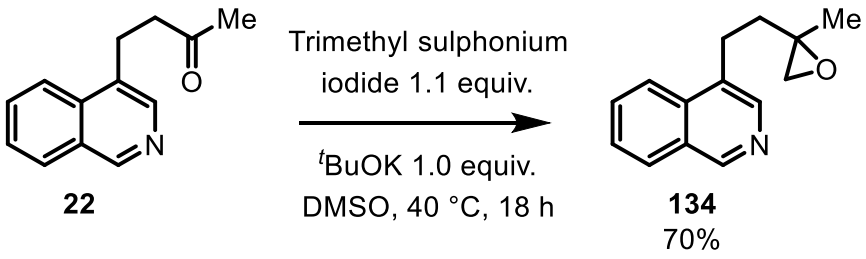
Scheme 2.27: Attempts towards a haloform oxidation.

A Shapiro reaction was performed, with tosyl hydrazone **132** synthesised in a good yield of 68% (Scheme 2.28).[39] Unfortunately attempts to complete the reaction with ^{n}BuLi and benzaldehyde as an electrophile produced only a complex mixture of decomposition products.



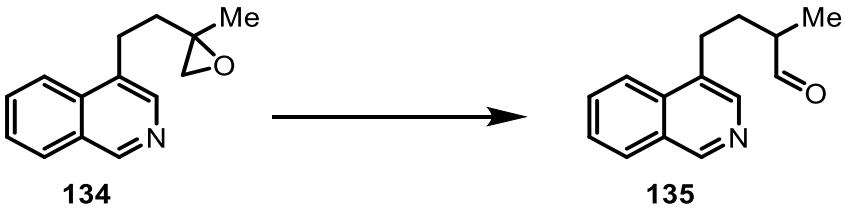
Scheme 2.28: Attempts towards a Shapiro reaction. Isolated yield is reported.

Finally, a Corey-Chaykovsky-Meinwald strategy was hypothesised, which would enable a terminal aldehyde to be fashioned from an epoxide rearrangement. Pleasingly the epoxide from the Corey-Chaykovsky reaction was formed in a good yield of 70% using literature conditions (Scheme 2.29).[40]



Scheme 2.29: Successful Corey-Chaykovsky epoxidation. Isolated yield is reported.

Taking the epoxide product **134**, several Lewis acids suggested by the literature were subsequently screened to produce a Meinwald re-arrangement (Table 2.8). Regrettably, all the literature combinations trialled, including a catalytic mix of $AuCl_3$ and $AgSbF_6$, $InCl_3$, $SnCl_4$ and BF_3 diethyl etherate, failed to effect the desired rearrangement, and merely returned starting material.[41-42]

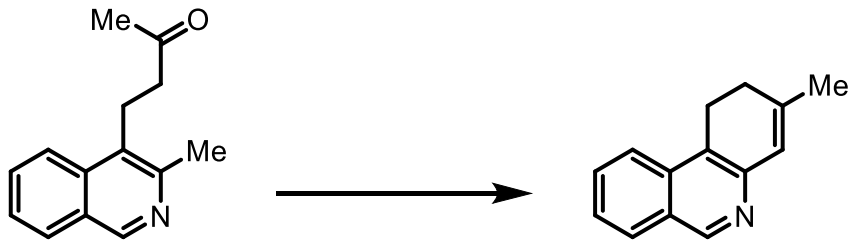


Entry	Reagent	Yield of 135 (%)
1	$AuCl_3$ + $AgSbF_6$	0
2	$InCl_3$	0
3	$SnCl_4$	0
4	BF_3 Et_2O	0

Table 2.8: Lewis acids screened for a proposed Meinwald rearrangement.

2.5.3 Annulation attempts with 3-Me isoquinoline 93

It was suggested that if 3-Me product **93** was treated with a base, it might be possible to deprotonate the isoquinoline methyl group and subsequently perform an aldol reaction onto the pendant carbonyl. Whilst these protons are not the most acidic in the molecule, it was hoped that even a minor component of the reaction mixture might allow the proposed cyclisation to occur.



93 **136**

Entry	Conditions	Temperature (°C)	Yield of 136 (%)
1	2.0 eq. ^{t}BuOK in ^{t}BuOH	80	0
2	2.0 eq. ^{t}BuOK in ^{t}BuOH	80	0
3	2.0 eq. ^{t}BuOK in DMF	80	0
4	5.0 eq. $NaHCO_2$, 0.5 equiv. Phase transfer catalyst	40	0
5	Excess NEt_3, 3Å MS	80	0
6	1.0 eq. AlO^{t}Bu in PhMe	110	0
7	Excess conc. HCl	80	0
8	Excess conc. H_2SO_4	80	0
9	2.0 eq. TsOH in PhMe	110	0

Table 2.9: Annulation attempts encompassing both basic and acidic conditions. Phase transfer catalyst used was CTAB; hexadecyltrimethylammonium bromide.

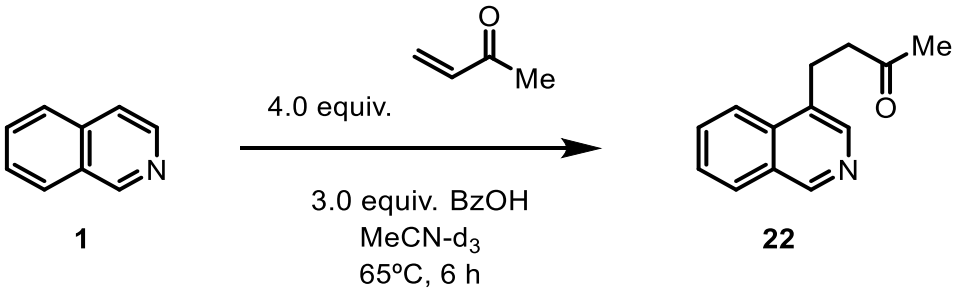
Using reversible basic conditions as a starting point, several variations of conditions were attempted with little success (Table 2.9, Entries 1-6). Most conditions attempted gave a complex mixture with no or few aromatic peaks in the ^{1}H NMR spectra.

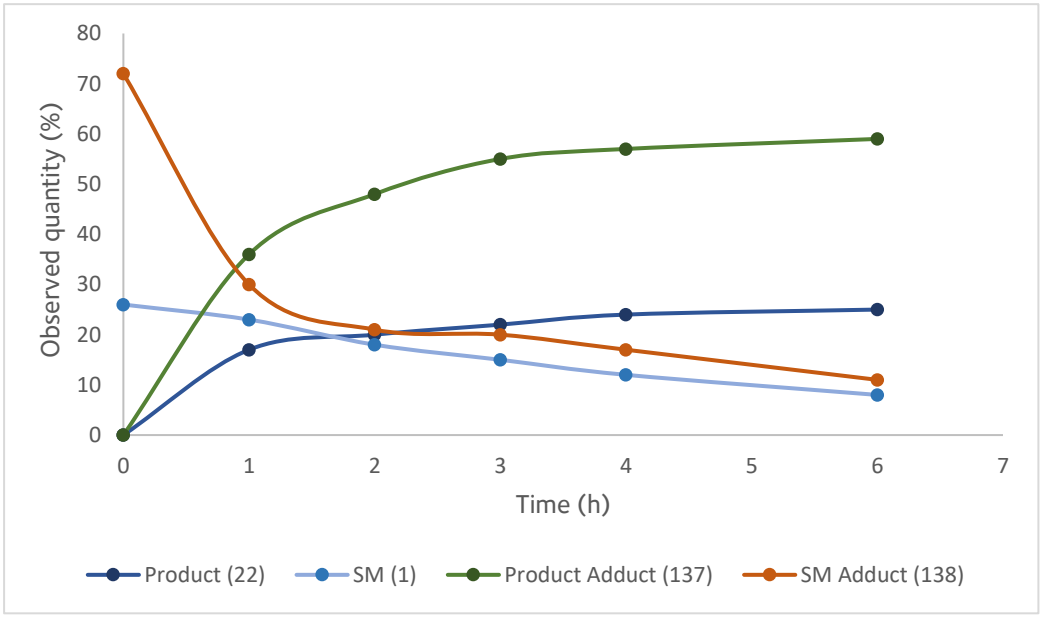
Next, we moved to acidic conditions (Table 2.9, Entries 7-9). Upon addition of any concentrated acid, a pale brown precipitate was observed, that persisted over the reaction time, addition of aqueous base on work up, however, dissolved this precipitate. It was postulated that the precipitate is the protonated salt of the starting material which is insoluble in the solvents used. Acidic conditions afforded no product and crude ^{1}H NMR spectra revealed only starting material, which bears out our hypothesis above. With no success and limited leads available this path of investigation was curtailed.

2.6 Mechanistic considerations

During the optimisation stages of this project, Dr A. Day performed a reaction in an NMR tube with 1.0 equivalent of an internal standard present. By cooling the reaction every hour and running a quantitative ^{1}H NMR spectrum, he observed the species present and their relative amounts (Figure 2.2).

It transpires that isoquinoline and methyl vinyl ketone very readily form a salt *via* 1,4-addition into the vinyl ketone. We hypothesise that this salt is not the reactive species and dissociation of this adduct must occur for the reaction to take place. After the desired reaction occurs, some of product **22** reforms the Michael adduct **137** with MVK, but some does not, remaining as the free molecule **22**. As expected, starting material decreases over time until a product maximum is reached.





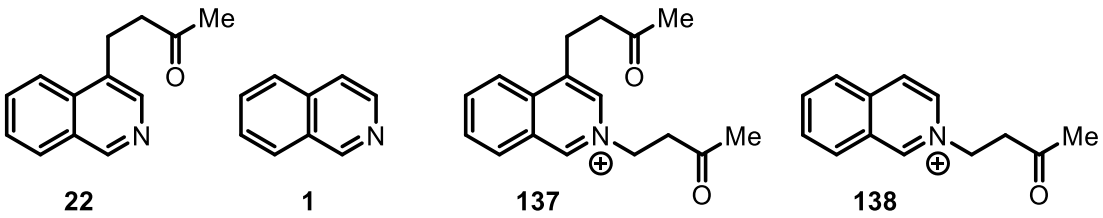


Figure 2.2: Relative amounts of reactive intermediates present in the reaction over time. The data quoted are approximate integrals from a series of quantitative ^{1}H NMR experiments conducted with 0.33 equiv. of 1,3,5-trimethoxybenzene present as an internal standard. Data obtained by Dr A. Day.

A mechanism was proposed by Dr A. Day to rationalise these observations (Figure 2.3). Formation of adduct **138** with MVK **16** is fast for isoquinoline **1**. Dissociation is required for the reaction to occur, thus only a small percentage of starting material exists as the reactive species. Upon formation, product can also quickly form adduct **137** with MVK. This proposed

regime would mean that the reaction rate is limited by the percentage of free isoquinoline present at any one time.

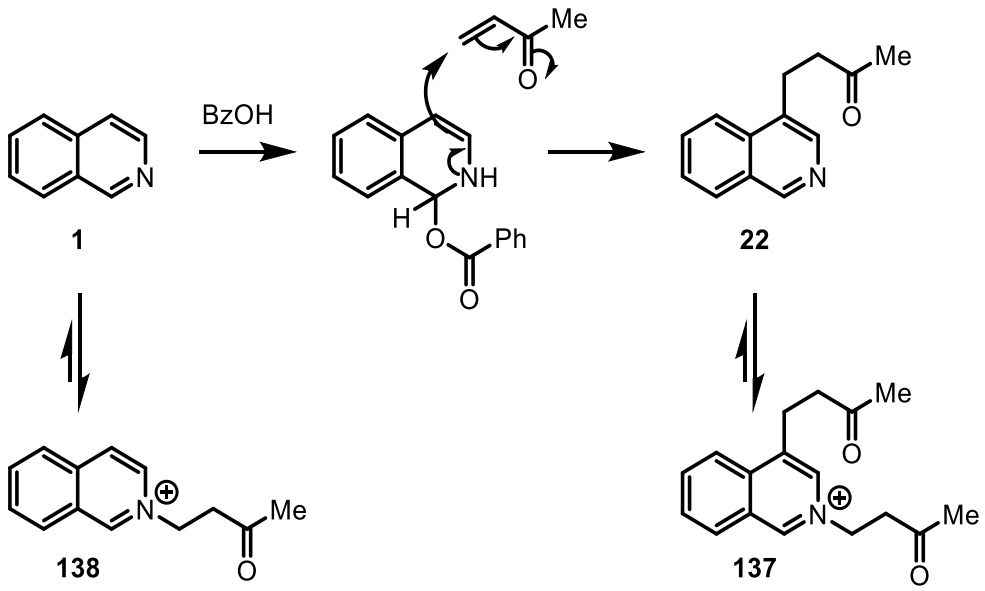
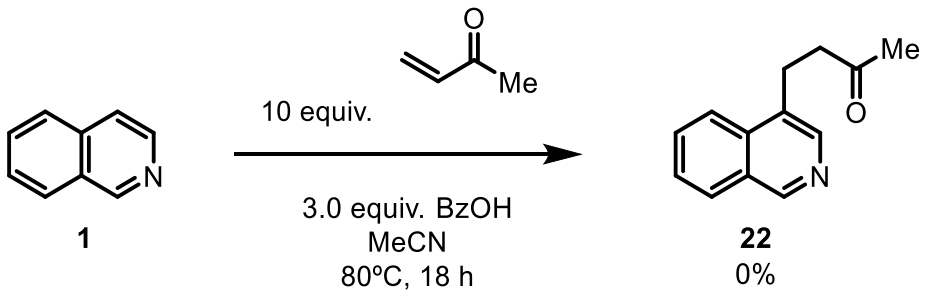


Figure 2.3: Equilibrium set up of the reaction, showing bias to adducts **137** and **138**.

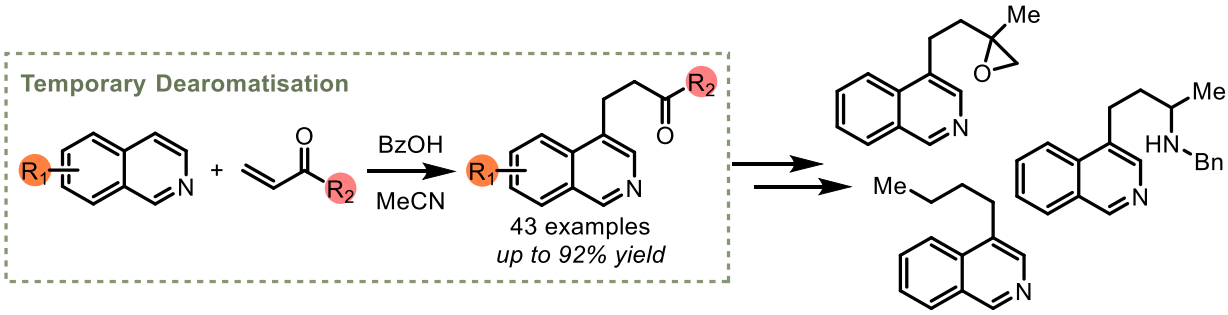
In order to test our hypothesis that the reactive species was the free isoquinoline, an experiment was performed with a large excess of MVK (Scheme 2.30). Ten equivalents of MVK were used in an attempt to ensure that as much of adduct **138** was formed as possible. Interestingly, no reactivity was observed, which we suggest provides evidence for our hypothesis.



Scheme 2.30: Mechanistic experiment with a large excess of electrophile.

2.7 Conclusion

We have developed a method that functionalises unactivated isoquinolines in a redox neutral process using a mild, cheap and non-toxic reagent under non-forcing conditions. It is an operationally simple four component reaction with a wide and tolerant isoquinoline scope but is limited to vinyl ketone electrophiles. We have explored the scope of aryl vinyl ketone electrophiles, as well as a short scope of alkyl vinyl ketones. It has been demonstrated that multiple product derivatisations are possible, and we have briefly investigated the mechanism by use of analytical techniques to examine the reaction intermediates. This method shows promise as a mild method for redox neutral functionalisation but is limited by the electrophile scope.



Scheme 2.31: Temporary dearomatisation strategy to access *β*-functionalised isoquinolines with product derivatisation to diverse functionality.

Chapter 3 – Oxidative debenzylation of partially saturated THIQs to isoquinolines

3.1 *N*-Heterocycle rearomatisation

3.1.1 The need for more unsaturated nitrogen heterocycles

Clinically successful pharmaceutical molecules are increasingly composed of sp^3 carbons, with saturated carbon centres replacing the more traditional aromatics and olefinic sp^2 carbons. This movement, partially driven by the increased metabolic stability of saturated sp^3 carbons in comparison to their sp^2 counterparts, was highlighted by Lovering and co-workers popularising the phrase 'Escape from Flatland'.[43] Through statistical analysis of drug molecules making their way through clinical trials, it was shown that a greater fraction of sp^3 carbons (Fsp^3) in a drug candidate is more likely to result in an approved medicine. Other related factors include increasing molecular complexity and the presence of one or more stereocentres.

These findings are reflected in many synthetic chemistry communications published in recent years, with an increasing number of methods available to the synthetic chemist to perform reductions of unsaturated cyclic moieties to form desired saturated sp^3 rings. These can often, in the case of heterocycles, be combined with a functionalisation reaction to afford a saturated species with significantly increased molecular complexity and consequently a higher Fsp^3. A recent review of the field by Donohoe and co-workers showed the variety of the reductive functionalisation reactions published in the literature, which can be used to generate a wide range of complex *N*-heterocycles from aromatic precursors.[19]

More recently, however, further analysis of pharmaceutical molecules making their way through testing and into the clinic have shown that successful drug candidates are becoming less saturated, in defiance of the predictions made by Lovering and co-workers.[44]

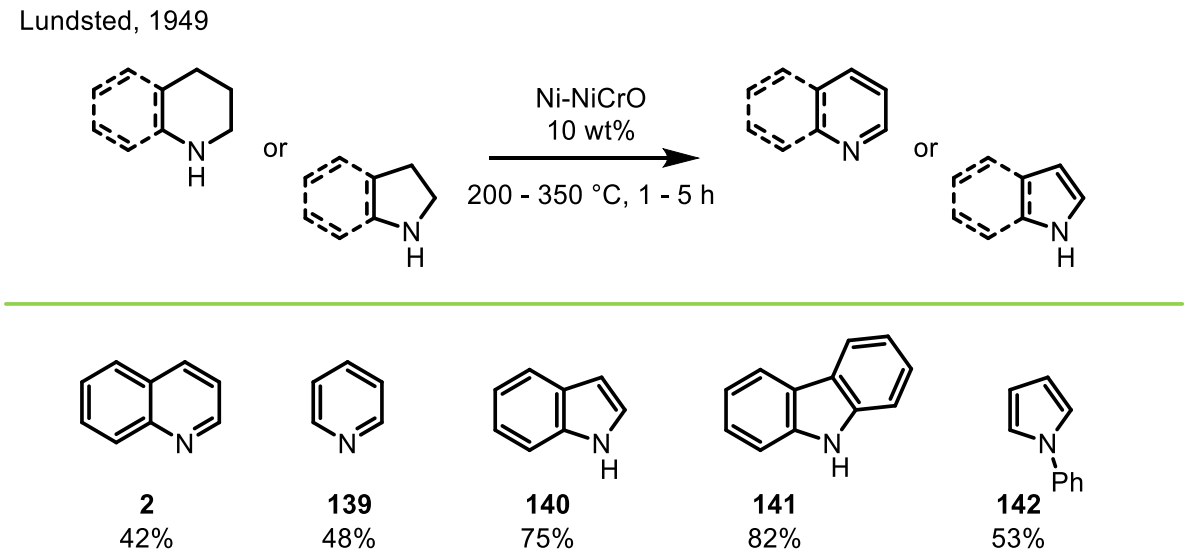
Analysis of the data shows that Fsp^3 is decreasing on average in recent years, with a conclusion proposed by the authors that Fsp^3 is not a useful metric to optimise as part of drug design, as the success of small molecule active pharmaceuticals is a largely complex problem, which is not well suited to distillation down to a single statistical parameter.

As previously discussed, however, functionalisation of pre-existing aromatic systems is highly challenging and can require extreme and harsh conditions (*vide supra*). Therefore, a useful synthetic transformation would be to oxidise a functionalised partially saturated *N*-heterocycle back to its parent aromatic molecule.

3.1.2 Oxidation of saturated and semi-saturated *N*-heterocycles to aromatics

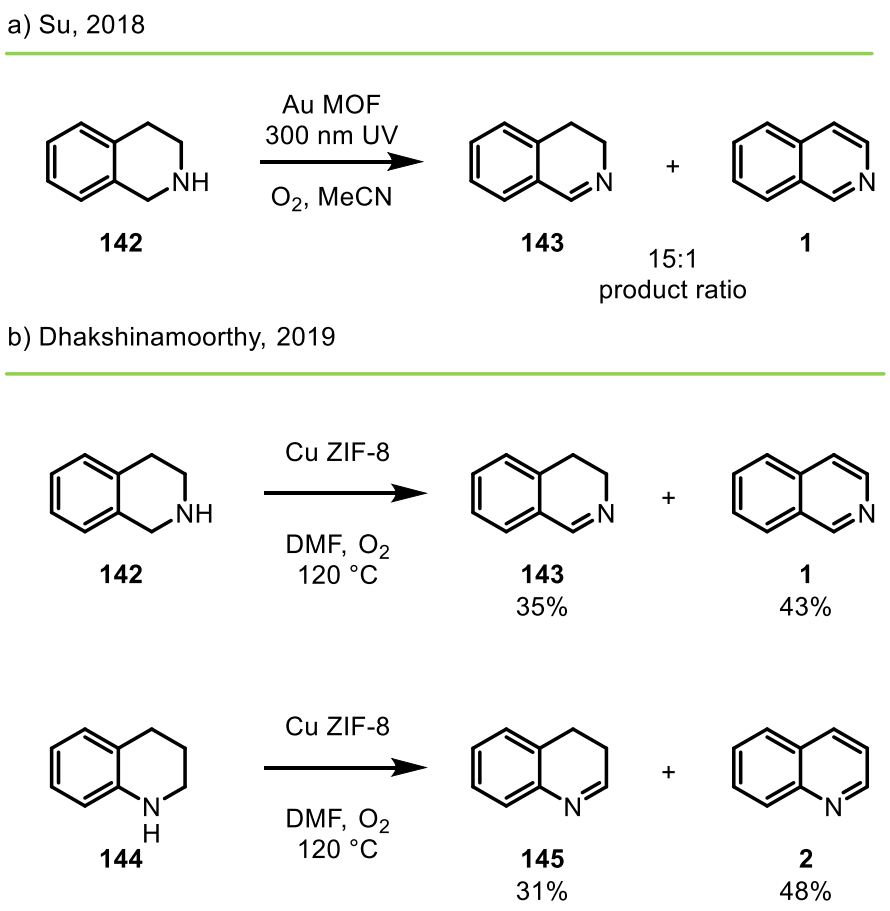
With a burgeoning interest in oxidation of *N*-heterocycles, various strategies have been developed to generate planar sp^2 based systems from a saturated precursor. Many techniques have been invoked in the literature, both catalytic and stoichiometric, including both homogenous and heterogeneous metal reagents, along with a handful of metal-free examples.

In 1949, Lundsted and co-workers employed a heterogeneous Ni-NiCrO catalyst and high temperatures to force the formation of aromatic *N*-heterocycles from their saturated analogues (Scheme 3.1).[45] Whilst the method is general and the catalyst robust, this method was unsuitable for use in late-stage functionalisation due to the harsh conditions used.



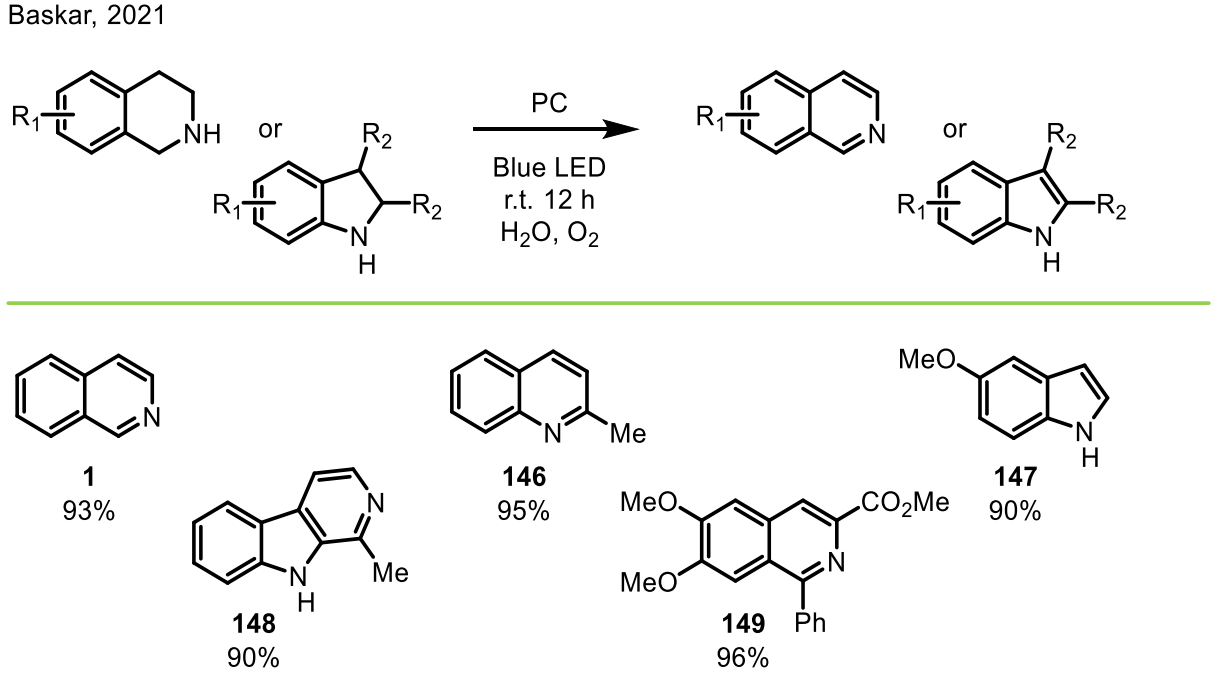
Scheme 3.1: Ni-NiCrO catalysed high temperature pyrolysis of saturated *N*-heterocycles to form aromatic analogues. Selected examples shown.

Adopting a milder approach, Su and co-workers showed in 2018 that immobilised Au(III) atoms held in a MOF could be used in a photochemical reaction to generate singlet oxygen.[46] The *in situ* generated singlet oxygen could then oxidise tetrahydroisoquinolines (THIQs) to dihydroisoquinolines with a small amount of fully oxidised isoquinoline (Scheme 3.2). The mechanism of the final oxidation to isoquinoline **1** was not discussed but may potentially be due to a further singlet oxygen oxidation. Dhakshinamoorthy and co-workers chose a related approach, with a Cu Zeolitic Imidazolate Framework (Cu-ZIF) catalyst (Scheme 3.2).[47] When partially saturated *N*-heterocycles such as tetrahydroisoquinoline **142** or tetrahydroquinoline **144** were heated in an oxygen atmosphere, the fully aromatic *N*-heterocycle was formed as the major product alongside other oxidation products. After mechanistic investigation, the authors proposed that a radical oxygen species was generated by the Cu(II)-ZIF which then abstracted a hydrogen atom, generating a C-centred radical. This radical can then form a bond with a second oxygen radical species to afford alcohol and ketone products.



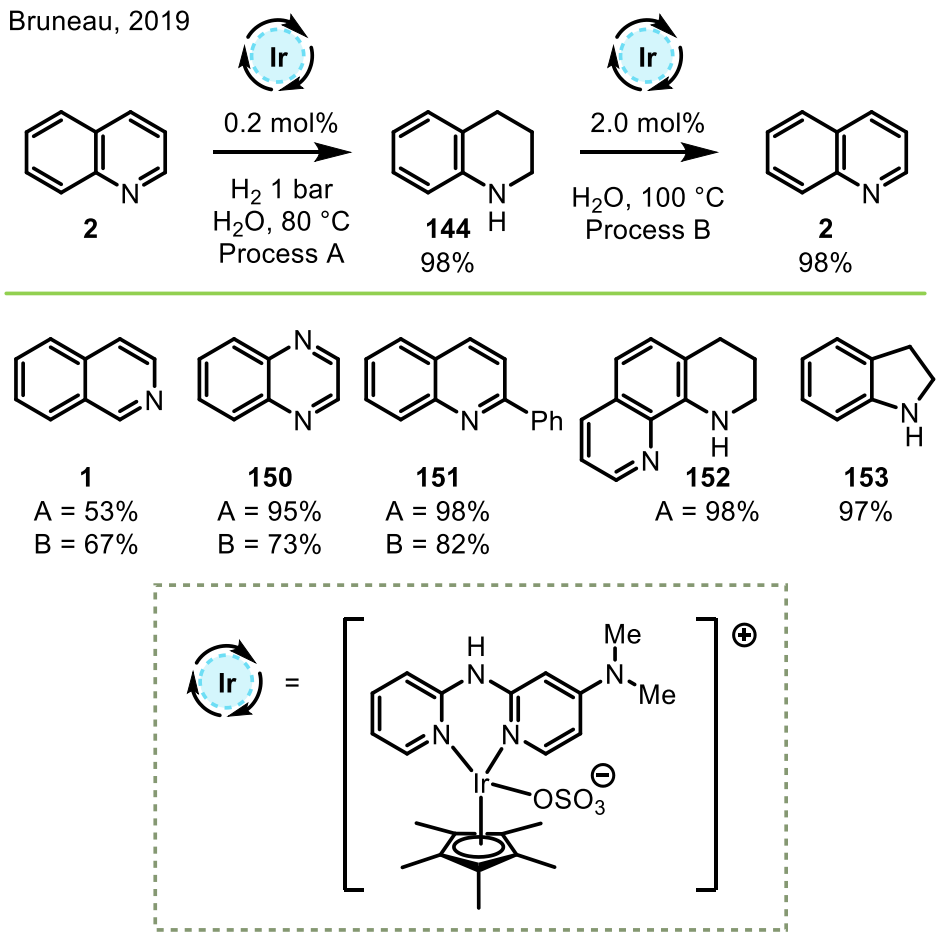
Scheme 3.2: a) Photochemical initiated oxidation of THIQ **142** using an Au MOF by Su and co-workers, 2018. b) Thermal Cu-ZIF oxidation of THIQ and THQ. Selected examples shown.

Using a related approach, Baskar and co-workers developed La-doped $NiWO_4$ nanoparticles that, under the activation of blue LED irradiation, generated radical oxygen species which oxidised tetrahydro-*N*-heterocycles to their fully aromatic analogues (Scheme 3.3).[48] This was demonstrated with THIQ and THQ substrates, producing isoquinoline **1** and quinoline **2**, amongst other scope products, in excellent yields. This method, although highly impressive and pleasingly general, nonetheless suffers from the same drawback as the previous two examples; each requires a complex catalyst which can be highly challenging to synthesise, store, handle and use without sufficient expertise and experience.



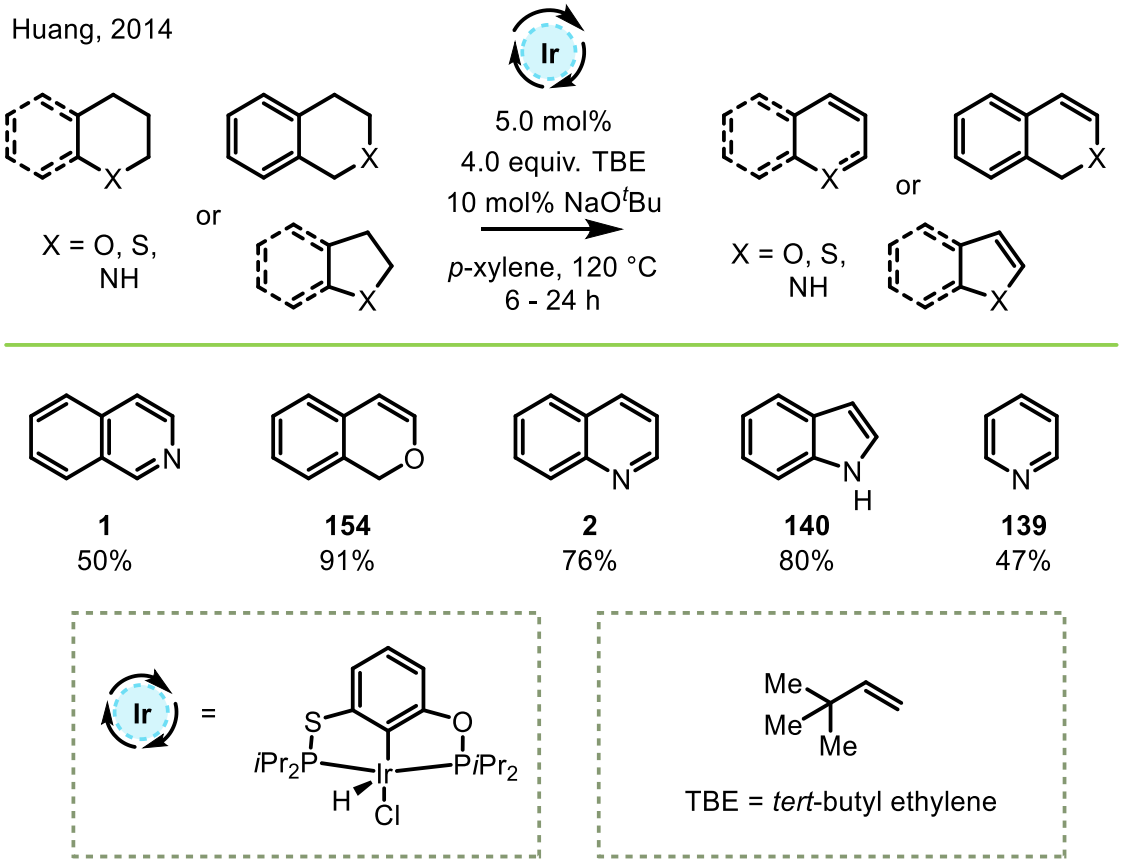
Scheme 3.3: Full oxidation of the heterocyclic ring in THIQs and THQs using La-doped $NiWO_4$ nanoparticle photocatalyst. Selected examples shown.

In 2019, Bruneau and co-workers reported an iridium-catalysed method for the interconversion of unsaturated and semi-saturated *N*-heterocycles (Scheme 3.4).[49] Although the method was optimised for the interconversion between quinolines and tetrahydroquinolines (THQs), the approach was shown to be applicable to other heterocycles such as indoles, isoquinolines and phenanthrenes. The presence or absence of hydrogen gas in the reaction was shown to give either hydrogenation or dehydrogenation respectively. The method is shown to be both high yielding, broadly applicable and able to oxidise or reduce several classes of *N*-heterocycle, however the method requires a bespoke iridium catalyst. The reversibility of hydrogenation demonstrates how a switch between unsaturated and semi-saturated *N*-heterocycles can be performed easily as a late-stage transformation on a wide variety of molecules, which would enable access to either the partially saturated or fully aromatic versions of drug candidates at a late stage in the development of the molecule.



Scheme 3.4: Sequential reduction and oxidation of *N*-heterocycles using Ir catalysis. Selected examples shown.

In a related transfer hydrogenation approach, Huang and co-workers used an iridium catalyst to oxidise semi-saturated *N*-heterocycles to their aromatic analogues (Scheme 3.5).[50] The method required a sacrificial alkene as the oxidant and could be extended to include oxygen and sulfur-based aromatics. It is worth noting, however, that the optimised conditions are fine-tuned between substrates to achieve the best yield possible, with catalyst loading increased from a minimum of 0.1 mol% to 5.0 mol%, a 50-fold increase. Moreover, the bespoke iridium catalyst reduces the accessibility of the method and the need for a sacrificial oxidant renders the atom economy of this process poor.

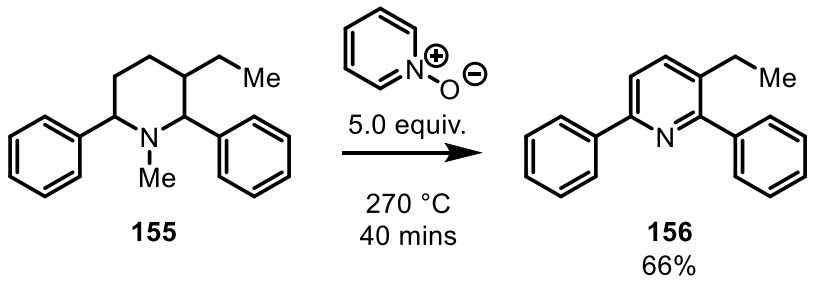


Scheme 3.5: Ir-catalysed transfer hydrogenation using *tert*-butyl ethylene as a sacrificial alkene. Selected examples shown.

3.1.3 Metal-free *N*-heterocycle dehydrogenation

An alternative, metal-free approach for the oxidation of *N*-heterocycles was reported by Vasil'ev and co-workers in 1977 (Scheme 3.6).[51] Using pyridine-*N*-oxide as a stoichiometric oxidant, a 2,6-substituted *N*-methyl piperidine **155** was aromatised to the corresponding pyridine **156**. Whilst this process is metal-free, extremely high temperatures are employed to achieve the desired transformation. The scope of the method was not fully explored, and only a handful of different piperidines and piperidones were subjected to the reaction conditions.

Vasil'ev, 1977



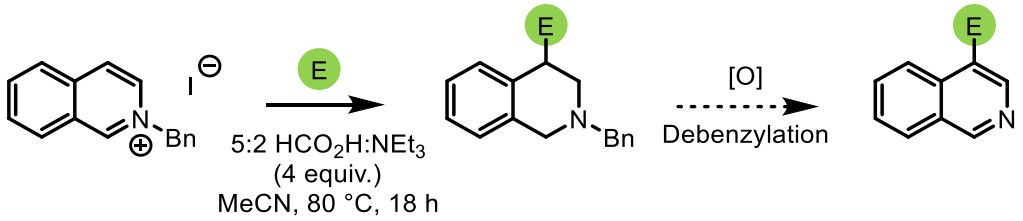
Scheme 3.6: Oxidation of *N*-methyl piperidine **155** to form pyridine **156** using pyridine-*N*-oxide as a stoichiometric oxidant.

3.2 Investigations towards a metal-free oxidative route to C4-functionalised isoquinolines

3.2.1 Project Aims

Reflecting on these publications, it was suggested that there was an opportunity to develop a general method for dehydrogenating semi-saturated *N*-heterocycles to form their unsaturated aromatic counterparts in a metal-free, easily accessible process. Such a process should have good atom economy, employ a cheap, readily available oxidant and the reaction conditions should be suitable for late-stage functionalisation.

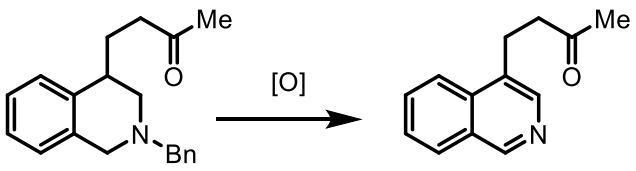
Our previous work with direct functionalisation of isoquinolines was limited in its electrophile scope (see Chapter 2), as such we aimed to develop a more widely applicable isoquinoline C4-functionalisation. The Donohoe group has previously reported a convenient method for the reductive functionalisation of quinolines and isoquinolines. The method employs the mildly acidic 5:2 HCO_2H:NEt_3 reductant system to form C4 functionalised THIQs from activated isoquinolinium salts (*vide supra*).[23] Given the broad scope of this method, we aimed to devise an approach to reoxidise the product THIQs to the corresponding isoquinolines. Taken in conjunction, this would then provide a strategy for a formal C4-functionalisation of isoquinolines over two steps (Scheme 3.7).



Scheme 3.7: Two-step strategy towards rearomative functionalisation.

3.2.2 Oxidant screening

Based on literature precedent, a range of oxidation conditions were trialled for the model reaction shown (Table 3.1).[51-56] Unfortunately, most of the oxidants screened gave either starting material or a complex mixture (Table 3.1, Entries 1-10). Pleasingly, when using pyridine-*N*-oxide **158** as an oxidant, a small amount of product **22** (6%) was observed in an otherwise complex mixture (Table 3.1, Entry 11). This demonstrated that both oxidation and cleavage of the benzyl activating group are possible in a one-pot process.



157 **22**

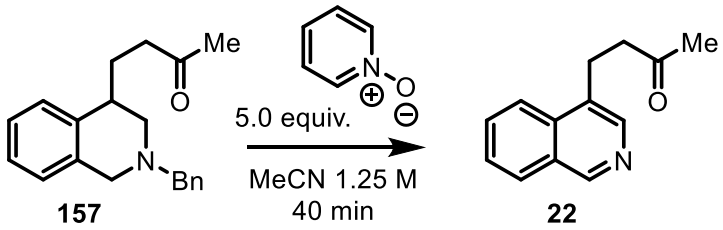
Entry	Oxidant	Oxidant Equivalents (Equiv.)	Temperature (°C)	Result
1	$CuCl_2$, $Pd(TFA)_2$, AgF O_2 balloon[52]	2.0, 5.0 mol%, 0.2	115	Complex mixture
2	^tBuOK[53]	3.0	140	Starting material
3	MnO_2[54]	0.25	85	Starting material
4	$CuBr_2$, DBU[55]	0.2, 2.0	r.t.	Starting material
5	DDQ	2.0	r.t.	Complex mixture
6	$FeCl_3$	3.0	80	Complex mixture
7	I_2, K_2CO_3	2.0, 5.0	80	Complex mixture
8	HNO_3	3.0	80	Complex mixture
9	CAN[56]	2.5	r.t.	Complex mixture
10	nitrobenzene	0.25 M	140	Starting material
11	**pyridine-*N*-oxide[51]**	**5.0**	**200**	**6% 22**

Table 3.1: Oxidant screening. Yields reported are determined by quantitative ^1H NMR spectroscopy. Reactions performed on 0.125 mmol scale.

3.3 Reaction Optimisation

It was posited that both addition of a solvent and reduction of the reaction temperature would reduce the observed decomposition and lead to a less complex reaction mixture, hopefully resulting in a greater yield. Subsequently, the reaction was performed at a range of lower temperatures using MeCN as a reaction solvent (Table 3.2). Disappointingly, no reactivity was observed at either of the two lower temperatures trialled, 100 and 150 °C, however pleasing amounts of reactivity were observed at our original reaction temperature of 200 °C with a yield

of 41% afforded (Table 3.2, Entries 1-3). We hypothesised that these results showed that high temperatures were required for the reaction to occur, but that dissolution of reactants limited the decomposition previously observed when the reaction was performed neat (*vide supra*).



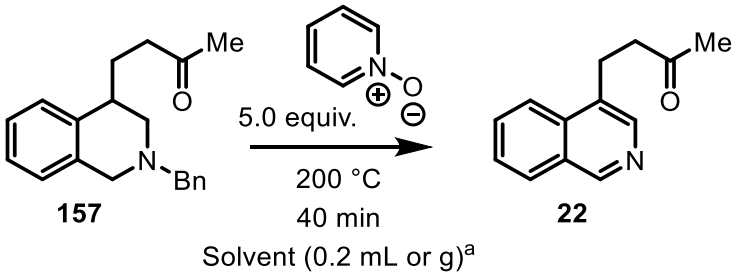
Entry	Temperature (°C)	Yield of 22 (%)
1	100	0
2	150	0
3	200	(41)

Table 3.2: Lower temperature investigations. Yields reported are calculated using reverse phase HPLC. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale.

Following this promising lead, the reaction was screened against a number of solvents (Table 3.3). All of the solvents screened afforded a higher yield than our initial hit under neat conditions, however the yields were highly varied. Interestingly, there was seemingly no correlation between yield and solvent boiling point, with some solvents affording good yields despite being heated well above their boiling point in a sealed vial, such as MeCN, which produced the second highest isolated yield of the screen.

Some lower boiling point solvents, such as MeCN and PhMe, afforded promising yields of 41% and 32% respectively, but then slightly higher boiling point solvents gave much lower yields, with DMA, DMSO and 1-Me-2-pyrrolidinone affording yields of 16%, 14% and 18% respectively (Table 3.3, Entries 1-5). Our highest yield of 52% was afforded when camphor was used as the reaction solvent, however nitrobenzene, a solvent with a very similar boiling point, gave only 40% yield (Table 3.3, Entries 6, 7). Finally, two further high boiling point

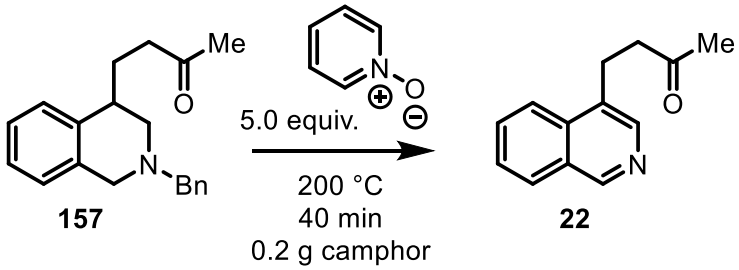
solvents, biphenyl and sulfolane, afforded disappointing isolated yields of 21% and 26% respectively (Table 3.3, Entries 8, 9). To investigate reaction concentration, the quantity of camphor used was increased from 0.2 g to 0.5 g, diluting the reaction, which caused the yield to decrease from 52% to 27%. All subsequent reactions were performed with 0.2 g of camphor (Table 3.3, Entry 6, 7). There appears to be no real trend between solvent polarity and yield, with highly polar solvents performing less well in some cases, such as DMSO which afforded only 14%, but better in others, such as MeCN which afforded 41% (Table 3.3, Entries 1, 4).



Entry	Solvent	Boiling Point (°C)	Yield of 22 (%)
1	MeCN	82	(41)
2	PhMe	110	(32)
3	DMA	165	26
4	DMSO	189	14
5	1-Me-2-pyrrolidinone	202	18
6	**camphor**	**209**	**(52)**
7[b]	camphor	209	24 (27)
8	nitrobenzene	211	(40)
9	biphenyl	255	25 (21)
10	sulfolane	285	28 (26)

Table 3.3: Solvent screen. Yields reported are calculated using reverse phase HPLC. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale in a sealed microwave vial. [a]Solvents which are solid at r.t. were measured by mass, whereas solvents that are liquid at r.t. were measured by volume. [b]Reaction performed with 0.5 g solvent.

The effect of the reaction atmosphere was investigated by the addition of a balloon containing varying gases to the reaction. Interestingly, the identity of the gas in the balloon was seemingly irrelevant, with oxygen, argon and nitrogen affording very similar HPLC yields of 40%, 39% and 36% respectively (Table 3.4, Entries 2-4). Although all of these yields are less than when the reaction was sealed, it was thought that the presence of a balloon would prevent the reaction vessel becoming over pressurised during the reaction, and therefore make our procedure safer (Table 3.4, Entry 1). Accordingly, subsequent investigations were conducted with a nitrogen balloon.



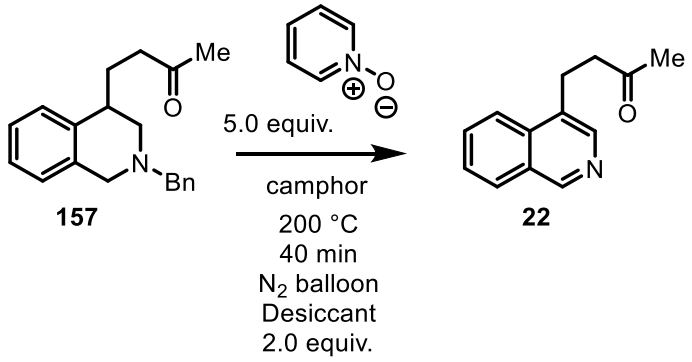
Entry	Differing conditions	Yield of 22 (%)
1	-	(41)
2	O_2 balloon	40 (33)
3	Ar balloon	39
4	N_2 balloon	36

Table 3.4: Investigating reaction concentration and headspace. Yields reported are calculated using reverse phase HPLC. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale.

It was proposed that the reduction of pyridine-*N*-oxide during the course of the reaction could potentially form water as a side product. To investigate if this had a detrimental effect on the reaction, a number of dehydrating agents were screened in an attempt to increase the yield (Table 3.5).

Pleasingly, addition of SiO_2, Na_2SO_4 and $CaCl_2$ all increased the yield to 45%, 48% and 51% respectively as compared to no addition of desiccant, potentially indicating that H_2O does have

a negative impact on our reaction yield (Table 3.5, Entries 1-4). The final desiccant screened, P_2O_5, afforded only a complex mixture (Table 3.5, Entry 5). Unfortunately, addition of an excess of water still produced reactivity, albeit in a marginally lower yield than with a dehydrating agent present (Table 3.5, Entry 6). Although a small increase in yield was observed when using dehydrating agents, the addition of superstoichiometric quantities of water did not shut down reactivity, which disproves our theory that production of water is supressing reactivity. As such, it was decided not to continue using dehydrating agents.



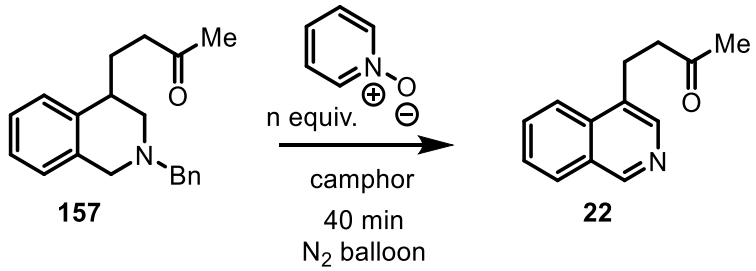
Entry	Desiccant	Yield of 22 (%)
1	-	36
2	SiO_2	45
3	Na_2SO_4	48 (53)
4	$CaCl_2$	51 (44)
5	P_2O_5	Complex mixture
6[a]	-	36

Table 3.5: Screening of desiccants. Yields reported are calculated using reverse phase HPLC. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale. [a]Sealed vessel, 5.0 equiv. H_2O added.

Inspired by the related paper by Vasil'ev and co-workers on the aromative formation of pyridines, it was noted that their reaction temperatures can be as high as 270 °C for some piperidine derived substrates. As such, we chose to investigate increasing our reaction temperature beyond 200 °C (Table 3.6). Pleasingly, increasing the temperature from 200 °C to

230 °C and then again to 250 °C showed a marked increase in yield from 36% to 66% and 62% respectively (Table 3.6, Entries 2-4). Interestingly, contrary to our previous investigation, when the reaction was again performed at 250 °C but without a balloon of N_2 a slight increase in yield to 66% was observed (Table 3.6, Entry 4). Increasing the temperature beyond 250 °C to 270 °C showed a reduction in yield to 37%, potentially due to decomposition of product and starting material (Table 3.6, Entry 5).

N.B. It was noted that the needles used to introduce a balloon of N_2 to our sealed vials failed when used with any reaction above 250 °C, with the components of the needle separating. Therefore, all reactions above that temperature were performed in a sealed microwave vial.

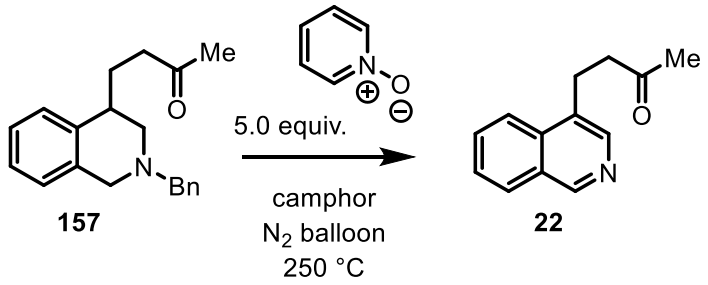


Entry	Temperature (°C)	pyridine-*N*-oxide equiv.	Yield of 22 (%)
1	200	5.0	36
2	230	5.0	66 (66)
3	250	5.0	(62)
4[a]	250	5.0	66[b]
5	270	5.0	37

Table 3.6: Higher temperature screening. Yields reported are calculated using reverse phase HPLC. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale. [a]Reaction performed without a N_2 balloon in a sealed vial. [b]Yield reported determined by quantitative ^{1}H NMR spectroscopy.

Next, we investigated the effect of varying the reaction time to show whether 40 minutes was allowing the reaction to reach maximum conversion (Table 3.7). Stopping the reaction at 20 minutes gave a significantly reduced yield of 48% (Table 3.7, Entry 1). Higher yields were

observed at reaction times of 30 and 40 minutes, affording yields of 63% and 74% respectively (Table 3.7, Entries 2, 3). Yields for longer reaction times were shown to be slightly reduced, with 62% and 66% desired product formation at 50 and 60 minutes respectively (Table 3.7, Entries 4, 5). This is perhaps due to product decomposition after reaction completion. 40 minutes was chosen as the optimum reaction time going forwards, as it was the longest reaction time before any yield reduction was observed.



Entry	Reaction time (min)	Yield of 22 (%)
1	20	48
2	30	76 (63)
3	40	74
4	50	(62)
5	60	66

Table 3.7: Reaction time investigations. Yields reported are calculated using reverse phase HPLC. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale.

3.3.1 Reproducibility issues

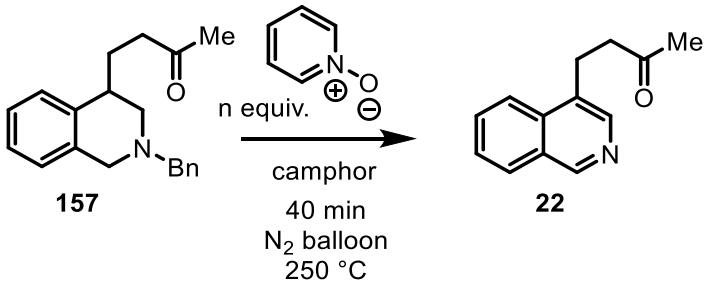
It was desired to assess the repeatability of our reaction conditions, and so three repeats of our 'best' conditions were performed (Table 3.8, Entry 1). Disappointingly, the yields varied greatly, with an excellent isolated yield of 88% produced by one reaction, but only 31% afforded by the other two, despite the identical conditions.

Our first hypothesis was that the hygroscopic nature of pyridine-*N*-oxide could be responsible for the observed irreproducibility; when added to the reaction, varying amounts of water present could result in a largely different amount of pyridine-*N*-oxide being added each time.

A screen of pyridine-*N*-oxide equivalents revealed a minimal difference in yield between 1.0, 3.0, 5.0 and 10 equivalents, affording 80%, 60%, 88% and 71% yields respectively (Table 3.8, Entries 2-4). We propose that this demonstrates that only 1.0 equivalent is required to perform our intended reaction, and that any amount over this quantity is unnecessary. This was reinforced by anecdotal evidence of our reaction, whereby experiments performed with three or more equivalents appeared charred and blackened, perhaps indicating that any excess reagent was decomposing at the reaction temperature.

Subsequent experiments with only 1.0 equivalent of pyridine-*N*-oxide showed a slight reduction in yield (58%, 66%, 62%) but slightly more concurrence between results (Table 3.8, Entry 5). The experiments were repeated once more in sealed vials which again showed a slight reduction in yields (70%, 63%, 68%) but increased repeatability (Table 3.8, Entry 6). We propose that the lack of reproducibility observed when a balloon is used is due to the needle becoming blocked by solidified camphor. This will occur at a different time for each reaction therefore introducing an uncontrollable variable.

In a last attempt to ensure repeatability, 1.5 equivalents of pyridine-*N*-oxide **158** were trialled to ensure that at least one equivalent was added to the reaction, irrespective of the quality of pyridine-*N*-oxide. Pleasingly, when trialled, our final conditions using 1.5 equivalents gave reasonable and repeatable yields of 69% and 65% respectively, representing a compromise between yield and repeatability (Table 3.8, Entry 7).



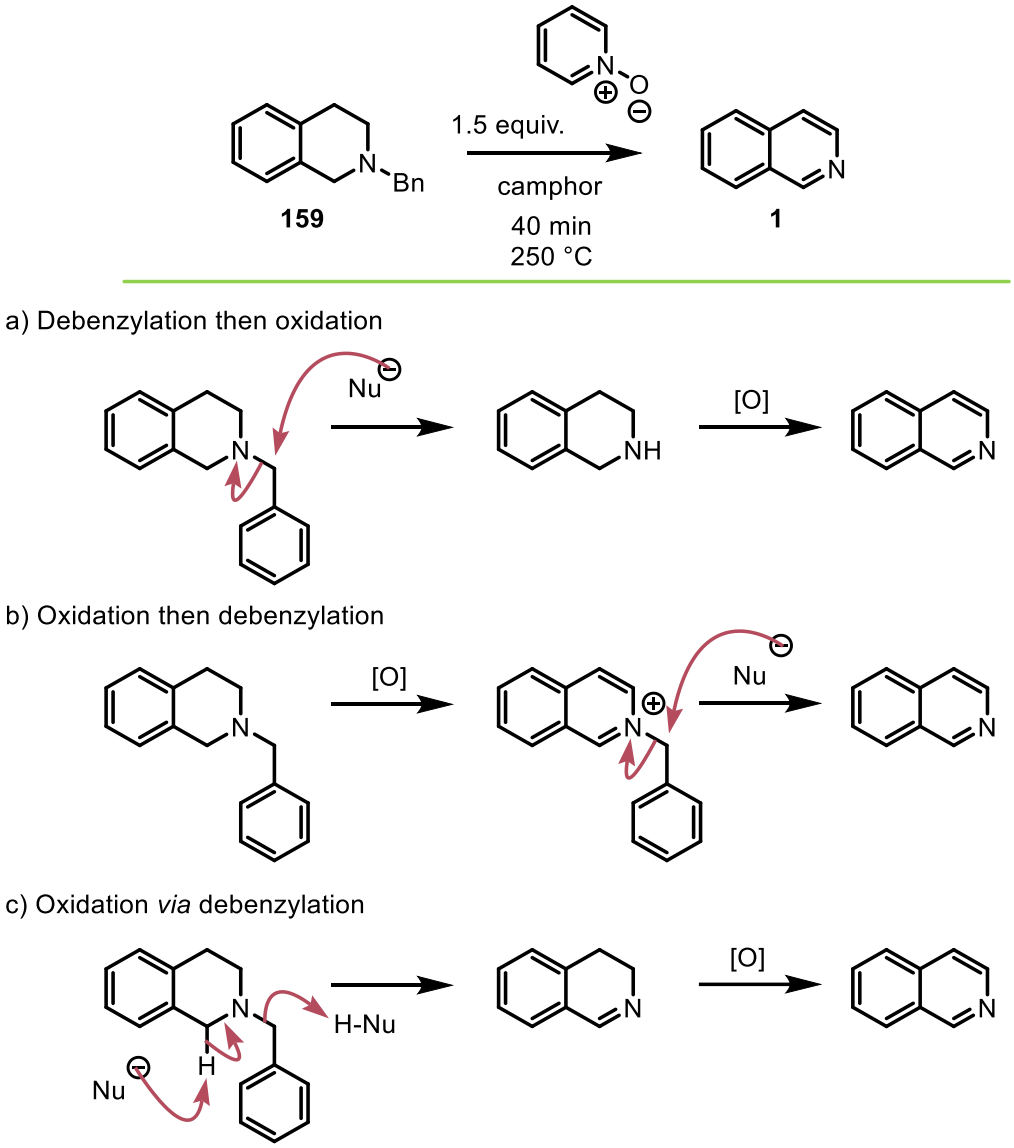
Entry	pyridine-*N*-oxide equivalents	Yield of 22 (%)
1	5.0	80 (88), 31, 31
2	1.0	73 (80)
3	3.0	60
4	10	78 (71)
5	1.0	(58), (66), 62
6[a]	1.0	70, 63, 68
7[a]	**1.5**	**(65), (69)**

Table 3.8: Assessing repeatability and varying pyridine-*N*-oxide equivalents. Yields reported are calculated using reverse phase HPLC. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale. [a]Reaction performed in a sealed vial.

3.4 Mechanistic Studies

3.4.1 Potential Mechanisms

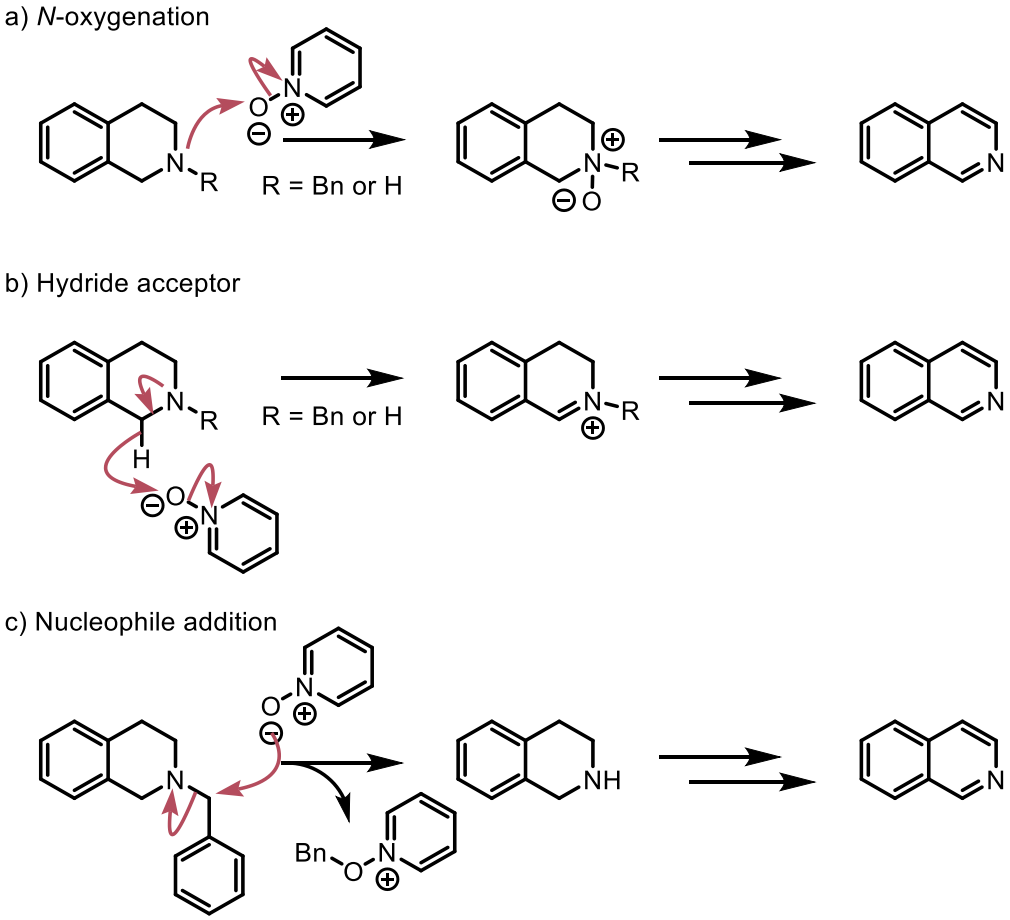
We considered several potential mechanisms for our transformation (Scheme 3.8). The reaction consists of two stages, debenzylation of the *N*-benzyl THIQ and oxidation to the isoquinoline. We wished to investigate the order of these steps, whether the benzyl activating group is removed first, (Scheme 3.8a) followed by oxidation of the free THIQ, or whether oxidation occurs first (Scheme 3.8b) then the resultant isoquinolinium salt is debenzylated afterwards. A third potential mechanism could be that the benzyl group is removed *via* proton removal at C1 of the THIQ, thereby partially oxidising the ring as well as debenzylating (Scheme 3.8c).



Scheme 3.8: Potential mechanisms for our transformation including a) Debenzylation then oxidation, b) Oxidation then debenzylation and c) Oxidation *via* debenzylation

As well as determining the reaction step order, we wished to discover the oxidation method that our oxidant, pyridine-*N*-oxide, was performing to transform the THIQ substrates into isoquinolines. We hypothesised three potential oxidation mechanisms, with pyridine-*N*-oxide acting as an oxygen atom donor (Scheme 3.9a), a hydride acceptor (Scheme 3.9b) or a nucleophile (Scheme 3.9c). If pyridine-*N*-oxide is acting as an oxygen atom donor, the acceptor atom is most likely to be nitrogen, as it is the most nucleophilic site in the molecule. An alternative proposal is that pyridine-*N*-oxide is acting as a hydride acceptor, generating

hydroxide as a side product. We find this proposal less likely due to the rarity of hydride transfer mechanisms in the literature. Finally, pyridine-*N*-oxide could act as a nucleophile, debenzylating the substrate to reveal a THIQ which is then oxidised to the corresponding isoquinoline.

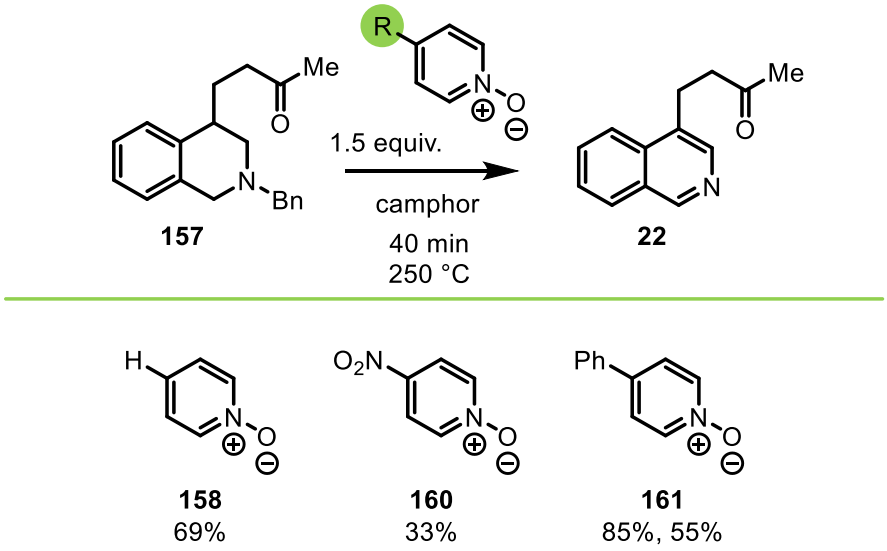


Scheme 3.9: Possibilities for pyridine-*N*-oxide mediated oxidation mechanisms; a) *N*-oxygenation b) hydride acceptance or c) nucleophile addition.

3.4.2 Role of pyridine-*N*-oxide

Our mechanistic studies began by exploring the three concepts detailed above. We hypothesised that if pyridine-*N*-oxide was functioning as an oxygen atom donor, the electron density of the pyridine ring should affect the reaction yield. Therefore, two C4 substituted pyridine-*N*-oxides, **160** and **161** were used as oxidants (Scheme 3.10). Addition of other groups

onto the pyridine ring such as nitro and phenyl groups substantially altered the yield, affording 33% and 85% respectively, as compared to our optimised yield of 69% with unsubstituted pyridine-*N*-oxide. This reinforces the theory of pyridine-*N*-oxide acting as an oxygen atom donor, as 4-nitro pyridine-*N*-oxide is a more electron poor aromatic ring, reducing the nucleophilicity at oxygen. Conversely, 4-phenyl pyridine-*N*-oxide **161** is a more electron rich aromatic ring and therefore more nucleophilic at oxygen, which is reflected in the higher yield of 85% observed.

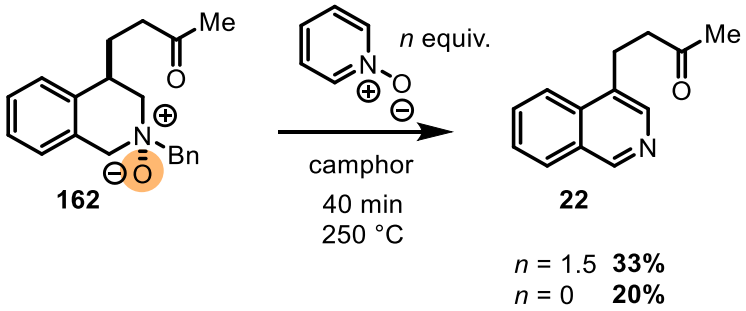


Scheme 3.10: Two examples of substituted pyridine-*N*-oxides, and reproducibility comparisons. Isolated yields are reported.

It is worth noting that although the yield obtained when using 4-phenyl pyridine-*N*-oxide as the active reagent was larger than when using pyridine-*N*-oxide, the yields were significantly less repeatable, with repeats of the reaction performed under identical conditions differing by as much as 40%, an effect not observed with pyridine-*N*-oxide (*vide supra*).

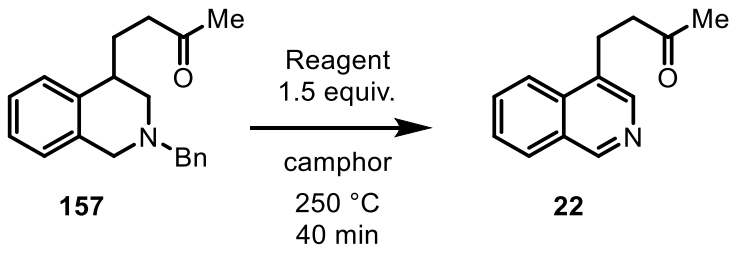
If pyridine-*N*-oxide was acting as an oxygen atom donor, compound **162** might be considered a putative intermediate in our reaction, assuming that oxidation occurs before debenzylation. Therefore, **162** was synthesised as a single diastereomer and subjected to the optimised reaction

conditions both in the presence and absence of pyridine-*N*-oxide (Scheme 3.11). However, in both cases, the desired product was formed in a low yield as part of a complex mixture of products (33% and 20% respectively). The low yields suggested that **162** is not an intermediate on our main reaction pathway.



Scheme 3.11: Subjection of putative intermediate **162** to the reaction conditions. Reactions performed on 0.25 mmol scale. Isolated yields are reported.

In order to further test our hypothesis that pyridine-*N*-oxide was acting as an oxygen atom donor, a number of other heteroatom oxide species were added to the reaction in place of pyridine-*N*-oxide (Table 3.9). Other *N*-oxides such as NMO and TMAO produced yields of 35% and 31% respectively, a slight improvement in conversion over the background reaction (Table 3.9, Entries 1-3). It is unclear why pyridine-*N*-oxide succeeds where other *N*-oxides fail, perhaps this is due to the leaving group ability of pyridine *vs* a trialkyl amine, demonstrated by their relative pKa values (5.23 and 10.78 respectively).[57-58] Moving away from *N*-oxides to other heteroatoms, a phosphorus oxide, Ph_3PO was trialled, with a disappointing yield of 21%, directly comparable with the background reaction observed (Table 3.9, Entry 4).



Entry	Reagent	Yield of 22 (%)
1	-	21
2	TMAO	31
3	NMO	35
4	Ph_3PO	21

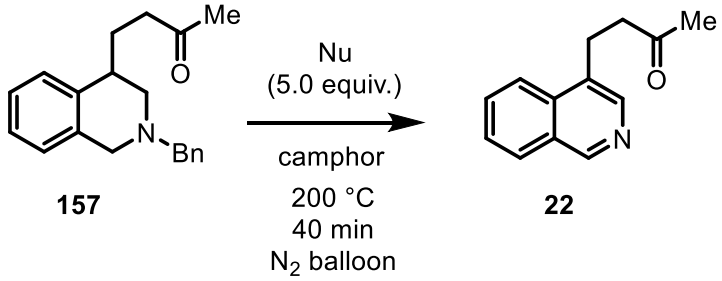
Table 3.9: Alternative oxide-based oxidants. Isolated yields are reported. Reactions performed on 0.25 mmol scale.

Pyridine-*N*-oxide may instead be acting as a nucleophile, promoting debenzylation through nucleophilic attack at the benzyl methylene carbon, which would reveal a THIQ that could then be oxidised.

To probe our hypothesis, a variety of nucleophiles were added to the reaction in place of pyridine-*N*-oxide (Table 3.10). Most nucleophiles screened gave a low yield of product, with imidazole, DMAP, phenol, BzOH and PPh_3 all producing a lower yield than when no additive was used; this suggests that their presence may inhibit reactivity (Table 3.10, Entries 1, 2, 3, 7, 8, 9). Some nucleophiles, such as KSCN, BnSH, H_2O and NaBr were shown to outperform the background reaction slightly (Table 3.10, Entries 1, 4, 5, 6, 10). These results showed that there was little benefit to adding a nucleophile over the background reaction, and suggests that neither pyridine-*N*-oxide or its potential reduction product, pyridine, are acting as nucleophiles in this reaction mechanism.

The only nucleophile that significantly outperformed the background reaction was NaI, which produced a yield of 34% (Table 3.10, Entry 11). This yield is comparable to the yield obtained

using pyridine-*N*-oxide under analogous reaction conditions. However, when the temperature was raised to 250 °C, only a modest improvement in the yield to 43% was observed, compared with the higher yield of 62% observed with pyridine-*N*-oxide under analogous conditions (Table 3.10, Entries 11-14). This result is an anomaly as compared to the other nucleophiles screened, but we suggest that the reason is unrelated to the nucleophilicity of the reagent due to the lack of reactivity shown by other nucleophiles.

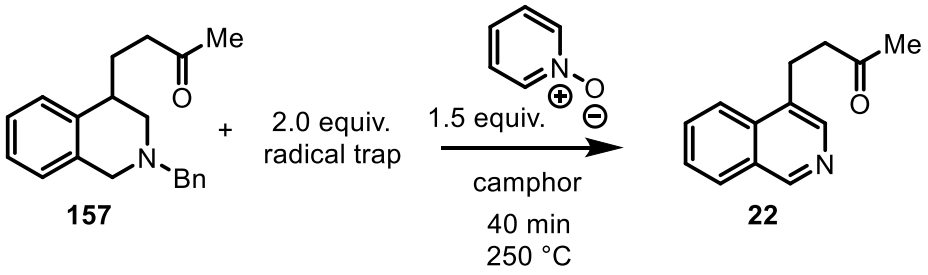


Entry	Nucleophile	Yield of 22 (%)
1	None	12
2	Imidazole	5
3	DMAP	8
4	KSCN	17
5	BnSH	18
6	H_2O	17
7	Phenol	7
8	BzOH	11
9	Ph_3P	1
10	NaBr	15
11	NaI	34
12[a]	NaI	(43)
13	pyridine-*N*-oxide	36
14[a]	pyridine-*N*-oxide	(62)

Table 3.10: Nucleophile screening. Yields reported are calculated using reverse phase HPLC. Reactions performed on 0.125 mmol scale. [a]Reaction performed at 250 °C.

3.4.3 Investigations into potential radical mechanisms

To investigate whether the reaction is a radical mediated process, the reaction was performed in the presence of radical trapping reagents (Table 3.11). Interestingly, none of the four reagents trialled showed strong evidence of yield reduction in the presence of a radical trapping agent. TEMPO and 1,1-diphenylethylene both afforded **22** in a 70% yield, directly comparable with our optimum yield of 69% (Table 3.11, Entries 1-3). Amylene and BHT both produced slightly reduced yields of 66% and 62% respectively, which is not consistent with a radical-based mechanism (Table 3.11, Entries 4-5). We hypothesise that these results imply that the reaction does not involve radical intermediates, however this may not be true if the mechanism is under diffusion control or occurs *via* an inner sphere mechanism, thereby preventing any external molecules from reacting with any radicals generated.



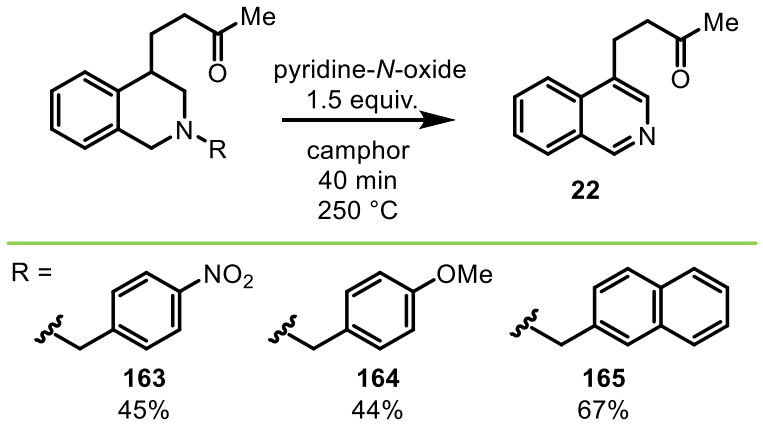
Entry	Radical trap	Yield of 22 (%)
1	None	69
2	TEMPO	70
3	1,1-Diphenyl ethylene	70
4	Amylene	66
5	BHT	62

Table 3.11: Radical trap screening. Isolated yields are reported.

3.4.4 Investigations into the fate of the benzyl activating group

Given that the product of the reaction is the free isoquinoline, at some point during the reaction progress the activating benzyl group is removed. We wished to investigate mechanistically how the benzyl group was removed and at what stage of the reaction; to do so, we desired to determine the fate of the group. Multiple attempts had been made to isolate any potential benzyl-containing side products with our optimisation substrate **157**, however no suitable products could be isolated by chromatographic techniques or detected by spectroscopic means.

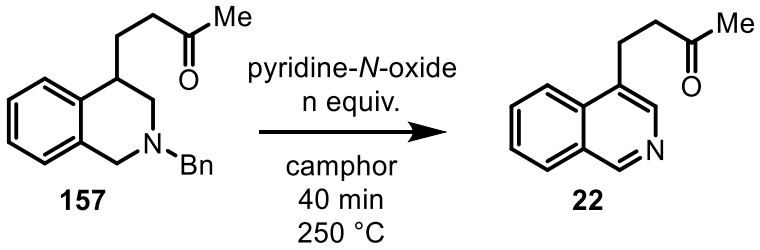
In an effort to combat this issue, several alternative activating groups were then trialled, in an attempt to make the departing group more spectroscopically detectable (Scheme 3.12). Unfortunately, changing the activating group to 4-methoxybenzyl **163**, 4-nitrobenzyl **164** or 2-methylene naphthyl **165** did not allow the detection of any activating group by-products by either isolation or spectroscopic means. It was also noted that all three different activating groups gave a lower yield of desired isoquinoline **22** in our oxidative rearomatisation than when using *N*-benzyl THIQ **157**, as such no correlation between activating group electronics and yield was observed.



Scheme 3.12: Activating group investigations: altering the activating group in an attempt to track by-products derived from the *N*-benzyl group. Isolated yields are reported.

3.4.5 Control experiments

Several control experiments were conducted, namely in the absence of pyridine-*N*-oxide, the absence of oxygen and the absence of both (Table 3.12). Conducting the reaction in the absence of oxygen somewhat reduced the yield, showing that oxygen is necessary for the reaction to occur to its full potential. Without any pyridine-*N*-oxide, (Table 3.12, Entry 3), the reaction showed a significantly diminished yield but still showed a larger background reaction than was anticipated (21% yield). When both oxygen and pyridine-*N*-oxide were excluded the reaction almost completely shut down, showing both are necessary for the reaction to occur; high temperature on its own is insufficient to promote the pyrolysis. When the atmosphere is replaced by oxygen, (Table 3.12, Entry 5), the reactivity is approximately that when the atmosphere is air, showing that oxygen is the reactive species in the air that is aiding the reaction.



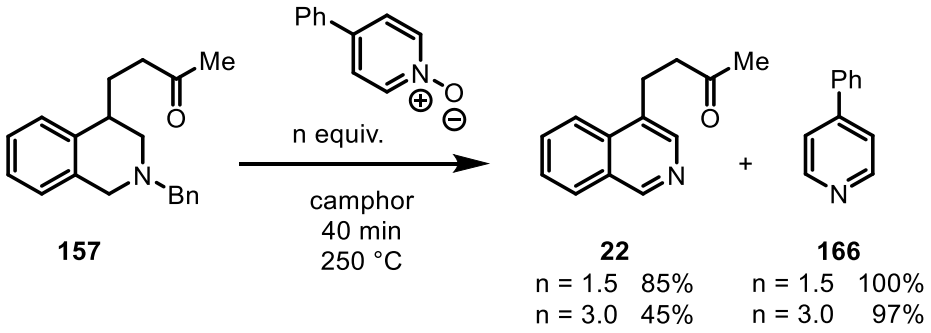
Entry	Atmosphere	pyridine-*N*-oxide equiv.	Yield of 22 (%)
1	Air	1.5	69
2	Argon	1.5	52
3	Air	0.0	21
4	Argon	0.0	3
5	Oxygen	1.5	68

Table 3.12: Control experiments. Isolated yields are reported.

3.4.6 Fate of pyridine-*N*-oxide

In order to more fully understand the fate of all reactants, the side product from pyridine-*N*-oxide was explored next. For these studies, it was decided to use 4-phenyl pyridine-*N*-oxide so that any by-products would be non-volatile and therefore isolable (Scheme 3.13). It was found that 4-phenyl pyridine could be isolated in quantitative yield with respect to the amount of 4-phenyl pyridine-*N*-oxide added. This result is still true even if the stoichiometry of the reagent is far in excess of the substrate, with 3.0 equivalents of 4-phenyl pyridine-*N*-oxide resulting in a 97% yield of the parent pyridine isolated.

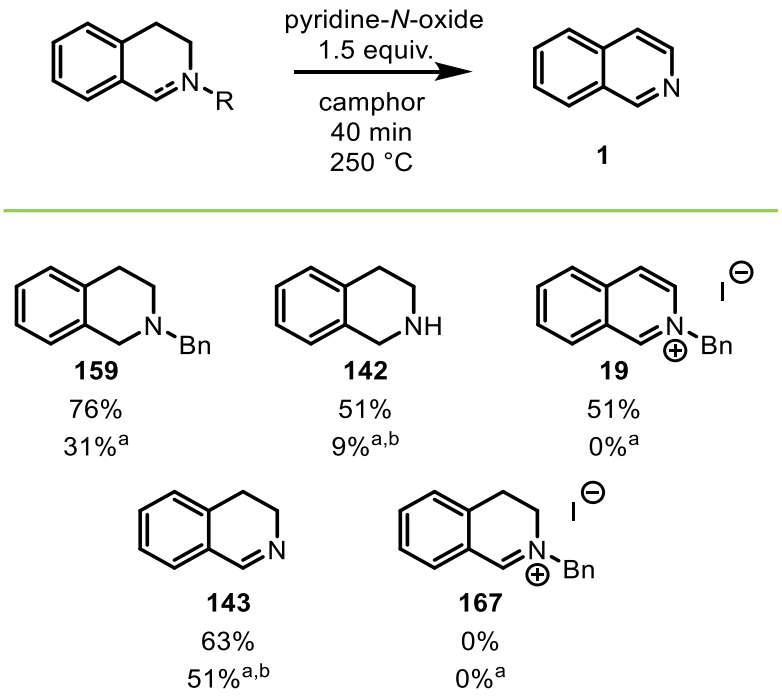
This observation could be explained by the decomposition of pyridine-*N*-oxide **161** at an elevated temperature to form 4-phenyl pyridine **166** and an oxygenated species, perhaps water. This has been previously observed in the decomposition of a related pyridine-*N*-oxide in a report by Mannan and co-workers.[59] The report by Mannan and co-workers was conducted over a period of many hours, however, with uncatalyzed decomposition occurring around 30 h. This observation does not completely explain the fate of the oxygen, with Mannan and co-workers noting a lack of clean conversion to a pyridine product and many side products observed.



Scheme 3.13: Isolation of pyridine-*N*-oxide side product. *n.b.* Yields of 4-phenyl pyridine are calculated with respect to the amount of 4-phenyl pyridine-*N*-oxide added. Isolated yields are reported. Reactions performed on 0.25 mmol scale.

3.4.7 Stability of proposed intermediates under reaction conditions

We wished to identify intermediate compounds likely to be formed during the reaction, so as to better understand the sequence of reactive events occurring. To achieve this, it was suggested that further putative intermediates should be synthesised and subjected to our reaction conditions, however the presence of a side chain at C4 rendered the synthesis of some of the proposed species challenging. In order to simplify the synthesis, a model system was employed, using parent THIQ **159** without a C4 side chain. Therefore, compounds **19**, **142**, **143**, **159** and **167** were synthesised and subjected to our reaction conditions (Scheme 3.14).



Scheme 3.14: Application of reaction conditions to putative intermediates of a related model system. Isolated yields are reported. Reactions performed on 0.25 mmol scale. [a]Reaction was conducted in the absence of pyridine-*N*-oxide. [b]Yield reported determined using quantitative ^{1}H NMR spectroscopy.

Compound **159**, the model for starting material **157**, pleasingly afforded a 76% yield of isoquinoline **1** when subjected to reaction conditions. In the absence of pyridine-*N*-oxide, the

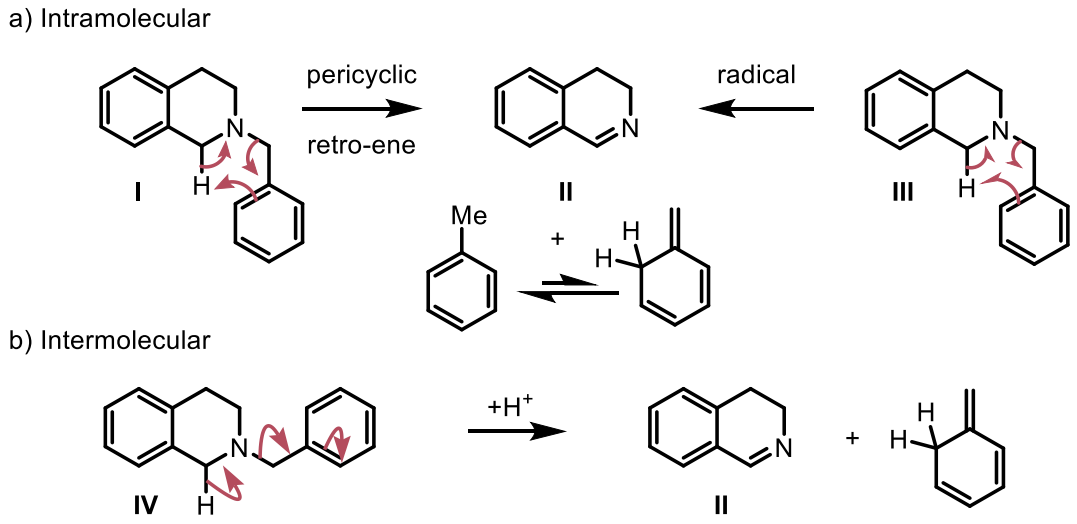
yield decreased to 31%, on par with the more complex substrate **157**. This suggested that the model system would be a good representation of our substrate of interest.

Deprotected THIQ **142** was oxidised in a 51% yield, perhaps suggesting that **142** may be an intermediate on our reaction pathway, however *N*-benzyl isoquinolinium **19** also produced a 51% yield which produces a contradiction. If THIQ **142** were an intermediate on our reaction pathway, the reaction would proceed first *via* benzyl group removal, followed by heterocyclic ring oxidation. However, if isoquinolinium **19** is an intermediate on the reaction pathway, this would entirely contradict this theory and instead suggest that oxidation of the heterocyclic ring occurred first, followed by benzyl removal. We propose that this contradicting data shows that there are several mechanisms occurring, but that neither **19** nor **142** are on the main reaction pathway. Both **19** and **142** showed little or no reactivity in the absence of pyridine-*N*-oxide, which suggests their transformations (oxidation and debenzylation respectively) require pyridine-*N*-oxide to occur.

Imine **143** was then trialled and gave isoquinoline **1** in a 63% yield, which supported the proposal that **143** was an intermediate on the main reaction pathway and suggested that the first oxidation which oxidises the C1 and N to form an iminium occurs as the first step, followed by benzyl removal to reveal imine **143**.

However, when the iodide salt of **167** was subjected to the reaction, no conversion was observed, either with pyridine-*N*-oxide or without, indicating that this species is not on the main reaction pathway. Therefore, we suggest that benzyl group removal and oxidation are occurring simultaneously and so propose the following mechanistic possibilities (Scheme 3.15).

Simultaneous benzyl group removal and oxidation could either occur *via* an intramolecular or an intermolecular process (Scheme 3.15a, 3.15b). Either possibility could be achieved through ionic or radical means, but in the ionic intramolecular case, the reaction would be pericyclic and could be classified as a retro-ene.

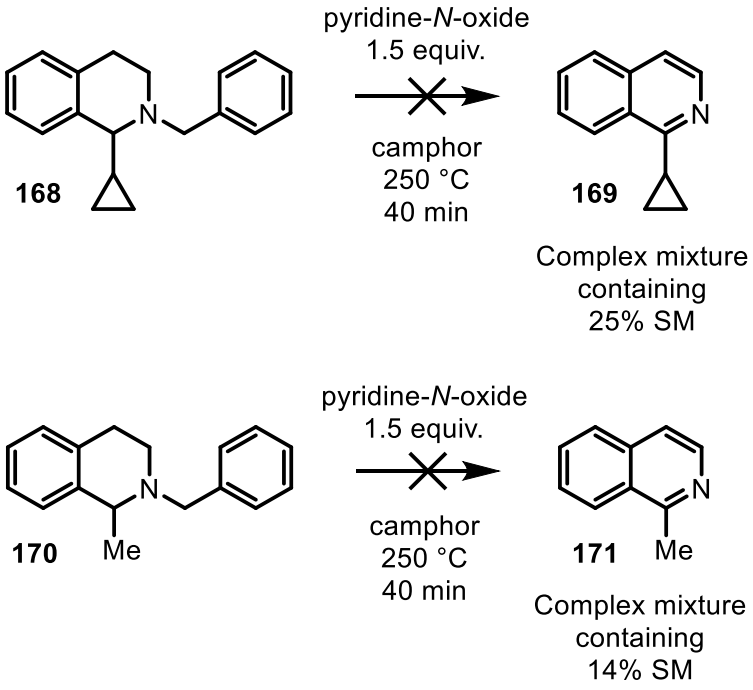


Scheme 3.15: Proposed mechanism possibilities for debenzylation of model substrate. a) Intramolecular possibilities, including pericyclic or radical reactivity. b) Unlikely intermolecular reaction showing creation of benzyl fragment upon removal of C1 proton.

3.4.8 C1 substituents

C1-cyclopropyl and C1-methyl *N*-benzyl THIQs **168** and **170** were then synthesised to investigate the effects of C1 substituents on the reaction, with the aim of learning more about the initial oxidation-debenzylation step. We hypothesised that the loss of a C1 proton plays a key mechanistic role, therefore a C1 substituted substrate should show significantly lower reaction rates and subsequently a lower yield of product in the same reaction time. Subjection of **168** and **170** to the reaction conditions regrettably gave complex mixtures in both cases, which indicates that no steric bulk at C1 is tolerated in the reaction (Scheme 3.16). A large steric presence at C1 would reduce the favourability of intramolecular debenzylation, therefore

this result could indicate that the debenzylation occurs *via* hydrogen removal at C1 in an intramolecular process. It is challenging to draw firm conclusions here, however, as no products could be isolated from the complex mixture of either reaction.

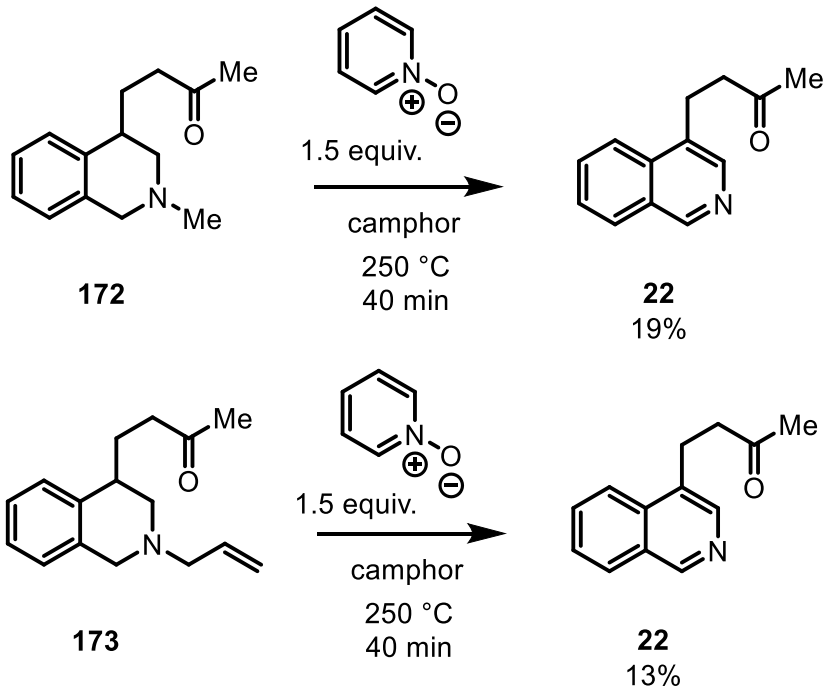


Scheme 3.16: Subjection of C1 cyclopropyl and C1 methyl substrates **168** and **170** to our reaction conditions. Yield reported determined by quantitative ^{1}H NMR spectroscopy.

It was hoped that subjecting C1-cyclopropyl substrate **168** to our reaction conditions might yield some radical derived rearrangement products, thus demonstrating the presence of C1 radicals. Unfortunately, as no distinct products could be isolated, this experiment does not prove or disprove this hypothesis. We believe that the debenzylation mechanism is intramolecular, as the drastic decrease in conversion in the presence of a C1 substituent strongly implies that the C1 proton is removed by a bulky species, such as the pendant *N*-benzyl.

3.4.9 Other *N*-activating groups

Interestingly, subjection of *N*-methyl substrate **172** to our reaction conditions gave a disappointing 19% yield of **22**, suggesting that the benzyl activating group is required for conversion. This could indicate that the debenzylation process is intramolecular (e.g. an ene-reaction), therefore requiring a nucleophile γ to nitrogen, which allows a 6-membered transition state, something unachievable by a methyl activating group. This result could also be explained by an intermolecular mechanism, which requires a leaving group that can stabilise an anion. Sadly, *N*-allyl substrate **173** performed similarly poorly, affording only a 13% yield, less than the background reaction observed in our model system, despite the electronic similarity of *N*-allyl to our *N*-benzyl model system.



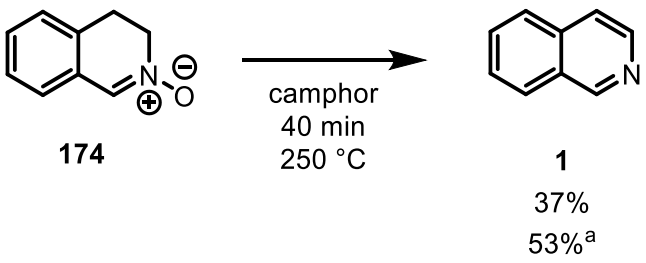
Scheme 3.17: Application of the reaction conditions to two varying *N*-activating groups **172** and **173**. Isolated yields are reported. Reactions performed on 0.25 mmol scale.

Accordingly, we propose that the mechanism is likely to occur *via* a pericyclic mechanism, due to the significantly lower yields observed with *N*-substituents other than benzyl, and the

unchanged reactivity indicated when radical trapping reagents are added to the reaction (*vide supra*). We also believe that the high temperature required for our reaction to occur indicates that at least part of the reaction is pericyclic, as other related pericyclic reactions often require high temperatures.[60-63]

3.4.10 Final oxidation step investigations

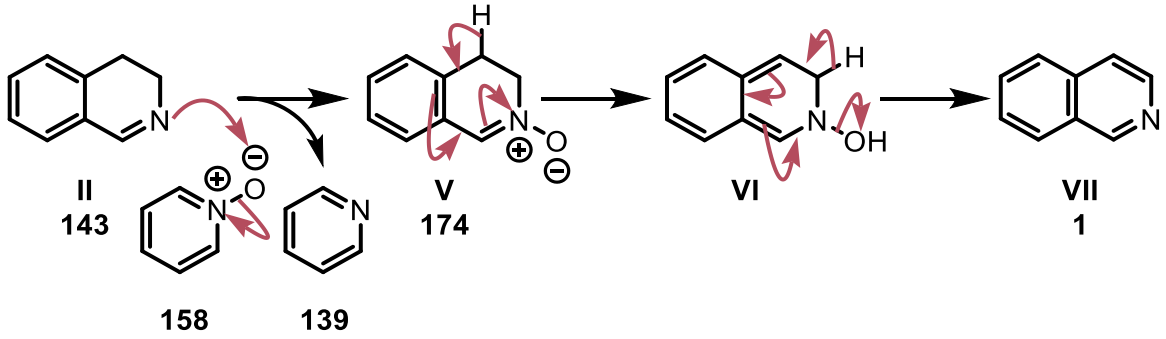
We propose that imine **143** can then be oxidised by pyridine-*N*-oxide to give product **1** *via* nitrone **174**. To test this hypothesis, **174** was synthesised and subjected to the reaction conditions in the absence of pyridine-*N*-oxide, which gave a somewhat disappointing yield of 37% (Scheme 3.18). This is a lower yield than we might expect for an intermediate on the productive reaction pathway. However, we recognised that although the final oxidation step could occur in the absence of pyridine-*N*-oxide, pyridine may be formed as a by-product and therefore will be present for this stage of the reaction. Therefore, pyridine was added to the reaction in order to more accurately replicate the reaction environment. Pleasingly, this afforded a much more promising yield of 53%, much closer to the expected yield of around 70-75%. We believe this is sufficient evidence that nitrone **174** is an intermediate.



Scheme 3.18: Application of the reaction conditions to putative intermediate nitrone **174**. Isolated yields are reported. Reaction performed on 0.25 mmol scale. [a]Reaction performed with 1.5 equiv. of pyridine added.

Once formed, we envisage that tautomerism of nitrone **174** (intermediate **V**, Scheme 3.19) will reveal an *N*-hydroxy enamine (intermediate **VI**, Scheme 3.19). This can then eliminate water

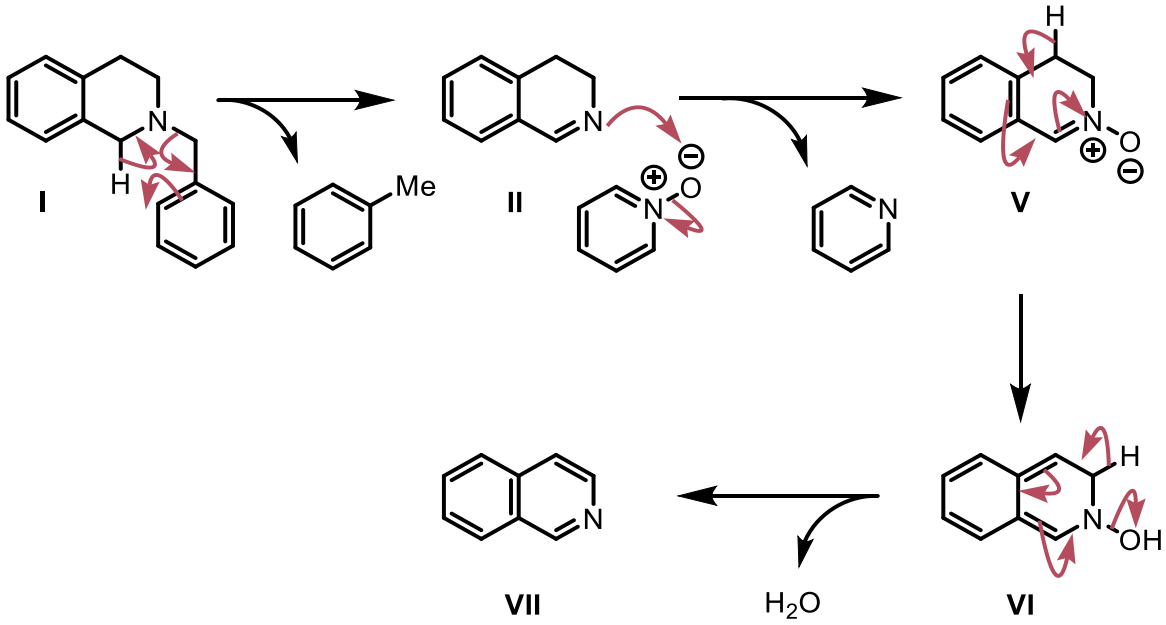
to reveal isoquinoline **1** (Scheme 3.19). We propose that pyridine is acting as a base to increase the rate of water elimination, thereby increasing conversion from nitrone **174** to isoquinoline **1**.



Scheme 3.19: Proposed mechanism for oxidation of imine **143** to isoquinoline **1**.

3.4.11 Complete proposed mechanism

In conclusion, we propose the following most probable mechanism for the overall transformation (Scheme 3.20). A pericyclic retro-ene reaction of *N*-benzyl THIQ **I** leads to imine **II**, a debenzylated and partially oxidised intermediate. **II** can then be oxidised by pyridine-*N*-oxide in an oxygen atom transfer event, giving nitrone **V**. Tautomerisation of nitrone **V** to *N*-hydroxy enamine **VI** then allows elimination of water to afford our product, isoquinoline **VII**.

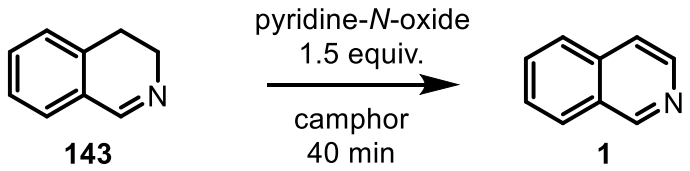


Scheme 3.20: Overall suggested mechanism for our oxidative benzylation reaction.

Although we have proposed the mechanism described above, a few experimental observations remain unexplained. Isolation of pyridine as a stoichiometric side product revealed that decomposition of our reagent was occurring over the reaction timescale. Our proposed mechanism involves a single oxidation event to imine **143**, which fails to completely account for the superstoichiometric quantities of pyridine isolated.

We have previously argued that the high temperature required to activate our reaction indicates that the pericyclic pathway is a more likely possibility for benzyl group removal (*vide supra*). This would then imply that the oxidation step detailed in Scheme 3.19 could occur at a lower temperature, since the high temperature is only required for the pericyclic debenzylation. A series of experiments were conducted to test this theory, with putative intermediate **143** subjected to reaction conditions at a range of temperatures lower than our optimised 250 °C (Table 3.13). Disappointingly, the yield of **1** was significantly diminished when the temperature was decreased even by 30 degrees to 220 °C (Table 3.13, Entries 2, 4) resulting in the yield more than halving from 63% to 30%. Only a small reduction in temperature to 240 °C showed

any yield comparable to our optimised conditions. These results show that imine **143** requires a high reaction temperature to undergo the oxidation step, which disproves the idea that the high temperature reaction conditions were only required for the initial debenzylation.



143 **1**

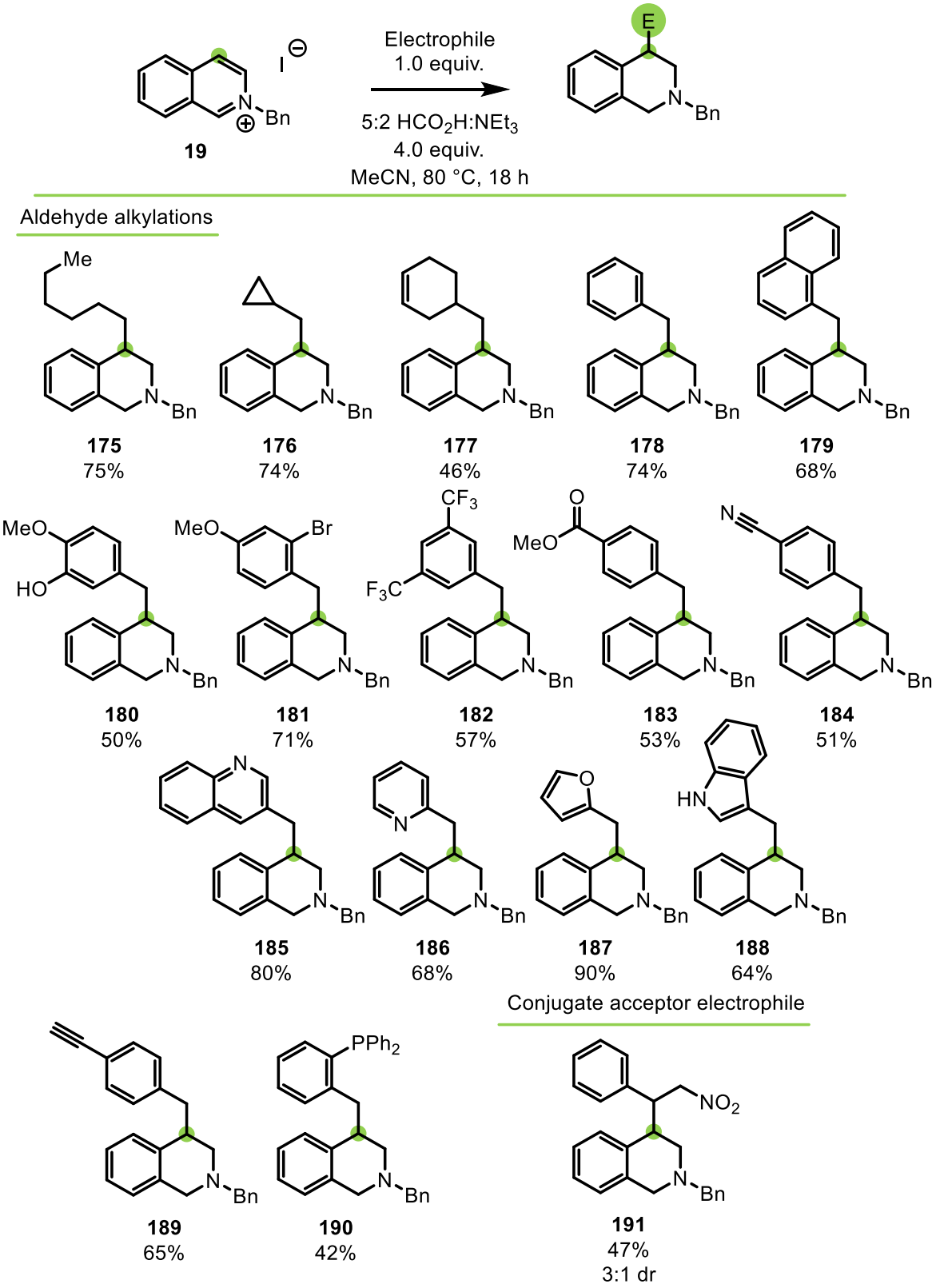
Entry	Temperature (°C)	Yield of 1 (%)
1	200	13
2	220	30
3	240	66 (65)
4	250	(63)

Table 3.13: Application of the reaction conditions to putative intermediate **143** at a range of temperatures. Yields reported are determined by quantitative ^{1}H NMR spectroscopy. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol.

3.5 Substrate scope

3.5.1 Synthesis of THIQ starting materials

Our aim was to develop an aromative approach for the formation of substituted isoquinolines from pre-functionalised THIQs to capitalise upon the large variety of reductive functionalisation methods present in the literature.[19] To this end, a range of THIQs were synthesised using the reductive functionalisation method first reported by Donohoe and co-workers (Scheme 3.21).[23] The method is very general and allows for a large number of functional groups to be installed in reasonable yields. Firstly, we made use of the method with aldehyde electrophiles, which allowed the synthesis of a varied scope of mono-C4-alkylated THIQs in yields varying from 42% to 90%.



Scheme 3.21: C4-mono substituted THIQ substrates synthesised using a reductive functionalisation method reported by Donohoe and co-workers.[23] Isolated yields are reported. Reactions performed on 0.5 mmol scale.

Although the yields were varied, they were similar to the yields reported by Donohoe and co-workers in their publication.[23] One further substrate, **191**, was obtained by using a conjugate acceptor electrophile, although regrettably in a lower-than-expected yield of 47%.

Next, two tricyclic annulated THIQs, **17** and **192**, were synthesised using the same method, utilising a variant of the method with *N*-benzyl-3-methyl isoquinolinium iodide **15** as a starting material (Scheme 3.22). The mechanism proceeds *via* an external enamine which allows vinyl ketone electrophiles to act as an ambident electrophile, facilitating a ring closure to reveal the tricyclic core. Two vinyl ketones were used to afford two tricyclic THIQ products.

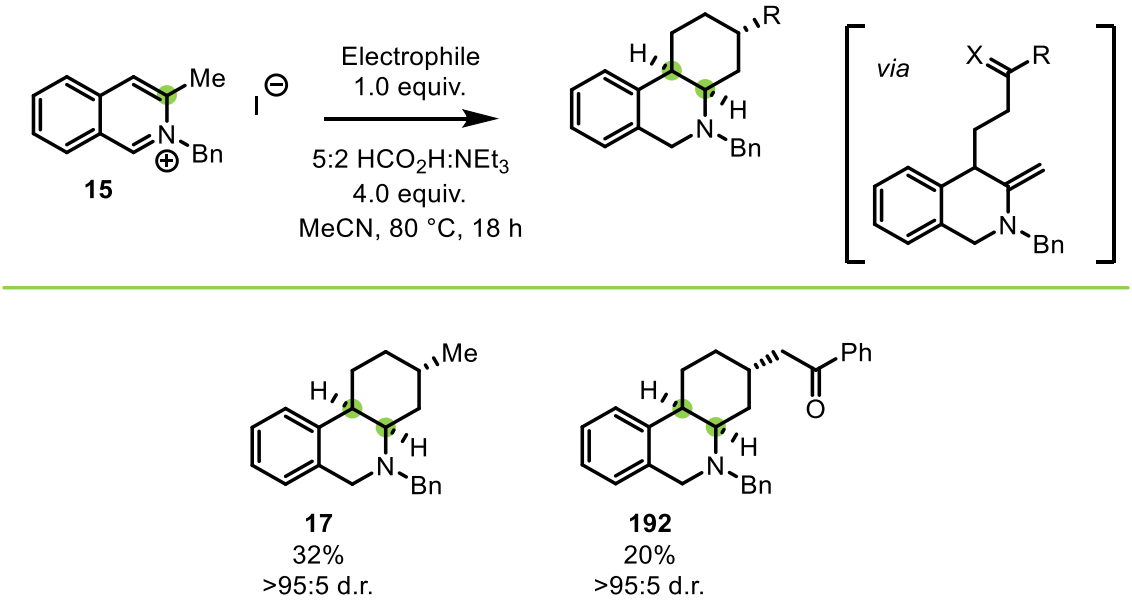
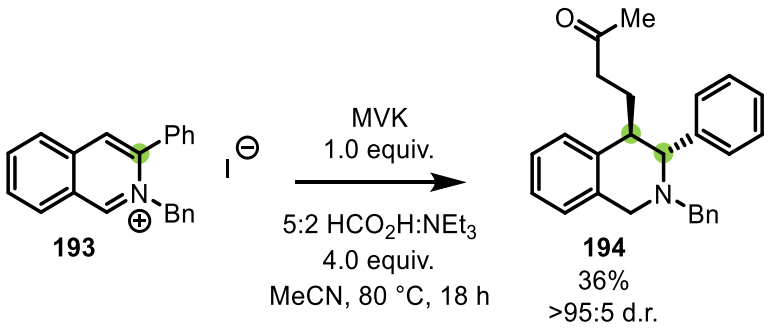


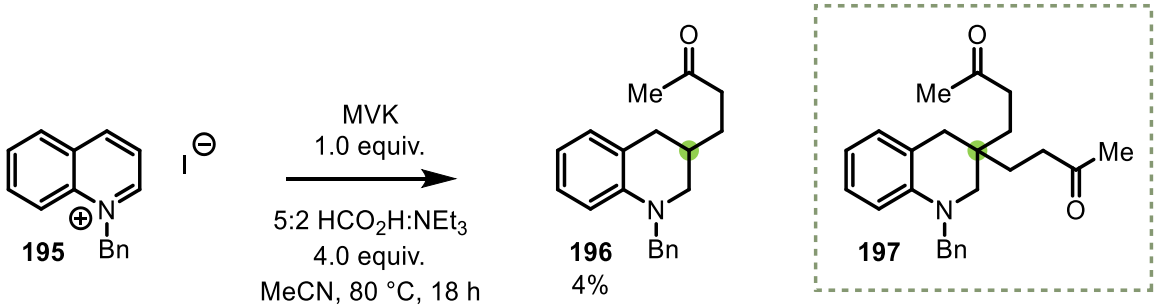
Table 3.22: Tricyclic THIQ substrates synthesised using reductive functionalisation reported by Donohoe and co-workers with a 3-Me isoquinolinium iodide salt.[23] Isolated yields are reported. Reactions performed on 0.5 mmol scale.

A C3, C4-di-substituted THIQ **194** was then synthesised utilising *N*-benzyl-3-phenyl isoquinolinium iodide **193** as the substrate (Scheme 3.23). The desired THIQ was afforded in a lower yield than expected (36%), demonstrating the limitations of the method with increased steric interactions around the heterocyclic ring.



Scheme 3.23: Synthesis of a C3-C4 di-substituted THIQ from *N*-benzyl-3-phenyl isoquinolinium iodide using reductive functionalisation.[23] Isolated yields are reported. Reaction performed on 0.5 mmol scale.

Finally, the method developed by Donohoe and co-workers was applied to a *N*-benzyl quinolinium iodide substrate **195**, which regrettably only afforded a 4% yield of **196** (Scheme 3.24). The reductive functionalisation method was optimised for a C3 pre-functionalised substrate with excess electrophile used to achieve a good yield. With a *N*-benzyl quinolinium iodide unfunctionalized at-C3 such as **195**, a limiting amount of electrophile is required to prevent excessive formation of the C3 di-substituted side product **197**, which accounts for the low yield. This demonstrates the limitation of our proposed two-step method to *β*-functionalised *N*-heterocycles, as the overall yield of the process can be limited by the THIQ or THQ starting material synthesis.



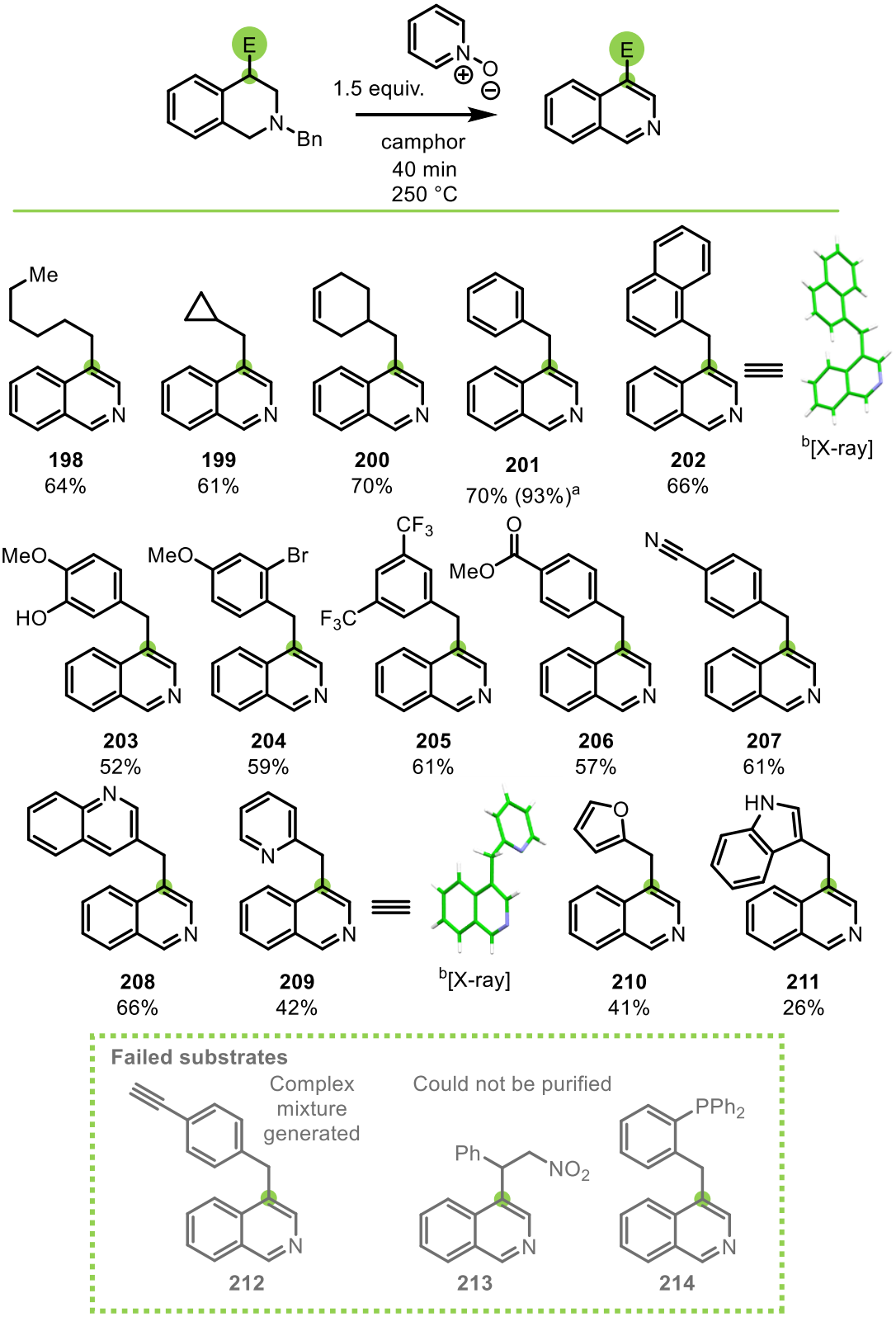
Scheme 3.24: Synthesis of a THQ substrate using reductive functionalisation. Isolated yield is reported. Reaction performed on 1.0 mmol scale.

3.5.2 Mono C4 substituted THIQ scope

With a range of C4 monosubstituted and C3-C4 disubstituted THIQ starting materials in hand, we investigated the scope of the developed rearomatisation reaction (Scheme 3.25). Pleasingly, the reaction conditions were shown to be tolerant of a broad range of functional groups in the THIQ side chain.

THIQs bearing simple aliphatic side chains and small rings were successful substrates, giving **198** and **199** in 64% and 61% yield respectively. Pleasingly, a cyclic internal alkene was also tolerated, affording **200** in 70% yield. Substituents containing undecorated aromatic systems were also tolerated, affording C4 benzyl substituted **201** in 70% yield and 1-naphthyl substituted **202** in a 66% yield. Moreover, the reaction to rearomatize substrate **178** could be scaled to 1.0 mmol, affording **201** in a 93% yield.

Side chain with aromatic rings bearing electron donating groups were well tolerated, affording **203** (notably with a free hydroxyl group) and **204** in 52% and 59% yields respectively. Substrates bearing electron deficient aryl rings were also successful, with examples including CF_3 groups, an ester and a nitrile affording the corresponding isoquinoline products **205**, **206**, and **207** in 61%, 57 and 61% yields respectively. A range of substrates bearing heterocyclic side chains were also examined; whilst a quinoline side chain was tolerated well to form **208** in a 66% yield, substrates bearing pyridine and furan side chains were less successful, affording **209** and **210** in 42% and 41% yield respectively. Unfortunately, inclusion of an indole within the side chain afforded isoquinoline product **211** in only 26% yield, demonstrating a lack of tolerance for more complex heterocyclic functionality.



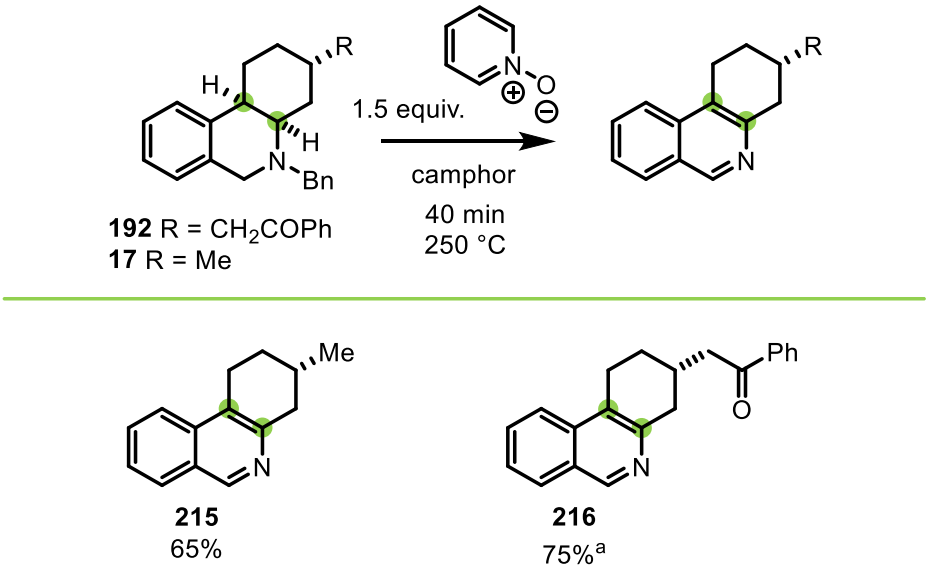
Scheme 3.25: Substrate scope of our rearomatisation reaction using C4 mono-functionalised THIQs. Isolated yields are reported. Reactions performed on 0.25 mmol scale. [a] Reaction performed on 1.0 mmol scale. [b] Determined by single crystal X-ray diffraction. Single crystal X-Ray analysis performed by T. C. Jenkins.

Only a few substrates failed to produce the desired isoquinoline products; THIQ **212** gave a complex reaction mixture presumably as a result of unwanted side reactions of the alkyne substituent. Compounds **213** and **214** were observed in trace amounts in their respective crude reaction mixtures by ^{1}H NMR spectroscopy, but unfortunately could not be isolated cleanly.

As a proof of structure, single crystal X-ray diffraction was used to elucidate the structures of **201**, **202** and **209** (for further information, see Appendix I, page 413).

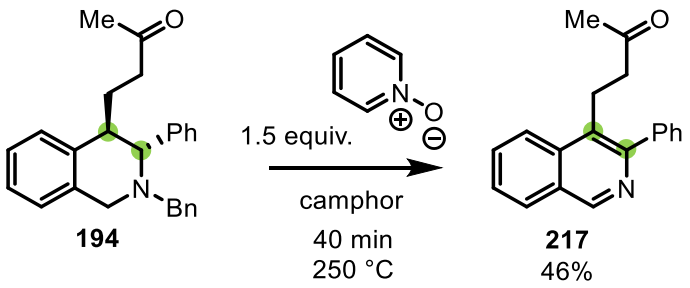
3.5.3 Further THIQ substrates

Related tricyclic annulated THIQs **17** and **192** were also subjected to our reaction conditions, pleasingly affording **215** and **216** in 65% and 75% yield respectively (Scheme 3.26).



Scheme 3.26: Tricyclic annulated THIQ substrates. Yields quoted are isolated. Reactions performed on 0.25 mmol scale. [a]Reaction performed on the 0.090 mmol scale.

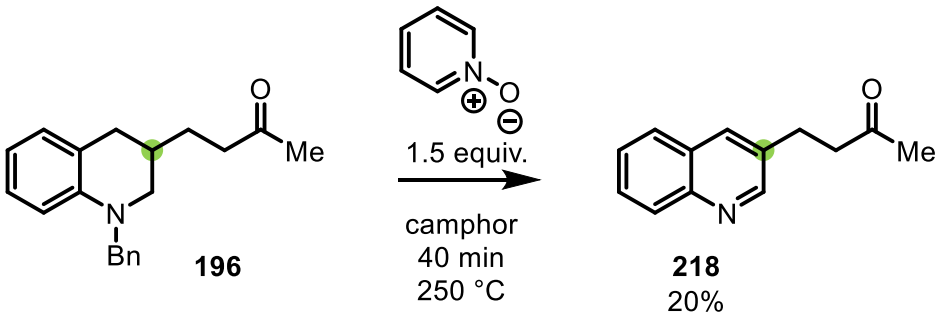
We then sought to prove that the process was also tolerant of less rigid substrates, providing a more general method for the formation of C3, C4 difunctionalised isoquinolines. Compound **194** was subsequently subjected to our reaction conditions and pleasingly isoquinoline **217** was afforded in 46% yield (Scheme 3.27).



Scheme 3.27: Rearomatization of C3-C4 di-substituted THIQ. Isolated yield is reported. Reaction performed on 0.15 mmol scale.

3.5.4 Tetrahydroquinolines

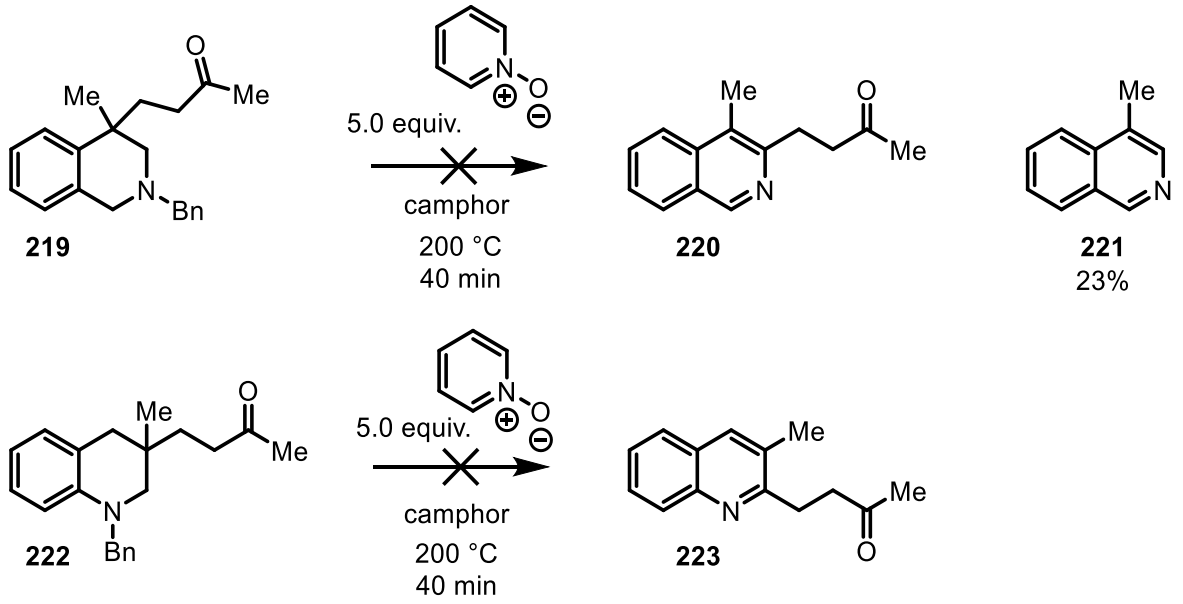
An example tetrahydroquinoline **196** was also subjected to our optimised rearomative conditions (Scheme 3.28). Unfortunately, this resulted in a disappointing yield of 20% of quinoline **218**. THQs are evidently less well tolerated than THIQs under the reaction conditions, which demonstrates the limitations of the method when applied to highly related substrates. As THQs are significantly harder to synthesise using the method published by Donohoe and co-workers, no further quinoline substrates were investigated.



Scheme 3.28: Expansion of reaction scope towards tetrahydroquinolines. Isolated yield is reported. Reaction performed on 0.05 mmol scale.

3.5.5 Limitation of method on C4 disubstituted THIQs

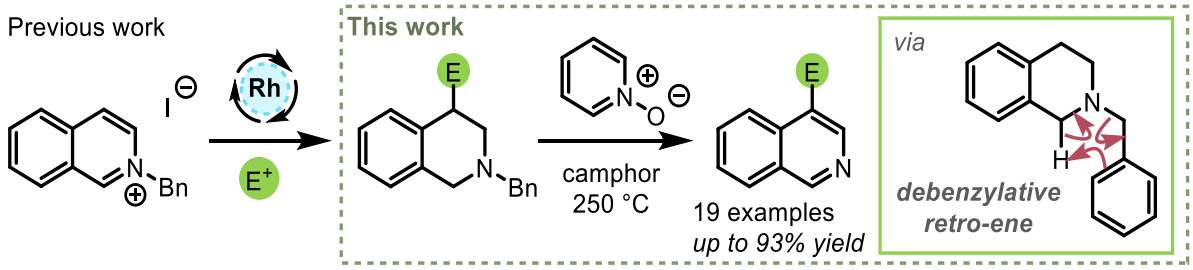
It was hypothesised that *N*-benzyl tetrahydroisoquinolines with two alkyl substituents at the C4-position might give some interesting reactivity, since the expected hydrogen loss to give aromaticity cannot occur. This may give the potential for migration of one or more of the alkyl groups to C3 to allow rearomatisation (Scheme 3.29). Disappointingly, when **219** and **222** were subjected to our rearomative reaction conditions a complex mixture was formed. The reaction using **219** as a substrate gave a 23% yield of the simple rearomatized product **221**, showing that rearomatisation is possible with loss of the previously added alkyl group, but no migration products were observed. This side product was not observed with our initial system, probably because rearomatisation is possible, thereby presenting a lower energy pathway than C4-side chain loss.



Scheme 3.29: Attempts at rearomatisation of double alkyl substituted *N*-heterocycles. Isolated yields are reported.

3.6 Conclusion

In this chapter, we have described the development of an aromative strategy to generate isoquinolines from THIQ starting materials. Taken in conjunction with the dearomative functionalisation methodology previously reported by the Donohoe group, this provides a facile two-step strategy for the synthesis of substituted isoquinolines by dearomative functionalisation and subsequent aromatisation. Despite the high reaction temperatures employed in the aromatisation step, a broad range of functional groups were tolerated, enabling the formation of functionalised isoquinolines without having to resort to *de novo* heterocycle synthesis. After mechanistic investigation, we propose that the reaction occurs *via* a debenzylative pericyclic retro-ene-type process to yield the corresponding imine, which is then further oxidised by pyridine-*N*-oxide to give the desired isoquinoline product in a single step procedure.



Scheme 3.30: Development of debenzylative rearomatisation reaction with 19 scope examples.

Chapter 4 – Reductive annulation to form a tricyclic THIQ skeleton

4.1 Tricyclic THIQ skeletons from isoquinolines

4.1.1 Selecting a desired transformation

Tricyclic THIQ skeletons feature in several natural product families such as the many and varied *Amaryllidaceae* alkaloids.[64] The majority of the families feature at their core a 6,6,6-tricyclic *N*-heterocycle system, which we noted could ultimately be prepared from a simpler *N*-heterocycle, such as an isoquinoline (Figure 4.1). Although this strategy is unconventional as compared to previous syntheses of other members of the *Amaryllidaceae* family, it would allow for a divergent synthesis route that could be used to produce a wide variety of alkaloids from a parent tricyclic compound.

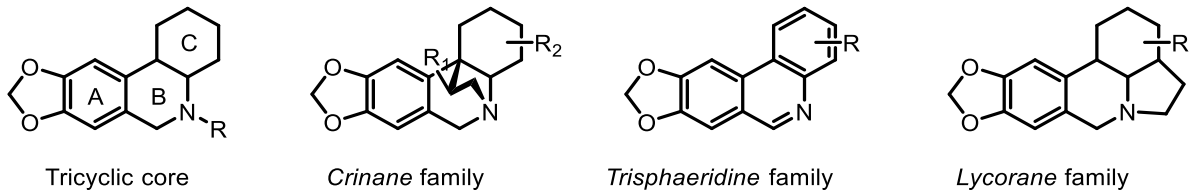
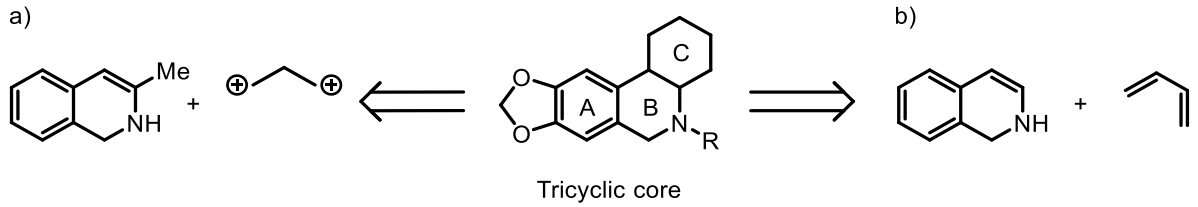


Figure 4.1: The tricyclic THIQ core of several *Amaryllidaceae* alkaloid families.

Further to our observation that the natural products of the *Amaryllidaceae* families could be synthesised from an isoquinoline starting material, we suspected that this might be achieved by a reductive functionalisation strategy, similar to processes previously developed in the group.[23] This method could be enacted with a 1,3-dicationic synthon, such as a vinyl ketone electrophile, and a C3-alkyl isoquinoline that is capable of forming external enamines (Scheme 4.1a), or a diene and an unfunctionalised isoquinoline that could be reduced *in situ* to reveal an enamine and therefore undergo Diels-Alder reactivity (Scheme 4.1b).

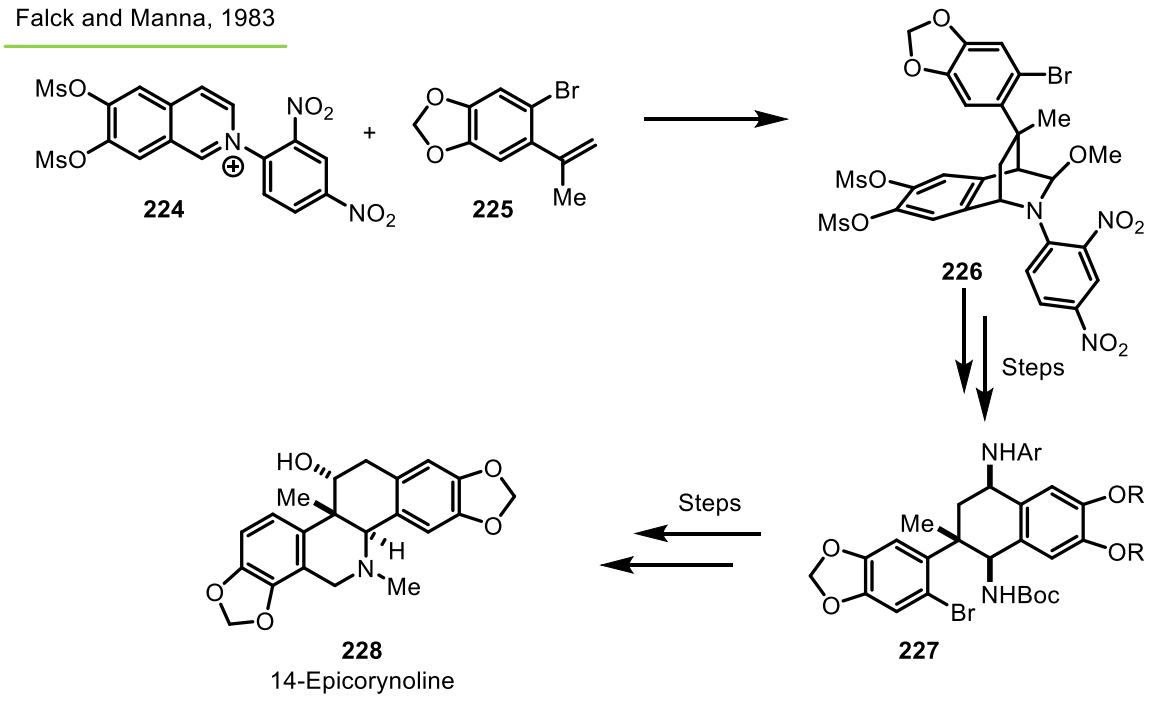


Scheme 4.1: Retrosynthesis of the *Amaryllidaceae* alkaloid tricyclic core to give either a) a C3-alkyl isoquinoline and a 1,3-dicationic synthon, or b) an unfunctionalised isoquinoline and a diene.

4.1.2 Different ring closure strategies for the synthesis of tricyclic compounds from isoquinolines

Reviewing the literature, methods for performing a ring synthesis at the C3 and C4 positions of an isoquinoline core are uncommon.

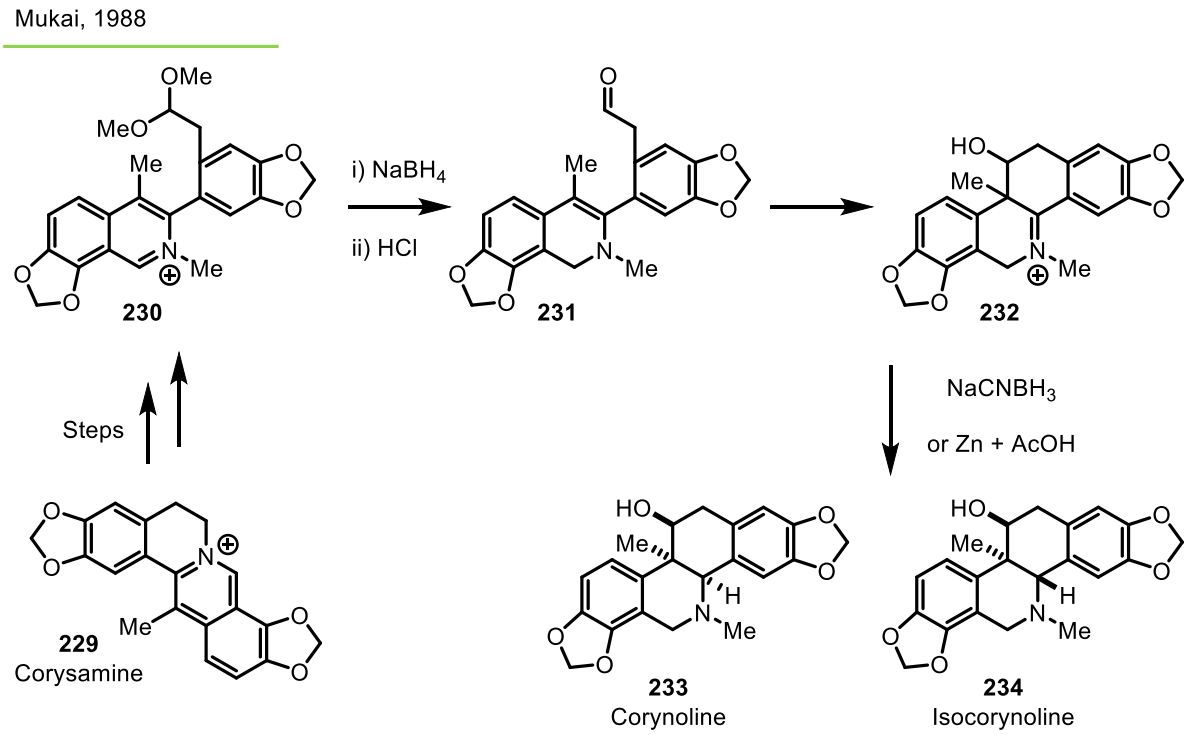
Falck and Manna produced a synthesis of 14-epicorynoline in 1983 which included a formal [4+2] cycloaddition between a styrene and an activated isoquinolinium (Scheme 4.2).[65] The bicycle formed was then opened to reveal an amine attached to the newly formed C ring, (intermediate **227**), which could then undergo a Pictet-Spengler reaction to close the B ring.



Scheme 4.2: [4+2] C ring forming strategy.

Mukai and co-workers published a related synthesis of both corynoline **233** and isocorynoline **234**, making use of an enamine-aldehyde C ring closure strategy (Scheme 4.3).[66] Enamine **231** was produced from the degradation of corysamine **229** to create isoquinolinium **230**. Reduction at C1 was performed by $NaBH_4$; then the masked aldehyde was deprotected with HCl to reveal enamine-aldehyde **231**. Attack by the enamine into the aldehyde produced iminium **232**, which can be reduced to form either Corynoline **233** or Isocorynoline **234** dependant on the reduction; a reduction by $NaCNBH_3$ produced Corynoline, whereas a reduction using Zn/AcOH afforded Isocorynoline.

The overall strategy differs largely from Falck and Manna, as closure of ring C is performed in a more conventional ionic process, using an enamine revealed by isoquinolinium reduction. The synthesis is substantially more efficient than that published by Falck and Manna, although Mukai and co-workers benefit from using natural product Corysamine **229** as their starting material, circumventing the need to construct rings A and B.



Scheme 4.3: Enamine-aldehyde strategy for C ring construction.

With this precedent in mind, we wished to develop a facile method that could construct the third ring of a 3,4-annulated THIQ in a one-pot-process. It was noted that use of reductive functionalisation conditions performed on an isoquinoline, coupled with an ambident electrophile, could ultimately generate the desired third ring annulated to the α and β positions of the *N*-heterocycle.

4.2 Previous work in the group

All data presented in this section was collected by Timothy Jenkins unless explicitly specified otherwise.

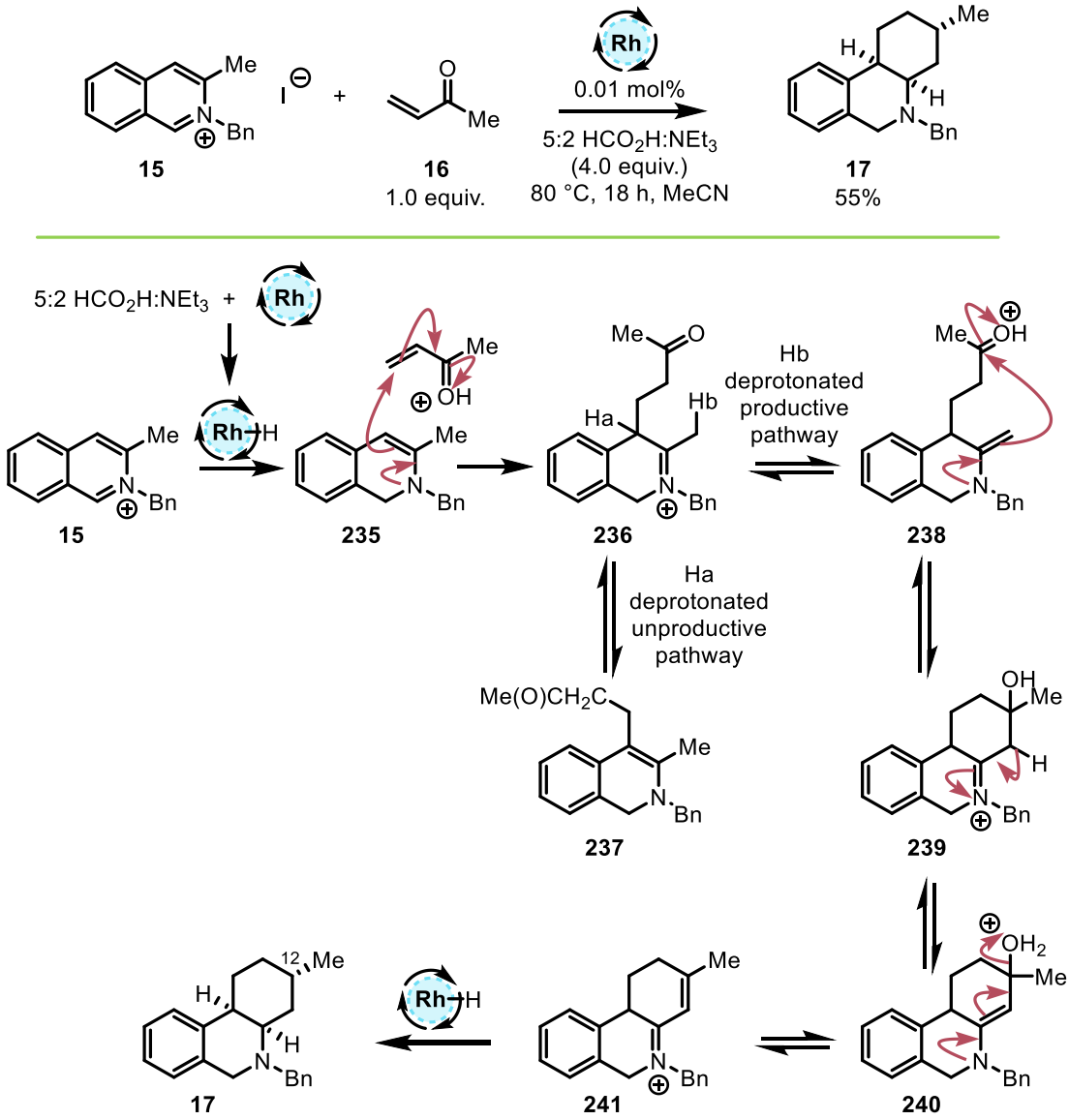
4.2.1 Reductive annulation reactions

Previous work in the group has been directed towards reductive functionalisation of *N*-heterocycles, using formic acid as a terminal reductant, which has allowed for the utilisation of a large scope of electrophiles.[23] This work has also produced several directly related annulation reactions which make use of an ambident electrophile such as MVK **16** (Scheme 4.4).

When a vinyl ketone is used, such as MVK **16**, the cyclisation proceeds *via* an external enamine **238**, which can attack the ambident electrophile again to form a new ring. This step produces an alcohol, which in turn is eliminated and the olefin reduced, leaving a partially saturated ring system (**17**, Scheme 4.4). The product **17** has cis-geometry across the 6,6-ring junction, caused by equatorial reduction of the iminium in intermediate **241**.

Unfortunately, electrophiles such as MVK **16** leave a methyl group at C_{12}, which is undesirable for applications of the method to synthesise *Amaryllidaceae* alkaloids as none of the alkaloids contain a C_{12} methyl group. Ideally, an electrophile used in this process would either leave the ring without any functionality (R = H), or with a functional group that could be used as a

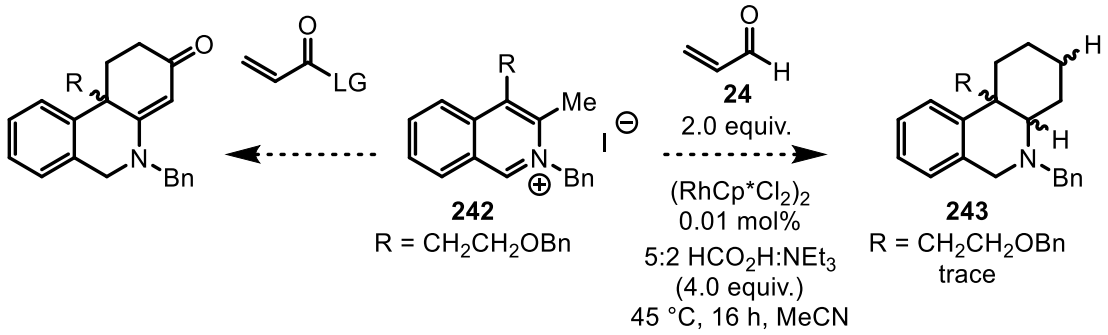
synthetic handle to divergently generate other compounds in future transformations (e.g. R = OR, NR_2).



Scheme 4.4: Previous work with formic acid promoted reductive annulation detailing headline result and mechanism.

Previous work by Dr. B. Marinic showed that the group's first strategy to overcome this issue, use of acrolein **24**, was regrettably unsuccessful, generating a mere 1% yield of **243** (Scheme 4.5).[67] Alternatively, it was suggested that use of a leaving group in place of a methyl in the electrophile structure would change the nature of the ring closing reaction and allow the

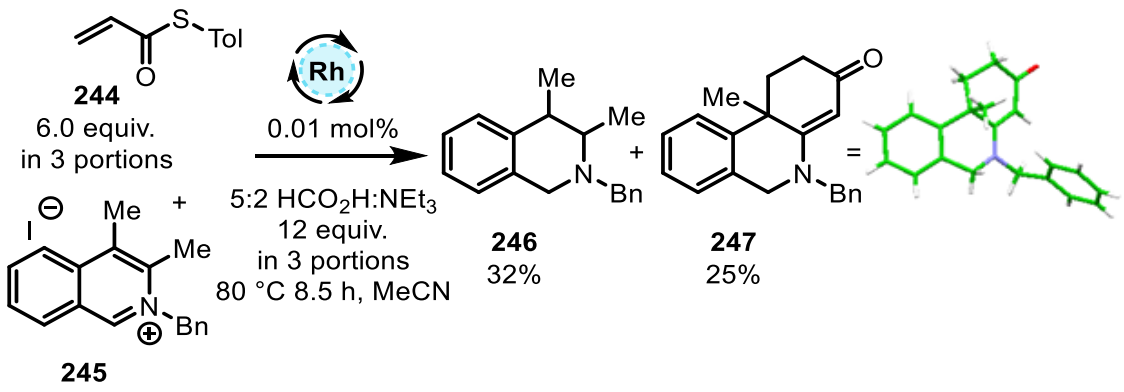
reaction to retain carbonyl functionality on the D ring, allowing further derivatisation and hopefully thereby making the process applicable to *Amaryllidaceae* alkaloid synthesis (Scheme 4.5).



Scheme 4.5: New ambident electrophile possibilities and the functional group patterns generated.

4.2.2 Optimisation using a vinyl thioester electrophile

A positive result was first obtained by Dr. B. Marinic with thioester **244** as the electrophile, which was then optimised by Dr. A. Day (Scheme 4.6). The major product obtained was vinylogous amide **247**, perhaps implying that the unsaturation of the vinylogous amide acts as a thermodynamic sink. Interestingly, it was found that the optimum yield of **247** was obtained when both electrophile and reductant are added in three portions over the course of the reaction time. It was shown that the large excess of reductant required led to formation of a reasonable yield of simple reduced THIQ **246**, which implies that the desired annulation reaction is occurring slowly compared to complete reduction of the heterocyclic ring. In order to minimise formation of **246**, a more potent electrophile should be utilised, in an attempt to increase the rate of our desired annulation reaction. The product identity was confirmed using single crystal X-ray analysis, showing the suspected vinylogous amide functionality (Scheme 4.6).



Scheme 4.6: Conditions optimised by Dr. A. Day to afford vinylogous amide **247** including single crystal X-ray structure of **247**. Isolated yields are reported. Reaction performed on 0.25 mmol scale. Single crystal X-Ray analysis performed by T. C. Jenkins.

4.3 Optimisation of the annulation including electrophile design

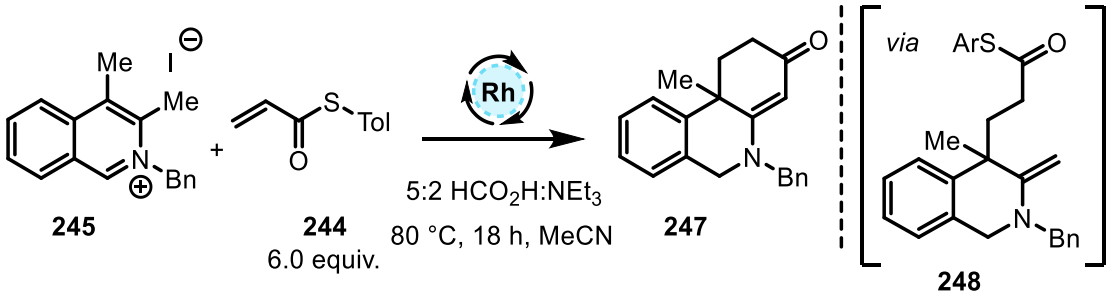
4.3.1 Replication of previous work and further optimisation with thioester 244

It was decided that a process without sequential additions of reagents would be the optimum reaction set up, and therefore we concentrated on single addition reactions. Further optimisation of the reaction of **245** to **247** was performed; with reductant equivalents and rhodium catalyst concentration varied (Table 4.1).

N.B. Starting material was present in most of the reactions detailed in Table 4.1, however the amount could not be quantitatively determined using ^{1}H NMR as the starting material was not fully soluble in $CDCl_3$.

Replicating the conditions used by Dr A. Day, a similar yield was obtained (Table 4.1, Entry 1). Decreasing the reductant equivalents to 1.0 and 2.0 equiv. drastically decreased the yield to 9% and 14% respectively, showing the necessity of a large excess of reductant (Table 4.1, Entries 2-3).

Neither decreasing nor increasing the catalyst loading by an order of magnitude had any noticeable effect on the reaction yield, with similar yields of 20% and 21% observed respectively (Table 4.1, Entries 4-5).



Entry	Reductant (Equiv.)	$(RhCp^*Cl_2)_2$ (mol%)	Concentration (M)	Yield of 247 (%)
1	8.0	0.02	0.625	20
2	1.0	0.02	0.625	9
3	2.0	0.02	0.625	14
4	8.0	0.002	0.625	20
5	8.0	0.2	0.625	21
6[a]	8.0	0.02	0.625	13
7	8.0	0.2	0.125	38
8	8.0	0.2	0.0625	38 (26)
9	8.0	0.02	0.0625	39
10	8.0	0.8	0.0625	44

Table 4.1: Further optimisation of reaction parameters. Yields reported are determined by quantitative ^{1}H NMR. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale. [a]Reaction performed with 2.0 equiv. KI present.

Addition of external KI has been previously shown in the group to increase the rate of reduction in rhodium catalysed reactions, however when used in our system it merely decreased the yield to 13% (Table 4.1, Entry 6). This is perhaps due to the increased iodide concentration favouring

fast reduction to the simple reduced product **246** before the enamine formed can add into any electrophile present.

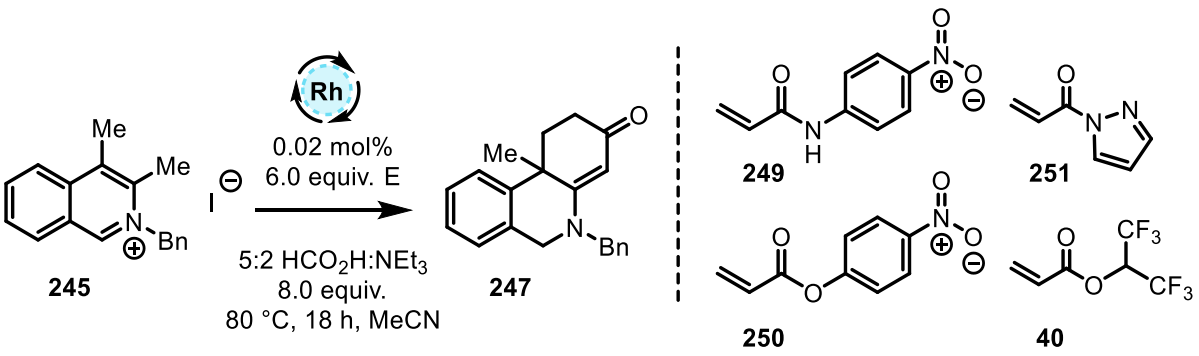
Increasing the solvent volume from 0.4 mL to 2.0 mL and 4.0 mL (0.0625 M, 0.125 M and 0.0625 M respectively), almost doubled the ^{1}H NMR yield to 38% in both cases, however this yield was decreased to 26% upon isolation in the case of the 4.0 mL reaction (Table 4.1, Entries 7-8). This can be attributed to difficulties encountered when isolating product **247** due to its surprisingly polar nature (*vide infra*).

Decreasing the catalyst loading but maintaining the low concentration produced a very similar yield of 39%, however largely increasing the catalyst loading four-fold to 0.8 mol% did show a slight increase in yield to 44% (Table 4.1, Entries 9-10).

4.3.2 Designing an improved electrophile

After a short optimisation, a maximum isolated yield of only 26% was obtained, which may be the limit obtainable with thioester **244**. It was desired to investigate alternative ambident electrophiles in an attempt to increase the reaction yield but also to potentially improve the physical properties of the electrophile to aid synthesis and handling. Ideally the reactant would be odourless, solid, and easily removable by chromatography.

A number of vinyl electrophiles were subsequently prepared and screened, with four potentially suitable electrophiles selected to represent distinct types of leaving group, namely stabilised esters and amides, and a *N*-heterocycle (Table 4.2). Vinyl pyrazole amides of this type have been previously used as electrophiles in the literature with reasonable success.[68]



Entry	Electrophile	Yield of 247 (%)
1	**249**	**0**
2	**250**	0
3	**251**	**65 (57)**
4	**HFIP acrylate, 40**	47

Table 4.2: Initial electrophile screen. Yields reported are determined by quantitative ^{1}H NMR. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale.

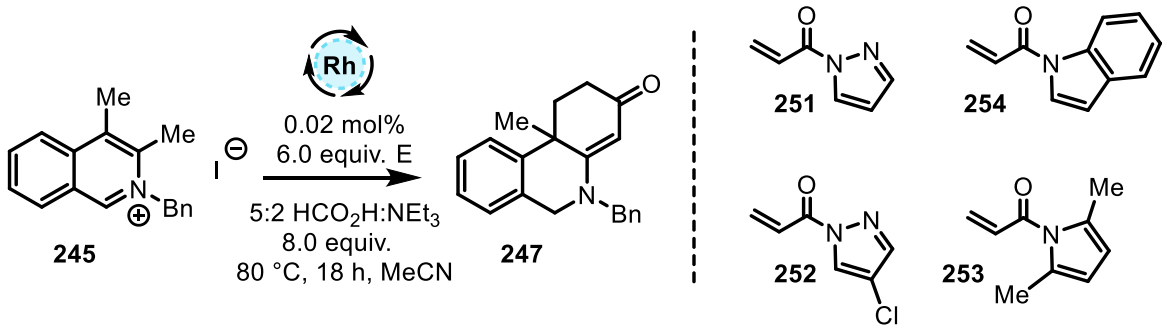
Vinyl pyrazole amide **251** showed excellent reactivity under the reaction conditions, with a 57% isolated yield recorded (Table 4.2, Entry 1). Regrettably, *p*-NO_2 phenyl amide **249** and ester **250**[69] showed no reactivity at all, merely generating a complex mixture (Table 4.2, Entries 2-3). This is explained in the case of amide **249** by the electrophile's poor solubility, however the explanation for ester **250** is less forthcoming. HFIP acrylate **40** performed well, producing a yield of 47%, although not quite as well as pyrazole amide **251** (Table 4.2, Entry 4).

As a result of this highly promising result with vinyl pyrazole amide **251**, a range of *N*-heterocycle vinyl amide electrophiles were synthesised and trialled under the model reaction conditions (Table 4.3).

Regrettably, both pyrrole derived compound **253** and indole derived compound **254** produced no product **247** when applied to the model system, potentially indicating the leaving groups

were not sufficiently stable as independent fragments to adequately function as ambident electrophiles (Table 4.3, Entries 3-4).

Pleasingly, **252**, derived from 4-chloropyrazole, produced a good ^{1}H NMR yield of 66%, similar to the previously trialled pyrazole derived amide **251** (Table 4.3, Entries 1-2). Chloropyrazole vinyl amide **252** is a white fluffy solid and is significantly easier to synthesise, handle and store than **251** which is a volatile oil. As a result of this advantageous set of physical properties, it was decided to continue the optimisation process using **252** as the electrophile.



Entry	Electrophile	Yield of 247 (%)
1	**251**	65 (57)
2	**252**	**66**
3	**253**	0
4	**254**	0

Table 4.3: Scope of *N*-heterocycle electrophiles investigated. Yields reported are determined by quantitative ^{1}H NMR. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale.

4.3.3 Optimisation of the annulation reaction using vinyl pyrazole amide 252

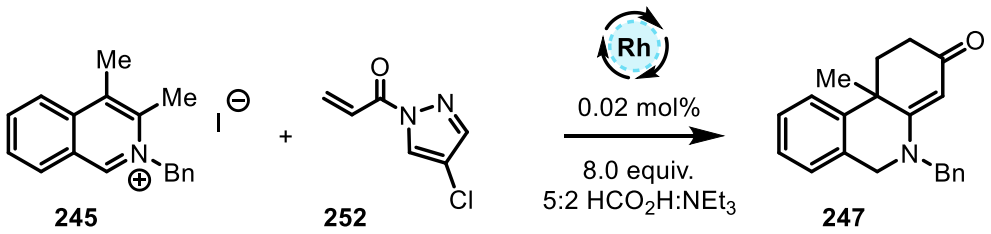
Further optimisation was then performed, first exploring equivalents of electrophile then proceeding to explore temperature, time and dilution (Table 4.4).

Pleasingly, decreasing the equivalents of electrophile from 6.0 to 4.0 and then 2.0 did not significantly decrease the yield (Table 4.4, Entries 1-3). This shows that this new electrophile is significantly more reactive to the system than the previous electrophile **251**, which showed sensitivity to deceasing electrophile equivalents. The reason for the slight decrease to a 45% isolated yield when using 4.0 equivalents of electrophile is unknown, but could be due to experimental error, since decreasing the equivalents still further to 2.0 produced a 60% isolated yield. As with experiments conducted with thioester electrophile **244**, increasing the volume of solvent to 4.0 mL (0.0625 M) increased the isolated yield to 76% (Table 4.4, Entry 4).

Performing the reaction with the same volume of solvent (4.0 mL) but with 10 times the catalyst loading (0.2%) did not significantly change the isolated yield (74%) showing that the amount of catalyst present is broadly unimportant (Table 4.4, Entry 5). A small solvent screen was then conducted, which showed that of the polar solvents trialled, MeCN afforded the highest ^{1}H NMR yield (Table 4.4, Entries 4, 6-9).

Reaction time was then explored, with eight hours affording the best isolated yield of 86% (Table 4.4, Entries 10-14). Extending the reaction time beyond eight hours to twenty four hours afforded a very similar yield (Table 4.4, Entry 14). Interestingly, the reaction is mostly complete after two hours (69%) with the final 20% taking six further hours to be produced.

As expected, decreasing the reaction temperature to 60 °C showed a significant decrease in ^{1}H NMR yield to 40%. Conversely, increasing the temperature to 100 °C did not increase the yield observed, therefore 80 °C was kept as a lowest optimum temperature (Table 4.4, Entries 12, 15-16).



Entry	Temperature (°C)	Electrophile Equiv.	Time (h)	Solvent	Concentration (M)	Yield of 247 (%)
1	80	6.0	18	MeCN	0.625	66
2	80	4.0	18	MeCN	0.625	51 (45)
3	80	2.0	18	MeCN	0.625	(60)
4	80	2.0	18	MeCN	0.0625	85 (76)
5[a]	80	2.0	18	MeCN	0.0625	81 (74)
6	80	2.0	18	MeOH	0.0625	3
7	80	2.0	18	Acetone	0.0625	50
8	80	2.0	18	DCE	0.0625	80
9	80	2.0	18	^{t}AmOH	0.0625	73
10	80	2.0	2	MeCN	0.0625	61 (69)
11	80	2.0	4	MeCN	0.0625	(72)
12	80	2.0	6	MeCN	0.0625	79 (77)
13	**80**	**2.0**	**8**	**MeCN**	**0.0625**	**84 (86)**
14	80	2.0	24	MeCN	0.0625	76 (81)
15	60	2.0	6	MeCN	0.0625	40
16	100	2.0	6	MeCN	0.0625	82
17	80	2.0	8	MeCN	0.250	50
18	80	2.0	8	MeCN	0.125	60
19	80	2.0	8	MeCN	0.0250	80
20	80	2.0	8	MeCN	0.0125	80

Table 4.4: Final optimisation steps of reductive annulation. Yields reported are determined by quantitative ^{1}H NMR. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale. [a]Reaction performed with 4.0 mL of Rh solution, giving a 0.2 mol% loading.

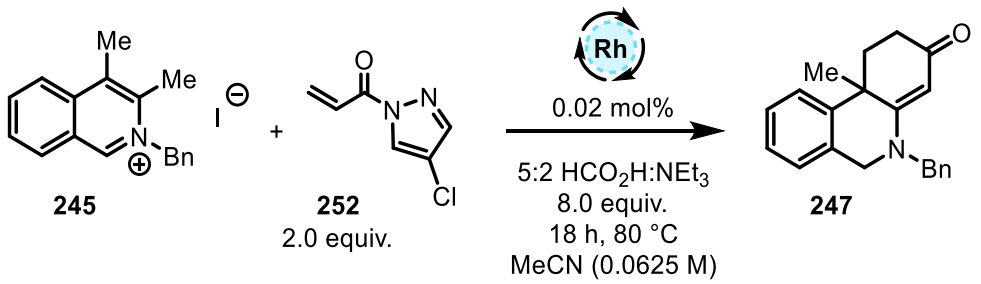
Finally, dilution was investigated more thoroughly, which showed that both 1.0 mL (0.25 M) and 2.0 mL (0.125 M) produced reduced ^{1}H NMR yields of 50% and 60% respectively (Table 4.4, Entries 17-18). Diluting the reaction further to 10 mL (0.025 M) and then 20 mL of solvent (0.0125 M) both afforded a ^{1}H NMR yield of 80%, slightly reduced from the best result of an 86% isolated yield, indicating that any beneficial effects of dilution on our reaction have plateaued (Table 4.4, Entries 19-20).

In conclusion, the optimised conditions are 2.0 equiv. of electrophile, using MeCN as the reaction solvent at a 0.0625 M concentration, for 8 h at 80 °C (Table 4.4, Entry 13).

4.3.4 Control experiments

A few control experiments were performed to investigate the need for certain reaction components (Table 4.5). Gratifyingly, removal of reductant (5:2 HCO_2H:NEt_3) shut down reactivity completely, showing no yield (Table 4.5, Entry 1). This demonstrates that reduction at C1 is indeed occurring due to a hydridic species, however it is unclear whether 5:2 HCO_2H:NEt_3 is reacting with $(RhCp^*Cl_2)_2$ to generate a rhodium hydride species, or whether the reductant is reacting with the isoquinolinium salt directly.

In an attempt to investigate this question, the reaction was performed in the absence of any Rh catalyst showing, a decrease in yield from 76% to 56%, perhaps indicating that although the yield is increased in the presence of Rh, a notable background reaction is occurring (Table 4.5, Entry 2). This result is consistent with previous work in the group with Rh catalysts that has shown that reductive functionalisation reactions can often occur without a Rh catalyst present, using *in situ* generated formate at the reducing agent, but that the reaction rate is slower.[23]

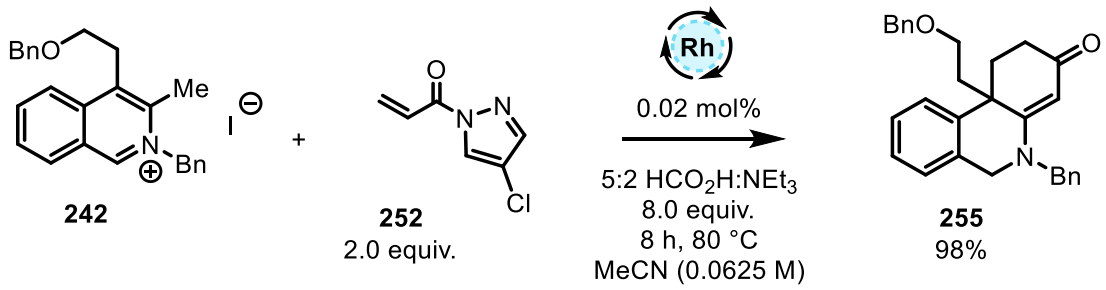


Entry	Differing Conditions	Yield of 247 (%)
1	No reductant (5:2 HCO_2H:NEt_3)	0
2	No Rh catalyst	(56)

Table 4.5: Control investigations. Yields reported are determined by quantitative ^{1}H NMR. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale.

4.3.5 Application of the optimised conditions to a second substrate

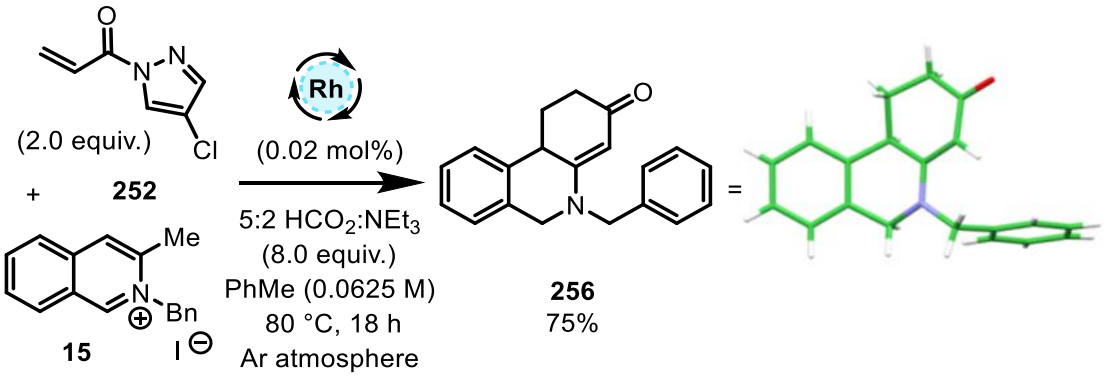
Pleasingly, the application of our optimised conditions to second model substrate with a larger C4 side chain **242** proved very successful, with our optimised conditions affording an isolated yield of 98% (Scheme 4.7). This is a highly promising result, as it shows that the reaction conditions are tolerant of a larger side chain with differing functionality. Should we wish to use this method to synthesise larger molecules or indeed use this method as a later stage step in a synthetic sequence, the ability to tolerate a diverse range of side chains would be highly advantageous.



Scheme 4.7: Application of our method to a second substrate, showing tolerance of differing side chain groups. Isolated yield is reported. Reaction performed on 0.25 mmol scale.

4.3.6 Application of reductive annulation conditions to other substrates

Work was performed on a related system by Mr. G. Blake, with a C4-unsubstituted model substrate **15** (Scheme 4.8). The reaction was re-optimised and was found to perform best with PhMe as a solvent and a rigorous Ar atmosphere (presumably to stop product autoxidation).



Scheme 4.8: Optimised reductive annulation conditions for C4 unsubstituted substrates including single crystal X-ray structure of **256**. 3-Me-*N*-benzyl isoquinolinium iodide was chosen as a model substrate. Reactions performed on 0.25 mmol scale. Isolated yield is reported. Single crystal X-Ray analysis performed by T. C. Jenkins.

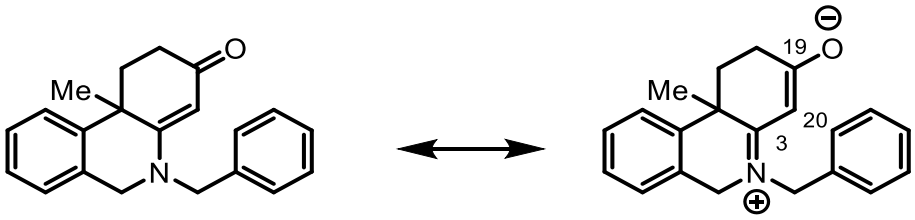
Although this work was highly promising, the lack of a substituent at C4 resulted in a much more unstable compound, **256**, which was observed to decompose after a few days at r.t. and exposed to air, in contrast to **247** which was bench stable. Further derivatisation of **256** was challenging and ultimately unsuccessful, therefore work on C4 unsubstituted annulated THIQs was curtailed. A single crystal X-ray structure of **256** showed the same tricyclic structure as with the C4-Me analogue, **247** (Scheme 4.8).

4.4 Reduction of vinylogous amide 247 to allow further derivatisation

4.4.1 Charge separated nature of vinylogous amide 247

Our attention was then directed towards the reduction of the model substrate **247**, which would allow us to remove the unwanted vinylogous amide functionality; however this presented

certain challenges due to its stability. We suggest that the charge separated resonance structure is the most accurate representation of the nature of compound **247** (RHS, Scheme 4.9), for which our evidence is three-fold. Firstly, the eluent required to purify a crude mixture is a surprisingly polar 3-8% EtOH in EtOAc. Secondly the ^{13}C chemical shift (δ_c) of C3, alpha to nitrogen, is 167.5 ppm, notably more deshielded and downfield than one might expect an olefin carbon, much more similar to an iminium chemical shift (typically 150-170 ppm).[70] By contrast, the carbonyl ^{13}C chemical shift (C_{19}) is 195.6 ppm, much more deshielded than expected from an amide carbonyl carbon, and the other olefin carbon (C_{20}) has a shift of 97.7 ppm, much lower and therefore shielded than expected for an olefinic carbon.[71] Thirdly, the primary IR stretch for compound **247** is a carbonyl peak at 1552 cm^{-1}, a very low shift for an amide, indicative of a significant proportion of nitrogen lone pair donation into the carbonyl and weakening the C-O pi bond.[72]



Scheme 4.9: Charge separated character of compound **247**.

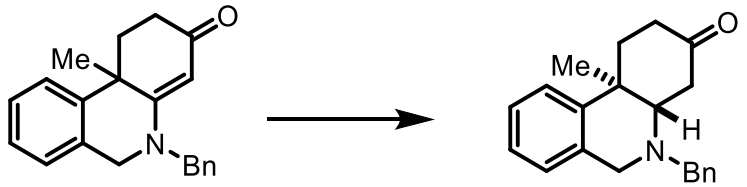
Armed with this evidence, we were prepared for the reduction of compound **247** to be more challenging than first thought, as this is not simply a reduction of a vinylogous amide, but essentially a reduction of an iminium ion in the presence of an enolate, which changes the electronics of the problem. Nonetheless, we were undeterred and first attempted to treat it as a conventional vinylogous amide to test its reactivity.

4.4.2 Hydrogenation reduction strategy

Three reduction strategies were attempted, being hydrogenation, single electron reductants and hydride addition. It was posited that a heterogenous catalyst might be found that would hydrogenate the alkene double bond as well as deprotect the tetrahydroisoquinoline nitrogen, however, attempts to find such a catalyst proved futile (Table 4.6).

The literature has previously shown that PtO_2 had been used for such purposes in related vinylogous amides before, however only starting material was returned upon application of the conditions to our substrate (Table 4.6, Entry 1).[73]

Similarly, use of more conventional hydrogenation catalysts such as rhodium on carbon and palladium on carbon, both with and without aqueous acid added merely returned starting material (Table 4.6, Entries 2-4).[74]



247 **257**

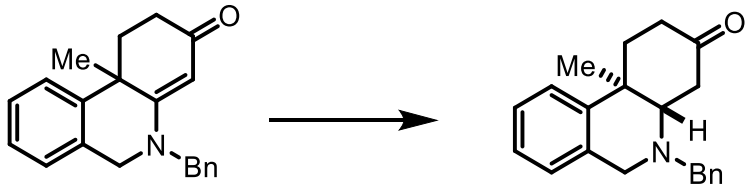
Entry	Conditions	Result
1	10 mol% PtO_2, H_2	SM returned
2	10 mol% Rh on C, H_2	SM returned
3	10 mol% Pd on C, H_2	SM returned
4	10 mol% Pd on C, H_2, cat. H^+	SM returned

Table 4.6: Heterogenous reduction approach for reduction of vinylogous amide **247**.

4.4.3 Single electron reduction reagents

Single electron reductants have previously been shown in the literature to be useful when dealing with challenging electronic manifolds, such as conjugated π-systems, pyridiniums and other *N*-heterocycles.[74-76] We thus decided to screen some single electron reductants (Table 4.7).

Zinc powder in acetic acid was suggested in the literature to be compatible with vinylogous amide reduction, however the reagent was unreactive to our substrate when the conditions were replicated (Table 4.7, Entry 1).[77] Elemental magnesium powder was also suggested by a literature procedure, however application to our substrate returned only starting material (Table 4.7, Entry 2).[78]



247 **257**

Entry	Conditions	Result
1	Zn powder in AcOH, reflux	SM returned
2	Mg powder in MeOH, r.t.	SM returned

Table 4.7: Single electron reductant strategy attempts.

4.4.4 Hydride reducing agents

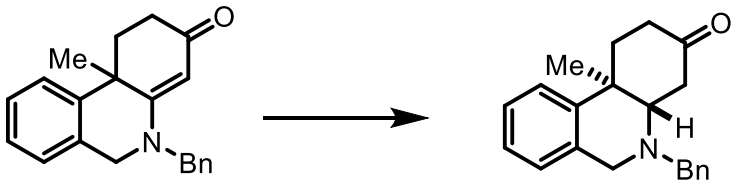
Our next line of enquiry was hydride based reducing agents, which we hoped could add into the amide in a 1,4-addition, thereby disrupting the conjugation.

L-Selectride has been used in related vinylogous amide systems before with good yields, however, use on our substrate showed no reactivity, only returning starting material (Table 4.8,

Entry 1).[79] DIBALH showed some reactivity to our substrate, however did not produce any observable product over the reaction timescale, simply partly decomposing our material (Table 4.8, Entry 2).

Luche conditions, a method traditionally used to provide a 'hard' hydride designed to favour 1,2-attack at a carbonyl centre, regrettably returned starting material (Table 4.8, Entry 3).

Similarly, both $NaBHEt_3$ or 'Superhydride' and $LiBH_4$ were unreactive to our substrate, again returning starting material (Table 4.8, Entry 4-5).



247 **257**

Entry	Reductant	Solvent	Temperature (°C)	Result
1	L-Selectride	THF	-78 then r.t.	SM returned
2	DIBAlH	THF	r.t.	Partly decomposed SM
3	$NaBH_4$ $CeCl_3$	MeOH	0 to 60	SM returned
4	1.0 equiv. $NaBHEt_3$	THF	0	SM returned
5	$LiBH_4$	MeOH	0	SM returned
6	1.0 equiv. BH_3 DMS	THF	66	SM returned
7	2.0 equiv. BH_3 DMS	THF	66	Complex mixture
8	0.5 equiv. Stryker's reagent	THF	r.t.	SM returned

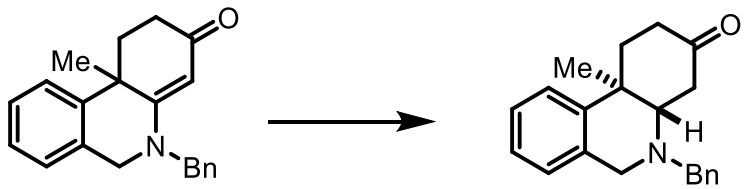
Table 4.8: Hydride reagents trialled.

BH_3 DMS complex, more commonly used to reduce carboxylic acids, did manage to produce reactivity with our substrate, with 1.0 equiv. returning starting material, but regrettably

2.0 equiv. generating a complex mixture (Table 4.8, Entries 6-7). Although it is promising to observe reactivity with our substrate, it was not possible to isolate or observe any useful species in the complex mixture produced, and so investigations with this reagent were not pursued further.

It was hypothesised that a softer hydride might be more appropriate, considering the failure of traditionally 'hard' hydride reagents, and so a substoichiometric amount of Stryker's reagent, a copper hydride source, was applied to our substrate (Table 4.8, Entry 8). Disappointingly, the substrate was unreactive to the reagent and starting material was returned unaltered.

It was hoped to achieve some level of reactivity, however minor that might be, and so a stronger hydride reducing agent, $LiAlH_4$, was suggested.[80] An initial reaction set up at -5 °C disappointingly returned only starting material, but undeterred, we performed the reaction again at a higher temperature (Table 4.9, Entries 1-2). Pleasingly, the complex mixture generated when the reaction was performed at 80 °C contained roughly 10% product **257** by quantitative ^1H NMR analysis of the crude reaction mixture. **257** was pleasingly formed as a single diastereomer.



247 **257**

Entry	Conditions	Yield of 257 (%)
1	$LiAlH_4$ at -5 °C	SM returned
2	$LiAlH_4$ at 80 °C for 5h	Complex mixture containing roughly 10% product. >95:5 d.r.
3	$LiAlH_4$ at r.t. for 15 mins	28% >95:5 d.r.

Table 4.9: Lithium aluminium hydride reduction attempts. Isolated yields are reported. Reactions performed on 0.25 mmol scale.

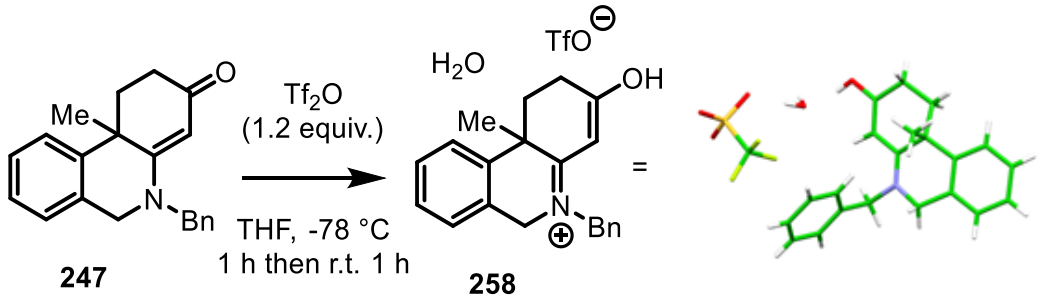
Performing the reduction at room temperature was much more successful, with the reaction able to be followed by TLC. TLC analysis showed that the reaction was complete in 30 minutes, and the product **257** was the only material observable (Table 4.9, Entry 3).

Regrettably, product **257** decomposed swiftly following isolation. Repeated ^{1}H NMR spectroscopic analysis showed decomposition after 30 minutes to form a variety of minority products, none of which were either isolatable by chromatography or possible to characterise by spectral means.

Interestingly, the ^{1}H NMR solution of the partially decomposed reaction mixture was a purple colour. It was proposed that the colour originated from the formation of a radical cation impurity generated through oxidation from the air, a theory borne out by the observation that the purple colour starts in the top portion of an NMR tube containing a crude mixture, slowly spreading throughout the tube with time. Despite these difficulties, it was possible to characterise the product, which conclusively showing a ketone carbon shift (^{13}C NMR) at 209.9 ppm.

4.4.5 Enolate trapping attempts

It was suggested that trapping the charge separated state of the starting material, then reducing the resultant triflate salt might control the process better, which could diminish the possibility of side products created by oxygenation after reduction (Scheme 4.10). Sadly, attempts to trap compound **247** with triflic anhydride were unsuccessful, however, after work-up and analysis by ^{1}H NMR, a single species was seen to precipitate out of the $CDCl_3$ solution, which was analysed by single crystal X-ray crystallography (Scheme 4.10).



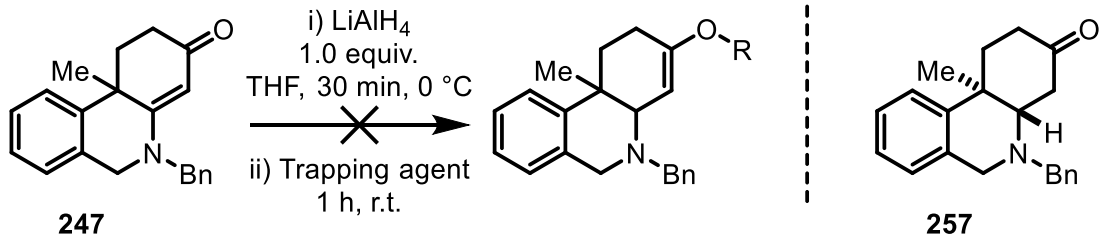
Scheme 4.10: Attempts to trap compound **247** using Tf_2O with single crystal X-ray analysis of the solid product. Single crystal X-Ray analysis performed by T. C. Jenkins.

The crystalline species was the *O*-protonated trifluoromethanesulfonate hydrate salt of starting material **247**, which clearly indicates the presence of moisture in our reaction, perhaps indicating that the triflic anhydride has partly decomposed during storage. Whilst this product (**258**) shows an unexpected mode of reactivity, it is sadly not synthetically useful, as treatment of this salt with any homogenous hydride reagents will simply deprotonate the salt and reveal our initial vinylogous amide **247**.

In a related vein, it was posited that reduction of compound **247** with $LiAlH_4$ (*vide supra*) would result in an enolate in solution, which then protonates upon quenching to reveal desired product **257**. This facet could be exploited by quenching instead with an electrophilic trapping

reagent, which could trap the enolate *in situ*, as opposed to protonation which a conventional aqueous quench would achieve.

Three electrophiles were subsequently trialled, regrettably with no success (Table 4.10, Entries 1-3). All electrophilic reagents did not react with any aluminium enolate produced, and upon working up each reaction with an aqueous quench, the major product observed by ^{1}H NMR in each case was ketone **257**.



247 **257**

Entry	Trapping reagent	Product
1	TMSCl	Untrapped **257**
2	TMSOTf	Untrapped **257**
3	$Me_3O\ BF_4$	Untrapped **257**

Table 4.10: Electrophilic trapping reagents.

With little success trapping any enolate, either formed *in situ* or naturally occurring in the molecule with anything other than a proton, this line of enquiry was curtailed.

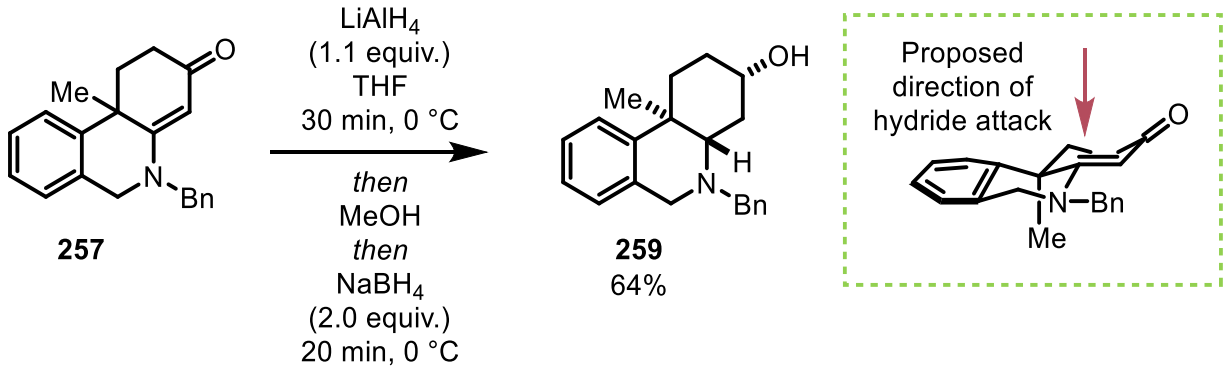
4.4.6 Borohydride work up strategy

It was suggested that by repeating the $LiAlH_4$ promoted reduction, but reducing the ketone further to an alcohol *in-situ* with a $NaBH_4$ quench, a stable intermediate might be reached. Normally, $NaBH_4$ reductions require a polar protic solvent to form the reactive species, which is incompatible with the original $LiAlH_4$ reagent, therefore this process must occur *via* sequential addition. After reduction of **247** in THF with $LiAlH_4$ had been observed to reach

completion by TLC analysis, an equivalent volume of MeOH was added slowly to the reaction. When effervescence ceased, 2.0 equiv. of $NaBH_4$ was then added in one portion.

Pleasingly, this technique afforded the desired compound **259** as a stable oil in 64% yield (Scheme 4.11). The single diastereomer produced was assigned by NOESY correlations and is trans annulated tricycle **259**. Happily, alcohol **259** showed greater stability than ketone **257**, providing a stable intermediate for future investigations.

The stereochemistry of the product has trans-geometry across the 6,6-ring junction, potentially due to Fürst-Plattner axial hydride addition. The resultant ketone is then reduced to give an equatorial alcohol.



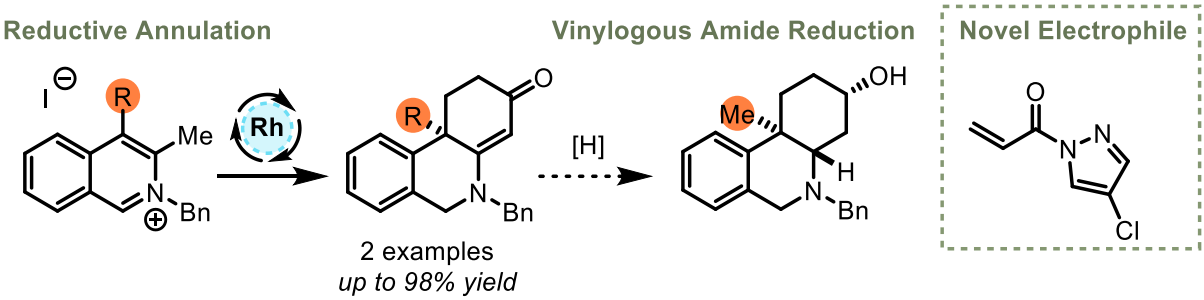
Scheme 4.11: Successful reduction of the vinylogous amide. Isolated yield is reported. Reaction performed on 0.25 mmol scale.

This result is gratifying, and shows that it is possible to further functionalise vinylogous amide **247** to produce tricyclic THIQ derivatives with functionality other than alkyl groups on the third ring.

4.5 Conclusion

In conclusion, a method for synthesising 3,4-annulated THIQs from isoquinolinium salts in a one-pot process has been developed, with a novel electrophile developed for our process which is easy to synthesise and has desirable physical properties. The method has been optimised to

a good yield on model substrate **247** and applied to two other model systems with slight modifications to afford excellent yields of both products. In the case of the primary model system, the product has been further reacted with a hydride reducing agent to produce a stable derivative, which shows promise for any future investigations into annulated vinylogous amides of this type.



Scheme 4.12: Development of a reductive annulation process making use of a novel ambident electrophile.

Chapter 5 – Application of a reductive annulation reaction towards the synthesis of Crinane-type alkaloids

5.1 Previous syntheses of the Crinane family of alkaloids

The diverse families of the *Amaryllidaceae* alkaloids are comprised of almost 500 compounds, with roughly 10% of them belonging to the Crinane family.[81] Most *Amaryllidaceae* alkaloids contain a 6,6,6-tricyclic core (ABC), however members of the Crinane family uniquely possess in a fourth bridging ring (D). This class of tetracyclic molecules are well represented in the total synthesis literature (Figure 5.1).[82]

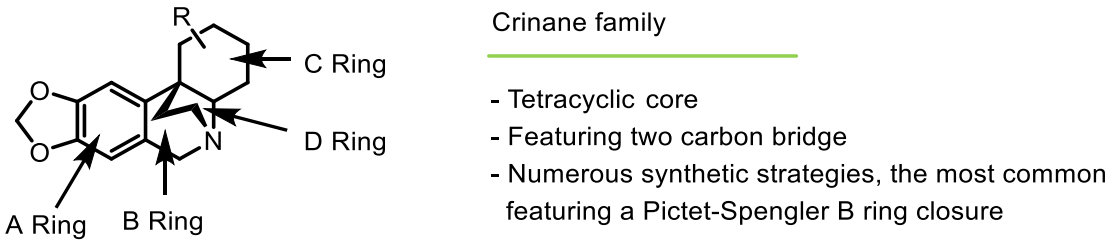
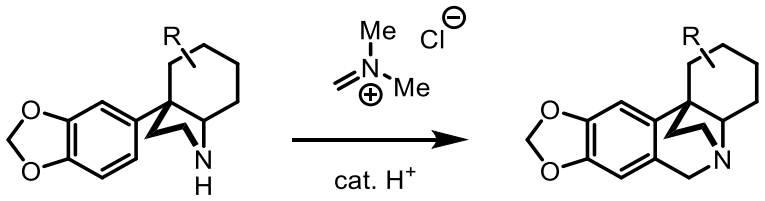


Figure 5.1: The tetracyclic structure of the Crinane family of alkaloids.

The numerous syntheses of Crinane-type alkaloids can be broadly divided into categories by their overarching synthetic strategies. The strategy most well represented in the literature includes a Pictet-Spengler cyclisation to close the B-ring, by way of Eschenmoser's salt as a one-carbon electrophile (Scheme 5.1).[83] The methods of constructing the C and D-rings, however, vary greatly, and provide ample opportunity to demonstrate a range of interesting and impressive transformations.

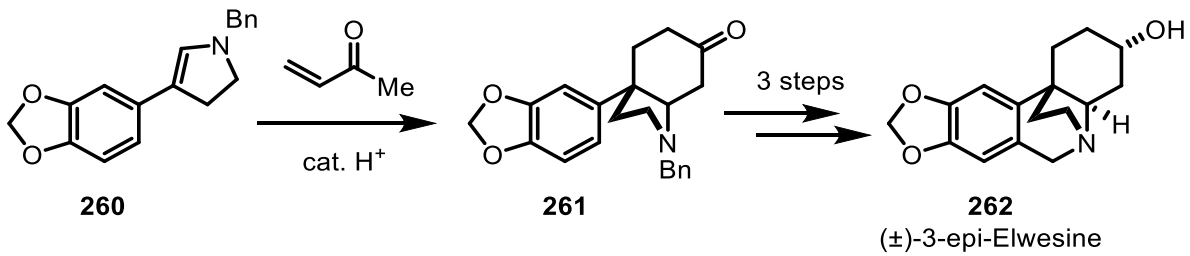
Pictet-Spengler B ring closing method



Scheme 5.1: Pictet-Spengler B-ring closure method that features in a large proportion of Crinane family alkaloid syntheses.

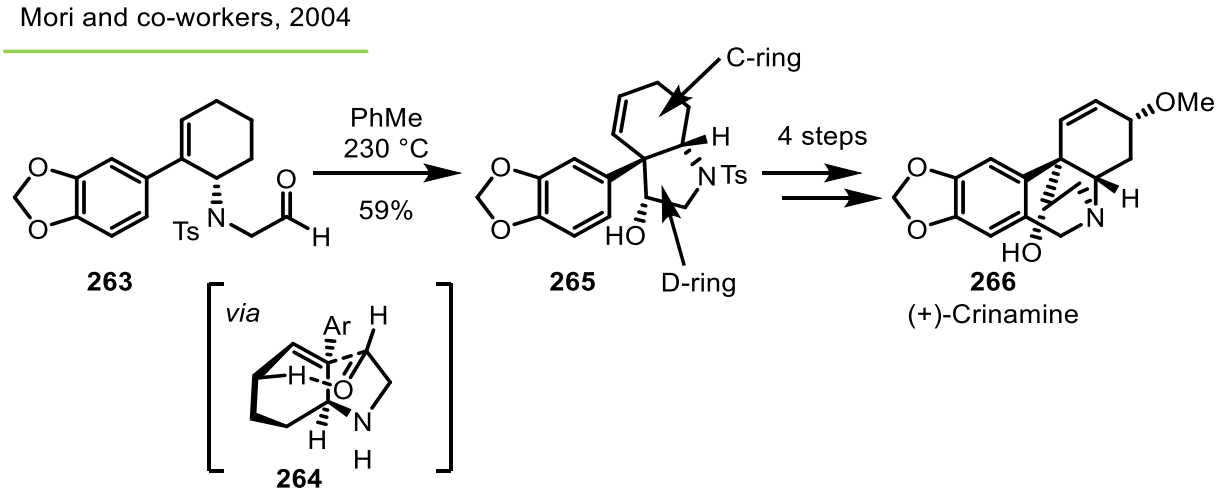
Stevens and DuPree reported a synthesis of (±)-3-epi-Elwesine in 1970, using the Pictet-Spengler B-ring-closing method described above.[84] The key step in their reaction sequence, however, was a formal [4+2] cycloaddition between an enamine **260** and MVK (Scheme 5.2). Whilst the reaction mechanism likely proceeds *via* stepwise addition of the enamine into MVK, followed by ring closure, the overall reaction can be considered as a formal cycloaddition. This reaction, which could be considered a modification to the Robinson ring annulation reaction, has been previously used by other researchers in the synthesis of alkaloids, for instance, by Evans in his synthesis of the Hasubanan skeleton.[85]

Stevens and DuPree, 1970



Scheme 5.2: Use of an annulation reaction to construct the C-ring of (±)-3-epi Elwesine **262**.

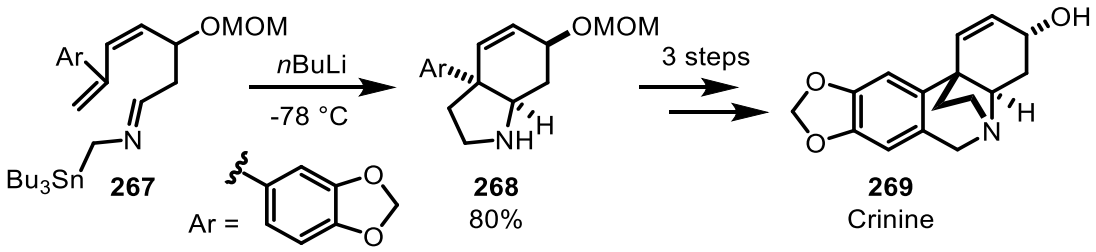
Mori and co-workers also used the popular Pictet-Spengler B-ring closure strategy as the final reaction in their synthesis of Crinamine, but their method of bridging D-ring construction was notable (Scheme 5.3).[86] Under forcing conditions (230 °C in a sealed tube), aldehyde **263** underwent a carbonyl-ene cyclisation, proposed by the authors to react *via* a 6-membered chair transition state (**264**). The bicyclic product **265** was then elaborated further to produce Crinamine **266**.



Scheme 5.3: Carbonyl-ene strategy to close the bridging D-ring before Pictet-Spengler B-ring closure.

In a related strategy, Person and Lovering used Crinine as a platform to demonstrate a [3+2] cycloaddition between a 2-azaallyl anion and an electron rich alkene (Scheme 5.4).[87] The 2-azaallyl anion was generated *in situ* by lithium-tin exchange, which then cyclised onto the pendant alkene to afford the 6,5-bicycle **268**, which represents the C and D-rings of Crinine. The synthesis was completed by B-ring closure in a very similar manner to the syntheses described above, to produce Crinine **269** in 8 steps.

Pearson and Lovering, 1994

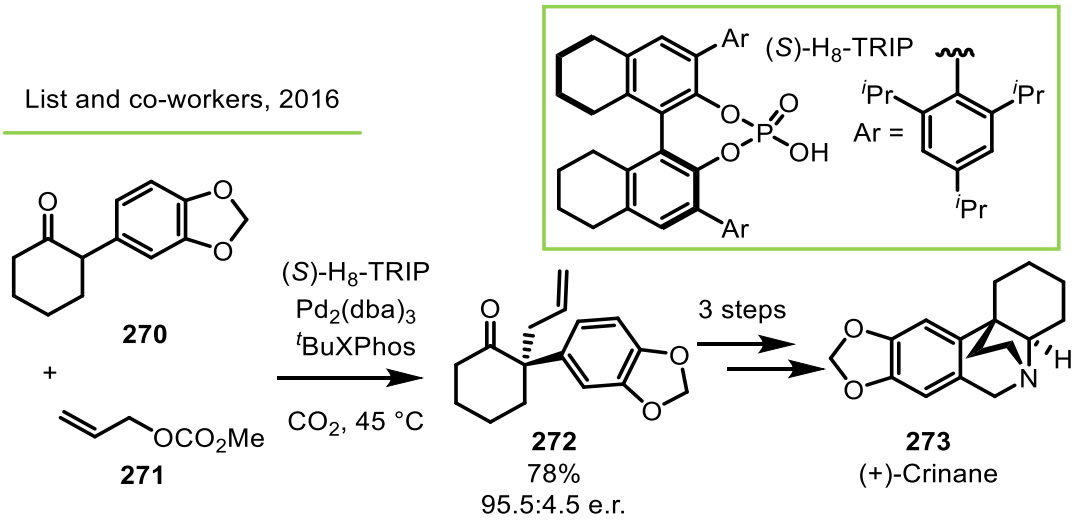


Scheme 5.4: A [3+2] 2-azaallyl anion cyclisation approach to construct the C and D-rings of Crinine before B-ring construction.

List and co-workers took a subtly different approach, applying their enantioselective ketone allylation protocol to construct the key quaternary stereocentres in (+)-Crinane (Scheme 5.5).[88-89]

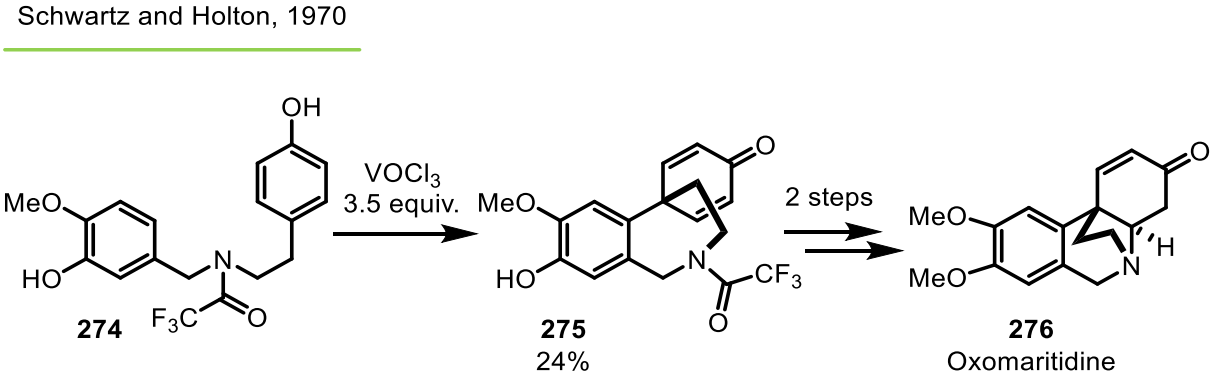
Upon treatment of racemic substrate **270** with allyl methyl carbonate under Pd/chiral phosphoric acid dual catalysis, **272** was accessed in 78% yield and with excellent enantioselectivity.

The α-allyl ketone **272** could then be derivatised to (+)-Crinane **273** in three steps, namely a Lemieux-Johnson oxidation, a reductive amination, and the familiar Pictet-Spengler B-ring closure utilising Eschenmoser's salt as the final carbon source. In this way, the allyl group added during the author's key step became the D-ring of Crinane, whilst the C and A-rings were derived from the commercial starting material.



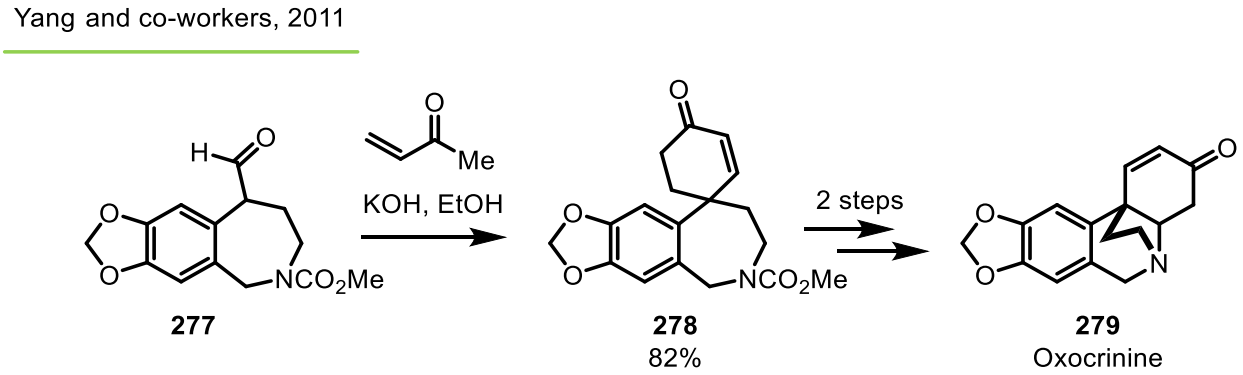
Scheme 5.5: Allylation using a chiral phosphoric acid to give an enantio-enriched α-quaternary ketone, that was further derivatised to (+)-Crinane **273**.

Employing a different B-ring closure strategy, Schwartz and Holton reported a biomimetic synthesis of the Crinane alkaloid family, starting from a tethered bisphenol **274** (Scheme 5.6).[90] Treatment of bisphenol **274** with an oxidant, $VOCl_3$, effected the desired *para-para* phenol coupling to forge the A to C-ring junction in **275**. Deprotection of the nitrogen then triggered conjugate addition into the dienone, constructing both the B and D-rings in tandem. Finally, methylation of the remaining free hydroxyl afforded Oxomaritidine **276**.



Scheme 5.6: A biomimetic approach to close the A to C-ring junction in Oxomaritidine **276**, employing a *para*-coupling of phenols.

In 2011, Yang and co-workers reported a synthesis of Oxocrinine **279**, employing a similar amine conjugate addition strategy to construct the bridged ring system (Scheme 5.7).[91] The cyclisation substrate **278** was readily constructed in 82% yield from **277** using a Robinson annulation, with MVK acting as the three-carbon fragment. The product was then transformed to Oxocrinine **279** in two further steps.



Scheme 5.7: Robinson ring annulation strategy to construct the C-ring from a pre-installed aldehyde.

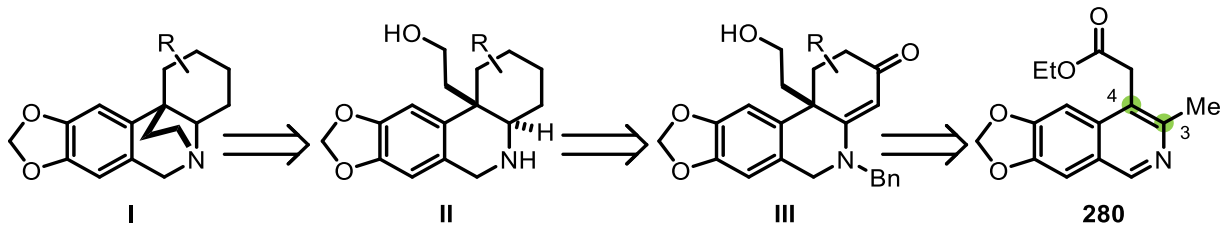
The methods detailed above represent a small fraction of the Crinane-type alkaloid syntheses which have been reported to date; methods using a B-ring closure strategy and assorted other routes are numerous and provide a rich source of inspiration for our synthetic campaign towards the Crinane family.[92]

5.2 A new route to the Crinane family of natural products

5.2.1 Retrosynthetic analysis

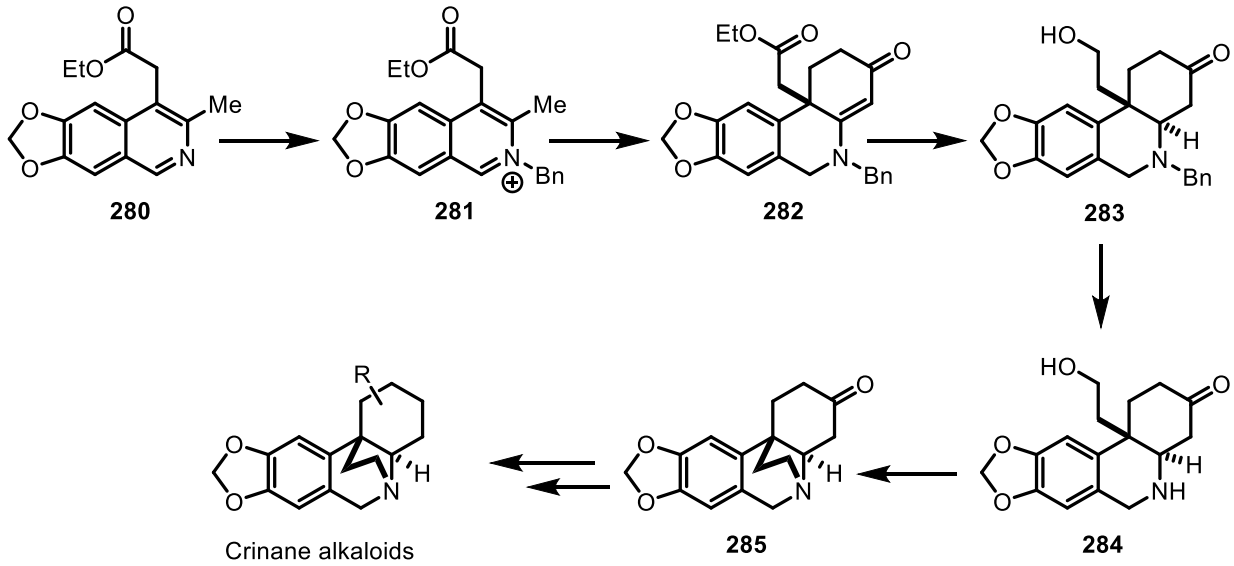
The Crinane family possesses a 6,6,6-ring structure as part of their tetracyclic core, which is reminiscent of the products derived from the reductive annulation reaction described in Chapter 4 (*vide supra*). We aimed to showcase this method in the context of a natural product synthesis, therefore the Crinane family were chosen as synthetic targets. We envisaged a set of

disconnections that would derive the Crinane natural products from an isoquinoline core **280** (Scheme 5.8). In the forward sense, isoquinoline **280** could be employed in our reductive annulation method to generate the C-ring required for the Crinane family. Our retrosynthetic analysis revealed that an isoquinoline with a C3 methyl group and a two-carbon C4 side chain was required. The two-carbon side chain would require a leaving group attached in order for the D-ring bridge closure step to occur, but this leaving group could be installed as a protected functionality which could be deprotected later in the synthetic sequence. We decided to adopt an ethyl ester as our target functionality, as it can be easily reduced and subsequently activated to become a good leaving group.



Scheme 5.8: Retrosynthetic analysis of a generic Crinane alkaloid to an accessible isoquinoline.

Working forwards, our identified isoquinoline **280** would need to be quaternised to form the benzyl isoquinolinium salt **281**, and then it could be subjected to the reductive annulation method to produce vinylogous amide intermediate **282** (Scheme 5.9). This functionality can be reduced, then debenzylation would reveal amino alcohol **284**, which would be set up for D-ring closure. Decoration of the C-ring to finish the synthesis of multiple members of the Crinane family could then occur *via* use of the ketone functionality retained from the vinylogous amide reduction.



Scheme 5.9: Planned synthetic route from isoquinoline **280** to the Crinane family of natural products.

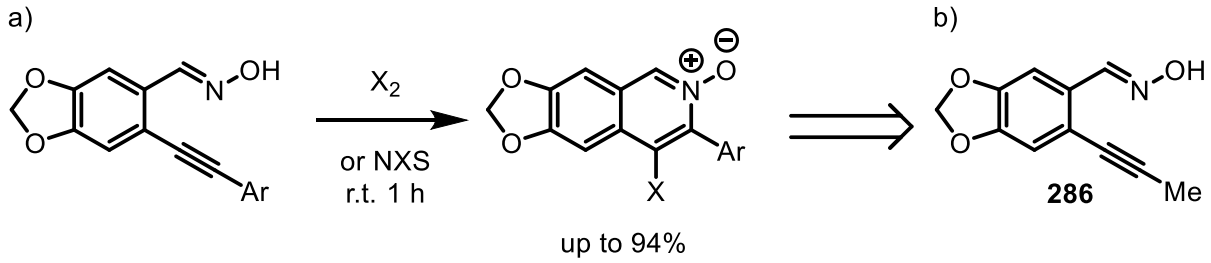
5.2.2 Choice of the synthetic route towards isoquinoline 280

Our model substrate synthesised in Chapter 4, **245**, was afforded using a halogenation approach, which introduced functionality onto the isoquinoline skeleton *via* harsh acidic conditions. The innate reactivity of 3-Me isoquinoline directs the halogen to C4, which was the desired site of side chain incorporation; for the purposes of reaction optimisation a methyl group was chosen (*vide supra*), however we have previously showed the annulation reaction's applicability to one other C4 side chain.

In order to render the same C4-functionality in our desired isoquinoline **280**, however, an alternative strategy was required. The electron rich nature of the dioxolane appended to the A-ring made the halogenation approach unsuitable. The B-ring therefore had to be constructed *de novo*, with a C4 two-carbon substituent and a C3 methyl built in *en route*.

As a first approach to the synthesis of desired isoquinoline **280**, a method reported by Ding and co-workers in 2008 was examined.[93] Their method utilises a halogen promoted cyclisation of

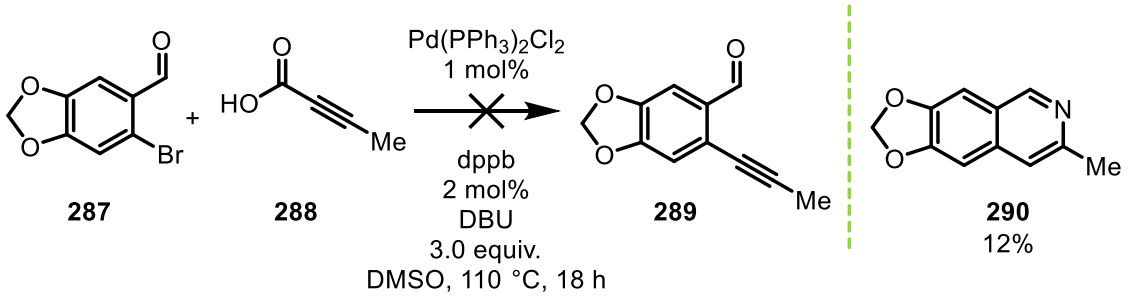
an oxime onto an aryl-capped alkyne to furnish a C4-halogenated C3-aryl isoquinoline-*N*-oxide (Scheme 5.10). This intermediate could then be cross coupled and reduced with good literature precedent to furnish a C4 substituted isoquinoline in three steps from the parent alkyne.



Scheme 5.10: a) Method developed by Ding and co-workers for halogen promoted cyclisation of aryl alkyne-oximes to form isoquinoline-*N*-oxides, and b) Alkyne **286** required to use the method to synthesise our desired isoquinoline **280**.

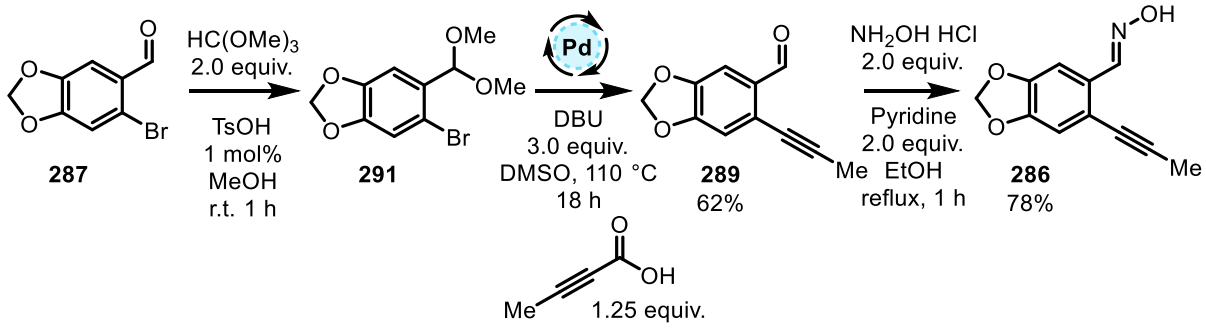
5.2.3 Synthesis of alkyne 286

To synthesise alkyne **286**, we opted to use butynoic acid as an alternative for gaseous and difficult-to-handle propyne. A literature procedure reported by Yang and co-workers used propiolic acid as a propyne surrogate in a decarboxylative cross coupling.[94] Unfortunately, when applied to benzaldehyde **287**, the reaction failed to product desired alkyne **289**, instead affording a 12% yield of an unintended side product **290**. We hypothesise that this product was generated due to the use of ammonium chloride solution in the work up (Scheme 5.11). The presence of isoquinoline **290** implies that a small amount of desired alkyne **289** was produced in the reaction, however the acidic work-up conditions suggested by the literature procedure are not well suited to our substrate, activating the molecule to ring closure in an undesired and uncontrolled manner. Moreover, the low yield (12%) of this product indicated that the cross coupling was not performing as well as intended.



Scheme 5.11: Attempts to apply the decarboxylative cross coupling conditions reported by Yang and co-workers to the synthesis of desired alkyne **289**, using butynoic acid as a propyne surrogate.

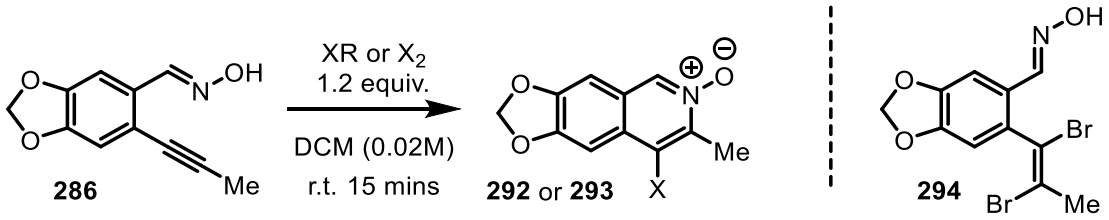
We therefore decided to protect the aldehyde as the corresponding dimethyl acetal. Pleasingly, upon protection to form acetal **291**, application of Yang's conditions afforded the desired product **289** in a 62% yield over 2 steps (Scheme 5.12). The acidic work up for the cross coupling conveniently deprotected the acetal group, thereby circumventing a separate deprotection step. The resultant aldehyde was then transformed into the corresponding oxime in a good yield of 78% (Scheme 5.12).[95]



Scheme 5.12: Successful application of Yang conditions to a protected substrate to afford alkyne **289,** and subsequent transformation to oxime **286**.

5.2.4 Attempted cyclisation of 286 towards isoquinoline 280

Cyclisation of the oxime **286** was then attempted using the aforementioned literature conditions reported by Ding and co-workers.[96] In the initial report, the optimum halogen electrophile was very substrate specific; hence, a variety of halogen sources were screened (Table 5.1).



Entry	Halogen source	Product Yield (%)	Yield of 294 (%)
1	NIS	Complex mixture	0
2	I_2	Complex mixture	0
3	ICl	Complex mixture	0
4	Br_2	None observed	49[a]
5	TBCA	None observed	0
6	DBDMH	Complex mixture	0
7	$TBABr_3$	None observed	10[b]
8	$Br_2/NaHCO_3$	Complex mixture	0
9	NaBr/Oxone	0	5[b]

Table 5.1: Attempts to cyclise oxime **286** to isoquinoline-*N*-oxide **292** or **293** with electrophilic trapping.

[a]Isolated yield is reported. [b]Yields reported determined by quantitative ^{1}H NMR spectroscopy.

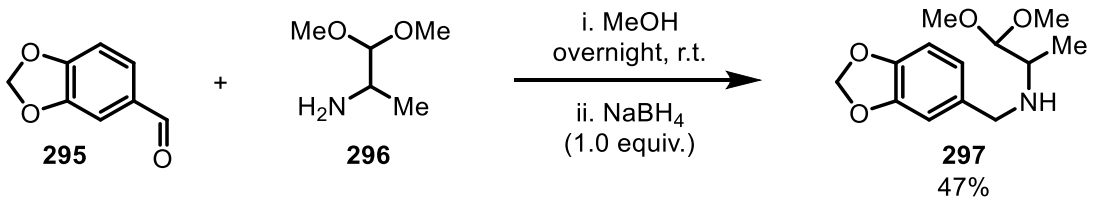
Unfortunately, all three trialled iodine sources produced a complex mixture, perhaps due to the highly reactive nature of the iodine cation. Bromine sources were then trialled in an attempt to reduce the electrophiles' reactivity: some produced complex mixtures as before (Table 5.1,

Entries 6, 8), however most bromine sources showed some reactivity, producing small to moderate amounts of brominated side product **294** (Table 5.1, Entries 4, 7, 9). Although this was promising, showing that electrophilic activation of the alkyne in **286** was possible, no intended product was observed with any reagent screened.

5.2.5 Second generation cyclisation route

Given the lack of success applying Ding's cyclisation conditions, an alternative strategy was required. Inspiration came from the work of Bobbit, Winter and Kiely, who reported an acid promoted 'interrupted' Pomeranz-Fritsch, in which the intermediate enamine is trapped by an aldehyde, affording C4-substituted isoquinolines directly.[97]

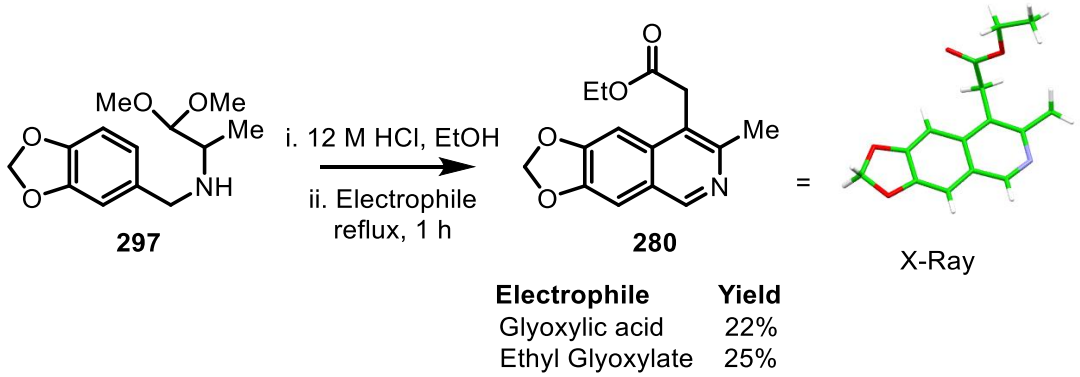
To test this methodology on our system, the necessary aldehyde **295** and amine **296** were coupled *via* reductive amination to afford **297** in 47% yield (Scheme 5.13).



295 **296** **297** 47%

Scheme 5.13: First-generation reductive amination conditions. Isolated yield is reported.

Compound **297** was then subjected to the interrupted Pomeranz-Fritsch conditions, using glyoxylic acid as an aldehyde electrophile (Scheme 5.14). Product **280** was isolated in a pleasing 22% yield, produced from the condensation of the EtOH solvent with the acid product under acidic conditions. The product identity was confirmed by single crystal X-Ray analysis. When repeated using ethyl glyoxylate as the electrophile, a similar yield of 25% was obtained.

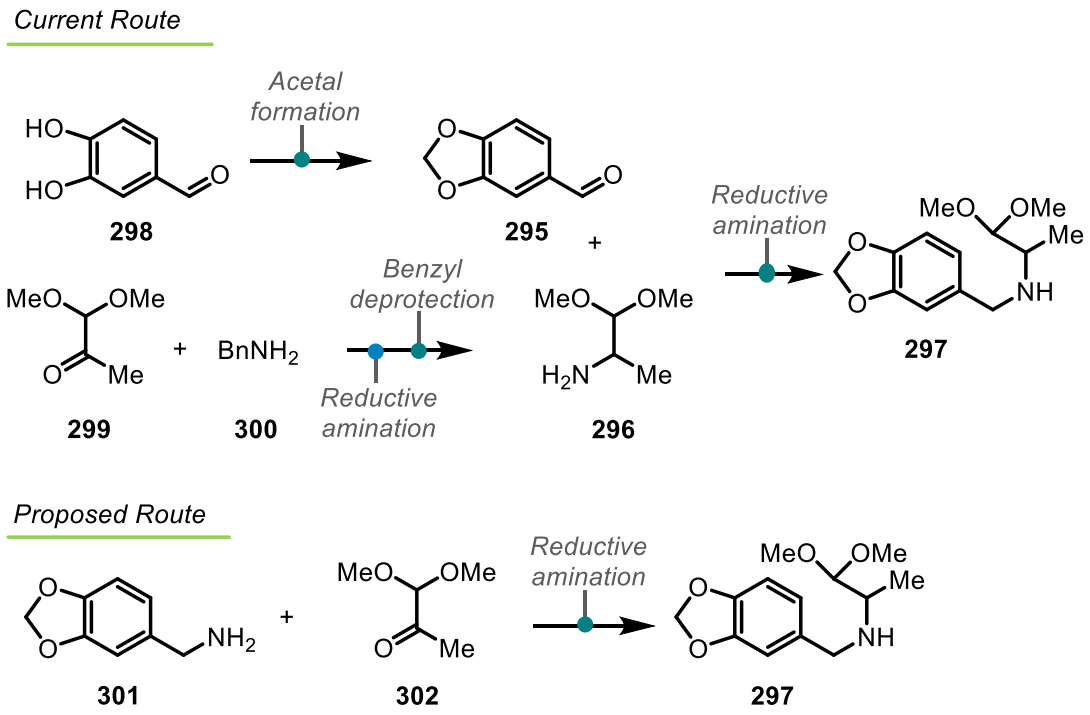


Scheme 5.14: First generation application of interrupted Pomeranz-Fritsch cyclisation conditions to amine **297** to afford isoquinoline **280**. Isolated yields are reported.

5.2.6 Optimisation of reductive amination

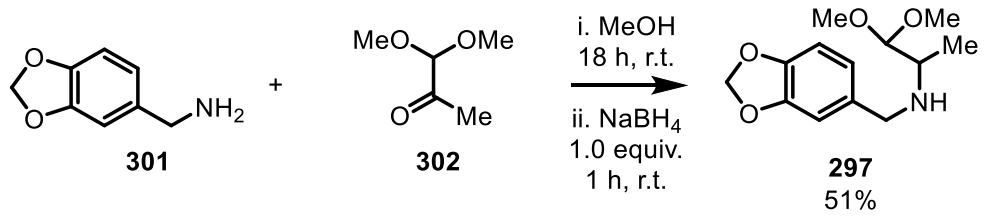
Having validated the feasibility of the interrupted Pomeranz-Fritsch cyclisation, our attention turned to the reductive amination of piperonal **295** and an acetal protected amino aldehyde **296**. The current best procedure involved stirring the two substrates overnight in MeOH to generate the imine, then adding 1.0 equiv. $NaBH_4$, affording a moderate yield of 47% (Scheme 5.15). It was posited that the lack of conversion was due to the low electrophilicity of the aldehyde which is adjacent to an electron-rich aromatic system.

A solution to this issue could be to invert the reactivity, by using amine **301** and ketone **302** (Scheme 5.15). By switching the functionality coupled by the reductive amination, the electron rich partner is now the nucleophile, rather than the electrophile, which should decrease the system energy and potentially increase yield. Both coupling partners are commercially available, therefore the proposed route would also shorten the longest linear sequence of the synthesis by two steps.



Scheme 5.15: Current and proposed routes towards amine **297**.

Pleasingly, application of the standard reductive amination conditions (*vide supra*) to **301** and **302** afforded an acceptable yield of **297** in 51% on 50 mmol scale (Scheme 5.16).



Scheme 5.16: Preparation of **297** from piperonyl amine **301**. Reaction performed on 50 mmol scale. Isolated yield is reported.

5.2.6.1 Initial optimisation of the new reductive amination

A short optimisation of the reaction was carried out, varying concentration, reactant equivalents, temperature and additives (Table 5.2). Previous optimisation screens have shown

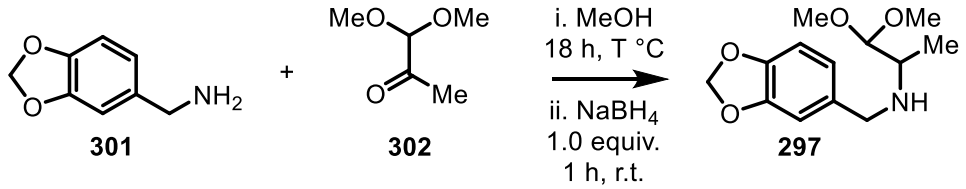
that similar reactions perform best in methanol, and it was desired to use a $NaBH_4$ quench after overnight stirring for operational ease.

Firstly, the equivalents of ketone **302** were varied, with a decrease in yield observed when 1.5 and 2.0 equivalents were used as compared to equal stoichiometry (Table 5.2, Entries 1-3). Next the concentration was increased from the current 0.25 M to a neat reaction (Table 5.2, Entries 4-7). Disappointingly, increasing the concentration decreased the observed ^{1}H NMR yield to 31% at 2.5 M. The reaction performed in the absence of solvent was diluted with MeOH immediately prior to addition of $NaBH_4$ to facilitate the reduction, which may explain the higher yield observed, as this would replicate the conditions used in Entry 1.

The temperature was then varied in the hope that an increased temperature may favour imine formation prior to reduction (Table 5.2, Entries 8-10). Disappointingly, increasing the reaction temperature decreased the product yield, with only 24% afforded at 80 °C.

A selection of Lewis acidic additives were screened, with limited success (Table 5.2, Entries 11-22). Most Lewis acids inhibited reactivity completely, producing little to no product, with only two ($Ti(O^iPr)_4$ and LiOTf) affording a reasonable amount of product, but less than without any Lewis acid present (Table 5.2, Entry 1).[98]

Finally, Entry 1 was replicated but with a basic work up with 1 M NaOH, in an attempt to limit any product sequestered into the aqueous layer as the protonated salt (Table 5.2, Entry 23). Disappointingly, the yield was only 34%, significantly less than without a basic work up.

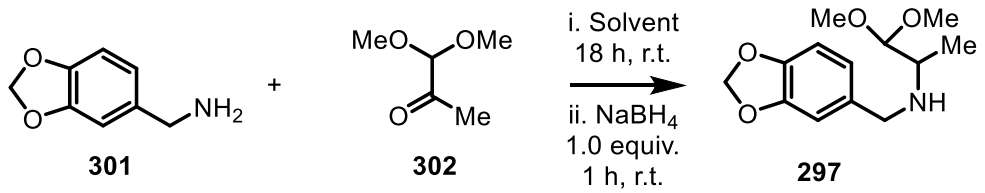


Entry	302 Equiv.	Temp (°C)	Concentration (M)	Additive (1.0 equiv.)	Yield of 297 (%)
1	1.0	r.t.	0.25	-	(58)
2	1.5	r.t.	0.25	-	42
3	2.0	r.t.	0.25	-	49
4	1.0	r.t.	0.50	-	38
5	1.0	r.t.	1.25	-	35
6	1.0	r.t.	2.50	-	31
7	1.0	r.t.	neat[a]	-	41
8	1.0	40	0.25	-	39
9	1.0	60	0.25	-	30
10	1.0	80	0.25	-	24
11	1.0	r.t.	0.25	$FeCl_2$	0
12	1.0	r.t.	0.25	$Sc(OTf)_3$	0
13	1.0	r.t.	0.25	$Yb(OTf)_3$	0
14	1.0	r.t.	0.25	$Bi(OTf)_3$	0
15	1.0	r.t.	0.25	$ZrCl_4$	0
16	1.0	r.t.	0.25	$Ti(O^iPr)_4$	37
17	1.0	r.t.	0.25	$CoCl_2 \cdot 6H_2O$	6
18	1.0	r.t.	0.25	CuCl	16
19	1.0	r.t.	0.25	$InCl_3$	0
20	1.0	r.t.	0.25	$CeCl_3$	0
21	1.0	r.t.	0.25	$Cu(OAc)_2$	4
22	1.0	r.t.	0.25	LiOTf	33
23[b]	1.0	r.t.	0.25	-	34

Table 5.2: Optimisation of the reductive amination with piperonyl amine. Yields determined by quantitative ^1H NMR spectroscopy. [a]The reaction was performed without solvent, however 1 mL of MeOH was added before addition of $NaBH_4$. [b]Work up performed with 1 M NaOH. Reactions performed on 0.25 mmol scale.

5.2.6.2 Solvent screen and final optimisation

Next, a solvent screen was conducted (Table 5.3, Entries 1-8). DME performed the best of all solvents screened, with a ^{1}H NMR yield of 66%, however EtOH performed almost as well, affording **297** in 64% isolated yield (Table 5.3, Entries 2, 3). Other less conventional solvents performed less well, with PhMe and DMA both affording no product at all, and THF and 1,2-DCE afforded yields of 55% and 30% respectively (Table 5.3, Entries 4-7). MeCN performed nearly as well as EtOH and better than MeOH however, affording a ^{1}H NMR yield of 60% (Table 5.3, Entry 8).



301 + **302** → **297**

Entry	Solvent	Yield of 297 (%)
1	MeOH	(58)
2	DME	66
3	EtOH	(64)
4	PhMe	0
5	DMA	0
6	THF	55
7	1,2-DCE	30
8	MeCN	60
9	IPA	41
10	Amyl alcohol	18
11	*n*-BuOH	35
12	*n*-PrOH	78 (73)

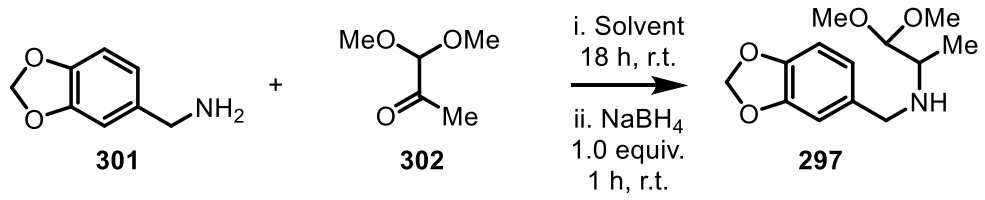
Table 5.3: Solvent screen for a reductive amination between amine **301** and ketone **302**. Yields determined by quantitative ^{1}H NMR spectroscopy. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale.

As both MeOH and EtOH performed well, and are the more traditional solvents used in a reductive amination, several more alcohols were trialled as solvents (Table 5.3, Entries 9-12). Longer chain or branched alcohols performed less well than EtOH, however the next alcohol in the homologous series, *n*-PrOH, produced a higher isolated yield of 73% (Table 5.3, Entry 12).

A few other parameters were optimised, such as concentration, equivalents and additives (Table 5.4). Doubling the dilution of the reaction when using MeOH as the solvent increased the yield from 58% to 65%, however increasing the dilution still further did not increase the yield again (Table 5.4, Entries 1, 3, 4). It was decided that 0.25 M was an appropriate compromise.

It was suggested that addition of a desiccant might drive the reaction equilibrium towards the products by removal of the water generated as a side product. Both Na_2SO_4 and powdered 3Å molecular sieves were trialled, with both showing a small increase in yield to 67 and 70% respectively (Table 5.4, Entries 1, 5, 6). Finally, increasing the equivalents of ketone **302** was attempted, although no yield increase was observed (Table 5.4, Entries 2, 7). The slight increase in yield observed with added desiccant when MeOH was used as a solvent was not replicated when *n*-PrOH was used instead, with 71% yield afforded in place of 73% in the absence of desiccant (Table 5.4, Entries 2, 8). This is perhaps due to the lower deliquescence of *n*-PrOH as compared to MeOH, resulting in a drier reaction mixture to begin with.

Finally, addition of desiccant to the reaction as well as use of 1.2 equiv. of ketone **302** afforded an identical yield to with 1.0 equiv. of **302** (71%), both lower yielding than the initial reaction conditions (Table 5.4, Entries 2, 8, 9).



301 302 297

Entry	Ketone 302 (equiv.)	Solvent	Concentration (M)	Additive (250 mg)	Yield of 297 (%)
1	1.0	MeOH	0.25	-	(58)
2	1.0	*n*-PrOH	0.25	-	78 (73)
3	1.0	MeOH	0.125	-	68 (65)
4	1.0	MeOH	0.0625	-	62
5	1.0	MeOH	0.25	Na_2SO_4	(67)
6	1.0	MeOH	0.25	Powdered 3 Å Mol Sieves	70
7	1.2	*n*-PrOH	0.25	-	68
8	1.0	*n*-PrOH	0.25	Na_2SO_4	71
9	1.2	*n*-PrOH	0.25	Na_2SO_4	71

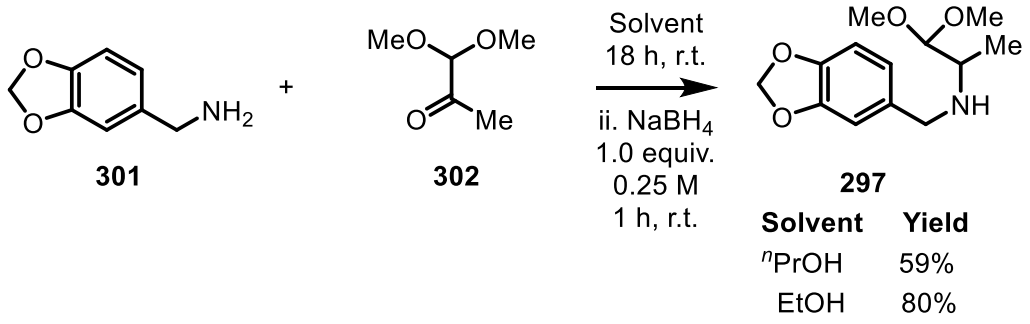
Table 5.4: Further optimisation of reductive amination reaction parameters. Yields determined by quantitative ^{1}H NMR spectroscopy. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale.

In conclusion, use of *n*-PrOH as reaction solvent without any further modifications increased the yield of **297** to 73% on 0.25 mmol scale.

5.2.6.4 Scaling up the optimised conditions

To demonstrate the yield increase, the reaction was scaled up to 40 mmol; disappointingly, the reaction on this scale only afforded **297** in 59% yield (Scheme 5.17). The lower yield observed upon scaling up was attributed to a challenging extraction, caused by the emulsifying ability of the solvent. It was decided to continue with the second highest yielding solvent, EtOH, which performed almost as well as *n*-PrOH at the 0.25 mmol scale (64%), but does not have the

extraction drawback on scale mentioned above. Pleasingly, when scaling the reaction up to 40 mmol with EtOH as the reaction solvent, an 80% yield of **297** was obtained.



301 + **302** → **297**

Solvent	Yield
^{n}PrOH	59%
EtOH	80%

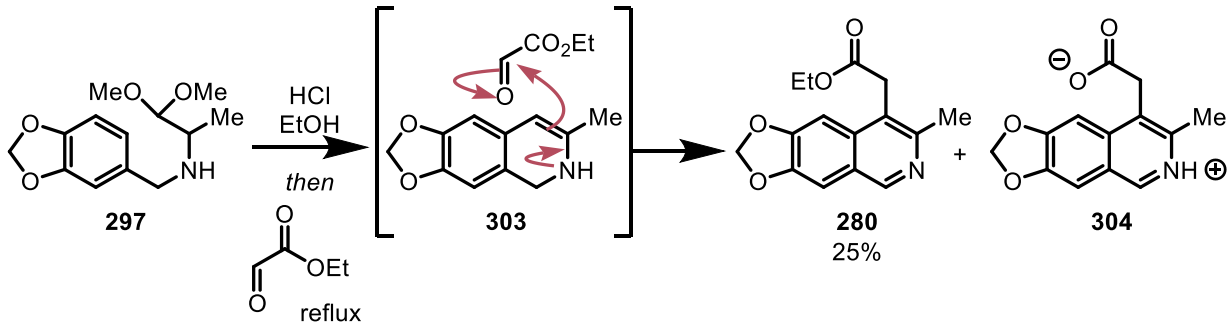
Scheme 5.17: Reductive amination to form amine **297** performed on 40 mmol scale with two solvents. Isolated yields are reported.

5.2.7 Optimisation of interrupted Pomeranz-Fritsch cyclisation

With sufficient quantities of amine **297** in hand, we sought to optimise the acid-promoted cyclisation of to form isoquinoline **280** (Scheme 5.18).[97]

In the reaction, concentrated acid is used to deprotect the acetal and promote a Pomeranz-Fritsch-type cyclisation to form the dihydroisoquinoline (DHIQ) **303**. The DHIQ can then attack ethyl glyoxylate, following which elimination of H_2O and tautomerisation reveals the isoquinoline product.

Issues observed during previous iterations of the cyclisation include *in situ* hydrolysis of the ester to form zwitterionic acid **304** (Scheme 5.18). This resided in the aqueous layer during the work up and proved very challenging to isolate.



Scheme 5.18: Current method for acid promoted cyclisation. Isolated yield is reported.

To prevent this side product forming, we aimed to develop a non-aqueous version of the reaction, either by generating acid *in situ* or by the use of non-aqueous acids.

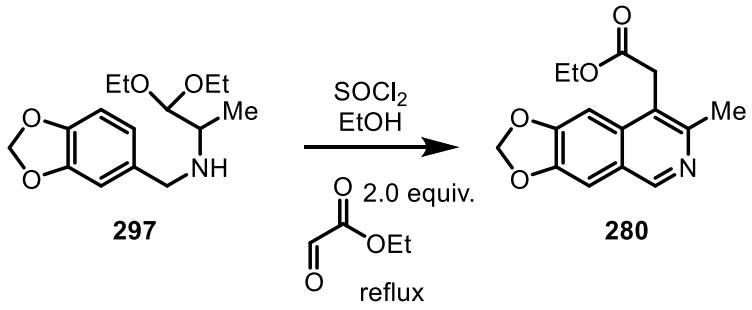
5.2.7.1 Use of $SOCl_2$ to generate acid *in situ*

Firstly, investigations turned to the possibility of generating an acidic environment *in situ* by addition of $SOCl_2$ to an ethanolic solution. This hypothesis was trialled with reactions in sealed microwave vials, heated to 100 °C. (Table 5.5).

We began by screening reaction times, and showed that the reaction yield appeared to plateau at around four hours, with a maximum yield of 25% afforded (Table 5.5, Entries 1-4). It was posited that decreasing the solvent volume would increase the acid concentration, however doing so merely decreased the yield further (Table 5.5, Entries 5-7). Conversely, increasing the solvent volume to 4.0 mL also decreased the reaction yield to trace amounts (Table 5.5, Entries 8-9).

Decreasing the equivalents of $SOCl_2$ to 5.0 equiv. had the predictable effect of decreasing the yield to 2%, but pleasingly increasing the equivalents of $SOCl_2$ to 20 increased the isolated yield to 33% (Table 5.5, Entries 10-11). Disappointingly, increasing the equivalents of $SOCl_2$ further to 30 resulted in a complex mixture (Table 5.5, Entry 12). Finally, doubling the

equivalents of electrophile to 4.0 equiv. did little to aid reactivity, with only a trace amount of product observed (Table 5.5, Entry 13).



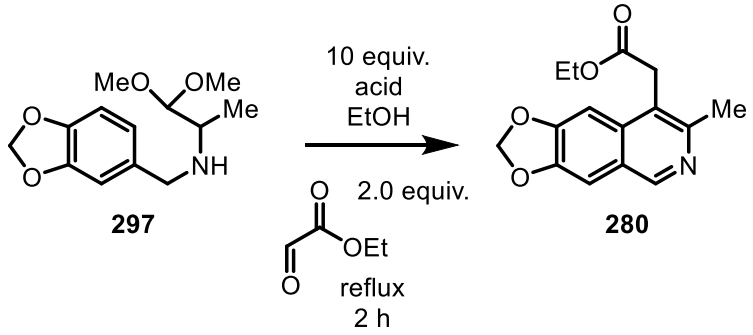
Entry	$SOCl_2$ (equiv.)	Time (h)	Solvent Volume (mL)	Yield of 280 (%)
1	10	1	1.0	15
2	10	2	1.0	20
3	10	3	1.0	23
4	10	4	1.0	25
5	10	2	0.5	14
6	10	2	0.2	6
7	10	2	0.1	2
8	10	2	2.0	6
9	10	2	4.0	1
10	5.0	2	1.0	2
11	**20**	**2**	**1.0**	**35 (33)**
12	30	2	1.0	Complex mixture
13[a]	10	2	1.0	trace

Table 5.5: Optimisation of interrupted Pomeranz-Fritsch using $SOCl_2$. Yields determined by quantitative ^1H NMR spectroscopy. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale.

[a]Reaction performed with 4.0 equiv. of ethyl glyoxylate.

5.2.7.2 Further screening of non-aqueous acids

Our attention then turned to the use of non-aqueous acids in the reaction and a small screen was performed (Table 5.6). Regrettably, nearly all acids screened produced no product, however sulfuric acid afforded 17% of **280**, a low yield compared to the best yield with our previous aqueous acid-based conditions and the best yield obtained with the $SOCl_2$ strategy (Table 5.5).



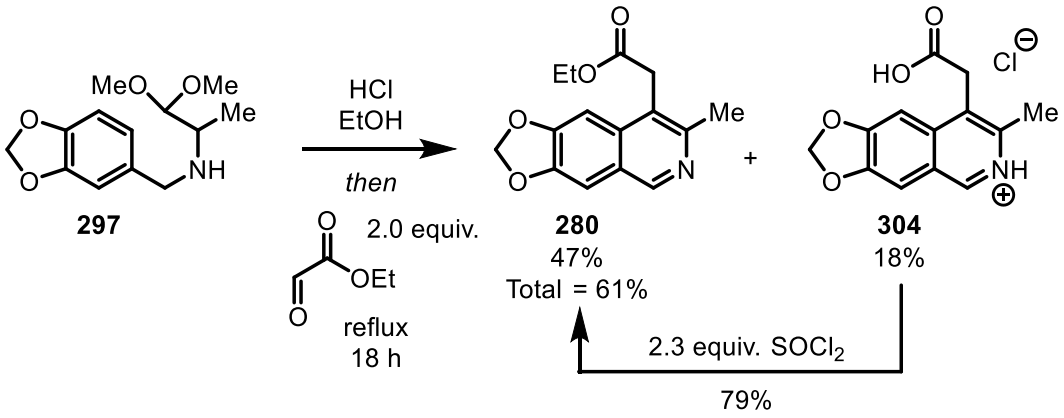
Entry	Acid	Yield of 280 (%)
1	H_2SO_4	17
2	AcOH	0
3	HNO_3	0
4	TFA	0
5	$HBF_4 \bullet OEt_2$	0
6	HCO_2H	0
7	$HClO_4$	0

Table 5.6: Further non-aqueous acid screening. Yields determined by quantitative ^1H NMR spectroscopy. Reactions performed on 0.25 mmol scale.

5.2.7.3 Practical modification to the optimal conditions

In conclusion, despite extensive optimisation, the best yield (33%) of **280** was obtained when performing the interrupted Pomeranz-Fritsch cyclisation using the $SOCl_2$ addition strategy.

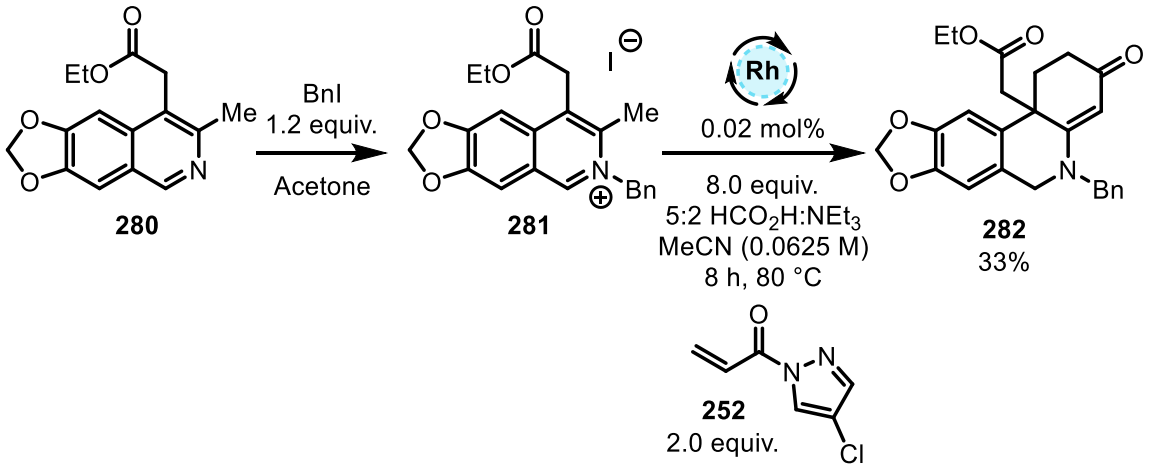
Since this was operationally more challenging than when using aqueous HCl, but not significantly higher yielding, we decided to return to the aqueous conditions. Careful repetition of the reaction on 30.5 mmol scale, with a few practical modifications, afforded an improved yield of 47% (Scheme 5.19). Changing the order of reagent addition and quenching the reaction at 0 °C *via* slow addition of solid Na_2CO_3 afforded a more controlled work up, with the reaction temperature more carefully managed. Refluxing the reaction for an extended period of eighteen hours allowed for clean conversion to the desired product, removing the need for purification. The HCl salt of the acid by-product **304** could be isolated from the aqueous layer by careful recrystallisation, delivering another 18% of isoquinoline product, which could then be esterified to afford the desired ester **280** in a 79% yield (Scheme 5.19). The cumulative yield of the process was therefore 61% of ester **280**.



Scheme 5.19: Highest yielding repeat of the interrupted Pomeranz-Fritsch cyclisation. The HCl salt of the acid side product could be isolated and esterified to produce more of the desired product. The initial Pomeranz-Fritsch reaction detailed on the left of the scheme was performed on 30.5 mmol scale.

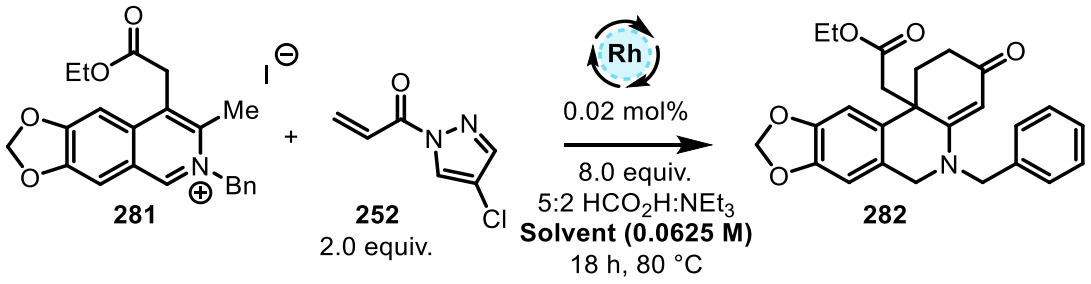
5.3 Re-optimisation of reductive annulation conditions

Continuing the planned synthetic sequence, product **280** was then benzylated with benzyl iodide to produce iodide salt **281** in a good yield of 86% (Scheme 5.20). The salt was then subjected to our optimised reductive annulation conditions.



Scheme 5.20: Preparation of and first attempt of reductive annulation with our real substrate **281**. Reaction performed on 0.25 mmol scale.

Pleasingly, the desired annulated product **282** was isolated in 33% yield. A short solvent screen was conducted using an extended reaction time of eighteen hours, which showed that 1,4-dioxane was the optimal solvent for this substrate (Table 5.7, Entry 5). The other solvents screened (MeCN, $CHCl_3$, acetone and DCE) afforded lower yields of 26%, 29%, 57% and 32% respectively (Table 5.7, Entries 1-4).



Entry	Solvent	Yield of 282 (%)
1	MeCN	26
2	$CHCl_3$	29
3	Acetone	57
4	DCE	32
5	**Dioxane**	**87 (80)**

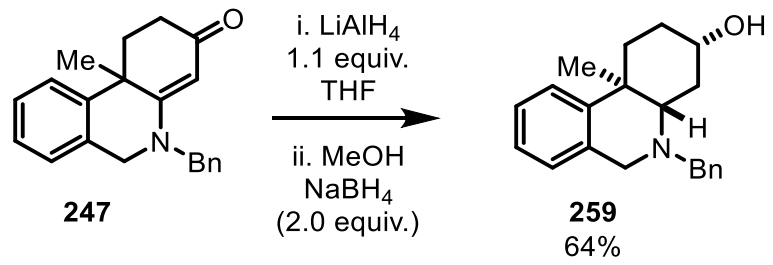
Table 5.7: Short solvent screen for reductive annulation of substrate **281**. Yields determined by quantitative ^{1}H NMR spectroscopy. Isolated yields are indicated by brackets. Reactions performed on 0.25 mmol scale.

5.4 Endgame of synthesis towards natural product targets

5.4.1 Reduction of the vinylogous amide of product 282

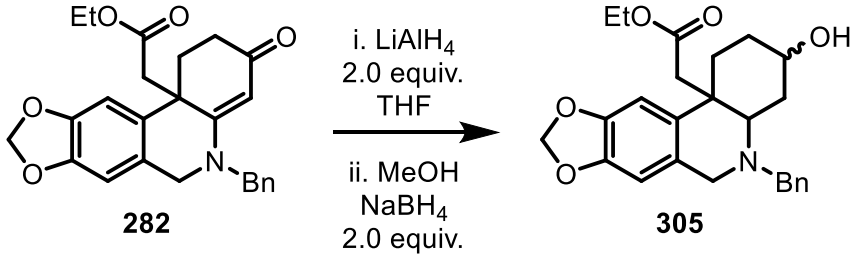
5.4.1.1 Application of model system reduction conditions

With the optimised conditions in hand, our attention turned to the next challenge in the synthetic sequence, namely the reduction of vinylogous amide **282**. Previous work on a model system **247** revealed $LiAlH_4$ to be the best reductant, which, when paired with a $NaBH_4$ work up afforded alcohol **259** in a respectable 64% yield *vide infra* (Scheme 5.21).



Scheme 5.21: Successful reduction of model compound **247** using $LiAlH_4$ followed by a $NaBH_4$ work up.

Unfortunately, when these conditions were applied to the more substituted system, a complex mixture of products was formed (Table 5.8, Entry 1). Upon repetition at a colder temperature of -78 °C, however, only starting material was obtained (Table 5.8, Entry 2). Further repetitions at intermediate temperatures similarly returned only starting material (Table 5.8, Entries 3-4).



Entry	Temperature (°C)	Result
1	0	Complex mixture
2	-78	SM returned
3	-40	SM returned
4	-10	SM returned

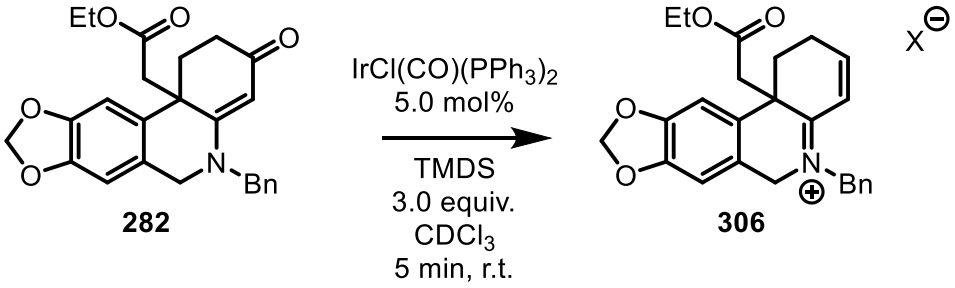
Table 5.8: Attempts at applying our optimised reduction conditions to the real system. Reactions performed on 0.25 mmol scale.

Further reduction techniques were screened on compound **282**, including high throughput screens of both homogeneous and heterogeneous hydrogenation strategies with pressures of

hydrogen of up to five bar used. Regrettably, no reactivity was observed in either case and investigations into the strategy were curtailed.

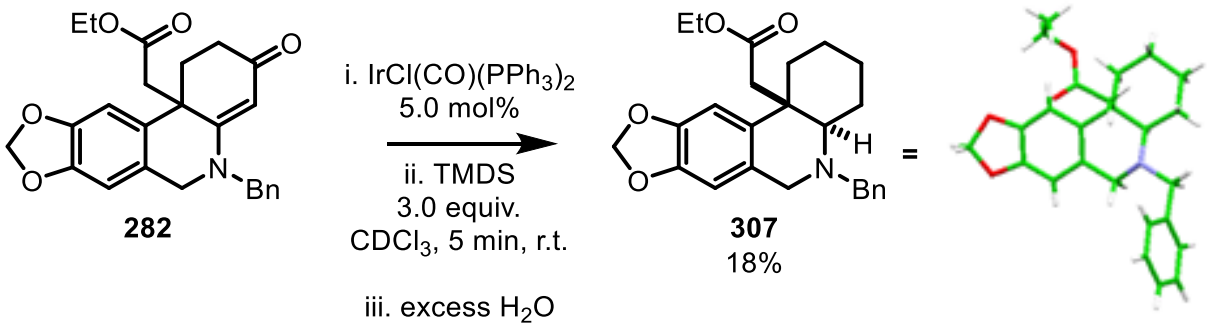
5.4.1.2 Vaska's complex as a reductant

Turning to the literature, it was noted that Vaska's complex has been used with great success to reduce simpler amide systems.[99] Use of Vaska's complex with a siloxane reductant can reduce amides to the corresponding hemi-aminal, which can collapse to afford an iminium. Attack with either hydride or a more complex nucleophile can then afford a variety of functionality. Application of literature conditions to this system afforded a highly promising crude ^{1}H NMR spectrum, with a major product clearly visible in under five minutes (Scheme 5.22). The crude NMR spectrum was characterised and revealed compound **306** as the major product. The counter-ion identity is unknown, but we assume it is a variety of siloxane or siloxide.



Scheme 5.22: Treatment of our real system with Vaska's complex and TMDS conditions.

Upon scaling up the reaction, we attempted to isolate **306** directly by performing an aqueous work up after five minutes (Scheme 5.23). The major product was reduced product **307**, albeit in a low yield of 18%. We hypothesise that **307** arises from conjugate hydride addition into iminium **306** followed by enamine protonation and iminium reduction, which we suggest occurs on proton addition to the mixture where iridium catalyst is still present.

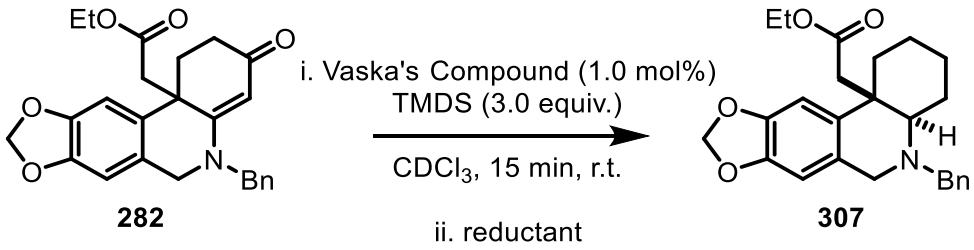


Scheme 5.23: Total reduction of **282** using Vaska's complex to give **307**. Stereochemistry was assigned by NOESY and confirmed by single crystal X-Ray analysis. Single crystal X-Ray analysis performed by T. C. Jenkins.

Compound **307** is an important intermediate on the synthetic route to Crinane, however lacks any of the peripheral functionality required to access any other member of the Crinane family. A more useful transformation would be to trap the enamine formed after reduction by either oxidation of the enamine, or 1,2-reduction of an iminium.

To complete the synthetic route to Crinane, we first attempted to optimise the iminium reduction, therefore a variety of reductants were screened (Table 5.9). To increase economy, the loading of Vaska's complex was reduced to 1.0 mol%, with reaction time increased to 15 min to compensate. No adverse effects were observed as a result of this compromise.

Without any reductant, but simply an aqueous work up, 18% of **307** was observed as the major product. It is unclear which species was causing reduction of iminium **306**, however isolation of only 18% of the intended product indicates that the reduction was inefficient and not going to completion (Table 5.9, Entry 1). Use of a mild reductant, 5:2 HCO_2H:NEt_3, produced a similar yield of 19%, indicating that the reagent choice was little better than a simple aqueous work up, or potentially not reducing iminium **306** at all, with the residual yield observed due to the background reactivity observed above (Table 5.9, Entry 2).



Entry	Reductant	Yield of 307 (%)
1	None	18
2	5:2 HCO_2H:NEt_3	19
3	$LiAlH_4$	Complex mixture
4	$NaBH(OAc)_3$	43
5	$NaBH_3CN$	50

Table 5.9: Attempts towards complete reduction of vinylogous amide **282** to form **307**. Isolated yields are reported.

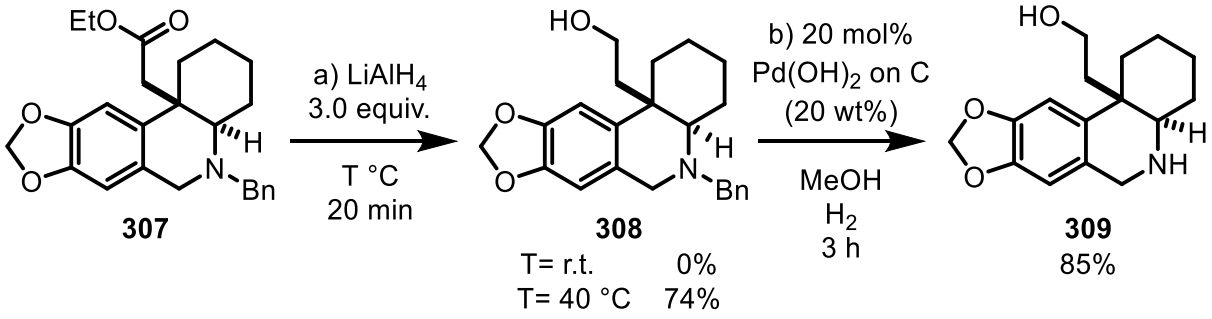
Application of a much stronger reductant, $LiAlH_4$, afforded a complex mixture of products, however, milder reductants such as $NaBH(OAc)_3$ and $NaBH_3CN$ afforded much more promising yields of 43% and 50% respectively (Table 5.9, Entries 3-5). [100-101]

5.4.2 Synthesis of Crinane

With successful total reduction conditions in hand, **307** was carried through three further steps to complete the synthesis of Crinane. Firstly, the ester moiety was reduced using $LiAlH_4$ to form alcohol **308** (Scheme 5.24).

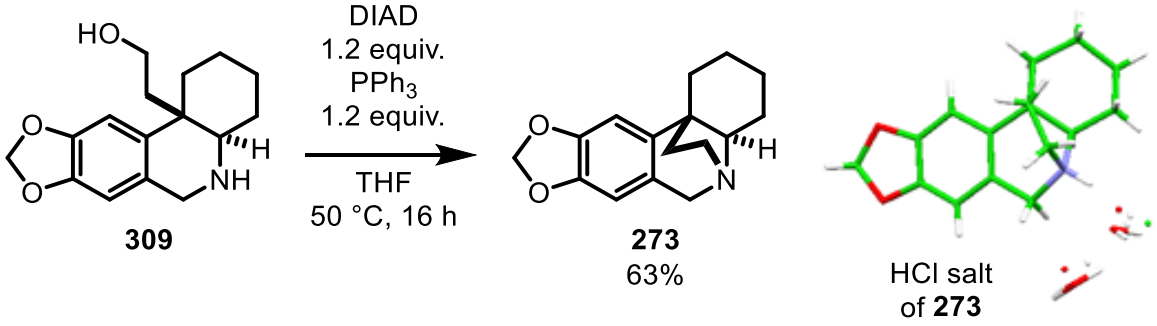
When the reaction was performed at room temperature only starting material was returned, however at 40 °C the reaction proceeded smoothly, and afforded a 74% yield on 0.2 mmol scale. The crude product after work up was sufficiently clean that no further purification was required.

Hydrogenation of alcohol **308** proceeded cleanly using Pearlman's catalyst, affording amino alcohol **309** in a good yield of 85% (Scheme 5.24). Pleasingly, the crude product was clean enough to proceed without further purification.



Scheme 5.24: Reduction of the ester moiety of **307** to give alcohol **308** then hydrogenation to afford amino alcohol **309**. Isolated yields are reported. Reactions a) performed on 0.2 mmol scale b) performed on 0.15 mmol scale.

With amino alcohol **309** in hand, we attempted the final ring closing step (Scheme 5.25). Pleasingly, under Mitsunobu conditions Crinane **273** was afforded in 63% yield after purification by flash column chromatography. Overall, the synthesis of Crinane **273** was completed in eight steps and 5 % overall yield.



Scheme 5.25: Ring closing reaction to afford Crinane **273**. Isolated yield is reported. Reaction performed on 0.13 mmol scale. Structure and relative stereochemistry confirmation carried out by single crystal X-ray analysis of the HCl salt of **273**. Single crystal X-Ray analysis performed by T. C. Jenkins.

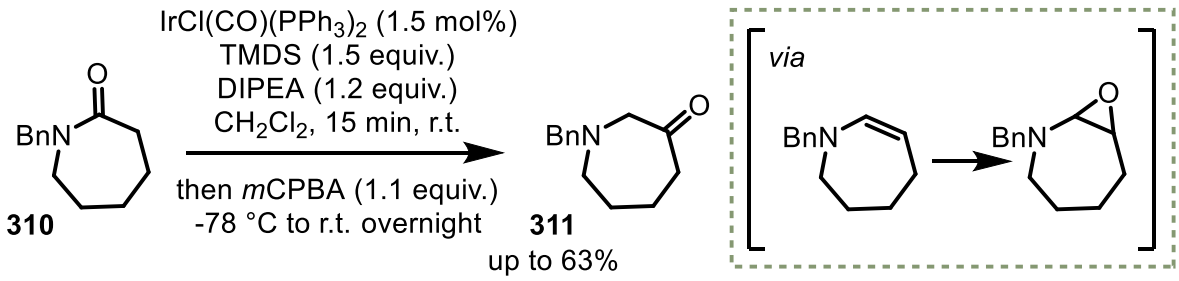
Crinane is not a natural product, but a tetracyclic core that represents the parent member of the alkaloid class. It was first synthesised in 1956 in a racemic manner by Wildman and co-workers using an entirely synthetic method. It has since been used as a common synthetic target to demonstrate method development in a total synthesis setting. The analytical data for the sample of Crinane **273** synthesised here matches literature data (see experimental section 8.6, pg. 335).

5.4.3 Strategies to allow decoration of the C-ring

5.4.3.1 Oxidation conditions

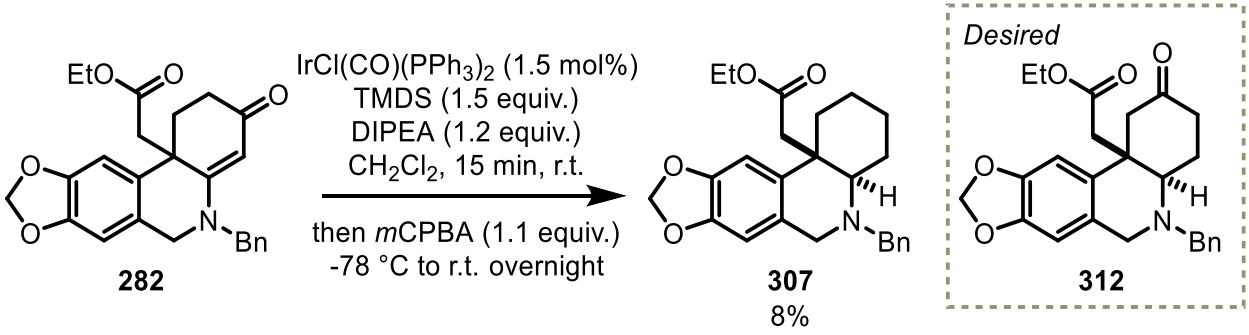
Having successfully completed the synthesis of Crinane, our efforts returned to the vinylogous amide reduction step, we aimed to use Vaska's complex to generate a metastable intermediate that could be further derivatised to form useful compounds as intermediates in the synthesis of the more complex members of the Crinane family.

It was hoped that use of oxidants following the Vaska's complex reduction might allow the carbonyl functionality to be returned, but without the conjugation that rendered compound **282** challenging to derivatise. A report by Dixon and co-workers. indicated that such a transformation might be possible, although the system described by the report was a simpler amide, as opposed to the more challenging vinylogous amide system (Scheme 5.26).[102]



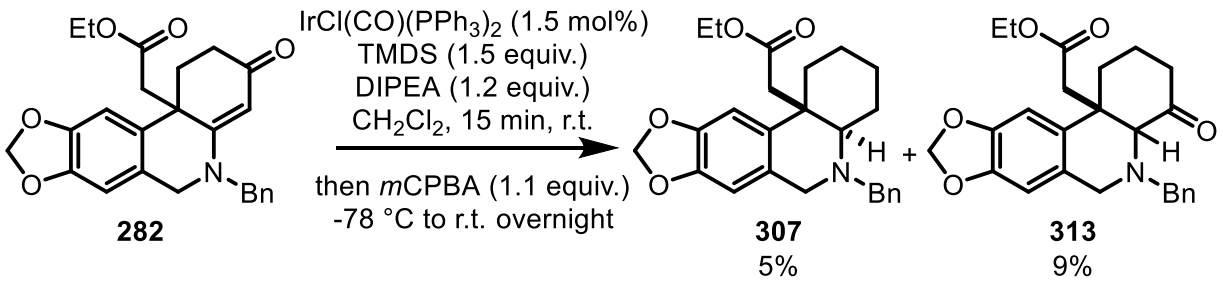
Scheme 5.26: Literature conditions for the redox transposition of tertiary amides.

Direct application of the literature conditions to our system produced disappointing results (Scheme 5.27). Although iminium **306** was produced *in situ*, the oxidation step proved more challenging with our system: 8% of totally reduced product **307** was afforded but no other products could be isolated cleanly and no evidence of desired product **312** could be observed. Analysis by crude ^{1}H NMR spectroscopy was regrettably not possible for this reaction due to the complex nature of the reaction mixture.



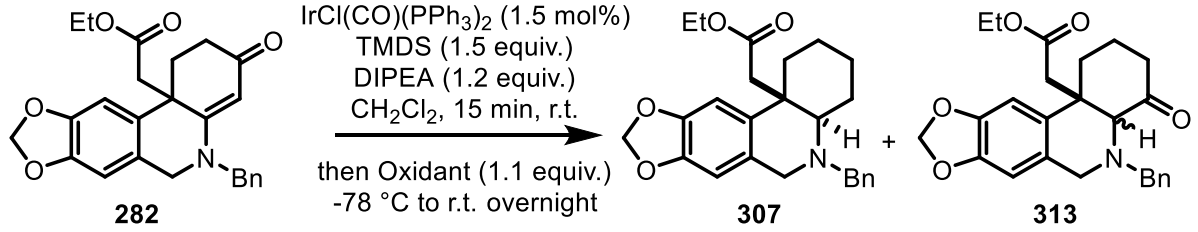
Scheme 5.27: Application of literature conditions to our vinylogous amide system. Isolated yield is reported. Reaction performed on 0.25 mmol scale.

Upon repetition, a similar quantity of **307** was produced, however a second compound was isolated in a 9% yield (Scheme 5.28). Compound **313** was not our intended product **312**; however, it does possess the desired carbonyl functionality. The complex nature of the crude ^{1}H NMR spectrum and the challenging purification process indicated that we are observing two of many minor products generated by this transformation which did not foster much hope for any optimisation process.



Scheme 5.28: Further products isolated upon replication of the reaction detailed in Scheme 5.27. Isolated yields are reported. Reaction performed on 0.25 mmol scale.

In an attempt to improve the product ratios, three further oxidants were trialled with disappointing results (Table 5.10). *In situ* generated DMDO afforded no totally reduced product **307**, but only produced 5% of **313**, with the remainder of the mass balance as a complex mixture (Table 5.10, Entry 2). Hydrogen peroxide and a softer equivalent species, $NaBO_3$, both afforded totally reduced product **307** as the major identifiable product, with no amount of **313** observed.



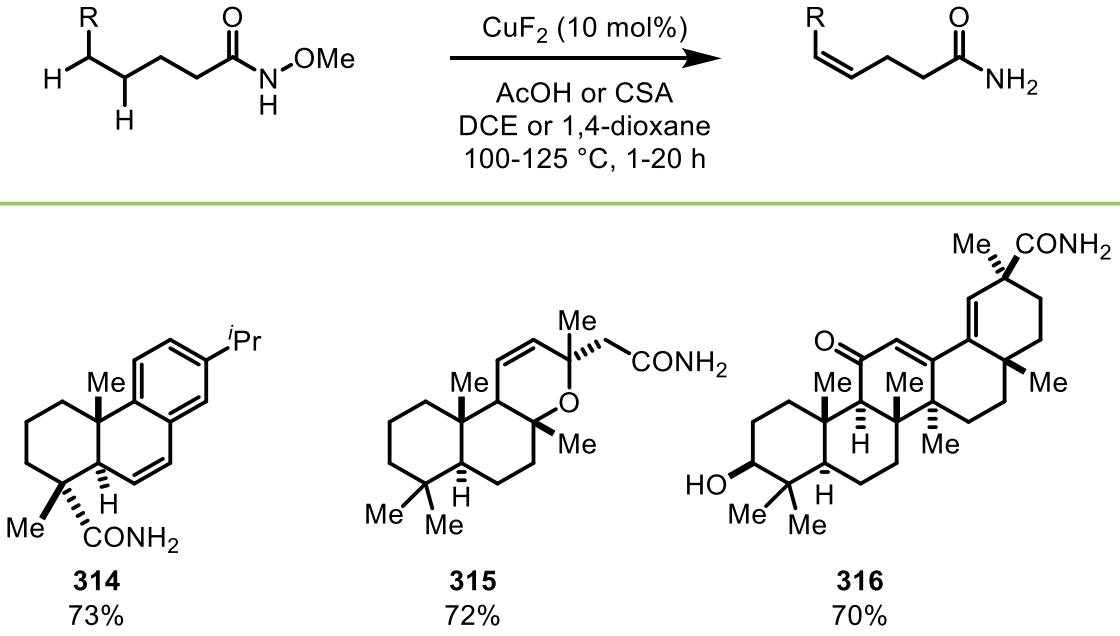
Entry	Oxidant	Yield of 307 (%)	Yield of 313 (%)
1	*m*CPBA	5	9
2	DMDO	0	5
3	$NaBO_3$	16	0
4	H_2O_2	6	0

Table 5.10: Application of several oxidants to our Vaska's intermediate. Isolated yields are reported. Reaction performed on 0.25 mmol scale. Relative stereochemistry of **313** is left unassigned.

5.4.3.2 C-H activation of reduced tricycle 307

It is possible that our previous strategies had attempted to work against the natural reactivity of our system; an alternative strategy would be to follow the system's natural reactivity to afford saturated tricyclic compound **307**. The desired decoration of the C-ring could then be achieved *via* C-H activation after reduction had occurred.

We were inspired by the work of Yu and co-workers, who used the copper-mediated *N*-*O* homolysis of an *N*-methoxy amide to achieve *γ*, *δ*-unsaturation in a large variety of systems, some with polycyclic structures similar to ours (Scheme 5.29).[103]



Scheme 5.29: C-H activation for *γ*, *δ*-unsaturation by Yu and co-workers.

We were excited by this method as although our compound of interest **307** has three *γ*-protons, H_a, H_b and H_c, the proton situated on the undesired site of C3, H_a, is on the opposite face of the molecule from the *N*-methoxy amide, thereby hopefully preventing abstraction (Figure 5.2).

This could favour abstraction of the more accessibly placed Hc, enabling the desired reaction to occur.

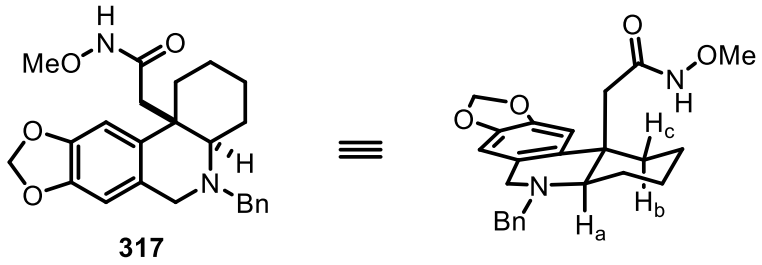
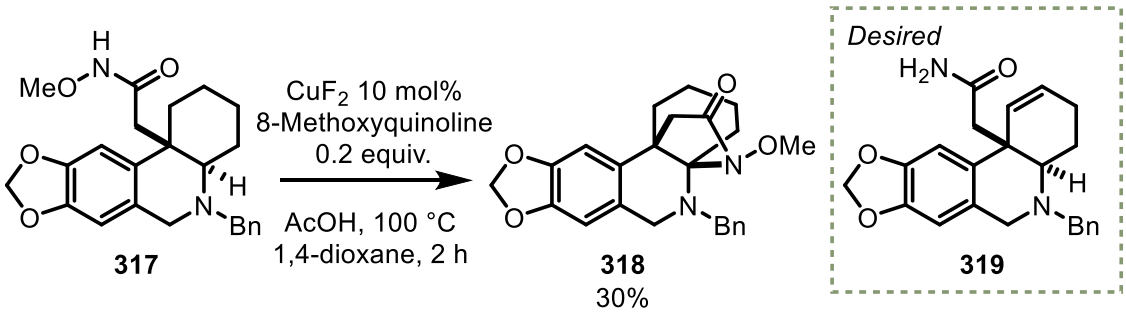


Figure 5.2: Considering relative stereochemistry of unwanted sites of activation

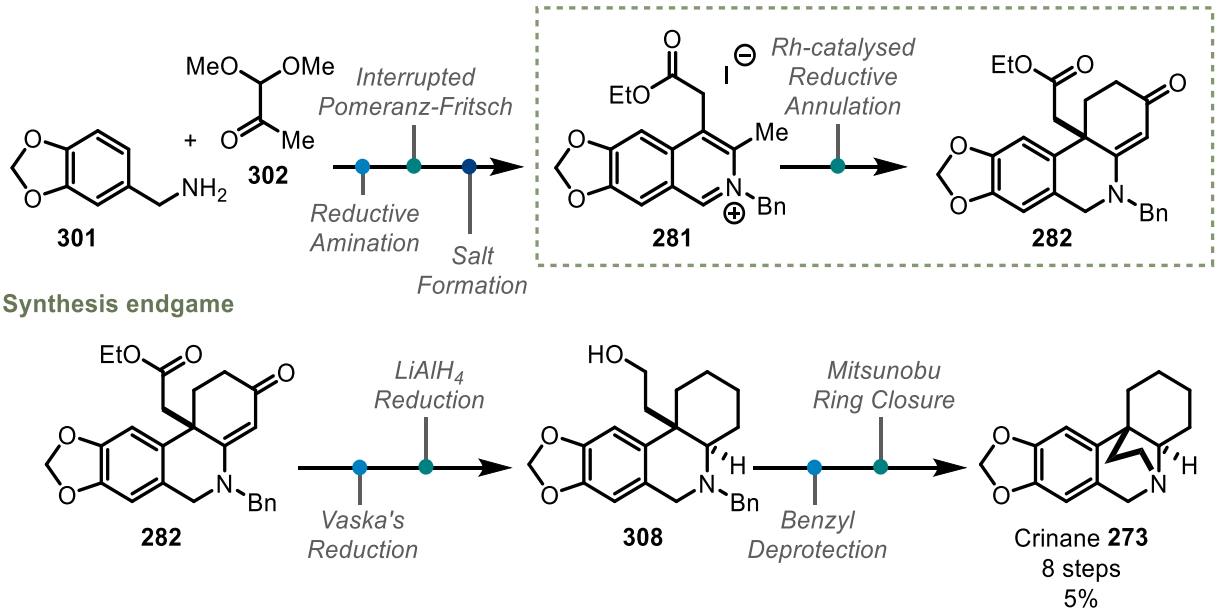
Regrettably, initial attempts to apply the method described above to our system resulted in the formation of **318** in a reasonable yield of 30% (Scheme 5.30). We believe this unexpected by-product formed as a result of oxidative abstraction of an H atom *α*-to nitrogen by a copper species, which was then further oxidised to form an iminium. The nitrogen of the *N*-methoxy amide is then free to attack the iminium, closing the ring to form **318**. It is unclear why this mode of reactivity was quicker or more favourable than the *N-O* homolysis reaction to generate desired product **319**. We assume that the terminal oxidant for the reaction is atmospheric oxygen.



Scheme 5.30: C-H activation of our compound of interest; application of literature conditions with unexpected side reactivity. Isolated yield is reported. Reaction performed on 0.25 mmol scale.

5.5 Conclusion

In this chapter, the reductive annulation method developed in Chapter 4 was applied to a more complex substrate **281**, enabling the total synthesis of Crinane **273**, the parent compound of the Crinane family of natural products. The synthesis was eight steps in total, with an overall yield of 5%. Extensive optimisation of the sequence was detailed and we also showed further investigations towards modifying the sequence to enable a divergent synthesis of multiple members of the Crinane family. Several strategies for diversification were investigated including a modified Vaska's reduction-functionalisation sequence and an attempt at a post reduction C-H activation strategy.

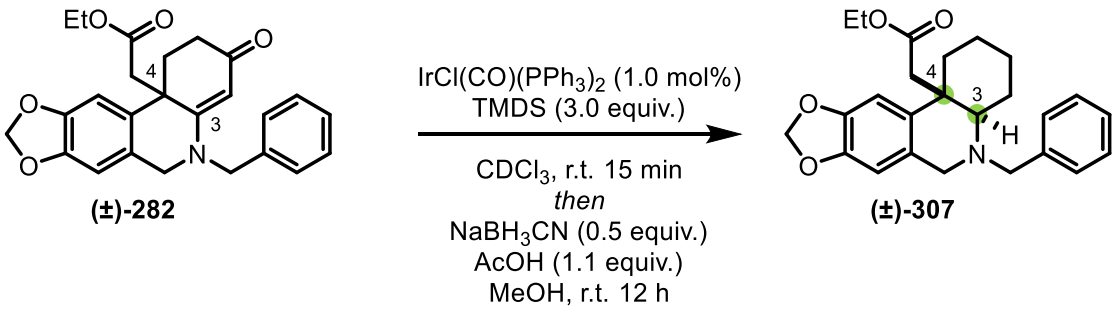


Scheme 5.31: Application of the reductive annulation reaction to the total synthesis of the Crinane family of natural products.

Chapter 6 – Investigations towards an enantioselective reductive annulation reaction

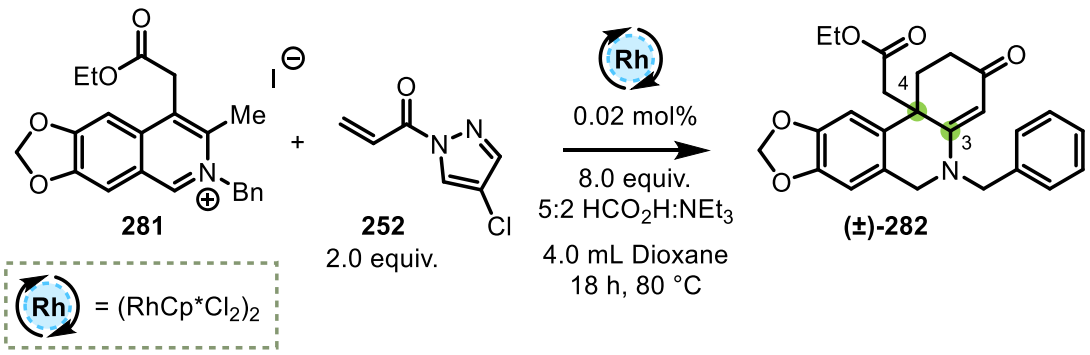
6.1 Exploring the challenges of making the enantiopure Crinane skeleton

The reductive annulation method described in Chapter 4 is a non-stereoselective reaction between two achiral building blocks. In order to synthesise natural examples of the Crinane family of alkaloids, the synthesis will have to be adapted to generate enantiopure products. The stereocentres that determine the enantiomer of the alkaloid are at C3 and C4 on the isoquinoline skeleton. The reduction of vinylogous amide **282** to form amine **307** proceeds with excellent diastereoselectivity (Scheme 6.1). The relative stereochemistry results from the preference of the final hydride addition to C3 to be delivered from the least hindered face. This stereochemistry represents axial addition to the final iminium ion.



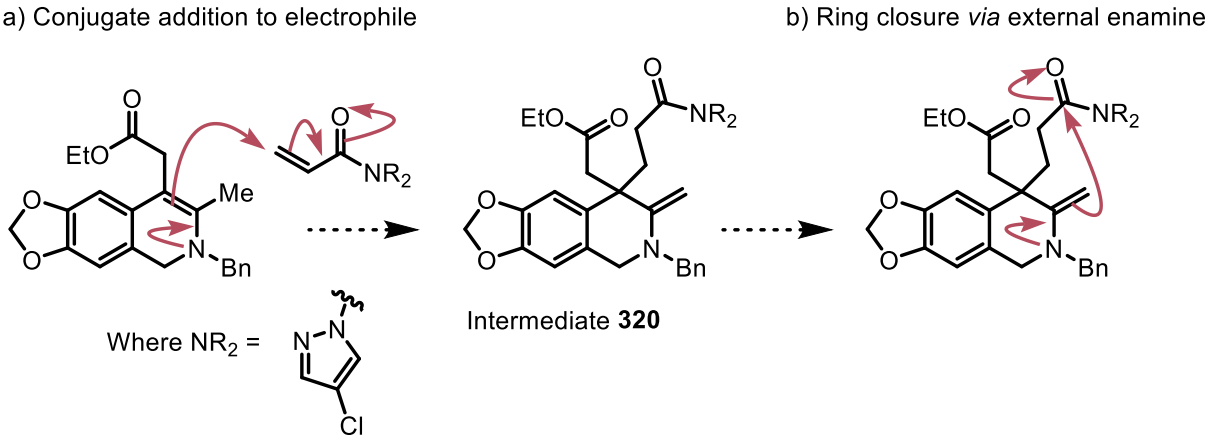
Scheme 6.1: Reduction of vinylogous amide **282** which determines the relative C3-C4 stereochemistry.

The absolute stereochemistry of the molecule at the C4-position is set in the reductive annulation reaction described in Chapter 4 (Scheme 6.2). In its current form, the reaction is not stereoselective and forms a racemic product.



Scheme 6.2: Non-stereoselective annulation reaction to produce the tricyclic skeleton of the Crinane natural products.

There are two possibilities as to the enantiodetermining step of the reaction, namely the initial addition of the endocyclic enamine to the conjugate acceptor electrophile (Scheme 6.3a), or the ring closure of the exocyclic enamine onto the carbonyl of the electrophile (Scheme 6.3b). Although the conjugate addition sets the stereochemistry at C4 (Scheme 6.3a), it is possible that this step is reversible and therefore the enantiomers generated after the initial addition to generate intermediate **320** are in equilibrium, and the ring closure event (Scheme 6.3b) sets the products' absolute stereochemistry.

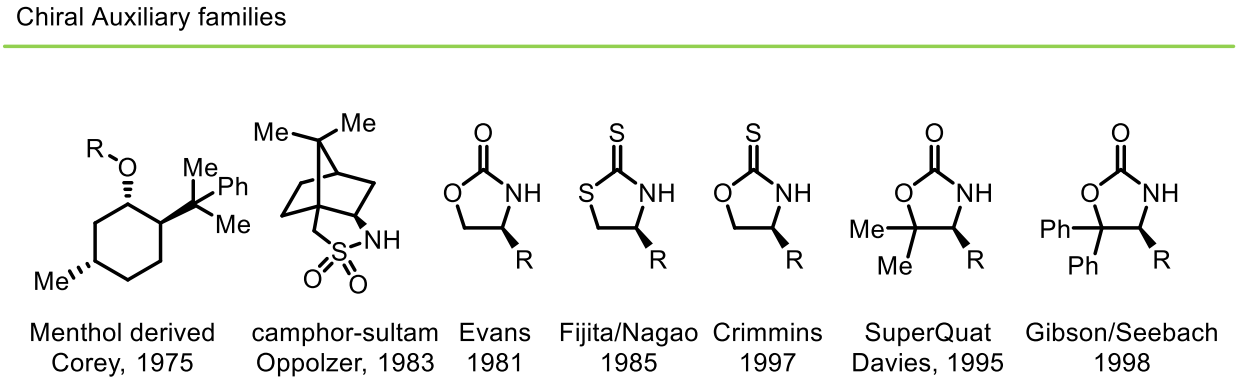


Scheme 6.3: Potential enantiodetermining steps in annulation mechanism. a) Conjugate addition to electrophile or b) ring closure *via* external enamine addition into electrophile carbonyl.

6.2 Previous studies towards enantioselective conjugate addition reactions

A multitude of methods have been employed previously to effect enantioselective conjugate additions between nucleophiles and α, β-unsaturated carbonyls to generate new C-C bonds.[104-106] There are many catalytic examples of this technique, but a commonly utilised strategy is to use chiral auxiliaries to impart stereogenic information on one or more components of the reaction.[107]

A chiral auxiliary is a group inserted into a molecule in order to impart stereoselectivity on a non-stereoselective reaction which is then removed after the fact. A good chiral auxiliary should be facile to add on to and remove from the molecule of interest, and afford high levels of stereoselectivity during the reaction of interest. Many have been synthesised and employed with great success including oxazolidinones, camphor sultams and menthol derivatives (Scheme 6.4).[108-110]

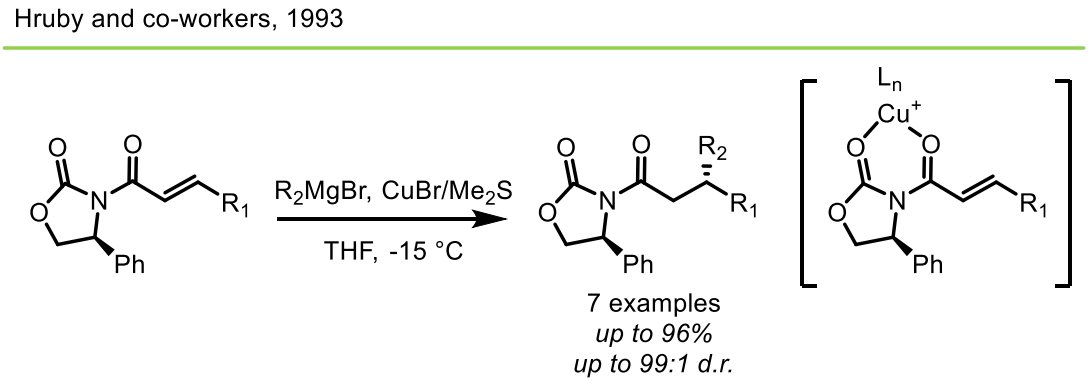


Scheme 6.4: A range of chiral auxiliary families including several oxazolidinone derived species.

The use of chiral auxiliaries to effect stereoselective conjugate additions is widespread, with numerous forms of auxiliaries utilised to achieve the C-C bond forming event with different substrates.[111] Stereocontrol of the α and β-stereocentres is common, using the steric bulk of an auxiliary substituent to bias the selectivity of an approaching reactant that is immediately adjacent to the auxiliary. Control of a γ-stereocentre using auxiliaries is much rarer, with the

ability of a bulky substituent to imprint stereogenic bias to a reaction falling with the distance between the substituent and the reactive centres. The main exception to this is the organo-catalysed Diels-Alder reaction, where α, β and γ-stereocentres are set in a single reaction.[109] However, it can be considered that the rigid structure generated and the pericyclic (or at least pseudo-concerted) nature of the reactivity results in stereochemistry set at the immediate α and β-centres first which proceeds to influence the γ-stereochemistry.

Hruby and co-workers were one of the first authors to utilise a chiral auxiliary approach to a conjugate addition, coupling an α, β-unsaturated carbonyl to an Evans auxiliary to give stereocontrol over a conjugate Grignard addition (Scheme 6.5).[112] The high levels of diastereoselectivity observed are attributed to the addition of a copper Lewis acid additive that can coordinate the two carbonyls present in the substrate, therefore giving a rigid and well-defined substrate with a larger difference in energy between diastereomer transition states.



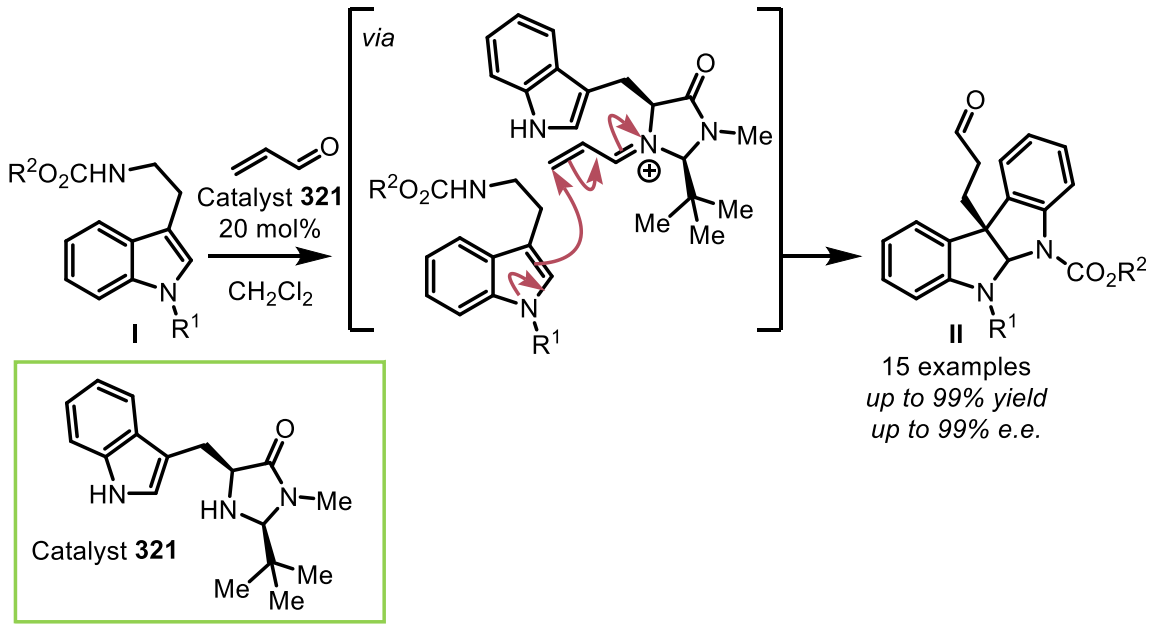
Scheme 6.5: Diastereoselective conjugate addition using a chiral auxiliary approach.

The field of organocatalysis has developed this concept, with more modern approaches to the issue taking the form of a re-usable catalyst that forms the reactive enantioenriched species *in situ* before performing the reaction, then hydrolysing to regenerate the organocatalyst. In many ways, organocatalysts can be considered *in situ* chiral auxiliaries, that are put on, impart stereoselectivity and are removed in a one-pot process, as opposed to three distinct reactions.

MacMillan and co-workers used organocatalysis to good effect in a functionalisation-cyclisation cascade with an indole substrate (Scheme 6.6).[113] Activation of the electrophile, an *α*, *β*- unsaturated aldehyde, by an imidazolidinone organocatalyst **321** formed an iminium which is attacked by the indole. The resultant iminium is then attacked by a pendant carbamate, thereby cyclising and functionalising in a one-pot process. The organocatalyst is then hydrolysed *in situ* to regenerate the catalytic species. This therefore makes the method the only known example of a conjugate addition-cyclisation reaction that sets the *α*, *β*, and *γ*-stereocentres in a single step.

The use of a bulky organocatalyst allows control of a *γ*-stereocentre with excellent yields and enantioselectivities reported of up to 99% each respectively. Regrettably this system for enantiocontrol could not be used on our substrate as the aldehyde oxidation state is wrong for the product we are seeking to synthesise, and the system is not designed for direct attack at the carbonyl.

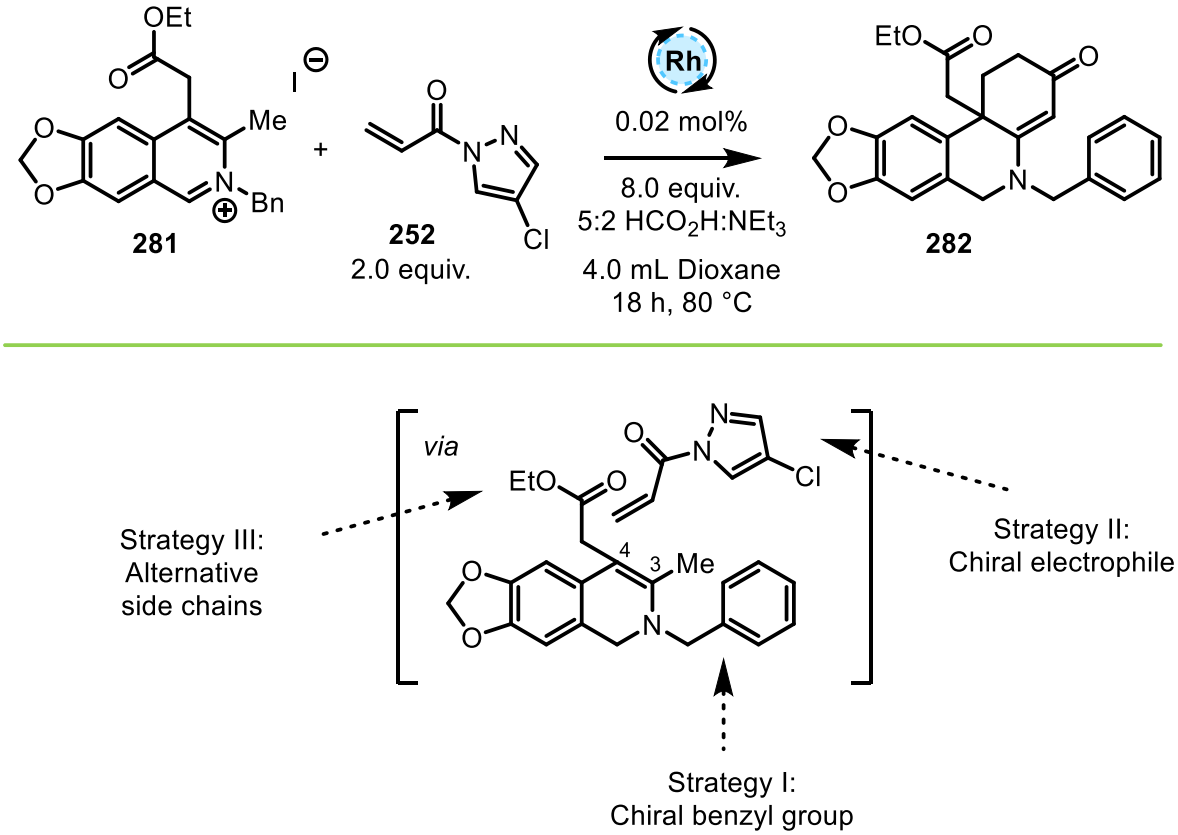
MacMillan, 2004



Scheme 6.6: Organocatalysed conjugate functionalisation coupled with an indole cyclisation.

6.3 Project aims

To render the annulation reaction enantioselective, we considered three possibilities: I) modification of the ambident electrophile, II) modification of the ester side chain, and III) modification of the benzyl activating group as good candidates to achieve stereoselectivity (Scheme 6.7). Bulkier side chains could also be appended to aid with strategies I and II.



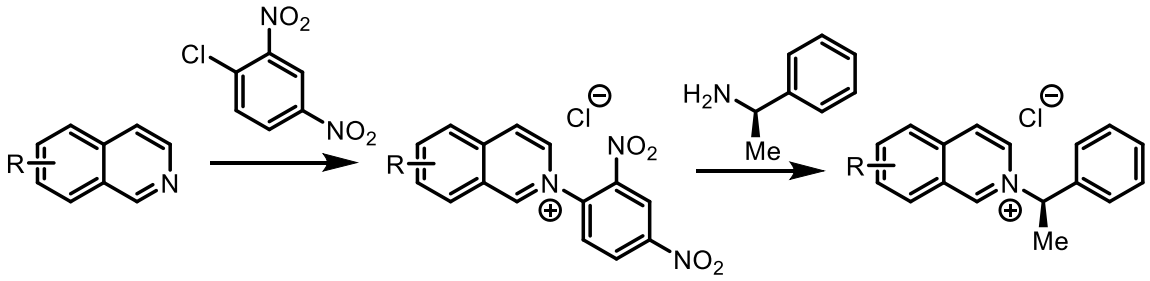
Scheme 6.7: Three strategies for substrate control of the reductive annulation. Strategy I: chiral benzyl activating group. Strategy II: chiral electrophiles. Strategy III: bulkier side chains.

6.4 Attempts towards rendering the annulation reaction enantioselective

6.4.1 Strategy I: Chiral benzyl activating group

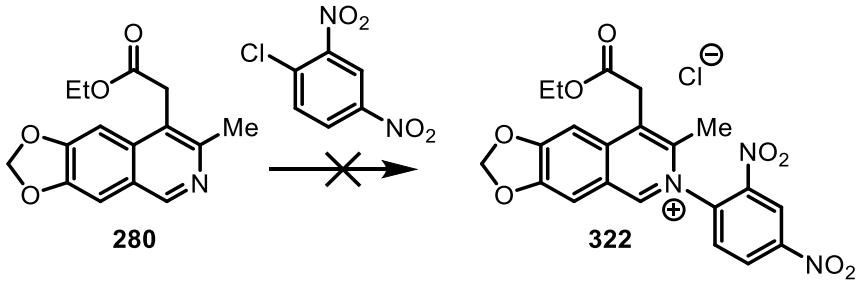
It was first suggested that an enantiopure benzylic sp^3 stereocentre on the benzyl activating group of salt **281** might allow some level of stereocontrol to the process, and so the synthesis of a single enantiomer of the salt was attempted. The literature method for synthesising related

substrates involves making the Zincke salt, then substituting the activated nitrogen for an enantioenriched, chiral amine (Scheme 6.8).[114]



Scheme 6.8: Literature procedure for enantiospecific synthesis of chiral isoquinolinium salts.

Unfortunately, application of this technique to isoquinoline **280** failed, where only starting material was recovered in the isoquinoline activation step (Scheme 6.9). It is thought that this is due to the increased steric bulk of **280** at C3 as compared to the isoquinolines used in the literature examples.

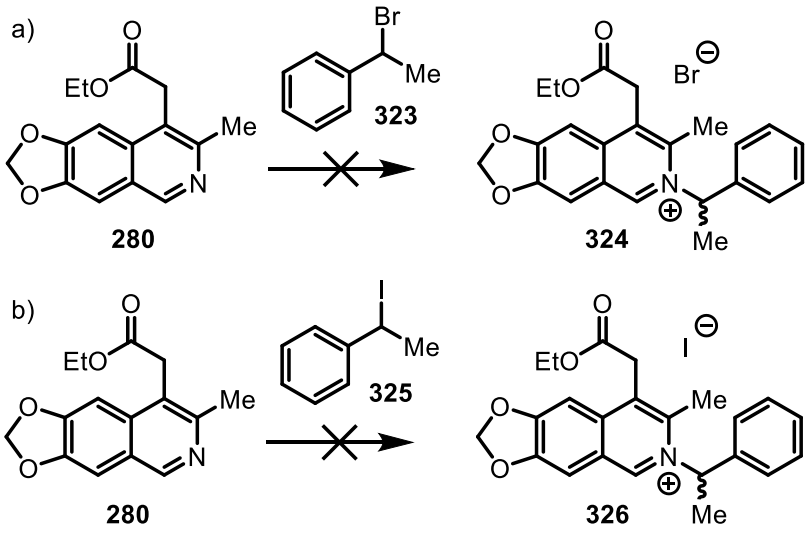


Scheme 6.9: Attempted application of literature conditions to isoquinoline **280**.

We hypothesised that even if a racemic mixture of α-methyl benzyl salt was used, some diastereomeric control might be observed. The racemic salt should be easier to synthesise, as it can be made using a more conventional S_N2 reaction.

We first attempted the reaction with the benzyl bromide, but unfortunately only starting material was returned (Scheme 6.10). The failure of this technique was similarly attributed to the steric bulk around the isoquinoline nitrogen, and so it was suggested that the reaction should be reattempted but with the corresponding benzyl iodide, as substitution with iodide is notably

faster than with the corresponding bromide (Scheme 6.10). Unfortunately, when attempted, the reaction generated a complex mixture from which no useful product could be isolated.

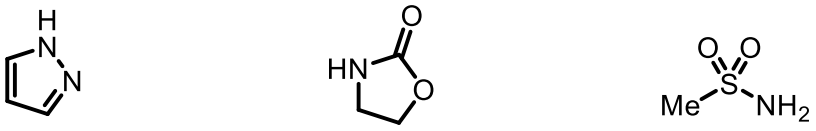


Scheme 6.10: Attempted synthesis of racemic α-methyl benzyl salt *via* a S_N2 reaction with a) a benzyl bromide **323** and b) a benzyl iodide **324**.

We concluded that the difficulty encountered when trying to synthesise an α-methyl benzyl salt indicated that this substrate was not well suited to this style of enantiocontrol, and so we proceeded to consider other approaches.

6.4.2 Strategy II: Reagent control through a chiral electrophile

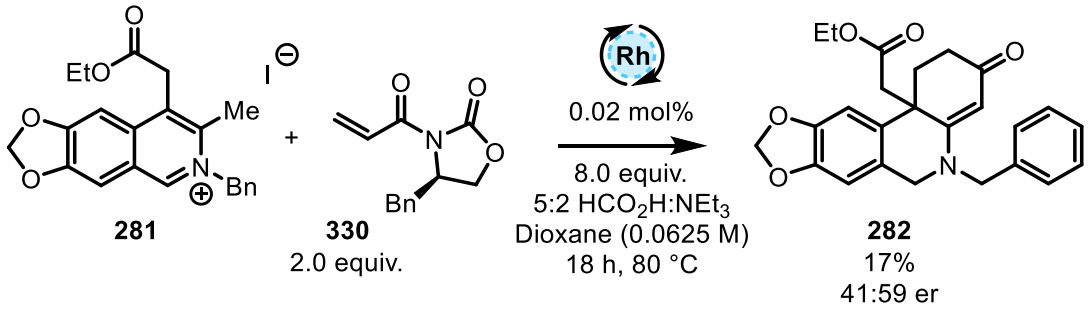
It was noted that electrophile **252** was successful due to the stability of the pyrazole leaving group. It was suggested that developing an enantioselective stereoselective variant of the transformation could be achieved by finding an enantioenriched, chiral equivalent to a pyrazole with a similar p*K*a. The p*K*a of pyrazole **327** is 19.8 (DMSO) (Figure 6.1), two species with similar p*K*a values are oxazolidinone **328** (20.8, DMSO) and methane sulfonamide **329** (17.5, DMSO). Oxazolidinone **328** is the basis for Evans's chiral auxiliaries; the similar p*K*a values and the wide precedent of using oxazolidinone groups in enolate chemistry justified exploring the use of this functional group in the reductive annulation.



	327	**328**	**329**
p*Ka*	19.8	20.8	17.5

Figure 6.1: pKa values for departing groups components of electrophiles.[115]

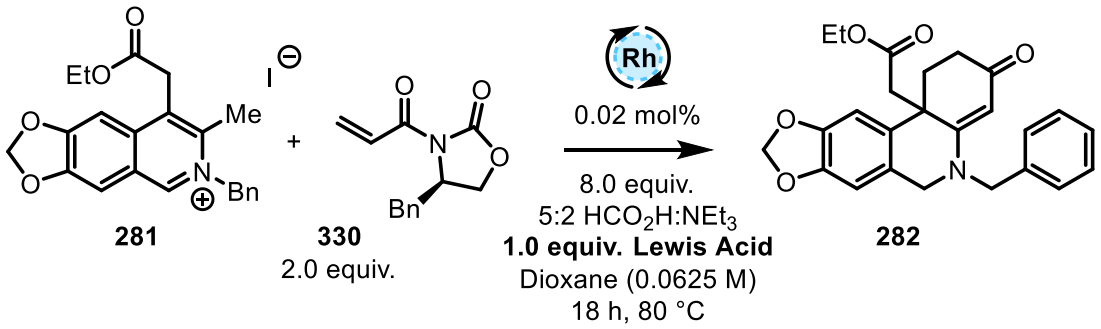
Oxazolidinone-based electrophile **330** was synthesised and subjected to the annulation reaction conditions. Pleasingly, a small amount (17%) of product was produced in low stereoselectivity of 41:59 e.r. (Scheme 6.11). e.r. were determined by SFC with a chiral stationary phase, with relative integration compared against a racemic standard (see experimental section for further details). Regrettably due to time constraints, the enantiomer identity of the product was not determined.



Scheme 6.11: Application of an Evans auxiliary-derived electrophile to the reductive annulation. Isolated yield reported. e.r. measured using SFC with a chiral stationary phase. Reaction performed on 0.25 mmol scale.

Our first strategy to improve upon this result was to use Lewis acid additives in an attempt to control the orientation of the reactants in the transition state through carbonyl co-ordination and thereby increase the enantioselective effects of the electrophile. A small screen of Lewis acid additives was subsequently performed (Table 6.1). Regrettably, the e.r. measured were either identical to that without an additive or substantially worse, and in one case the product was racemic (Table 6.1, Entry 5). The lack of any improvement indicates that either increased

co-ordination disrupts the transition state required to induce enantioselectivity, or that the initial conjugate addition is not the enantiodetermining step.



Entry	Lewis acid	Yield of 282 (%)	e.r.
1	None	17	41:59
2	LiCl	29	44:56
3	$MgCl_2$	24	41:59
4	$Ti(O^iPr)_4$	34	45:55
5	$Sc(OTf)_3$	14	50:50
6	$Zn(OTf)_2$	15	45:55

Table 6.1: Addition of Lewis acids to the enantioselective annulation reaction in an attempt to increase co-ordination in the transition state. Yields determined by quantitative ^{1}H NMR spectroscopy. e.r. were determined using SFC with a chiral stationary phase. Reactions performed on 0.25 mmol scale.

Several chiral auxiliaries were used to synthesise a range of ambident vinyl ketone-type electrophiles and subjected to the reaction conditions (Scheme 6.12).[109] The auxiliaries were chosen for ease of sourcing and price, so the specific enantiomer is not consistent.

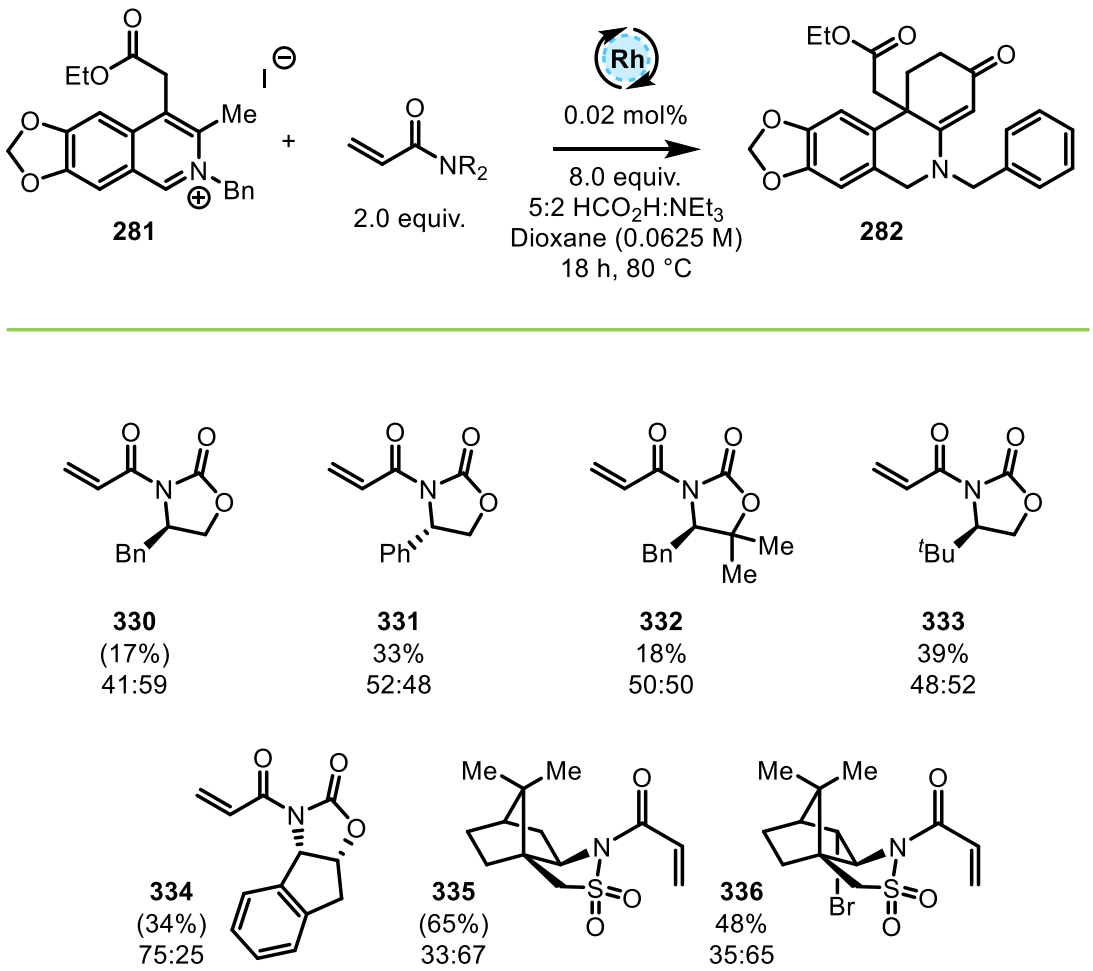
All electrophiles screened afforded some product, however the product **282** e.r. varied quite drastically between R groups. Decreasing the length of the side chain to a phenyl group (**331**) decreased the e.r. to racemic within experimental error, perhaps showing that the effectiveness of the auxiliary scales with side chain size.

Dimethyl substituted electrophile **332** has traditionally been used to increase the enantioselective effects of the side chain, as the presence of two geminal methyl groups is presumed to push the side chain further from the Evans ring and towards the reaction transition state.[116] Disappointingly, when applied in the reductive annulation reaction, the product was obtained as a racemic mixture.

Electrophile **333** with a ^{t}Bu side chain afforded **282** in a 39% yield but with a negligible e.r. (within experimental error of being racemic). A more rigid indane derived electrophile **334** fared much better, affording a 34% yield with an e.r. of 75:25. We believe this much improved e.r. is due to the rigid nature of the skeleton, suggesting that the bulk of the electrophile is much deeper into the reaction transition state and is therefore imprinting a much larger enantioselectivity on the system.

Lastly, Oppolzer's camphor-sultam auxiliary was used to synthesise an ambident electrophile, **335**, which produced an excellent isolated yield of 66% with an e.r. of 33:67.

Although the e.r. when **335** was used is much lower than with indane-based electrophile **334**, the high yield observed with **335** made it a promising candidate for optimisation. It was hoped that by modifying the skeleton of the electrophile to become more sterically bulky, the e.r. might be improved (Scheme 6.12). Regrettably, introduction of a bromine atom to the skeleton to form **336** made little difference to either the e.r. or the yield, affording product in a 48% yield with an e.r. of 35:65, very similar to the ratio of 33:67 obtained when unbrominated **335** was used as the electrophile. This perhaps implies that the bromine atom is on the wrong face and therefore pointing away from the reaction transition state. If the introduction of a bromine atom created sufficient steric bulk so as to prevent the formation of the required transition state, one would expect a lower yield and a drastically reduced e.r. which is not observed here.



Scheme 6.12: Screen of different chiral auxiliary derived electrophiles in the reductive annulation. Yields determined by quantitative ^{1}H NMR spectroscopy. Isolated yields are indicated by brackets. e.r. were determined using SFC with a chiral stationary phase. Reactions performed on 0.25 mmol scale.

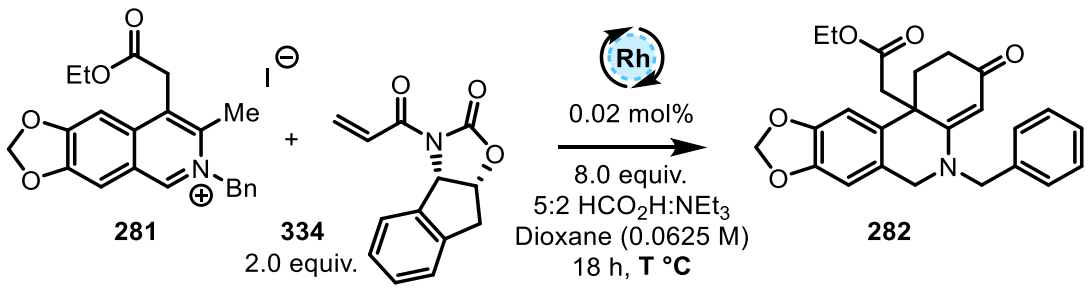
We believe the reason for the improved yield with electrophiles **335** and **336** lies with the p*K*a of the leaving group. In the optimised reductive annulation, the leaving group is a pyrazole anion, which has a p*K*a of 19.8. A cyclic carbamate, such as an Evans's auxiliary, has a p*K*a of 20.8, an order of magnitude larger than the pyrazole. A sultam is potentially much more similar to the pyrazole p*K*a, and therefore more readily able to leave as the reaction progresses. Methyl sulfonamide, a related species to camphor sultam, has a p*K*a of 17.5, perhaps indicating that the leaving groups in electrophiles **335** and **336** are much more stable as the conjugate base than an Evan's oxazolidinone, and therefore more appropriate as a component of an ambident

electrophile. A secondary possibility is that if the initial conjugate addition is rate determining, the sulfonamide functionality is a better electron withdrawing group than an oxazolidinone, resulting in a more electrophilic conjugate acceptor.

6.4.3 Further optimisation of the reaction with electrophiles 334, 335 and 336

Continuing with indane-derived electrophile **334**, our next optimisation strategy was to lower the reaction temperature, as it has been previously shown that lowering temperature increases enantioselectivity, due to the differences in energy between the transitions state structures that form the two enantiomers (Table 6.2).[117-119] Pleasingly, although the yield obtained decreased from 34% at 80 °C to 30% at 60 °C and then finally 15% at 40 °C, the e.r. observed increased to a highly promising 83:17 at 40 °C (Table 6.2, Entries 1-3). Regrettably, decreasing the reaction temperature below 40 °C prevented reactivity, thereby giving us a lower limit to the envelope of reaction viability (Table 6.2, Entries 4-5). This is consistent with observations made with the non-stereoselective reaction using pyrazole electrophile **252** (*vide supra*).

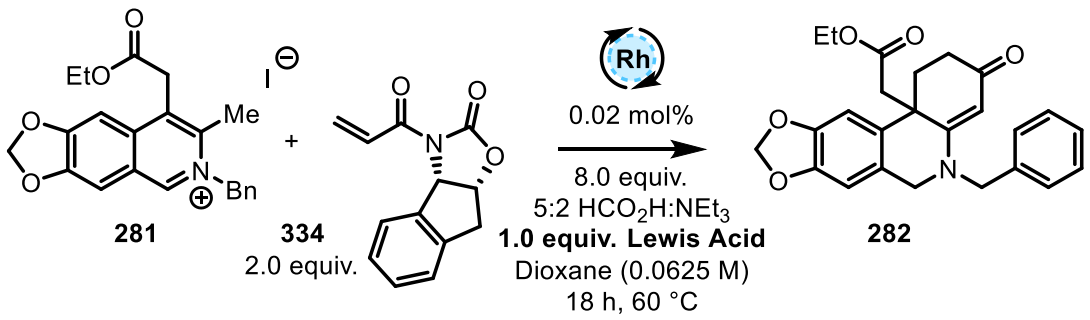
Given that there was starting material remaining in the reaction at 40 °C, the reaction was repeated but left for 66 h. Disappointingly, only a small increase in yield was observed to 21%, with the same e.r. of 83:17 (Table 6.2, Entry 6).



Entry	Temperature (°C)	Yield of 282 (%)	e.r.
1	80	(34)	75:25
2	60	30	77:23
3	40	15	84:16
4	30	0	-
5	20	0	-
6[a]	40	21	83:17

Table 6.2: Temperature variations using rigid electrophile **334**. Yields determined by quantitative ^{1}H NMR spectroscopy. Isolated yields are indicated by brackets. e.r. were determined using SFC with a chiral stationary phase. [a]Reaction time increased to 66 h. Reactions performed on 0.25 mmol scale.

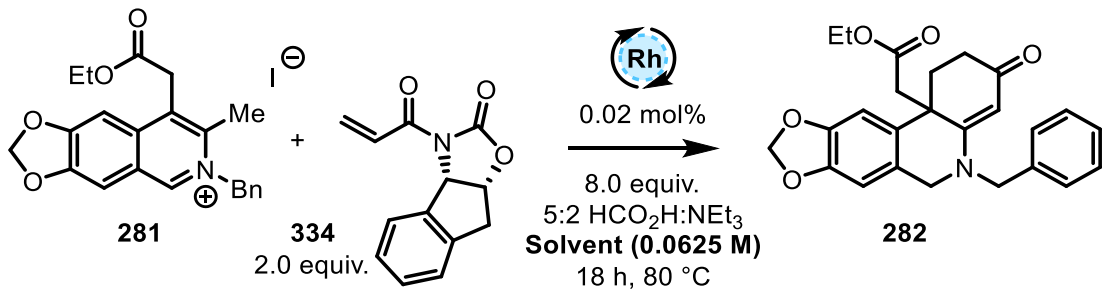
It was suggested that further optimisation of the reaction using **334** could be achieved by the addition of Lewis acids, perhaps succeeding where we had failed with electrophile **330** (Table 6.3). Regrettably, of the three Lewis acids screened, yields and e.r. were broadly unaffected, affording yields of 32% and 27% respectively for $Ti(O^{i}Pr)_4$ and Al_2O_3, with an e.r. of 78:22 for both. Contrary to this is $SnCl_4$, which prevented reactivity altogether (Table 6.3, Entry 4).



Entry	Lewis acid	Yield of 282 (%)	e.r.
1	-	30	77:23
2	$Ti(O^iPr)_4$	32	78:22
3	Al_2O_3	27	78:22
4	$SnCl_4$	0	-

Table 6.3: Addition of Lewis acids with electrophile **334**. Yields determined by quantitative ^{1}H NMR spectroscopy. e.r. were determined using SFC with a chiral stationary phase. Reactions performed on 0.25 mmol scale.

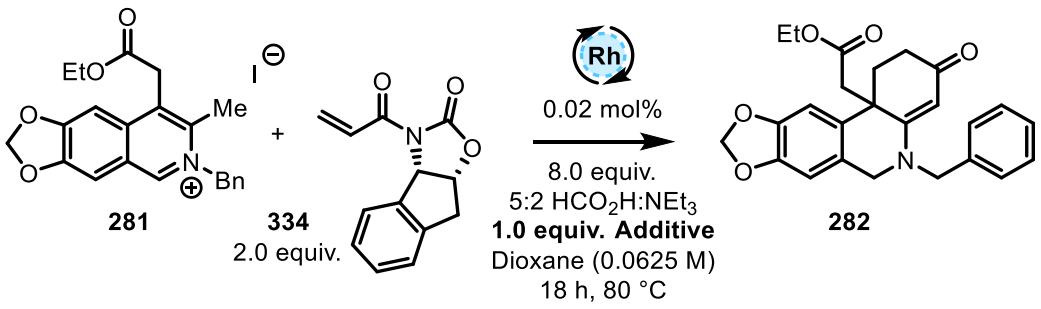
Next, we attempted to screen the reaction solvent, with a range of solvents chosen to represent a variety of polarity. Regrettably, compared to the original reaction solvent of 1,4-dioxane (Table 6.4, Entry 1), the solvents screened produced largely reduced e.r. and yields. MeCN rendered only a small e.r. (58:42), much less than with 1,4-dioxane, and a mere 14% yield (Table 6.4, Entry 2) and acetone as the solvent prevented reactivity altogether (Table 6.4, Entry 3). Polar solvents such as $CHCl_3$ and DCE fared a little better, with similar yields to MeCN (18% and 12% respectively) but improved e.r. more in line with 1,4-dioxane (73:27, 69:31 respectively) (Table 6.4, Entries 4, 6). PhMe produced the most promising result of the solvents trialled, however, with a 22% yield and an e.r. of 78:22. However, this result is still worse than when 1,4-dioxane was used as the reaction solvent, and so investigations were continued with 1,4-dioxane as the solvent.



Entry	Solvent	Yield of 282 (%)	e.r.
1	1,4-Dioxane	(34)	75:25
2	MeCN	14	58:42
3	Acetone	0	-
4	$CHCl_3$	18	73:27
5	PhMe	22 (21)	78:22
6	DCE	12	69:31

Table 6.4: Solvent screen of the enantioselective annulation. Yields determined by quantitative ^{1}H NMR spectroscopy. Isolated yields are indicated by brackets. e.r. were determined using SFC with a chiral stationary phase. Reactions performed on 0.25 mmol scale.

It was suggested that an alternative counter-ion might improve reactivity, and so two potential candidates were added to the reaction (Table 6.5).[120] AgOTf, which should undergo salt metathesis with the *N*-benzyl substrate to form the triflate, showed a reduction in both the e.r. and yield to 70:30 and 24% respectively (Table 6.5, Entry 2). $NaBAr^F_4$, a phase-transfer catalyst, was trialled next, in the hope that the large, non-co-ordinating anion might aid in reactivity.[121] Regrettably, although the e.r. was similar (73:27), the yield was lower, at 23%.

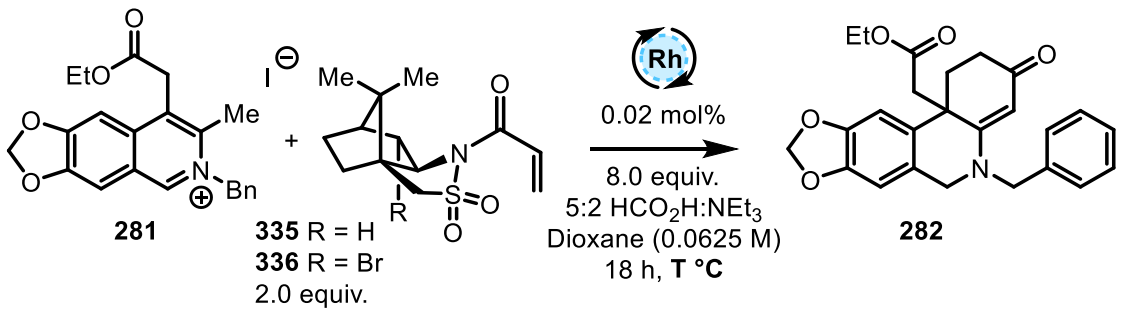


Entry	Additive	Yield of 282 (%)	e.r.
1	-	(34)	75:25
2	AgOTf	24	70:30
3[a]	$NaBAr^F_4$	23	73:27

Table 6.5: Addition of additives to the enantioselective annulation. Yields determined by quantitative ^{1}H NMR spectroscopy. Isolated yields are indicated by brackets. e.r. were determined using SFC with a chiral stationary phase. [a]Reaction performed with 0.1 equiv. $NaBAr^F_4$. Reactions performed on 0.25 mmol scale.

Finally, the camphor sultam derived electrophiles **335** and **336** were revisited, in the hope that the lower e.r. could be optimised whilst retaining the high reactivity (Table 6.6). Subjecting both **335** and **336** to the lowest feasible reaction temperature of 40 °C afforded a reasonable amount of product, 53% and 52% yield respectively. However, the e.r. observed were regrettably unchanged, at 33:67 and 36:64 respectively.

The lack of any significant e.r. change with temperature is concerning, as these results are not consistent with those recorded for equivalent experiments with indane-derived electrophile **334** (Table 6.2). This implies that the two electrophiles show different characteristics, where the enantiodetermining step is affected by temperature in one, but independent of temperature in the other.

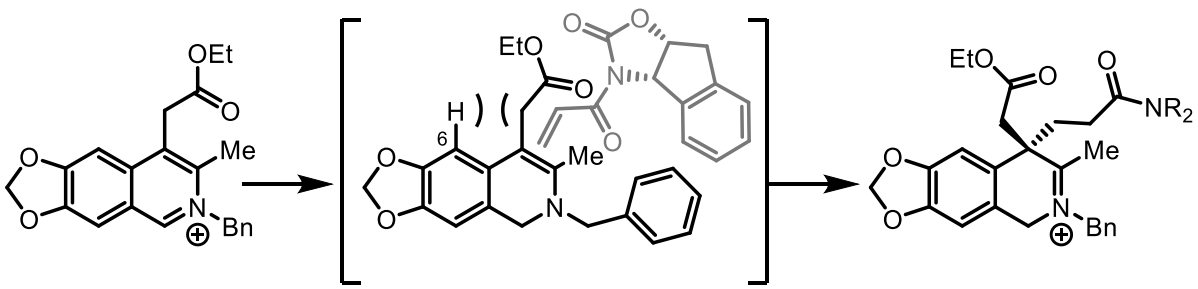


Entry	R	T	Yield of 282 (%)	e.r.
1	H	80	65	33:67
2	H	40	53	33:67
3	Br	80	48[a]	35:65
4	Br	40	52	36:64

Table 6.6: Lower temperature investigations with electrophiles **335** and **336**. [a]Yield determined by quantitative ^{1}H NMR spectroscopy. e.r. were determined using SFC with a chiral stationary phase. Reactions performed on 0.25 mmol scale.

6.4.4 Strategy III: Adapting the ester side chain

Based on our observations, we propose a pre-transition assembly for the initial conjugate addition of the enamine generated *in situ* to the electrophile (Scheme 6.13). In the model proposed, the ester is pointing away from the isoquinoline core due to unfavourable peri-interactions with the proton at the C6-position.

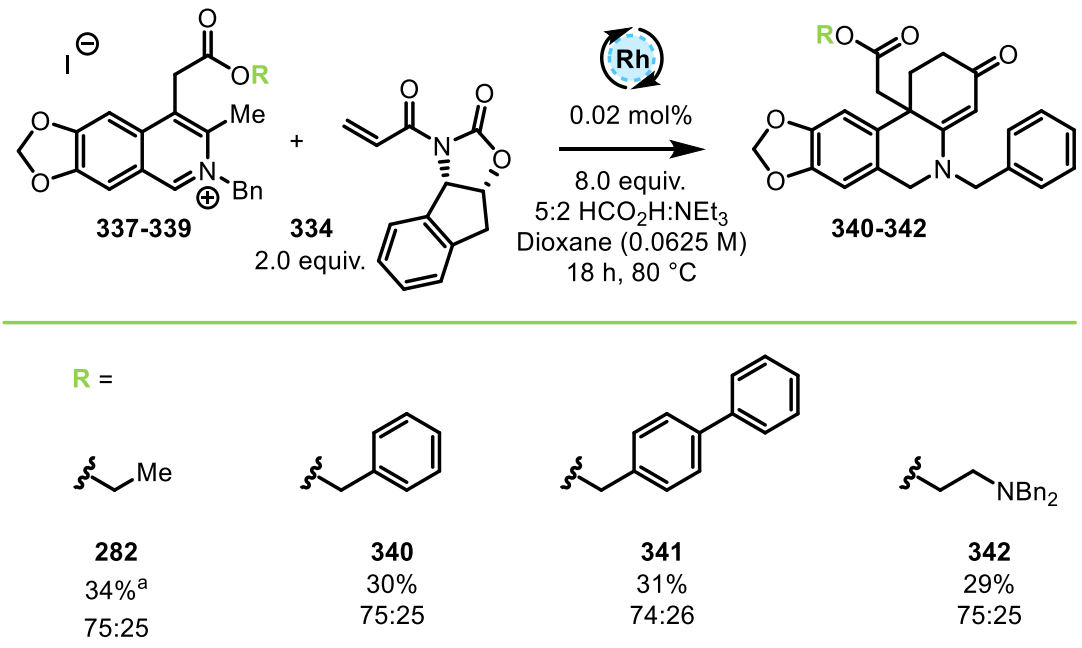


Scheme 6.13: Suggested pre-transition assembly for the conjugate addition of enamine into electrophile.

Not enough is known about the system to accurately predict the transition state for the reaction, as it is acyclic, with unknown orientations of the components. DFT could be used to inform this model further, but was not in this instance due to time constraints. The suggested pre-transition assembly in Scheme 6.13 is included for clarity but should not be interpreted as an accurate representation of the reaction.

Subsequently to this, it was hypothesised that the enantioselectivity of the reductive annulation could be increased by making either the ester side chain or the benzyl group larger; this would hopefully increase the selectivity of the reaction by creating a larger steric environment to bias the formation of one enantiomer over the other.

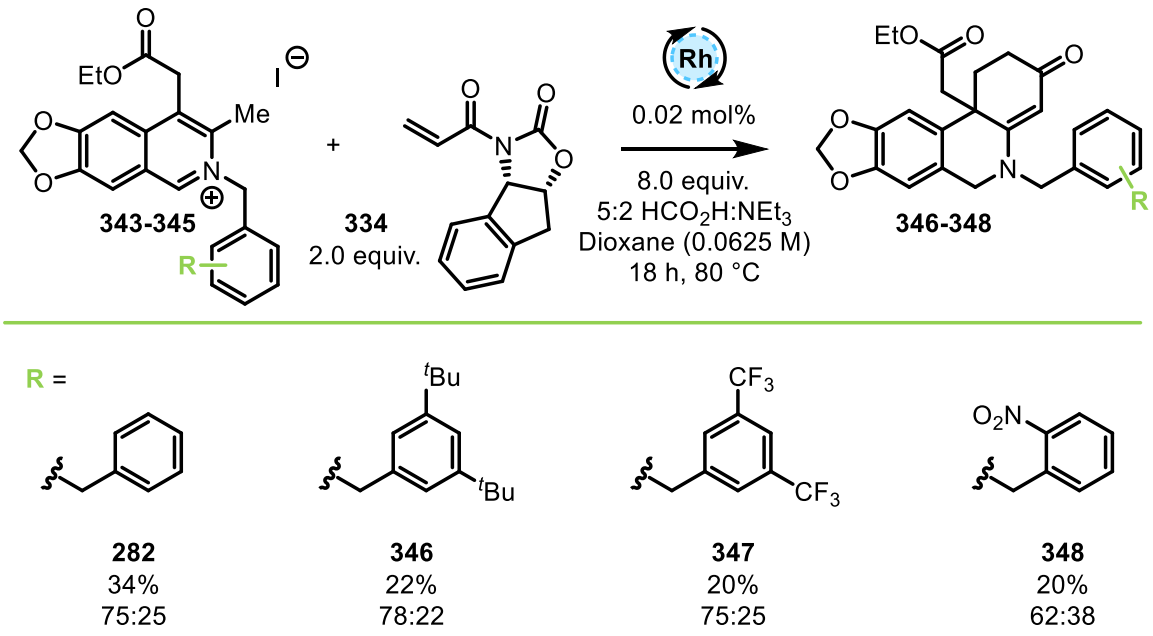
Compounds **337**, **338** and **339** were synthesised, each with a distinct side chain bulkier than the original ethyl side chain in **281**, and were subjected to the reductive annulation conditions (Scheme 6.14). Pleasingly, the yields afforded were only slightly reduced from **281** with an ethyl side chain. Regrettably, however, the enantiomeric ratios observed were the same, within experimental error, of the model system. These data suggests that our transition state model is incorrect in some way, and the ester side chain is pointing away from the centre of reactivity. Accordingly, modifying the sterics of the alkyl group of the ester will not impact the stereoselectivity of the reaction.



Scheme 6.14: Screen of ester side chain substituents in an attempt to increase the bulk of the transition state. Isolated yields are reported. e.r. were determined using SFC with a chiral stationary phase. Reactions performed on 0.10 mmol scale. [a]Reaction performed on 0.25 mmol scale.

6.4.5 Strategy III: Adapting the benzyl activating group

Further to our work altering the ester side chain, we wished to explore the effects of adapting the benzyl activating group to be more sterically demanding. Substrates bearing three different activating groups were synthesised (**343**, **344** and **345**, Scheme 6.15) and subjected to the reductive annulation conditions. Regrettably, all three afforded a lower yield than with original compound **281** as the substrate, giving 22%, 20% and 20% yields respectively. Enantiomeric ratios were broadly unimproved; **346** showed a slightly higher level of selectivity (e.r. = 78:22), **347** was consistent with unsubstituted **282** affording an e.r. of 75:25 and *ortho*-nitro benzyl derived **348** gave a much lower e.r. of 62:38. We propose this indicates that slightly bulkier benzyl groups have a negligible effect on the difference in energy between the two transition state structures that form the two enantiomers, perhaps because the benzyl substituent is pointing sufficiently away from the reaction transition state to have negligible steric effects.



282	**346**	**347**	**348**
34%	22%	20%	20%
75:25	78:22	75:25	62:38

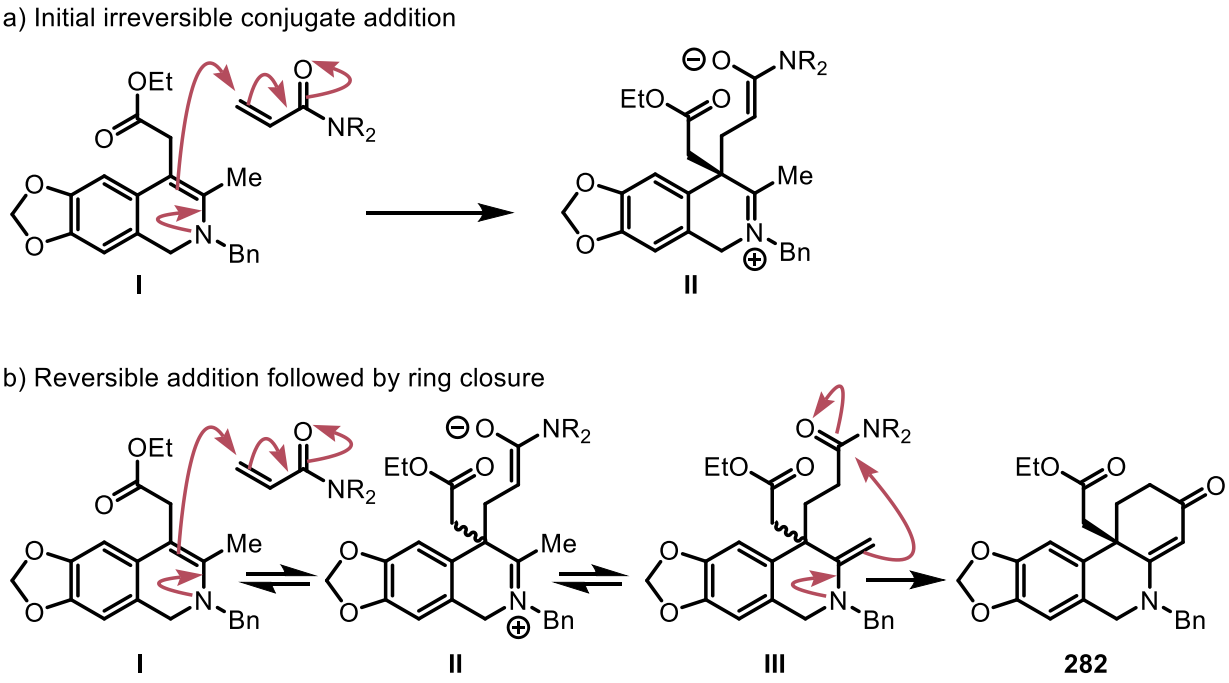
Scheme 6.15: Screen of benzyl activating groups in an attempt to increase the bulk of the transition state. Isolated yields are reported. e.r. were determined using SFC with a chiral stationary phase. Reactions performed on 0.25 mmol scale.

6.5 Investigations into the mechanism of enantioselective annulation

We wanted to determine the enantiodetermining step of the reaction; there are two possibilities, either the initial conjugate addition into the chiral electrophile, or the ring closure attack at the electrophile carbonyl (Scheme 6.16).

The first possibility is that the initial conjugate addition of the *in situ* generated enamine into the chiral electrophile (Scheme 6.16a). Were this to be the enantiodetermining step, the reaction would have to be irreversible. We consider this is the simplest and most likely of the two options, as Donohoe and co-workers have shown that a range of C4-functionalised products can be obtained with a variety of different electrophiles.

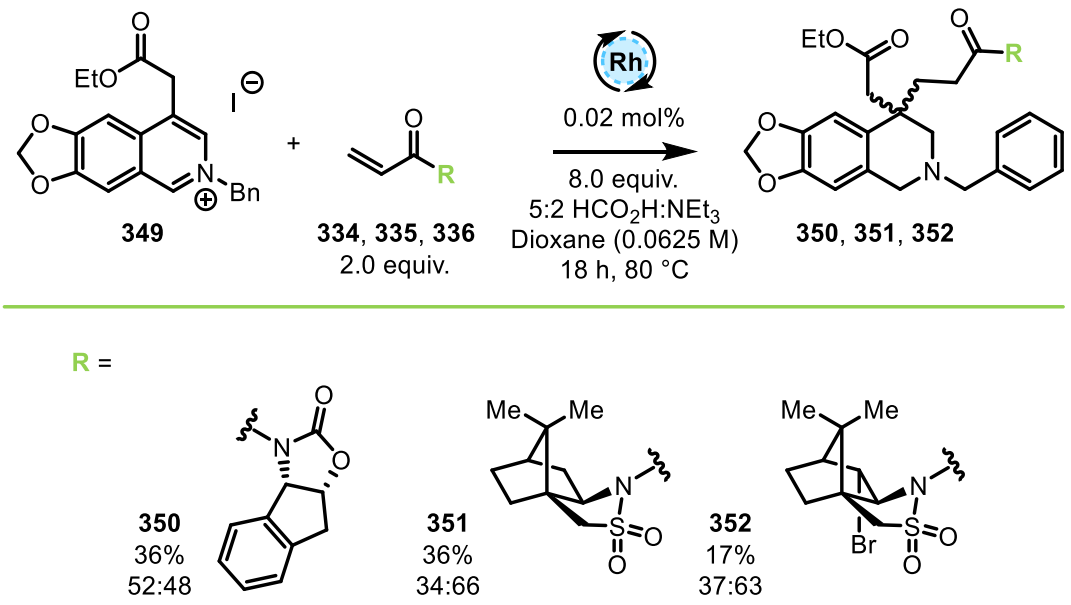
The alternative to this is that the initial conjugate addition itself is reversible, and the stereochemistry is determined by a second faster ring closure step (Scheme 6.16b).



Scheme 6.16: Two possibilities for the enantiodetermining step in the enantioselective annulation: a) Initial irreversible conjugate addition and b) Reversible addition followed by irreversible ring closure.

In order to show if the first step in enantiodetermining, a control experiment was proposed with isoquinoline **349**, which lacks a C3-methyl group (Scheme 6.17). The lack of an α-methyl group prevents the second cyclisation step from occurring, which will result in the isolation of the analogue of intermediate **320** (Scheme 6.3, Scheme 6.16). If the isolated intermediate has a d.r. similar to the e.r. produced when the electrophile is used in the annulation reaction, this suggests that the initial conjugate addition is irreversible and therefore enantiodetermining. If the product has a substantially different d.r. to the corresponding e.r. of the annulation reaction, this suggests that the initial addition is reversible and therefore the addition reaction is under thermodynamic control.

Three electrophiles (**334**, **335** and **336**) were chosen for this control experiment as the expected yield was high enough to hopefully ensure clean isolation of the product and the expected d.r. should be large enough to be noticeable by spectroscopic means (Scheme 6.17).



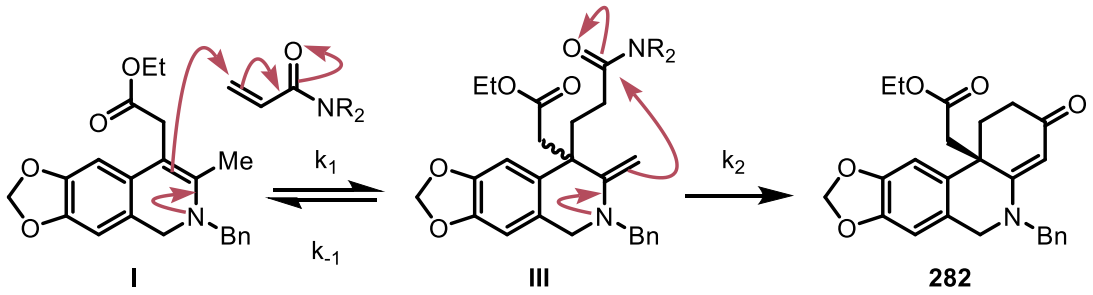
Scheme 6.17: Subjection of control compound **349** to the annulation conditions to test for the enantiodetermining step by isolating **350**, **351**, and **352**. Isolated yields are reported. d.r. determined by relative ^{1}H NMR integration of the isolated product and verified by relative ^{1}H NMR integration of the crude mixture. Reactions performed on 0.25 mmol scale.

Pleasingly, both products **351** and **352** were isolable in yields of 36% and 17% respectively. Their diastereomeric ratios were measurable by relative integration of their ^{1}H spectra and were shown to be 34:66 and 37:63 respectively. This ratio is similar to the e.r. observed in the annulation reaction (33:67), supporting the proposal that the initial conjugate addition with these two electrophiles (**335** and **336**), is both irreversible and enantiodetermining. Contrary to this conclusion, when electrophile **334** was used with substrate **349** under reductive annulation conditions, product **350** was isolated in 36% yield with a d.r. of 52:48.

Although the first two data points support our hypothesis of the initial conjugate addition being the enantiodetermining step, the possibility of our hypothesis being incorrect cannot be discounted for two reasons. **349** is a distinct substrate, and could therefore react very differently under the reductive annulation conditions. The two diastereomeric intermediates formed are again different to any intermediates formed in the reductive annulation reaction with **281** as the

substrate, therefore it is hard to assess if both diastereomers will undergo any side reactions at different rates; since they cannot cyclise fully, the two intermediates are present under the reaction conditions for significantly longer than any analogues formed in the reaction with **281**. The low yields of the products suggest that there could be side products formed which could arise from diastereoselective side reactions, which would give a false d.r. for the overall reaction.

We propose that when **334** is used as the electrophile, the departing oxazolidinone anion is sufficiently less stable to make the second step (k_2) slow (Scheme 6.18). This then implies that k_2 is the enantiodetermining step and therefore k_1 is reversible, which would account for the 52:48 d.r. observed.

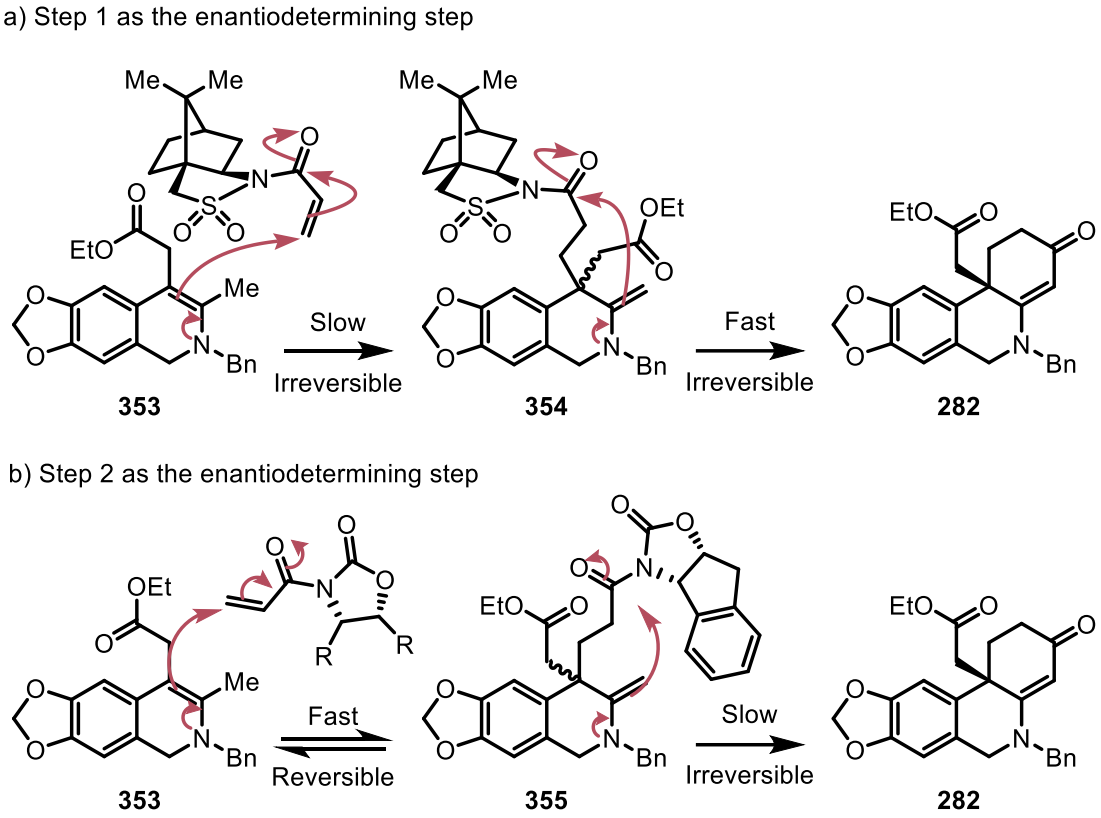


Scheme 6.18: Reductive annulation mechanism with the rates of the two steps considered.

With this theory in hand, the two potential mechanisms for the reaction are as follows (Scheme 6.19). Mechanism a) as exemplified by camphor-sultam derived electrophile **335**, involves fast substitution at the carbonyl in the second direct addition step. This then means that the initial conjugate addition is irreversible and slow in comparison, determining the reaction enantioselectivity.

Mechanism b) as exemplified by Evans auxiliary derived electrophile **334**, involves slow substitution at the carbonyl, which results in a faster reversible conjugate addition step,

generating a thermodynamic mixture of diastereomers of **355**. The final direct addition is therefore the enantiodetermining step.

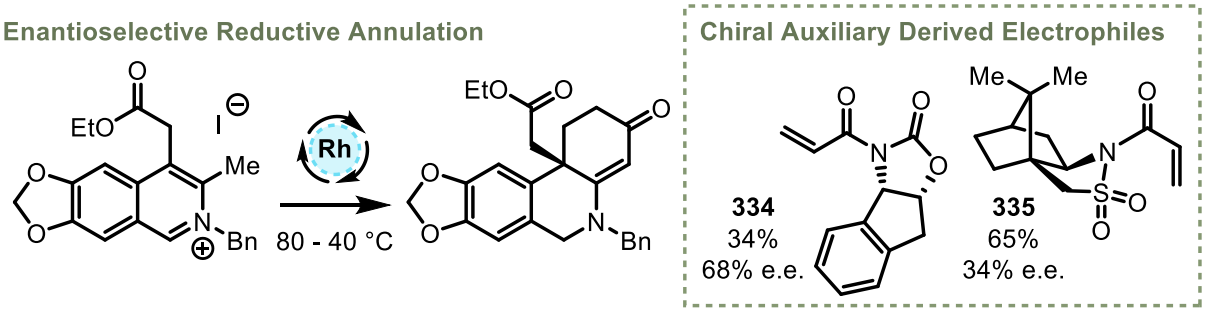


Scheme 6.19: Two possible mechanism for the reaction a) Step 1 is the enantiodetermining step with fast substitution at the carbonyl. b) Step 2 is the enantiodetermining step with slow substitution at the carbonyl.

6.6 Conclusion

In this chapter, we have made significant progress towards performing the reductive annulation reaction described in Chapter 4 as an enantioselective variant. Use of chiral auxiliaries, such as Evan's oxazolidinone and Oppolzer's camphor-sultam have enabled the development of further ambident electrophiles to effect the transformation with stereoselectivity. Optimisation of the reaction conditions and the electrophile skeleton have led to an e.e. of 68%. Investigations into the reaction mechanism have shown that the two auxiliaries mentioned

above proceed by different mechanisms, with a theory proposed that different steps in the mechanism can be enantiodetermining depending on the auxiliary used.



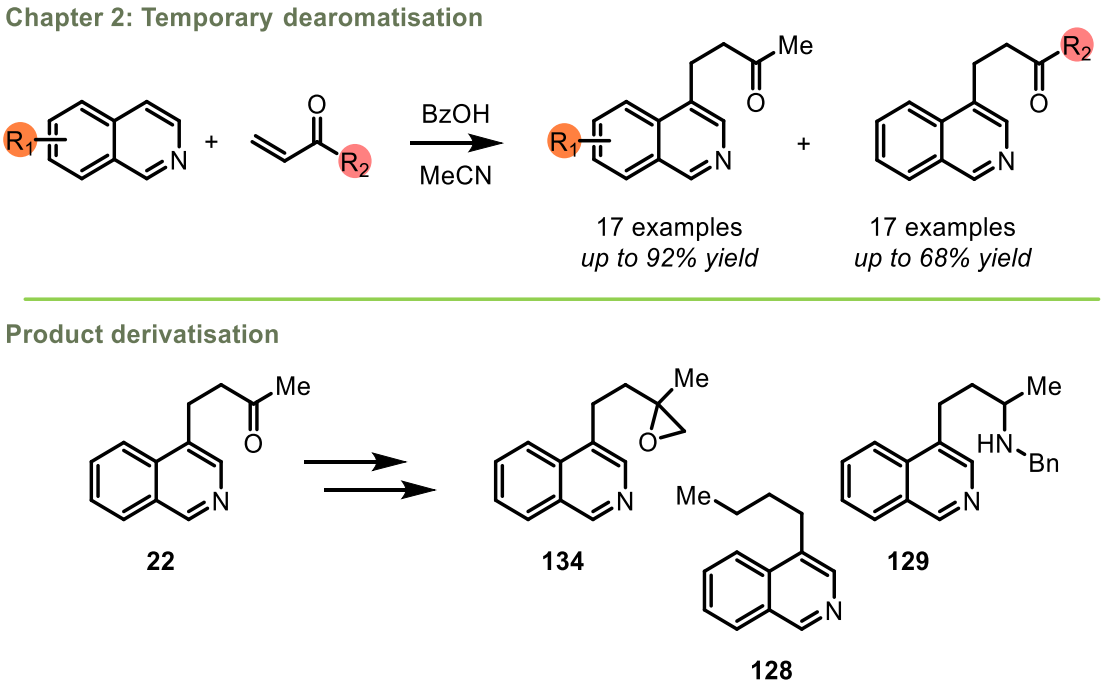
Scheme 6.20: Development of the stereoselective reductive annulation reaction.

Chapter 7 – Conclusions and Future Work

7.1 Thesis Summary

In this thesis, three distinct techniques for performing *β*-functionalisation of isoquinolines have been explored, with applications to natural product synthesis.

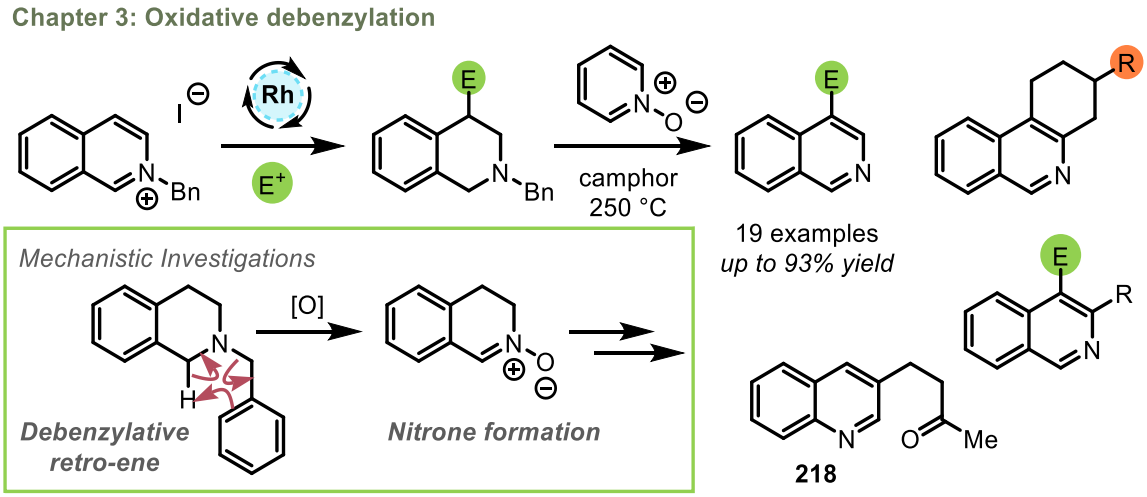
In Chapter 2, a temporary dearomatisation strategy towards the direct *β*-functionalisation of isoquinolines was explored, making use of benzoic acid as a mild activating agent. It was proposed that the acid acts as a nucleophile, dearomatising the isoquinoline substrate to reveal enamine functionality, which is then free to add into a conjugate acceptor. The scope of the reaction was explored, showing the wide range of isoquinoline functionality tolerated, and a small scope of vinyl ketones was described. Mechanistic experiments revealed that the reaction likely proceeds through the free isoquinoline.



Scheme 7.1: Temporary dearomatisation strategy towards *β*-functionalised isoquinolines.

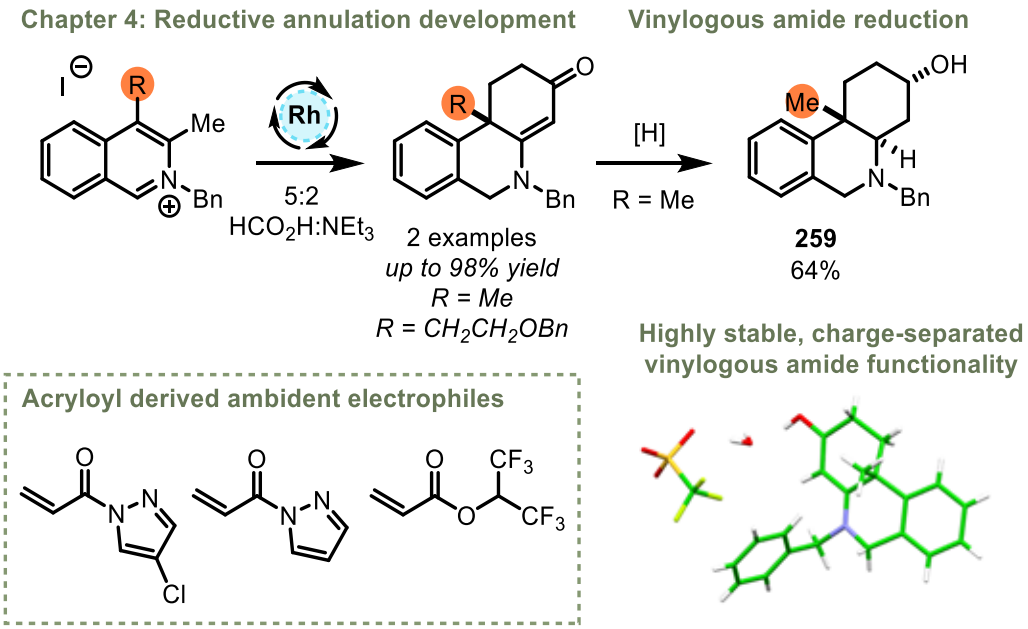
Chapter 3 detailed a different approach for achieving *β*-functionalised isoquinolines, building upon the reductive functionalisation chemistry developed previously within the group, which

provided a facile route to a wide range of *β*-functionalised THIQs. An oxidative debenzylation reaction was used to effect the required transformation, which furnished a two-step sequence to *β*-functionalised isoquinolines. A scope was explored, including both simple mono-functionalised THIQs and more complex tricyclic systems as well as extending to other types of heterocycles. Mechanistic studies indicate that the mechanism probably proceeds *via* a debenzylative retro-ene reaction followed by further oxidation.



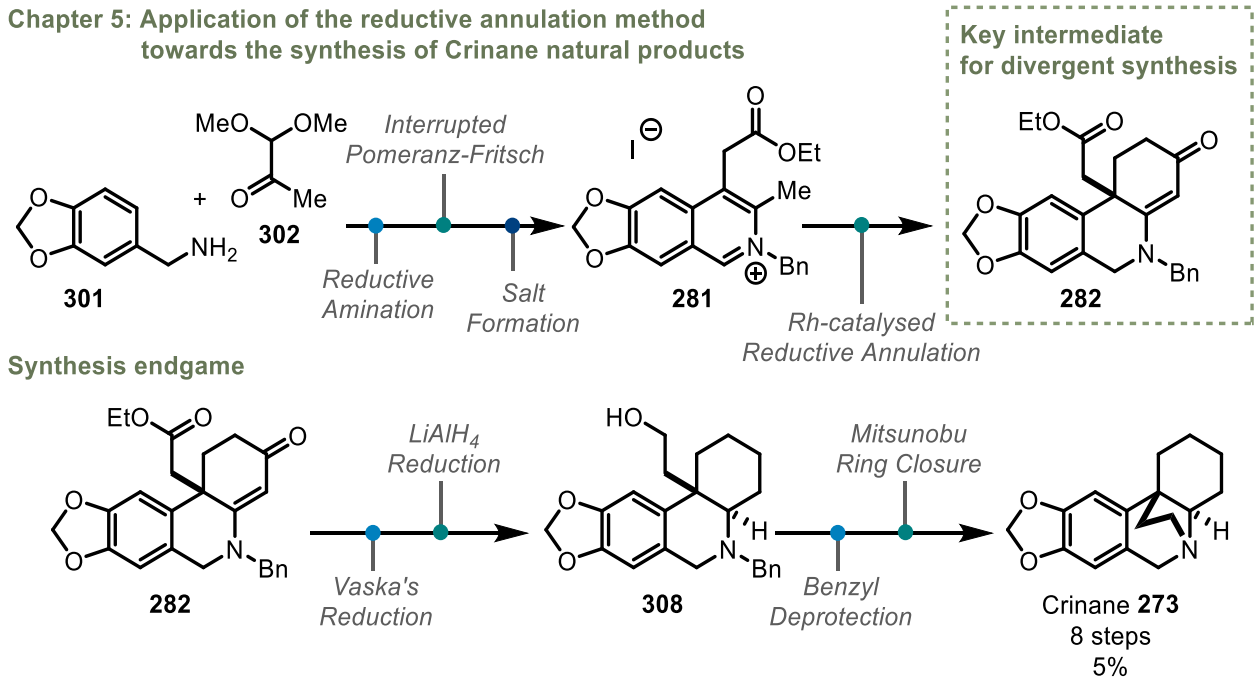
Scheme 7.2: Oxidative debenzylation strategy to synthesise *β*-functionalised isoquinolines from THIQs.

Building on the group's previous work with acidic reductive functionalisation conditions, Chapter 4 describes the development and optimisation of a reductive annulation reaction, making use of ambident electrophiles to achieve the one-pot transformation. The tricyclic vinylogous amide product was then derivatised to alcohol **259**, providing proof-of-concept that the unusual, charge-separated vinylogous amide motif was amenable to downstream functionalisation.



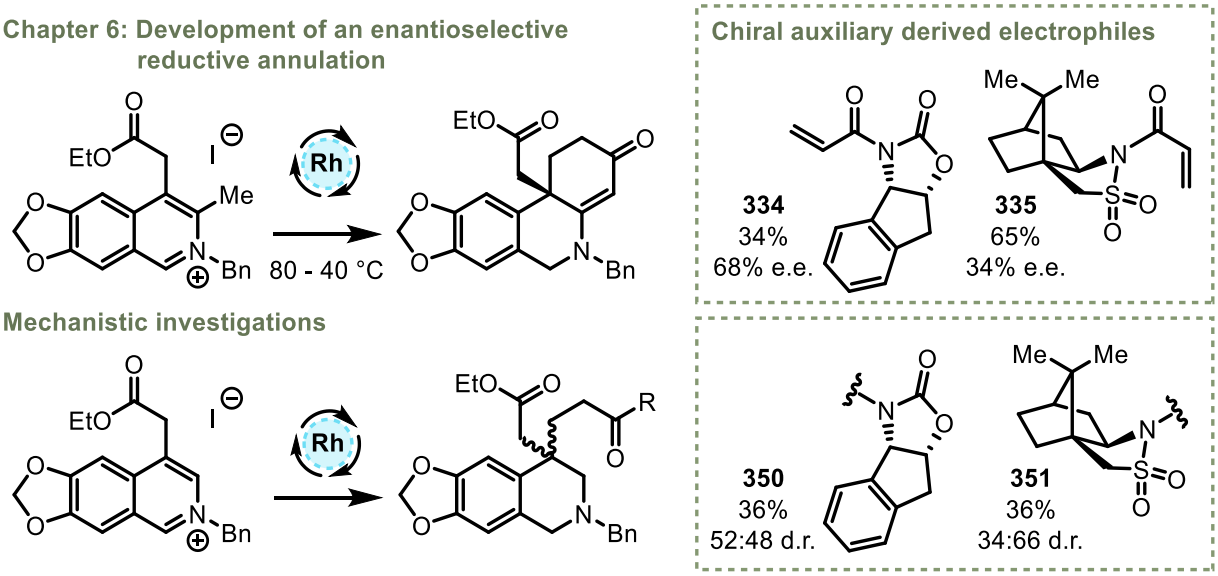
Scheme 7.3: Development of a reductive annulation reaction to produce a tricyclic THIQ skeleton.

Chapter 5 showed the application of the reductive annulation reaction developed in Chapter 4 to an electron-rich isoquinoline system, aimed towards the synthesis of the Crinane family of natural products. The synthesis of key intermediate **281** was optimised, including a reductive amination and an interrupted Pomeranz-Fritsch isoquinoline synthesis. A concise and efficient synthesis endgame subsequently afforded the family's parent compound Crinane, in eight steps and 5% overall yield. Further exploration of several alternative endgame strategies were explored to enable future syntheses of other family members.



Scheme 7.4: Application of the reductive annulation reaction to the total synthesis of the Crinane alkaloid family skeleton.

Finally, in Chapter 6 the reductive annulation reaction developed in Chapter 4 was modified in an effort to render it enantioselective. Several approaches were trialled, with the greatest success arising from the use of chiral auxiliaries in the place of the pyrazole moiety in the ambident electrophile. Various derivatives of both Evan's oxazolidinone and Oppolzer's camphor-sultam were used during the optimisation, affording varying degrees of selectivity. Preliminary mechanistic investigations were conducted using a model substrate without a C3 methyl group, thereby forcing the reaction to stop half-way. In this way, the reaction with three chiral auxiliary derived electrophiles, **334**, **335** and **336** were shown to proceed *via* distinct mechanisms with different enantiodetermining steps, which was proposed to relate to the acidity of the relevant leaving group.



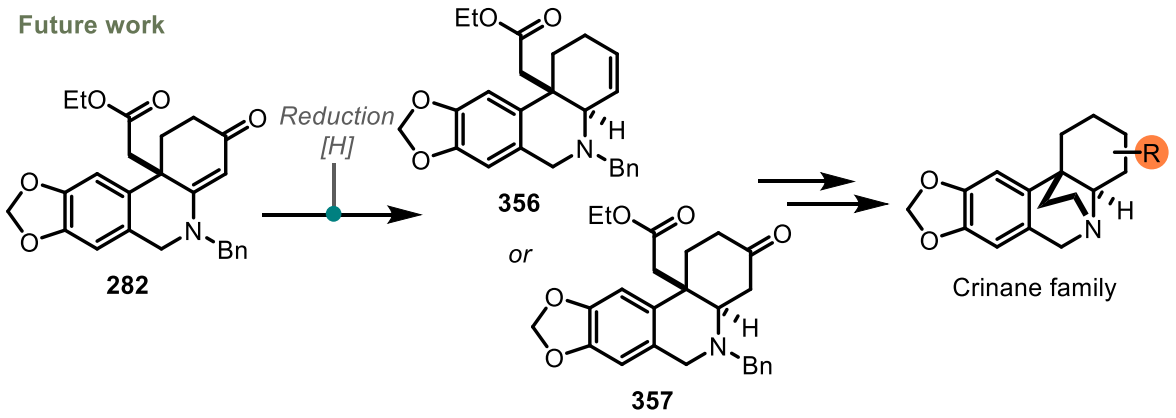
Scheme 7.5: Development of an enantioselective variant of the reductive annulation, making use of chiral auxiliary-derived electrophiles.

7.2 Future work

Due to time constraints, syntheses of other members of the Crinane family of alkaloids were not exhaustively investigated. Further optimisation of the vinylogous amide reduction could be undertaken to potentially generate more favourable intermediates, perhaps *via* an alkene reduction leaving the carbonyl intact, or perhaps a partial reduction of an elimination product, to give alkene **356** (Scheme 7.6). Either of these intermediates could then be derivatised to afford several members of the Crinane family.

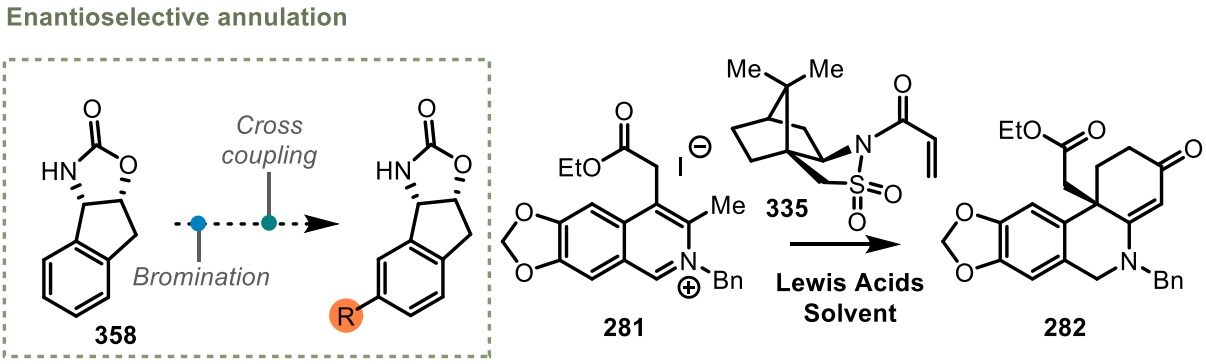
Most members of the Crinane family feature oxygenation in the C ring, a functionality currently impossible to access *via* the route described in Chapter 5. Partial reduction by some other means to form ketone **357** would be favourable, as the oxygenation site is consistent with the oxygenated members of the family. A milder reduction is therefore required to remove the amide C-C double bond without reducing the carbonyl. This was successfully achieved with a model system in Chapter 4, but regrettably when the optimised conditions were applied to amide **282**, only product decomposition was observed. This result should be pursued further,

perhaps investigating whether alternative hard hydride sources or perhaps differing solvents would allow the desired transformation to occur on vinylogous amide **282**.



Scheme 7.6: Future work optimising the vinylogous amide reduction to give more favourable intermediates, enabling syntheses of more diverse members of the Crinane family.

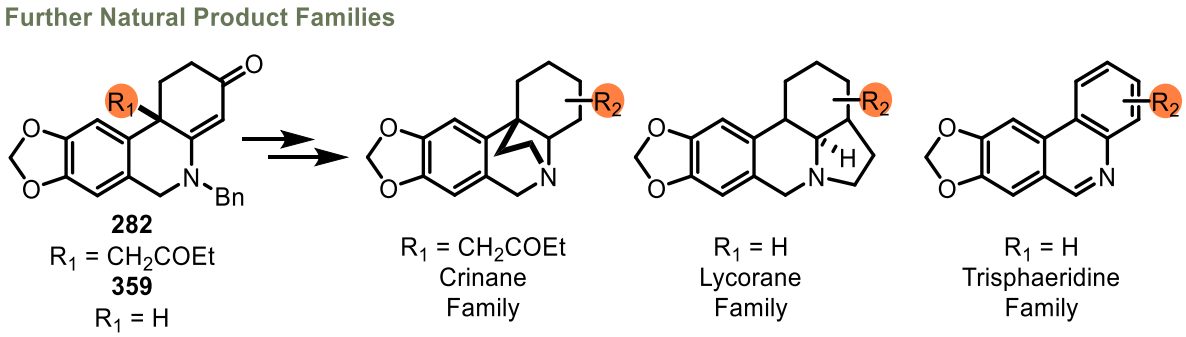
The optimisation of an enantioselective version of the reductive annulation was also curtailed due to time constraints. The selectivity of the reaction could be further optimised by exploring derivatives of electrophile **334** which achieved the highest level of selectivity to date (Scheme 7.7). The skeleton of the auxiliary is an indane motif that is often used to synthesise chiral PyBox ligands, used for transition metal catalysis. Previous investigations in the literature have shown syntheses of a number of functionalised analogues of indane-derived **358**, generated through site-selective bromination followed by palladium-catalysed cross coupling. This sequence could be used to generate a small array of larger chiral auxiliaries to explore the reaction and therefore hopefully increase the enantioselectivity. Our proposed transition state model shows that the chiral electrophile is directed towards the N and C1 atoms of the isoquinolinium salt, therefore a further aromatic substituent may stabilise the transition state by π-π interactions and thus increase selectivity.



Scheme 7.7: Future work on increasing the enantioselectivity of the reductive annulation.

Further to this, we have hypothesised that the other successful chiral electrophile, a camphor-sultam-derived species, may be reacting *via* a different mechanism. We propose that this causes the initial conjugate addition to be irreversible and enantiodetermining. The transition state for this reaction may be stabilised by co-ordination, for instance from a Lewis acid. Whilst screening solvents and Lewis acids did not previously provide a substantial improvement, altering the electrophile to **335** may afford more promising results, due to the differing hypothesised mechanisms.

Combining these two projects would enable many members of the Crinane family of natural products to be synthesised in high enantiopurity *via* a divergent route from a common intermediate. Other *Amaryllidaceae* alkaloids could also be accessed in a similar fashion (Scheme 7.8). Studies have already shown that use of a C4-unsubstituted isoquinolinium salt can lead to amide **359**, which could be further derivatised to access members of the Lycorane family. Formation of an alternative exocyclic D-ring would be required, which could be achieved post reduction using an α-carbonyl alkylation strategy.



Scheme 7.8: Further *Amaryllidaceae* natural product families that could be synthesised using a highly related divergent approach with a reductive annulation step to construct the C ring.

Similarly, the Trisphaeridine family could be accessed from amide **359**, using a global oxidation strategy. The debenzylative oxidation described in Chapter 3 could be useful in this regard, however reduction of the vinylogous amide would have to occur first, a challenge in this system that has not yet been overcome but could be targeted in future synthetic campaigns.

Chapter 8 – Experimental

8.1 General experimental details

Chemicals and solvents: Chemicals were purchased from commercial suppliers (Sigma Aldrich, Fluorochem and Alfa Aesar) and used without further purification. Solvents were dried either by filtration through activated alumina purification columns in house, or over pre-activated 4 Å molecular sieves.

Chromatography: TLC analysis was performed using pre-coated silica gel aluminium sheets (Merck TLC Silica Gel 60 F254), with spots visualised either under UV light or by staining with either a solution of $KMnO_4$, ninhydrin in acidic ethanol (ninhydrin stain), bromocresol green stain or vanillin in acidic ethanol (vanillin stain). Flash column chromatography was performed using Merck Geduran® Silica Gel 60 (40-63 μm) or (15-40 μm) using gaseous nitrogen to generate head pressure. Deactivated Silica refers to pre-basified silica: silica (400 g), pentane (250 mL), Et_2O (250 mL) and NEt_3 (5 mL) were combined in a 1 L beaker and stirred for 15 min. The solvent was allowed to evaporate overnight and the resulting silica could be stored in a sealed bottle for a few weeks.

Glassware: Reactions were carried out in standard glassware under an atmosphere of air unless stated otherwise. Microwave vials and vial caps (containing a resealing Silicone/PTFE septum) were purchased from Kinesis (Cole-Palmer) and were used without flame-drying.

Reaction Temperatures: Room temperature (r.t.) refers to 20-25 °C. Temperatures of 0 °C were obtained using an ice/water bath and temperatures of -78 °C were obtained using a dry ice/acetone bath. Temperatures elevated above r.t. were achieved using a heating block mounted on an IKA basic stirrer hotplate. Where reactions were performed in a round bottomed flask, the block took the form of a commercial Asynt DrySyn® Multi-E kit heating block. Reactions performed in a microwave vial were heated using a cuboidal aluminium block

manufactured in-house for Biotage® 5 mL glass microwave vials. The block has dimensions of 47.5 by 75.0 by 50.0 mm, with 6 bores of 17.0 mm diameter, and depth 30.0 mm.

NMR Spectroscopy: NMR spectroscopy was carried out using a Bruker 400, 500 or 600 MHz spectrometer in the deuterated solvent stated, using the residual non-deuterated solvent signal as an internal reference. The instruments used to collect NMR data were either:

AVF400 (400MHz) is a Bruker Avance III HD nanobay NMR equipped with a 9.4 T magnet. ^{1}H 400.3MHz, ^{11}B 128.4MHz, ^{19}F 376.6MHz, ^{13}C 100.7MHz, ^{31}P 162.0MHz

AVX500 is a Bruker Avance III HD NMR equipped with a 11.75 T magnet. ^{1}H 500.3 MHz, ^{13}C 125.8 MHz, ^{31}P 202.5 MHz, ^{19}F 470.8 MHz, ^{11}B 60.5 MHz

NEO600 is a Bruker NEO 600 with broadband helium cryoprobe equipped with a 14.1 T magnet. ^{1}H 600.4MHz ^{13}C 151.0MHz, ^{19}F 565.0 MHz, ^{31}P 243.1 MHz, ^{11}B 192.6 MHz, ^{29}Si 119.3 MHz

AV600 is a Bruker Avance III HD 600 with BB-F/1H Prodigy nitrogen cryoprobe equipped with a 14.1 T magnet. ^{1}H 600.2MHz ^{13}C 150.9MHz, ^{31}P 243.0 MHz

AV700 is a Bruker Avance III 700 with a 1H(13C/15N) inverse TCI cryoprobe equipped with a 16.44 T magnet. ^{1}H 699.9MHz, ^{13}C 176,0MHz, ^{15}N 70.9MHz

Chemical shifts, δ, are recorded to the nearest 0.01 ppm (^{1}H NMR) or 0.1 ppm (^{13}C NMR) and referenced to residual solvent peaks. Splitting patterns are classified as a singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), hextet (h), heptet (hept), multiplet (m) or combinations thereof. Chemical shifts and splitting patterns were recorded as observed and left uncorrected for fidelity purposes. ^{1}H NMR yields were calculated by using 0.33 equiv. of 1,3,5-trimethoxy benzene as an internal standard, added to the crude reaction mixture after work up and concentration *in vacuo*. Quantitative ^{1}H NMR spectra were recorded using a Bruker AVIII HD 400 Spectrometer with a 25 s relaxation time and samples measured in $CDCl_3$.

Mass Spectrometry: LRMS were obtained using an Agilent 6120 Quadrupole LC-MS spectrometer with electro spray ionisation conditions (ESI). HRMS were recorded on a Thermo Exactive orbitrap spectrometer equipped with a Waters Equity LC system, with a flow rate of 0.2 mL/min using water:methanol:formic acid (10:89.9:0.1) as eluent. The system uses a heated electrospray ionisation (HESI-II) probe for ESI^+ and has a resolution of 50,000 FWHM under conditions for maximum sensitivity, with an accuracy of better than 5 ppm for 24 h following external calibration on the day of analysis. The mass reported is that containing the most abundant isotopes, with each value rounded to 4 decimal places and within 5 ppm of the calculated mass.

HPLC: Reverse phase HPLC yields were obtained using a Dionex UltiMate 3000 system equipped with UV-Vis variable wavelength detector, fitted with an Agilent InfinityLab Poroshell 120 EC-C18 column (0.46 cm x 150 mm, 4 μm pore size). 2-Naphthol was used as an internal standard, with 1.0 equiv. added after work up and concentration *in vacuo*.

Chiral SFC (supercritical fluid chromatography): separations were conducted on a Waters Acquity UPC2 system using Waters Empower software. Chiralpak® columns (150 x 3 mm, particle size 3 μm) were used as specified in the text. Solvents used were of HPLC grade (Fisher Scientific, Sigma Aldrich or Rathburn).

X-Ray Diffraction: Single crystal X-ray data collection and structure determination were performed by Timothy C. Jenkins in the Chemistry Research Laboratory, University of Oxford. Crystals were mounted on MiTeGen loops using perfluoropolyether oil and rapidly transferred to a goniometer head on a diffractometer fitted with an Oxford CryoSystems CryoStream open-flow nitrogen cooling device.[122] Data collections were carried out at 150 K using an (Rigaku) Oxford Diffraction Supernova A diffractometer using mirror-monochromated Cu Kα radiation (λ = 1.54184 Å) and data were processed using

CryAlisPro. The structure was solved using charge-flipping algorithm (SUPERFLIP) and refined by full-matrix least squares using CRYSTALS.[123-125] Structures are visualised and represented using Mercury.

Melting Point and IR Data: Melting points were measured using a Gallenkamp Griffin melting point apparatus. Fourier Transform Infrared (FTIR) spectra were recorded using a Bruker Tensor 27 spectrometer with absorption maxima quoted in wavenumbers (cm^{-1}).

Compound Numbering and Structure Depiction: Chiral compounds and images depicting chiral compounds refer to racemic mixtures unless stated otherwise. Compounds were numbered using Perkin Elmer ChemDraw software, numbering is for the purpose of assignment only and does not correspond to formal compound numbering patterns.

8.2 General Procedures

General Procedure A:

The corresponding isoquinoline (0.125 mmol, 1.00 equiv.) was placed in a 2 mL vial with benzoic acid (46 mg, 0.38 mmol, 3.0 equiv.), MVK (41 μL, 0.50 mmol, 4.0 equiv.) and a stirrer bar. The mixture was dissolved in acetonitrile (0.1 mL) and stirred at 80 $^{\circ}$C for 18 h. The reaction mixture was diluted with CH_2Cl_2 and washed with sat. aq. Na_2CO_3. The aqueous layer was extracted twice more with CH_2Cl_2 then the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

General Procedure B:

The corresponding isoquinoline (0.25 mmol, 1.0 equiv.) was placed in a 2 mL vial with benzoic acid (92 mg, 0.75 mmol, 3.0 equiv.), the corresponding electrophile (1.0 mmol, 4.0 equiv.) and a stirrer bar. The mixture was dissolved in acetonitrile (0.2 mL) and stirred at 100 $^{\circ}$C for 18 h. The reaction mixture was diluted with CH_2Cl_2 and washed with sat. aq. Na_2CO_3. The aqueous layer was extracted twice more with CH_2Cl_2 then the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*.

General Procedure C: According to a procedure reported by Donohoe and co-workers:[23] Benzyl isoquinolinium iodide (170 mg, 0.50 mmol, 1.0 equiv.) was dissolved in MeCN (0.40 mL) with 5:2 HCO_2H:NEt_3 (0.17 mL, 2.0 mmol, 4.0 equiv.) and an electrophile (0.50 mmol, 1.0 equiv.). The solution was heated to 80 °C for 18 h, cooled to r.t., diluted with CH_2Cl_2, and washed with sat. aq. Na_2CO_3. The layers were partitioned, the aqueous layer washed twice with CH_2Cl_2, the organic layers combined, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

General Procedure D: Tetrahydroisoquinoline (0.25 mmol, 1.0 equiv.) was placed in a microwave vial with pyridine-*N*-oxide (36 mg, 0.38 mmol, 1.5 equiv.) and camphor (0.20 g, 1.3 mmol, 5.3 equiv.), sealed, heated to 250 °C for 40 min then cooled to r.t.

N.B. For this project, when the reactions were performed in a sealed vessel, a blast shield was used for safety purposes, although it is worth noting that no reactions exploded, uncontrollably released their contents or otherwise failed during the reaction time. When MeCN was used as the reaction solvent, the PTFE seal in the microwave cap swelled and hardened, indicating a significant build-up of pressure, but did not fail. When camphor was used as the solvent, no such deformation was observed. The height of the microwave vial above the aluminium block used to provide heat allowed the vial itself to act as a reflux condenser, with the camphor visibly condensing on the walls of the vial above the block and dripping back down into the reaction. Mitigating factor were adopted to minimise the risk of any reaction seal failing, such as using only intact, undamaged microwave vials, use of a blast shield and cooling the reaction vials fully before opening. When the reaction was performed at 270 °C, the reaction was incompatible with a balloon, as the glue bonding the metal needle to its plastic mounting repeatedly failed. Subsequently, reactions performed at 270 °C were done so in a sealed vessel in the absence of a balloon.

General Procedure E:

Isoquinoline was dissolved in acetone (0.2 M) with BnI (1.2 equiv.) and stirred at 60 °C for 18 h. The mixture was cooled to r.t. then the suspension triturated with Et_2O and the precipitate filtered off.

General Procedure F:

Following a procedure reported by Czekelius and co-workers:[126] Acrylic acid (0.70 mL, 10 mmol, 1.4 equiv.) was dissolved in anhydrous THF (30 mL) and cooled to -20 °C. NEt_3

(2.60 mL, 18.5 mmol, 2.50 equiv.) was added dropwise, followed by acryloyl chloride (0.80 mL, 9.5 mmol, 1.3 equiv.), then the reaction was stirred at -20 °C for 2.5 h. LiCl (370 mg, 8.76 mmol, 1.20 equiv.) and a chiral auxiliary (7.3 mmol, 1.0 equiv.) were added, then the reaction was allowed to warm to r.t. overnight. The reaction was quenched by addition of excess 0.2 M HCl, then the crude reaction mixture was concentrated to remove excess THF. The mixture was then diluted with EtOAc and H_2O, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc, then the combined organic extracts washed once each with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

General Procedure G:

Ethyl 2-(7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate **280** (546 mg, 2.00 mmol, 1.00 equiv.) was dissolved in acetone (20 mL) with a benzyl iodide and stirred at 60 °C overnight. After cooling to r.t. the mixture was triturated with Et_2O until a precipitate was observed. The precipitate was filtered under vacuum then dried *in vacuo*.

General Procedure H:

Ethyl 2-(7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate **280** (546 mg, 2.00 mmol, 1.00 equiv.) was placed in a vial with K_2CO_3 (276 mg, 2.00 mmol, 1.00 equiv.) and an alcohol (20 mmol, 10 equiv.) then heated to 135 °C with stirring for 18 h. Upon cooling to r.t. the reaction was diluted with EtOAc and H_2O, shaken and the layers partitioned. The aqueous layer was extracted twice with EtOAc then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

General Procedure I:

0.25 mmol scale:

An isoquinolinium iodide (0.25 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (3.75 mL) with 1-(4-chloro-1H-pyrazol-1-yl)prop-2-en-1-one **252** (78 mg, 0.50 mmol, 2.0 equiv.), 5:2 HCO_2H:NEt_3 (0.17 mL, 2.0 mmol, 8.0 equiv.) and an aliquot of a premade solution of $(RhCp^*Cl)_2$ in 1,4-dioxane (0.25 mL, 0.020 mol%, 3.1 mg in 25 mL) was added. The mixture was stirred at 80 °C for 18 h, then cooled, diluted with EtOAc, washed with sat. aq. Na_2CO_3 and the layers partitioned. The aqueous layer was extracted twice with EtOAc then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

0.10 mmol scale:

An isoquinolinium iodide (0.10 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (1.5 mL) with 1-(4-chloro-1H-pyrazol-1-yl)prop-2-en-1-one **252** (32 mg, 0.20 mmol, 2.0 equiv.), 5:2 HCO_2H:NEt_3 (0.07 mL, 0.8 mmol, 8 equiv.) and an aliquot of a premade solution of $(RhCp^*Cl)_2$ in 1,4-dioxane (0.10 mL, 0.020 mol%, 3.1 mg in 25 mL) was added. The mixture was stirred at 80 °C for 18 h, then cooled, diluted with EtOAc, washed with sat. aq. Na_2CO_3 and the layers partitioned. The aqueous layer was extracted twice with EtOAc then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

General Procedure J:

0.25 mmol scale:

An isoquinolinium iodide (0.25 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (3.75 mL) with (3aS,8aR)-3-acryloyl-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazol-2-one **334** (115 mg,

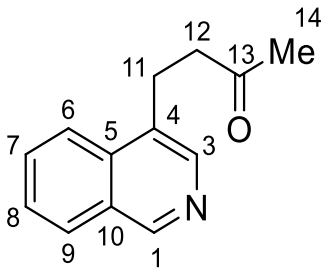
0.5 mmol, 2.0 equiv.), 5:2 HCO_2H:NEt_3 (0.17 mL, 2.0 mmol, 8.0 equiv.) and an aliquot of a premade solution of $(RhCp^*Cl)_2$ in 1,4-dioxane (0.25 mL, 0.020 mol%, 3.1 mg in 25 mL) was added. The mixture was stirred at 80 °C for 18 h, then cooled, diluted with EtOAc, washed with sat. aq. Na_2CO_3 and the layers partitioned. The aqueous layer was extracted twice with EtOAc then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

0.10 mmol scale:

An isoquinolinium iodide (0.10 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (1.5 mL) with (3aS,8aR)-3-acryloyl-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazol-2-one **334** (46 mg, 0.20 mmol, 2.0 equiv.), 5:2 HCO_2H:NEt_3 (0.07 mL, 0.8 mmol, 8 equiv.) and an aliquot of a premade solution of $(RhCp^*Cl)_2$ in 1,4-dioxane (0.10 mL, 0.020 mol%, 3.1 mg in 25 mL) was added. The mixture was stirred at 80 °C for 18 h, then cooled, diluted with EtOAc, washed with sat. aq. Na_2CO_3 and the layers partitioned. The aqueous layer was extracted twice with EtOAc then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

8.3 Experimental data for Chapter 2

4-(Isoquinolin-4-yl)butan-2-one (22):



The title compound was prepared using **General Procedure A** with isoquinoline (16 mg, 0.13 mmol, 1.0 equiv.). Purification by flash column chromatography (5% acetone in Et_2O) afforded **22** as a pale-yellow oil (17 mg, 66%).

4-(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one **157** (37.0 mg, 0.125 mmol, 1.00 equiv.) was placed in a microwave vial with pyridine-*N*-oxide (18 mg, 0.19 mmol, 1.5 equiv.) and camphor (0.20 g), sealed with a crimped cap, heated to 250 °C for 40 min then cooled to r.t. Purification by flash column chromatography (60-80% EtOAc in pentane) afforded **22** as a pale-yellow oil (17 mg, 69%).

For experiments conducted with a non-air headspace, the microwave vial was charged with reactants, sealed with a crimped cap, then attached to a vacuum manifold *via* a needle. The reaction vial was evacuated and backfilled with the replacement gas three times. After the last backfill the needle was removed, then the reaction was heated, cooled and purified as above.

4-(2-(4-Nitrobenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one **163** (85 mg, 0.25 mmol, 1.0 equiv.) was added to a microwave vial with pyridine-*N*-oxide (36 mg, 0.38 mmol, 1.5 equiv.) and camphor (0.2 g), sealed with a crimped cap and heated to 250 °C for 40 min. After cooling to r.t. purification by flash column chromatography (60-80% EtOAc in pentane) afforded **22** as a pale-yellow oil (22 mg, 45%).

4-(2-(4-Methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one **164** (81 mg, 0.25 mmol, 1.0 equiv.) was added to a microwave vial with pyridine-*N*-oxide (36 mg, 0.38 mmol, 1.5 equiv.) and camphor (0.2 g), sealed with a crimped cap and heated to 250 °C for 40 min. After cooling to r.t. purification by flash column chromatography (60-80% EtOAc in pentane) afforded **22** as a pale-yellow oil (22 mg, 44%).

4-(2-(Naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one **165** (86 mg, 0.25 mmol, 1.0 equiv.) was added to a microwave vial with pyridine-*N*-oxide (36 mg, 0.38 mmol, 1.5 equiv.) and camphor (0.2 g), sealed with a crimped cap and heated to 250 °C for 40 min. After cooling to r.t. purification by flash column chromatography (60-80% EtOAc in pentane) afforded **22** as a pale-yellow oil (33 mg, 67%).

2-Benzyl-4-(3-oxobutyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide **162** (77 mg, 0.25 mmol, 1.0 equiv.) was added to a microwave vial with pyridine-*N*-oxide (36 mg, 0.38 mmol, 1.5 equiv.) and camphor (0.2 g), sealed with a crimped cap and heated to 250 °C for 40 min. After cooling to r.t. purification by flash column chromatography (60-80% EtOAc in pentane) afforded **22** as a pale-yellow oil (16 mg, 33%).

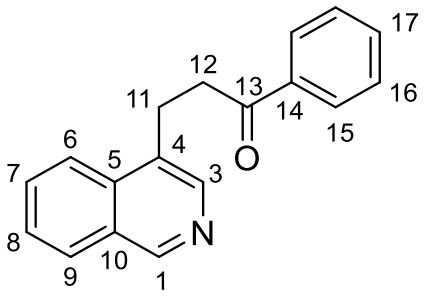
4-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one **172** (54 mg, 0.25 mmol, 1.0 equiv.) was added to a microwave vial with pyridine-*N*-oxide (36 mg, 0.38 mmol, 1.5 equiv.) and camphor (0.2 g), sealed with a crimped cap and heated to 250 °C for 40 min. After cooling to r.t. purification by flash column chromatography (60-80% EtOAc in pentane) afforded **22** as a pale-yellow oil (9.5 mg, 19%).

4-(2-Allyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one **173** (61 mg, 0.25 mmol, 1.0 equiv.) was added to a microwave vial with pyridine-*N*-oxide (36 mg, 0.38 mmol, 1.5 equiv.) and camphor (0.2 g), sealed with a crimped cap and heated to 250 °C for 40 min. After cooling to

r.t. purification by flash column chromatography (60-80% EtOAc in pentane) afforded **22** as a pale-yellow oil (6.5 mg, 13%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.12 (1H, s, H_1), 8.37 (1H, s, H_3), 7.99 – 7.91 (2H, m, H_6, H_9), 7.72 (1H, dddt, *J* = 8.2, 6.9, 2.5, 1.3 Hz, H_7), 7.59 (1H, dddt, *J* = 8.1, 6.9, 2.4, 1.2 Hz, H_8), 3.28 (2H, td, *J* = 7.7, 3.3 Hz, H_{11}), 2.87 (2H, td, *J* = 7.8, 2.9 Hz, H_{12}), 2.16 (3H, s, H_{14}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 207.2 (C_{13}), 151.6 (C_1), 142.5 (C_3), 134.4 (C_5), 130.5 (C_7), 130.2 (C_4), 128.5 (2C, C_9, C_{10}), 127.0 (C_8), 122.6 (C_6), 44.0 (C_{12}), 30.1 (C_{14}), 23.7 (C_{11}); **IR** (neat) cm^{-1}: 1713, 1653, 1623, 1585, 1504, 1411, 1391, 1366, 1293, 1231, 1165, 1109, 902, 882, 785, 754; **HRMS** (ESI^+) m/z calcd. for $C_{13}H_{14}NO$ $[M+H]^+$ 200.1070; found at 200.1067 Δ - 1.50 ppm. Spectroscopic data were consistent with the literature data for this compound.[127]

3-(Isoquinolin-4-yl)-1-phenylpropan-1-one (45):

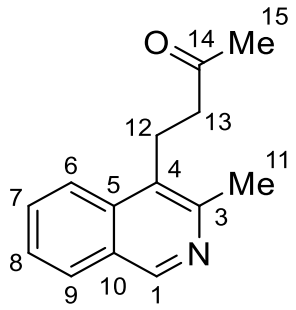


The title compound was prepared using **General Procedure B** with isoquinoline (16 mg, 0.125 mmol, 1.0 equiv.) and phenyl vinyl ketone **23** (66 μL, 0.50 mmol, 4.0 equiv.). Purification by flash column chromatography (80% Et_2O in pentane) afforded **45** as a pale-yellow solid (5.9 mg, 18%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.15 (1H, s, H_1), 8.46 (1H, s, H_3), 8.03 (1H, d, *J* = 8.5 Hz, H_6), 8.00 (1H, d, *J* = 8.2 Hz, H_9), 7.98 – 7.93 (2H, m, H_{15}), 7.75 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz, H_7), 7.62 (1H, ddd, *J* = 8.1, 6.8, 1.1 Hz, H_8), 7.59 – 7.53 (1H, m, H_{17}), 7.48 – 7.42 (2H, m, H_{16}), 3.54 – 3.46 (2H, m, H_{11}, H_{11}'), 3.46 – 3.40 (2H, m, H_{12}, H_{12}'); **^{13}C NMR** (151 MHz, $CDCl_3$):

δ_C = 198.8 (C_{13}), 151.8 (C_1), 142.9 (C_3), 136.8 (C_{14}), 134.6 (C_5), 133.4 (C_{17}), 130.7 (C_7), 130.5 (C_4), 128.8 (C_{16}), 128.6 (2C,C_9, C_{10}), 128.2 (C_{15}), 127.1 (C_8), 122.8 (C_6), 39.4 (C_{12}), 24.3 (C_{11}); **IR** (neat) cm^{-1}: 2917, 1684, 1623, 1597, 1503, 1449, 1364, 1296, 1226, 1205, 976, 887, 786, 743, 690, 664, 650, 647, 638, 626, 606, 601; **HRMS** (ESI^+) m/z calc. for $C_{18}H_{16}NO$ $[M+H]^+$ 262.1226; found at 262.1222 Δ -1.53 ppm; **m.p.** = 101-102 °C.

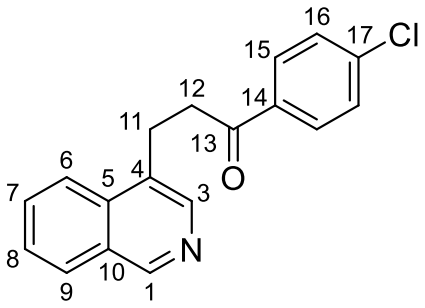
4-(3-Methylisoquinolin-4-yl)butan-2-one (93):



The title compound was prepared using **General Procedure A** with 3-methyl isoquinoline (18.0 mg, 0.125 mmol, 1.00 equiv.) and MVK (41 μL, 0.5 mmol, 4.0 equiv.). Purification by flash column chromatography (5% acetone in Et_2O) afforded **93** as a pale-brown oil (19 mg, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.05 (1H, s, H_1), 7.96 – 7.85 (2H, m, H_6, H_9), 7.68 (1H, ddd, *J* = 8.4, 6.8, 1.4 Hz, H_7), 7.52 (1H, ddd, *J* = 8.0, 6.8, 1.1 Hz, H_8), 3.35 – 3.26 (H, m, H_{12}), 2.79 – 2.71 (2H, m, H_{13}), 2.70 (3H, s, H_{11}), 2.19 (3H, s, H_{15}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 207.7 (C_{14}), 150.5 (C_1), 149.3 (C_3), 135.0 (C_5), 130.6 (C_7), 128.5 (C_9), 127.4 (C_{10}), 126.9 (C_4), 126.0 (C_8), 122.3 (C_6), 43.3 (C_{13}), 30.1 (C_{15}), 22.3 (C_{11}), 22.0 (C_{12}); **IR** (neat) cm^{-1}: 2980, 2360, 2342, 1712, 1623, 1577, 1501, 1446, 1422, 1362, 1286, 1247, 1162, 1027, 916, 886, 786, 752; **HRMS** (ESI^+) m/z calc. for $C_{14}H_{16}NO$ $[M+H]^+$ 214.1226; found at 214.1224 Δ -0.93 ppm.

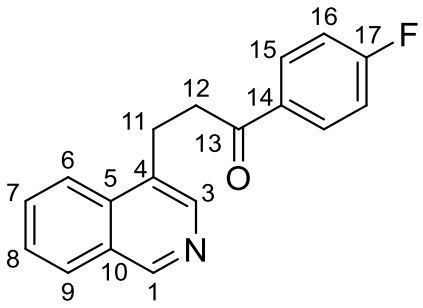
1-(4-Chlorophenyl)-3-(isoquinolin-4-yl)propan-1-one (54):



The title compound was prepared using **General Procedure A** with isoquinoline (32 mg, 0.25 mmol, 1.0 equiv.) and 1-(4-chlorophenyl)prop-2-en-1-one **53** (170 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **54** as a pale-brown solid (27 mg, 37%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.14 (1H, s, H_1), 8.44 (1H, s, H_3) 8.02 – 7.97 (2H, m, H_6, H_9), 7.88 (2H, d, *J* = 1.6 Hz, H_{15}), 7.74 (1H, ddd, *J* = 8.4, 6.8, 1.4 Hz, H_7), 7.61 (1H, ddd, *J* = 8.0, 6.9, 1.2 Hz, H_8), 7.41 (2H, d, *J* = 1.5 Hz, H_{16}), 3.47 (2H, dd, *J* = 8.7, 6.6 Hz, H_{11}), 3.38 (2H, dd, *J* = 9.0, 6.7 Hz, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 197.5 (C_{13}), 151.8 (C_1), 142.8 (C_3), 139.8 (C_{17}), 135.0 (C_{14}), 134.5 (C_5), 130.7 (C_7), 130.3 (C_4), 129.5 (C_{15}), 129.1 (C_{16}), 128.6 (C_9), 128.6 (C_{10}), 127.1 (C_8), 122.6 (C_6), 39.3 (C_{12}), 24.2 (C_{11}); **IR** (neat) cm^{-1}: 1684, 1622, 1588, 1571, 1504, 1488, 1452, 1399, 1362, 1339, 1362, 1339, 1297, 1262, 1226, 1204, 1176, 1148, 1091, 1051, 1013, 978, 933, 888, 838, 820, 799, 785, 750, 731; **HRMS** (ESI^+) m/z calc. for $C_{18}H_{15}{}^{35}ClNO$ $[M+H]^+$ 296.0837; found at 296.0836 Δ -0.34 ppm; **m.p.** = 96-98 °C.

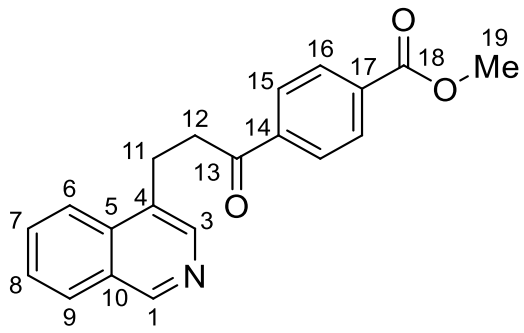
1-(4-Fluorophenyl)-3-(isoquinolin-4-yl)propan-1-one (56):



The title compound was prepared using **General Procedure B** with isoquinoline (32 mg, 0.25 mmol, 1.0 equiv.) and 1-(4-fluorophenyl)prop-2-en-1-one **55** (150 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **56** as a pale-brown solid (18 mg, 25%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.15 (1H, s, H_1), 8.45 (1H, s, H_3), 8.05 – 7.93 (4H, m, H_6, H_9, H_{15}), 7.77 – 7.71 (1H, m, H_7), 7.66 – 7.58 (1H, m, H_8), 7.10 (2H, ddt, *J* = 9.0, 6.7, 1.2 Hz, H_{16}), 3.48 (2H, t, *J* = 7.6 Hz, H_{11}), 3.39 (2H, ddd, *J* = 9.9, 6.8, 1.2 Hz, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 197.2 (C_{13}), 165.9 (d, *J* = 255.4 Hz, C_{17}), 151.8 (C_1), 142.8 (C_3), 134.6 (C_5), 133.2 (d, *J* = 3.0 Hz, C_{14}), 130.8 (d, *J* = 9.3 Hz, C_{15}), 130.7 (C_7), 130.4 (C_4), 128.6 (2C, C_9, C_{10}), 127.2 (C_8), 122.7 (C_6), 115.9 (d, *J* = 21.8 Hz, C_{16}), 39.3 (C_{12}), 24.2 (C_{11}); **^{19}F NMR** (377 MHz, $CDCl_3$): δ_F = -104.84 (tt, *J* = 8.4, 5.4 Hz); **IR** (neat) cm^{-1}: 1684, 1622, 1598, 1505, 1410, 1364, 1300, 1227, 1204, 1157, 1099, 979, 889, 842, 801, 784, 751, 701, 616; **HRMS** (ESI^+) m/z calc. for $C_{18}H_{15}FNO$ $[M+H]^+$ 280.1132; found at 280.1132 Δ 0.00 ppm; **m.p.** = 93-94 °C.

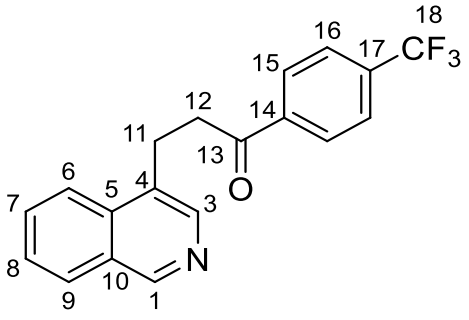
Methyl 4-(3-(isoquinolin-4-yl)propanoyl)benzoate (58):



The title compound was prepared using **General Procedure B** with isoquinoline (32 mg, 0.25 mmol, 1.0 equiv.) and methyl 4-acryloylbenzoate **57** (190 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **58** as an orange solid (18 mg, 23%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.15 (1H, s, H_1), 8.46 (1H, s, H_3), 8.12 – 8.07 (2H, m, H_{15}), 8.04 – 7.97 (4H, m, H_6, H_9, H_{16}), 7.78 – 7.72 (1H, m, H_7), 7.65 – 7.60 (1H, m, H_8), 3.93 (3H, s, H_{19}), 3.53 – 3.47 (2H, m, H_{11}), 3.45 (2H, dd, *J* = 8.4, 6.4 Hz, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 198.3 (C_{13}), 166.3 (C_{18}), 151.9 (C_1), 142.8 (C_3), 139.9 (C_{14}), 134.6 (C_5), 134.2 (C_{17}), 130.7 (C_7), 130.2 (C_4), 130.0 (C_{15}), 128.7 (C_9), 128.6 (C_{10}), 128.1 (C_{16}), 127.2 (C_8), 122.7 (C_6), 52.6 (C_{19}), 39.8 (C_{12}), 24.1 (C_{11}); **IR** (neat) cm^{-1}: 1674, 1600, 1511, 1259, 1171, 1029, 911, 839, 733; **HRMS** (ESI$^+$) m/z calc. for $C_{20}H_{18}NO_3$ $[M+H]^+$ 320.1281; found at 320.1277 Δ -1.25 ppm; **m.p.** = 124-125 °C.

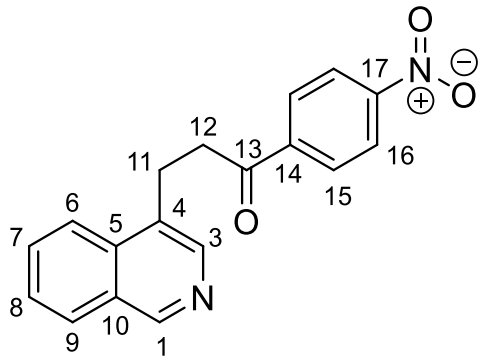
3-(Isoquinolin-4-yl)-1-(4-(trifluoromethyl)phenyl)propan-1-one (60):



The title compound was prepared using **General Procedure B** with isoquinoline (32 mg, 0.25 mmol, 1.0 equiv.) and 1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **59** (200 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **60** as a pale-yellow solid (40 mg, 48%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.14 (1H, s, H_1), 8.45 (1H, s, H_3), 8.03 (2H, d, *J* = 8.0 Hz, H_{15}), 8.01 – 7.97 (2H, m, H_6, H_9), 7.74 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz, H_7), 7.71 – 7.66 (2H, m, H_{16}), 7.61 (1H, ddd, *J* = 7.9, 6.8, 1.1 Hz, H_8), 3.49 (2H, ddd, *J* = 8.5, 6.5, 1.7 Hz, H_{11}), 3.43 (2H, ddd, *J* = 8.4, 6.7, 1.7 Hz, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 197.8 (C_{13}), 151.9 (C_1), 142.9 (C_3), 139.3 (C_{14}), 135.0 – 134.1 (2C, m, C_5, C_{17}), 130.7 (C_7), 130.1 (C_4), 128.6 (C_9, 128.6 (C_{10}), 128.5 (C_{15}), 127.2 (C_8), 125.8 (q, *J* = 3.7 Hz, C_{16}), 123.5 (q, *J* = 272.5 Hz, C_{18}), 122.6 (C_6), 39.6 (C_{12}), 24.0 (C_{11}); **^{19}F NMR** (377 MHz, $CDCl_3$): δ_F = -63.13; **IR** (neat) cm^{-1}: 1694, 1412, 1331, 1202, 1119, 1107, 1070, 988, 844, 772, 750, 731; **HRMS** (ESI^+) m/z calc. for $C_{19}H_{15}F_3NO$ $[M+H]^+$ 330.1100; found at 330.1099 Δ -0.40 ppm; **m.p.** = 136-138 °C .

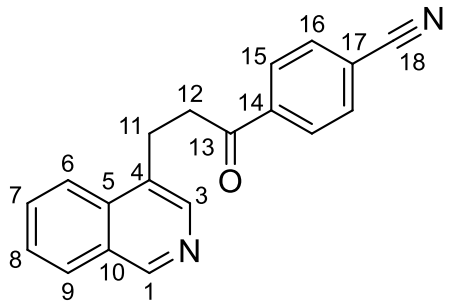
3-(Isoquinolin-4-yl)-1-(4-nitrophenyl)propan-1-one (62):



The title compound was prepared using **General Procedure B** with isoquinoline (32 mg, 0.25 mmol, 1.0 equiv.) and 1-(4-nitrophenyl)prop-2-en-1-one **61** (180 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **62** as a pale-orange solid (23 mg, 30%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.18 (1H, s, H_1), 8.48 (1H, s, H_3), 8.27 (2H, d, *J* = 8.7 Hz, H_{16}), 8.08 (2H, d, *J* = 8.7 Hz, H_{15}), 8.03 – 7.98 (2H, m, H_6, H_9), 7.79 – 7.73 (1H, m, H_7), 7.66 – 7.58 (1H, m, H_8), 3.55 – 3.44 (4H, m, H_{11}, H_{11}', H_{12}, H_{12}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 197.2 (C_{13}), 152.0 (C_1), 150.5 (C_{17}), 142.9 (C_3), 141.1 (C_{14}), 134.5 (C_5), 130.8 (C_7), 130.0 (C_4), 129.2 (C_{15}), 128.7 (C_9), 127.3 (C_8), 124.0 (C_{16}), 122.5 (C_6), 39.9 (C_{12}), 24.0 (C_{11}), C_{10} was not observed; **IR** (neat) cm^{-1}: 1691, 1603, 1523, 1346, 1319, 1200, 982, 855, 786, 740, 687, 603; **HRMS** (ESI^+) m/z calc. for $C_{18}H_{15}N_2O_3$ $[M+H]^+$ 307.1077; found at 307.1073 Δ -1.30 ppm; **m.p.** = 139-142 °C.

4-(3-(Isoquinolin-4-yl)propanoyl)benzonitrile (64):

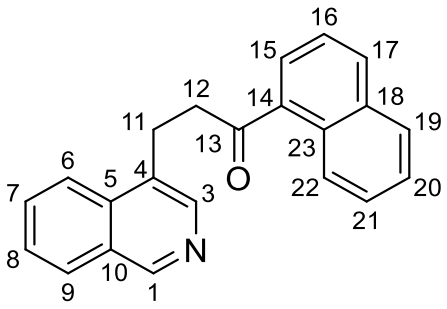


The title compound was prepared using **General Procedure B** with isoquinoline (32 mg, 0.25 mmol, 1.0 equiv.) and 4-acryloylbenzonitrile **63** (160 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **64** as an off-white solid (18 mg, 25%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.15 (1H, s, H_1), 8.45 (1H, s, H_3), 8.04 – 7.97 (4H, m, H_6, H_9, H_{15}), 7.78 – 7.70 (3H, m, H_7, H_{16}), 7.63 (1H, t, *J* = 7.5 Hz, H_8), 3.53 – 3.47 (2H, m, H_{11}), 3.46 – 3.40 (2H, m, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 197.4 (C_{13}), 151.9 (C_1), 142.8 (C_3), 139.6 (C_{18}), 134.5 (C_5), 132.7 (C_{16}), 130.8 (C_7), 129.9 (C_4), 128.7 (C_9), 128.6 (2C, C_{15}, C_{10}), 127.3 (C_8), 122.5 (C_6), 117.9 (C_{14}), 116.7 (C_{17}), 39.7 (C_{12}), 24.0 (C_{11}); **IR** (neat) cm^{-1}: 2229, 1690, 1439, 1402, 1370, 1340, 1295, 1262, 1225, 1017, 981, 911, 885, 845, 799, 751;

HRMS (ESI^+) m/z calc. for $C_{19}H_{15}N_2O$ $[M+H]^+$ 287.1179; found at 287.1178 Δ 0.35 ppm; **m.p.** = melted with decomposition at 156 °C.

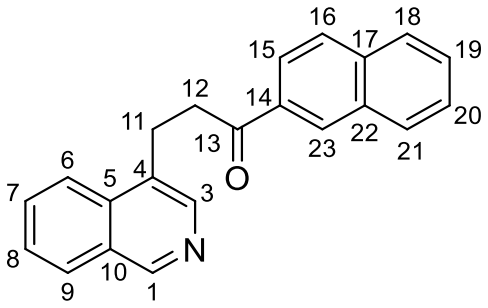
3-(Isoquinolin-4-yl)-1-(naphthalen-1-yl)propan-1-one (66):



The title compound was prepared using **General Procedure B** with isoquinoline (32 mg, 0.25 mmol, 1.0 equiv.) and 1-(naphthalen-1-yl)prop-2-en-1-one **65** (180 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **66** as an orange oil (15 mg, 19%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.17 (1H, *br*.s, H_1), 8.65 (1H, dd, *J* = 8.5, 1.2 Hz, H_{22}), 8.49 (1H, *br*.s, H_3), 8.06 (1H, d, *J* = 8.5 Hz, H_6), 8.03 – 7.96 (2H, m, H_9, H_{17}), 7.88 (1H, dt, *J* = 8.1, 1.0 Hz, H_{19}), 7.84 (1H, dd, *J* = 7.2, 1.2 Hz, H_{15}), 7.76 (1H, ddd, *J* = 8.4, 6.8, 1.3 Hz, H_7), 7.66 – 7.49 (2H, m, H_8, H_{21}), 7.54 (1H, ddd, *J* = 8.1, 6.8, 1.2 Hz, H_{20}), 7.46 (1H, dd, *J* = 8.2, 7.2 Hz, H_{16}), 3.62 – 3.54 (2H, m, H_{11}), 3.54 – 3.49 (2H, m, H_{12}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 202.9 (C_{13}), 151.8 (C_1), 142.8 (C_3), 135.6 (C_{14}), 134.6 (C_5), 134.1 (C_{18}), 133.1 (C_{17}), 130.7 (C_7), 130.5 (C_4), 130.3 (C_{23}), 128.6 (3C, C_9, C_{10}, C_{19}), 128.2 (C_{21}), 127.8 (C_{15}), 127.2 (C_8), 126.7 (C_{20}), 125.9 (C_{22}), 124.5 (C_{16}), 122.8 (C_6), 42.7 (C_{12}), 24.8 (C_{11}); **IR** (neat) cm^{-1}:1679, 1622, 1507, 1229, 1173, 1098, 909, 800, 779, 732; **HRMS** (ESI^+) m/z calc. for $C_{22}H_{18}NO$ $[M+H]^+$ 312.1383; found at 312.1378 Δ -1.61 ppm.

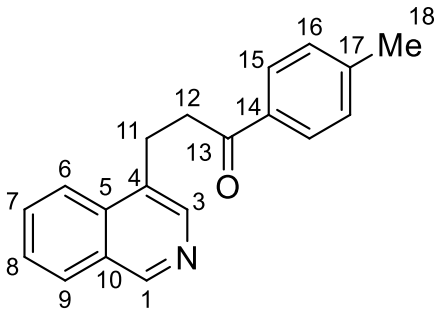
3-(Isoquinolin-4-yl)-1-(naphthalen-2-yl)propan-1-one (68):



The title compound was prepared using **General Procedure B** with isoquinoline (32 mg, 0.25 mmol, 1.0 equiv.) and 1-(naphthalen-2-yl)prop-2-en-1-one **67** (180 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **68** as an orange solid (29 mg, 37%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.16 (1H, s, H_1), 8.50 (1H, s, H_3), 8.46 – 8.41 (1H, m, H_{23}), 8.06 (1H, d, *J* = 8.5 Hz, H_6), 8.03 (1H, dd, *J* = 8.6, 1.8 Hz, H_{15}), 7.99 (1H, d, *J* = 8.2 Hz, H_9), 7.94 – 7.88 (2H, m, H_{16}, H_{21}), 7.85 (1H, d, *J* = 8.2 Hz, H_{18}), 7.75 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz, H_7), 7.62 (1H, ddd, *J* = 8.0, 6.8, 1.0 Hz, H_8), 7.58 (1H, ddd, *J* = 8.2, 6.8, 1.2 Hz, H_{19}), 7.52 (1H, ddd, *J* = 8.1, 6.9, 1.3 Hz, H_{20}), 3.54 (4H, s, H_{11}, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 198.7 (C_{13}), 151.8 (C_1), 142.8 (C_3), 135.7 (C_{17}), 134.6 (C_5), 134.1 (C_{14}), 132.6 (C_{22}), 130.6 (C_7), 130.6 (C_{10}), 129.8 (C_{23}), 129.6 (C_{21}), 128.6 (2C, C_{16}, C_{19}), 128.6 (2C, C_4, C_9), 127.9 (C_{18}), 127.1 (C_8), 126.9 (C_{20}), 123.8 (C_{15}), 122.8 (C_6), 39.5 (C_{12}), 24.4 (C_{11}); **IR** (neat) cm^{-1}: 1679, 1625, 1300, 1184, 1123, 1020, 910, 862, 748; **HRMS** (ESI^+) m/z calc. for $C_{22}H_{18}NO$ $[M+H]^+$ 312.1383; found at 312.1380 Δ -0.95 ppm; **m.p.** = 92-93 °C.

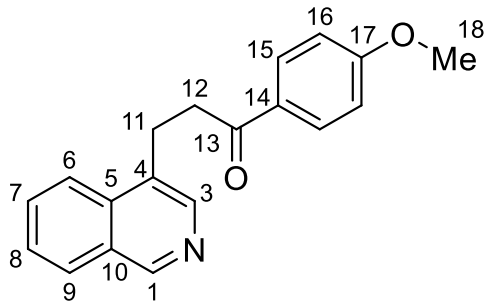
3-(Isoquinolin-4-yl)-1-(*p*-tolyl)propan-1-one (70):



The title compound was prepared using **General Procedure B** with isoquinoline (32 mg, 0.25 mmol, 1.0 equiv.) and 1-(*p*-tolyl)prop-2-en-1-one **69** (150 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **70** as a brown solid (11 mg, 16%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.15 (1H, s, H_1), 8.46 (1H, s, H_3), 8.03 (1H, d, *J* = 8.5 Hz, H_6), 8.01 – 7.97 (1H, m, H_9), 7.88 – 7.83 (2H, m, H_{15}), 7.74 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz, H_7), 7.62 (1H, ddd, *J* = 8.1, 6.8, 1.1 Hz, H_8), 7.24 (2H, d, *J* = 8.0 Hz, H_{16}), 3.48 (2H, dd, *J* = 9.0, 6.5 Hz, H_{11}), 3.39 (2H, dd, *J* = 9.3, 6.7 Hz, H_{12}), 2.40 (3H, s, H_{18}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 198.5 (C_{13}), 151.8 (C_1), 144.2 (C_{17}), 142.8 (C_3), 134.6 (C_5), 134.3 (C_{14}), 130.6 (2C, C_4, C_7), 129.5 (C_{16}), 128.6 (C_{10}), 128.6 (C_9), 128.3 (C_{15}), 127.1 (C_8), 122.8 (C_6), 39.3 (C_{12}), 24.4 (C_{11}), 21.8 (C_{18}); **IR** (neat) cm^{-1}: 1680, 1607, 1503, 1409, 1362, 1298, 1262, 1227, 1203, 1181, 1019, 974, 889, 798, 752, 700; **HRMS** (ESI^+) m/z calc. for $C_{19}H_{18}NO$ $[M+H]^+$ 276.1383; found at 276.1382 Δ -0.36 ppm; **m.p.** = 96-97 °C.

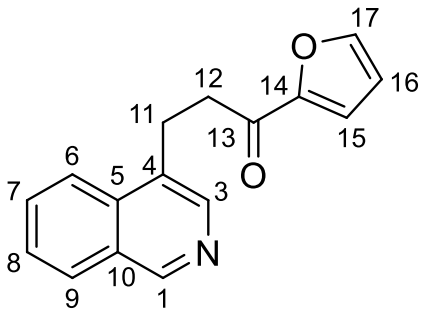
3-(Isoquinolin-4-yl)-1-(4-methoxyphenyl)propan-1-one (72):



The title compound was prepared using **General Procedure B** with isoquinoline (32 mg, 0.25 mmol, 1.0 equiv.) and 1-(4-methoxyphenyl)prop-2-en-1-one **71** (160 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **72** as an orange solid (7.0 mg, 9%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.15 (1H, s, H_1), 8.46 (1H, s, H_3), 8.04 (1H, d, *J* = 8.5 Hz, H_6), 8.02 – 7.98 (1H, m, H_9), 7.97 – 7.91 (2H, m, H_{15}), 7.75 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz, H_7), 7.62 (1H, ddd, *J* = 8.0, 6.8, 1.1 Hz, H_8), 6.95 – 6.89 (2H, m, H_{16}), 3.86 (3H, s, H_{18}), 3.48 (2H, dd, *J* = 9.1, 6.5 Hz, H_{11}), 3.41 – 3.34 (2H, m, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 197.4 (C_{13}), 163.8 (C_{17}), 151.7 (C_1), 142.8 (C_3), 134.7 (C_5), 130.7 (C_4), 130.7 (C_7), 130.5 (C_{15}), 129.9 (C_{14}), 128.6 (C_{10}), 128.6 (C_9), 127.1 (C_8), 122.8 (C_6), 114.1 (C_{16}), 55.6 (C_{18}), 39.1 (C_{12}), 24.5 (C_{11}); **IR** (neat) cm^{-1}: 1674, 1600, 1511, 1420, 1308, 1258, 1210, 1171, 1029, 911, 839, 733; **HRMS** (ESI^+) m/z calc. for $C_{19}H_{18}NO_2$ $[M+H]^+$ 292.1332; found at 292.1331 Δ -0.34 ppm; **m.p.** = 66-69 °C.

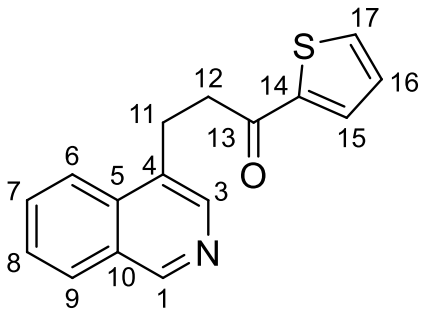
1-(Furan-2-yl)-3-(isoquinolin-4-yl)propan-1-one (76):



The title compound was prepared using **General Procedure B** with isoquinoline (32 mg, 0.25 mmol, 1.0 equiv.) and 1-(furan-2-yl)prop-2-en-1-one **75** (120 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **76** as an orange solid (42 mg, 68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.11 (1H, s, H_1), 8.42 (1H, s, H_3), 8.01 (1H, d, *J* = 8.5 Hz, H_6), 7.96 (1H, d, *J* = 8.2 Hz, H_9), 7.72 (1H, ddd, *J* = 8.4, 6.9, 1.3 Hz, H_7), 7.59 (1H, ddd, *J* = 8.0, 6.8, 1.1 Hz, H_8), 7.54 (1H, d, *J* = 1.7 Hz, H_{17}), 7.15 (1H, d, *J* = 3.6 Hz, H_{15}), 6.49 (1H, dd, *J* = 3.5, 1.7 Hz, H_{16}), 3.43 (2H, dd, *J* = 8.9, 6.8 Hz, H_{11}), 3.25 (2H, dd, *J* = 8.9, 6.8 Hz, H_{12}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 188.0 (C_{13}), 152.5 (C_{14}), 151.7 (C_1), 146.5 (C_{17}), 142.7 (C_3), 134.5 (C_5), 130.6 (C_7), 130.1 (C_4), 128.5 (C_9), 128.5 (C_{10}), 127.1 (C_8), 122.7 (C_6), 117.2 (C_{15}), 112.4 (C_{16}), 39.0 (C_{12}), 24.1 (C_{11}); **IR** (neat) cm^{-1}:1672, 1623, 1585, 1504, 1468, 1394, 1364, 1306, 1268, 1230, 1162, 1108, 1085, 1047, 1021, 978, 907, 883, 862, 755, 698; **HRMS** (ESI^+) m/z calc. for $C_{16}H_{14}NO_2$ $[M+H]^+$ 252.1019; found at 252.1019 Δ 0.00 ppm; **m.p.** = 71-72 °C.

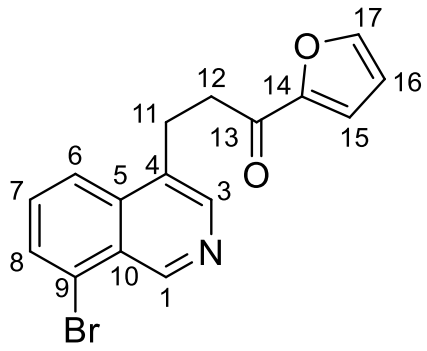
3-(Isoquinolin-4-yl)-1-(thiophen-2-yl)propan-1-one (78):



The title compound was prepared using **General Procedure B** with isoquinoline (32 mg, 0.25 mmol, 1.0 equiv.) and 1-(thiophen-2-yl)prop-2-en-1-one **77** (140 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **78** as an orange solid (26 mg, 39%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.14 (1H, s, H_1), 8.44 (1H, s, H_3), 8.05 – 8.00 (1H, m, H_6), 7.98 (1H, dd, *J* = 8.1, 1.3 Hz, H_9), 7.74 (1H, ddd, *J* = 8.6, 6.9, 1.4 Hz, H_7), 7.65 (1H, dt, *J* = 4.0, 1.2 Hz, H_{15}), 7.63 – 7.59 (2H, m, H_8, H_{17}), 7.12 – 7.06 (1H, m, H_{16}), 3.48 (2H, dd, *J* = 8.8, 6.8 Hz, H_{11}), 3.34 (2H, dd, *J* = 10.1, 5.6 Hz, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 191.7 (C_{13}), 151.8 (C_1), 144.0 (C_{14}), 142.8 (C_3), 134.5 (C_5), 133.9 (C_{17}), 132.0 (C_{15}), 130.7 (C_7), 130.2 (C_4), 128.6 (C_9), 128.5 (C_{10}), 128.2 (C_{16}), 127.1 (C_8), 122.7 (C_6), 40.0 (C_{12}), 24.5 (C_{11}); **IR** (neat) cm^{-1}: 1660, 1622, 1585, 1569, 1518, 1505, 1452, 1415, 1392, 1355, 1301, 1263, 1231, 1209, 1173, 1148, 1108, 1082, 1060, 1021, 933, 905, 889, 858, 796, 785, 726; **HRMS** (ESI^+) m/z calc. for $C_{16}H_{14}NOS$ $[M+H]^+$ 268.0791; found at 268.0790 Δ -0.37 ppm; **m.p.** = 70-71 °C.

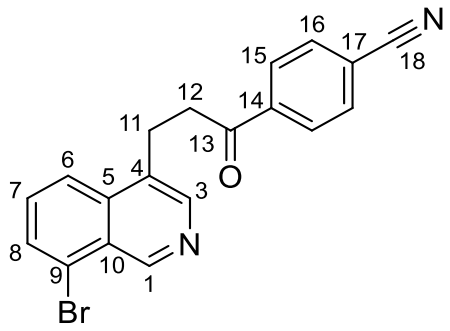
3-(8-Bromoisoquinolin-4-yl)-1-(furan-2-yl)propan-1-one (111):



The title compound was prepared using **General Procedure A** with 8-bromo isoquinoline (52 mg, 0.25 mmol, 1.0 equiv.) and 1-(furan-2-yl)prop-2-en-1-one **75** (120 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **111** as an off-white solid (19 mg, 23%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.54 (1H, s, H_1), 8.53 (1H, s, H_3), 8.02 (1H, d, *J* = 8.5 Hz, H_6), 7.85 (1H. d, *J* = 7.4 Hz, H_8), 7.60 – 7.55 (2H, m, H_7, H_{17}), 7.18 (1H, d, *J* = 3.6 Hz, H_{15}), 6.53 (1H, dd, *J* = 3.6, 1.7 Hz, H_{16}), 3.47 (2H, dd, *J* = 8.7, 6.9 Hz, H_{11}), 3.27 (2H, dd, *J* = 8.8, 6.9 Hz, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 187.8 (C_{13}), 152.6 (C_{14}), 151.3 (C_1), 146.6 (C_{17}), 143.9 (C_3), 136.2 (C_5), 131.3 (C_8), 130.9 (C_7), 129.9 (C_4), 126.8 (C_{10}), 123.7 (C_9), 122.7 (C_6), 117.3 (C_{15}), 112.5 (C_{16}), 39.1 (C_{12}), 24.1 (C_{11}); **IR** (neat) cm^{-1}: 1674, 1611, 1568, 1550, 1468, 1393, 1362, 1304, 1266, 1227, 1162, 1085, 1015, 979, 883, 809, 762; **HRMS** (ESI^+) m/z calc. for $C_{16}H_{13}NO_2{}^{79}Br$ $[M+H]^+$ 330.0124; found at 330.0123 Δ -0.30 ppm; **m.p.** = melted with decomposition at 145 °C.

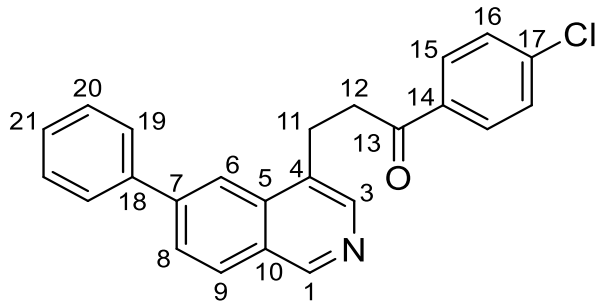
4-(3-(8-Bromoisoquinolin-4-yl)propanoyl)benzonitrile (112):



The title compound was prepared using **General Procedure A** with 8-bromo isoquinoline (52 mg, 0.25 mmol, 1.0 equiv.) and 4-acryloylbenzonitrile **63** (160 mg, 1.0 mmol, 4.0 equiv.). Purification by flash column chromatography (1% Acetone in Et_2O) afforded **112** as an off-white solid (29 mg, 31%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.55 (1H, s, H_1), 8.54 (1H, s, H_3), 8.04 – 8.00 (2H, m, H_{15}), 7.98 (1H, dt, *J* = 8.5, 1.0 Hz, H_8), 7.87 (1H, dd, *J* = 7.4, 1.0 Hz, H_6), 7.78 – 7.74 (2H, m, H_{16}), 7.58 (1H, dd, *J* = 8.5, 7.4 Hz, H_7), 3.51 (2H, t, *J* = 7.2 Hz, H_{11}), 3.43 (2H, dd, *J* = 8.2, 6.4 Hz, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 197.1 (C_{13}), 151.5 (C_1), 143.9 (C_3), 139.5 (C_{18}), 136.1 (C_5), 132.7 (C_{16}), 131.4 (C_6), 131.0 (C_7), 129.6 (C_4), 128.6 (C_{15}), 126.8 (C_{10}), 123.8 (C_9), 122.5 (C_8), 117.9 (C_{14}), 116.8 (C_{17}), 39.6 (C_{12}), 23.9 (C_{11}); **IR** (neat) cm^{-1}: 1697, 1609, 1552, 1494, 1436, 1407, 1394, 1372, 1304, 1263, 1227, 1202, 990, 854, 840, 812, 768, 745; **HRMS** (ESI^+) m/z calc. for $C_{19}H_{14}N_2O^{79}Br$ $[M+H]^+$ 365.0284; found at 365.0283 Δ -0.27 ppm; **m.p.** = melted with decomposition at 198 °C.

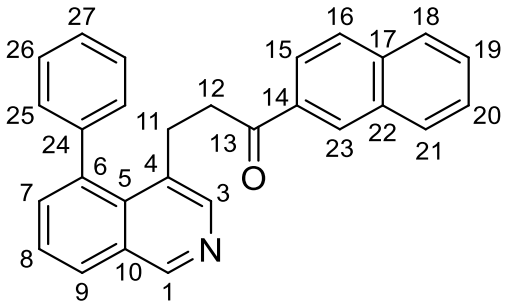
1-(4-Chlorophenyl)-3-(6-phenylisoquinolin-4-yl)propan-1-one (116):



The title compound was prepared according to **General Procedure A** using 6-phenyl isoquinoline (26.0 mg, 0.125 mmol, 1.00 equiv.) and 1-(4-chlorophenyl)prop-2-en-1-one **53** (84 mg, 0.50 mmol, 4.0 equiv.). Purification by flash column chromatography (0.5% Acetone in Et_2O) afforded **116** as a colourless solid (14 mg, 31%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.17 (1H, s, H_1), 8.48 (1H, s, H_3), 8.14 (1H, d, *J* = 1.7 Hz, H_6), 8.07 (1H, d, *J* = 8.4 Hz, H_9), 7.92 – 7.85 (3H, m, H_8, H_{15}), 7.73 – 7.68 (2H, m, H_{19}), 7.52 (2H, t, *J* = 7.6 Hz, H_{20}), 7.44 (1H, t, *J* = 7.4 Hz, H_{21}), 7.41 (2H, d, *J* = 8.5 Hz, H_{16}), 3.54 (2H, t, *J* = 7.7 Hz, H_{11}), 3.42 (2H, dd, *J* = 8.7, 6.7 Hz, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 197.6 (C_{13}), 151.6 (C_1), 143.6 (C_7), 143.2 (C_3), 140.6 (C_{20}), 139.9 (C_{17}), 135.1 (C_{14}), 134.9 (C_5), 130.5 (C_4), 129.6 (C_{15}), 129.2 (C_{20}), 129.2 (C_9), 129.1 (C_{16}), 128.4 (C_{21}), 127.9 (C_{19}), 127.6 (C_{10}), 127.1 (C_8), 120.5 (C_6), 39.4 (C_{12}), 24.3 (C_{11}); **IR** (neat) cm^{-1}: 1685, 1623, 1588, 1488, 1454, 1401, 1360, 1297, 1224, 1204, 1177, 1092, 1013, 979, 893, 822, 760, 734, 698; **HRMS** (ESI^+) m/z calc. for $C_{24}H_{19}NO^{35}Cl$ $[M+H]^+$ 372.1150; found at 372.1157 Δ 1.9 ppm; **m.p.** = 153 °C.

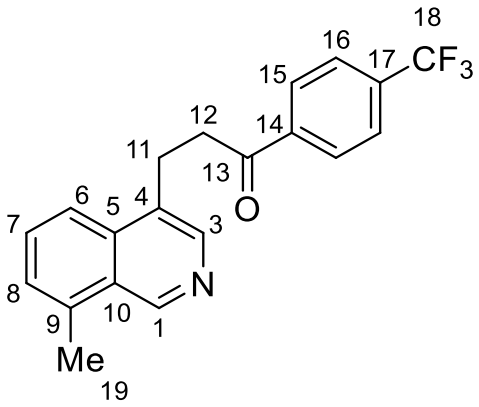
1-(Naphthalen-2-yl)-3-(5-phenylisoquinolin-4-yl)propan-1-one (117):



The title compound was prepared according to **General Procedure A** using 5-phenyl isoquinoline (26.0 mg, 0.125 mmol, 1.00 equiv.) and 1-(naphthalen-2-yl)prop-2-en-1-one **67** (180 mg, 0.50 mmol, 4.0 equiv.). Purification by flash column chromatography (0.5% Acetone in Et_2O) afforded **117** as an off-white solid (12 mg, 24%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.21 (1H, s, H_1), 8.41 (1H, s, H_3), 8.22 (1H, d, *J* = 1.3 Hz, H_{23}), 8.03 (1H, dd, *J* = 8.1, 1.4 Hz, H_9), 7.88 (1H, d, *J* = 8.2 Hz, H_{21}), 7.86 (1H, d, *J* = 7.6 Hz, H_{18}), 7.84 – 7.83 (2H, m, H_{15}, H_{16}), 7.63 (1H, dd, *J* = 8.1, 7.0 Hz, H_8), 7.58 (2H, ddd, *J* = 8.1, 6.8, 1.3 Hz, H_{19}), 7.54 (1H, dd, *J* = 4.3, 1.4 Hz, H_7), 7.54 – 7.51 (1H, m, H_{20}), 7.38 – 7.31 (3H, m, H_{25}, H_{27}), 7.30 – 7.26 (2H, m, H_{26}), 3.06 – 3.00 (2H, m, H_{12}), 2.96 – 2.90 (2H, m, H_{11}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 198.2 (C_{13}), 152.7 (C_1), 145.6 (C_3), 142.7 (C_{24}), 139.2 (C_6), 135.6 (C_{17}), 134.2 (2C, C_7, C_{14}), 132.9 (C_5), 132.6 (C_{22}), 131.6 (C_4), 129.9 (C_{10}), 129.6 (C_{21}), 129.4 (C_{23}), 129.3 (C_{25}), 128.9 (C_9), 128.5 (2C, C_{16}, C_{19}), 128.2 (C_{26}), 127.9 (2C, C_{18}, C_{27}), 126.9 (C_{20}), 126.1 (C_8), 123.9 (C_{15}), 40.7 (C_{12}), 27.1 (C_{11}); **IR** (neat) cm^{-1}: 3058, 1682, 1627, 1580, 1496, 1468, 1443, 1406, 1384, 1369, 1323, 1303, 1283, 1183, 1155, 1123, 1074, 979, 942, 912, 893, 863, 826, 826, 797, 764, 705, 668, 655, 643, 629, 610; **HRMS** (ESI^+) m/z calc. for $C_{28}H_{22}NO$ $[M+H]^+$ 388.1696; found at 388.1681 Δ -3.9 ppm; **m.p.** = 78-80 °C.

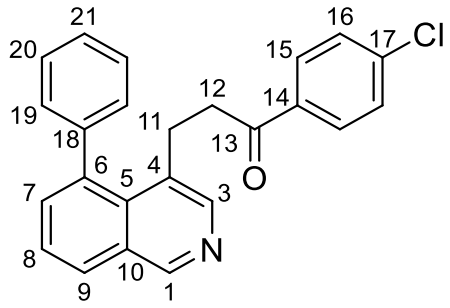
3-(8-Methylisoquinolin-4-yl)-1-(4-(trifluoromethyl)phenyl)propan-1-one (118):



The title compound was prepared according to **General Procedure A** using 8-methyl isoquinoline (18.0 mg, 0.125 mmol, 1.00 equiv.) and 1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **59** (100 mg, 0.50 mmol, 4.0 equiv.). Purification by flash column chromatography (0.5% Acetone in Et_2O) afforded **118** as a colourless solid (5.0 mg, 12%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.39 (1H, s, H_1), 8.49 (1H, s, H_3), 8.04 (2H, d, *J* = 8.1 Hz, H_{15}), 7.87 (1H, d, *J* = 8.5 Hz, H_6), 7.71 (2H, d, *J* = 8.1 Hz, H_{16}), 7.64 (1H, dd, *J* = 8.4, 7.0 Hz, H_7), 7.42 (1H, d, *J* = 7.1 Hz, H_8), 3.54 – 3.48 (2H, m, H_{11}), 3.47 – 3.41 (2H, m, H_{12}), 2.81 (3H, s, H_{19}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 197.9 (C_{13}), 148.5 (C_1), 142.6 (C_3), 139.4 (C_{14}), 136.6 (C_9), 134.9 (C_5), 134.71 (q, *J* = 32.7 Hz, C_{17}), 130.7 (C_7), 130.4 (C_4), 128.5 (C_{15}), 128.2 (C_8), 127.6 (C_{10}), 125.9 (q, *J* = 3.6 Hz, C_{16}), 124.44 (q, *J* = 272.1 Hz, C_{18}), 120.8 (C_6), 39.8 (C_{12}), 24.4 (C_{11}), 19.0 (C_{19}); **^{19}F NMR** (377 MHz, $CDCl_3$): δ_F = -63.15; **IR** (neat) cm^{-1}: 1688, 1142, 1338, 1229, 1203, 1174, 1136, 1109, 1071, 1019, 992, 913, 886, 854, 840, 774, 758, 733; **HRMS** (ESI^+) m/z calc. for $C_{20}H_{17}F_3NO$ $[M+H]^+$ 344.1257; found at 344.1256 Δ -0.29 ppm; **m.p.** = 136-137 °C.

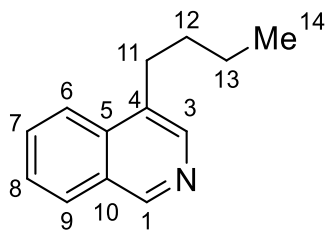
1-(4-Chlorophenyl)-3-(5-phenylisoquinolin-4-yl)propan-1-one (119):



The title compound was prepared according to **General Procedure A** using 5-phenyl isoquinoline (26.0 mg, 0.125 mmol, 1.00 equiv.) and 1-(4-chlorophenyl)prop-2-en-1-one **53** (84 mg, 0.50 mmol, 4.0 equiv.). Purification by flash column chromatography (0.5% Acetone in Et_2O) afforded **119** as an off-white solid (12 mg, 25%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.19 (1H, s, H_1), 8.36 (1H, s, H_3), 8.02 (1H, dt, *J* = 8.1, 1.1 Hz, H_9), 7.69 – 7.64 (2H, m, H_{15}), 7.62 (1H, ddd, *J* = 8.0, 7.0, 0.8 Hz, H_8), 7.53 (1H, dt, *J* = 7.0, 1.1 Hz, H_7), 7.38 – 7.35 (2H, m, H_{16}), 7.35 – 7.32 (3H, m, H_{19}, H_{21}), 7.32 – 7.28 (2H, m, H_{20}), 2.91 – 2.81 (4H, m, H_{11}, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 197.1 (C_{13}), 152.7 (C_1), 145.6 (C_3), 142.7 (C_{18}), 139.4 (C_{17}), 139.0 (C_6), 135.1 (C_{14}), 134.2 (C_7), 132.8 (C_5), 131.3 (C_4), 129.8 (C_{10}), 129.4 (C_{15}), 129.3 (C_{19}), 129.0 (C_9), 128.9 (C_{16}), 128.2 (C_{20}), 127.9 (C_{21}), 126.2 (C_8), 40.6 (C_{12}), 26.9 (C_{11}); **IR** (neat) cm^{-1}: 1686, 1588, 1486, 1443, 1401, 1384, 1362, 1323, 1306, 1224, 1204, 1177, 1154, 1092, 1013, 977, 913, 892, 837, 796, 764, 705, 667, 650, 626; **HRMS** (ESI^+) m/z calc. for $C_{24}H_{19}NO^{35}Cl$ $[M+H]^+$ 372.1150; found at 372.1155 Δ 1.3 ppm; **m.p.** = 101-102 °C.

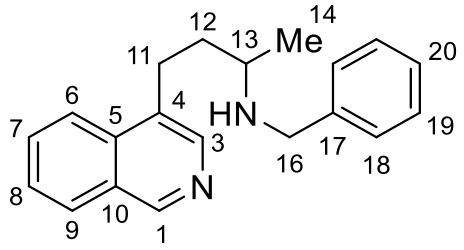
4-Butylisoquinoline (128):



The title compound was prepared according to a literature procedure first published by Kamenka and Cauquil-Caubère:[128] 4-(Isoquinolin-4-yl)butan-2-one **22** (50 mg, 0.25 mmol, 1.0 equiv.) was dissolved in ethylene glycol (0.5 mL) and added to a stirred solution of potassium hydroxide (56 mg, 1.0 mmol, 4.0 equiv.) and hydrazine monohydrate (50 mg, 1.0 mmol, 4.0 equiv.) in ethylene glycol (0.5 mL). The solution was stirred at 180 °C for 7 h then diluted with EtOAc and quenched with sat. aq. NH_4Cl. The suspension was shaken, the layers partitioned and the aqueous layer extracted twice more with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (90% Et_2O in pentane) afforded **128** as a dark orange oil (28 mg, 61%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.11 (1H, s, H_1), 8.37 (1H, s, H_3), 7.99 (1H, d, *J* = 8.5 Hz, H_6), 7.96 (1H, dd, *J* = 8.3, 1.4 Hz, H_9), 7.74 – 7.68 (1H, m, H_7), 7.61 – 7.55 (1H, m, H_8), 3.01 (2H, t, *J* = 7.8 Hz, H_{11}), 1.76 – 1.68 (2H, m, H_{12}), 1.50 – 1.41 (2H, m, H_{13}), 0.97 (3H, t, *J* = 7.4 Hz, H_{14}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 151.2 (C_1), 142.7 (C_3), 134.8 (C_5), 131.9 (C_4), 130.2 (C_7), 128.6 (C_{10}), 128.4 (C_9), 126.8 (C_8), 123.1 (C_6), 32.9 (C_{12}), 29.9 (C_{11}), 22.9 (C_{13}), 14.0 (C_{14}); **IR** (neat) cm^{-1}: 2957, 2931, 2870, 1701, 1685, 1653, 1623, 1583, 1569, 1540, 1503, 1465, 1457, 1389, 1379, 1266, 1249, 1230, 1166, 1148, 1106, 1020, 961, 903, 885, 860, 785, 751; **HRMS** (ESI$^+$) m/z calc. for $C_{13}H_{16}N$ $[M+H]^+$ 186.1277; found at 186.1277 Δ 0 ppm. Spectroscopic data were consistent with the literature data for this compound.[129]

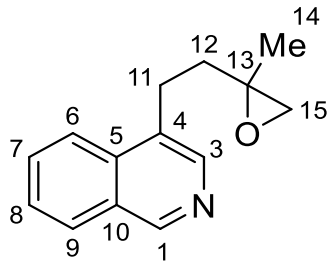
(*RS*)-*N*-Benzyl-4-(isoquinolin-4-yl)butan-2-amine (129):



4-(Isoquinolin-4-yl)butan-2-one **22** (50 mg, 0.25 mmol, 1.0 equiv.) was dissolved in MeOH (0.20 mL) with benzylamine (30 μL, 0.28 mmol, 1.1 equiv.), $NaCNBH_3$ (20 mg, 0.33 mmol, 1.3 equiv.) and powdered 3Å molecular sieves. Acetic acid (29 μL, 0.50 mmol, 2.0 equiv.) was added dropwise to the stirred mixture at 0 °C, after which the mixture was stirred at r.t. for 3 h. The reaction mixture was quenched with sat. aq. Na_2CO_3, diluted with EtOAc and the layers partitioned. The aqueous phase was extracted twice, then the combined organic phases were dried over Na_2SO_4, filtered under gravity and concentrated *in vacuo*. Purification by column chromatography (2-10% acetone in EtOAc) afford **129** as a pale-orange oil (48 mg, 66%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.04 (1H, s, H_1), 8.29 (1H, s, H_3), 7.93 (1H, d, *J* = 8.5 Hz, H_6), 7.89 (1H, d, *J* = 8.1 Hz, H_9), 7.65 – 7.60 (1H, m, H_7), 7.54 – 7.48 (1H, m, H_8), 7.29 – 7.21 (4H, m, H_{18}, H_{19}), 7.20 – 7.15 (1H, m, H_{20}), 3.79 (1H, d, *J* = 13.0 Hz, H_{16}), 3.69 (1H, d, *J* = 13.0 Hz, H_{16}'), 3.00 (2H, t, *J* = 8.1 Hz, H_{11}), 2.76 (1H, h, *J* = 6.1 Hz, H_{13}), 1.86 – 1.77 (1H, m, H_{12}), 1.72 (1H, ddt, *J* = 13.3, 8.9, 6.6 Hz, H_{12}'), 1.15 (3H, d, *J* = 6.3 Hz, H_{14}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 151.3 (C_1), 142.6 (C_3), 140.8 (C_{17}), 134.7 (C_5), 131.8 (C_4), 130.2 (C_7), 128.6 (C_{10}), 128.5 (C_{19}), 128.4 (C_9), 128.2 (C_{18}), 127.0 (C_{20}), 126.9 (C_8), 123.0 (C_6), 52.4 (C_{13}), 51.5 (C_{16}), 38.0 (C_{12}), 26.5 (C_{11}), 20.5 (C_{14}); **IR** (neat) cm^{-1}: 1653, 1623, 1505, 1455, 1376, 1148, 1027, 886, 787, 749, 698; **HRMS** (ESI^+) m/z calc. for $C_{20}H_{23}N_2$ $[M+H]^+$ 291.1856; found at 291.1862 Δ 2.06 ppm.

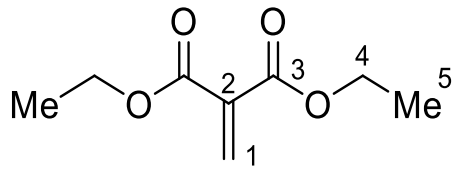
(*RS*)-4-(2-(2-Methyloxiran-2-yl)ethyl)isoquinoline (134):



The title compound was prepared according to a literature procedure first reported by Kosjek and co-workers:[130] Trimethylsulfonium iodide (224 mg, 1.10 mmol, 1.10 equiv.) and potassium *tert*-butoxide (112 mg, 1.00 mmol, 1.00 equiv.) were stirred in DMSO (1.5 mL) at r.t. for 15 min. 4-(Isoquinolin-4-yl)butan-2-one **22** (200 mg, 1.0 mmol, 1.0 equiv.) was dissolved in DMSO (0.50 mL) and added to the reaction mixture, which was then stirred at 40 °C for 18 h. The reaction was quenched with sat. aq. NH_4Cl, diluted with CH_2Cl_2, shaken and the layers partitioned. The aqueous layer was extracted twice more with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (5% acetone in Et_2O) afforded **134** as a pale-orange oil (150 mg, 70%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.12 (1H, s, H_1), 8.37 (1H, s, H_3), 8.04 – 7.92 (2H, m, H_6, H_9), 7.72 (1H, ddt, *J* = 8.2, 6.8, 1.2 Hz, H_7), 7.67 – 7.54 (1H, m, H_8), 3.16 – 3.05 (2H, m, H_{11}), 2.66 (1H, d, *J* = 4.7 Hz, H_{15}), 2.64 (1H, d, *J* = 4.7 Hz, H_{15}'), 2.04 – 1.93 (2H, m, H_{12}), 1.45 (3H, s, H_{14}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 151.6 (C_1), 142.6 (C_3), 134.5 (C_5), 130.8 (C_4), 130.5 (C_7), 128.5 (C_{10}), 128.5 (C_9), 127.0 (C_8), 122.8 (C_6), 56.8 (C_{13}), 54.0 (C_{15}), 37.6 (C_{12}), 25.6 (C_{11}), 21.2 (C_{14}); **IR** (neat) cm^{-1}: 1623, 1585, 1504, 1455, 1390, 1300, 1254, 1230, 1147, 1107, 1078, 1021, 892, 863, 788, 752, 695, 645, 610; **HRMS** (ESI$^+$) m/z calc. for $C_{14}H_{16}NO$ $[M+H]^+$ 214.1226; found at 214.1225 Δ -0.47 ppm.

Diethyl 2-methylenemalonate (33):

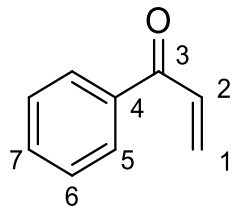


The title compound was prepared according to the literature procedure by Matziari, Nasopoulou and Yiotakis:[131] Diethyl malonate (2.4 mL, 16 mmol, 1.0 equiv.), $Cu(OAc)_2$

(0.32 g, 1.8 mmol, 11 mol%) and prilled paraformaldehyde (0.32 g, 11 mmol, 0.70 equiv.) were dissolved in acetic acid (10 mL) and heated to reflux for 2 h. The reaction was cooled to r.t. and a second addition of prilled paraformaldehyde (0.32 g, 11 mmol, 0.7 equiv.) was added. The mixture was heated to reflux for 6 h then concentrated *in vacuo*. The crude mixture was dissolved in diethyl ether (25 mL), then washed successively with 1.0 M aq. HCl, sat. aq. $NaHCO_3$, 1.0 M aq. HCl, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography (20% Et_2O in pentane) afforded **33** as a viscous yellow oil (0.34 g, 12%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 6.50 (2H, s, H_1), 4.28 (4H, q, J = 7.1 Hz, H_4), 1.32 (6H, t, J = 7.1 Hz, H_5); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 164.1 (C_3), 135.3 (C_2), 134.1 (C_1), 61.6 (C_4), 14.1 (C_5); **IR** (neat) cm^{-1}: 2984, 1727, 1467, 1445, 1369, 1300, 1243, 1182, 1127, 1020, 883, 857, 765. Spectroscopic data were consistent with the literature data for this compound.[131]

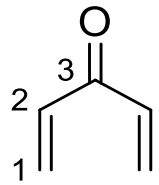
1-Phenylprop-2-en-1-one (23):



A 100 mL flask was flame dried then charged with anhydrous THF (30 mL). *N*-MeO-*N*-Me-benzamide (2.0 g, 12 mmol, 1.0 equiv.) was added and the solution cooled to 0 °C. Vinyl magnesium bromide (14 mL, 1.0 M in THF, 14 mmol, 1.2 equiv.) was added dropwise and the solution stirred at r.t. for 1 h. The reaction was quenched with 2.0 M aq. HCl, diluted with Et_2O, shaken and the layers partitioned. The aqueous layer extracted twice more with Et_2O, then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (10% Et_2O in pentane) afforded **23** as a pale-yellow oil (0.62 g, 78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.99 – 7.92 (2H, m, H_5), 7.63 – 7.54 (1H, m, H_7), 7.54 – 7.44 (2H, m, H_6), 7.16 (1H, dd, *J* = 17.2, 10.6 Hz, H_2), 6.44 (1H, dd, *J* = 17.1, 1.7 Hz, H_1), 5.94 (1H, dd, *J* = 10.5, 1.7 Hz, H_1'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 191.2 (C_3), 137.4 (C_4), 133.1 (C_7), 132.6 (C_2), 130.3 (C_1), 128.9 (C_5), 128.8 (C_6); **IR** (neat) cm^{-1}: 1672, 1609, 1596, 1580, 1448, 1404, 1287, 1233, 1180, 1003, 994, 727, 689, 668, 655. Spectroscopic data were consistent with the literature data for this compound.[132]

Penta-1,4-dien-3-one (38):



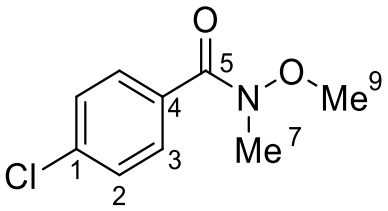
Vinyl magnesium bromide (22 mL, 1.0 M in THF, 22 mmol, 2.2 equiv.) was placed in a flame dried flask with a stirrer bar and cooled to 0 °C. Methyl formate (0.62 mL, 10 mmol, 1.0 equiv.) was dissolved in anhydrous THF (1.0 mL) and added dropwise to the above solution. The solution was stirred at r.t. for 1 h, then quenched with sat. aq. NH_4Cl, and extracted twice with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered under gravity and concentrated *in vacuo* to afford a yellow oil (0.71 g, 84%) which was used immediately without further purification.

The oil was dissolved in Et_2O (5 mL) and DDQ (2.1 g, 9.2 mmol, 1.1 equiv.) was added with stirring. After 24 h, the reaction mixture was poured into pentane, and filtered under gravity, the solid residue was washed twice more with pentane, then the combined pentane extracts were concentrated carefully *in vacuo*, with a 25 °C water bath. The resultant yellow oil **38** was used without further purification (0.16 g, 23%, 19% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 6.64 (2H, dd, *J* = 17.5, 10.7 Hz, H_2), 6.32 (1H, dd, *J* = 17.5, 1.3 Hz, H_1), 5.89 (1H, dd, *J* = 10.7, 1.3 Hz, H_1'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 190.4

(C_3), 134.5 (C_2), 129.5 (C_1); **IR** (neat) cm^{-1}: 2360, 1717, 1671, 1419, 992, 920. Spectroscopic data were consistent with the literature data for this compound.[133]

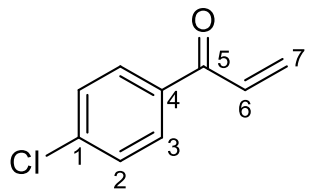
4-Chloro-*N*-methoxy-*N*-methylbenzamide (S53):



The title compound was prepared according to a literature procedure reported by Nelson and co-workers:[134] 4-Chloro benzoyl chloride (1.8 g, 10 mmol, 1.0 equiv.) and *N,O*−dimethylhydroxylamine hydrochloride (1.2 g, 12 mmol, 1.2 equiv.) were dissolved in CH_2Cl_2 (25 mL) at 0 °C. NEt_3 (3.5 mL, 25 mmol, 2.5 equiv.) was added to the solution dropwise, then the reaction mixture was warmed to r.t. and stirred for 1 hr. The solution was diluted with H_2O, shaken and the layers partitioned. The aqueous layer was extracted twice with CH_2Cl_2, the organic layers were combined, dried over Na_2SO_4, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (40% Et_2O in pentane) afforded **S53** as a colourless oil (1.5 g, 73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.70 – 7.61 (2H, m, H_2), 7.41 – 7.33 (2H, m, H_3), 3.53 (3H, s, H_9), 3.35 (3H, s, H_7); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 168.8 (C_5), 136.9 (C_1), 132.4 (C_4), 130.0 (C_2), 128.4 (C_3), 61.3 (C_9), 33.7 (C_7); **IR** (neat) cm^{-1}: 2361, 1643, 1594, 1459, 1417, 1379, 1213, 1177, 1091, 1064, 1016, 979, 887, 840, 746, 691; **LRMS** (ESI^+) m/z calc. for $C_9H_{11}ClNO_2$ $[M+H]^+$ 200.0; found at 200.0 Δ 0 ppm. Spectroscopic data were consistent with the literature data for this compound.[137]

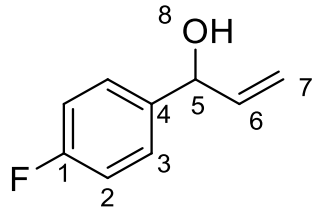
1-(4-Chlorophenyl)prop-2-en-1-one (53):



The title compound was prepared according to the literature procedure reported by Nelson and co-workers:[134] 4-chloro-*N*-methoxy-*N*-methylbenzamide **S53** (1.4 g, 7.3 mmol, 1.0 equiv.) was dissolved in anhydrous THF (15 mL) in a flame dried flask and cooled to 0 °C. Vinyl magnesium bromide (8.7 mL, 1.0 M in THF, 8.7 mmol, 1.2 equiv.) was added dropwise, the reaction mixture was stirred at r.t. for 1 h then the solution was cooled to 0 °C and quenched with 3.0 M aq. HCl. The layers were partitioned and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (30% Et_2O in pentane) afforded **53** as a pale-yellow oil (0.82 g, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.94 – 7.83 (2H, m, H_2), 7.50 – 7.41 (2H, m, H_3), 7.12 (1H, dd, *J* = 17.1, 10.6 Hz, H_6), 6.44 (1H, dd, *J* = 17.1, 1.6 Hz, H_7), 5.95 (1H, dd, *J* = 10.6, 1.6 Hz, H_7'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 189.9 (C_5), 139.6 (C_1), 135.7 (C_4), 132.1 (C_6), 130.8 (C_7), 130.3 (C_2), 129.1 (C_3); **IR** (neat) cm^{-1}: 1670, 1641, 1609, 1590, 1571, 1407, 1352, 1290, 1236, 1093, 998, 980, 777: **LRMS** (ESI$^+$) m/z calc. for C_9H_8ClO $[M+H]^+$ 167.0; found at 167.0 Δ 0 ppm. Spectroscopic data were consistent with the literature data for this compound.[136]

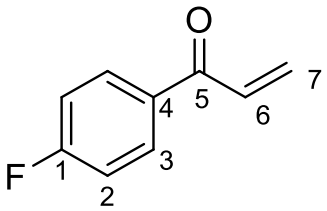
(*RS*)-1-(4-Fluorophenyl)prop-2-en-1-ol (S55):



4-Fluoro benzaldehyde (1.2 g, 10 mmol, 1.0 equiv.) was dissolved in THF (15 mL) and cooled to 0 °C. Vinyl magnesium bromide (12 mL, 1.0 M in THF, 12 mmol, 1.2 equiv.) was added dropwise and the resultant solution was stirred for 2 h. The reaction was quenched with 2.0 M aq. HCl and extracted three times with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered under gravity and concentrated *in vacuo* to afford **S55** as an orange oil (1.5 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.41 – 7.29 (2H, m, H_3), 7.18 – 6.95 (2H, m, H_2), 6.02 (1H, ddd, *J* = 17.2, 10.3, 6.1 Hz, H_6), 5.34 (1H, dt, *J* = 17.1, 1.4 Hz, H_7), 5.26 – 5.16 (2H, m, H_5, H_7'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 162.5 (d, *J* = 245.7 Hz, C_1), 140.2 (C_6), 138.4 (d, *J* = 3.2 Hz, C_4), 128.2 (d, *J* = 8.1 Hz) (C_3), 115.6 – 115.4 (2C, m, C_2, C_7), 74.8 (C_5); **^{19}F NMR** (377 MHz, $CDCl_3$): δ_F = -114.83 (tt, *J* = 8.6, 5.4 Hz); **IR** (neat) cm^{-1}: 3339 (br), 1604, 1509, 1417, 1223, 1157, 1095, 1014, 990, 928, 854, 835, 788. Spectroscopic data were consistent with the literature data for this compound.[146]

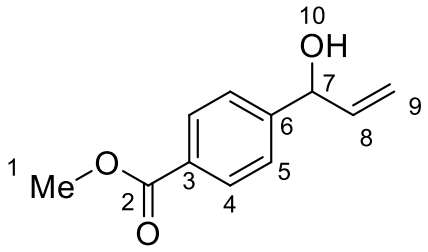
1-(4-Fluorophenyl)prop-2-en-1-one (55):



The title compound was prepared according to a literature procedure reported by Molander and Jean-Gerard:[140] 1-(4-Fluorophenyl)prop-2-en-1-ol **S55** (1.5 g, 10 mmol, 1.0 equiv.) was dissolved in THF (8.0 mL) and the resultant solution added to a stirred suspension of IBX (3.4 g, 12 mmol, 1.2 equiv.) in DMSO (25 mL). The suspension was stirred at r.t. for 3 h, then diluted with H_2O and extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (5% Et_2O in pentane) afforded **55** as a pale-yellow oil (0.69 g, 47%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.04 – 7.87 (2H, m, H_3), 7.19 – 7.09 (3H, m, H_2, H_6), 6.44 (1H, dd, *J* = 17.1, 1.6 Hz, H_7), 5.94 (1H, dd, *J* = 10.6, 1.6 Hz, H_7'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 189.5 (C_5), 165.9 (d, *J* = 254.9 Hz, C_1), 133.8 (d, *J* = 2.9 Hz, C_4), 132.2 (C_6), 131.5 (d, *J* = 9.3 Hz, C_3), 130.5 (C_7), 115.9 (d, *J* = 21.9 Hz, C_2); **^{19}F NMR** (377 MHz, $CDCl_3$): δ_F = -105.17 (tt, *J* = 8.2, 5.4 Hz); **IR** (neat) cm^{-1}: 1671, 1597, 1507, 1411, 1284, 1232, 1158, 1100, 1000, 854, 785. Spectroscopic data were consistent with the literature data for this compound.[136]

(*RS*)-Methyl 4-(1-hydroxyallyl)benzoate (S57):

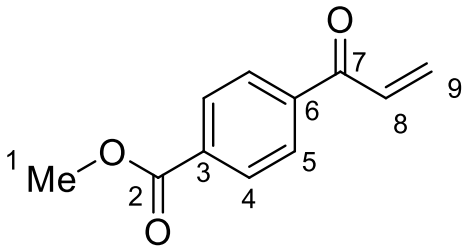


The title compound was prepared according to a procedure reported by Kikuchi and co-workers:[147] 4-Methyl terephthalaldehydeate (1.6 g, 10 mmol, 1.0 equiv.) was dissolved in THF (20 mL) and cooled to -78 °C. Vinyl magnesium bromide (12 mL, 1.0 M in THF, 12 mmol, 1.2 equiv.) was added dropwise and the resultant solution was stirred for 30 min. The reaction was quenched with sat. aq. NH_4Cl, warmed to r.t. and extracted three times with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc in pentane) afforded **S57** as a colourless oil (1.5 g, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.06 – 7.98 (2H, m, H_4), 7.49 – 7.41 (2H, m, H_5), 6.08 – 5.95 (1H, m, H_8), 5.43 – 5.31 (1H, m, H_9), 5.26 (1H, t, *J* = 4.8 Hz, H_7), 5.25 – 5.14 (1H, m, H_9'), 3.91 (3H, s, H_1); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 167.1 (C_2), 147.6 (C_3), 139.8 (C_8), 130.0 (C_4), 129.6 (C_6), 126.3 (C_5), 116.1 (C_9), 75.2 (C_7), 52.3 (C_1); **IR** (neat) cm^{-1}: 3435 (br)**,**

2360, 1720, 1611, 1437, 1280, 1193, 1114, 1018, 991, 929, 863, 814, 762, 713. Spectroscopic data were consistent with the literature data for this compound.[148]

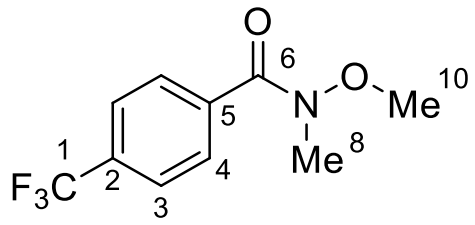
Methyl 4-acryloylbenzoate (57):



The title compound was prepared according to a literature procedure reported by Walker, Werrel and Donohoe:[148] Methyl 4-(1-hydroxyallyl)benzoate **S57** (1.3 g, 6.9 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (40 mL) and cooled to 0 °C. DMP (4.5 g, 11 mmol, 1.5 equiv.) and $NaHCO_3$ (5.9 g, 70 mmol, 10 equiv.) were added portion wise over 15 min to give an off-white suspension, which was stirred for a further 15 min. The reaction was allowed to warm to r.t. and stirred for 16 h, after which it was quenched with sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$ and stirred for 30 min. The reaction was shaken vigorously, then the layers partitioned and the aqueous layer extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (15% EtOAc in cyclohexane) afforded **57** as an off-white gel (0.75 g, 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.13 (2H, q, *J* = 7.7, 1.9 Hz, H_{Ar}), 7.97 (2H, dq, *J* = 8.3, 1.7 Hz, H_{Ar}), 7.14 (1H, ddd, *J* = 17.0, 10.6, 1.8 Hz, H_8), 6.45 (1H, dt, *J* = 16.8, 1.7 Hz, H_9), 5.99 (1H, dt, *J* = 10.5, 1.9 Hz, H_9'), 3.95 (3H, d, *J* = 2.0 Hz, H_1); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 190.8 (C_7), 166.4 (C_2), 140.8 (C_6), 133.9 (C_3), 132.4 (C_8), 131.3 (C_9), 130.0 (C_{Ar}), 128.7 (C_{Ar}), 52.6 (C_1); **IR** (neat) cm^{-1}: 1727, 1671, 1605, 1505, 1439, 1412, 1278, 1227, 1195, 1110, 740; **LRMS** (ESI$^+$) m/z calc. for C_9H_7O [M-CO_2CH_3]$^+$ 131.0; found at 131.0 Δ 0.0 ppm. Spectroscopic data were consistent with the literature data for this compound.[148]

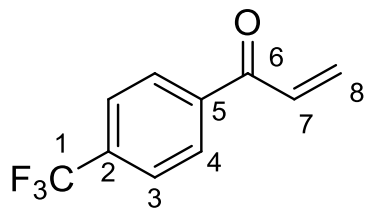
***N*-Methoxy-*N*-methyl-4-(trifluoromethyl)benzamide (S59):**



The title compound was prepared according to a literature procedure reported by Nelson and co-workers:[134] *p*-Trifluoromethyl benzoyl chloride (2.1 g, 10 mmol, 1.0 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride (1.2 g, 12 mmol, 1.2 equiv.) were dissolved in CH_2Cl_2 (25 mL) at 0 °C. NEt_3 (3.5 mL, 25 mmol, 2.5 equiv.) was added to the solution dropwise, then the reaction mixture was warmed to r.t. and stirred for 1 h. The solution was diluted with H_2O, shaken and the layers partitioned. The aqueous layer was extracted twice with CH_2Cl_2, the organic layers were combined, dried over Na_2SO_4, filtered under gravity and concentrated *in vacuo* to afford **S59** as a beige oil (2.3 g, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.78 (2H, d, *J* = 8.0 Hz, H_4), 7.67 (2H, d, *J* = 8.0 Hz, H_3), 3.53 (3H, s, H_{10}), 3.38 (3H, s, H_8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 168.7 (C_6), 137.7 (C_5), 132.4 (q, *J* = 32.6 Hz, C_2), 128.7 (C_4), 125.2 (q, *J* = 3.8 Hz, C_3), 123.0 (q, *J* = 273.1 Hz, C_1), 61.4 (C_{10}), 33.5 (C_8); **^{19}F NMR** (565 MHz, $CDCl_3$): δ_F = -62.97; **IR** (neat) cm^{-1}. Spectroscopic data were consistent with the literature data for this compound.[149]

1-(4-(Trifluoromethyl)phenyl)prop-2-en-1-one (59):

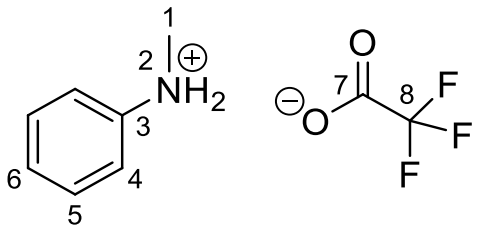


The title compound was prepared according to a literature procedure reported by Nelson and co-workers:[134] *N*-Methoxy-*N*-methyl-4-(trifluoromethyl)benzamide **S59** (2.3 g, 9.9 mmol,

1.0 equiv.) was dissolved in anhydrous THF (15 mL) in a flame dried flask and cooled to 0 °C. Vinyl magnesium bromide (12 mL, 1.0 M in THF, 12 mmol, 1.2 equiv.) was added dropwise, then the reaction mixture was stirred at r.t. for 1 h, after which the solution was cooled to 0 °C and quenched with 3.0 M aq. HCl. The layers were partitioned and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (10% Et_2O in pentane) afforded **59** as a yellow oil (0.63 g, 32%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.06 – 7.99 (2H, m, H_4), 7.75 (1H, dt, *J* = 8.1, 0.8 Hz, H_3), 7.13 (1H, dd, *J* = 17.2, 10.6 Hz, H_7), 6.47 (1H, dd, *J* = 17.2, 1.5 Hz, H_8), 6.02 (1H, dd, *J* = 10.6, 1.4 Hz, H_8'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 190.4 (C_6), 140.2 (C_5), 134.4 (q, *J* = 32.7 Hz, C_2), 132.3 (C_7), 131.6 (C_8), 129.1 (C_4), 125.8 (q, *J* = 3.7 Hz, C_3), 123.8 (q, *J* = 272.7 Hz, C_1); **^{19}F NMR** (377 MHz, $CDCl_3$): δ_F = -63.12; **IR** (neat) cm^{-1}: 1679, 1414, 1326, 1229, 1170, 1128, 1067, 1001, 789. Spectroscopic data were consistent with the literature data for this compound.[150]

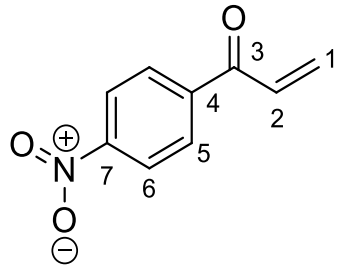
***N*-Methyl benzenaminium 2,2,2-trifluoroacetate (S61):**



The title compound was prepared according to the literature procedure first reported by Bugarin, Jones and Connell;[152] *N*-Methyl aniline (11 mL, 100 mmol, 1.0 equiv.) was dissolved in diethyl ether (100 mL) at 0 °C and trifluoro acetic acid (7.7 mL, 100 mmol, 1.0 equiv.) was added dropwise. The mixture was stirred for 5 min, then the precipitate was filtered, washed with diethyl ether cooled to 0 °C and dried under vacuum for 3 h, affording **S61** as a fluffy white solid (11 g, 50% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 10.73 (2H, s, H_2), 7.47 – 7.38 (5H, m, H_4, H_5, H_6), 2.96 (3H, d, *J* = 0.9 Hz, H_1); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 162.7 (q, *J* = 35.8 Hz, C_7), 138.1 (C_3), 130.3 (C_4), 129.1 (C_6), 122.0 (C_5), 116.6 (q, *J* = 290.2 Hz, C_8), 37.7 (C_1); **IR** (neat) cm^{-1}: 1671, 1602, 1498, 1202, 1133, 837, 798, 756, 722, 693, 668, 619; **m.p.** = 60-62 °C. Spectroscopic data were consistent with the literature data for this compound.[152]

1-(4-Nitrophenyl)prop-2-en-1-one (61):

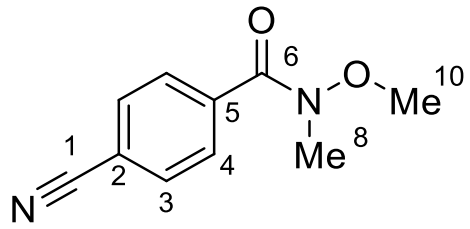


The title compound was prepared according to a literature procedure reported by Duan, Zhou, Lin and Xiao:[153] Prilled paraformaldehyde (3.8 g, 130 mmol, 5.0 equiv.), *N*-methyl benzenaminium 2,2,2-triflouroacetate **S61** (5.5 g, 25 mmol, 1.0 equiv.) and 4-NO_2 phenyl acetone (4.1 g, 25 mmol, 1.0 equiv.) were placed in a flask with a stirrer bar and flushed with N_2 (g). THF (25 mL) was added and the resultant mixture heated to reflux under N_2 (g) for 15 h. The reaction mixture was concentrated *in vacuo*, dissolved in EtOAc, washed with H_2O, 1.0 M aq. HCl, H_2O, dried over Na_2SO_4 and concentrated to dryness. Purification by flash column chromatography (5% Et_2O in pentane) afforded **61** as a cream solid (110 mg, 3.0%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.38 – 8.28 (2H, m, H_{Ar}), 8.13 – 8.03 (2H, m, H_{Ar}), 7.12 (1H, dd, *J* = 17.2, 10.6 Hz, H_2), 6.48 (1H, dd, *J* = 17.2, 1.4 Hz, H_1), 6.07 (1H, dd, *J* = 10.6, 1.4 Hz, H_1'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 189.8 (C_3), 150.4 (C_7), 142.1 (C_4), 132.3 (C_1), 132.1 (C_2), 129.8 (C_6), 124.0 (C_5); **IR** (neat) cm^{-1}: 1730, 1667, 1600, 1520, 1415, 1401, 1363, 1344, 1324, 1228, 1002, 980, 873, 855, 802, 757, 728, 681; **LRMS** (ESI^+) m/z calc. for

$C_9H_7NO_3Na$ $[M+Na]^+$ 200.0; found at 200.0 Δ 0 ppm; **m.p.** = 85-87 °C. Spectroscopic data were consistent with the literature data for this compound.[154]

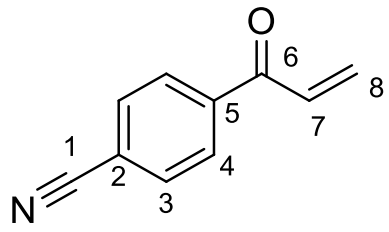
4-Cyano-*N*-methoxy-*N*-methylbenzamide (S63):



The title compound was prepared according to a literature procedure reported by Wallace and Gibb:[143] *p*-Cyano benzoic acid (1.47 g, 10.0 mmol, 1.00 equiv.), *N*,*O*-dimethylhydroxylamine hydrochloride (1.07 g, 11.0 mmol, 1.10 equiv.), 2-hydroxy benzotriazole (400 mg, 3.00 mmol, 30.0 mol%) and EDC (2.30 g, 12.0 mmol, 1.20 equiv.) were dissolved in MeCN (15.0 mL) at r.t. under an atmosphere of nitrogen. NEt_3 (1.53 mL, 11.0 mmol, 1.10 equiv.) was added dropwise, and the solution was stirred overnight. The reaction was quenched by addition of 2.0 M aq. NaOH and extracted three times with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered under gravity and concentrated *in vacuo* to afford **S63** as a beige oil (787 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.80 – 7.74 (2H, m, H_4), 7.74 – 7.67 (2H, m, H_3), 3.52 (3H, s, H_{10}), 3.37 (3H, s, H_8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 168.1 (C_6), 138.4 (C_5), 132.0 (C_3), 129.0 (C_4), 118.3 (C_1), 114.3 (C_2), 61.5 (C_{10}), 33.4 (C_8); **IR** (neat) cm^{-1}: 1644, 1423, 1215, 983, 850, 754. Spectroscopic data were consistent with the literature data for this compound.[151]

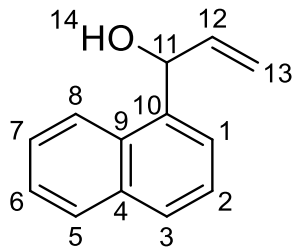
4-Acryloylbenzonitrile (63):



The title compound was prepared according to a literature procedure reported by Nelson and co-workers:[134] 4-Cyano-*N*-methoxy-*N*-methylbenzamide **S63** (0.79 g, 4.1 mmol, 1.0 equiv.) was dissolved in anhydrous THF (10 mL) in a flame dried flask and cooled to 0 °C. Vinyl magnesium bromide (5.0 mL, 1.0 M in THF, 4.9 mmol, 1.2 equiv.) was added dropwise, then the reaction mixture was stirred at r.t. for 1 h, after which the solution was cooled to 0 °C and quenched with 3.0 M aq. HCl. The layers were partitioned and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo* to afford **63** as a pale-brown solid (0.60 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.05 – 7.97 (2H, m, H_4), 7.85 – 7.74 (2H, m, H_3), 7.10 (1H, dd, *J* = 17.2, 10.6 Hz, H_7), 6.47 (1H, ddd, *J* = 17.2, 1.4, 0.6 Hz, H_8), 6.04 (1H, dd, *J* = 10.6, 1.2 Hz, H_8'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 189.9 (C_6), 140.6 (C_5), 132.7 (C_3), 132.1 (C_8), 131.9 (C_7), 129.2 (C_4), 118.1 (C_1), 116.4 (C_2); **IR** (neat) cm^{-1}: 2231, 1668, 1610, 1412, 1293, 1230, 1001, 862, 782. **m.p.** = 51-52 °C. Spectroscopic data were consistent with the literature data for this compound.[136]

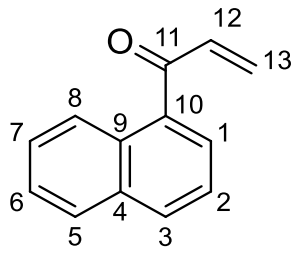
(*RS*)-1-(Naphthalen-1-yl)prop-2-en-1-ol (S65):



The title compound was prepared according to a literature procedure reported by Wang and co-workers:[138] 1-Napthaldehyde (1.6 g, 10 mmol, 1.0 equiv.) was dissolved in anhydrous THF (20 mL) in a flame dried flask and cooled to 0 °C. Vinyl magnesium bromide (12 mL, 1.0 M in THF, 12 mmol, 1.2 equiv.) was added dropwise, after which the solution was warmed to r.t. and stirred for 2 h. The solution was quenched with sat. aq. NH_4Cl and extracted twice with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered under gravity and concentrated *in vacuo* to afford **S65** as an orange oil (1.8 g, 96%) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.25 – 8.16 (1H, m, H_8), 7.88 (1H, dd, *J* = 8.0, 1.6 Hz, H_3), 7.81 (1H, d, *J* = 8.2 Hz, H_5), 7.68 – 7.60 (1H, m, H_1), 7.58 – 7.41 (3H, m, H_2, H_6, H_7), 6.26 (1H, dddd, *J* = 17.1, 10.4, 5.4, 1.3 Hz, H_{12}), 5.95 (1H, d, *J* = 5.3 Hz, H_{11}), 5.46 (1H, dt, *J* = 17.2, 1.5 Hz, H_{13}), 5.29 (1H, dt, *J* = 10.4, 1.4 Hz, H_{13}'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 139.8 (C_{12}), 138.2 (C_{10}), 134.1 (C_4), 130.9 (C_9), 129.0 (C_3), 128.7 (C_5), 126.3 (C_1), 125.8 (C_7), 125.6 (C_6), 124.1 (C_8), 123.9 (C_2), 115.8 (C_{13}), 72.5 (C_{11}); **IR** (neat) cm^{-1}: 3356 (br), 3050, 2361, 2341, 1510, 989, 926, 802, 736. Spectroscopic data were consistent with the literature data for this compound.[139]

1-(Naphthalen-1-yl)prop-2-en-1-one (65):

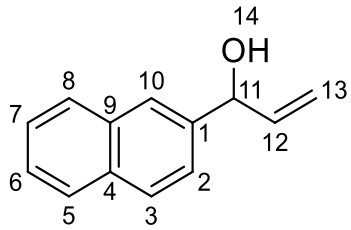


The title compound was prepared according to a literature procedure reported by Molander and Jean-Gerard:[140] 1-(Naphthalen-1-yl)prop-2-en-1-ol **S65** (1.8 g, 10 mmol, 1.0 equiv.) was dissolved in THF (8 mL) and the resultant solution added to a stirred suspension of IBX (3.4 g,

12 mmol, 1.2 equiv.) in DMSO (25 mL). The suspension was stirred at r.t. for 3 h, then diluted with H_2O and extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (7% Et_2O in pentane) afforded **65** as a yellow oil (0.73 g, 40%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.34 (1H, dq, *J* = 8.7, 0.9 Hz, H_8), 7.98 (1H, dt, *J* = 8.3, 1.1 Hz, H_3), 7.92 – 7.86 (1H, m, H_5), 7.73 (1H, dd, *J* = 7.1, 1.2 Hz, H_1), 7.57 (1H, ddd, *J* = 8.5, 6.8, 1.6 Hz, H_7), 7.54 (1H, ddd, *J* = 8.1, 6.8, 1.4 Hz, H_6), 7.51 (1H, dd, *J* = 8.2, 7.1 Hz, H_2), 6.95 (1H, dd, *J* = 17.4, 10.6 Hz, H_{12}), 6.27 (1H, dd, *J* = 17.4, 1.3 Hz, H_{13}), 6.05 (1H, dd, *J* = 10.6, 1.3 Hz, H_{13}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 196.0 (C_{11}), 137.1 (C_{12}), 135.9 (C_{10}), 134.0 (C_4), 132.1 (C_3), 131.5 (C_{13}), 130.7 (C_9), 128.6 (C_5), 127.9 (C_1), 127.7 (C_7), 126.6 (C_6), 125.7 (C_8), 124.5 (C_2); **IR** (neat) cm^{-1}: 1664, 1603, 1508, 1404, 1290, 1252, 1233, 1181, 1102, 947, 785, 646. Spectroscopic data were consistent with the literature data for this compound.[142]

(*RS*)-1-(Naphthalen-2-yl)prop-2-en-1-ol (S67):

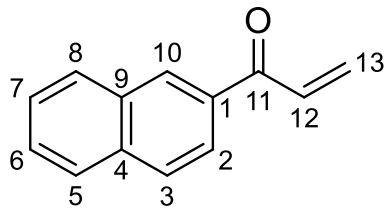


The title compound was prepared according to a literature procedure reported by Wang and co-workers:[138] 2-napthaldehyde (1.6 g, 10 mmol, 1.0 equiv.) was dissolved in anhydrous THF (20 mL) in a flame dried flask and cooled to 0 °C. Vinyl magnesium bromide (12 mL, 1.0 M in THF, 12 mmol, 1.2 equiv.) was added dropwise, after which the solution was warmed to r.t. and stirred for 2 h. The solution was quenched with sat. aq. NH_4Cl and extracted twice with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered under gravity and

concentrated *in vacuo* to afford **S67** as an orange oil (1.8g, *quant.*) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.89 – 7.78 (5H, m, H_2, H_3, H_5, H_8, H_{10}), 7.55 – 7.43 (2H, m, H_6, H_7), 6.13 (1H, dddd, *J* = 17.0, 10.3, 6.0, 0.7 Hz, H_{12}), 5.47 – 5.36 (2H, m, H_{11}, H_{13}), 5.25 (1H, ddt, *J* = 10.2, 1.8, 0.9 Hz, H_{13}'), 1.49 (1H, *br*.s, H_{14}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 140.3 (C_{12}), 140.1 (C_1), 133.5 (C_4), 133.2 (C_9), 128.5 (C_{10}), 128.2 (C_8), 127.8 (C_3), 126.3 (C_6), 126.1 (C_5), 125.1 (C_7), 124.7 (C_2), 115.6 (C_{13}), 75.6 (C_{11}); **IR** (neat) cm^{-1}: 3353 (br), 3053, 2361, 2341, 1508, 1419, 1363, 1271, 1167, 1124, 1020, 990, 927, 895, 857, 818, 781, 715. Spectroscopic data were consistent with the literature data for this compound.[139]

1-(Naphthalen-2-yl)prop-2-en-1-one (67):

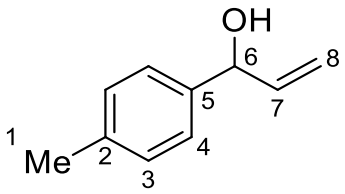


The title compound was prepared according to a literature procedure reported by Molander and Jean-Gerard:[140] 1-(Naphthalen-2-yl)prop-2-en-1-ol **S67** (1.7 g, 9.0 mmol, 1.0 equiv.) was dissolved in THF (7.0 mL) and the resultant solution added to a stirred suspension of IBX (3.0 g, 11 mmol, 1.2 equiv.) in DMSO (20 mL). The suspension was stirred at r.t. for 3 h, then diluted with H_2O and extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (7% Et_2O in pentane) afforded **67** as a yellow oil (0.79 g, 43%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.47 (1H, d, *J* = 1.6 Hz, H_{10}), 8.04 (1H, dd, *J* = 8.6, 1.8 Hz, H_2), 7.99 – 7.95 (1H, m, H_8), 7.92 (1H, d, *J* = 8.6 Hz, H_3), 7.89 (1H, dd, *J* = 8.1, 1.2 Hz, H_5), 7.61 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz, H_6), 7.56 (1H, ddd, *J* = 8.1, 6.9, 1.3 Hz, H_7), 7.33 (1H, dd,

J = 17.0, 10.5 Hz, H_{12}), 6.51 (1H, dd, *J* = 17.1, 1.6 Hz, H_{13}), 5.98 (1H, dd, *J* = 10.6, 1.6 Hz, H_{13}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 191.0 (C_{11}), 135.7 (C_4), 134.8 (C_1), 132.6 (C_9), 132.5 (C_{12}), 130.5 (C_{10}), 130.2 (C_{13}), 129.7 (C_8), 128.8 (C_3), 128.7 (C_6), 128.0 (C_5), 127.0 (C_7), 124.6 (C_2); **IR** (neat) cm^{-1}: 1693, 1666, 1627, 1608, 1468, 1401, 1351, 1277, 1255, 1222, 1181, 1125, 1000, 978, 942, 866, 826, 791, 765. Spectroscopic data were consistent with the literature data for this compound.[141]

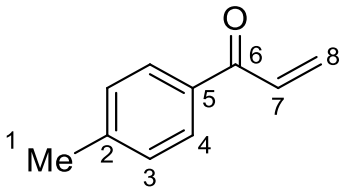
(*RS*)-1-(*p*-Tolyl)prop-2-en-1-ol (S69):



p-Methyl benzaldehyde (1.2 g, 10 mmol, 1.0 equiv.) was dissolved in anhydrous THF (20 mL) in a flame dried flask and cooled to 0 °C. Vinyl magnesium bromide (12 mL, 1.0 M in THF, 12 mmol, 1.2 equiv.) was added dropwise, then the resultant solution was stirred at r.t. for 1 h, after which it was quenched with sat. aq. NH_4Cl. The mixture was extracted three times with Et_2O then the combined organic extracts were dried over Na_2SO_4, filtered under gravity and concentrated *in vacuo* to give **S69** as a pale-orange oil (1.5 g, *quant.*) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.30 – 7.22 (2H, m, H_4), 7.21 – 7.12 (2H, m, H_3), 6.10 – 5.98 (1H, m, H_7), 5.33 (1H, dt, *J* = 16.9, 1.3 Hz, H_8), 5.21 – 5.14 (2H, m, H_6, H_8'), 2.34 (3H, s, H_1); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 140.6 (C_7), 139.9 (C_5), 137.6 (C_2), 129.4 (C_3), 126.4 (C_4), 114.9 (C_8), 75.3 (C_6), 21.2 (C_1); **IR** (neat) cm^{-1}: 3347 (br), 1513, 1411, 1108, 1030, 989, 924, 848, 816, 774, 733. Spectroscopic data were consistent with the literature data for this compound.[139]

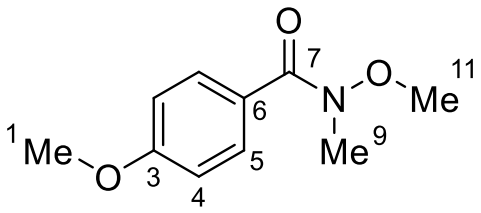
1-(*p*-Tolyl)prop-2-en-1-one (69):



The title compound was prepared according to a literature procedure reported by Molander and Jean-Gerard:[140] 1-(*p*-Tolyl)prop-2-en-1-ol **S69** (1.5 g, 10 mmol, 1.0 equiv.) was dissolved in THF (8.0 mL) and the resultant solution added to a stirred suspension of IBX (3.4 g, 12 mmol, 1.2 equiv.) in DMSO (25 mL). The suspension was stirred at r.t. for 3 h, then diluted with H_2O and extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (7% Et_2O in pentane) afforded **69** as a yellow oil (0.67 g, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.91 – 7.83 (2H, m, H_4), 7.35 – 7.22 (2H, m, H_3), 7.16 (1H, dd, *J* = 17.1, 10.5 Hz, H_7), 6.43 (1H, dd, *J* = 17.1, 1.8 Hz, H_8), 5.90 (1H, dd, *J* = 10.5, 1.7 Hz, H_8'), 2.42 (3H, s, H_1); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 190.7 (C_6), 144.0 (C_2), 134.9 (C_5), 132.5 (C_7), 129.8 (C_8), 129.5 (C_3), 129.0 (C_4), 21.8 (C_1); **IR** (neat) cm^{-1}: 1668, 1604, 1571, 1410, 1399, 1293, 1237, 1212, 1182, 1121, 1002, 982, 846, 771. Spectroscopic data were consistent with the literature data for this compound.[136]

***N*,*O*-Dimethoxy-*N*-methylbenzamide (S71):**

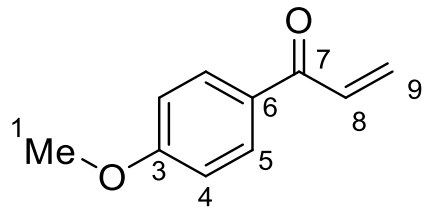


The title compound was prepared according to a literature procedure reported by Nelson and co-workers:[134] *p*-Methoxy benzoyl chloride (3.4 g, 20 mmol, 1.0 equiv.) and

N,O-dimethylhydroxylamine hydrochloride (2.4 g, 24 mmol, 1.2 equiv.) were dissolved in CH_2Cl_2 (50 mL) at 0 °C. NEt_3 (7.0 mL, 50 mmol, 2.5 equiv.) was added to the solution dropwise, then the reaction mixture was warmed to r.t. and stirred for 1 h. The solution was diluted with H_2O, shaken and the layers partitioned. The aqueous layer was extracted twice with CH_2Cl_2, the organic layers were combined, dried over Na_2SO_4, filtered under gravity and concentrated *in vacuo* to afford **S71** as an orange oil (3.8 g, 98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.72 (2H, dq, *J* = 8.3, 1.0 Hz, H_5), 6.99 – 6.80 (2H, m, H_4), 3.84 (3H, d, *J* = 1.5 Hz, H_1), 3.56 (3H, d, *J* = 1.3 Hz, H_{11}), 3.35 (3H, d, *J* = 1.4 Hz, H_9); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 169.5 (C_7), 161.7 (C_6), 130.7 (C_5), 126.2 (C_3), 113.4 (C_4), 61.0 (C_{11}), 55.4 (C_1), 34.0 (C_9); **IR** (neat) cm^{-1}: 1634, 1608, 1512, 1421, 1374, 1304, 1254, 1173, 1029, 978, 909, 841, 797, 756, 730. Spectroscopic data were consistent with the literature data for this compound.[151]

1-(4-Methoxyphenyl)prop-2-en-1-one (71):

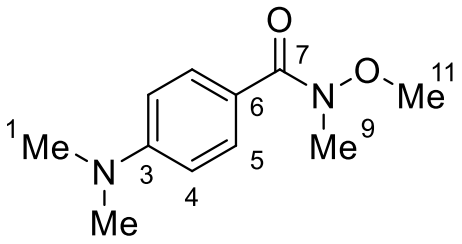


The title compound was prepared according to a literature procedure reported by Nelson and co-workers:[134] *N,O*-Dimethoxy-*N*-methylbenzamide **S71** (3.8 g, 20 mmol, 1.0 equiv.) was dissolved in anhydrous THF (30 mL) in a flame dried flask and cooled to 0 °C. Vinyl magnesium bromide (24 mL, 1.0 M in THF, 24 mmol, 1.2 equiv.) was added dropwise, then the reaction mixture was stirred at r.t. for 1 h, after which the solution was cooled to 0 °C and quenched with 3.0 M aq. HCl. The layers were partitioned and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered under gravity

and concentrated *in vacuo* to afford **71** as an orange solid (2.7 g, 83%) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.00 – 7.89 (2H, m, H_5), 7.16 (1H, dd, *J* = 17.0, 10.5 Hz, H_8), 6.99 – 6.88 (2H, m, H_4), 6.41 (1H, dd, *J* = 17.0, 1.8 Hz, H_9), 5.85 (1H, dd, *J* = 10.5, 1.8 Hz, H_9'), 3.86 (3H, s, H_1); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 189.3 (C_7), 163.7 (C_6), 132.7 (C_8), 131.1 (C_5), 130.3 (C_3), 129.3 (C_9), 114.0 (C_4), 55.6 (C_1); **IR** (neat) cm^{-1}: 1657, 1605, 1586, 1510, 1463, 1444, 1420, 1401, 1332, 1310, 1267, 1238, 1173, 1119, 1029, 1012, 993, 984, 854, 806, 791, 728, 711, 631; **m.p.** = 24-26 °C. Spectroscopic data were consistent with the literature data for this compound.[136]

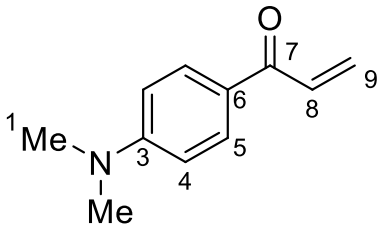
4-(Dimethylamino)-*N*-methoxy-*N*-methylbenzamide (S73):



The title compound was prepared according to a literature procedure reported by Wallace and Gibb:[143] 4-Dimethylamino benzoic acid (1.65 g, 10.0 mmol, 1.00 equiv.), *N*,*O*-dimethylhydroxylamine hydrochloride (1.07 g, 11.0 mmol, 1.10 equiv.), 2-hydroxy benzotriazole (400 mg, 3.00 mmol, 30.0 mol%) and EDC (2.3 g, 12 mmol, 1.2 equiv.) were dissolved in MeCN (15.0 mL) at r.t. under an atmosphere of nitrogen. NEt_3 (1.53 mL, 11.0 mmol, 1.10 equiv.) was added dropwise, and the solution was stirred overnight. The reaction was quenched by addition of 2.0 M aq. NaOH and extracted three times with EtOAc. The combined organic extracts were dried with Na_2SO_4, filtered under gravity and concentrated *in vacuo* to afford **S73** as a pale-orange oil (794 mg, 38%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.77 – 7.69 (2H, m, H_5), 6.69 – 6.61 (2H, m, H_4), 3.59 (3H, s, H_{11}), 3.34 (3H, s, H_9), 3.02 (3H, s, H_1); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 170.1 (C_7), 152.2 (C_3), 130.8 (C_5), 120.6 (C_6), 110.8 (C_4), 60.8 (C_{11}), 40.2 (C_1), 34.4 (C_9); **IR** (neat) cm^{-1}: 1604, 1527, 1411, 1360, 1186, 1169, 826, 756; **LRMS** (ESI$^+$) m/z calc. for $C_{11}H_{16}N_2O_2Na$ $[M+Na]^+$ 231.1; found at 231.2 Δ 433 ppm. Spectroscopic data were consistent with the literature data for this compound.[144]

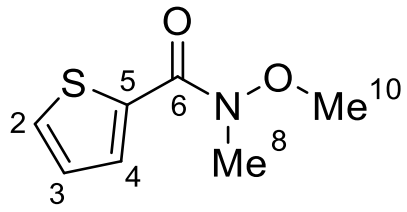
1-(4-(Dimethylamino)phenyl)prop-2-en-1-one (73):



4-(Dimethylamino)-*N*-methoxy-*N*-methylbenzamide **S73** (0.79 g, 3.8 mmol, 1.0 equiv.) was dissolved in THF (15 mL) and cooled to 0 °C. Vinyl magnesium bromide (4.6 mL, 1.0 M in THF, 4.6 mmol, 1.2 equiv.) was added dropwise and the resultant solution was stirred for 2 h. The reaction was quenched with 2.0 M aq. HCl and extracted three times with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo* to afford **73** as an orange solid (0.46 g, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.97 – 7.90 (2H, m, H_5), 7.21 (1H, dd, *J* = 17.0, 10.5 Hz, H_8), 6.70 (2H, d, *J* = 8.7 Hz, H_4), 6.40 (1H, dd, *J* = 17.0, 2.0 Hz, H_9), 5.79 (1H, dd, *J* = 10.5, 2.1 Hz, H_9'), 3.08 (3H, s, H_1); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 188.5 (C_7), 153.5 (C_6), 132.4 (C_8), 131.2 (C_5), 128.0 (C_9), 124.8 (C_3), 111.1 (C_4), 40.3 (C_1); **IR** (neat) cm^{-1}: 1651, 1612, 1591, 1548, 1529, 1435, 1399, 1378, 1328, 1265, 1232, 1196, 981, 786; **m.p.** = 88-89 °C. Spectroscopic data were consistent with the literature data for this compound.[145]

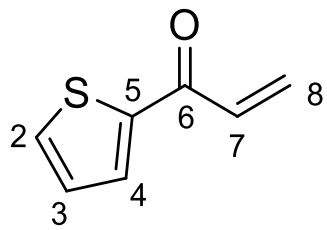
***N*-Methoxy-*N*-methylthiophene-2-carboxamide (S77):**



The title compound was prepared according to a literature procedure reported by Nelson and co-workers:[134] Thiophene carbonyl chloride (1.5 g, 10 mmol, 1.0 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride (1.2 g, 12 mmol, 1.2 equiv.) were dissolved in CH_2Cl_2 (25 mL) at 0 °C. NEt_3 (3.5 mL, 25 mmol, 2.5 equiv.) was added to the solution dropwise, then the reaction mixture was warmed to r.t. and stirred for 1 hr. The solution was diluted with H_2O, shaken and the layers partitioned. The aqueous layer was extracted twice with CH_2Cl_2, the organic layers were combined, dried over Na_2SO_4, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (25% EtOAc in pentane) afforded **S77** as a pale-orange oil (1.4 g, 84%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.96 (1H, dd, *J* = 3.9, 1.3 Hz, H_2), 7.54 (1H, dd, *J* = 5.1, 1.3 Hz, H_4), 7.10 (1H, dd, *J* = 5.1, 3.8 Hz, H_3), 3.77 (3H, s, H_{10}), 3.37 (3H, s, H_8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 162.4 (C_6), 134.5 (C_2), 133.4 (C_5), 132.3 (C_4), 126.9 (C_3), 61.7 (C_{10}), 33.2 (C_8); **IR** (neat) cm^{-1}: 2361, 1622, 1517, 1421, 1382, 1340, 1227, 1207, 1061, 1035, 978, 854, 839, 726, 660; **LRMS** (ESI$^+$) m/z calc. for $C_7H_{10}NO_2S$ $[M+H]^+$ 172.0; found at 172.0 Δ 0 ppm. Spectroscopic data were consistent with the literature data for this compound.[135]

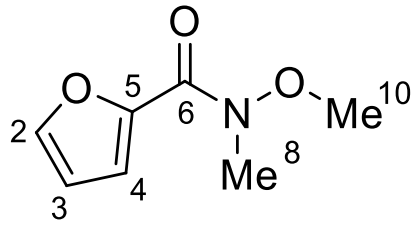
1-(Thiophen-2-yl)prop-2-en-1-one (77):



The title compound was prepared according to a literature procedure reported by Nelson and co-workers:[134] *N*-Methoxy-*N*-methylthiophene-2-carboxamide **S77** (1.4 g, 8.0 mmol, 1.0 equiv.) was dissolved in anhydrous THF (15 mL) in a flame dried flask and cooled to 0 °C. Vinyl magnesium bromide (10 mL, 10 mmol, 1.0 M in THF, 1.2 equiv.) was added dropwise, then the reaction mixture was stirred at r.t. for 1 h, after which the solution was cooled to 0 °C and quenched with 3.0 M aq. HCl. The layers were partitioned and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (20% Et_2O in pentane) afforded **77** as a pale-yellow oil (0.60 g, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.78 (1H, dd, *J* = 3.8, 1.2 Hz, H_4), 7.68 (1H, dd, *J* = 4.9, 1.1 Hz, H_2), 7.16 (1H, dd, *J* = 5.0, 3.8 Hz, H_3), 7.08 (1H, dd, *J* = 17.0, 10.5 Hz, H_7), 6.51 (1H, dd, *J* = 17.0, 1.6 Hz, H_8), 5.88 (1H, dd, *J* = 10.5, 1.6 Hz, H_8'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 182.6 (C_6), 144.7 (C_5), 134.4 (C_2), 132.6 (C_4), 132.0 (C_7), 129.6 (C_8), 128.4 (C_3); **IR** (neat) cm^{-1}: 2360, 1649, 1605, 1515, 1415, 1354, 1289, 1245, 1067, 977, 934, 856, 783, 725, 647. Spectroscopic data were consistent with the literature data for this compound.[136]

***N*-Methoxy-*N*-methylfuran-2-carboxamide (S75):**

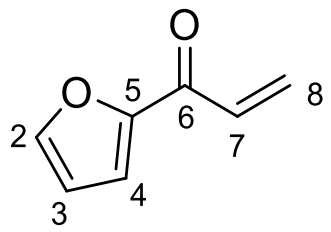


The title compound was prepared according to a literature procedure reported by Nelson and co-workers:[134] Furoyl chloride (1.3 g, 10 mmol, 1.0 equiv.) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.2 g, 12 mmol, 1.2 equiv.) were dissolved in CH_2Cl_2 (25 mL) at 0 °C. NEt_3 (3.5 mL, 25 mmol, 2.5 equiv.) was added to the solution dropwise, then the reaction mixture was warmed to r.t. and stirred for 1 hr. The solution was diluted with H_2O, shaken and the

layers partitioned. The aqueous layer was extracted twice with CH_2Cl_2, the organic layers were combined, dried over Na_2SO_4, filtered under gravity and concentrated *in vacuo* to afford **S75** as a pale-red oil (1.6 g, *quant.*) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.58 (1H, dt, *J* = 1.5, 0.7 Hz, H_2), 7.14 (1H, dt, *J* = 3.5, 0.7 Hz, H_4), 6.53 – 6.46 (1H, m, H_3), 3.76 (3H, d, *J* = 0.6 Hz, H_{10}), 3.35 (3H, d, *J* = 0.6 Hz, H_8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 159.3 (C_6), 145.8 (C_5), 145.4 (C_2), 117.5 (C_4), 111.7 (C_3), 61.5 (C_{10}), 33.3 (C_8); **IR** (neat) cm^{-1}: 1640, 1562, 1476, 1418, 1390, 1231, 1178, 1115, 1070, 1024, 980, 932, 886, 859, 762, 745, 668. Spectroscopic data were consistent with the literature data for this compound.[135]

1-(Furan-2-yl)prop-2-en-1-one (75):

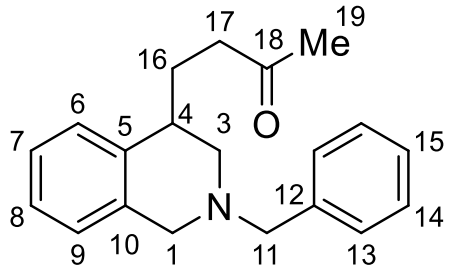


The title compound was prepared according to a literature procedure reported by Nelson and co-workers:[134] *N*-Methoxy-*N*-methylfuran-2-carboxamide **S75** (1.4 g, 10 mmol, 1.0 equiv.) was dissolved in anhydrous THF (15 mL) in a flame dried flask and cooled to 0 °C. Vinyl magnesium bromide (12 mL, 1.0 M in THF, 12 mmol, 1.2 equiv.) was added dropwise, then the reaction mixture was stirred at r.t. for 1 h, after which the solution was cooled to 0 °C and quenched with 3.0 M aq. HCl. The layers were partitioned and the aqueous layer was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo* to afford **75** as a pale-yellow oil (1.1 g, 88%) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.63 (1H, dd, *J* = 1.7, 0.8 Hz, H_2), 7.27 (1H, dd, *J* = 3.6, 0.8 Hz, H_4), 7.06 (1H, dd, *J* = 17.2, 10.5 Hz, H_7), 6.56 (1H, d, *J* = 1.6 Hz, H_3), 6.55 (1H, dd, *J* = 20.5, 1.8 Hz, H_8), 5.87 (1H, dd, *J* = 10.5, 1.7 Hz, H_8'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 178.2 (C_6), 153.1 (C_5), 147.1 (C_2), 131.5 (C_7), 129.6 (C_8), 118.4 (C_4), 112.6 (C_3); **IR** (neat) cm^{-1}: 1666, 1608, 1567, 1465, 1408, 1271, 1225, 1164, 1087, 1032, 1004, 983, 911, 898, 883, 764, 731, 637. Spectroscopic data were consistent with the literature data for this compound.[136]

8.4 Experimental data for Chapter 3

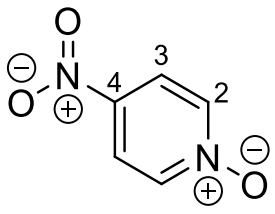
(*RS*)-4-(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one (157):



The title compound was prepared according to **General Procedure C** on 1.4 mmol scale using MVK (120 μL, 1.4 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (10% Et_2O in pentane) afforded **157** as a pale-yellow oil (260 mg, 62%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.39 (2H, d, *J* = 6.8 Hz, H_{13}), 7.34 (2H, t, *J* = 7.5 Hz, H_{14}), 7.28 (1H, s, H_{15}), 7.20 – 7.14 (2H, m, H_6, H_7), 7.12 (1H, td, *J* = 7.3, 1.8 Hz, H_8), 7.00 (1H, d, *J* = 7.5 Hz, H_9), 3.81 (1H, d, *J* = 14.8 Hz, H_1), 3.75 (1H, d, *J* = 13.0 Hz, H_{11}), 3.56 (1H, d, *J* = 13.0 Hz, H_{11}'), 3.48 (1H, d, *J* = 14.8 Hz, H_1'), 2.80 (1H, dq, *J* = 8.5, 4.2 Hz, H_4), 2.72 – 2.67 (1H, m, H_3), 2.54 (1H, dd, *J* = 11.6, 4.3 Hz, H_3'), 2.39 (1H, ddd, *J* = 16.3, 9.4, 6.4 Hz, H_{17}), 2.28 (1H, ddd, *J* = 16.7, 9.6, 5.5 Hz, H_{17}'), 2.07 (3H, s, H_{19}), 2.06 – 1.94 (2H, m, H_{16}, H_{16}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 209.1 (C_{18}), 138.8 (C_{12}), 138.4 (C_5), 135.1 (C_{10}), 129.2 (C_{13}), 128.5 (C_6), 128.4 (C_{14}), 127.3 (C_{15}), 126.6 (C_9), 126.4 (C_7), 126.0 (C_8), 62.9 (C_{11}), 56.9 (C_1), 53.9 (C_3), 41.4 (C_{17}), 38.0 (C_4), 30.0 (C_{19}), 30.0 (C_{16}); **IR** (neat) cm^{-1}: 3026, 2798, 1714, 1493, 1453, 1392, 1367, 1266, 1240, 1160, 1096, 1071, 1028, 977, 912, 741, 701, 669, 651, 635; **LRMS** (ESI^+) m/z calc. for $C_{20}H_{24}NO$ $[M + H]^+$ 294.2; found at 294.2 Δ 0 ppm. Spectroscopic data were consistent with the literature data for this compound.[23]

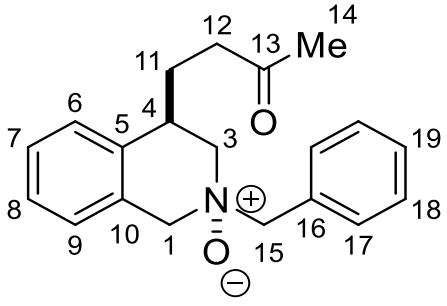
4-Nitropyridine 1-oxide (160):



Pyridine-*N*-oxide (2.4 g, 25 mmol, 1.0 equiv.) was stirred with conc. HNO_3 (1.9 mL, 46 mmol, 1.8 equiv.) and conc. H_2SO_4 (7.0 mL, 140 mmol, 5.6 equiv.) at 130 °C for 3 h. The solution was poured onto ice, then neutralised with solid Na_2CO_3 and diluted with CH_2Cl_2. The mixture was shaken, the layers were partitioned, then the aqueous phase extracted twice with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered under gravity then concentrated in vacuo to give a pale-yellow powder. Recrystallisation from boiling acetone afforded **160** as bright yellow crystals (1.9 g, 54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.30 – 8.19 (2H, m, H_3), 8.15 – 8.07 (2H, m, H_2); **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C = 142.3 (C_4), 140.3 (C_3), 121.0 (C_2); **IR** (neat) cm^{-1}: 1603, 1588, 1511, 1461, 1363, 1346, 1284, 1267, 1233, 1198, 1174, 1121, 1097, 1019, 961, 863, 829, 749, 681, 647; **HRMS** (ESI^+) m/z calc. for $C_5H_5N_2O_3$ $[M+H]^+$ 141.0295; Molecule could not be observed by ESI MS; **m.p.** = 148-149 °C. Spectroscopic data were consistent with the literature data for this compound.[155]

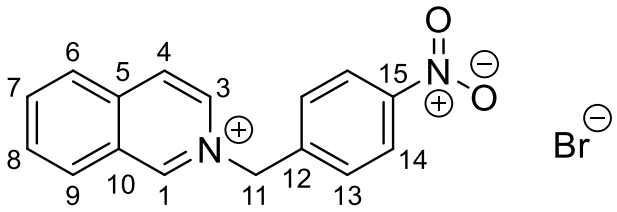
(*RS, RS*)-2-Benzyl-4-(3-oxobutyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide (162):



4-(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one **162** (100 mg, 0.34 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (5.0 mL) and cooled to -78 °C with stirring. 3-Chloroperoxybenzoic acid (65 mg, 0.38 mmol, 1.1 equiv.) was added portionwise and the solution allowed to warm slowly to r.t. overnight. Sat. aq. $Na_2S_2O_3$ was added and the mixture was diluted with CH_2Cl_2. The layers were partitioned and the aqueous layer extracted twice with CH_2Cl_2. The combined organic layers were washed with 2.0 M aq. NaOH, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Column chromatography (initial flush with 50% Et_2O in pentane followed by final flush with 5% MeOH in CH_2Cl_2) afforded **162** as a pale-orange oil as a single diastereomer (94 mg, 89%, 90% purity).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.50 – 7.45 (2H, m, H_{17}), 7.36 – 7.27 (3H, m, H_{18}, H_{19}), 7.22 (1H, d, *J* = 7.8 Hz, H_6), 7.11 (1H, t, *J* = 7.6 Hz, H_7), 7.02 (1H, t, *J* = 7.5 Hz, H_8), 6.79 (1H, d, *J* = 7.7 Hz, H_9), 4.48 – 4.38 (3H, m, H_1, H_{15}), 3.93 (1H, d, *J* = 14.5 Hz, H_1'), 3.68 (1H, qd, *J* = 9.8, 6.3 Hz, H_4), 3.34 (1H, ddd, *J* = 11.5, 5.9, 2.5 Hz, H_3), 3.02 (1H, t, *J* = 11.4 Hz, H_3'), 2.36 – 2.30 (2H, m, H_{12}, H_{12}'), 2.13 (1H, dtd, *J* = 15.2, 7.6, 3.4 Hz, H_{11}), 1.99 (3H, s, H_{14}), 1.85 (1H, dq, *J* = 15.4, 7.7 Hz, H_{11}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 207.5 (C_{13}), 134.6 (C_5), 132.4 (C_{17}), 129.6 (C_{16}), 129.5 (C_{19}), 128.9 (C_{10}), 128.5 (C_{18}), 127.5 (C_7), 127.1 (C_9), 126.4 (C_8), 125.8 (C_6), 76.4 (C_{15}), 65.6 (C_1), 65.5 (C_3), 40.0 (C_{12}), 32.8 (C_4), 29.9 (C_{14}), 24.2 (C_{11}); **IR** (neat) cm^{-1}:1713, 1497, 1456, 911, 731, 702; **HRMS** (ESI$^+$) m/z calc. for $C_{20}H_{24}NO_2$ $[M+H]^+$ 310.1802; found at 310.1801 Δ -0.19 ppm.

2-(4-Nitrobenzyl)isoquinolin-2-ium bromide (S163):

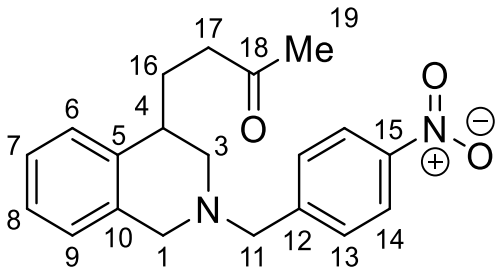


Isoquinoline (2.58 g, 20.0 mmol, 1.00 equiv.) was dissolved in acetone (30 mL) with *para*-nitrobenzyl bromide (5.18 g, 24.0 mmol, 1.20 equiv.) and stirred at 60 °C for 1 h. The resultant slurry was filtered *in vacuo*, then the solid was suspended in Et_2O and stirred for 3 h. The solid was collected and dried *in vacuo* to afford **S163** as an off-white solid (6.28 g, 91%).

N.B. The title compound was extremely insoluble in most common organic NMR solvents, therefore the quality of the data obtained was poor. The peak shape was broad in all cases and challenging to characterise. The multiplicity of the peaks is recorded as observed but may not be truly representative of the nature of the coupling.

^{1}H NMR (600 MHz, DMSO): δ_H = 10.59 – 10.26 (1H, m, H_1), 8.96 – 8.81 (1H, m, H_3), 8.69 – 8.62 (1H, m, H_4), 8.55 (1H, d, *J* = 8.1 Hz, H_9), 8.42 – 8.36 (1H, m, H_6), 8.33 – 8.23 (3H, m, H_7, H_{14}), 8.11 (1H, ddt, *J* = 10.7, 7.0, 2.4 Hz, H_8), 7.92 – 7.81 (2H, m, H_{13}), 6.27 – 6.15 (2H, m, H_{11}); **^{13}C NMR** (151 MHz, DMSO): δ_C = 150.8 (C_1), 147.9 (C_{15}), 141.3 (C_{12}), 137.3 (C_7), 137.2 (C_5), 135.0 (C_3), 131.4 (C_8), 130.7 (C_9), 130.2 (C_{13}), 127.4 (2C, C_6, C_{10}), 126.4 (C_4), 124.1 (C_{14}), 62.0 (C_{11}); **IR** (neat) cm^{-1}: 3494, 3458, 1643, 1609, 1534, 1403, 1349, 869, 855, 839, 812, 759, 719; **HRMS** (ESI$^+$) m/z calc. for $C_{16}H_{13}N_2O_2$ $[M]^+$ 265.0972; found at 265.0970 Δ -0.75 ppm; **m.p.** = 192-194 °C. Spectroscopic data were consistent with the literature data for this compound.[156]

(*RS*)-4-(2-(4-Nitrobenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one (163):

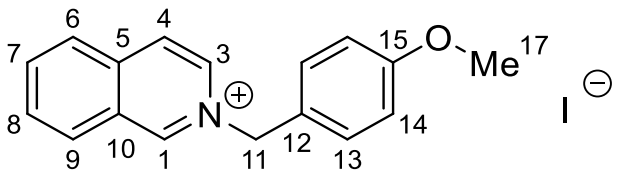


The title compound was prepared according to **General Procedure C** using 2-(4-nitrobenzyl)isoquinolin-2-ium bromide **S163** (516 mg, 1.50 mmol, 1.00 equiv.) and MVK

(126 μL, 1.25 mmol, 1.00 equiv.) as the electrophile. Purification by flash column chromatography (5-20% EtOAc in pentane) afforded **163** as a pale-orange oil (32 mg, 6%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.20 – 8.17 (2H, m, H_{14}), 7.59 – 7.55 (2H, m, H_{13}), 7.22 – 7.16 (2H, m, H_6, H_7), 7.13 (1H, td, *J* = 7.3, 1.8 Hz, H_8), 7.00 – 6.96 (1H, m, H_9), 3.82 – 3.75 (2H, m, H_1, H_{11}), 3.70 (1H, d, *J* = 14.0 Hz, H_{11}'), 3.48 (1H, d, *J* = 14.7 Hz, H_1'), 2.83 (1H, dq, *J* = 7.9, 4.4 Hz, H_4), 2.69 – 2.61 (2H, m, H_3, H_3'), 2.47 – 2.30 (2H, m, H_{17}, H_{17}'), 2.10 (3H, s, H_{19}), 2.04 (2H, tdd, *J* = 7.3, 5.9, 2.2 Hz, H_{16}, H_{16}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 208.7 (C_{18}), 147.4 (C_{12}), 146.7 (C_{15}), 137.9 (C_5), 134.5 (C_{10}), 129.6 (C_{13}), 128.5 (C_6), 126.6 (C_9), 126.5 (C_7), 126.1 (C_6), 123.7 (C_{14}), 62.2 (C_{11}), 56.6 (C_1), 54.7 (C_3), 41.4 (C_{17}), 37.9 (C_4), 30.1 (C_{19}), 29.8 (C_{16}); **IR** (neat) cm^{-1}:1713, 1605, 1519, 1344, 1161, 1145, 1107, 1095, 912, 859, 739; **HRMS** (ESI$^+$) m/z calc. for $C_{20}H_{23}N_2O_3$ $[M+H]^+$ 339.1703; found at 339.1707 Δ 1.18 ppm.

2-(4-Methoxybenzyl)isoquinolin-2-ium iodide (S164):

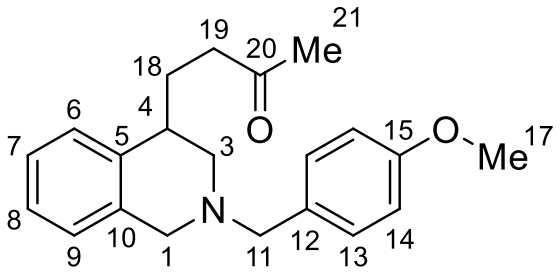


Isoquinoline (1.29 g, 10.0 mmol, 1.00 equiv.) was dissolved in acetone (40 mL) with 4-methoxybenzyl chloride (1.88 g, 12.0 mmol, 1.20 equiv.) and KI (3.32 g, 20.0 mmol, 2.00 equiv.) then stirred at r.t. for 4 h. The resultant precipitate was isolated by filtration, washed with H_2O and acetone, then dried *in vacuo* to give **S164** as a pale-yellow solid (3.27 g, 87%).

^{1}H NMR (600 MHz, DMSO): δ_H = 10.33 (1H, s, H_1), 8.84 (1H, dt, *J* = 6.9, 1.3 Hz, H_3), 8.60 (1H, d, *J* = 6.8 Hz, H_4), 8.53 (1H, dd, *J* = 8.4, 1.2 Hz, H_9), 8.35 (1H, dd, *J* = 8.4, 1.1 Hz, H_6), 8.26 (1H, ddd, *J* = 8.3, 7.0, 1.2 Hz, H_7), 8.08 (1H, ddd, *J* = 8.2, 6.9, 1.1 Hz, H_8), 7.64 – 7.58

(2H, m, H_{13}), 7.03 – 6.97 (2H, m, H_{14}), 5.92 (2H, s, H_{11}), 3.75 (3H, s, H_{17}); **^{13}C NMR** (151 MHz, DMSO): δ_C = 160.0 (C_{15}), 149.7 (C_1), 137.0 (C_7), 137.0 (C_5), 134.5 (C_3), 131.3 (C_8), 130.7 (C_{13}), 130.5 (C_9), 127.3 (C_6), 127.2 (C_{10}), 126.2 (C_4), 126.0 (C_{12}), 114.5 (C_{14}), 62.9 (C_{11}), 55.3 (C_{17}); **IR** (neat) cm^{-1}: 1644, 1605, 1512, 1471, 1444, 1398, 1364, 1307, 1283, 1249, 1208, 1187, 1146, 1108, 1013, 988, 968, 944, 883, 858, 838, 822, 777, 765, 740, 700; **HRMS** (ESI$^+$) m/z calc. for $C_{17}H_{16}NO$ $[M]^+$ 250.1226; found at 250.1220 Δ -2.58 ppm; m/z calc. for I $[I]^-$ 126.9050; found at 126.9051 Δ 0.79 ppm; **m.p.** = 206-208 °C. Spectroscopic data were consistent with the literature data for this compound.[157]

(*RS*)-4-(2-(4-Methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one (164):

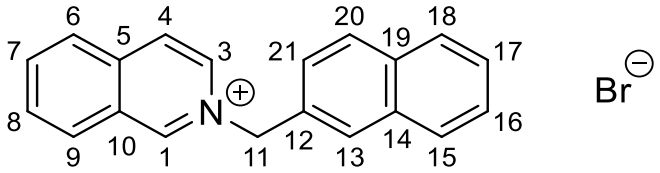


The title compound was prepared according to **General Procedure C** using 2-(4-methoxybenzyl)isoquinolin-2-ium iodide **S164** (1.13 g, 3.00 mmol, 1.00 equiv.) and MVK (252 μL, 3.00 mmol, 1.00 equiv.) as the electrophile. Purification by flash column chromatography (15-50% EtOAc in pentane) afforded **164** as a pale-yellow oil (275 mg, 28%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.32 – 7.28 (2H, m, H_{13}), 7.18 (1H, dd, *J* = 7.7, 1.8 Hz, H_6), 7.17 – 7.14 (1H, m, H_7), 7.11 (1H, td, *J* = 7.3, 1.8 Hz, H_8), 7.03 – 6.97 (1H, m, H_9), 6.91 – 6.84 (2H, m, H_{14}), 3.81 (3H, s, H_{17}), 3.80 – 3.75 (1H, m, H_1), 3.69 (1H, d, *J* = 12.8 Hz, H_{11}), 3.48 (2H, m, H_1', H_{11}'), 2.81 (1H, dt, *J* = 8.6, 4.1 Hz, H_4), 2.71 – 2.65 (1H, m, H_3), 2.53 (1H, dd, *J* = 11.7, 4.3 Hz, H_3'), 2.39 (1H, ddd, *J* = 16.2, 9.3, 6.5 Hz, H_{19}), 2.28 (1H, ddd, *J* = 16.8, 9.4, 5.6 Hz, H_{19}'), 2.08 (3H, s, H_{21}), 2.05 – 1.94 (2H, m, H_{18}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 209.1 (C_{20}), 159.0 (C_{15}), 138.4 (C_5), 135.1 (C_{10}), 130.6 (C_{12}), 130.4 (C_{13}), 128.5 (C_6), 126.6

(C_9), 126.4 (C_7), 126.0 (C_8), 113.8 (C_{14}), 62.1 (C_{11}), 56.7 (C_1), 55.4 (C_{17}), 53.8 (C_3), 41.4 (C_{19}), 37.8 (C_4), 30.0 (C_{21}), 29.9 (C_{18}); **IR** (neat) cm^{-1}: 2932, 2796, 1714, 1612, 1513, 1464, 1454, 1367, 1302, 1248, 1172, 1094, 1036, 835, 739, 646, 633; **HRMS** (ESI^+) m/z calc. for $C_{21}H_{26}NO_2$ $[M+H]^+$ 324.1958; found at 324.1973 Δ 4.63 ppm.

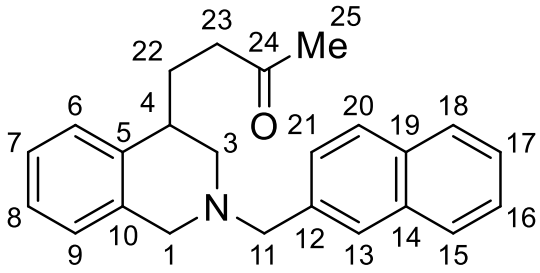
2-(Naphthalen-2-ylmethyl)isoquinolin-2-ium bromide (S165):



Isoquinoline (0.65 g, 5.0 mmol, 1.0 equiv.) was dissolved in acetone (25 mL) along with 2-bromomethylnaphthalene (1.4 g, 6.0 mmol, 1.2 equiv.) and stirred at r.t. for 3 h. The resultant precipitate was filtered *in vacuo* to afford **S165** as a pale-yellow solid (0.67 g, 38%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 11.19 (1H, d, *J* = 1.4 Hz, H_1), 8.94 (1H, dd, *J* = 6.8, 1.4 Hz, H_3), 8.54 (1H, dt, *J* = 8.5, 1.0 Hz, H_9), 8.27 (1H, d, *J* = 1.8 Hz, H_{13}), 8.13 (1H, d, *J* = 6.8 Hz, H_4), 7.93 – 7.87 (2H, m, H_6, H_7), 7.78 – 7.69 (3H, m, H_8, H_{15}, H_{21}), 7.68 – 7.62 (2H, m, H_{18}, H_{20}), 7.41 – 7.33 (2H, m, H_{16}, H_{17}), 6.54 (2H, s, H_{11}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 150.2 (C_1), 137.2 (C_6), 137.0 (C_5), 134.5 (C_3), 133.4 (C_{19}), 133.1 (C_{14}), 131.2 (C_8), 131.1 (C_9), 130.7 (C_{12}), 129.7 (C_{13}), 129.6 (C_{20}), 128.4 (C_{15}), 127.7 (C_{18}), 127.7 (C_{10}), 127.2 (C_7), 127.0 (C_{17}), 126.8 (C_{16}), 126.2 (C_4), 126.1 (C_{21}), 63.8 (C_{11}); **IR** (neat) cm^{-1}: 1644, 1508, 1470, 1442, 1399, 1366, 1338, 1182, 1118, 998, 973, 938, 883, 870, 838, 778, 760, 698; **HRMS** (ESI^+) m/z calc. for $C_{20}H_{16}N$ $[M]^+$ 270.1277; found at 270.1275 Δ -0.74 ppm; **m.p.** = 183-184 °C. Spectroscopic data were consistent with the literature data for this compound.[158]

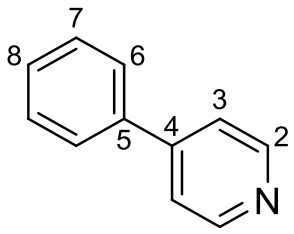
(*RS*)-4-(2-(Naphthalen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one (165):



The title compound was prepared according to **General Procedure C** using 2-(naphthalen-2-ylmethyl)isoquinolin-2-ium bromide **S165** (352 mg, 1.00 mmol, 1.00 equiv.) and MVK (84.0 μL, 1.00 mmol, 1.00 equiv.) as the electrophile. Purification by flash column chromatography (5-10% acetone in pentane) afforded **165** as a pale-yellow oil (188 mg, 55%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.86 – 7.80 (4H, m, H_{13}, H_{15}, H_{17}, H_{20}), 7.58 (1H, dd, *J* = 8.4, 1.6 Hz, H_{21}), 7.54 – 7.43 (2H, m, H_{16}, H_{18}), 7.20 (1H, dd, *J* = 7.8, 1.6 Hz, H_6), 7.19 – 7.15 (1H, m, H_7), 7.13 (1H, td, *J* = 7.3, 1.8 Hz, H_8), 7.00 (1H, dd, *J* = 7.4, 1.4 Hz, H_9), 3.93 (1H, d, *J* = 13.0 Hz, H_{11}), 3.87 (1H, d, *J* = 14.8 Hz, H_1), 3.73 (1H, d, *J* = 13.0 Hz, H_{11}'), 3.56 (1H, d, *J* = 14.9 Hz, H_1'), 2.83 (1H, dq, *J* = 8.7, 4.2 Hz, H_4), 2.75 (1H, dd, *J* = 11.7, 3.9 Hz, H_3), 2.62 (1H, dd, *J* = 12.0, 4.1 Hz, H_3'), 2.37 (1H, ddd, *J* = 16.2, 9.5, 6.3 Hz, H_{23}), 2.25 (1H, ddd, *J* = 16.9, 9.6, 5.4 Hz, H_{23}'), 2.11 – 2.00 (2H, m, H_{22}'), 2.00 (3H, s, H_{25}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 209.0 (C_{24}), 138.3 (C_5), 136.1 (C_{12}), 134.9 (C_{10}), 133.5 (C_{14}), 133.0 (C_{19}), 128.5 (C_6), 128.1 (C_{15}), 127.8 (C_{18}), 127.8 (C_{20}), 127.8 (C_{13}), 127.4 (C_{21}), 126.6 (C_9), 126.5 (C_7), 126.2 (C_{18}), 126.0 (C_8), 125.8 (C_{16}), 62.9 (C_{11}), 56.8 (C_1), 53.9 (C_3), 41.4 (C_{23}), 37.8 (C_4), 30.0 (C_{25}), 29.8 (C_{22}); **IR** (neat) cm^{-1}: 3059, 1713, 1450, 1368, 1160, 1095, 911, 858, 821, 742; **HRMS** (ESI$^+$) m/z calc. for $C_{24}H_{26}NO$ $[M+H]^+$ 344.2009; found at 344.2013 Δ 1.16 ppm.

4-Phenyl pyridine (166):



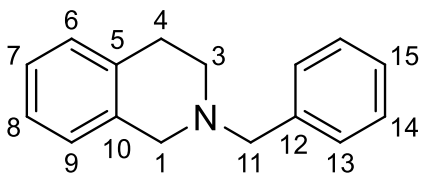
4-Phenyl pyridine was isolated as a side product of a reaction to produce 4-(isoquinolin-4-yl)butan-2-one **22** from 4-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one **157**.

4-(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one **157** (37.0 mg, 0.125 mmol, 1.00 equiv.) was placed in a microwave vial with 4-phenyl pyridine-*N*-oxide **161** (32.0 mg, 0.188 mmol, 1.50 equiv.) and camphor (0.20 g), sealed with a crimped cap, heated to 250 °C for 40 min then cooled to r.t. Purification by flash column chromatography (60-80% EtOAc in pentane) afforded **22** as a pale-yellow oil (21 mg, 85%) and 4-phenyl pyridine, **166**, as a pale-brown solid (29 mg, quant.).

Characterisation data for **166**:

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.70 – 8.63 (2H, m, H_2), 7.67 – 7.60 (2H, m, H_6), 7.53 – 7.39 (5H, m, H_3, H_7, H_8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 150.4 (C_2), 148.5 (C_4), 138.3 (C_5), 129.2 (C_7), 129.2 (C_8), 127.1 (C_6), 121.8 (C_3). Spectroscopic data were consistent with the literature data for this compound.[159]

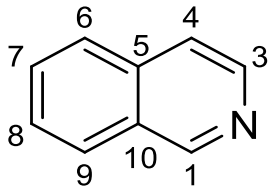
2-Benzyl-1,2,3,4-tetrahydroisoquinoline (159):



1,2,3,4-Tetrahydroisoquinoline (1.25 mL, 10.0 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (20 mL) with NEt_3 (4.2 mL, 30 mmol, 3.0 equiv.). BnBr (1.78 mL, 15.0 mmol, 1.50 equiv.) was added dropwise, then the solution was stirred at r.t. overnight. The reaction was quenched with H_2O, diluted with CH_2Cl_2, shaken and the layers partitioned. The aqueous phase was extracted twice with CH_2Cl_2, then the combined organic layers were washed once with brine, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. The residue was passed through a short silica plug to afford **159** as a pale-yellow oil (1.63 g, 73%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.43 – 7.39 (2H, m, H_{13}), 7.38 – 7.32 (2H, m, H_{14}), 7.30 – 7.26 (1H, m, H_{15}), 7.16 – 7.07 (3H, m, H_6, H_7, H_8), 7.01 – 6.97 (1H, m, H_9), 3.70 (2H, s, H_{11}), 3.65 (2H, s, H_1), 2.91 (2H, t, *J* = 6.0 Hz, H_4), 2.76 (2H, t, *J* = 5.9 Hz, H_3); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 138.6 (C_{12}), 135.1 (C_{10}), 134.6 (C_5), 129.2 (C_{13}), 128.8 (C_6), 128.4 (C_{14}), 127.2 (C_{15}), 126.7 (C_9), 126.2 (C_7), 125.7 (C_8), 63.0 (C_{11}), 56.3 (C_1), 50.8 (C_3), 29.3 (C_4); **IR** (neat) cm^{-1}: 3025, 2917, 2801, 1496, 1454, 1368, 1344, 1131, 1094, 935, 740, 699; **HRMS** (ESI^+) m/z calc. for $C_{16}H_{18}N$ $[M+H]^+$ 224.1434; found at 224.1438 Δ 1.88 ppm. Spectroscopic data were consistent with the literature data for this compound.[160]

Isoquinoline (1):



The title compound was prepared according to **General Procedure D** with *N*-benzyl tetrahydroisoquinoline **159** (56 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (20% EtOAc in pentane) afforded **1** as a brown solid (25 mg, 76%).

N-benzyl tetrahydroisoquinoline **159** (56 mg, 0.25 mmol, 1.0 equiv.) was heated to 250 °C in a microwave vial for 40 min with camphor (0.20 g), sealed with a crimped cap. Flash column chromatography (20% EtOAc in pentane) afforded **1** as a brown solid (10 mg, 31%).

The title compound was prepared according to **General Procedure D** with 1,2,3,4-tetrahydroisoquinoline **142** (33 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (20% EtOAc in pentane) afforded **1** as a brown solid (16 mg, 51%).

1,2,3,4-Tetrahydroisoquinoline **142** (33 mg, 0.25 mmol, 1.0 equiv.) was heated to 250 °C in a microwave vial for 40 min with camphor (0.20 g), sealed with a crimped cap. Flash column chromatography (20% EtOAc in pentane) afforded **1** as a brown solid (2.9 mg, 9%).

The title compound was prepared according to **General Procedure D** with 2-benzylisoquinolin-2-ium iodide **19** (87 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (20% EtOAc in pentane) afforded **1** as a brown solid (16 mg, 51%).

2-Benzylisoquinolin-2-ium iodide **19** (87 mg, 0.25 mmol, 1.0 equiv.) was heated to 250 °C in a microwave vial for 40 min with camphor (0.20 g), sealed with a crimped cap. Flash column chromatography (20% EtOAc in pentane) failed to afford any product.

The title compound was prepared according to **General Procedure B** with 3,4-dihydroisoquinoline **143** (33 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (20% EtOAc in pentane) afforded **1** as a brown solid (20 mg, 63%).

3,4-Dihydroisoquinoline **143** (33 mg, 0.25 mmol, 1.0 equiv.) was heated to 250 °C in a microwave vial for 40 min with camphor (0.20 g), sealed with a crimped cap. Flash column chromatography (20% EtOAc in pentane) afforded **1** as a brown solid (16 mg, 51%).

2-Benzyl-3,4-dihydroisoquinolin-2-ium iodide **167** (87 mg, 0.25 mmol, 1.0 equiv.) was placed in a microwave vial with pyridine-*N*-oxide (36 mg, 0.38 mmol, 1.5 equiv.) and camphor

(0.20 g), then heated to 250 °C in a microwave vial sealed with a crimped cap for 40 min. Purification by flash column chromatography (20% EtOAc in pentane) failed to afford any product.

2-Benzyl-3,4-dihydroisoquinolin-2-ium iodide **167** (87 mg, 0.25 mmol, 1.0 equiv.) was placed in a microwave vial with camphor (0.20 g), then heated to 250 °C in a microwave vial sealed with a crimped cap for 40 min. Purification by flash column chromatography (20% EtOAc in pentane) failed to afford any product.

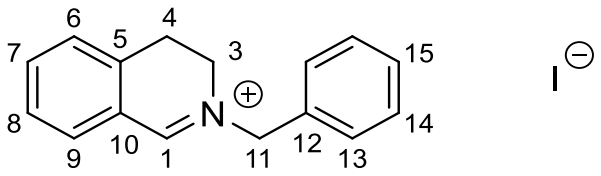
The title compound was prepared according to **General Procedure D** with 3,4-dihydroisoquinoline-2-oxide **174** (37 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (20% EtOAc in pentane) afforded **1** as a brown solid (9.0 mg, 28%).

3,4-Dihydroisoquinoline-2-oxide **174** (37 mg, 0.25 mmol, 1.0 equiv.) was heated to 250 °C in a microwave vial for 40 min with camphor (0.20 g), sealed with a crimped cap. Flash column chromatography (20% EtOAc in pentane) afforded **1** as a brown solid (12 mg, 37%).

3,4-Dihydroisoquinoline-2-oxide **174** (37 mg, 0.25 mmol, 1.0 equiv.) was heated to 250 °C in a microwave vial for 40 min with camphor (0.20 g), and pyridine (30.0 μL, 0.375 mmol, 1.50 equiv.) sealed with a crimped cap. Flash column chromatography (20% EtOAc in pentane) afforded **1** as a brown solid (17 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.24 (1H, s, H_1), 8.51 (1H, d, J = 5.8 Hz, H_3), 7.94 (1H, dd, J = 8.1, 1.1 Hz, H_9), 7.79 (1H, dd, J = 8.2, 1.2 Hz, H_6), 7.66 (1H, ddd, J = 8.3, 6.8, 1.3 Hz, H_7), 7.62 (1H, d, J = 5.7 Hz, H_4), 7.57 (1H, ddd, J = 8.1, 6.8, 1.2 Hz, H_8); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 152.6 (C_1), 143.0 (C_3), 135.8 (C_5), 130.4 (C_7), 128.7 (C_{10}), 127.7 (C_9), 127.3 (C_8), 126.5 (C_6), 120.5 (C_4). Spectroscopic data were consistent with the literature data for this compound.[161]

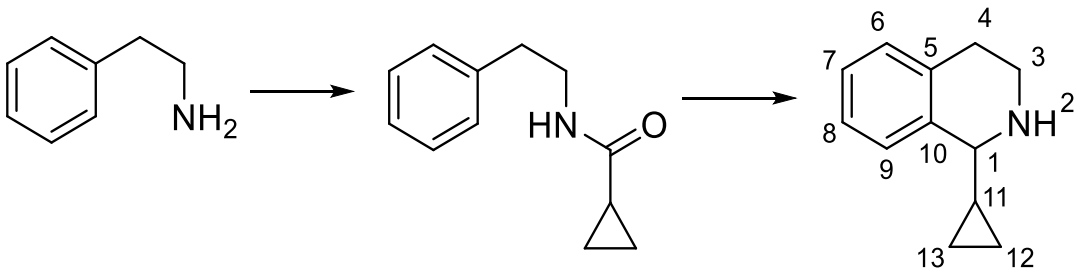
2-Benzyl-3,4-dihydroisoquinolin-2-ium iodide (167):



3,4-Dihydroisoquinoline (262 mg, 2.00 mmol, 1.00 equiv.) was dissolved in acetone (5.0 mL) with BnI (523 mg, 2.40 mmol, 1.20 equiv.) and stirred at r.t. overnight, then triturated with Et_2O. The precipitate was filtered under vacuum to afford **167** as a pale-yellow solid (657 mg, 94%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 10.33 (1H, s, H_1), 8.09 (1H, d, *J* = 7.7 Hz, H_9), 7.65 (1H, t, *J* = 7.6 Hz, H_7), 7.62 (2H, dd, *J* = 6.6, 2.9 Hz, H_{13}), 7.43 – 7.36 (4H, m, H_8, H_{14}, H_{15}), 7.30 (1H, d, *J* = 7.6 Hz, H_6), 5.54 (2H, s, H_{11}), 4.00 (2H, t, *J* = 8.1 Hz, H_3), 3.25 (2H, t, *J* = 8.1 Hz, H_4); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 166.1 (C_1), 138.3 (C_7), 136.1 (C_5), 135.0 (C_9), 130.6 (C_{12}), 130.1 (C_{15}), 130.0 (C_{13}), 129.7 (C_{14}), 128.8 (C_8), 128.3 (C_6), 124.6 (C_{10}), 64.1 (C_{11}), 48.5 (C_3), 25.6 (C_4); **IR** (neat) cm^{-1}: 3006 (br), 1654, 1603, 1572, 1491, 1445, 1415, 1361, 1312, 1286, 1227, 1152, 1134, 1087, 1051, 1003, 783, 773, 717, 702; **HRMS** (ESI$^+$) m/z calc. for $C_{16}H_{16}N$ $[M]^+$ 222.1277; found at 222.1282 Δ 2.12 ppm; **LRMS** (ESI$^+$) m/z calc. for I $[I]^-$ 126.9; found at 126.9 Δ 0.00 ppm.

(*RS*)-1-Cyclopropyl-1,2,3,4-tetrahydroisoquinoline (S168):



The title compound was prepared according to a literature procedure published by Zheng and co-workers:[162] Phenethylamine (1.3 mL, 10 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2

(50 mL) with NEt_3 (5.5 mL, 40 mmol, 4.0 equiv.) and cooled to 0 °C. Cyclopropane carbonyl chloride (1.0 mL, 11 mmol, 1.1 equiv.) was added dropwise, then the solution was allowed to warm to r.t. and stirred for 1 h. The mixture was quenched with H_2O, shaken and the layers partitioned. The aqueous phase was extracted twice with CH_2Cl_2, then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

The residue was added to polyphosphoric acid (20 g) and heated with stirring to 160 °C for 4 h. After cooling to r.t. the mixture was poured onto ice, then basified with NH_4OH to pH 9. The mixture was then diluted with CH_2Cl_2, shaken and the layers partitioned. The aqueous phase was extracted twice with CH_2Cl_2, then the combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

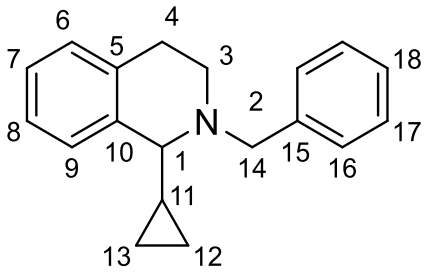
The residue was dissolved in MeOH (20 mL) and cooled to 0°C. $NaBH_4$ (380 mg, 10 mmol, 1.0 equiv.) was added in one portion and the mixture stirred for 1 h. The mixture was then quenched with H_2O, diluted with EtOAc, shaken and the layers partitioned. The aqueous layer was extracted twice with EtOAc, the organic layers were then combined, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (10-20% EtOH in EtOAc) afforded **S168** as a pale-orange oil (590 mg, 34%).

N.B. It was not possible to distinguish between C_{12} and C_{13} on the cyclopropyl ring and therefore assignments are used only to indicate carbon and proton coupling, the atom identities should be considered interchangeable.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.54 (1H, dd, *J* = 5.4, 3.7 Hz, H_9), 7.20 – 7.12 (2H, m, H_7, H_8), 7.12 – 7.08 (1H, m, H_6), 3.37 – 3.28 (1H, m, H_3), 3.11 (1H, d, *J* = 9.5 Hz, H_1), 3.03 – 2.92 (2H, m, H_3', H_4), 2.81 – 2.72 (1H, m, H_4'), 2.25 (1H, br s, H_2), 1.11 (1H, dddd, *J* = 13.0, 9.5, 8.0, 5.0 Hz, H_{11}), 0.87 – 0.78 (1H, m, H_{12}), 0.61 (1H, dq, *J* = 9.5, 5.0 Hz, H_{13}), 0.57 (1H, ddt, *J* = 8.9, 8.0, 5.0 Hz, H_{12}'), 0.38 – 0.31 (1H, m, H_{13}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 139.3

(C_{10}), 134.9 (C_5), 129.2 (C_6), 126.4 (C_9), 126.2 (C_7), 125.7 (C_8), 62.1 (C_1), 42.7 (C_3), 29.9 (C_4), 18.0 (C_{11}), 5.6 (C_{12}), 2.0 (C_{13}); **IR** (neat) cm^{-1}: 1490, 1454, 1396, 1295, 1127, 1020, 758, 741, 638; **HRMS** (ESI^+) m/z calc. for $C_{12}H_{16}N$ $[M+H]^+$ 174.1277; found at 174.1270 Δ -4.19 ppm. Spectroscopic data were consistent with the literature data for this compound.[163]

(*RS*)-2-Benzyl-1-cyclopropyl-1,2,3,4-tetrahydroisoquinoline (168):

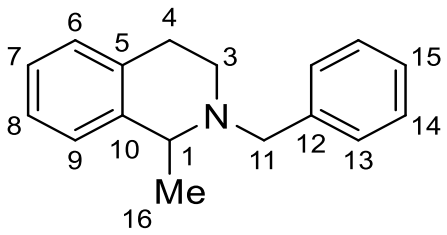


1-Cyclopropyl-1,2,3,4-tetrahydroisoquinoline **S168** (590 mg, 3.4 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (10 mL) with NEt_3 (1.40 mL, 10.2 mmol, 3.00 equiv.). BnBr (0.61 ml, 5.1 mmol, 1.5 equiv.) was added dropwise and the reaction stirred at r.t. overnight. The reaction was diluted with H_2O, shaken and the layers partitioned. The aqueous layer was extracted twice with CH_2Cl_2, then the combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (5-10 % EtOAc in pentane) afforded **168** as a pale-orange oil (481 mg, 54%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.39 (2H, d, *J* = 7.5 Hz, H_{16}), 7.32 (2H, t, *J* = 7.5 Hz, H_{17}), 7.29 – 7.25 (1H, m, H_{18}), 7.21 – 7.16 (2H, m, H_8, H_9), 7.16 – 7.11 (2H, m, H_6, H_7), 3.89 – 3.80 (2H, m, H_{14}, H_{14}), 3.42 – 3.34 (1H, m, H_3), 3.12 (1H, d, *J* = 8.3 Hz, H_1), 2.97 (1H, ddd, *J* = 16.4, 10.0, 6.5 Hz, H_4), 2.93 – 2.87 (1H, m, H_3'), 2.74 – 2.66 (1H, m, H_4'), 1.17 (1H, tq, *J* = 8.1, 4.0 Hz, H_{11}), 0.64 – 0.54 (2H, m, $H_{12/13}$), 0.42 – 0.33 (2H, m, $H_{12/13}$); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 139.9 (C_{15}), 138.2 (C_{10}), 134.5 (C_5), 129.1 (C_6), 129.0 (C_{16}), 128.3 (C_{17}), 128.2 (C_9), 127.0 (C_{18}), 126.4 (C_8), 125.6 (C_7), 64.6 (C_1), 57.8 (C_{14}), 44.3 (C_3), 25.7 (C_4), 15.7 (C_{11}), 4.4 ($C_{12/13}$), 4.1 ($C_{12/13}$); **IR** (neat) cm^{-1}: 3062, 3024, 2913, 2831, 1493, 1453, 1361, 1022, 911,

761, 742, 699; **HRMS** (ESI$^+$) m/z calc. for $C_{19}H_{21}N$ $[M+H]^+$ 264.1747; found at 264.1749 Δ 0.84 ppm.

(*RS*)-2-Benzyl-1-methyl-1,2,3,4-tetrahydroisoquinoline (170):



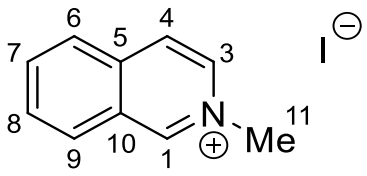
2-Benzyl-1-methylisoquinolin-2-ium bromide **S170** (314 mg, 1.00 mmol, 1.00 equiv.) was dissolved in MeCN (1.0 mL) with 5:2 HCO_2H:NEt_3 (0.34 mL, 4.0 mmol, 4.0 equiv.) then the mixture was stirred at 80 °C for 18 h. After cooling to r.t. the mixture was diluted with EtOAc, quenched with sat. aq. Na_2CO_3, shaken and the layers partitioned. The aqueous layer was extracted twice with EtOAc, then the combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography afforded **170** as a pale-orange oil (146 mg, 62%).

S170 was kindly provided by Mr A. Tinkler.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.45 – 7.37 (2H, m, H_{13}), 7.36 – 7.29 (2H, m, H_{14}), 7.30 – 7.21 (1H, m, H_{15}), 7.18 – 7.12 (2H, m, H_7, H_8), 7.13 – 7.09 (1H, m, H_6), 7.09 – 7.04 (1H, m, H_9), 3.92 (1H, q, *J* = 6.7 Hz, H_1), 3.84 (1H, d, *J* = 13.6 Hz, H_{11}), 3.73 (1H, d, *J* = 13.6 Hz, H_{11}'), 3.14 – 3.06 (1H, m, H_3), 2.92 (1H, ddd, *J* = 15.2, 9.3, 6.0 Hz, H_4), 2.78 – 2.67 (2H, m, H_3', H_4'), 1.42 (3H, d, *J* = 6.7 Hz, H_{16}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 140.4 (C_{10}), 139.5 (C_{12}), 134.4 (C_5), 129.0 (C_6), 128.9 (C_{13}), 128.4 (C_{14}), 127.6 (C_9), 127.1 (C_{15}), 126.0 (C_7), 125.8 (C_8), 58.3 (C_{11}), 56.4 (C_1), 43.9 (C_3), 27.5 (C_4), 19.9 (C_{16}); **IR** (neat) cm^{-1}: 3025, 2971, 2087, 1494, 1453, 1366, 1138, 1102, 759, 738, 699; **HRMS** (ESI$^+$) m/z calc. for $C_{17}H_{20}N$ $[M+H]^+$

238.1590; found at 238.1588 Δ -0.95 ppm. Spectroscopic data were consistent with the literature data for this compound.[164]

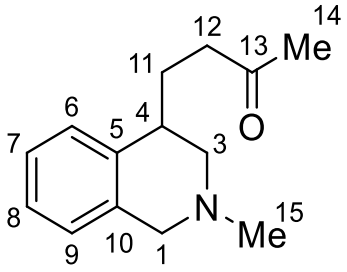
2-Methylisoquinolin-2-ium iodide (172):



The title compound was prepared according to a procedure reported by Donohoe and co-workers:[23] Isoquinoline (1.3 g, 10 mmol, 1.0 equiv.) was dissolved in acetone (20 mL) with methyl iodide (1.2 mL, 20 mmol, 2.0 equiv.) and stirred at r.t. in the dark overnight. The resultant suspension was triturated with Et_2O, filtered under reduced pressure, then the filter cake washed further with Et_2O. The solid was dried *in vacuo* to afford **S172** as a fluffy yellow solid (2.6 g, 96%).

^{1}H NMR (400 MHz, DMSO): δ_H = 10.02 (1H, s, H_1), 8.70 (1H, d, *J* = 1.5 Hz, H_3), 8.57 (1H, d, *J* = 6.8 Hz, H_4), 8.48 (1H, dd, *J* = 8.3, 1.1 Hz, H_9), 8.34 (1H, d, *J* = 1.0 Hz, H_6), 8.25 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz, H_7), 8.07 (1H, ddd, *J* = 8.3, 7.0, 1.2 Hz, H_8), 4.48 (3H, s, H_{11}); **^{13}C NMR** (101 MHz, DMSO): δ_C = 150.7 (C_1), 136.7 (C_7), 136.6 (C_5), 135.9 (C_3), 131.2 (C_8), 130.2 (C_9), 127.2 (C_6), 127.0 (C_{10}), 125.4 (C_4), 47.9 (C_{11}); **IR** (neat) cm^{-1}: 1651, 1396, 1184, 813, 758, 618; **HRMS** (ESI$^+$) m/z calc. for $C_{10}H_{10}N$ $[M]^+$ 144.0808; found at 144.0805 Δ -1.98 ppm; **LRMS** (ESI$^+$) m/z calc. for I $[I]^-$ 126.9; found at 126.9 Δ 0 ppm; **m.p.** = 145-146 °C. Spectroscopic data were consistent with the literature data for this compound.[165]

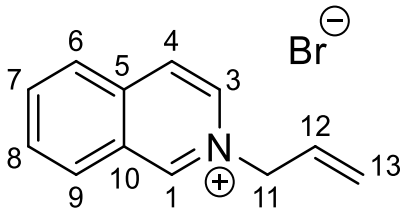
(*RS*)-4-(2-Methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one (172):



2-Methylisoquinolin-2-ium iodide **S172** (1.4 g, 5.0 mmol, 1.0 equiv.) was dissolved in MeCN (4.0 mL) along with MVK (0.41 mL, 5.0 mmol, 1.0 equiv.) and 5:2 HCO_2H:NEt_3 (1.2 mL, 20 mmol, 4.0 equiv.). The solution was heated to 80 °C for 18 h, then cooled, diluted with CH_2Cl_2 and quenched with sat. aq. Na_2CO_3. The layers were partitioned and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (100% EtOAc) afforded **172** as a pale-orange oil (0.43 g, 40%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.20 (1H, dd, *J* = 7.7, 1.6 Hz, H_6), 7.16 (1H, td, *J* = 7.4, 1.5 Hz, H_7), 7.12 (1H, td, *J* = 7.3, 1.6 Hz, H_8), 7.04 – 6.99 (1H, m, H_9), 3.67 (1H, d, *J* = 14.8 Hz, H_1), 3.39 (1H, d, *J* = 14.8 Hz, H_1'), 2.90 (1H, dq, *J* = 9.0, 4.6 Hz, H_4), 2.57 (2H, t, *J* = 4.1 Hz, H_3), 2.55 – 2.49 (1H, m, H_{12}), 2.46 – 2.39 (1H, m, H_{12}), 2.38 (3H, s, H_{15}), 2.12 (4H, s, H_{11}, H_{14}), 1.96 (1H, dtd, *J* = 14.2, 8.4, 5.8 Hz, H_{11}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 208.8 (C_{13}), 137.5 (C_5), 135.2 (C_{10}), 128.3 (C_6), 126.4 (2C, C_7, C_9), 126.0 (C_8), 58.5 (C_1), 57.4 (C_3), 46.3 (C_{15}), 41.2 (C_{12}), 37.7 (C_4), 30.1 (C_{14}), 29.7 (C_{11}); **IR** (neat) cm^{-1}: 2781, 1715, 1493, 1451, 1380, 1357, 1253, 1161, 1146, 1129, 1104, 1038, 1003, 769, 742; **HRMS** (ESI$^+$) m/z calc. for $C_{14}H_{20}NO$ $[M]^+$ 218.1539; found at 218.1536 Δ -1.38 ppm.

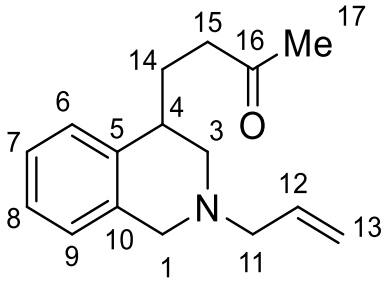
2-Allylisoquinolin-2-ium bromide (S173):



Isoquinoline (0.65 g, 5.0 mmol, 1.0 equiv.) was dissolved in acetone (20 mL) with allyl bromide (0.50 mL, 6.0 mmol, 1.2 equiv.) and stirred at r.t. overnight. The precipitate formed was then filtered under reduced pressure, then dried *in vacuo* to afford **S173** as an off-white solid (1.1 g, 88%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 11.01 (1H, s, H_1), 8.85 (1H, dd, *J* = 6.8, 1.5 Hz, H_3), 8.64 (1H, d, *J* = 8.3 Hz, H_9), 8.38 (1H, d, *J* = 6.8 Hz, H_4), 8.14 (1H, d, *J* = 8.3 Hz, H_6), 8.07 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz, H_7), 7.89 (1H, ddd, *J* = 8.2, 7.0, 1.2 Hz, H_8), 6.19 (1H, ddt, *J* = 16.8, 10.0, 6.6 Hz, H_{12}), 5.75 (2H, d, *J* = 6.6 Hz, H_{11}, H_{11}'), 5.69 (1H, d, *J* = 17.0 Hz, H_{13}), 5.46 (1H, d, *J* = 10.1 Hz, H_{13}'); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 150.4 (C_1), 137.5 (C_5), 137.2 (C_7), 134.5 (C_3), 131.4 (C_8), 131.2 (C_9), 130.4 (C_{12}), 127.8 (C_{10}), 127.2 (C_6), 126.4 (C_4), 124.1 (C_{13}), 62.9 (C_{11}); **IR** (neat) cm^{-1}: 3425 (br), 1647, 1514, 1398, 1286, 1159, 1111, 953, 923, 880, 829, 763, 727; **HRMS** (ESI^+) m/z calc. for $C_{12}H_{12}N$ $[M]^+$ 170.0964; found at 170.0958 Δ -3.68 ppm; **m.p.** = 37-38 °C. Spectroscopic data were consistent with the literature data for this compound.[166]

(*RS*)-4-(2-Allyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one (173):

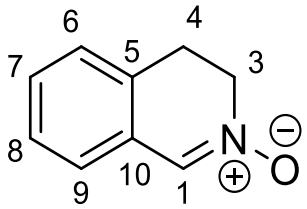


2-Allylisoquinolin-2-ium bromide **S173** (125 mg, 0.500 mmol, 1.00 equiv.) was dissolved in MeCN (0.4 mL) in a 5 mL microwave vial with 5:2 HCO_2H:NEt_3 (0.17 mL, 2.0 mmol, 4.0 equiv.), MVK (42 μL, 0.50 mmol, 1.0 equiv.), then sealed and stirred at 80 °C for 18 h. The reaction was performed in parallel with 6 reactions run simultaneously, then combined for extraction and purification. The reaction mixtures were diluted with EtOAc and sat. aq.

Na_2CO_3, shaken and the layers partitioned. The aqueous layer was extracted twice with EtOAc, then the combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (2-5% MeOH in CH_2Cl_2) afforded **173** as a pale-yellow oil (88 mg, 12%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.20 (1H, dd, *J* = 7.7, 1.6 Hz, H_6), 7.16 (1H, td, *J* = 7.4, 1.5 Hz, H_7), 7.12 (1H, td, *J* = 7.4, 1.6 Hz, H_8), 7.02 (1H, dd, *J* = 7.4, 1.4 Hz, H_9), 5.92 (1H, ddt, *J* = 16.9, 10.2, 6.5 Hz, H_{12}), 5.26 (1H, dq, *J* = 17.2, 1.6 Hz, H_{13}), 5.20 (1H, ddt, *J* = 10.1, 2.1, 1.2 Hz, H_{13}'), 3.71 (1H, d, *J* = 14.8 Hz, H_1), 3.47 (1H, d, *J* = 14.8 Hz, H_1'), 3.17 (1H, ddt, *J* = 13.5, 6.2, 1.4 Hz, H_{11}), 3.08 (1H, ddt, *J* = 13.4, 6.7, 1.3 Hz, H_{11}'), 2.87 (1H, dq, *J* = 9.0, 4.6 Hz, H_4), 2.65 (1H, ddd, *J* = 11.5, 4.7, 1.1 Hz, H_3), 2.60 (1H, dd, *J* = 11.6, 4.7 Hz, H_3'), 2.53 (1H, ddd, *J* = 17.0, 9.1, 6.5 Hz, H_{15}), 2.48 – 2.39 (1H, m, H_{15}'), 2.13 (3H, s, H_{17}), 2.07 (1H, dddd, *J* = 13.7, 9.1, 6.6, 4.4 Hz, H_{14}), 2.04 – 1.95 (1H, m, H_{14}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 209.0 (C_{16}), 138.0 (C_5), 135.5 (C_{12}), 135.2 (C_{10}), 128.3 (C_6), 126.6 (C_9), 126.4 (C_7), 126.0 (C_8), 117.9 (C_{13}), 61.6 (C_{11}), 56.7 (C_1), 54.7 (C_3), 41.4 (C_{15}), 37.7 (C_4), 30.1 (C_{17}), 29.7 (C_{14}); **IR** (neat) cm^{-1}: 2790, 1714, 1492, 1358, 1160, 1142, 1096, 1037, 996, 922, 767, 743; **HRMS** (ESI^+) m/z calc. for $C_{16}H_{22}NO$ $[M+H]^+$ 244.1696; found at 244.1686 Δ -4.06 ppm.

3,4-Dihydroisoquinoline-2-oxide (174):

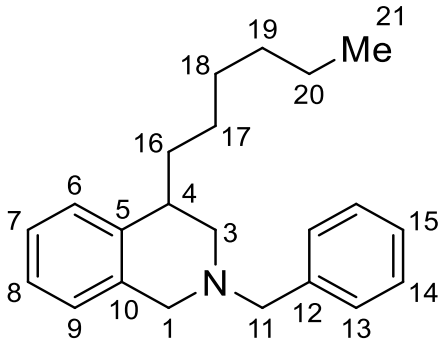


1,2,3,4-Tetrahydroisoquinoline (1.3 g, 10 mmol, 1.0 equiv.) was dissolved in MeOH (30 mL) with H_2O_2 (4.1 mL, 40 mmol, 4.0 equiv. 34.5-36.5% w/w) and heated to 50 °C overnight. The solution was then cooled to r.t. and diluted with H_2O. The mixture was extracted three times with CH_2Cl_2, the organic layers combined, dried over $MgSO_4$, filtered under gravity and

concentrated *in vacuo*. Purification by flash column chromatography (5-10% EtOH in EtOAc) afforded **174** as a pale-orange oil (260 mg, 18%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.74 (1H, s, H_1), 7.29 – 7.23 (2H, m, H_7, H_8), 7.23 – 7.17 (1H, m, H_6), 7.13 – 7.07 (1H, m, H_9), 4.09 (2H, td, *J* = 7.9, 2.5 Hz, H_3), 3.17 (2H, td, *J* = 7.8, 2.7 Hz, H_4); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 134.2 (C_1), 130.2 (C_5), 129.5 (C_7), 128.5 (C_{10}), 127.8 (C_8), 127.4 (C_6), 125.6 (C_9), 58.1 (C_3), 27.9 (C_4); **IR** (neat) cm^{-1}: 3420 (br), 1595, 1562, 1490, 1445, 1308, 1285, 1262, 1210, 1175, 1111, 900, 763, 660; **HRMS** (ESI$^+$) m/z calc. for $C_9H_{10}NO$ $[M+H]^+$ 148.0757; could not be observed by ESI MS. Spectroscopic data were consistent with the literature data for this compound.[167]

(*RS*)-2-Benzyl-4-hexyl-1,2,3,4-tetrahydroisoquinoline (175):

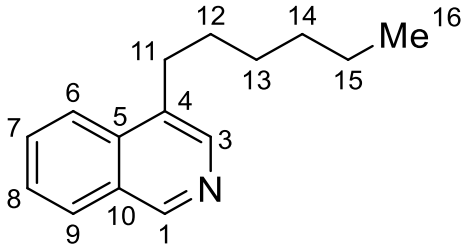


The title compound was prepared according to **General Procedure C** using hexanal (60 μL, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (3% EtOAc in pentane) afforded **175** as a pale-orange oil (115 mg, 75%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.40 (1H, d, *J* = 7.5 Hz, H_{13}), 7.33 (2H, t, *J* = 7.5 Hz, H_{14}), 7.30 – 7.27 (1H, m, H_{15}), 7.20 – 7.12 (2H, m, H_6, H_7), 7.10 (1H, t, *J* = 7.4 Hz, H_8), 6.98 (1H, d, *J* = 7.6 Hz, H_9), 3.79 – 3.73 (2H, m, H_1, H_{11}), 3.58 (1H, d, *J* = 13.2 Hz, H_{11}), 3.51 (1H. d, *J* = 14.8 Hz, H_1'), 2.78 (1H, s, H_4), 2.73 – 2.67 (1H, m, H_3), 2.66 – 2.59 (1H, m, H_3'), 1.77 (1H, dq, *J* = 17.4, 5.9 Hz, H_{16}), 1.67 (1H, dt, *J* = 15.0, 7.3 Hz, H_{16}'), 1.34 – 1.18 (8H, m, H_{17}, H_{18}, H_{19}, H_{20}), 0.88 (3H, t, *J* = 6.9 Hz, H_{21}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 139.5 (C_5), 138.8

(C_{12}), 134.9 (C_{10}), 129.0 (C_{13}), 128.2 (2C, C_6, C_{14}), 127.1 (C_{15}), 126.4 (C_9), 126.1 (C_7), 125.5 (C_8), 62.9 (C_{11}), 56.8 (C_1), 54.2 (C_3), 38.7 (C_4), 36.0 (C_{16}), 31.8 (C_{19}), 29.5 (C_{17}), 27.4 (C_{18}), 22.7 (C_{20}), 14.1 (C_{21}); **IR** (neat) cm^{-1}: 2928, 2856, 1494, 1454, 1096, 743, 699; **HRMS** (ESI^+) m/z calc. for $C_{22}H_{30}N$ $[M+H]^+$ 308.2373; found at 308.2370 Δ -0.97 ppm. Spectroscopic data were consistent with the literature data for this compound.[23]

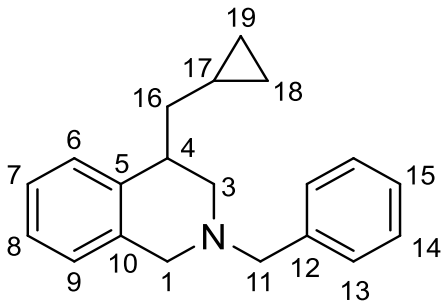
4-Hexylisoquinoline (198):



The title compound was prepared according to **General Procedure D** with 2-benzyl-4-hexyl-1,2,3,4-tetrahydroisoquinoline **175** (77 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (10% EtOAc in pentane) afforded **198** as an orange oil (34 mg, 64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.11 (1H, s, H_1), 8.37 (1H, s, H_3), 8.03 – 7.93 (2H, m, H_6, H_9), 7.72 (1H, ddd, *J* = 8.4, 6.8, 1.4 Hz, H_7), 7.59 (1H, ddd, *J* = 8.0, 6.8, 1.1 Hz, H_8), 3.05 – 2.96 (2H, m, H_{11}), 1.80 – 1.68 (2H, m, H_{12}), 1.49 – 1.39 (2H, m, H_{13}), 1.38 – 1.27 (4H, m, H_{14}, H_{15}), 0.95 – 0.82 (3H, m, H_{16}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 151.2 (C_1), 142.7 (C_3), 134.8 (C_5), 131.9 (C_4), 130.2 (C_7), 128.6 (C_{10}), 128.4 (C_9), 126.8 (C_8), 123.1 (C_6), 31.8 (C_{14}), 30.8 (C_{12}), 30.3 (C_{11}), 29.5 (C_{13}), 22.8 (C_{15}), 14.2 (C_{16}); **IR** (neat) cm^{-1}: 2930, 2858, 1623, 1583, 1503, 1466, 1390, 1229, 1149, 896, 787, 751; **HRMS** (ESI^+) m/z calc. for $C_{15}H_{20}N$ $[M+H]^+$ 214.1590; found at 214.1599 Δ 4.08 ppm. Spectroscopic data were consistent with the literature data for this compound.[168]

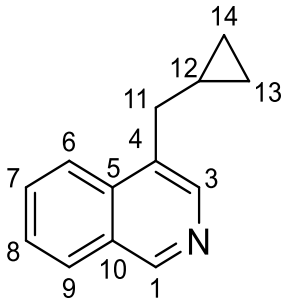
(*RS*)-2-Benzyl-4-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinoline (176):



The title compound was prepared according to **General Procedure C** using cyclopropane carbaldehyde (35 μL, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (5% EtOAc in pentane) afforded **176** as a pale-orange oil (103 mg, 74%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.42 (2H, d, *J* = 6.9 Hz, H_{13}), 7.40 – 7.31 (2H, m, H_{14}), 7.31 – 7.26 (1H, m, H_{15}), 7.19 (1H, dd, *J* = 7.7, 1.5 Hz, H_6), 7.15 (1H, td, *J* = 7.4, 1.4 Hz, H_7), 7.10 (1H, td, *J* = 7.4, 1.5 Hz, H_8), 7.01 – 6.96 (1H, m, H_9), 3.80 – 3.71 (2H, m, H_1, H_{11}), 3.64 (1H, d, *J* = 13.0 Hz, H_{11}'), 3.48 (1H, d, *J* = 14.8 Hz, H_1'), 2.97 – 2.89 (2H, m, H_3, H_4), 2.74 – 2.68 (1H, m, H_3'), 1.73 (1H, ddd, *J* = 13.7, 9.4, 6.9 Hz, H_{16}), 1.58 (1H, ddd, *J* = 13.8, 7.0, 4.2 Hz, H_{16}'), 0.72 – 0.62 (1H, m, H_{17}), 0.46 – 0.37 (2H, m, H_{18}, H_{19}), 0.05 – 0.00 (2H, m, H_{18}', H_{19}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 139.3 (C_5), 138.9 (C_{12}), 135.0 (C_{10}), 129.2 (C_{13}), 128.5 (C_9), 128.4 (C_{14}), 127.2 (C_{15}), 126.5 (C_9), 126.1 (C_7), 125.6 (C_8), 63.2 (C_{11}), 56.8 (C_1), 54.8 (C_3), 41.3 (C_{18}), 39.7 (C_4), 9.6 (C_{17}), 5.5 ($C_{18/19}$), 4.3 ($C_{18/19}$); **IR** (neat) cm^{-1}: 2798, 1494, 1454, 1146, 1095, 1016, 742, 700; **HRMS** (ESI^+) m/z calc. for $C_{20}H_{24}N$ $[M+H]^+$ 278.1903; found at 278.1894 Δ -3.24 ppm. Spectroscopic data were consistent with the literature data for this compound.[23]

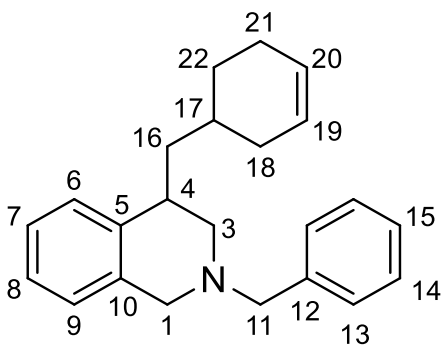
4-(Cyclopropylmethyl)isoquinoline (199):



The title compound was prepared according to **General Procedure D** with 2-benzyl-4-(cyclopropylmethyl)-1,2,3,4-tetrahydroisoquinoline **176** (69 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (15% EtOAc in pentane) afforded **199** as an orange oil (28 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.13 (1H, s, H_1), 8.47 (1H, s, H_3), 8.02 (1H, dq, *J* = 8.5, 1.0 Hz, H_6), 7.96 (1H, dt, *J* = 8.1, 1.1 Hz, H_9), 7.71 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz, H_7), 7.58 (1H, ddd, *J* = 8.0, 6.8, 1.1 Hz, H_8), 2.93 (2H, d, *J* = 6.7 Hz, H_{11}), 1.15 (1H, ttt, *J* = 8.0, 6.7, 4.9 Hz, H_{12}), 0.63 – 0.51 (2H, m, H_{13}, H_{14}), 0.27 (2H, dt, *J* = 6.0, 4.6 Hz, H_{13}', H_{14}'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 151.3 (C_1), 142.4 (C_3), 134.9 (C_5), 131.0 (C_4), 130.2 (C_7), 128.4 (C_{10}), 128.3 (C_9), 126.8 (C_8), 123.1 (C_6), 34.5 (C_{11}), 11.0 (C_{12}), 5.3 (2C, C_{13}, C_{14}); **IR** (neat) cm^{-1}: 1623, 1583, 1504, 1390, 1046, 932, 900, 828, 798, 779, 750; **HRMS** (ESI^+) m/z calc. for $C_{13}H_{14}N$ $[M+H]^+$ 184.1121; found at 184.1117 Δ -2.17 ppm.

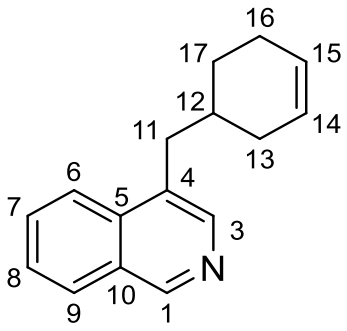
(*RS*, *RS*) and (*RS*, *SR*)-2-Benzyl-4-(cyclohex-3-en-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (177):



The title compound was prepared according to **General Procedure C** using 3-cyclohexene-1-carbaldehyde (55 mg, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (2% EtOAc in pentane) afforded **177** as a 1:1 mixture of diastereomers as a pale-orange oil (72.2 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.43 – 7.37 (2H, m, H_{13}), 7.36 – 7.29 (2H, m, H_{14}), 7.29 – 7.23 (1H, m, H_{15}), 7.17 – 7.12 (2H, m, H_6, H_7), 7.10 (1H, ddd, *J* = 8.7, 5.8, 2.8 Hz, H_8), 6.99 (1H, ddt, *J* = 7.5, 2.2, 1.2 Hz, H_9), 5.69 – 5.60 (2H, m, H_{19}, H_{20}), 3.85 – 3.74 (2H, m, H_1, H_{11}), 3.60 – 3.45 (2H, m, H_1', H_{11}'), 2.89 (1H, ddq, *J* = 17.9, 11.2, 3.8 Hz, H_4), 2.79 – 2.67 (1H, m, H_3), 2.55 (1H, ddd, *J* = 15.6, 11.4, 4.3 Hz, H_3'), 2.22 – 2.12 (1H, m, H_{18}), 2.12 – 1.92 (3H, m, H_{18}', H_{21}, H_{21}'), 1.92 – 1.77 (2H, m, H_{16}, H_{22}), 1.76 – 1.70 (1H, m, H_{18}''), 1.70 – 1.60 (2H, m, H_{18}''', H_{22}'), 1.59 – 1.38 (2H, m, H_{16}', H_{17}), 1.31 – 1.16 (2H, m, H_{22}'', H_{22}'''); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 140.1 (C_{5a}), 140.0 (C_{5b}), 139.0 (C_{12a}), 138.9 (C_{12b}), 135.1 (C_{10a}), 135.1 (C_{10b}), 129.1 (C_{13a}), 129.1 (C_{13b}), 128.5 (C_{6a}), 128.5 (C_{6b}), 128.3 (C_{14a+b}), 127.4 (C_{15a+b}), 127.2 (C_{20a}), 127.2 (C_{20b}), 127.1 (C_{19a}), 126.9 (C_{19b}), 126.6 (C_{9a}), 126.5 (C_{9b}), 126.4 (C_{7a}), 126.3 (C_{7b}), 125.6 (C_{8a+b}), 63.0 (C_{11a}), 62.8 (C_{11b}), 57.0 (C_{1a}), 56.9 (C_{1b}), 54.4 (C_{3a}), 53.8 (C_{3b}), 43.9 (C_{16a}), 43.2 (C_{16b}), 36.0 (C_{4a}), 35.9 (C_{4b}), 33.0 (C_{18a}), 31.4 (C_{18b}), 31.1 (C_{17a}), 30.9 (C_{17b}), 30.2 (C_{22a}), 28.1 (C_{22b}), 25.4 (C_{21a}), 25.2 (C_{21b}); **IR** (neat) cm^{-1}: 2914, 1702, 1494, 1454, 1144, 1095, 914, 743, 699, 654; **HRMS** (ESI^+) m/z calc. for $C_{23}H_{28}N$ $[M+H]^+$ 318.2216; found at 318.2219 Δ 0.943 ppm.

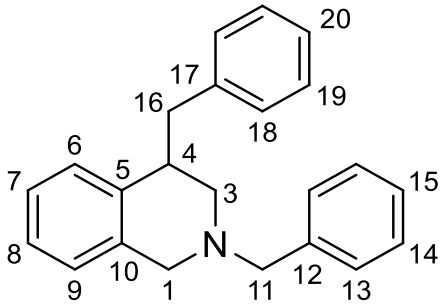
(*RS*)-4-(Cyclohex-3-en-1-ylmethyl)isoquinoline (200):



The title compound was prepared according to **General Procedure D** with 2-benzyl-4-(cyclohex-3-en-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline **177** (79 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (20% EtOAc in pentane) afforded **200** as a pale-yellow oil (35 mg, 63%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.12 (1H, s, H_1), 8.35 (1H, s, H_3), 7.98 (1H, d, *J* = 8.5 Hz, H_6), 7.96 (1H, d, *J* = 8.2 Hz, H_9), 7.70 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz, H_7), 7.58 (1H, t, *J* = 7.5 Hz, H_8), 5.68 – 5.59 (2H, m, H_{14}, H_{15}), 3.01 – 2.89 (2H, m, H_{11}), 2.12 – 1.91 (4H, m, H_{12}, H_{13}, H_{16}, H_{16}'), 1.88 – 1.75 (2H, m, H_{13}', H_{17}), 1.38 (1H, dtd, *J* = 12.9, 10.5, 5.7 Hz, H_{17}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 151.3 (C_1), 143.5 (C_3), 135.1 (C_5), 130.2 (C_7), 130.1 (C_4), 128.6 (C_{10}), 128.4 (C_9), 127.2 (C_{15}), 126.8 (C_8), 126.1 (C_{14}), 123.3 (C_6), 36.9 (C_{11}), 34.7 (C_{12}), 32.0 (C_{13}), 28.9 (C_{17}), 25.1 (C_{16}); **IR** (neat) cm^{-1}: 3022, 2916, 1622, 1582, 1502, 1452, 1335, 1390, 1225, 1042, 1020, 962, 896, 861, 797, 782, 751, 715, 700, 656, 619; **HRMS** (ESI^+) m/z calc. for $C_{16}H_{18}N$ $[M+H]^+$ 224.1434; found at 224.1424 Δ -4.46 ppm.

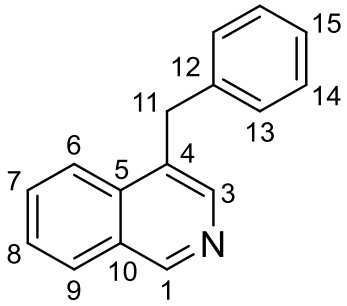
(*RS*)-2,4-Dibenzyl-1,2,3,4-tetrahydroisoquinoline (178):



The title compound was prepared according to **General Procedure C** (1.0 mmol scale), using benzaldehyde (100 μL, 1.0 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (3% EtOAc in pentane) afforded **178** as a colourless solid (232 mg, 74%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.46 – 7.41 (2H, m, H_{13}), 7.40 – 7.35 (2H, m, H_{14}), 7.33 (1H, dt, *J* = 5.8, 2.0 Hz, H_{15}), 7.25 – 7.11 (6H, m, H_6, H_7, H_8, H_{19}, H_{20}), 7.05 – 6.99 (3H, m, H_9, H_{18}), 3.88 (1H, d, *J* = 14.8 Hz, H_1), 3.72 (1H, d, *J* = 12.9 Hz, H_{11}), 3.57 – 3.52 (1H, m, H_{11}'), 3.45 (1H, d, *J* = 14.9 Hz, H_1'), 3.06 – 2.96 (3H, m, H_4, H_{16}), 2.78 (1H, d, *J* = 11.5 Hz, H_3), 2.38 (1H, d, *J* = 11.3 Hz, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 141.2 (C_{17}), 138.8 (2C, C_5, C_{12}), 135.2 (C_{10}), 129.6 (C_{13}), 129.5 (C_{18}), 128.9 (C_6), 128.5 (C_{14}), 128.4 (C_{19}), 127.3 (C_{15}), 126.6 (C_9), 126.3 (C_{20}), 126.0 (2C, C_7, C_8), 63.1 (C_{11}), 56.9 (C_1), 53.1 (C_3), 42.9 (C_{16}), 41.6 (C_4); **IR** (neat) cm^{-1}: 1602, 1494, 1454, 1368, 1342, 1140, 1094, 1029, 912, 753, 721, 699; **HRMS** (ESI^+) m/z calc. for $C_{23}H_{24}N$ $[M+H]^+$ 314.1903; found at 314.1894 Δ -2.86 ppm; **m.p.** = 73-75 °C. Spectroscopic data were consistent with the literature data for this compound.[23]

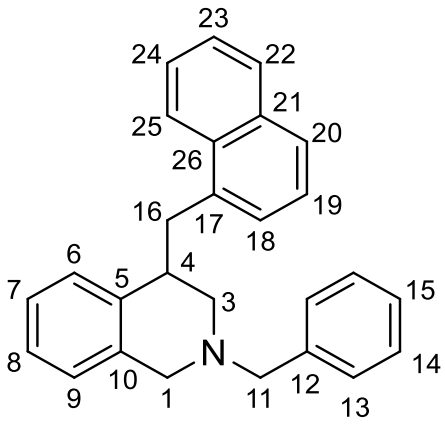
4-Benzylisoquinoline (201):



The title compound was prepared according to **General Procedure D** with 2,4-dibenzyl-1,2,3,4-tetrahydroisoquinoline **178** (78 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (10-15% EtOAc in pentane) afforded **201** as a colourless solid (39 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.24 (1H, s, H_1), 8.48 (1H, s, H_3), 8.02 (1H, dt, *J* = 8.0, 1.1 Hz, H_9), 7.96 (1H, dt, *J* = 8.4, 1.0 Hz, H_6), 7.68 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz, H_7), 7.61 (1H, ddd, *J* = 8.0, 6.9, 1.2 Hz, H_8), 7.38 – 7.28 (2H, m, H_{14}), 7.28 – 7.20 (3H, m, H_{13}, H_{15}), 4.43 (2H, s, H_{11}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_{C} = 152.0 (C_1), 143.9 (C_3), 139.8 (C_{12}), 134.9 (C_5), 130.5 (C_7), 129.7 (C_4), 128.7 (2C, C_{10}, C_{13}), 128.6 (C_{14}), 128.3 (C_9), 127.0 (C_8), 126.4 (C_{15}), 123.6 (C_6), 36.3 (C_{11}); **IR** (neat) cm^{-1}: 1622, 1584, 1500, 1493, 1150, 1440, 1392, 1255, 911, 805, 796, 782, 756, 745, 714, 656; **HRMS** (ESI^+) m/z calc. for $C_{16}H_{14}N$ $[M+H]^+$ 220.1121; found at 220.1123 Δ 0.909 ppm; **m.p.** = 103-106 °C. Spectroscopic data were consistent with the literature data for this compound.[170]

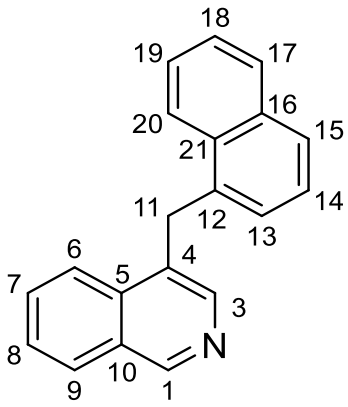
(*RS*)-2-Benzyl-4-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (179):



The title compound was prepared according to **General Procedure C** using 1-naphthaldehyde (78 mg, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (1% EtOAc in pentane) afforded **179** as a pale-orange solid (124 mg, 68%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.37 – 8.31 (1H, m, H_{25}), 7.92 – 7.86 (1H, m, H_{22}), 7.73 (1H, t, *J* = 6.3 Hz, H_{20}), 7.60 – 7.53 (1H, m, H_{24}), 7.53 – 7.46 (3H, m, H_{13}, H_{23}), 7.45 – 7.39 (2H, m, H_{14}), 7.39 – 7.34 (2H, m, H_6, H_{15}), 7.28 (1H, ddd, *J* = 8.6, 5.3, 1.8 Hz, H_{19}), 7.24 (1H, d, *J* = 6.8 Hz, H_7), 7.20 (1H, t, *J* = 7.5 Hz, H_8), 7.07 (1H, t, *J* = 6.1 Hz, H_9), 7.03 – 6.96 (1H, m, H_{18}), 4.00 – 3.93 (1H, m, H_1), 3.72 – 3.58 (2H, m, H_{11}, H_{11}'), 3.56 – 3.47 (2H, m, H_{16}, H_{16}'), 3.46 – 3.37 (1H, m, H_1'), 3.22 (1H, s, H_4), 2.88 – 2.82 (1H, m, H_3), 2.38 – 2.33 (1H, m, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 139.0 (C_5), 138.8 (C_{12}), 137.0 (C_{21}), 135.2 (C_{10}), 134.1 (C_{17}), 132.4 (C_{26}), 129.5 (C_{13}), 129.0 (C_{22}), 128.8 (C_6), 128.5 (C_{14}), 128.0 (C_{18}), 127.3 (C_{15}), 126.9 (C_{20}), 126.7 (C_9), 126.4 (C_7), 126.1 (C_8), 125.9 (C_{24}), 125.6 (C_{19}), 125.5 (C_{23}), 124.2 (C_{25}), 63.2 (C_{11}), 56.8 (C_1), 53.4 (C_3), 40.4 (C_4), 39.9 (C_{16}); **IR** (neat) cm^{-1}: 3062, 1493, 1454, 1395, 1367, 1344, 1262, 1237, 1198, 1139, 1088, 1059, 1026, 963, 949, 920, 869, 857, 818, 799, 791, 781, 758, 747, 731, 702; **HRMS** (ESI^+) m/z calc. for $C_{27}H_{26}N$ $[M+H]^+$ 364.2060; found at 364.2067 Δ 0.19 ppm; **m.p.** = 79-81 °C.

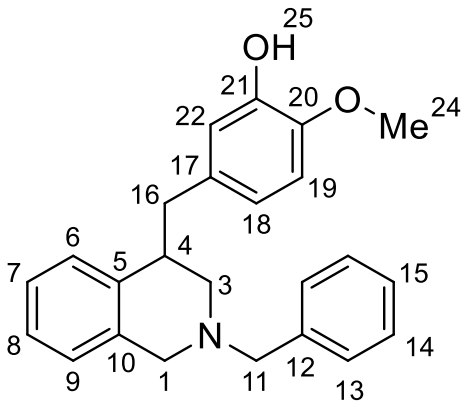
4-(Naphthalen-1-ylmethyl)isoquinoline (202):



The title compound was prepared according to **General Procedure D** with 2-benzyl-4-(naphthalen-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline **179** (91 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (20% EtOAc in pentane) afforded **202** as an orange solid (44 mg, 66%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.23 (1H, s, H_1), 8.28 (1H, s, H_3), 8.14 – 8.08 (1H, m, H_{20}), 8.05 – 8.00 (1H, m, H_9), 7.95 – 7.89 (2H, m, H_6, H_{17}), 7.77 (1H, d, *J* = 8.2 Hz, H_{15}), 7.64 (1H, ddd, *J* = 8.4, 6.9, 1.5 Hz, H_7), 7.61 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz, H_8), 7.57 – 7.51 (2H, m, H_{18}, H_{19}), 7.31 (1H, dd, *J* = 8.2, 7.1 Hz, H_{14}), 7.01 (1H, dt, *J* = 7.1, 1.1 Hz, H_{13}), 4.82 (2H, s, H_{11}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 151.9 (C_1), 144.0 (C_3), 135.2 (C_{12}), 135.1 (C_5), 133.9 (C_{16}), 132.0 (C_{21}), 130.6 (C_7), 129.3 (C_4), 129.0 (C_{17}), 128.5 (C_{10}), 128.4 (C_9), 127.4 (C_{15}), 127.1 (C_8), 126.8 (C_{13}), 126.4 (C_{19}), 125.9 (C_{14}), 125.6 (C_{18}), 123.6 (C_{20}), 123.3 (C_6), 33.0 (C_{11}); **IR** (neat) cm^{-1}: 3056, 1623, 1597, 1584, 1437, 1355, 907, 789, 752, 734; **HRMS** (ESI^+) m/z calc. for $C_{20}H_{16}N$ $[M+H]^+$ 270.1277; found at 270.1278 Δ 0.37 ppm; **m.p.** = 128-131 °C. Spectroscopic data were consistent with the literature data for this compound.[171]

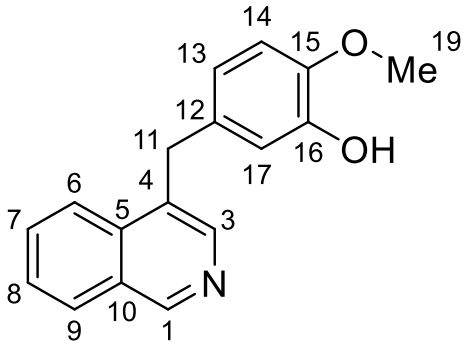
(*RS*)-5-((2-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-2-methoxyphenol (180):



The title compound was prepared according to **General Procedure C** using isovanillin (76 mg, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (10% EtOAc in pentane) afforded **180** as a pale-orange oil (88.9 mg, 50%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.44 – 7.39 (2H, m, H_{13}), 7.38 – 7.34 (2H, m, H_{14}), 7.32 – 7.28 (1H, m, H_{15}), 7.19 (1H, dd, *J* = 7.6, 1.6 Hz, H_6), 7.18 – 7.14 (1H, m, H_7), 7.12 (1H, td, *J* = 7.3, 1.6 Hz, H_8), 7.00 (1H, dd, *J* = 7.4, 1.5 Hz, H_9), 6.71 (1H, d, *J* = 2.1 Hz, H_{22}), 6.67 (1H, d, *J* = 8.1 Hz, H_{19}), 6.45 (1H, dd, *J* = 8.1, 2.1 Hz, H_{18}), 5.52 (1H, br s, H_{25}), 3.86 (3H, s, H_{24}), 3.83 (1H, d, *J* = 14.7 Hz, H_1), 3.69 (1H, d, *J* = 12.9 Hz, H_{11}), 3.56 (1H, d, *J* = 12.9 Hz, H_{11}'), 3.41 (1H, d, *J* = 14.8 Hz, H_1'), 3.00 – 2.94 (1H, m, H_4), 2.90 (2H, dd, *J* = 7.4, 3.3 Hz, H_{16}, H_{16}'), 2.77 (1H, ddd, *J* = 11.6, 2.9, 1.4 Hz, H_3), 2.39 (1H, dd, *J* = 11.5, 3.9 Hz, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 145.5 (C_{21}), 145.0 (C_{20}), 138.9 (C_{12}), 138.8 (C_5), 135.2 (C_{10}), 134.5 (C_{17}), 129.5 (C_{13}), 128.8 (C_6), 128.4 (C_{14}), 127.2 (C_{15}), 126.6 (C_9), 126.3 (C_7), 125.9 (C_8), 121.0 (C_{18}), 115.4 (C_{22}), 110.6 (C_{19}), 63.2 (C_{11}), 56.8 (C_1), 56.1 (C_{24}), 53.4 (C_3), 42.3 (C_{16}), 41.5 (C_4); **IR** (neat) cm^{-1}: 1591, 1510, 1454, 1274, 1238, 1130, 1029, 910, 784, 734, 701; **HRMS** (ESI^+) m/z calc. for $C_{24}H_{26}NO_2$ $[M+H]^+$ 360.1958; found at 360.1949 Δ -2.50 ppm.

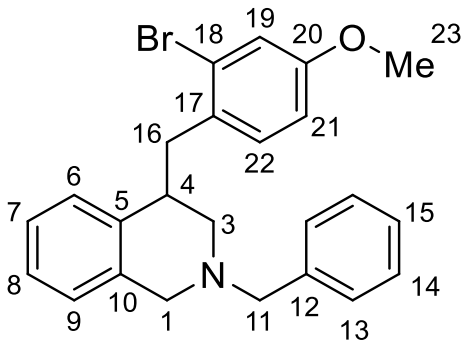
5-(Isoquinolin-4-ylmethyl)-2-methoxyphenol (203):



The title compound was prepared according to **General Procedure D** with 5-((2-benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)-2-methoxyphenol **180** (78 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (40% - 60% EtOAc in pentane) afforded **203** as a beige solid (31 mg, 52%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.12 (1H, s, H_1), 8.37 (1H, s, H_3), 7.99 – 7.89 (2H, m, H_6, H_9), 7.66 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz, H_7), 7.58 (1H, ddd, *J* = 8.1, 6.8, 1.1 Hz, H_8), 6.76 (1H, d, *J* = 6.3 Hz, H_{14}), 6.75 (1H, s, H_{17}), 6.68 (1H, dd, *J* = 8.1, 2.1 Hz, H_{13}), 4.29 (2H, s, H_{11}), 3.84 (3H, s, H_{19}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 151.4 (C_1), 146.1 (C_{16}), 145.5 (C_{15}), 142.8 (C_3), 135.2 (C_5), 132.9 (C_{12}), 130.9 (C_7), 130.6 (C_4), 128.7 (C_{10}), 128.5 (C_9), 127.3 (C_8), 123.8 (C_6), 119.9 (C_{13}), 115.1 (C_{17}), 111.0 (C_{14}), 56.1 (C_{19}), 35.8 (C_{11}); **IR** (neat) cm^{-1}: 2931, 1625, 1531, 1434, 1391, 1283, 1268, 1247, 1224, 1133, 1109, 1033, 864, 787, 750, 714; **HRMS** (ESI^+) m/z calc. for $C_{17}H_{16}NO_2$ $[M+H]^+$ 266.1176; found at 266.1172 Δ -1.50 ppm; **m.p.** = 108-109 °C.

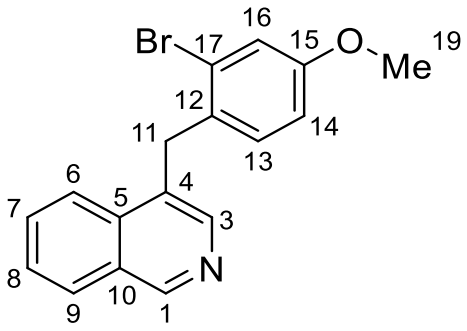
(*RS*)-2-Benzyl-4-(2-bromo-4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (181):



The title compound was prepared according to **General Procedure C** using 4-methoxy-2-bromo benzaldehyde (108 mg, 0.500 mmol, 1.00 equiv.) as the electrophile. Purification by flash column chromatography (2% EtOAc in pentane) afforded **181** as an orange solid (150 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.47 – 7.42 (2H, m, H_{13}), 7.42 – 7.37 (3H, m, H_6, H_{14}), 7.37 – 7.33 (1H, m, H_{15}), 7.19 (1H, td, *J* = 7.5, 1.5 Hz, H_7), 7.15 (1H, td, *J* = 7.4, 1.5 Hz, H_8), 7.10 (1H, d, *J* = 2.6 Hz, H_{19}), 7.03 (1H, dd, *J* = 7.5, 1.5 Hz, H_9), 6.53 (1H, dd, *J* = 8.4, 2.6 Hz, H_{21}), 6.45 (1H, d, *J* = 8.5 Hz, H_{22}), 3.94 (1H, d, *J* = 14.8 Hz, H_1), 3.83 – 3.69 (4H, m, H_{11}, H_{23}), 3.52 (1H, d, *J* = 12.7 Hz, H_{11}'), 3.45 (1H, d, *J* = 14.8 Hz, H_1'), 3.15 – 3.06 (1H, m, H_4), 3.06 – 2.96 (2H, m, H_{16}, H_{16}'), 2.84 – 2.76 (1H, m, H_3), 2.30 (1H, dd, *J* = 11.8, 3.8 Hz, H_3'); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 158.5 (C_{20}), 138.8 (2C, C_5, C_{12}), 135.1 (C_{10}), 132.5 (C_{22}), 132.2 (C_{17}), 129.8 (C_{13}), 129.0 (C_6), 128.5 (C_{14}), 127.3 (C_{15}), 126.4 (C_9), 126.4 (C_7), 126.0 (C_8), 125.0 (C_{18}), 118.0 (C_{19}), 113.4 (C_{21}), 63.1 (C_{11}), 57.2 (C_1), 55.6 (C_{23}), 52.3 (C_3), 42.2 (C_{16}), 39.0 (C_4); **IR** (neat) cm^{-1}: 1653, 1493, 1454, 1440, 1281, 1242, 1093, 1030, 911, 864, 842, 796, 751, 701, 639; **HRMS** (ESI^+) m/z calc. for $C_{24}H_{25}{}^{79}BrNO$ $[M+H]^+$ 422.1114; found at 422.1108 Δ -1.43 ppm; **m.p.** = 56-58 °C.

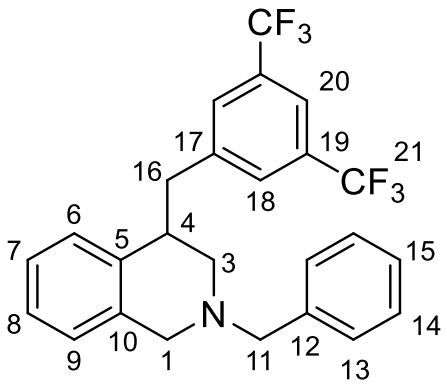
4-(2-Bromo-4-methoxybenzyl)isoquinoline (204):



The title compound was prepared according to **General Procedure D** with 2-benzyl-4-(2-bromo-4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline **181** (106 mg, 0.250 mmol, 1.00 equiv.). Flash column chromatography (30% EtOAc in pentane) afforded **204** as a viscous brown oil (48.6 mg, 59%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.19 (1H, s, H_1), 8.28 (1H, s, H_3), 7.99 (1H, dd, *J* = 8.1, 1.3 Hz, H_9), 7.84 (1H, d, *J* = 8.5 Hz, H_6), 7.67 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz, H_7), 7.59 (1H, ddd, *J* = 8.0, 6.8, 1.1 Hz, H_8), 7.19 (1H, d, *J* = 2.6 Hz, H_{16}), 6.76 (1H, d, *J* = 8.6 Hz, H_{13}), 6.67 (1H, dd, *J* = 8.6, 2.6 Hz, H_{14}), 4.40 (2H, s, H_{11}), 3.75 (3H, s, H_{19}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 158.8 (C_{15}), 152.0 (C_1), 143.7 (C_3), 134.9 (C_5), 130.8 (C_{13}), 130.8 (C_{12}), 130.7 (C_7), 129.1 (C_4), 128.6 (C_{10}), 128.4 (C_9), 127.2 (C_8), 124.8 (C_{17}), 123.4 (C_6), 118.2 (C_{16}), 113.7 (C_{14}), 55.6 (C_{19}), 35.4 (C_{11}); **IR** (neat) cm^{-1}: 1605, 1568, 1493, 1461, 1439, 1390, 1317, 1285, 1235, 1184, 1148, 1037, 908, 861, 842, 791, 779, 747, 647, 629; **HRMS** (ESI^+) m/z calc. for $C_{17}H_{15}{}^{79}BrNO$ $[M+H]^+$ 328.0332; found at 328.0338 Δ -2.30 ppm;

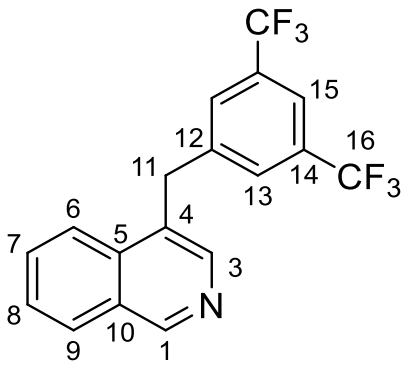
(*RS*)-2-Benzyl-4-((3,5-bis(trifluoromethyl)cyclohexyl)methyl)-1,2,3,4-tetrahydroisoquinoline (182):



The title compound was prepared according to **General Procedure C** using 3,5-bis CF_3 benzaldehyde (121 mg, 0.500 mmol, 1.00 equiv.) as the electrophile. Purification by flash column chromatography (10% EtOAc in pentane) afforded **182** as a pale-orange oil (130 mg, 57%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.71 (1H, d, *J* = 2.0 Hz, H_{20}), 7.51 – 7.48 (2H, m, H_{18}), 7.41 – 7.38 (2H, m, H_{13}), 7.38 – 7.33 (2H, m, H_{14}), 7.32 – 7.28 (1H, m, H_{15}), 7.20 – 7.13 (2H, m, H_7, H_8), 7.08 – 7.01 (2H, m, H_6, H_9), 3.91 (1H, d, *J* = 14.9 Hz, H_1), 3.72 (1H, d, *J* = 12.9 Hz, H_{11}), 3.56 (1H, d, *J* = 12.9 Hz, H_{11}'), 3.46 (1H, d, *J* = 14.9 Hz, H_1'), 3.19 (1H, dd, *J* = 13.7, 9.8 Hz, H_{16}), 3.11 (1H, dd, *J* = 13.7, 4.8 Hz, H_{16}'), 3.06 – 2.99 (1H, m, H_4), 2.70 (1H, ddd, *J* = 11.7, 2.6, 1.4 Hz, H_3), 2.45 (1H, dd, *J* = 11.6, 3.8 Hz, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 143.6 (C_{17}), 138.3 (C_{12}), 137.4 (C_{10}), 135.2 (C_5), 131.6 (q, *J* = 33.0 Hz, C_{19}), 129.6 (q, *J* = 3.6 Hz, C_{18}), 129.2 (C_{13}), 128.8 (C_6), 128.5 (C_{14}), 127.6 (C_{15}), 126.8 (C_9), 126.5 ($C_{7/8}$), 126.4 ($C_{7/8}$), 123.5 (q, *J* = 272.7 Hz, C_{21}), 120.2 (hept, *J* = 3.9 Hz, C_{20}), 63.0 (C_{11}), 56.7 (C_1), 53.3 (C_3), 42.6 (C_{16}), 41.2 (C_4); **^{19}F NMR** (377 MHz, $CDCl_3$): δ_F = -62.68; **IR** (neat) cm^{-1}: 1378, 1279, 1132, 1109, 778, 748, 723, 702, 683; **HRMS** (ESI^+) m/z calc. for $C_{25}H_{22}F_6N$ $[M+H]^+$ 450.1651; found at 450.1653 Δ 0.444 ppm.

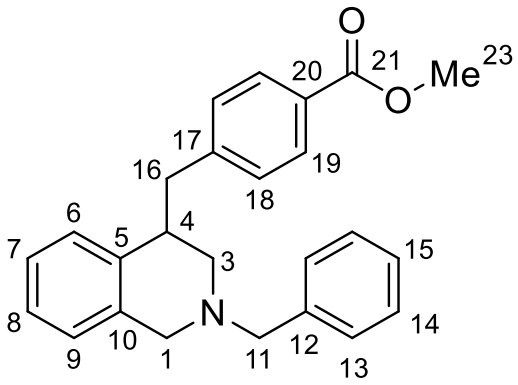
4-(3,5-Bis(trifluoromethyl)benzyl)isoquinoline (205):



The title compound was prepared according to **General Procedure D** with 2-benzyl-4-((3,5-bis(trifluoromethyl)cyclohexyl)methyl)-1,2,3,4-tetrahydroisoquinoline **182** (110 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (20% EtOAc in pentane) afforded **205** as an off white solid (54 mg, 61%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.24 (1H, s, H_1), 8.41 (1H, s, H_3), 8.02 (1H, dd, *J* = 8.1, 1.2 Hz, H_9), 7.80 (1H, d, *J* = 8.4 Hz, H_6), 7.73 (1H, s, H_{15}), 7.70 (1H, ddd, *J* = 8.4, 6.8, 1.4 Hz, H_7), 7.65 (2H, s, H_{13}), 7.62 (1H, ddd, *J* = 8.1, 6.9, 1.1 Hz, H_8), 4.50 (2H, s, H_{11}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 152.9 (C_1), 143.9 (C_3), 142.3 (C_{12}), 134.5 (C_5), 132.1 (q, *J* = 33.2 Hz, C_{14}), 131.1 (C_7), 128.8 – 128.6 (3C, m, C_9, C_{10}, C_{13}), 127.7 (C_4), 127.5 (C_8), 124.4 (q, *J* = 273.8 Hz, C_{16}), 122.8 (C_6), 120.8 (hept, *J* = 3.8 Hz, C_{15}), 36.0 (C_{11}); **^{19}F NMR** (377 MHz, $CDCl_3$): δ_F = -62.87; **IR** (neat) cm^{-1}: 1623, 1376, 1279, 1172, 1129, 906, 886, 843, 788, 750, 731, 706, 683; **HRMS** (ESI^+) m/z calc. for $C_{18}H_{12}F_6N$ $[M+H]^+$ 356.0868; found at 356.0863 Δ -1.37 ppm; **m.p.** = 90-92 °C.

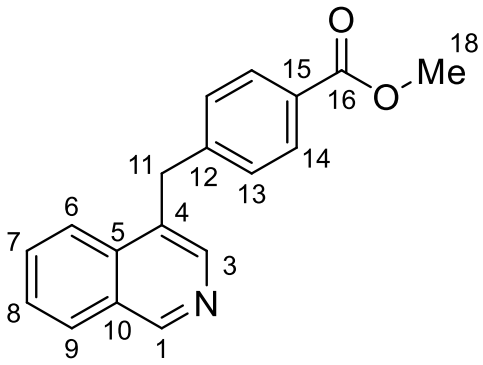
(*RS*)-Methyl 4-((2-benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)benzoate (183):



The title compound was prepared according to **General Procedure C** using methyl terephthalaldehyde (74 mg, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (3% EtOAc in pentane) afforded **183** as a colourless solid (99 mg, 53%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.88 – 7.84 (2H, m, H_{19}), 7.41 (2H, dd, *J* = 7.9, 1.7 Hz, H_{13}), 7.39 – 7.32 (3H, m, H_{14}, H_{15}), 7.18 – 7.14 (3H, m, H_6, H_7, H_8), 7.06 – 7.01 (3H, m, H_9, H_{18}), 3.93 – 3.88 (4H, m, H_1, H_{23}), 3.73 (1H, d, *J* = 12.8 Hz, H_{11}), 3.52 – 3.42 (2H, m, H_1', H_{11}'), 3.06 (1H, dd, *J* = 13.8, 11.2 Hz, H_{16}), 3.03 – 2.95 (2H, m, H_4, H_{16}'), 2.72 (1H, dt, *J* = 11.6, 1.9 Hz, H_3), 2.34 (1H, dd, *J* = 11.7, 3.8 Hz, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 167.3 (C_{21}), 146.7 (C_{17}), 138.7 (C_{12}), 138.3 (C_5), 135.2 (C_{10}), 129.7 (C_{19}), 129.6 (C_{18}), 129.5 (C_{13}), 128.8 (C_6), 128.5 (C_{14}), 128.0 (C_{21}), 127.4 (C_{15}), 126.7 (C_9), 126.3 (C_7), 126.1 (C_8), 63.0 (C_{11}), 57.0 (C_1), 52.8 (C_3), 52.1 (C_{23}), 42.9 (C_{16}), 41.5 (C_4); **IR** (neat) cm^{-1}: 1720, 1609, 1435, 1279, 1179, 1103, 760, 701; **HRMS** (ESI^+) m/z calc. for $C_{25}H_{26}NO_2$ $[M+H]^+$ 372.1958; found at 372.1956 Δ -0.54 ppm; **m.p.** = 80-81 °C. Spectroscopic data were consistent with the literature data for this compound.[23]

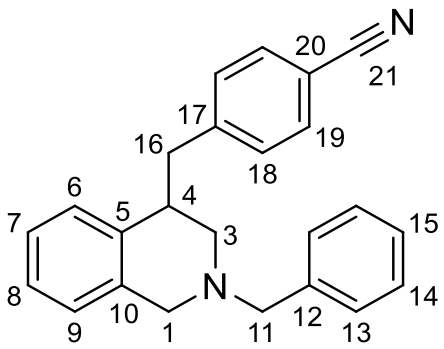
Methyl 4-(isoquinolin-4-ylmethyl)benzoate (206):



The title compound was prepared according to **General Procedure D** with methyl 4-((2-benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)benzoate **183** (93 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (30% EtOAc in pentane) afforded **206** as a pale-brown solid (40 mg, 57%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.22 (1H, s, H_1), 8.42 (1H, s, H_3), 8.02 (1H, dt, *J* = 8.0, 1.1 Hz, H_9), 7.96 – 7.91 (2H, m, H_{14}), 7.87 – 7.82 (1H, m, H_6), 7.66 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz, H_7), 7.61 (1H, ddd, *J* = 8.0, 6.8, 1.2 Hz, H_8), 7.26 (2H, d, *J* = 8.3 Hz, H_{13}), 4.44 (2H, s, H_{11}), 3.88 (3H, s, H_{18}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 166.9 (C_{16}), 151.9 (C_1), 145.0 (C_{12}), 143.2 (C_3), 134.9 (C_5), 130.9 (C_7), 130.0 (C_{13}), 129.2 (C_4), 128.6 (2C, C_{14}, C_{15}), 128.5 (C_9), 128.5 (C_{10}), 127.3 (C_8), 123.3 (C_6), 52.1 (C_{18}), 36.4 (C_{11}); **IR** (neat) cm^{-1}: 1720, 1611, 1436, 1283, 1180, 1110, 1020, 753, 723; **HRMS** (ESI^+) m/z calc. for $C_{18}H_{16}NO_2$ $[M+H]^+$ 278.1176; found at 278.1165 Δ -3.96 ppm; **m.p.** = 80-82 °C. Spectroscopic data were consistent with the literature data for this compound.[172]

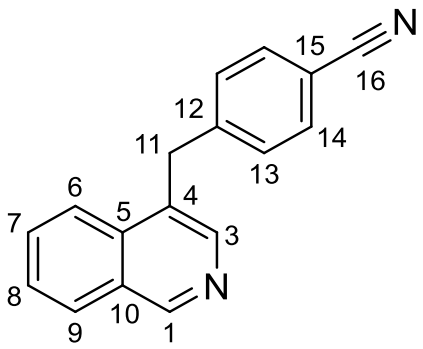
(*RS*)-4-((2-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)benzonitrile (184):



The title compound was prepared according to **General Procedure C** using 4-CN benzaldehyde (66 mg, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (7% EtOAc in pentane) afforded **184** as a colourless solid (87 mg, 51%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.46 – 7.42 (2H, m, H_{19}), 7.42 – 7.34 (5H, m, H_{13}, H_{14}, H_{15}), 7.22 – 7.15 (2H, m, H_7, H_8), 7.14 (1H, d, *J* = 2.8 Hz, H_6), 7.06 (1H, dd, *J* = 6.6, 2.3 Hz, H_9), 6.98 (2H, d, *J* = 7.9 Hz, H_{18}), 3.96 (1H, d, *J* = 14.8 Hz, H_1), 3.79 (1H, d, *J* = 12.7 Hz, H_{11}), 3.49 (1H, d, *J* = 14.9 Hz, H_1'), 3.45 (1H, d, *J* = 12.7 Hz, H_{11}'), 3.06 (1H, dd, *J* = 12.8, 10.2 Hz, H_{16}), 3.00 – 2.92 (2H, m, H_4, H_{16}'), 2.69 (1H, dt, *J* = 11.5, 1.9 Hz, H_3), 2.32 (1H, dd, *J* = 11.6, 3.7 Hz, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 146.7 (C_{17}), 138.5 (C_{12}), 137.8 (C_{10}), 135.1 (C_5), 132.0 (C_{19}), 130.1 (C_{18}), 129.7 (C_{13}), 128.7 (C_6), 128.4 (C_{14}), 127.3 (C_{15}), 126.6 (C_9), 126.3 (C_7), 126.2 (C_8), 119.2 (C_{21}), 109.7 (C_{20}), 62.8 (C_{11}), 57.1 (C_1), 52.1 (C_3), 42.9 (C_{16}), 41.3 (C_4); **IR** (neat) cm^{-1}: 2802, 1606, 1494, 1454, 1092, 1030, 911, 851, 821, 776, 749, 728, 701; **HRMS** (ESI^+) m/z calc. for $C_{24}H_{23}N_2$ $[M+H]^+$ 339.1856; found at 339.1853 Δ -0.88 ppm; **m.p.** = 91- 93 °C. Spectroscopic data were consistent with the literature data for this compound.[23]

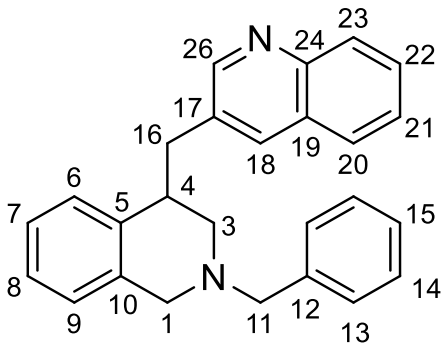
4-(Isoquinolin-4-ylmethyl)benzonitrile (207):



The title compound was prepared according to **General Procedure D** with 4-((2-benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)benzonitrile **184** (84 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (30-40% EtOAc in pentane) afforded **207** as a pale-orange powder (37 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.21 (1H, s, H_1), 8.41 (1H, s, H_3), 8.01 (1H, ddd, *J* = 8.0, 1.5, 0.8 Hz, H_9), 7.77 (1H, dq, *J* = 8.4, 0.9 Hz, H_6), 7.66 (1H, ddd, *J* = 8.4, 6.9, 1.5 Hz, H_7), 7.61 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz, H_8), 7.57 – 7.52 (2H, m, H_{14}), 7.32 – 7.27 (2H, m, H_{13}), 4.44 (2H, s, H_{11}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 152.7 (C_1), 145.5 (C_{16}), 144.0 (C_3), 134.7 (C_5), 132.6 (C_{14}), 130.9 (C_7), 129.4 (C_{13}), 128.8 (C_{10}), 128.6 (C_9), 128.2 (C_4), 127.4 (C_8), 123.1 (C_6), 118.9 (C_{12}), 110.5 (C_{15}), 36.5 (C_{11}); **IR** (neat) cm^{-1}: 2229, 1608, 1584, 1504, 1391, 1230, 1021, 904, 818, 787, 754, 620; **HRMS** (ESI^+) m/z calc. for $C_{17}H_{13}N_2$ $[M+H]^+$ 245.1073; found at 245.1067 Δ -2.45 ppm; **m.p.** = 101-103 °C. Spectroscopic data were consistent with the literature data for this compound.[169]

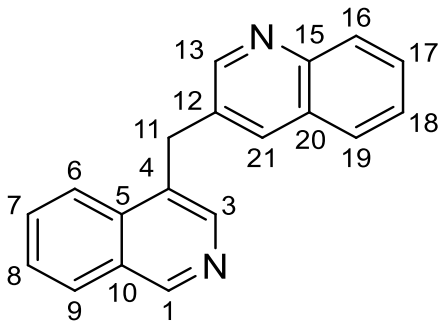
(*RS*)-3-((2-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)quinoline (185):



The title compound was prepared according to **General Procedure C** using quinoline-3-carbaldehyde (79 mg, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (20% EtOAc in pentane) afforded **185** as a pale-orange oil (146 mg, 80%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.76 (1H, d, *J* = 2.2 Hz, H_{26}), 8.07 (1H, d, *J* = 8.4 Hz, H_{23}), 7.70 – 7.59 (2H, m, H_{20}, H_{22}), 7.54 – 7.48 (2H, m, H_{18}, H_{21}), 7.45 – 7.41 (2H, m, H_{13}), 7.40 – 7.34 (3H, m, H_{14}, H_{15}), 7.24 – 7.13 (3H, m, H_6, H_7, H_8), 7.08 – 7.03 (1H, m, H_9), 3.94 (1H, d, *J* = 14.8 Hz, H_1), 3.76 (1H, d, *J* = 12.9 Hz, H_{11}), 3.54 – 3.45 (2H, m, H_1', H_{11}'), 3.25 – 3.18 (1H, m, H_{16}), 3.14 (1H, dd, *J* = 13.7, 4.3 Hz, H_{16}'), 3.10 – 3.04 (1H, m, H_4), 2.79 (1H, dt, *J* = 11.7, 1.9 Hz, H_3), 2.39 (1H, dd, *J* = 11.6, 3.9 Hz, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 152.6 (C_{26}), 146.9 (C_{24}), 138.8 (C_{12}), 138.0 (C_5), 135.5 (C_{18}), 135.2 (C_{10}), 133.8 (C_{17}), 129.6 (C_{13}), 129.3 (C_{23}), 128.9 (C_6), 128.8 (C_{22}), 128.5 (C_{14}), 128.1 (C_{19}), 127.6 (C_{15}), 127.5 (C_{20}), 126.7 (C_9), 126.6 (C_{21}), 126.4 (C_8), 126.3 (C_7), 63.0 (C_{11}), 57.0 (C_1), 52.8 (C_3), 41.3 (C_4), 40.3 (C_{16}); **IR** (neat) cm^{-1}: 1494, 1454, 911, 793, 745, 701; **HRMS** (ESI^+) m/z calc. for $C_{26}H_{25}N_2$ $[M+H]^+$ 365.2012; found at 365.2003 Δ -2.46 ppm.

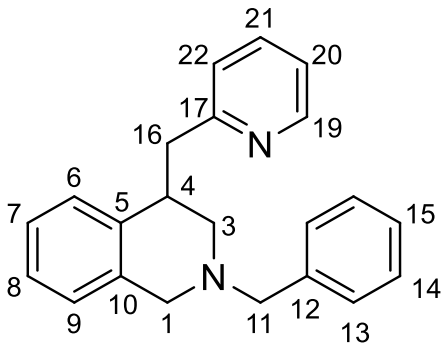
3-(Isoquinolin-4-ylmethyl)quinoline (208):



The title compound was prepared according to **General Procedure D** with 3-((2-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)quinoline **185** (91 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (80% - 100% EtOAc in pentane) afforded **208** as a beige solid (39 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.25 (1H, s, H_1), 8.93 (1H, d, *J* = 2.2 Hz, H_{13}), 8.50 (1H, s, H_3), 8.08 (1H, d, *J* = 8.4 Hz, H_6), 8.03 (1H, dt, *J* = 8.1, 1.1 Hz, H_9), 7.88 (1H, d, *J* = 8.4 Hz, H_{16}), 7.81 – 7.77 (1H, m, H_{21}), 7.68 – 7.63 (3H, m, H_7, H_{17}, H_{19}), 7.60 (1H, ddd, *J* = 8.1, 7.0, 1.2 Hz, H_8), 7.48 (1H, ddd, *J* = 8.1, 6.9, 1.2 Hz, H_{18}), 4.57 (2H, s, H_{11}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 152.4 (C_1), 151.4 (C_{13}), 147.0 (C_{15}), 143.6 (C_3), 135.0 (C_{21}), 134.8 (C_5), 132.6 (C_{12}), 131.1 (C_7), 129.3 (C_{17}), 129.2 (C_6), 128.8 (C_4), 128.7 (2C, C_9, C_{10}), 128.1 (C_{20}), 127.6 (C_{19}), 127.5 (C_8), 127.0 (C_{18}), 123.3 (C_{16}), 33.8 (C_{11}); **IR** (neat) cm^{-1}: 1653, 1496, 1437, 1420, 1232, 911, 865, 791, 752, 733; **HRMS** (ESI^+) m/z calc. for $C_{19}H_{15}N_2$ $[M+H]^+$ 271.1230; found at 271.1223 Δ -2.58 ppm; **m.p.** = 133-134 °C.

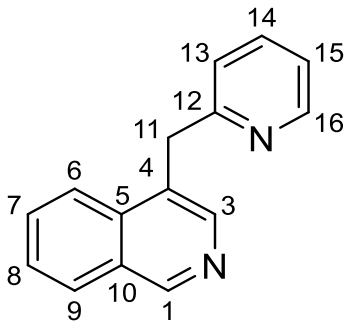
(*RS*)-2-Benzyl-4-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (186):



The title compound was prepared according to **General Procedure C** using 2-pyridinecarbaldehyde (48 μL, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (20% EtOAc in pentane) afforded **186** as a pale-yellow oil (215 mg, 68%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.56 (1H, dt, *J* = 4.8, 1.5 Hz, H_{19}), 7.42 – 7.38 (3H, m, H_{13}, H_{21}), 7.37 – 7.32 (2H, m, H_{14}), 7.32 – 7.28 (1H, m, H_{15}), 7.22 – 7.18 (1H, m, H_6), 7.17 – 7.12 (2H, m, H_7, H_8), 7.07 (1H, ddd, *J* = 7.5, 4.9, 1.2 Hz, H_{20}), 7.03 (1H, dd, *J* = 6.8, 2.2 Hz, H_9), 6.69 (1H, d, *J* = 7.7 Hz, H_{22}), 3.92 (1H, d, *J* = 14.8 Hz, H_1), 3.74 (1H, d, *J* = 12.8 Hz, H_{11}), 3.53 – 3.45 (2H, m, H_1', H_{11}'), 3.41 – 3.33 (1H, m, H_4), 3.22 – 3.11 (2H, m, H_{16}, H_{16}'), 2.71 (1H, ddd, *J* = 11.6, 2.8, 1.4 Hz, H_3), 2.42 (1H, dd, *J* = 11.6, 4.0 Hz, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 160.6 (C_{17}), 149.5 (C_{19}), 138.7 (C_{12}), 138.5 (C_5), 136.2 (C_{21}), 135.0 (C_{10}), 129.5 (C_{13}), 128.9 (C_6), 128.4 (C_{14}), 127.2 (C_{15}), 126.5 (C_9), 126.3 (C_7), 126.0 (C_8), 124.4 (C_{22}), 121.1 (C_{20}), 62.9 (C_{11}), 56.9 (C_1), 53.4 (C_3), 45.1 (C_{16}), 39.5 (C_4); **IR** (neat) cm^{-1}: 1591, 1495, 1473, 1394, 1368, 1146, 1093, 910, 755, 735, 700; **HRMS** (ESI^+) m/z calc. for $C_{22}H_{23}N_2$ $[M+H]^+$ 315.1856; found at 315.1845 Δ -3.41 ppm. Spectroscopic data were consistent with the literature data for this compound.[23]

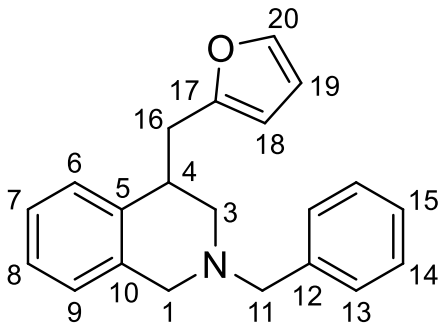
4-(Pyridin-2-ylmethyl)isoquinoline (209):



The title compound was prepared according to **General Procedure D** with 2-benzyl-4-(pyridin-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline **186** (79 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (20% EtOAc in pentane) afforded **209** as a dark brown solid (23 mg, 42%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.18 (1H, s, H_1), 8.58 – 8.54 (1H, m, H_{16}), 8.48 (1H, s, H_3), 8.00 (1H, d, *J* = 8.5 Hz, H_6), 7.96 (1H, ddd, *J* = 8.2, 2.1, 1.1 Hz, H_9), 7.64 (1H, ddt, *J* = 8.3, 7.1, 1.3 Hz, H_7), 7.57 (1H, ddt, *J* = 8.2, 6.9, 1.3 Hz, H_8), 7.49 (1H, td, *J* = 7.7, 2.0 Hz, H_{14}), 7.12 – 7.07 (1H, m, H_{15}), 7.00 (1H, dd, *J* = 7.9, 1.4 Hz, H_{13}), 4.55 (2H, s, H_{11}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 160.0 (C_{12}), 152.2 (C_1), 149.4 (C_{16}), 143.7 (C_3), 136.7 (C_{14}), 135.1 (C_5), 130.7 (C_7), 128.9 (C_4), 128.7 (C_{10}), 128.3 (C_9), 127.2 (C_8), 123.9 (C_6), 123.0 (C_{13}), 121.6 (C_{15}), 39.5 (C_{11}); **IR** (neat) cm^{-1}: 1622, 1591, 1569, 1503, 1474, 1433, 1229, 1193, 1050, 994, 903, 797, 785, 776, 751; **HRMS** (ESI^+) m/z calc. for $C_{15}H_{13}N_2$ $[M+H]^+$ 221.1073; found at 221.1070 Δ -1.36 ppm; **m.p.** = 70-74 °C.

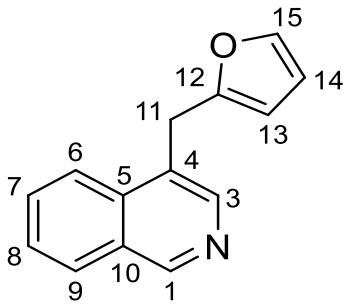
(*RS*)-2-Benzyl-4-(furan-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (187):



The title compound was prepared according to **General Procedure C** using furfural (42 μL, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (3% EtOAc in pentane) afforded **187** as a pale-orange oil (136 mg, 90%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.41 (2H, d, *J* = 7.5 Hz, H_{13}), 7.35 (2H, t, *J* = 7.6 Hz, H_{14}), 7.31 – 7.27 (2H, m, H_{15}, H_{20}), 7.18 – 7.08 (3H, m, H_6, H_7, H_8), 7.01 (1H, dd, *J* = 7.0, 1.9 Hz, H_9), 6.21 (1H, dd, *J* = 3.1, 1.9 Hz, H_{19}), 5.69 (1H, d, *J* = 3.1 Hz, H_{18}), 3.85 (1H, d, *J* = 14.8 Hz, H_1), 3.73 (1H, d, *J* = 13.0 Hz, H_{11}), 3.57 (1H, d, *J* = 12.9 Hz, H_{11}'), 3.45 (1H, d, *J* = 14.8 Hz, H_1'), 3.16 – 3.06 (2H, m, H_4, H_{16}), 2.99 – 2.92 (1H, m, H_{16}), 2.79 (1H, d, *J* = 11.5 Hz, H_3), 2.50 – 2.45 (1H, m, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 154.8 (C_{17}), 141.1 (C_{20}), 138.9 (C_{12}), 138.1 (C_{10}), 135.3 (C_5), 129.4 (C_{13}), 128.8 (C_6), 128.4 (C_{14}), 127.2 (C_{15}), 126.6 (C_9), 126.3 (C_7), 126.1 (C_8), 110.2 (C_{19}), 106.7 (C_{18}), 63.0 (C_{11}), 56.8 (C_1), 53.9 (C_3), 38.6 (C_4), 35.1 (C_{16}); **IR** (neat) cm^{-1}: 1493, 1454, 1146, 1095, 1029, 1010, 923, 728, 699; **HRMS** (ESI^+) m/z calc. for $C_{21}H_{22}NO$ $[M+H]^+$ 304.1696; found at 304.1689 Δ -2.30 ppm. Spectroscopic data were consistent with the literature data for this compound.[23]

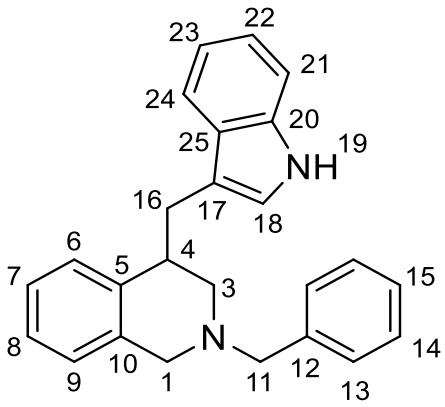
4-(Furan-2-ylmethyl)isoquinoline (210):



The title compound was prepared according to **General Procedure D** with 2-benzyl-4-(furan-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline **187** (76 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (15% EtOAc in pentane) afforded **210** as an orange oil (21 mg, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.19 (1H, s, H_1), 8.42 (1H, s, H_3), 7.96 – 7.87 (2H, m, H_6, H_9), 7.71 (1H, ddd, *J* = 8.3, 6.9, 1.4 Hz, H_7), 7.61 (1H, ddd, *J* = 8.1, 6.9, 1.1 Hz, H_8), 7.33 (1H, dd, *J* = 1.9, 0.8 Hz, H_{15}), 6.26 (1H, dd, *J* = 3.3, 1.9 Hz, H_{14}), 5.93 (1H, dq, *J* = 3.1, 1.0 Hz, H_{13}), 4.36 (2H, s, H_{11}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 153.4 (C_{12}), 152.3 (C_1), 143.5 (C_3), 141.6 (C_{15}), 134.9 (C_5), 130.6 (C_7), 128.6 (C_{10}), 128.4 (C_9), 127.5 (C_4), 127.2 (C_8), 123.3 (C_6), 110.6 (C_{14}), 106.9 (C_{13}), 29.3 (C_{11}); **IR** (neat) cm^{-1}: 1624, 1586, 1505, 1391, 1228, 1148, 1073, 1011, 876, 790, 753, 658; **HRMS** (ESI^+) m/z calc. for $C_{14}H_{12}NO$ $[M+H]^+$ 210.0913; found at 210.0916 Δ -1.43 ppm. Spectroscopic data were consistent with the literature data for this compound.[24]

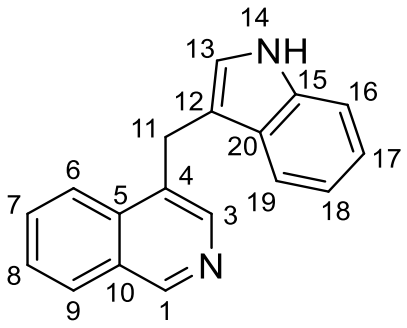
(*RS*)-4-((1H-Indol-3-yl)methyl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (188):



The title compound was prepared according to **General Procedure C** using indole-3-carbaldehyde (73 mg, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (5% EtOAc in pentane) afforded **188** as a fluffy, colourless solid (112 mg, 64%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.86 (1H, s, H_{19}), 7.78 (1H, d, *J* = 7.8 Hz, H_{24}), 7.48 (2H, d, *J* = 7.0 Hz, H_{13}), 7.43 – 7.38 (3H, m, H_6, H_{14}), 7.38 – 7.34 (2H, m, H_{15}, H_{21}), 7.29 – 7.16 (4H, m, H_7, H_8, H_{22}, H_{23}), 7.09 (1H, d, *J* = 7.6 Hz, H_9), 6.44 (1H, d, *J* = 2.2 Hz, H_{18}), 3.95 (1H, d, *J* = 14.7 Hz, H_1), 3.79 (1H, d, *J* = 12.9 Hz, H_{11}), 3.58 – 3.49 (2H, m, H_1', H_{11}'), 3.23 (1H, dd, *J* = 15.2, 11.9 Hz, H_{16}), 3.19 – 3.12 (2H, m, H_4, H_{16}'), 2.90 (1H, dt, *J* = 11.5, 1.9 Hz, H_3), 2.41 (1H, dd, *J* = 11.4, 3.8 Hz, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 139.2 (C_5), 139.1 (C_{12}), 136.4 (C_{20}), 135.2 (C_{10}), 129.6 (C_{13}), 129.0 (C_6), 128.4 (C_{14}), 127.7 (C_{17}), 127.2 (C_{15}), 126.5 (C_9), 126.3 (C_7), 125.9 (C_8), 122.8 (C_{18}), 121.9 (C_{22}), 119.3 (C_{23}), 119.0 (C_{24}), 115.0 (C_{25}), 111.2 (C_{21}), 63.0 (C_{11}), 57.1 (C_1), 53.3 (C_3), 39.8 (C_4), 32.3 (C_{16}); **IR** (neat) cm^{-1}: 3422, 1493, 1455, 1342, 1093, 740, 700; **HRMS** (ESI^+) m/z calc. for $C_{25}H_{25}N_2$ $[M+H]^+$ 353.2012; found at 353.2007 Δ -1.42 ppm; **m.p.** = 46-47 °C.

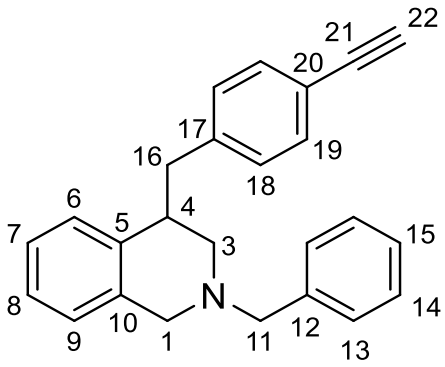
4-((1H-Indol-3-yl)methyl)isoquinoline (211):



The title compound was prepared according to **General Procedure D** with 4-((1H-indol-3-yl)methyl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline **188** (88 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (20% EtOAc in pentane) afforded **211** as a brown solid (17 mg, 26%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.19 (1H, s, H_1), 8.47 (1H, s, H_3), 8.29 (1H, s, H_{14}), 8.04 (1H, d, *J* = 8.4 Hz, H_6), 7.99 (1H, dd, *J* = 8.4, 1.3 Hz, H_9), 7.70 – 7.63 (2H, m, H_7, H_{16}), 7.59 (1H, ddd, *J* = 8.0, 6.8, 1.2 Hz, H_8), 7.36 (1H, dd, *J* = 8.1, 1.0 Hz, H_{19}), 7.21 (1H, ddd, *J* = 8.2, 7.0, 1.2 Hz, H_{18}), 7.14 (1H, ddd, *J* = 8.0, 7.0, 1.1 Hz, H_{17}), 6.67 (1H, dd, *J* = 2.4, 1.2 Hz, H_{13}), 4.50 (2H, s, H_{11}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 151.3 (C_1), 142.6 (C_3), 136.5 (C_{15}), 135.3 (C_5), 130.7 (C_7), 130.5 (C_4), 128.6 (C_{10}), 128.4 (C_9), 127.3 (C_{12}), 127.2 (C_8), 123.8 (C_6), 122.9 (C_{13}), 122.4 (C_{18}), 119.7 (C_{17}), 118.9 (C_{16}), 114.5 (C_{20}), 111.4 (C_{19}), 26.4 (C_{11}); **IR** (neat) cm^{-1}: 1623, 1457, 1228, 909, 739; **HRMS** (ESI^+) m/z calc. for $C_{18}H_{16}N_2$ $[M+2H]^{2+}$ 260.1263; found at 260.1259 Δ -1.54 ppm; **m.p.** = 125-129 °C.

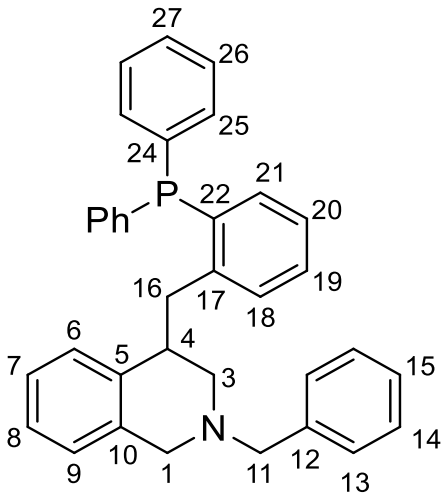
(*RS*)-2-Benzyl-4-(4-ethynylbenzyl)-1,2,3,4-tetrahydroisoquinoline (189):



The title compound was prepared according to **General Procedure C** using 4-ethynylbenzaldehyde (65 mg, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (2% EtOAc in pentane) afforded **189** as an orange gum (109 mg, 65%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.48 – 7.45 (2H, m, H_{13}), 7.45 – 7.41 (2H, m, H_{14}), 7.41 – 7.35 (3H, m, H_{15}, H_{19}), 7.24 – 7.18 (3H, m, H_6, H_7, H_8), 7.11 – 7.06 (1H, m, H_9), 6.96 (2H, d, *J* = 1.4 Hz, H_{18}), 3.95 (1H, d, *J* = 14.8 Hz, H_1), 3.78 (1H, d, *J* = 12.8 Hz, H_{11}), 3.54 (1H, d, *J* = 12.8 Hz, H_{11}'), 3.50 (1H, d, *J* = 14.8 Hz, H_1'), 3.10 (1H, s, H_{22}), 3.06 (1H, dd, *J* = 13.6, 11.2 Hz, H_{16}), 3.03 – 2.97 (2H, m, H_4, H_{16}'), 2.79 (1H, dt, *J* = 11.5, 1.7 Hz, H_3), 2.39 (1H, dd, *J* = 11.6, 3.7 Hz, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 142.2 (C_{17}), 138.7 (C_{12}), 138.4 (C_5), 135.2 (C_{10}), 132.1 (C_{19}), 129.6 (C_{13}), 129.5 (C_{18}), 128.8 (C_6), 128.5 (C_{14}), 127.3 (C_{15}), 126.6 (C_9), 126.3 (C_7), 126.0 (C_8), 119.6 (C_{20}), 84.0 (C_{21}), 76.8 (C_{22}), 63.0 (C_{11}), 57.0 (C_1), 52.8 (C_3), 42.8 (C_{16}), 41.5 (C_4); **IR** (neat) cm^{-1}: 3291, 1505, 1494, 1454, 1093, 1058, 967, 946, 849, 821, 748, 729, 700; **HRMS** (ESI^+) m/z calc. for $C_{25}H_{24}N$ $[M+H]^+$ 338.1903; found at 338.1900 Δ -0.887 ppm.

(*RS*)-2-Benzyl-4-(2-(diphenylphosphaneyl)benzyl)-1,2,3,4-tetrahydroisoquinoline (190):

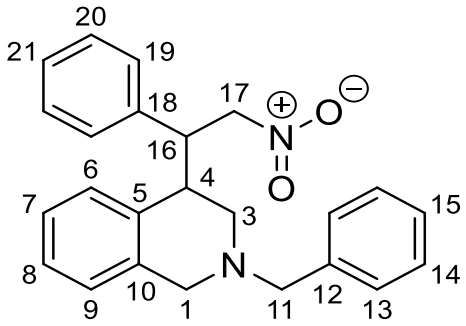


The title compound was prepared according to **General Procedure C** using 2-PPh_2 benzaldehyde (145 mg, 0.500 mmol, 1.00 equiv.) as the electrophile. Purification by flash column chromatography (5% EtOAc in pentane) afforded **190** as a colourless powder (104 mg, 42%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.48 – 7.42 (3H, m, H_6, H_{13}), 7.41 – 7.35 (2H, m, H_{14}), 7.35 – 7.30 (4H, m, H_{15}, H_{26}, H_{27}), 7.30 – 7.26 (2H, m, H_{25}), 7.15 (1H, t, *J* = 7.5 Hz, H_7), 7.12 – 7.04 (3H, m, H_8, H_{19}, H_{20}), 6.97 (1H, d, *J* = 7.6 Hz, H_9), 6.93 (1H, ddt, *J* = 7.0, 3.0, 1.3 Hz, H_{21}), 6.75 – 6.69 (1H, m, H_{18}), 3.87 (1H, d, *J* = 14.8 Hz, H_1), 3.67 (1H, d, *J* = 12.8 Hz, H_{11}), 3.57 (1H, d, *J* = 12.8 Hz, H_{11}'), 3.42 – 3.36 (2H, m, H_1', H_{16}), 3.20 – 3.09 (2H, m, H_4, H_{16}'), 2.85 (1H, dd, *J* = 11.6, 2.1 Hz, H_3), 2.28 (1H, dd, *J* = 11.7, 3.8 Hz, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 145.9 (d, *J* = 25.8 Hz, C_{22}), 139.2 (C_5), 139.0 (C_{12}), 137.4 (dd, *J* = 34.4, 10.9 Hz, C_{24}), 135.9 (d, *J* = 13.6 Hz, C_{17}), 135.0 (C_{10}), 134.4 (C_{21}), 133.9 (dd, *J* = 40.1, 19.5 Hz, C_{25}), 131.3 (d, *J* = 5.5 Hz, C_{18}), 129.7 (C_{13}), 129.1 (d, *J* = 4.0 Hz, C_{19}), 128.9 (C_6), 128.8 – 128.6 (m, C_{26}, C_{27}), 128.5 (C_{14}), 127.3 (C_{15}), 126.5 (C_9), 126.3 (C_{20}), 126.3 (C_7), 125.8 (C_8), 63.2 (C_{11}), 57.0 (C_1), 52.8 (C_3), 41.8 (d, *J* = 17.0 Hz, C_{16}), 40.3 (d, *J* = 4.2 Hz, C_4); **^{31}P NMR** (162 MHz, $CDCl_3$): δ_P = -16.25; **IR** (neat) cm^{-1}: 1510, 1281, 1249, 1224, 1133, 1023, 787, 744, 698;

HRMS (ESI^+) m/z calc. for $C_{35}H_{33}NP$ $[M+H]^+$ 498.2345; found at 498.2351 Δ 1.20 ppm; **m.p.** = 65-67 °C.

(*RS*, *RS*) and (*RS*, *SR*)-2-Benzyl-4-(2-nitro-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (191a and 191b):



The title compound was prepared according to **General Procedure C** using *β*-nitrostyrene (75 mg, 0.5 mmol, 1.0 equiv.) as the electrophile. Flash column chromatography (2-3% EtOAc in pentane) afforded **191** as two separable diastereomers in a 1:3 ratio:

Minor diastereomer **191a**:

Pale-orange solid (20 mg, 11%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.48 (2H, t, *J* = 7.0 Hz, H_{14}), 7.46 – 7.41 (3H, m, H_{13}, H_{15}), 7.37 – 7.32 (1H, m, H_6), 7.28 – 7.23 (1H, m, H_8), 7.22 (1H, td, *J* = 7.5, 1.5 Hz, H_7), 7.19 – 7.14 (3H, m, H_{20}, H_{21}), 7.09 (1H, d, *J* = 7.4 Hz, H_9), 6.79 (2H, dd, *J* = 7.5, 1.9 Hz, H_{19}), 5.20 (1H, dd, *J* = 14.1, 12.1 Hz, H_{17}), 4.20 (1H, dd, *J* = 14.1, 3.7 Hz, H_{17}'), 4.06 – 3.99 (2H, m, H_1, H_{16}), 3.84 (1H, d, *J* = 12.2 Hz, H_{11}), 3.42 (1H, d, *J* = 14.8 Hz, H_1'), 3.32 (1H, d, *J* = 12.1 Hz, H_{11}'), 3.04 – 3.00 (1H, m, H_4), 2.92 (1H, d, *J* = 12.3 Hz, H_3), 2.08 (1H, dd, *J* = 12.4, 4.4 Hz, H_3'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 138.9 (C_{18}), 138.0 (C_{12}), 135.8 (C_{10}), 135.1 (C_5), 130.2 (C_{13}), 128.9 (C_{20}), 128.8 (C_{14}), 128.6 (C_6), 127.8 (C_{19}), 127.8 (C_{15}), 127.2 (C_{21}), 127.0 (C_8), 127.0 (C_7), 126.7 (C_9), 75.4 (C_{17}), 63.1 (C_{11}), 57.4 (C_1), 50.4 (C_{16}), 49.2 (C_3), 43.8 (C_4); **IR** (neat) cm^{-1}: 1548, 1496, 1454, 1383, 1089, 911, 778, 756, 737, 702; **HRMS** (ESI^+) m/z calc.

for $C_{24}H_{25}N_2O_2$ $[M+H]^+$ 373.1911; found at 373.1911 Δ 0.12 ppm; **m.p.** = 78-79 °C. Spectroscopic data were consistent with the literature data for this compound.[23]

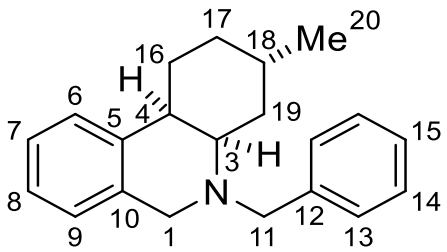
Major diastereomer **191b**:

Yellow solid (66 mg, 36%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.43 – 7.38 (4H, m, H_{13}, H_{14}), 7.37 – 7.33 (1H, m, H_{15}), 7.28 (2H, dd, *J* = 8.1, 6.3 Hz, H_{20}), 7.26 – 7.20 (2H, m, H_8, H_{21}), 7.19 – 7.14 (3H, m, H_7, H_{19}), 7.08 (1H, d, *J* = 7.6 Hz, H_9), 7.00 (1H, d, *J* = 7.6 Hz, H_6), 4.74 – 4.69 (2H, m, H_{17}), 4.13 (1H, td, *J* = 9.7, 6.1 Hz, H_{16}), 4.03 (1H, d, *J* = 15.4 Hz, H_1), 3.57 (2H, s, H_{11}), 3.36 (1H, d, *J* = 15.4 Hz, H_1'), 3.03 (1H, d, *J* = 9.2 Hz, H_4), 2.77 (1H, d, *J* = 11.5 Hz, H_3), 2.41 (1H, dd, *J* = 11.5, 3.2 Hz, $H_{3'}$); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 139.6 (C_{18}), 138.2 (C_{12}), 135.9 (C_{10}), 134.3 (C_5), 129.8 (C_6), 129.4 (C_{13}), 128.9 (C_{20}), 128.6 (C_{14}), 128.2 (C_{19}), 127.5 (C_{21}), 127.5 (C_{15}), 127.4 (C_9), 127.2 (C_8), 125.8 (C_7), 80.0 (C_{17}), 63.1 (C_{11}), 56.0 (C_1), 53.5 (C_3), 48.4 (C_{16}), 43.9 (C_4); **IR** (neat) cm^{-1}: 1552, 1494, 1455, 1379, 911, 735, 702, 649; **HRMS** (ESI^+) m/z calc. for $C_{24}H_{25}N_2O_2$ $[M+H]^+$ 373.1911; found at 373.1908 Δ -0.80 ppm; **m.p.** = 92-94 °C. Spectroscopic data were consistent with the literature data for this compound.[23]

The relative stereochemistry of the two isomers was challenging to assign based on spectroscopic data and was therefore left unassigned.

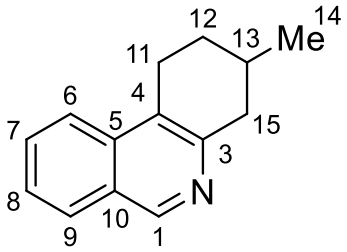
(*RS*, *RS*, *SR*)-*N*-Benzyl-3-methyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (17):



The title compound was prepared according to a literature procedure reported by Donohoe and co-workers: 2-Benzyl-3-methylisoquinolin-2-ium iodide **15**(181 mg, 0.50 mmol, 1.00 equiv.) was placed in a microwave vial with MVK (41.0 μL, 0.50 mmol, 1.0 equiv.), formic acid triethylamine complex 5:2 (168 μL, 2.00 mmol, 4.00 equiv.), and an aliquot of a premade solution of $(RhCp^*Cl_2)_2$ in MeCN (0.400 mL, 0.0100 mol%, 3.86 mg in 50.0 mL). The mixture was stirred at 80 °C for 18 h, then cooled to r.t. and diluted with CH_2Cl_2. The solution was washed with sat. aq. Na_2CO_3, the layers partitioned and the aqueous phase extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (2% EtOAc in pentane) afforded **17** as a colourless oil as a single diastereomer (61 mg, 42%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.48 (2H, dd, *J* = 7.1, 1.9 Hz, H_{13}), 7.38 (2H, td, *J* = 7.7, 2.5 Hz, H_{14}), 7.33 – 7.28 (1H, m, H_{15}), 7.19 – 7.12 (2H, m, H_6, H_7), 7.10 (1H, td, *J* = 7.4, 3.9 Hz, H_8), 6.91 (1H, d, *J* = 7.6 Hz, H_9), 4.38 (1H, dd, *J* = 13.0, 2.5 Hz, H_{11}), 3.85 (1H, dd, *J* = 15.5, 2.6 Hz, H_1), 3.28 (1H, dd, *J* = 15.4, 2.4 Hz, H_1'), 3.11 (1H, dd, *J* = 13.1, 2.3 Hz, H_{11}'), 2.88 (1H, q, *J* = 3.1 Hz, H_3), 2.72 (1H, dt, *J* = 11.8, 3.4 Hz, H_4), 2.31 (1H, dq, *J* = 14.7, 2.9 Hz, H_{19}), 2.20 (1H, dddd, *J* = 16.2, 13.0, 8.2, 3.4 Hz, H_{16}), 1.96 – 1.84 (2H, m, H_{17}, H_{18}), 1.79 (1H, dp, *J* = 13.5, 3.4 Hz, H_{16}), 1.34 (1H, ddt, *J* = 14.8, 11.9, 2.7 Hz, H_{19}'), 1.28 – 1.18 (1H, m, H_{17}'), 0.96 (3H, dd, *J* = 6.6, 2.5 Hz, H_{20}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 140.8 (C_5), 140.4 (C_{12}), 134.6 (C_{10}), 128.7 (C_{13}), 128.4 (C_{14}), 128.1 (C_6), 126.9 (C_{15}), 126.1 (C_9), 126.0 (C_7), 125.6 (C_8), 58.3 (C_3), 56.8 (C_{11}), 56.1 (C_1), 42.5 (C_4), 37.5 (C_{19}), 35.6 (C_{17}), 32.4 (C_{16}), 26.0 (C_{18}), 22.7 (C_{20}); **IR** (neat) cm^{-1}: 2924, 1494, 1455, 1379, 1188, 1069, 1029, 910, 738, 699; **HRMS** (ESI^+) m/z calc. for $C_{21}H_{26}N$ $[M+H]^+$ 292.2060; found at 292.2049 Δ -3.80 ppm. Spectroscopic data were consistent with the literature data for this compound.[23]

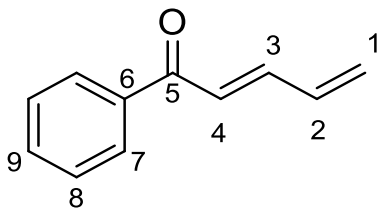
(*RS*)-3-Methyl-1,2,3,4-tetrahydrophenanthridine (215):



The title compound was prepared according to **General Procedure D** with *N*-benzyl-3-methyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridine **17** (78 mg, 0.25 mmol, 1.0 equiv.). Flash column chromatography (20% EtOAc in pentane) afforded **215** as a brown oil (32 mg, 65%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.04 (1H, s, H_1), 7.91 – 7.84 (2H, m, H_6, H_9), 7.66 (1H, ddt, *J* = 8.2, 6.9, 1.3 Hz, H_7), 7.50 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz, H_8), 3.25 – 3.10 (2H, m, H_{11}, H_{15}), 3.03 – 2.91 (1H, m, H_{11}'), 2.70 (1H, ddt, *J* = 17.2, 10.0, 1.8 Hz, H_{15}'), 2.11 – 1.94 (2H, m, H_{12}, H_{13}), 1.50 (1H, dddd, *J* = 12.7, 9.6, 6.1, 4.9 Hz, H_{12}'), 1.14 (3H, d, *J* = 6.5 Hz, H_{14}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 150.2 (C_1), 149.8 (C_3), 135.3 (C_5), 130.2 (C_7), 128.2 (C_9), 127.0 (C_{10}), 125.9 (C_8), 124.2 (C_4), 122.1 (C_6), 41.2 (C_{15}), 30.8 (C_{12}), 29.2 (C_{13}), 24.6 (C_{11}), 21.7 (C_{14}); **IR** (neat) cm^{-1}: 2950, 2922, 1623, 1582, 1500, 14554, 1430, 1381, 1361, 1228, 1155, 774, 751; **HRMS** (ESI^+) m/z calc. for $C_{14}H_{16}N$ $[M+H]^+$ 198.1277; found at 198.1273 Δ -2.17 ppm.

(*E*)-1-Phenylpenta-2,4-dien-1-one (S192):

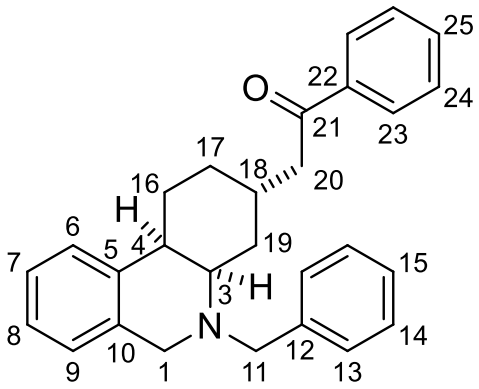


The title compound was synthesised according to a procedure published by Jørgensen and co-workers:[173] Fresh LDA was prepared by adding *n*BuLi (11.2 mL, 2.50 M in hexanes, 28.0 mmol, 1.10 equiv.) dropwise so a stirred solution of diisopropylamine (4.05 mL,

28.0 mmol, 1.10 equiv.) in anhydrous THF (30 mL) at -78 °C. Acetophenone (2.92 mL, 25.0 mmol, 1.00 equiv.) dissolved in anhydrous THF (5.0 mL) was added dropwise, and the solution stirred for 1 h. Acrolein (1.87 mL, 28.0 mmol, 1.10 equiv.) dissolved in anhydrous THF (5.0 mL) was added dropwise and the solution stirred for 5 min, after which the reaction was quenched with sat. aq. NH_4Cl, poured onto Et_2O and the layers partitioned. The aqueous layer was extracted twice with Et_2O and the combined organic layers washed with brine, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (25 mL) and TsOH (2.40 g, 14.2 mmol, 0.570 equiv.) was added, after which the mixture was heated to reflux for 3 h. The reaction was cooled to r.t., diluted with CH_2Cl_2, washed with water and the layers partitioned. The aqueous layer was extracted twice with CH_2Cl_2 then the combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Flash column chromatography (1-5% EtOAc in pentane) afforded **S192** as a pale-yellow oil (1.05 g, 27%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.97 – 7.93 (2H, m, H_7), 7.61 – 7.52 (1H, m, H_9), 7.51 – 7.45 (2H, m, H_8), 7.40 (1H, ddt, *J* = 15.2, 11.0, 0.8 Hz, H_3), 6.99 (1H, dd, *J* = 15.1, 0.8 Hz, H_4), 6.60 (1H, dddd, *J* = 16.9, 10.8, 10.0, 0.7 Hz, H_2), 5.72 (1H, ddt, *J* = 16.9, 1.5, 0.8 Hz, H_1), 5.59 (1H, ddt, *J* = 10.0, 1.4, 0.7 Hz, H_1'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 190.9 (C_5), 144.9 (C_3), 138.1 (C_6), 135.5 (C_2), 132.9 (C_9), 128.7 (C_8), 128.6 (C_7), 127.0 (C_1), 126.4 (C_4); **IR** (neat) cm^{-1}: 1665, 1614, 1598, 1276, 1221, 1018, 785, 707, 688, 664. Spectroscopic data were consistent with the literature data for this compound.[173]

(*RS*, *RS*, *RS*)-2-(*N*-Benzyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridin-3-yl)-1-phenylethan-1-one (192):

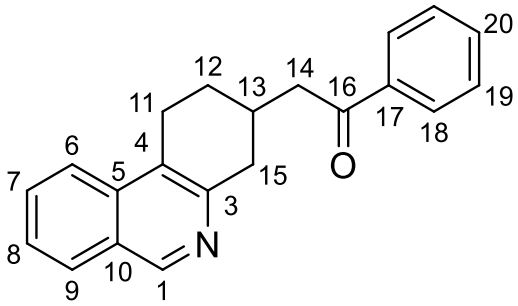


The title compound was prepared according to **General Procedure C** using 2-benzyl-3-methylisoquinolin-2-ium iodide **15** (180 mg, 0.50 mmol, 1.0 equiv.), and (*E*)-1-phenylpenta-2,4-dien-1-one **S192** (80 mg, 0.50 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (2% EtOAc in pentane) afforded **192** as a pale-orange solid as a single diastereomer (39 mg, 20%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.00 – 7.93 (2H, m, H_{23}), 7.57 – 7.50 (1H, m, H_{25}), 7.48 – 7.41 (4H, m, H_{13}, H_{24}), 7.37 – 7.32 (2H, m, H_{14}), 7.29 (1H, ddt, *J* = 7.4, 6.2, 1.5 Hz, H_{15}), 7.19 – 7.06 (3H, m, H_6, H_7, H_8), 6.90 (1H, d, *J* = 7.5 Hz, H_9), 4.50 (1H, d, *J* = 12.7 Hz, H_{11}), 3.83 (1H, d, *J* = 15.4 Hz, H_1), 3.27 (1H, d, *J* = 15.4 Hz, H_1'), 3.06 (1H, d, *J* = 12.7 Hz, H_{11}'), 2.99 (1H, dd, *J* = 16.2, 5.5 Hz, H_{20}), 2.95 – 2.85 (2H, m, H_3, H_{20}'), 2.79 – 2.72 (1H, m, H_4), 2.58 (1H, ddtq, *J* = 11.6, 8.5, 5.9, 3.2 Hz, H_{18}), 2.51 – 2.44 (1H, m, H_{19}), 2.25 (1H, qd, *J* = 13.0, 3.4 Hz, H_{16}), 2.01 – 1.92 (1H, m, H_{17}), 1.82 (1H, dq, *J* = 13.4, 3.7 Hz, H_{16}'), 1.48 – 1.34 (2H, m, H_{17}', H_{19}'); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 199.9 (C_{21}), 140.4 (C_5), 140.2 (C_{12}), 137.3 (C_{22}), 134.6 (C_{10}), 133.0 (C_{25}), 128.9 (C_{13}), 128.7 (C_{24}), 128.3 (C_{14}), 128.1 (C_{23}), 128.0 (C_6), 126.8 (C_{15}), 126.2 (C_9), 126.0 (C_7), 125.7 (C_8), 58.0 (C_3), 56.8 (C_{11}), 55.9 (C_1), 45.9 (C_{20}), 42.5 (C_4), 35.3 (C_{19}), 33.7 (C_{17}), 32.2 (C_{16}), 27.8 (C_{18}); **IR** (neat) cm^{-1}: 1683, 1494, 1449, 910, 739, 700, 691; **HRMS** (ESI^+) m/z calc. for $C_{28}H_{30}NO$ $[M+H]^+$ 396.2322; found at 396.2322

Δ 0.00 ppm; **m.p.** = 113-114 °C. Spectroscopic data were consistent with the literature data for this compound.[23]

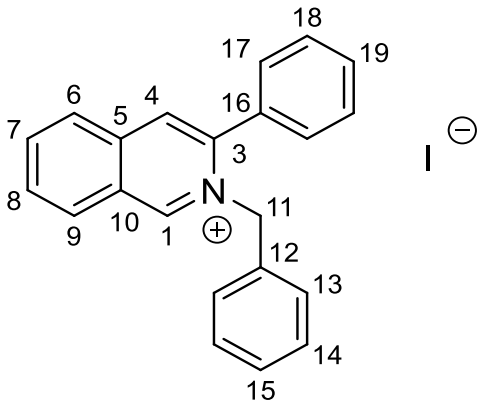
(*RS*)-1-Phenyl-2-(1,2,3,4-tetrahydrophenanthridin-3-yl)ethan-1-one (216):



The title compound was prepared according to **General Procedure D** (0.090 mmol scale), with 2-(*N*-benzyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridin-3-yl)-1-phenylethan-1-one **192** (36 mg, 0.09 mmol, 1.0 equiv.). Flash column chromatography (40% EtOAc in pentane) afforded **216** as a pale-orange solid (21 mg, 75%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.06 (1H, s, H_1), 8.04 – 7.98 (1H, m, H_{18}), 7.92 (1H, dd, *J* = 8.1, 1.2 Hz, H_9), 7.90 (1H, dd, *J* = 8.5, 1.2 Hz, H_6), 7.70 (1H, ddd, *J* = 8.4, 6.9, 1.3 Hz, H_7), 7.59 – 7.52 (2H, m, H_8, H_{20}), 7.47 (1H, dd, *J* = 8.3, 7.1 Hz, H_{19}), 3.32 – 3.20 (2H, m, H_{11}, H_{15}), 3.17 (1H, dd, *J* = 16.2, 5.8 Hz, H_{14}), 3.12 – 3.03 (2H, m, H_{11}', H_{14}'), 2.89 (1H, ddt, *J* = 17.0, 10.0, 1.7 Hz, H_{15}'), 2.73 – 2.61 (1H, m, H_{13}), 2.23 (1H, dtt, *J* = 12.6, 5.8, 2.4 Hz, H_{12}), 1.65 (1H, dtd, *J* = 13.0, 10.7, 5.6 Hz, H_{12}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 199.5 (C_{16}), 150.3 (C_1), 148.8 (C_3), 137.4 (C_{17}), 135.4 (C_5), 133.2 (C_{20}), 130.6 (C_7), 128.8 (C_{19}), 128.3 (C_9), 128.3 (C_{18}), 127.1 (C_{10}), 126.2 (C_8), 124.5 (C_4), 122.2 (C_6), 44.6 (C_{14}), 39.2 (C_{15}), 30.7 (C_{13}), 28.6 (C_{12}), 24.3 (C_{11}); **IR** (neat) cm^{-1}: 2922, 1684, 1623, 1597, 1581, 1449, 1431, 1358, 1303, 1261, 1212, 1001, 775, 753, 738, 691; **HRMS** (ESI^+) m/z calc. for $C_{21}H_{20}NO$ $[M+H]^+$ 302.1539; found at 302.1530 Δ -2.98 ppm; **m.p.** = 133-135 °C.

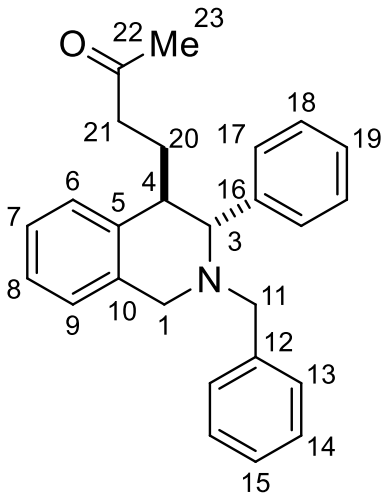
2-Benzyl-3-phenylisoquinolin-2-ium iodide (193):



3-Phenyl isoquinoline (226 mg, 1.10 mmol, 1.00 equiv.) was dissolved in acetone (20 mL) with benzyl iodide (288 mg, 1.30 mmol, 1.20 equiv.) and stirred at 60 °C overnight. Precipitate was filtered *in vacuo*, washed with cold Et_2O and dried to afford **193** as a pale-yellow powder (250 mg, 54%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 11.17 (1H, s, H_1), 8.81 (1H, dt, *J* = 8.3, 1.0 Hz, H_9), 8.14 (1H, ddd, *J* = 8.2, 7.0, 1.2 Hz, H_7), 8.09 – 8.04 (2H, m, H_4, H_6), 7.96 (1H, ddd, *J* = 8.2, 7.0, 1.1 Hz, H_8), 7.64 – 7.58 (1H, m, H_{19}), 7.57 – 7.51 (2H, m, H_{18}), 7.46 – 7.41 (2H, m, H_{17}), 7.29 – 7.25 (1H, m, H_{15}), 7.24 – 7.20 (2H, m, H_{14}), 7.04 – 6.99 (2H, m, H_{13}), 6.15 (2H, s, H_{11}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 152.2 (C_1), 146.1 (C_3), 138.0 (C_5), 137.8 (C_6), 133.2 (C_{12}), 131.8 (C_{16}), 131.7 (C_9), 131.4 (C_8), 131.1 (C_{19}), 130.0 (C_{17}), 129.5 (2C, C_{14}, C_{18}), 129.3 (C_{15}), 128.6 (C_{13}), 127.4 (C_{10}), 127.3 (C_4), 126.8 (C_6), 61.9 (C_{11}); **IR** (neat) cm^{-1}: 1641, 1495, 918, 764, 734, 703; **HRMS** (ESI^+) m/z calc. for $C_{22}H_{18}N$ $[M]^+$ 296.1434; found at 296.1444 Δ 3.45 ppm; **m.p.** = 150 °C.

(*RS*, *RS*)-4-(2-Benzyl-3-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one (194):



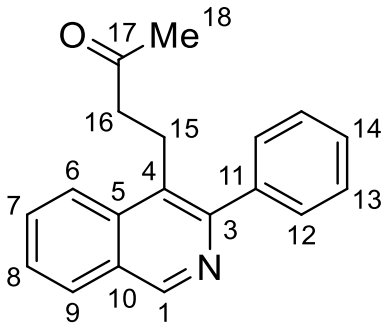
2-Benzyl-3-phenylisoquinolin-2-ium iodide **193** (210 mg, 0.50 mmol, 1.0 equiv.) was dissolved in MeCN (0.40 mL) with MVK (42 μL, 0.50 mmol, 1.0 equiv.) and 5:2 HCO_2H:NEt_3 (0.17 mL, 2.0 mmol, 4.0 equiv.) then stirred at 80 °C for 18 h. The crude mixture was cooled to r.t., diluted with sat. aq. Na_2CO_3 then extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Flash column chromatography (3-10% EtOAc in pentane) afforded **194** as a pale-orange oil as a single diastereomer (67 mg, 36%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.43 (2H, d, *J* = 7.6 Hz, H_{13}), 7.37 (2H, td, *J* = 7.6, 1.8 Hz, H_{14}), 7.34 – 7.15 (9H, m, H_6, H_7, H_8, H_{15}, H_{17}, H_{18}, H_{19}), 7.03 (1H, d, *J* = 7.3 Hz, H_9), 4.09 (1H, d, *J* = 4.6 Hz, H_3), 3.87 – 3.78 (2H, m, H_1, H_{11}), 3.68 (1H, d, *J* = 15.8 Hz, $H_{1'}$), 3.48 (1H, d, *J* = 13.9 Hz, $H_{11'}$), 3.24 (1H, q, *J* = 6.4 Hz, H_4), 2.44 (1H, ddd, *J* = 14.5, 9.7, 4.8 Hz, H_{21}), 2.33 – 2.19 (2H, m, H_{20}, $H_{21'}$), 1.99 (3H, s, H_{23}), 1.75 – 1.63 (1H, m, $H_{20'}$); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 208.8 (C_{22}), 139.3 (C_{12}), 138.1 (C_5), 137.7 (C_{16}), 135.3 (C_{10}), 129.4 (C_{17}), 128.6 (C_{13}), 128.5 (C_{14}), 128.2 (C_{18}), 127.4 (C_{19}), 127.0 (C_{15}), 126.7 (C_6), 126.4 (C_9), 126.4 (C_7), 126.1 (C_8), 65.7 (C_3), 59.9 (C_{11}), 52.4 (C_1), 42.7 (C_4), 41.6 (C_{21}), 29.9 (C_{23}), 23.9 (C_{20}); **IR**

(neat) cm^{-1}: 1715, 1494, 1454, 1361, 911, 735, 702; **HRMS** (ESI^+) m/z calc. for $C_{26}H_{28}NO$ $[M+H]^+$ 370.2165; found at 370.2181 Δ 4.20 ppm.

Stereochemistry assigned based on size of J-coupling between H_3 and H_4 (J = 4.6 Hz), which indicates a large dihedral angle close to 120 °, consistent with a trans geometry. NOESY correlations were unrevealing in this case. Attempts to further confirm this relationship through NOESY correlations were unsuccessful.

4-(3-Phenylisoquinolin-4-yl)butan-2-one (217):

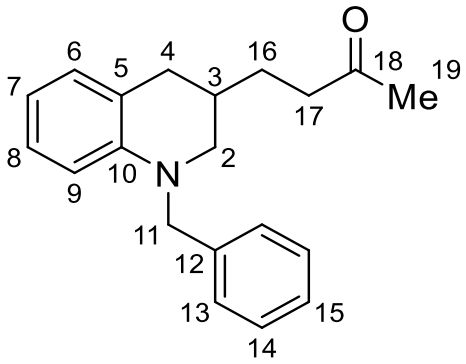


4-(2-Benzyl-3-phenyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one **194** (67 mg, 0.18 mmol, 1.0 equiv.) was placed in a microwave vial with pyridine-*N*-oxide (26 mg, 0.27 mmol, 1.5 equiv.) and camphor (0.20 g), then heated to 250 °C for 40 min. Purification by flash column chromatography (20-40% EtOAc in pentane) afforded **217** as a pale-brown oil (23 mg, 46%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 9.20 (1H, s, H_1), 8.04 – 8.01 (1H, m, H_9), 8.00 (1H, dd, J = 8.6, 1.0 Hz, H_6), 7.77 (1H, ddd, J = 8.4, 6.9, 1.3 Hz, H_7), 7.63 (1H, ddd, J = 8.0, 6.8, 1.0 Hz, H_8), 7.50 – 7.45 (4H, m, H_{12}, H_{13}), 7.44 – 7.39 (1H, m, H_{14}), 3.37 – 3.31 (2H, m, H_{15}), 2.73 – 2.67 (2H, m, H_{16}), 2.07 (3H, s, H_{18}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 207.4 (C_{17}), 152.4 (C_3), 150.6 (C_1), 141.1 (C_{11}), 135.2 (C_5), 131.1 (C_7), 129.2 (C_{12}), 128.7 (C_9), 128.5 (C_{13}), 128.0 (C_{14}), 127.9 (C_{10}), 127.6 (C_4), 127.0 (C_8), 123.2 (C_6), 44.5 (C_{16}), 29.9 (C_{18}), 22.5 (C_{15});

IR (neat) cm^{-1}: 3434, 1776, 1713, 1620, 1575, 1498, 1446, 1422, 1364, 1235, 1164, 768, 703; **HRMS** (ESI^+) m/z calc. for $C_{19}H_8NO$ $[M+H]^+$ 276.1383; found at 276.1388 Δ 1.83 ppm.

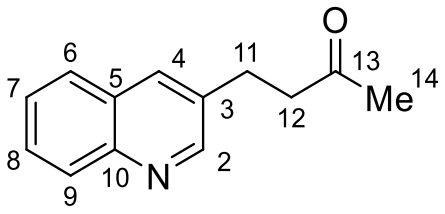
(*RS*)-4-(1-Benzyl-1,2,3,4-tetrahydroquinolin-3-yl)butan-2-one (196):



The title compound was prepared according to **General Procedure C** using 1-benzylquinolin-1-ium iodide **195** (347 mg, 1.00 mmol, 1.00 equiv.) and MVK (82 μL, 1.0 mmol, 1.0 equiv.) as the electrophile. Purification by flash column chromatography (10-50% EtOAc in pentane) afforded **196** as a pale-yellow oil (12 mg, 4%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.34 – 7.29 (2H, m, H_{14}), 7.27 – 7.22 (3H, m, H_{13}, H_{15}), 7.01 – 6.95 (2H, m, H_6, H_8), 6.59 (1H, td, *J* = 7.3, 1.1 Hz, H_7), 6.55 – 6.50 (1H, m, H_9), 4.52 – 4.42 (2H, m, H_{11}), 3.32 (1H, ddd, *J* = 11.3, 3.9, 2.0 Hz, H_2), 3.07 (1H, dd, *J* = 11.3, 9.2 Hz, H_2'), 2.92 – 2.84 (1H, m, H_4), 2.59 – 2.44 (3H, m, H_4', H_{17}, H_{17}'), 2.14 (3H, s, H_{19}), 2.06 – 1.96 (1H, m, H_3), 1.73 – 1.57 (2H, m, H_{16}, H_{16}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 208.7 (C_{18}), 145.4 (C_{10}), 139.0 (C_{12}), 129.4 (C_6), 128.7 (C_{14}), 127.4 (C_8), 127.0 (C_{15}), 126.8 (C_{13}), 121.3 (C_5), 116.2 (C_7), 111.0 (C_9), 55.3 (C_{11}), 55.0 (C_2), 41.2 (C_{17}), 34.4 (C_4), 32.1 (C_3), 30.1 (C_{19}), 27.4 (C_{16}); **IR** (neat) cm^{-1}: 2922, 1715, 1603, 1507, 1452, 1357, 1294, 1245, 1169, 745, 698; **HRMS** (ESI^+) m/z calc. for $C_{20}H_{24}NO$ $[M+H]^+$ 294.1852; Molecule could not be observed by ESI MS.

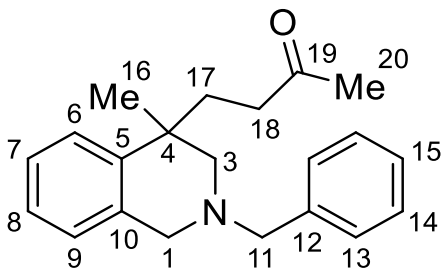
4-(Quinolin-3-yl)butan-2-one (218):



The title compound was prepared according to **General Procedure D** with 4-(1-benzyl-1,2,3,4-tetrahydroquinolin-3-yl)butan-2-one **196** (14 mg, 0.050 mmol, 1.0 equiv.). Flash column chromatography (60% EtOAc in pentane) afforded **218** as a dark brown oil (2.0 mg, 20%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.82 (1H, d, *J* = 2.2 Hz, H_2), 8.22 (1H, d, *J* = 8.5 Hz, H_9), 8.11 (1H, d, *J* = 2.2 Hz, H_4), 7.82 (1H. dd, *J* = 8.2, 1.4 Hz, H_6), 7.73 (1H, ddd, *J* = 8.5, 6.9, 1.4 Hz, H_8), 7.59 (1H, ddd, *J* = 8.2, 6.8, 1.1 Hz, H_7), 3.12 (2H, t, *J* = 7.2 Hz, H_{11}), 2.90 (2H, t, *J* = 7.3 Hz, H_{12}), 2.17 (3H, s, H_{14}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 206.9 (C_{13}), 150.2 (C_2), 145.0 (C_{10}), 136.8 (C_4), 134.2 (C_2), 130.1 (C_8), 128.3 (C_5), 127.8 (C_9), 127.6 (C_7), 127.6 (C_6), 44.4 (C_{12}), 30.2 (C_{14}), 26.9 (C_{11}); **IR** (neat) cm^{-1}:1715, 1496, 1367, 1164, 913, 788, 757; **HRMS** (ESI^+) m/z calc. for $C_{13}H_{14}NO$ $[M+H]^+$ 200.1070; found at 200.1065 Δ -2.65 ppm. Spectroscopic data were consistent with the literature data for this compound.[127]

(*RS*)-4-(2-Benzyl-4-methyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one (219):

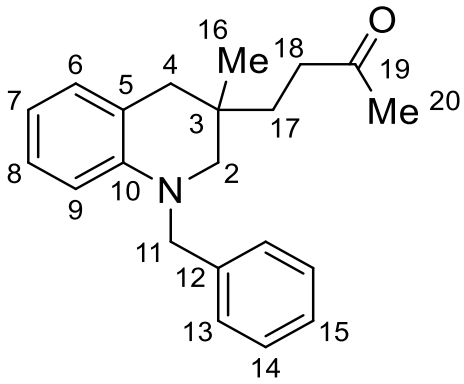


The title compound was prepared according to **General Procedure C** on 0.25 mmol scale, using 4-Me isoquinolinium iodide (90 mg, 0.25 mmol, 1.0 equiv.) as the substrate and MVK

(41 μL, 0.50 mmol, 2.0 equiv.) as the electrophile. Purification with flash column chromatography (5% EtOAc in pentane) afforded **219** as a pale-orange oil (67 mg, 87%).

^{1}H NMR (700 MHz, $CDCl_3$): δ_H = 7.38 (2H, d, *J* = 7.2 Hz, H_{13}), 7.34 (2H, dd, *J* = 8.3, 6.8 Hz, H_{14}), 7.30 – 7.26 (1H, m, H_{15}), 7.24 (1H, dd, *J* = 7.8, 1.3 Hz, H_6), 7.21 – 7.16 (1H, m, H_7), 7.11 (1H, td, *J* = 7.4, 1.3 Hz, H_8), 7.00 (1H, d, *J* = 7.6 Hz, H_9), 3.70 (1H, d, *J* = 14.6 Hz, H_1), 3.65 (1H, d, *J* = 12.9 Hz, H_{11}), 3.58 (1H, d, *J* = 13.0 Hz, H_{11}'), 3.54 (1H, d, *J* = 14.6 Hz, H_1'), 2.57 (1H, d, *J* = 11.4 Hz, H_3), 2.46 (1H, ddd, *J* = 16.6, 12.1, 4.8 Hz, H_{18}), 2.30 (1H, d, *J* = 11.5 Hz, H_3'), 2.11 – 2.04 (2H, m, H_{17}, H_{18}), 2.03 (3H, s, H_{20}), 1.79 (1H, ddd, *J* = 15.4, 12.1, 4.9 Hz, H_{17}'), 1.24 (3H, s, H_{16}); **^{13}C NMR** (176 MHz, $CDCl_3$): δ_C = 209.5 (C_5), 142.2 (C_{12}), 138.6 (C_{10}), 134.9 (C_{13}), 129.2 (C_{14}), 128.4 (C_{15}), 127.3 (C_7), 126.7 (C_9), 126.5 (C_6), 126.2 (C_8), 125.8 (C_{11}), 62.9 (C_3), 61.7 (C_3), 57.6 (C_1), 39.7 (C_{18}), 37.7 (C_4), 35.9 (C_{17}), 30.1 (C_{20}), 27.8 (C_{16}); **IR** (neat) cm^{-1}: 1715, 1493, 1453, 1365, 1162, 1097, 1075, 1029, 761, 700; **HRMS** (ESI^+) m/z calc. for $C_{21}H_{26}NO$ $[M+H]^+$ 308.2009; found at 308.2000 Δ -2.92 ppm. Spectroscopic data were consistent with the literature data for this compound.[23]

(*RS*)-4-(1-Benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-3-yl)butan-2-one (222):



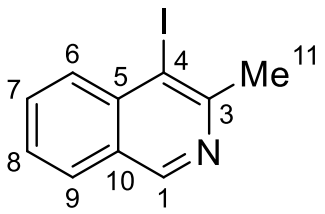
The title compound was prepared according to **General Procedure C** on 0.25 mmol scale, using 3-Me quinolinium iodide (90 mg, 0.25 mmol, 1.0 equiv.) as the substrate and MVK

(100 μL, 1.3 mmol, 5.0 equiv.) as the electrophile. Purification with flash column chromatography (5% EtOAc in pentane) afforded **222** as a pale-orange oil (60 mg, 78%).

^{1}H NMR (700 MHz, $CDCl_3$): δ_H = 7.31 (2H, dd, *J* = 8.2, 6.8 Hz, H_{14}), 7.28 – 7.22 (3H, m, H_{13}. H_{15}), 7.01 – 6.98 (1H, m, H_8), 6.98 – 6.95 (1H, m, H_6), 6.60 (1H, tt, *J* = 7.3, 1.0 Hz, H_7), 6.55 (1H, d, *J* = 8.2 Hz, H_9), 4.52 – 4.43 (2H, m, H_{11}), 3.02 (2H, q, *J* = 11.4 Hz, H_2), 2.59 (2H, s, H_4), 2.48 – 2.34 (2H, m, H_{18}), 2.11 (3H, s, H_{20}), 1.62 (2H, dddd, *J* = 41.3, 14.0, 11.2, 5.2 Hz, H_{17}), 0.97 (3H, s, H_{16}); **^{13}C NMR** (176 MHz, $CDCl_3$): δ_C = 209.1 (C_{19}), 144.6 (C_{10}), 139.1 (C_{12}), 129.8 (C_6), 128.6 (C_{14}), 127.2 (C_8), 126.9 (C_{15}), 126.7 (C_{13}), 120.4 (C_5), 116.3 (C_7), 110.8 (C_9), 59.7 (C_2), 55.4 (C_{11}), 40.5 (C_4), 38.3 (C_{17}), 32.3 (C_{18}), 30.7 (C_{20}), 30.0 (C_3), 23.3 (C_{16}); **IR** (neat) cm^{-1}: 1716, 1603, 1505, 1452, 1355, 1284, 1249, 1167, 745, 698, 651; **HRMS** (ESI^+) m/z calc. for $C_{21}H_{26}NO$ $[M+H]^+$ 308.2009; found at 308.2004 Δ -1.62 ppm. Spectroscopic data were consistent with the literature data for this compound.[23]

8.5 Experimental data for Chapter 4

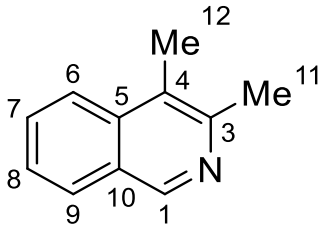
4-Iodo-3-methylisoquinoline (360):



3-Methyl isoquinoline (1.43 g, 10.0 mmol, 1.00 equiv.) was dissolved in glacial acetic acid (50.0 mL) with NIS (2.48 g, 11.0 mmol, 1.10 equiv.) and heated to 80 °C with stirring for 16 h. Upon cooling the mixture was quenched with solid Na_2CO_3 at 0 °C, then extracted three times with CH_2Cl_2. The combined organic extracts were washed once each with sat. aq. $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Flash column chromatography (15-25% EtOAc in pentane) afforded **360** as a pale-yellow solid (1.43 g, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.02 (1H, s, H_1), 8.06 (1H, dq, *J* = 8.5, 0.8 Hz, H_6), 7.86 (1H, dt, *J* = 8.1, 1.0 Hz, H_9), 7.73 (1H, ddd, *J* = 8.4, 6.9, 1.3 Hz, H_7), 7.57 (1H, ddd, *J* = 8.1, 6.9, 1.1 Hz, H_8), 2.98 (3H, s, H_{11}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 154.8 (C_3), 151.7 (C_1), 138.4 (C_5), 132.1 (C_8), 131.1 (C_6), 128.0 (C_9), 127.6 (C_{10}), 127.3 (C_7), 99.4 (C_4), 30.3 (C_{11}); **IR** (neat) cm^{-1}: 1620, 1572, 1553, 1480, 1438, 1413, 1370, 1330, 1307, 1257, 1238, 1200, 1139, 1031, 1014, 952, 921, 890, 855, 822, 770, 748, 731, 651, 640; **HRMS** (ESI^+) m/z calc. for $C_{10}H_9IN$ $[M+H]^+$ 269.9774; found at 269.9766 Δ -2.98 ppm; **m.p.** = 60-62 °C. Spectroscopic data were consistent with the literature data for this compound.[174]

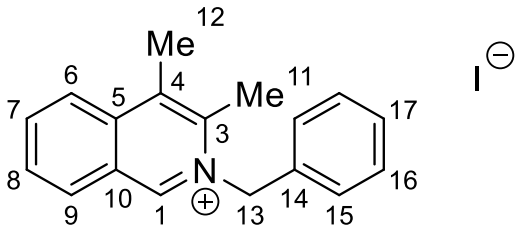
3,4-Dimethylisoquinoline (361):



4-Iodo-3-methylisoquinoline **360** (2.17 g, 8.10 mmol, 1.00 equiv.) was dissolved in a 2:1 v/v mixture of 1,4-dioxane and H_2O (80 mL) with $MeB(OH)_2$ (0.97 g, 16.2 mmol, 2.00 equiv.), K_3PO_4 (6.90 g, 32.4 mmol, 4.0 equiv.), and SPhos (33 mg, 81 μmol, 1.0 mol%). The solution was sparged with argon for 30 min, then $Pd_2(dba)_3$ (37.0 mg, 40.5 μmol, 0.50 mol%) was added and the resultant suspension stirred at 110 °C overnight. The mixture was then cooled, diluted with H_2O and extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Flash column chromatography (10-40% EtOAc in pentane) afforded **361** as a pale-orange oil (1.05 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 9.04 (1H, s, H_1), 7.95 (1H, dq, J = 8.6, 1.0 Hz, H_6), 7.90 (1H, dt, J = 8.1, 1.1 Hz, H_9), 7.68 (1H, ddd, J = 8.4, 6.8, 1.2 Hz, H_7), 7.51 (1H, ddd, J = 8.1, 6.9, 1.0 Hz, H_8), 2.71 (3H, s, H_{11}), 2.57 (3H, s, H_{12}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 149.6 (C_1), 149.2 (C_3), 135.9 (C_5), 130.2 (C_7), 128.2 (C_9), 127.1 (C_{10}), 125.8 (C_8), 124.1 (C_4), 122.8 (C_6), 22.8 (C_{11}), 14.0 (C_{12}); **IR** (neat) cm^{-1}: 1624, 1580, 1501, 1448, 1385, 1246, 977, 917, 880, 779, 750. Spectroscopic data were consistent with the literature data for this compound.[175]

2-Benzyl-3,4-dimethylisoquinolin-2-ium iodide (245):

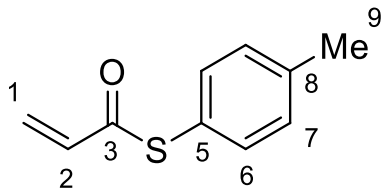


The title compound was synthesised according to **General Procedure E** with 3,4-dimethylisoquinoline **361** (1.1 g, 6.7 mmol, 1.0 equiv.) to afford **245** as a pale-yellow powder (2.2 g, 86%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 10.96 (1H, s, H_1), 8.71 (1H, d, J = 8.2 Hz, H_9), 8.17 (1H, d, J = 8.6 Hz, H_6), 8.11 (1H, ddd, J = 8.5, 6.8, 1.3 Hz, H_7), 7.87 (1H, dd, J = 8.3, 6.8 Hz, H_8),

7.35 – 7.28 (3H, m, H_{16}, H_{17}), 7.27 – 7.22 (2H, m, H_{15}), 6.36 (2H, s, H_{13}), 2.82 (3H, s, H_{11}), 2.74 (3H, s, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 150.0 (C_1), 141.9 (C_3), 138.1 (C_5), 137.2 (C_7), 133.4 (C_4), 132.7 (C_{14}), 131.9 (C_9), 130.3 (C_8), 129.6 (C_{16}), 129.3 (C_{17}) 127.7 (C_{15}), 126.2 (C_{10}), 123.7 (C_6), 62.8 (C_{13}), 17.5 (C_{11}), 15.6 (C_{12}); **IR** (neat) cm^{-1}: 1633, 1604, 1497, 1382, 1184, 917, 776, 761, 745, 711, 696; **HRMS** (ESI^+) m/z calc. for $C_{18}H_{18}N$ $[M]^+$ 248.1434; found at 248.1441 Δ 2.82 ppm; **m.p.** = 225-226 °C.

***S*-(*p*-Tolyl) prop-2-enethioate (244):**

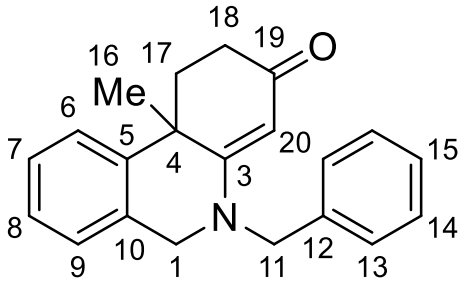


NaOH (4.1 g, 100 mmol, 1.7 equiv.) was dissolved in H_2O (25 mL) then thiocresol (7.4 g, 60 mmol, 1.0 equiv.) and $NaBH_4$ (68 mg, 1.8 mmol, 3.0 mol%) were added and the mixture stirred for 3 h. BHT (200 mg, 0.90 mmol, 1.5 mol%) and acryloyl chloride (7.3 mL, 90 mmol, 1.5 equiv.) dissolved in cyclohexane (30 mL) was added dropwise, then the mixture stirred for 2 h at 55 °C. The reaction was then cooled, diluted with Et_2O and the layers partitioned. The aqueous layer was extracted twice more with Et_2O then the combined organic layers were washed with sat. aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by column chromatography afforded **244** as a pale-yellow oil (3.3 g, 31%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.36 – 7.31 (2H, m, H_6), 7.27 – 7.22 (2H, m, H_7), 6.46 (1H, dd, *J* = 17.2, 9.6 Hz, H_2), 6.38 (1H, dd, *J* = 17.2, 1.6 Hz, H_1), 5.76 (1H, dd, *J* = 9.6, 1.6 Hz, H_1'), 2.39 (3H, s, H_9); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 189.1 (C_3), 139.9 (C_5), 134.7 (C_6), 134.5 (C_2), 130.2 (C_7), 127.3 (C_1), 123.8 (C_8), 21.5 (C_9); **IR** (neat) cm^{-1}: 1684, 1613, 1494, 1395, 1162, 1116, 989, 941, 808, 723; **HRMS** (ESI^+) m/z calc. for $C_{10}H_{11}OS$ $[M+H]^+$

179.0525; found at 179.0525 Δ 0.00 ppm. Spectroscopic data were consistent with the literature data for this compound.[176]

(*RS*)-5-Benzyl-10b-methyl-1,5,6,10b-tetrahydrophenanthridin-3(2H)-one (247):

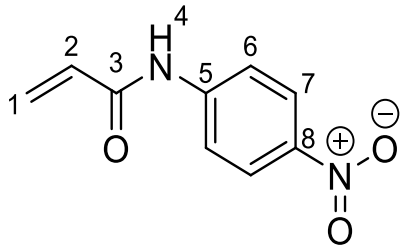


2-Benzyl-3,4-dimethylisoquinolin-2-ium iodide **245** (94 mg, 0.25 mmol, 1.0 equiv.) was dissolved in MeCN (3.6 mL) with 1-(4-chloro-1H-pyrazol-1-yl)prop-2-en-1-one **244** (78 mg, 0.5 mmol, 2.0 equiv.), 5:2 HCO_2H:NEt_3 (0.17 mL, 2.0 mmol, 8.0 equiv.) and an aliquot of a premade solution of $(RhCp^*Cl)_2$ in MeCN (0.40 mL, 0.020 mol%, 3.9 mg in 50 mL) was added. The mixture was stirred at 80 °C for 8 h, then cooled, diluted with EtOAc, washed with sat. aq. Na_2CO_3 and the layers partitioned. The aqueous layer was washed twice more with EtOAc, the organic layers combined, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (3-8% EtOH in EtOAc) afforded **247** as a colourless solid (65 mg, 86%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.45 (1H, dd, *J* = 7.9, 1.2 Hz, H_6), 7.41 – 7.34 (1H, m, H_7), 7.33 – 7.19 (4H, m, H_8, H_{14}, H_{15}), 7.14 – 7.07 (3H, m, H_9, H_{13}), 5.30 (1H, s, H_{20}), 4.74 (1H, d, *J* = 16.2 Hz, H_1), 4.70 – 4.57 (2H, m, H_{11}), 4.34 (1H, d, *J* = 16.2 Hz, H_1'), 2.67 (1H, ddd, *J* = 17.1, 14.2, 5.1 Hz, H_{18}), 2.63 – 2.56 (1H, m, H_{17}), 2.50 (1H, ddd, *J* = 17.1, 4.9, 2.0 Hz, H_{18}), 2.36 (1H, td, *J* = 13.5, 4.9 Hz, H_{17}), 1.46 (3H, s, H_{16}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 195.6 (C_{19}), 167.5 (C_3), 140.9 (C_5), 135.2 (C_{12}), 131.5 (C_{10}), 129.1 (C_{14}), 128.6 (C_7), 127.7 (C_{15}), 126.8 (C_8), 126.5 (C_{13}), 125.6 (C_9), 123.5 (C_6), 97.7 (C_{20}), 55.8 (C_{11}), 52.1 (C_1), 38.7 (C_4), 33.1 (C_{17}), 32.3 (C_{18}), 24.9 (C_{16}); **IR** (neat) cm^{-1}: 1710, 1588, 1552, 1496, 1454, 1361,

1331, 1297, 1270, 1232, 1212, 814, 765, 735, 707; **HRMS** (ESI^+) m/z calc. for $C_{21}H_{22}NO$ $[M+H]^+$ 304.1696; found at 304.1705 Δ 2.93 ppm; **m.p.** = 142-143 °C.

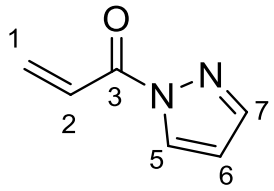
***N*-(4-Nitrophenyl)acrylamide (249):**



K_2CO_3 (2.8 g, 20 mmol, 1.0 equiv.) was dissolved in acetone (20 mL) and H_2O (5.0 mL), the flask purged with Ar and cooled to 0 °C. Acryloyl chloride (1.6 mL, 20 mmol, 2.0 equiv) was added dropwise, the 4-nitroaniline (1.4 g, 10 mmol, 1.0 equiv) was added in a single portion. The reaction was stirred for 1 h, then filtered *in vacuo*. The precipitate was washed with ice cold Et_2O then dried under vacuum for 1 h to give **249** as a beige solid (1.2 g, 63%).

^{1}H NMR (400 MHz, DMSO): δ_H = 8.28 – 8.18 (2H, m, H_7), 7.96 – 7.88 (2H, m, H_6), 6.49 (1H, ddd, *J* = 17.0, 10.1, 2.4 Hz, H_2), 6.34 (1H, dd, *J* = 17.0, 2.0 Hz, H_1), 5.85 (1H, dt, *J* = 9.9, 2.2 Hz, H_1'); **^{13}C NMR** (101 MHz, DMSO): δ_C = 163.9 (C_3), 145.3 (C_8), 142.4 (C_5), 131.3 (C_2), 128.6 (C_1), 125.0 (C_7), 119.1 (C_6); **IR** (neat) cm^{-1}: 1672, 1614, 1566, 1502, 1413, 1344, 1257, 1199, 1180, 1117, 1071, 852, 833, 811, 794, 752, 723, 704; **HRMS** (ESI^+) m/z calc. for $C_9H_9N_2O_3$ $[M+H]^+$ 193.0608; found at 193.0613 Δ 2.75 ppm; **m.p.** = 180-182 °C. Spectroscopic data were consistent with the literature data for this compound.[177]

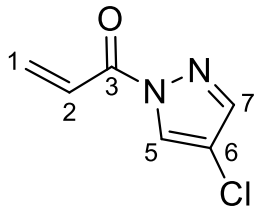
1-(1H-Pyrazol-1-yl)prop-2-en-1-one (251):



The title compound was prepared according to a literature procedure published by Lattanzi and co-workers:[178] Pyrazole (680 mg, 10 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (50 mL) with acrylic acid (0.82 mL, 12 mmol, 1.2 equiv.), DMAP (61 mg, 0.5 mmol, 5.0 mol%) and EDC HCl (2.3 g, 12 mmol, 1.2 equiv.). The solution was stirred for 1h, then concentrated *in vacuo*. The crude oil was purified by column chromatography (5-25% EtOAc in pentane) to afford **251** as a colourless oil (330 mg, 27%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.34 (1H, ddd, *J* = 2.9, 1.5, 0.7 Hz, H_5), 7.75 (1H, d, *J* = 1.7 Hz, H_7), 7.56 (1H, ddd, *J* = 17.3, 10.5, 1.3 Hz, H_2), 6.75 (1H, dt, *J* = 17.3, 1.6 Hz, H_1), 6.48 (1H, dt, *J* = 3.0, 1.5 Hz, H_6), 6.09 (1H, dt, *J* = 10.5, 1.6 Hz, H_1'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 163.2 (C_3), 144.3 (C_7), 133.7 (C_1), 128.9 (C_5), 126.5 (C_2), 110.2 (C_6); **IR** (neat) cm^{-1}: 1718, 1623, 1422, 1401, 1384, 1342, 1246, 1203, 1162, 1094, 1035, 987, 919, 769; **HRMS** (ESI^+) m/z calc. for $C_6H_7N_2O$ $[M+H]^+$ 123.0553; Molecule could not be observed by ESI MS. Spectroscopic data were consistent with the literature data for this compound.[179]

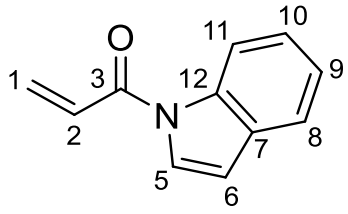
1-(4-Chloro-1H-pyrazol-1-yl)prop-2-en-1-one (252):



β-Bromo propionyl chloride (0.50 mL, 5.0 mmol, 1.0 equiv.) was added dropwise to a mixture of 4-chloro pyrazole (520 mg, 5.0 mmol, 1.0 equiv.) and K_2CO_3 (1.4 g, 10 mmol, 2.0 equiv.) in THF (20 mL) at 0 °C, then stirred at r.t. for 2 h. NEt_3 (2.8 mL, 20 mmol, 4.0 equiv.) was added dropwise at 0 °C, then the mixture stirred at r.t. for 30 min. Solvent was removed *in vacuo*, then purification by flash column chromatography (2-8% EtOAc in pentane) afforded **252** as a colourless fluffy solid (650 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.29 (1H, d, *J* = 0.8 Hz, H_7), 7.70 – 7.64 (1H, m, H_5), 7.50 (1H, dd, *J* = 17.3, 10.5 Hz, H_2), 6.76 (1H, dd, *J* = 17.3, 1.5 Hz, H_1), 6.12 (1H, dd, *J* = 10.5, 1.5 Hz, H_1'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 162.4 (C_3), 142.9 (C_5), 134.5 (C_1), 126.4 (C_7), 125.4 (C_2), 116.1 (C_6); **IR** (neat) cm^{-1}: 3129, 1718, 1619, 1557, 1418, 1393, 1343, 1300, 1246, 1192, 1173, 986, 977, 963, 926, 879, 826, 790, 735, 649; **HRMS** (ESI^+) m/z calc. for $C_6H_6ClN_2O$ $[M+H]^+$ 157.0163; Molecule could not be observed by ESI MS; **m.p.** = 61-62 °C.

1-(1H-Indol-1-yl)prop-2-en-1-one (254):

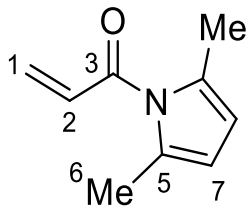


The title compound was prepared according to a literature procedure published by Kerr and co-workers:[180] Indoline (1.2 g, 10 mmol, 1.0 equiv.) was dissolved in THF (25 mL) with K_2CO_3 (2.8 g, 20 mmol, 2.0 equiv.) and cooled to 0 °C. Acryloyl chloride (0.89 mL, 11 mmol, 1.1 equiv.) was added dropwise, and the reaction stirred at 0 °C for 20 min. The mixture was then poured onto ice water and stirred for 1 h. The suspension was diluted with EtOAc, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc, the combined organic layers dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. The residue was dissolved in dry PhMe (50 mL), DDQ (3.0 g, 13 mmol, 1.3 equiv.) was added and the mixture heated to reflux under an Ar atmosphere for 6 h. The mixture was then cooled, diluted with EtOAc and washed twice with H_2O and once with brine. The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (5% EtOAc in pentane) afforded **254** as a red solid (1.2 g, 72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.52 (1H, dd, *J* = 8.2, 1.0 Hz, H_{11}), 7.59 (1H, dt, *J* = 7.5, 1.1 Hz, H_8), 7.52 (1H, d, *J* = 3.8 Hz, H_5), 7.38 (1H, ddd, *J* = 8.4, 7.2, 1.4 Hz, H_{10}), 7.31 (1H,

td, J = 7.5, 1.1 Hz, H_9), 6.97 (1H, dd, J = 16.8, 10.4 Hz, H_2), 6.74 – 6.64 (2H, m, H_1, H_6), 6.05 (1H, dd, J = 10.4, 1.5 Hz, H_1'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 164.0 (C_3), 135.9 (C_{12}), 132.2 (C_1), 130.7 (C_7), 128.0 (C_2), 125.3 (C_{10}), 124.7 (C_5), 124.1 (C_9), 121.0 (C_8), 117.0 (C_{11}), 109.5 (C_6); **IR** (neat) cm^{-1}: 1694, 1619, 1539, 1473, 1454, 1411, 1339, 1291, 1227, 1207, 1158, 1143, 1110, 1090, 1057, 1017, 976, 931, 791, 768, 752, 729; **m.p.** = 43-44 °C. Spectroscopic data were consistent with the literature data for this compound.[181]

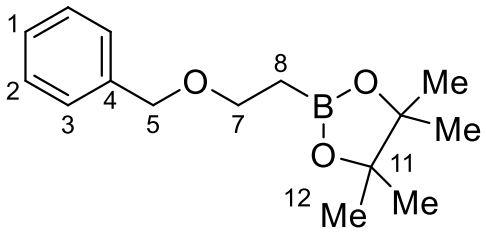
1-(2,5-Dimethyl-1H-pyrrol-1-yl)prop-2-en-1-one (253):



The title compound was prepared according to a literature procedure published by McErlean and Law:[182] Acrylamide (2.1 g, 30 mmol, 3.0 equiv.) was dissolved in PhMe (150 mL) with 2,5-hexanedione (1.2 mL, 10 mmol, 1.0 equiv.) and *p*-TSA (170 mg, 1.0 mmol, 0.1 equiv.) then the mixture heated to reflux for 24 h. The mixture was cooled, diluted with EtOAc, washed three times with H_2O, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (4-6% EtOAc in pentane) afforded **253** as a bright yellow oil (160 mg, 11%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 6.69 (1H, dd, J = 17.0, 10.3 Hz, H_2), 6.47 (1H, dd, J = 17.0, 1.4 Hz, H_1), 5.95 (1H, dd, J = 10.3, 1.4 Hz, H_1'), 5.85 (2H, s, H_7), 2.35 (6H, s, H_6); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 167.2 (C_3), 132.2 (C_2), 131.5 (C_1), 130.2 (C_5), 111.2 (C_7), 15.8 (C_6); **IR** (neat) cm^{-1}: 1699, 1620, 1540, 1406, 1390, 1367, 1325, 1302, 1264, 1074, 1045, 997, 978, 799, 777; **HRMS** (ESI^+) m/z calc. for $C_9H_{12}NO$ $[M+H]^+$ 150.0913; found at 150.0910 Δ -2.45 ppm. Spectroscopic data were consistent with the literature data for this compound.[183]

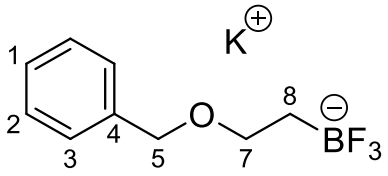
2-(2-(Benzyloxy)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (362):



The title compound was prepared according to a literature procedure published by Molander and co-workers:[184] B_2Pin_2 (3.8 g, 15 mmol, 1.5 equiv.), LiOMe (760 mg, 20 mmol, 2.0 equiv.), CuI (190 mg, 1.0 mmol, 10 mol%) and polymer mounted PPh_3 (340 mg, 1.3 mmol, 13 mol%) was added to a flask which was subsequently evacuated and backfilled with N_2 three times. DMF (50 mL) and ((2-bromoethoxy)methyl)benzene (2.2 g, 10 mmol, 1.0 equiv.) were added, then the mixture was stirred vigorously at r.t. for 20 h, diluted with CH_2Cl_2 and filtered through a celite pad. The filtrate was concentrated, diluted with sat. aq. NH_4Cl, shaken and the layers partitioned. The aqueous phase was extracted twice more with EtOAc, then the combined organic layers were washed once each with H_2O, brine, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo* to afford **362** as a pale-orange oil (2.4 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.38 – 7.24 (5H, m, H_1, H_2, H_3), 4.51 (2H, s, H_5), 3.63 (2H, t, *J* = 7.9 Hz, H_7), 1.30 – 1.19 (14H, m, H_8, H_{12}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 139.0 (C_4), 128.4 (C_2), 127.7 (C_3), 127.5 (C_1), 83.3 (C_{11}), 72.7 (C_5), 67.2 (C_7), 25.0 (C_{12}); **IR** (neat) cm^{-1}: 2978, 1372, 1323, 1259, 1215, 1168, 1147, 1114, 1097, 968; **HRMS** (ESI^+) m/z calc. for $C_{15}H_{24}BO_3$ $[M+H]^+$ 263.1813; found at 263.1822 Δ 3.40 ppm; Spectroscopic data were consistent with the literature data for this compound.[184]

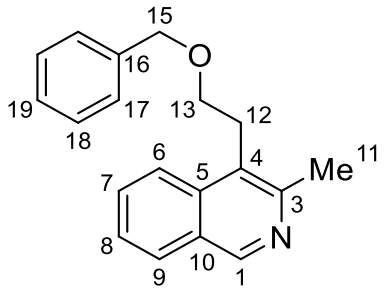
Potassium (2-(benzyloxy)ethyl)trifluoroborate (363):



The title compound was prepared according to a literature procedure published by Molander and co-workers:[184] 2-(2-(Benzyloxy)ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **362** (2.4 g, 9.3 mmol, 1.0 equiv.) was dissolved in THF (40 mL) and H_2O (5.0 mL) with KHF_2 (3.1 g, 40 mmol, 4.3 equiv.). The mixture was stirred at r.t. for 2 h, then concentrated to dryness. The residue was washed with boiling acetone three times, then the washings collected and concentrated to afford **363** as an off-white solid (2.3 g, Quant).

^{1}H NMR (400 MHz, DMSO): δ_H = 7.36 – 7.20 (5H, m, H_1, H_2, H_3), 4.35 (2H, s, H_5), 3.44 – 3.32 (2H, m, H_7), 0.49 – 0.35 (2H, m, H_8); **^{13}C NMR** (101 MHz, DMSO): δ_C = 139.8 (C_4), 128.1 (C_3), 127.4 (C_2), 127.0 (C_1), 71.1 (C_5), 70.8 (C_7), 25.0 (C_8); **^{19}F NMR** (377 MHz, DMSO): δ_F = -136.04; **IR** (neat) cm^{-1}: 2981, 1609, 1526, 1516, 1399, 1345, 1257, 1187, 1115, 1094, 1075, 1055, 1032, 1004, 976, 922, 880, 855, 834, 811, 757, 739, 723, 701; **HRMS** (ESI$^+$) m/z calc. for $C_9H_{11}BF_3O$ [M]$^-$ 203.0860; found at 203.0861 Δ 0.49 ppm; **m.p.** = 98-102 °C. Spectroscopic data were consistent with the literature data for this compound.[184]

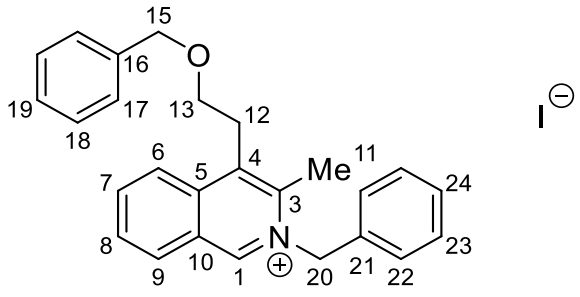
4-(2-(Benzyloxy)ethyl)-3-methylisoquinoline (S242):



The title compound was prepared according to a literature procedure published by Molander and co-workers:[184] 4-Iodo-3-methylisoquinoline **360** (1.4 g, 5.3 mmol, 1.0 equiv.) was placed in a round bottomed flask with potassium (2-(benzyloxy)ethyl)trifluoroborate **363** (1.4 g, 5.8 mmol, 1.1 equiv.), Cs_2CO_3 (5.1 g, 16 mmol, 3.0 equiv.) and $PdCl_2(Amphos)_2$ (190 mg, 0.26 mmol, 5.0 mol%) then the flask was evacuated and backfilled with an inert atmosphere three times. Degassed PhMe (20 mL) and deionised H_2O (5.0 mL) were added then the solution stirred at 100 °C for 24 h. After cooling, the solution was diluted with H_2O and extracted three times with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered under gravity, concentrated *in vacuo* then purified by flash column chromatography (10-40% EtOAc in pentane) to afford **S242** as a pale-orange oil (340 mg, 24%).

^{1}H NMR (700 MHz, $CDCl_3$): δ_H = 9.07 (1H, s, H_1), 7.99 (1H, d, *J* = 8.7 Hz, H_6), 7.93 (1H, d, *J* = 8.1 Hz, H_9), 7.69 (1H, ddd, *J* = 8.4, 6.7, 1.4 Hz, H_7), 7.53 (1H, ddd, *J* = 8.0, 6.8, 1.0 Hz, H_8), 7.37 – 7.25 (5H, m, H_{17}, H_{18}, H_{19}), 4.53 (2H, s, H_{15}), 3.73 (2H, t, *J* = 7.6 Hz, H_{13}), 3.41 (2H, t, *J* = 7.6 Hz, H_{12}), 2.75 (3H, s, H_{11}); **^{13}C NMR** (176 MHz, $CDCl_3$): δ_C = 150.3 (C_1), 149.9 (C_3), 138.3 (C_{16}), 135.8 (C_5), 130.7 (C_7), 128.5 (C_{18}), 128.4 (C_9), 127.8 (C_{19}), 127.7 (C_{17}), 127.3 (C_{10}), 126.1 (C_8), 125.0 (C_4), 122.8 (C_6), 73.3 (C_{15}), 69.4 (C_{13}), 28.9 (C_{12}), 22.3 (C_{11}); **IR** (neat) cm^{-1}: 2860, 1624, 1578, 1497, 1454, 1362, 1247, 1103, 1028, 788, 750, 735, 698; **HRMS** (ESI^+) m/z calc. for $C_{19}H_{20}NO$ $[M+H]^+$ 278.1539; found at 278.1537 Δ -0.88 ppm.

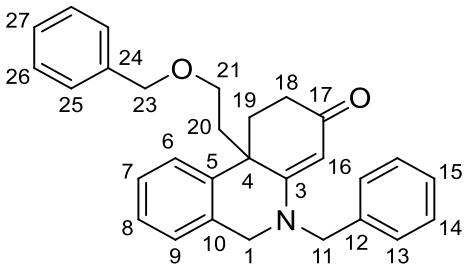
2-Benzyl-4-(2-(benzyloxy)ethyl)-3-methylisoquinolin-2-ium iodide (242):



The title compound was synthesised according to **General Procedure E** with 4-(2-(benzyloxy)ethyl)-3-methylisoquinoline **S242** (383 mg, 1.40 mmol, 1.00 equiv.) to afford **242** as a pale-yellow powder (453 mg, 65%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 11.02 (1H, s, H_1), 8.71 (1H, dd, *J* = 8.3, 1.3 Hz, H_9), 8.16 (1H, d, *J* = 8.7 Hz, H_6), 8.07 (1H, ddd, *J* = 8.5, 6.9, 1.3 Hz, H_7), 7.84 (1H, ddd, *J* = 8.0, 6.8, 0.9 Hz, H_8), 7.31 – 7.26 (3H, m, H_{19}, H_{23}), 7.25 – 7.17 (5H, m, H_{18}, H_{22}, H_{24}), 7.10 – 7.03 (2H, m, H_{17}), 6.33 (2H, s, H_{20}, H_{20}'), 4.38 (2H, s, H_{15}), 3.78 (2H, t, *J* = 6.4 Hz, H_{13}), 3.47 (2H, t, *J* = 6.4 Hz, H_{12}), 2.82 (3H, s, H_{11}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 150.4 (C_1), 143.0 (C_3), 138.0 (C_5), 137.5 (C_{16}), 137.2 (C_7), 134.7 (C_4), 132.6 (C_{21}), 131.9 (C_9), 130.2 (C_8), 129.5 (C_{23}), 129.2 (C_{19}), 128.5 (C_{18}), 127.9 (C_{24}), 127.5 ($C_{17/22}$), 127.5 ($C_{17/22}$), 126.4 (C_{10}), 123.8 (C_6), 73.4 (C_{15}), 68.7 (C_{13}), 62.5 (C_{20}), 29.7 (C_{12}), 17.4 (C_{11}); **IR** (neat) cm^{-1}: 3452 (br), 1633, 1496, 1455, 1362, 1101, 918, 783, 735, 708, 638; **HRMS** (ESI^+) m/z calc. for $C_{26}H_{26}NO$ $[M]^+$ 368.2009; found at 368.2020 Δ 3.00 ppm; **m.p.** = 178-180 °C.

(*RS*)-5-Benzyl-10b-(2-(benzyloxy)ethyl)-1,5,6,10b-tetrahydrophenanthridin-3(2H)-one (255):

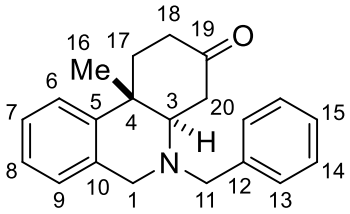


2-Benzyl-4-(2-(benzyloxy)ethyl)-3-methylisoquinolin-2-ium iodide **242** (124 mg, 0.25 mmol, 1.0 equiv.) was dissolved in MeCN (3.6 mL) with 1-(4-chloro-1H-pyrazol-1-yl)prop-2-en-1-one **252** (78 mg, 0.5 mmol, 2.0 equiv.), 5:2 HCO_2H:NEt_3 (0.17 mL, 2.0 mmol, 8.0 equiv.) and an aliquot of a premade solution of $(RhCp^*Cl)_2$ in MeCN (0.40 mL, 0.020 mol%, 3.9 mg in 50 mL) was added. The mixture was stirred at 80 °C for 8 h, then cooled, diluted with EtOAc,

washed with sat. aq. Na_2CO_3 and the layers partitioned. The aqueous layer was washed twice more with EtOAc, the organic layers combined, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (3-8% EtOH in EtOAc) afforded **255** as a brown oil (103 mg, 98%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.37 – 7.11 (11H, m, H_6, H_7, H_8, H_{14}, H_{15}, H_{25}, H_{26}, H_{27}), 7.09 – 6.99 (3H, m, H_9, H_{13}), 5.28 (1H, s, H_{16}), 4.66 – 4.58 (1H, m, H_1), 4.58 – 4.43 (2H, m, H_{11}, H_{11}'), 4.38 – 4.19 (3H, m, H_1', H_{23}, H_{23}'), 3.33 – 3.23 (1H, m, H_{21}), 3.22 – 3.14 (1H, m, H_{21}'), 2.86 – 2.78 (1H, m, H_{19}), 2.73 – 2.61 (1H, m, H_{18}), 2.46 – 2.37 (1H, m, H_{18}'), 2.30 – 2.21 (1H, m, H_{20}), 2.15 – 2.02 (1H, m, H_{19}'), 1.92 (1H, dt, *J* = 15.2, 5.8 Hz, H_{20}'); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 195.5 (C_{17}), 167.0 (C_3), 137.7 ($C_{Ar, Quat}$), 137.5 (C_5), 134.9 (C_{12}), 131.4 (C_{10}), 128.6 ($C_{Ar, 2CH}$), 128.1 ($C_{Ar, 2CH}$), 127.6 ($C_{Ar, CH}$), 127.3 ($C_{Ar, CH}$), 127.3 ($C_{Ar, CH}$), 127.3 ($C_{Ar, 2CH}$), 126.7 ($C_{Ar, CH}$), 126.2 (C_{13}), 125.4 (C_9), 125.0 (C_6), 97.7 (C_{16}), 72.7 (C_{23}), 66.2 (C_{21}), 55.3 (C_{11}), 51.8 (C_1), 41.1 (C_4), 33.4 (C_{20}), 32.1 (C_{18}), 29.5 (C_{19}); **IR** (neat) cm^{-1}: 1608, 1552, 1454, 1331, 1232, 1104, 909, 814, 729, 698, 645; **HRMS** (ESI$^+$) m/z calc. for $C_{29}H_{30}NO_2$ $[M+H]^+$ 424.2271; found at 424.2276 Δ 1.16 ppm.

(*RS*, *RS*)-5-Benzyl-10b-methyl-1,4,4a,5,6,10b-hexahydrophenanthridin-3(2H)-one (257):

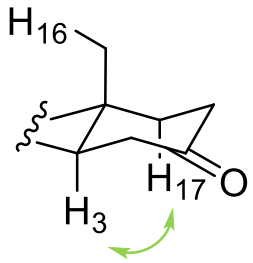


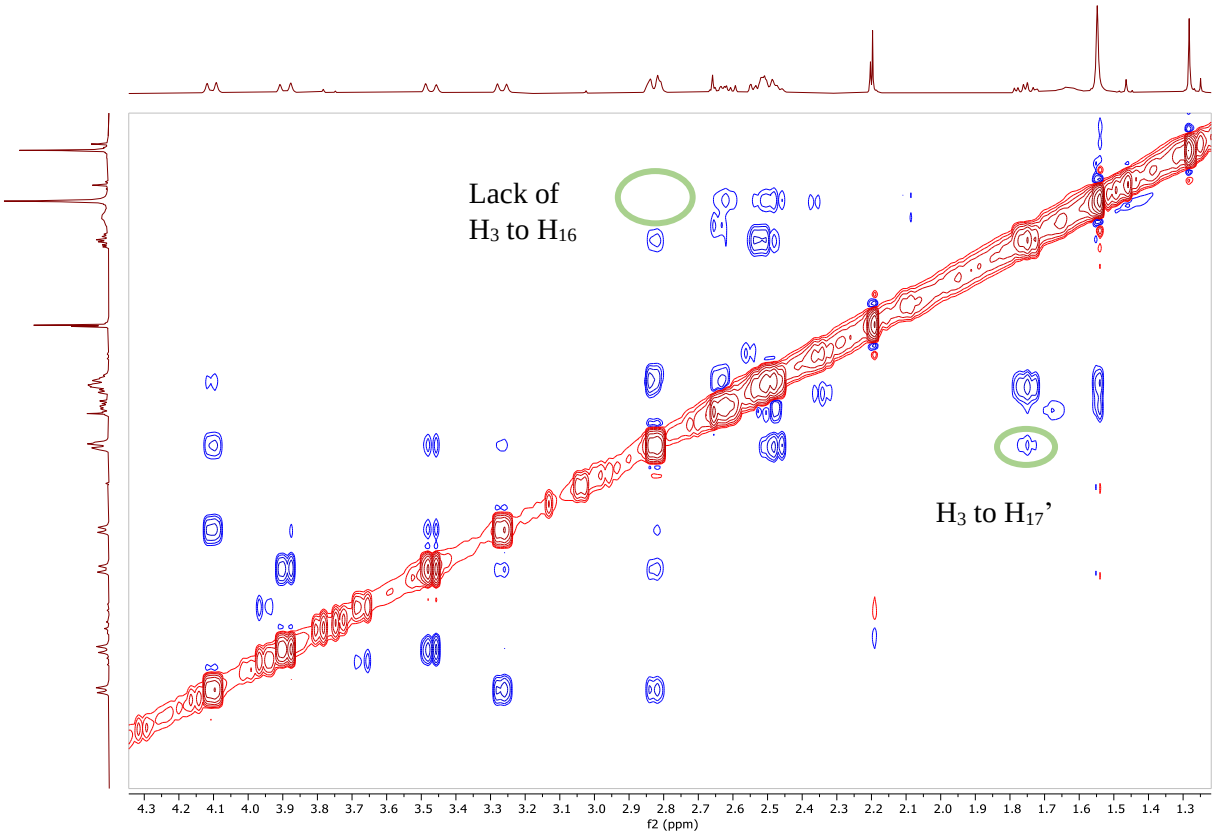
5-Benzyl-10b-methyl-1,5,6,10b-tetrahydrophenanthridin-3(2H)-one **247** (76 mg, 0.25 mmol, 1.0 equiv.) was dissolved in anhydrous THF (5 mL), $LiAlH_4$ (10 mg, 0.25 mmol, 1.0 equiv.) was added and the mixture stirred at r.t. for 15 min. The reaction was then quenched by addition of NH_4Cl, after which the mixture was filtered under gravity, dried with $MgSO_4$, filtered under gravity again then

concentrated *in vacuo*. Purification by flash column chromatography (2-10% EtOAc in pentane) afforded **257** as a pale-yellow oil (21 mg, 28%).

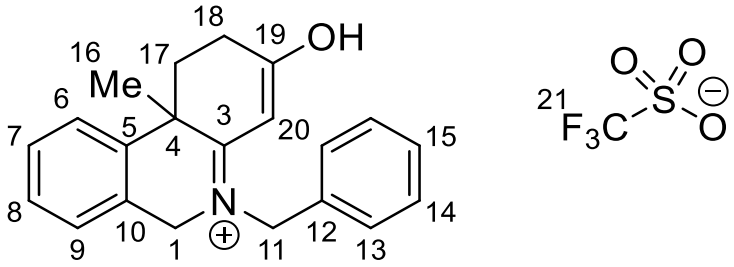
^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.39 (2H, d, *J* = 7.5 Hz, H_{13}), 7.35 – 7.28 (3H, m, H_6, H_{14}), 7.28 – 7.23 (1H, m, H_{15}), 7.18 (1H, t, *J* = 7.8 Hz, H_7), 7.13 – 7.08 (1H, m, H_8), 6.92 (1H, d, *J* = 7.6 Hz, H_9), 4.08 (1H, d, *J* = 13.2 Hz, H_{11}), 3.87 (1H, d, *J* = 15.5 Hz, H_1), 3.45 (1H, d, *J* = 15.4 Hz, H_1'), 3.24 (1H, d, *J* = 13.2 Hz, H_{11}'), 2.85 – 2.77 (3H, m, H_3, H_{20}), 2.65 – 2.56 (1H, m, H_{18}), 2.54 – 2.42 (3H, m, H_{17}, H_{18}', H_{20}'), 1.73 (1H, td, *J* = 13.8, 5.6 Hz, H_{17}'), 1.52 (3H, s, H_{16}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 209.9 (C_{19}), 143.9 (C_5), 139.9 (C_{12}), 133.7 (C_{10}), 128.5 (C_{13}), 128.5 (C_{14}), 127.1 (C_{15}), 126.6 (C_9), 126.6 (C_7), 126.2 (C_8), 125.1 (C_6), 65.3 (C_3), 57.4 (C_1), 57.1 (C_{11}), 42.6 (C_{20}), 38.6 (C_4), 37.6 (C_{18}), 33.5 (C_{17}), 21.8 (C_{16}); **IR** (neat) cm^{-1}: 2962, 1715, 1494, 1454, 1372, 1261, 1124, 1077, 911, 762, 732, 701, 644, 610; **HRMS** (ESI^+) m/z calc. for $C_{21}H_{24}NO$ $[M+H]^+$ 306.1852; found at 306.1855 Δ 0.83 ppm.

Stereochemistry was assigned based on NOESY peaks observed between H_3 and H_{17}' but a lack of any NOESY peaks between H_3 and H_{16}.





(*RS*)-5-Benzyl-3-((tert-butyldimethylsilyl)oxy)-10b-methyl-1,2,6,10b-tetrahydrophenanthridin-5-ium trifluoromethanesulfonate (258):

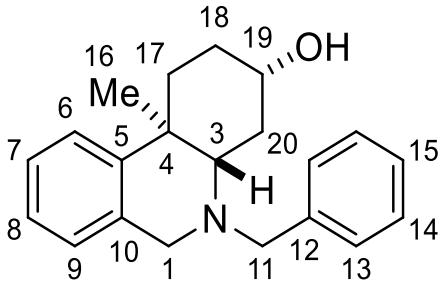


5-Benzyl-10b-methyl-1,5,6,10b-tetrahydrophenanthridin-3(2H)-one **247** (76 mg, 0.25 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (5.0 mL) and cooled to 0 °C. TBSOTf (0.15 mL, 0.50 mmol, 2.0 equiv.) was added dropwise, and the reaction stirred at 0 °C for 1 h then at r.t. for 1 h. The crude mixture was quenched by dropwise addition of H_2O, then diluted with CH_2Cl_2, the mixture shaken and the layers partitioned. The aqueous layer was extracted twice

more with CH_2Cl_2, then the organic layers were combined, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo* to afford a crude orange oil (49 mg, impure). Crystals of the monohydrate of **258** formed from the oil upon standing, which were characterised by single crystal X-Ray analysis.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.43 – 7.37 (2H, m, H_6, H_{15}), 7.30 – 7.26 (2H, m, H_8, H_{14}), 7.26 – 7.22 (1H, m, H_7), 7.19 (1H, d, *J* = 7.6 Hz, H_9), 7.17 – 7.13 (2H, m, H_{13}), 6.01 (1H, s, H_{20}), 5.00 – 4.90 (3H, m, H_1, H_{11}, H_{11}'), 4.67 (1H, d, *J* = 17.5 Hz, H_1'), 2.81 (1H, ddd, *J* = 18.8, 13.3, 5.3 Hz, H_{18}), 2.72 – 2.63 (2H, m, H_{17}, H_{18}'), 2.25 (1H, td, *J* = 13.3, 5.3 Hz, H_{17}'), 1.40 (3H, s, H_{16}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 189.8 (C_{19}), 175.8 (C_3), 138.0 (C_5), 133.1 (C_{12}), 129.4 (C_{10}), 129.3 (2C, C_{14}, C_{15}), 128.6 (C_7), 127.7 (C_8), 127.1 (C_{13}), 125.9 (C_9), 123.2 (C_6), 120.5 (q, *J* = 319.6 Hz, C_{21}), 95.6 (C_{20}), 57.2 (C_{11}), 53.5 (C_1), 39.5 (C_4), 31.7 (C_{17}), 27.6 (C_{18}), 23.7 (C_{16}); **IR** (neat) cm^{-1}: 2956, 1567, 1472, 1256, 1164, 1076, 1030, 910, 838, 782, 736, 638; **HRMS** (ESI^+) m/z calc. for $C_{21}H_{22}NO$ $[M]^+$ 304.1696; found at 304.1700 Δ 1.33 ppm.

(*RS*, *RS*, *RS*)-5-Benzyl-10b-methyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridin-3-ol (259):

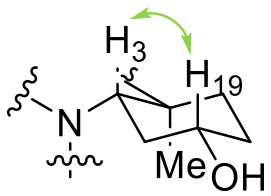


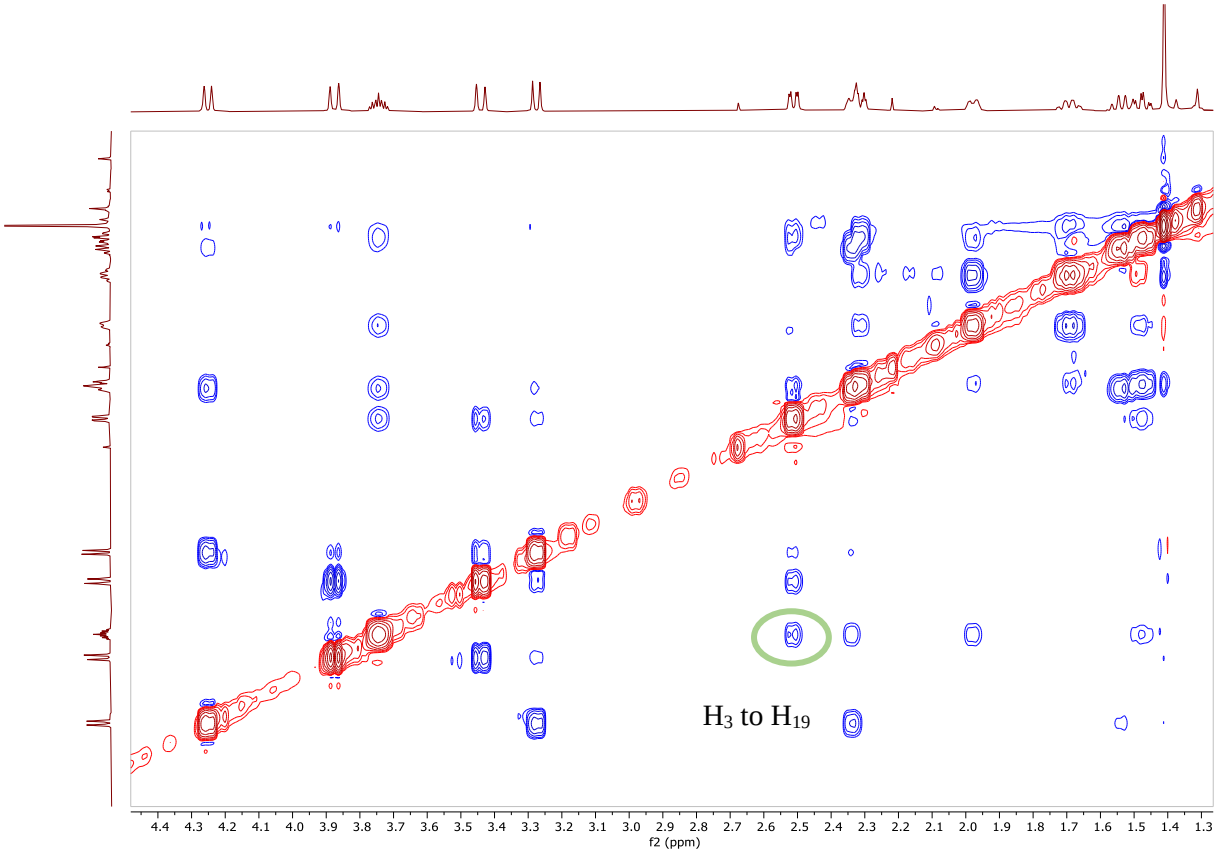
5-Benzyl-10b-methyl-1,5,6,10b-tetrahydrophenanthridin-3(2H)-one **247** (76 mg, 0.25 mmol, 1.0 equiv.) was dissolved in anhydrous THF (5.0 mL) and cooled to 0 °C. $LiAlH_4$ (11 mg, 0.28 mmol, 1.1 equiv.) was added and the mixture stirred for 30 min. MeOH (5.0 mL) was added dropwise, then $NaBH_4$ (19 mg, 0.5 mmol, 2.0 equiv.) was added in one portion and the mixture stirred for 20 min. 2.0 M aq. HCl was added dropwise, then the mixture was diluted

with EtOAc and H_2O, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc then the organic layers were combined, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (20-30% EtOAc in pentane) afforded **259** as a pale-brown oil (49 mg, 64%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.43 – 7.39 (2H, m, H_{13}), 7.35 – 7.30 (2H, m, H_{14}), 7.30 – 7.23 (2H, m, H_6, H_{15}), 7.17 (1H, td, *J* = 7.6, 1.4 Hz, H_7), 7.13 – 7.05 (1H, m, H_8), 6.90 (1H, dd, *J* = 7.7, 1.3 Hz, H_9), 4.22 (1H, d, *J* = 13.1 Hz, H_{11}), 3.85 (1H, d, *J* = 15.4 Hz, H_1), 3.72 (1H, tt, *J* = 11.2, 4.8 Hz, H_{19}), 3.41 (1H, d, *J* = 15.4 Hz, H_1'), 3.25 (1H, d, *J* = 13.1 Hz, H_{11}'), 2.48 (1H, dd, *J* = 12.7, 3.4 Hz, H_3), 2.35 – 2.22 (2H, m, H_{17}, H_{20}), 2.00 – 1.91 (1H, m, H_{18}), 1.66 (1H, dddt, *J* = 15.0, 12.9, 7.7, 3.9 Hz, H_{18}'), 1.57 – 1.40 (2H, m, H_{17}', H_{20}'), 1.38 (3H, s, H_{16}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 145.7 (C_5), 140.5 (C_{12}), 133.9 (C_{10}), 128.5 (C_{13}), 128.4 (C_{14}), 126.9 (C_{15}), 126.4 (C_9), 126.2 (C_7), 125.6 (C_8), 124.9 (C_6), 70.7 (C_{19}), 64.4 (C_3), 57.4 (C_1), 57.1 (C_{11}), 38.6 (C_4), 34.7 (C_{20}), 33.2 (C_{17}), 30.9 (C_{18}), 22.8 (C_{16}); **IR** (neat) cm^{-1}: 3393 (br), 2939, 1493, 1452, 1370, 1129, 1043, 910, 731, 700; **HRMS** (ESI$^+$) m/z calc. for $C_{21}H_{26}NO$ $[M+H]^+$ 308.2009; found at 308.2002 Δ -2.25 ppm.

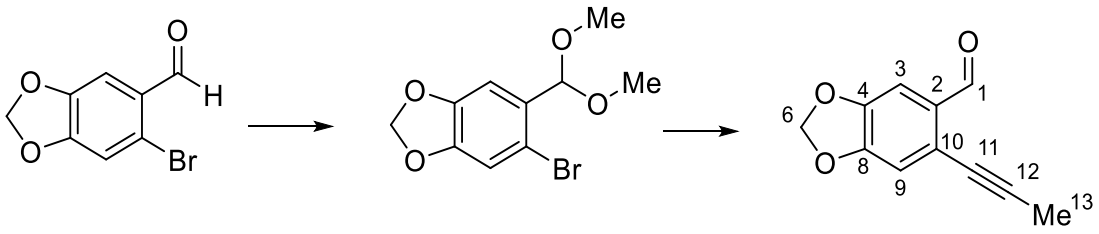
Stereochemistry assigned by NOESY peaks observed between H_{19} and H_3 with a lack of any NOESY peak between H_{16} and either H_3 or H_{19}.




H3 to H19
4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3
f2 (ppm)

8.6 Experimental data for Chapter 5

6-(Prop-1-yn-1-yl)benzo[d][1,3]dioxole-5-carbaldehyde (289):



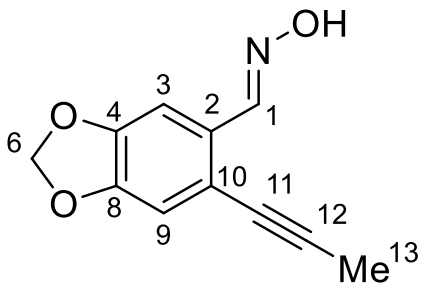
6-Bromo piperonal (2.29 g, 10.0 mmol, 1.00 equiv.) was dissolved in MeOH (20 mL) with trimethyl orthoformate (2.2 mL, 20 mmol, 2.0 equiv.) and TsOH (17 mg, 0.10 mmol, 1.0 mol%). The resultant solution was stirred at r.t. for 1 h, then quenched by addition of $NaHCO_3$ (aq). The solution was extracted three times with EtOAc, then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

The residue was then dissolved in DMSO (30 mL) with butynoic acid (1.05 g, 12.5 mmol, 1.25 equiv.), dppb (86 mg, 0.20 mmol, 2.0 mol%) and $Pd(PPh_3)_2Cl_2$ (70 mg, 0.10 mmol, 1.0 mol%). The flask containing the resultant suspension was evacuated and backfilled with Ar three times, after which DBU (4.5 mL, 30 mmol, 3.0 equiv.) was added. The suspension was stirred at 110 °C overnight, then cooled to r.t. and quenched by addition of excess 2M aq. HCl and diluted with EtOAc. The mixture was shaken, the layers partitioned and the aqueous layer extracted twice with EtOAc. The combined organic extracts were washed three times with 1 wt% aq. LiCl, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Recrystallisation from EtOH afforded **289** as a pale-brown solid (1.17 g, 62%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 10.34 (1H, s, H_1), 7.29 (1H, s, H_3), 6.88 (1H, s, H_9), 6.04 (2H, s, H_6), 2.10 (3H, s, H_{13}); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C = 190.7 (C_1), 152.5 (C_8), 148.2 (C_4), 132.3 (C_2), 124.8 (C_{10}), 112.3 (C_9), 106.0 (C_3), 102.4 (C_6), 92.3 (C_{12}), 75.4 (C_{11}), 4.6 (C_{13}); **IR** (neat) cm^{-1}: 1680, 1611, 1504, 1487, 1436, 1407, 1359, 1272, 1230, 1191, 1119,

1083, 1038, 928, 892, 854, 789, 737; **HRMS** (ESI^+) m/z calc. for $C_{11}H_9O_3$ $[M+H]^+$ 189.0546; found at 189.0543 Δ -1.72 ppm; **m.p.** = 108-109 °C.

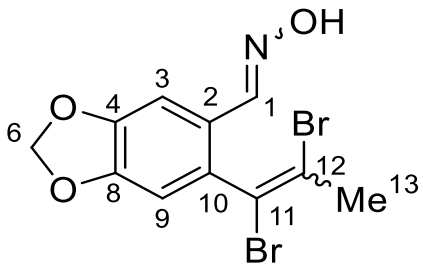
6-(Prop-1-yn-1-yl)benzo[d][1,3]dioxole-5-carbaldehyde oxime (286):



6-(Prop-1-yn-1-yl)benzo[d][1,3]dioxole-5-carbaldehyde **289** (1.24 g, 6.61 mmol, 1.00 equiv.) was dissolved in EtOH (20 mL) with NH_2OH HCl (920 mg, 13.2 mmol, 2.00 equiv.) and pyridine (1.10 mL, 13.7 mmol, 2.10 equiv.). The solution was heated to reflux for 1 h, then cooled to r.t. and concentrated to dryness. The residue was dissolved in EtOAc, quenched with H_2O and the layers partitioned. The aqueous layer was extracted twice with EtOAc, washed three times with 10 wt% aq. $CuSO_4$ then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo* to afford **286** as a pale-brown solid (1.05 g, 78%).

^{1}H NMR (600 MHz, Acetone): δ_H = 8.46 (1H, s, H_1), 7.22 (1H, s, H_3), 6.83 (1H, s, H_9), 6.05 (2H, s, H_6), 2.08 (3H, s, H_{13}); **^{13}C NMR** (151 MHz, Acetone): δ_C = 149.6 (C_8), 148.9 (C_4), 147.6 (C_1), 129.9 (C_2), 118.6 (C_{10}), 111.9 (C_9), 104.5 (C_3), 102.9 (C_6), 91.0 (C_{12}), 77.2 (C_{11}), 4.0 (C_{13}); **IR** (neat) cm^{-1}: 3313 (br), 1702, 1503, 1482, 1436, 1365, 1330, 1260, 1196, 1088, 1038, 968, 950, 936, 874; **HRMS** (ESI^+) m/z calc. for $C_{11}H_{10}NO_3$ $[M+H]^+$ 204.0655; found at 204.0660 Δ 2.33 ppm; **m.p.** = 138 °C.

6-(1,2-Dibromoprop-1-en-1-yl)benzo[d][1,3]dioxole-5-carbaldehyde oxime (294):

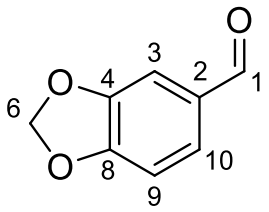


6-(Prop-1-yn-1-yl)benzo[d][1,3]dioxole-5-carbaldehyde oxime **286** (2.88 g, 14.2 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (100 mL) and Br_2 (1.50 mL, 28.4 mmol, 2.0 equiv.) added dropwise at 0 °C. After 15 min, the mixture was diluted with CH_2Cl_2 and quenched with sat. aq. $Na_2S_2O_3$. The mixture was shaken, the layers partitioned, then the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (5-20% EtOAc in pentane) afforded **294** as a pale orange solid as a single diastereomer (2.54 g, 49%).

The stereochemistry of the alkene was not determined and therefore undefined stereochemistry is depicted.

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.14 (1H, s, H_1), 7.30 (1H, s, H_3), 6.67 (1H, s, H_9), 6.03 – 5.98 (2H, m, H_6), 2.60 (3H, s, H_{13}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 149.3 (C_8), 148.6 (C_4), 147.5 (C_1), 135.4 (C_{10}), 123.9 (C_2), 121.2 (C_{12}), 113.6 (C_{11}), 108.9 (C_9), 105.1 (C_3), 102.0 (C_6), 28.8 (C_{13}); **IR** (neat) cm^{-1}: 3331 (br), 1706, 1503, 1482, 1427, 1363, 1256, 1074, 1039, 968, 936, 911, 874, 813, 735, 692; **HRMS** (ESI^+) m/z calc. for $C_{11}H_{10}{}^{79}Br_2NO_3$ $[M+H]^+$ 361.9022; found at 361.9009 Δ -3.58 ppm; **m.p.** = 116-118 °C.

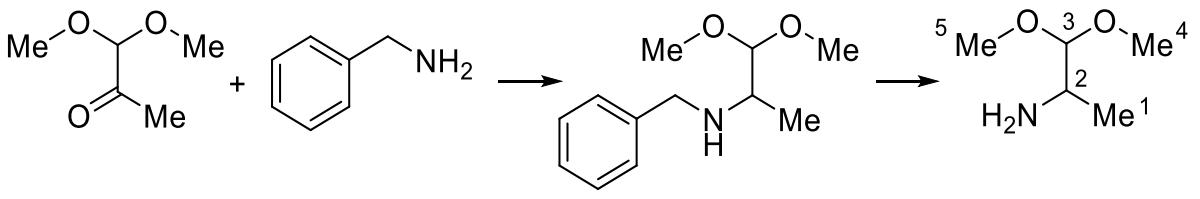
Piperonal (295):



3,4-Dihydroxybenzaldehyde (2.8 g, 20 mmol, 1.0 equiv.) was dissolved in DMF (150 mL) with CH_2Cl_2 (21 mL, 320 mmol, 16 equiv.) and K_2CO_3 (3.9 g, 28 mmol, 1.4 equiv.) then heated with stirring at 120 °C for 2 h. The reaction was cooled to r.t., diluted with H_2O and EtOAc, shaken and the layers partitioned. The aqueous layer was extracted twice with EtOAc, then the combined organic extracts dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (20-30% EtOAc in pentane) afforded **295** as a pale-yellow solid (2.4 g, 79%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 9.80 (1H, s, H_1), 7.40 (1H, dd, J = 7.9, 1.6 Hz, H_{10}), 7.32 (1H, d, J = 1.6 Hz, H_3), 6.92 (1H, d, J = 7.9 Hz, H_9), 6.06 (2H, s, H_6); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 190.4 (C_1), 153.2 (C_4), 148.8 (C_8), 132.0 (C_2), 128.8 (C_{10}), 108.5 (C_9), 107.0 (C_3), 102.2 (C_6); **IR** (neat) cm^{-1}: 1672, 1601, 1494, 1450, 1260, 1097, 1038, 929, 865, 815, 787; **HRMS** (ESI$^+$) m/z calc. for $C_8H_7O_3$ $[M+H]^+$ 151.0390; found at 151.0392 Δ 1.49 ppm; **m.p.** = 30-32 °C. Spectroscopic data were consistent with the literature data for this compound.[185]

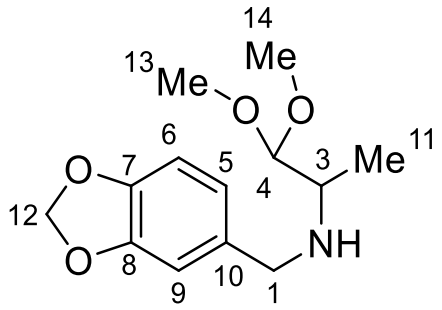
(*RS*)-1,1-Dimethoxypropan-2-amine (296):



Benzylamine (4.4 mL, 40 mmol, 1.0 equiv.) was dissolved in MeOH (20 mL) with dimethylpyruvate acetal (4.8 mL, 40 mmol, 1.0 equiv.) and stirred at r.t. overnight. The solution was then cooled to 0 °C and $NaBH_4$ (1.5 g, 40 mmol, 1.0 equiv.) was added portionwise. After stirring for 90 min at 0 °C, the reaction was quenched with H_2O, diluted with EtOAc, shaken and the layers partitioned. The aqueous layer was extracted twice with EtOAc, then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. The residue was dissolved in MeOH (20 mL) and 6 drops of aq. HCl (2M) were added. The solution was degassed using successive pump/fill cycles, backfilling with Ar. Palladium on carbon (10 wt%, 420 mg, 0.04 mmol, 1.00 mol%) was added, the reaction vessel partially evacuated and then backfilled with H_2. The reaction was stirred at 60 °C for 2 h, then cooled, filtered through celite and concentrated *in vacuo* to afford **296** as an orange oil (3.4 g, 71%).

^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 4.00 (1H, d, *J* = 5.9 Hz, H_3), 3.42 (3H, s, H_4), 3.39 (3H, s, H_5), 3.12 – 2.90 (1H, m, H_2), 1.09 (3H, d, *J* = 6.6 Hz, H_1); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 109.0 (C_3), 55.3 (C_5), 54.9 (C_4), 48.5 (C_2), 18.0 (C_1); **IR** (neat) cm^{-1}: 3413 (br), 2989, 1710, 1497, 1466, 1193, 1112, 1076, 978, 702, 647; **HRMS** (ESI^+) Molecule could not be observed by ESI MS. Spectroscopic data were consistent with the literature data for this compound.[186]

(*RS*)-*N*-(Benzo[d][1,3]dioxol-5-ylmethyl)-1,1-dimethoxypropan-2-amine (297):

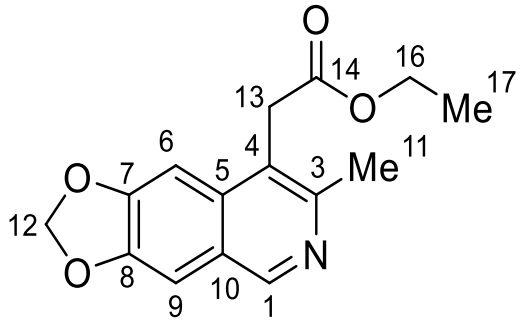


Piperonyl amine (5.0 mL, 40 mmol, 1.0 equiv.) was dissolved in EtOH (150 mL) with 1,1-dimethoxypropan-2-one (4.8 mL, 40 mmol, 1.0 equiv.) and stirred at r.t. overnight. The

reaction was cooled to 0 °C, then $NaBH_4$ (1.5 g, 40 mmol, 1.0 equiv.) was added portionwise, and the mixture stirred for 30 min. The reaction was quenched by slow addition of excess H_2O, then the mixture was diluted with EtOAc, shaken and layers partitioned. The aqueous layer was extracted twice with EtOAc, then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. The residue was passed through a short silica plug, eluting with EtOAc, then the filtrate was again concentrated *in vacuo* to afford **297** as an orange oil (8.1 g, 80%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 6.84 (1H, d, *J* = 1.5 Hz, H_9), 6.79 – 6.72 (2H, m, H_5, H_6), 5.93 (2H, s, H_{12}), 4.14 (1H, d, *J* = 6.3 Hz, H_4), 3.80 (1H, d, *J* = 13.0 Hz, H_1), 3.62 (1H, d, *J* = 13.0 Hz, H_1'), 3.39 (3H, s, H_{13}), 3.36 (3H, s, H_{14}), 2.82 (1H, p, *J* = 6.4 Hz, H_3), 1.09 (3H, d, *J* = 6.4 Hz, H_{11}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 147.8 (C_8), 146.7 (C_7), 134.3 (C_{10}), 121.4 (C_5), 108.9 (C_9), 108.3 (C_6), 108.0 (C_4), 101.0 (C_{12}), 54.9 (C_{13}), 54.8 (C_{14}), 53.6 (C_3), 51.0 (C_1), 15.0 (C_{11}); **IR** (neat) cm^{-1}: 2985, 2891, 2834, 1504, 1491, 1444, 1252, 1112, 1073, 1042, 937, 811; **HRMS** (ESI^+) m/z calc. for $C_{13}H_{20}NO_4$ $[M+H]^+$ 254.1387; found at 254.1388 Δ 0.44 ppm.

Ethyl 2-(7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate (280):



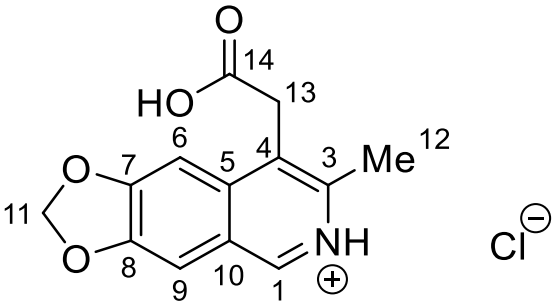
N-(Benzo[d][1,3]dioxol-5-ylmethyl)-1,1-dimethoxypropan-2-amine **297** (7.72 g, 30.5 mmol, 1.00 equiv.) was dissolved in EtOH (80 mL), then 12 M HCl (80 mL) was added and the solution was stirred at r.t. for 5 min. Ethyl glyoxylate (12.4 g, 61.0 mmol, 2.00 equiv., 50 wt%

solution in PhMe) was added and the solution stirred at 100 °C for 18 h. After cooling to 0 °C, the reaction was neutralised with solid K_2CO_3 and the mixture extracted three times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo* to afford **280** as a pale-yellow solid (3.92 g, 47%).

8-(Carboxymethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium chloride **304** (245 mg, 0.872 mmol, 1.00 equiv.) was suspended in EtOH (3 mL) and $SOCl_2$ (145 μL, 2.00 mmol, 2.29 equiv.) was added dropwise. The mixture was heated to reflux for 3 h, cooled to r.t. then diluted with EtOAc and sat. aq. Na_2CO_3. The mixture was shaken and the layers partitioned. The aqueous layer was extracted twice with EtOAc, then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo* to afford **280** as a colourless solid (188 mg, 79%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.85 (1H, s, H_1), 7.26 (1H, s, H_6), 7.17 (1H, s, H_9), 6.10 (2H, s, H_{12}), 4.15 (2H, q, *J* = 7.1 Hz, H_{16}), 3.95 (2H, s, H_{13}), 2.73 (3H, s, H_{11}), 1.23 (3H, t, *J* = 7.1 Hz, H_{17}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 170.7 (C_{14}), 152.2 (C_7), 149.3 (C_3), 148.3 (C_1), 147.9 (C_8), 134.8 (C_5), 124.7 (C_{10}), 121.6 (C_4), 103.8 (C_9), 101.9 (C_{12}), 99.6 (C_6), 61.4 (C_{16}), 34.9 (C_{13}), 22.3 (C_{11}), 14.3 (C_{17}); **IR** (neat) cm^{-1}: 1732, 1496, 1469, 1256, 1233, 1185, 1039, 944, 847, 737; **HRMS** (ESI$^+$) m/z calc. for $C_{15}H_{16}NO_4$ $[M+H]^+$ 274.1074; found at 274.1067 Δ -2.52 ppm; **m.p.** = 108-110 °C.

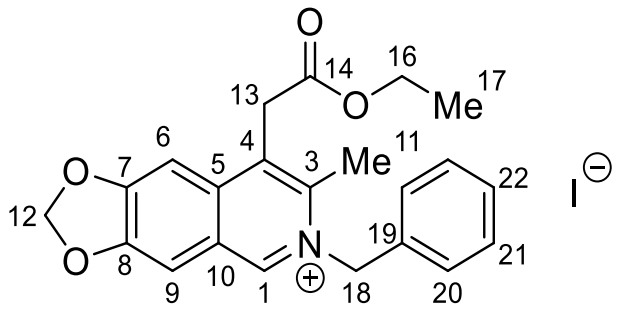
8-(Carboxymethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium chloride (304):



(*R*, *S*)-*N*-(Benzo[d][1,3]dioxol-5-ylmethyl)-1,1-dimethoxypropan-2-amine **297** (7.72 g, 28.2 mmol, 1.00 equiv.) was dissolved in EtOH (75 mL), then 12M HCl (75 mL) was added and the solution was stirred at r.t. for 5 min. Ethyl glyoxylate (11.5 g, 56.4 mmol, 2.00 equiv., 50 wt% solution in PhMe) was added and the solution stirred at 100 °C for 18 h. After cooling to 0 °C, the reaction was neutralised with solid K_2CO_3 and the mixture extracted three times with EtOAc. The aqueous layer was transferred to a crystallisation dish, and stirred at 40 °C under a stream of nitrogen until precipitation was observed. The precipitate was filtered under reduced pressure, then suspended in H_2O and 2M aq. HCl added dropwise. With dropwise HCl addition, the suspension dissolved, then a precipitate was observed. The precipitate was filtered under reduced pressure and dried *in vacuo* to afford **304** as a pale-brown solid (1.44 g, 18%).

^{1}H NMR (600 MHz, DMSO): δ_H = 9.30 (1H, s, H_1), 7.76 (1H, s, H_9), 7.70 (1H, s, H_6), 6.39 (2H, s, H_{11}), 4.18 (2H, s, H_{13}), 2.74 (3H, s, H_{12}); **^{13}C NMR** (151 MHz, DMSO): δ_C = 170.8 (C_{14}), 156.2 (C_7), 149.8 (C_8), 140.9 (C_1), 140.7 (C_3), 138.4 (C_5), 127.2 (C_4), 123.9 (C_{10}), 104.4 (C_9), 103.8 (C_{11}), 100.3 (C_6), 33.4 (C_{13}), 16.9 (C_{12}); **IR** (neat) cm^{-1}: 2624 (br), 1712, 1485, 1460, 1302, 1285, 1232, 1202, 1160, 1026, 926, 905, 880, 856; **HRMS** (ESI$^+$) m/z calc. for $C_{13}H_{11}NO_4$ $[M]^+$ 246.0761; found at 246.0757 Δ -1.69 ppm; **m.p.** = melted with decomposition at 227 °C

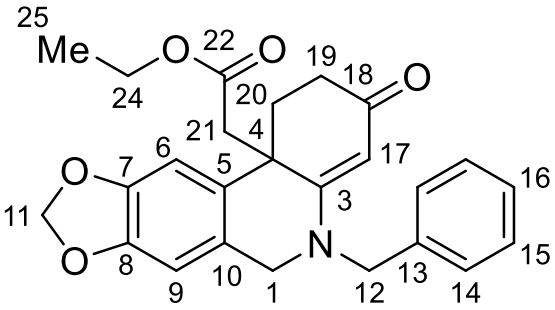
6-Benzyl-8-(2-ethoxy-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium (281):



The title compound was prepared according to **General Procedure E** with ethyl 2-(7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate **280** (2.71 g, 9.93 mmol, 1.00 equiv.) to afford **281** as a pale-yellow solid (4.2 g, 86%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 10.68 (1H, s, H_1), 7.93 (1H, s, H_9), 7.40 – 7.31 (3H, m, H_6, H_{21}), 7.24 – 7.19 (2H, m, H_{20}), 6.30 (2H, s, H_{12}), 6.20 (2H, s, H_{18}), 4.17 (2H, q, *J* = 7.1 Hz, H_{16}), 4.06 (2H, s, H_{13}), 2.76 (3H, s, H_{11}), 1.23 (3H, t, *J* = 7.1 Hz, H_{17}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 168.7 (C_{14}), 157.8 (C_7), 150.9 (C_8), 147.7 (C_1), 142.5 (C_3), 138.6 (C_5), 132.8 (C_{19}), 129.7 (C_{21}), 129.3 (C_{22}), 128.1 (C_4), 127.4 (C_{20}), 124.8 (C_{10}), 106.4 (C_9), 103.9 (C_{12}), 100.3 (C_6), 62.3 (C_{16}), 63.2 (C_{18}), 35.5 (C_{13}), 17.3 (C_{11}), 14.3 (C_{17}); **IR** (neat) cm^{-1}: 1734, 1468, 1218, 1033, 735; **HRMS** (ESI^+) m/z calc. for $C_{22}H_{22}NO_4$ $[M]^+$ 364.1543; found at 364.1551 Δ 2.09 ppm; **LRMS** (ESI^+) m/z calc. for I $[I]^-$ 126.9; found at 126.9; **m.p.** = 152 °C.

(*RS*)-Ethyl 2-(5-benzyl-3-oxo-2,3,5,6-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate (282):



The title compound was synthesised according to **General Procedure I** with 6-benzyl-8-(2-ethoxy-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **281** (123 mg, 0.250 mmol, 1.00 equiv.). Purification by flash column chromatography (3-5% EtOH in EtOAc) afforded **282** as an orange oil (84 mg, 80%).

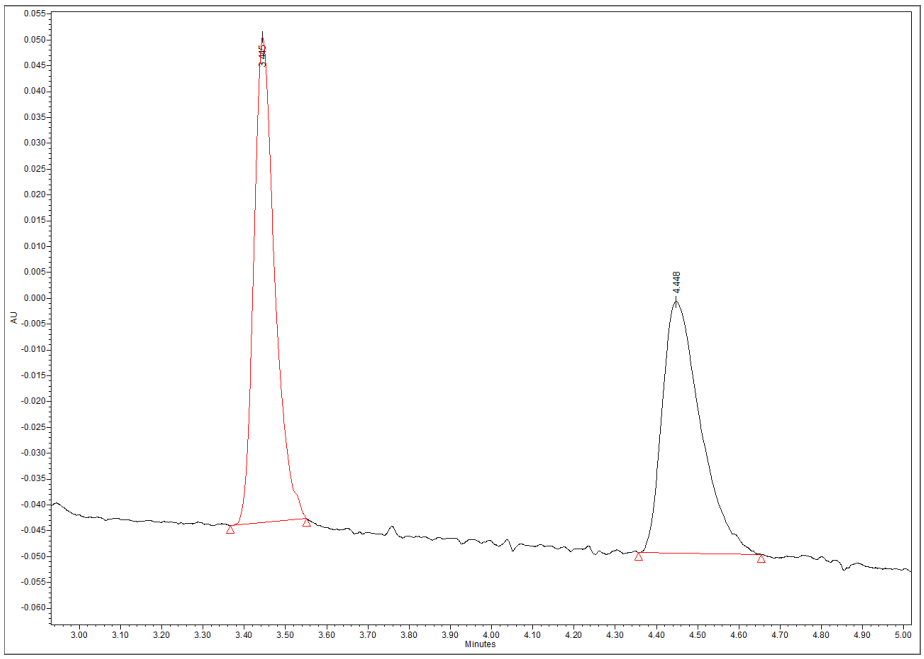
6-Benzyl-8-(2-ethoxy-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **281** (5.20 g, 10.6 mmol, 1.00 equiv.) was dissolved in 1,4-dioxane (160 mL) with 1-(4-chloro-1H-

pyrazol-1-yl)prop-2-en-1-one **252** (3.30 g, 21.2 mmol, 2.00 equiv.), 5:2 HCO_2H:NEt_3 (7.10 mL, 84.8 mmol, 8.00 equiv.) and an aliquot of a premade solution of $(RhCp^*Cl)_2$ in 1,4-dioxane (10.6 mL, 0.0200 mol%, 3.10 mg in 25.0 mL) was added. The mixture was stirred at 80 °C for 18 h, then cooled, diluted with EtOAc and sat. aq. Na_2CO_3, shaken and the layers partitioned. The aqueous layer was washed twice with EtOAc, the organic layers combined, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (3-5% EtOH in EtOAc) afforded **282** as a pale-orange solid (3.78 g, 85%).

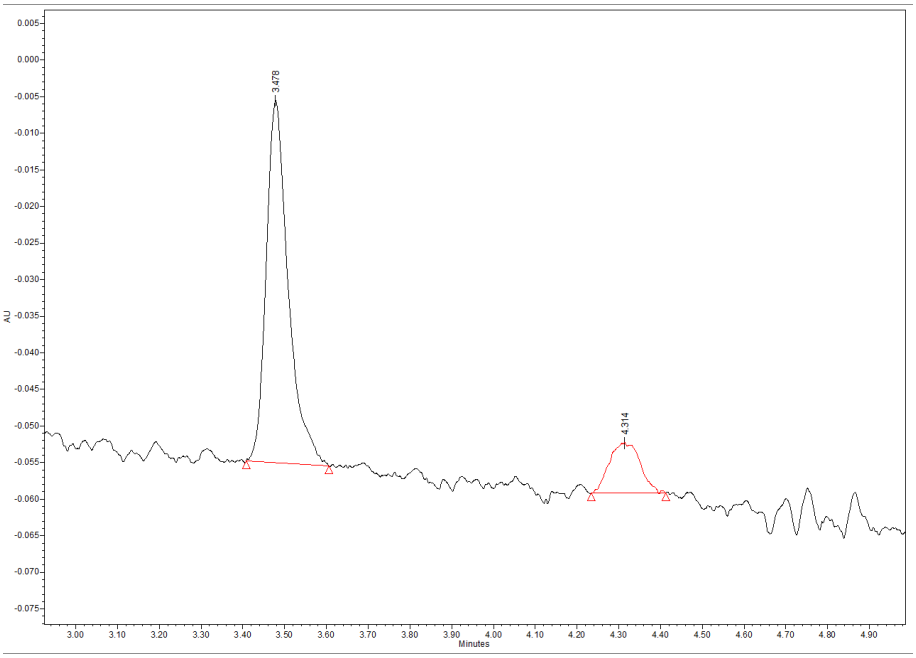
The title compound was synthesised according to **General Procedure J** with 6-benzyl-8-(2-ethoxy-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **281** (123 mg, 0.100 mmol, 1.00 equiv.) with the reaction performed at 40 °C. Purification by flash column chromatography (3-5% EtOH in EtOAc) afforded **282** as a pale-orange solid (7 mg, 7%, 84:16 e.r.).

^{1}H NMR (700 MHz, $CDCl_3$): δ_H = 7.30 – 7.25 (2H, m, H_{15}), 7.25 – 7.19 (1H, m, H_{16}), 7.09 – 7.05 (2H, m, H_{14}), 6.87 (1H, s, H_6), 6.54 (1H, s, H_9), 5.93 (1H, d, *J* = 3.1 Hz, H_{11}), 5.91 (1H, d, *J* = 3.1 Hz, H_{11}'), 5.26 (1H, s, H_{17}), 4.64 (1H, d, *J* = 2.5 Hz, H_1), 4.56 (2H, s, H_{12}), 4.23 (1H, d, *J* = 2.4 Hz, H_1'), 3.92 (2H, q, *J* = 2.1 Hz, H_{24}), 2.98 (1H, ddd, *J* = 13.3, 5.0, 2.5 Hz, H_{20}), 2.78 (1H, d, *J* = 15.1 Hz, H_{21}), 2.67 – 2.60 (2H, m, H_{19}, H_{21}'), 2.47 (1H, ddd, *J* = 17.7, 4.9, 2.6 Hz, H_{19}'), 2.21 – 2.11 (1H, m, H_{20}'), 1.05 (3H, t, *J* = 1.9 Hz, H_{25}); **^{13}C NMR** (176 MHz, $CDCl_3$): δ_C = 195.4 (C_{18}), 169.4 (C_{22}), 165.1 (C_3), 147.7 (C_7), 146.8 (C_8), 134.9 (C_{13}), 130.4 (C_5), 129.0 (C_{15}), 127.7 (C_{16}), 126.4 (C_{14}), 125.4 (C_{10}), 106.0 (C_6), 105.6 (C_9), 101.4 (C_{11}), 98.3 (C_{17}), 60.7 (C_{24}), 55.7 (C_{12}), 52.0 (C_1), 40.7 (C_4), 39.1 (C_{21}), 32.2 (C_{19}), 29.9 (C_{20}), 14.0 (C_{25}); **IR** (neat) cm^{-1}: 1728, 1613, 1558, 1488, 1327, 1246, 1150, 1039, 913, 732; **HRMS** (ESI^+) m/z calc. for $C_{25}H_{26}NO_5$ $[M+H]^+$ 420.1806; found at 420.1813 Δ 1.77 ppm; **m.p.** = 65-67 °C; **SFC** Chiralpak IA; 1500 psi; 30 °C; flow 1.5 mL/min; from 0% to 50% ^{i}PrOH in 7 min; 68% e.e.

(major enantiomer t_R = 3.45 min; minor enantiomer t_R = 4.45 min); $[\alpha]_D^{20}$ = -101.2 (c = 0.00340 gmL^{-1}, $CHCl_3$).

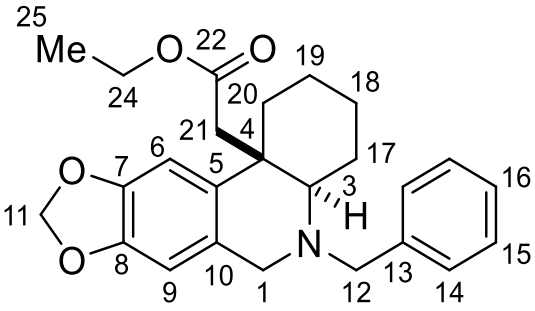


Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (μV*sec)	% Area
3.445							331894	51.28
4.448							315374	48.72



Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (μV*sec)	% Area
3.478							181870	83.84
4.314							35048	16.16

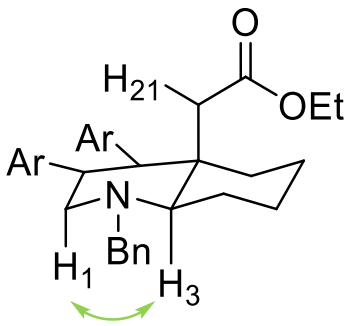
(*RS*, *RS*)-Ethyl 2-(5-benzyl-2,3,4,4a,5,6-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate (307):



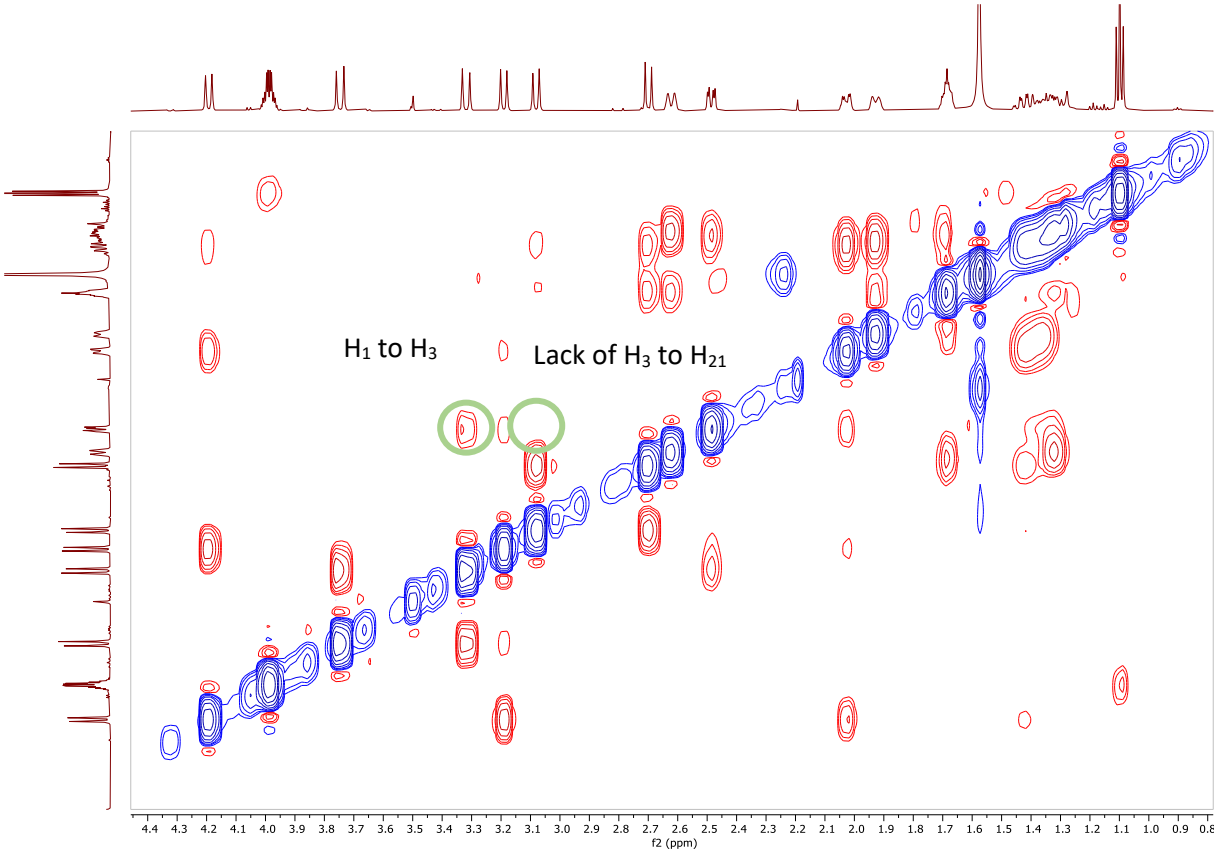
(*RS*)-Ethyl 2-(5-benzyl-3-oxo-2,3,5,6-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate **282** (105 mg, 0.25 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (2.5 mL) with Vaska's complex (2.0 mg, 2.5 μmol, 1.0 mol%) then TMDS (130 μL, 0.75 mmol, 3.0 equiv.) was added dropwise at r.t. and the solution stirred for 10 min. MeOH (2.5 mL) was added dropwise, then $NaBH_3CN$ (8.0 mg, 0.13 mmol, 0.50 equiv.) and AcOH (15 μL, 0.26 mmol, 1.1 equiv.) were added sequentially. The mixture was stirred at r.t. for 12 h, then diluted with CH_2Cl_2 and sat. aq. Na_2CO_3, shaken and the layers partitioned. The aqueous layer was extracted twice with CH_2Cl_2, then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (3-8% EtOAc in pentane) afforded **307** as a pale-yellow oil that solidified upon standing (51 mg, 50%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.36 (2H, d, *J* = 7.6 Hz, H_{14}), 7.31 (2H, t, *J* = 7.5 Hz, H_{15}), 7.24 (1H, m, H_{16}), 6.70 (1H, s, H_6), 6.33 (1H, s, H_9), 5.85 (1H, d, *J* = 1.5 Hz, H_{11}), 5.83 (1H, d, *J* = 1.5 Hz, H_{11}'), 4.17 (1H, d, *J* = 13.0 Hz, H_{12}), 3.96 (2H, qt, *J* = 6.9, 3.5 Hz, H_{24}), 3.72 (1H, d, *J* = 15.2 Hz, H_1), 3.30 (1H, d, *J* = 15.1 Hz, H_1'), 3.17 (1H, d, *J* = 12.9 Hz, H_{12}'), 3.06 (1H, d, *J* = 13.0 Hz, H_{21}), 2.68 (1H, d, *J* = 13.0 Hz, H_{21}'), 2.60 (1H, dq, *J* = 13.4, 2.9 Hz, H_{19}),

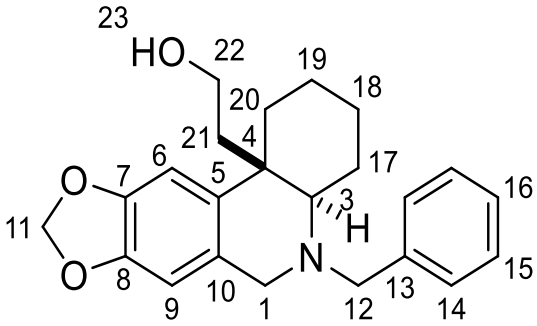
2.46 (1H, dd, *J* = 11.9, 3.7 Hz, H_3), 2.04 – 1.98 (1H, m, H_{17}), 1.94 – 1.87 (1H, m, H_{18}), 1.70 – 1.63 (2H, m, H_{20}), 1.46 – 1.23 (3H, m, H_{17}', H_{18}', H_{19}'), 1.08 (3H, t, *J* = 7.2 Hz, H_{25}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 173.2 (C_{22}), 145.9 ($C_{7 \text{ or } 8}$), 145.7 ($C_{7 \text{ or } 8}$), 140.4 (C_{13}), 135.7 (C_5), 128.8 (C_{14}), 128.4 (C_{15}), 127.8 (C_{10}), 127.0 (C_{16}), 106.1 ($C_{6 \text{ or } 9}$), 106.0 ($C_{6 \text{ or } 9}$), 100.7 (C_{11}), 67.2 (C_3), 60.0 (C_{24}), 57.1 ($C_{1 \text{ or } 12}$), 57.0 ($C_{1 \text{ or } 12}$), 41.8 (C_4), 39.0 (C_{21}), 33.4 (C_{19}), 25.5 ($C_{17 \text{ or } 18}$), 25.3 ($C_{17 \text{ or } 18}$), 21.2 (C_{20}), 14.3 (C_{25}); **IR** (neat) cm^{-1}: 2962, 1725, 1504, 1487, 1262, 1240, 1096, 1041, 913, 808; **HRMS** (ESI^+) m/z calc. for $C_{25}H_{30}NO_4$ $[M+H]^+$ 408.2169; found at 408.2190 Δ 4.07 ppm; **m.p.** = 84-85 °C.



Stereochemistry assigned by NOESY due to enhancement observed between H_3 and H_1, and a lack of any enhancement between H_3 and H_{21}.



(*RS*, *RS*)-2-(5-Benzyl-2,3,4,4a,5,6-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)ethan-1-ol (308):



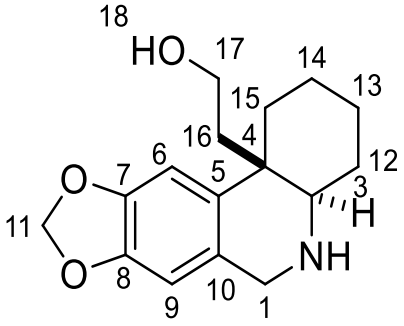
(*RS*, *RS*)-Ethyl 2-(5-benzyl-2,3,4,4a,5,6-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate **307** (136 mg, 0.333 mmol, 1.00 equiv.) was dissolved in THF (3.0 mL) then $LiAlH_4$ (25 mg, 0.666 mmol, 2.0 equiv.) was added in one portion. The suspension was stirred at 40 °C for 20 min, then cooled to r.t. and MeOH was added dropwise. The suspension was diluted with EtOAc and sat. aq. NH_4Cl, shaken and the layers partitioned. The aqueous layer was extracted twice with EtOAc, then the combined organic extracts were dried over

$MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (30-50% EtOAc in pentane) afforded **308** as a colourless solid (54 mg, 45%).

Relative stereochemistry assigned by induction assuming retention from compound **307**.

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.41 – 7.27 (5H, m, H_{14}, H_{15}, H_{16}), 6.64 (1H, s, H_6), 6.31 (1H, s, H_9), 5.87 (1H, d, *J* = 1.5 Hz, H_{11}), 5.86 (1H, d, *J* = 1.5 Hz, H_{11}'), 4.36 (1H, d, *J* = 11.8 Hz, H_{12}), 3.60 (1H, d, *J* = 14.9 Hz, H_1), 3.39 – 3.30 (1H, m, H_{22}), 3.19 (1H, dd, *J* = 15.0, 1.1 Hz, H_1'), 3.07 (1H, d, *J* = 11.8 Hz, H_{12}'), 2.89 (1H, td, *J* = 11.6, 1.2 Hz, H_{22}'), 2.61 (1H, ddd, *J* = 14.9, 11.6, 3.1 Hz, H_{21}), 2.44 (1H, dd, *J* = 12.5, 3.4 Hz, H_3), 2.15 (1H, dd, *J* = 13.2, 3.6 Hz, H_{17}), 2.11 – 2.05 (1H, m, H_{20}), 2.03 – 1.97 (1H, m, H_{18}), 1.86 (1H, qd, *J* = 12.8, 4.1 Hz, H_{17}'), 1.80 – 1.67 (1H, m, H_{19}), 1.65 – 1.60 (1H, m, H_{19}'), 1.52 (1H, td, *J* = 13.4, 4.1 Hz, H_{20}'), 1.47 – 1.38 (1H, m, H_{18}'), 1.35 (1H, dd, *J* = 15.2, 3.4 Hz, H_{21}'); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 146.9 (C_7), 145.9 (C_8), 137.0 (C_{13}), 134.6 (C_5), 129.9 (C_{14}), 128.9 (C_{15}), 127.7 (C_{16}), 126.9 (C_{10}), 106.2 (C_9), 105.0 (C_6), 100.9 (C_{11}), 67.6 (C_3), 58.6 (C_{22}), 58.1 (C_{12}), 56.6 (C_1), 43.3 (C_4), 40.1 (C_{20}), 39.3 (C_{21}), 26.0 (C_{18}), 23.9 (C_{17}), 20.8 (C_{19}); **IR** (neat) cm^{-1}: 2945, 1673, 1503, 1487, 1364, 1240, 1113, 1069, 1038, 933, 869, 748, 703; **HRMS** (ESI^+) m/z calc. for $C_{23}H_{28}NO_3$ $[M+H]^+$ 366.2064; found at 366.2064 Δ 0.07 ppm; **m.p.** = 158-160 °C. Spectroscopic data were consistent with the literature data for this compound.[187]

(*RS*, *RS*)-2-(2,3,4,4a,5,6-Hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)ethan-1-ol (309):

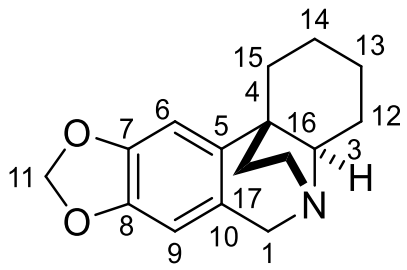


(*RS*, *RS*)-2-(5-Benzyl-2,3,4,4a,5,6-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)ethan-1-ol **308** (55.5 mg, 0.152 mmol, 1.00 equiv.) was dissolved in MeOH (3 mL) and the vessel evacuated and backfilled with N_2. $Pd(OH)_2$ on carbon (21 mg, 20 mol%, 20 wt%) was added, and an atmosphere of H_2 was introduced. The reaction was stirred at 65 °C for 3 h, then diluted with MeOH, eluted through a short plug of celite with excess MeOH and concentrated *in vacuo* to afford **309** as a colourless oil (36 mg, 85%).

Relative stereochemistry assigned by induction assuming retention from compound **308**.

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 6.63 (1H, s, H_6), 6.46 (1H, s, H_9), 5.89 (1H, d, *J* = 2.0 Hz, H_{11}), 5.88 (1H, d, *J* = 2.0 Hz, H_{11}'), 4.15 (1H, d, *J* = 14.8 Hz, H_1), 4.00 (1H, d, *J* = 14.8 Hz, H_1'), 3.34 (1H, dt, *J* = 12.0, 3.5 Hz, H_{17}), 2.87 (1H, t, *J* = 11.5 Hz, H_{17}'), 2.71 (1H, dd, *J* = 12.1, 3.4 Hz, H_3), 2.47 (1H, ddd, *J* = 14.8, 11.4, 2.7 Hz, H_{16}), 1.99 (1H, dt, *J* = 13.2, 3.3 Hz, H_{15}), 1.90 – 1.79 (2H, m, H_{12}, H_{13}), 1.68 (1H, tt, *J* = 13.8, 3.9 Hz, H_{14}), 1.64 – 1.55 (2H, m, H_{12}', H_{14}'), 1.49 – 1.34 (2H, m, H_{13}', H_{15}'), 1.34 – 1.28 (1H, m, H_{16}'); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 146.9 (C_7), 146.0 (C_8), 135.0 (C_5), 126.7 (C_{10}), 106.1 (C_9), 105.1 (C_6), 101.0 (C_{11}), 60.5 (C_3), 58.1 (C_{17}), 48.6 (C_1), 42.1 (C_4), 38.7 (C_{16}), 38.6 (C_{15}), 27.5 (C_{12}), 25.3 (C_{13}), 21.4 (C_{14}); **IR** (neat) cm^{-1}: 2934, 1504, 1486, 1237, 1041, 937, 911, 734; **HRMS** (ESI^+) m/z calc. for $C_{16}H_{22}NO_3$ $[M+H]^+$ 276.1594; found at 276.1608 Δ 4.98 ppm. Spectroscopic data were consistent with the literature data for this compound.[187]

(*RS*, *RS*)-(2,3,4,4a-Tetrahydro-1H,6H-5,11b-ethano[1,3]dioxolo[4,5-j]phenanthridine (273):



(*RS*, *RS*)-2-(2,3,4,4a,5,6-Hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)ethan-1-ol **309** (35.7 mg, 0.130 mmol, 1.00 equiv.) was dissolved in anhydrous THF (1.0 mL) with Ph_3P (41 mg, 0.16 mmol, 1.2 equiv.) and DIAD (31 μL, 0.16 mmol, 1.2 equiv.) then stirred at 50 °C overnight. The mixture was then diluted with CH_2Cl_2 and 2 M aq. NaOH, shaken and the layers partitioned. The aqueous layer was extracted twice with CH_2Cl_2, then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (2-10% MeOH in CH_2Cl_2) afforded **273** as a pale-brown oil (21 mg, 63%).

Relative stereochemistry assigned by induction assuming retention from compound **309** and re-enforced by single crystal X-ray analysis (see Appendix I).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 6.69 (1H, s, H_6), 6.44 (1H, s, H_9), 5.87 (2H, s, H_{11}), 4.33 (1H, d, *J* = 16.7 Hz, H_1), 3.73 (1H, d, *J* = 16.7 Hz, H_1'), 3.32 (1H, ddd, *J* = 13.5, 10.3, 3.9 Hz, H_{16}), 2.79 (1H, ddd, *J* = 13.0, 10.8, 6.2 Hz, H_3, H_{16}'), 2.33 (1H, ddt, *J* = 13.1, 3.9, 1.9 Hz, H_{15}), 2.24 – 2.17 (1H, m, H_{17}), 1.82 – 1.66 (4H, m, H_{12}, H_{13}, H_{14}, H_{17}'), 1.61 (1H, td, *J* = 13.0, 3.9 Hz, H_{15}'), 1.49 (1H, qt, *J* = 11.8, 2.1 Hz, H_{14}'), 1.31 – 1.14 (2H, m, H_{12}', H_{13}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 146.3 (C_7), 145.6 (C_8), 142.4 (C_5), 126.2 (C_{10}), 106.3 (C_9), 103.4 (C_6), 100.8 (C_{11}), 67.5 (C_3), 62.3 (C_1), 52.1 (C_{16}), 42.9 (C_4), 38.0 (C_{17}), 29.1 (C_{15}), 27.7 (C_{12}), 24.5 (C_{13}), 21.9 (C_{14}); **IR** (neat) cm^{-1}: 2934, 1504, 1482, 1233, 1041, 937, 912, 735; **HRMS** (ESI^+) m/z calc. for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489; found at 258.1477 Δ -4.48 ppm. Spectroscopic data were consistent with the literature data for this compound.[188]

Comparison of ^{1}H NMR data:

Data Collected ($CDCl_3$)	**Literature Data ($CDCl_3$)**	**Δ ppm from Literature Data**
6.69 (s)	6.71 (s)	-0.02
6.44 (s)	6.46 (s)	-0.02
5.87 (s)	5.89 (d, *J* = 1.8 Hz)	-0.02
4.33 (d, *J* = 16.7 Hz)	4.36 (d, *J* = 16.7 Hz)	-0.03
3.73 (d, *J* = 16.7 Hz)	3.76 (d, *J* = 16.7 Hz)	-0.03
3.32 (ddd, *J* = 13.5, 10.3, 3.9 Hz)	3.36 (ddd, *J* = 13.4, 10.4, 3.9 Hz)	-0.04
2.79 (ddd, *J* = 13.0, 10.8, 6.2 Hz)	2.91 - 2.67 (m)	-
2.33 (ddt, *J* = 13.1, 3.9, 1.9 Hz)	2.34 (ddd, *J* = 11.8, 4.2, 1.9 Hz)	-0.01
2.24 - 2.17 (m)	2.22 (ddd, *J* = 12.2 10.4 6.2 Hz)	-
1.82 – 1.66 (m)	1.85 – 1.70 (m)	-
1.61 (td, *J* = 13.0, 3.9 Hz)	1.62 (td, *J* = 13.1, 4.2 Hz)	-0.01
1.49 (qt, *J* = 11.8, 2.1 Hz)	1.50 (tdd, *J* = 13.1, 9.6, 3.6 Hz)	-0.01
1.31 – 1.14 (m)	1.30-1.18 (m)	-

Table 8.1: Comparison of literature ^{1}H NMR data with data collected for Crinane **273**.[188]

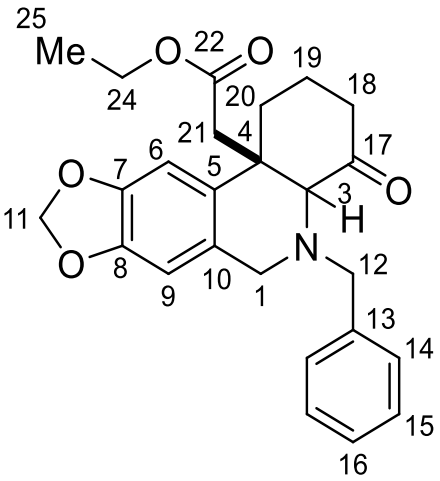
Comparison of ^{13}C NMR data:

Data Collected ($CDCl_3$)	**Literature Data ($CDCl_3$)**	**Δ ppm from Literature Data**
146.3	146.4	-0.1
145.6	145.7	-0.1
142.4	142.3	+0.1
126.2	126.0	+0.2
106.3	106.4	-0.1
103.4	103.4	0.0
100.8	100.8	0.0
67.5	67.5	0.0
62.3	62.2	+0.1

52.1	52.1	0.0
42.9	43.0	-0.1
38.0	37.9	+0.1
29.1	29.1	0.0
27.7	27.6	+0.1
24.5	24.5	0.0
21.9	21.9	0.0

Table 8.2: Comparison of literature ^{13}C NMR data with data collected for Crinane **273**.[188]

(*RS*)-Ethyl 2-(5-benzyl-4-oxo-2,3,4,4a,5,6-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate (313):



According to a literature procedure published by Dixon and co-workers:[102] (*RS*)-Ethyl 2-(5-benzyl-3-oxo-2,3,5,6-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate **282** (105 mg, 0.25 mmol, 1.00 equiv.) was placed in a Schlenk flask which was then evacuated and backfilled with argon three times. In a separate vial, Vaska's complex (3.0 mg, 3.8 μmol, 1.5 mol%) was dissolved in anhydrous CH_2Cl_2 (3.0 mL) with Hünig's base (52 μL, 0.3 mmol, 1.2 equiv.), then the mixture was added dropwise to the Schlenk tube. TMDS (66.0 μL, 0.375 mmol, 1.50 equiv.) was added dropwise, then the solution was stirred at r.t. for 15 min, after which time it was cooled to -78 °C. Purified *m*-CPBA (*vide infra*) (48.0 mg, 0.275 mmol,

1.10 equiv.) was dissolved in anhydrous CH_2Cl_2 (3.0 mL) then added to the Schlenk flask dropwise, after which the reaction was stirred for 5 min at -78 °C, then allowed to warm to r.t. overnight. The reaction was then diluted with EtOAc and sat. aq. $NaHCO_3$, shaken and the layers partitioned. The aqueous layer was extracted twice with EtOAc, then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (20-50% EtOAc in pentane) afforded **313** as a pale-yellow oil as a single diastereomer (9.0 mg, 9%).

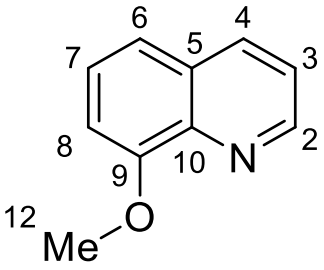
m-CPBA was purified by dissolving commercial *m*-CPBA (5.0 g) in Et_2O (30 mL), then washing the solution with a buffer solution of pH 7.5 (NaOH (412 mg, 10.3 mmol) and KH_2PO_4 (1.71 g, 12.6 mmol) in H_2O (250 mL)) three times. The solution was then dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. The purified *m*-CPBA was stored under argon at 4 °C until usage.

Relative stereochemistry at C3 and C4 was left unassigned.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.38 – 7.34 (2H, m, H_{14}), 7.32 – 7.28 (2H, m, H_{15}), 7.24 (1H, m, H_{16}), 6.67 (1H, s, H_6), 6.40 (1H, s, H_9), 5.92 – 5.83 (2H, m, H_{11}), 4.24 – 4.18 (2H, m, H_1, H_{12}), 4.08 (2H, q, *J* = 7.1 Hz, H_{24}), 4.02 (1H, d, *J* = 13.4 Hz, H_{12}'), 3.81 (1H, s, H_3), 3.70 (1H, d, *J* = 15.5 Hz, H_1'), 3.08 (1H, d, *J* = 14.6 Hz, H_{21}), 2.61 (1H, d, *J* = 14.6 Hz, H_{21}'), 2.52 (1H, dq, *J* = 14.5, 2.9 Hz, H_{20}), 2.33 – 2.21 (2H, m, H_{18}, H_{18}'), 2.19 – 2.10 (1H, m, H_{20}'), 1.80 (1H, ddq, *J* = 13.0, 6.3, 3.3 Hz, H_{19}), 1.50 (1H, qdd, *J* = 13.4, 5.1, 3.1 Hz, H_{19}'), 1.21 (3H, t, *J* = 7.1 Hz, H_{25}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 211.4 (C_{17}), 171.8 (C_{22}), 146.6 ($C_{7\text{ or }8}$), 146.5 ($C_{7\text{ or }8}$), 139.8 (C_{13}), 130.0 ($C_{5\text{ or }10}$), 129.9 ($C_{5\text{ or }10}$), 129.1 (C_{14}), 128.4 (C_{15}), 127.1 (C_{16}), 106.9 (C_9), 104.7 (C_6), 101.0 (C_{11}), 70.1 (C_3), 60.3 (C_{12}), 60.3 (C_{24}), 50.5 (C_1), 46.9 (C_4), 46.7 (C_{21}), 41.9 (C_{18}), 32.7 (C_{20}), 21.3 (C_{19}), 14.4 (C_{25}); **IR** (neat) cm^{-1}: 1716, 1505, 1487, 1262,

1235, 1096, 1040, 911, 861, 806, 735, 701; **HRMS** (ESI^+) m/z calc. for $C_{25}H_{28}NO_5$ $[M+H]^+$ 422.1962; found at 422.1969 Δ 1.65 ppm.

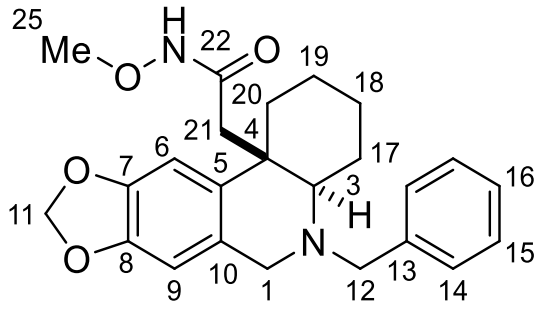
8-Methoxyquinoline (364):



8-Quinolinol (1.45 g, 10.0 mmol, 1.00 equiv.) was dissolved in acetone (20 mL) with MeI (0.75 mL, 12 mmol, 1.2 equiv.) and K_2CO_3 (2.1 g, 15 mmol, 1.5 equiv.), then stirred at r.t. for 72 h. The mixture was filtered with a celite plug, which was washed with acetone. The combined filtrates were concentrated *in vacuo*, then purification by flash column chromatography (80-100% EtOAc in pentane) afforded **364** as a yellow solid (1.29 g, 81%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 8.92 (1H, dd, *J* = 4.2, 1.7 Hz, H_2), 8.12 (1H, dd, *J* = 8.3, 1.7 Hz, H_4), 7.49 – 7.35 (3H, m, H_3, H_7, H_8), 7.05 (1H, dd, *J* = 7.6, 1.3 Hz, H_6), 4.09 (3H, s, H_{12}); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 155.5 (C_9), 149.4 (C_2), 140.4 (C_{10}), 136.0 (C_4), 129.5 (C_5), 126.8 (C_7), 121.8 (C_3), 119.7 (C_8), 107.6 (C_6), 56.1 (C_{12}); **IR** (neat) cm^{-1}: 1501, 1473, 1377, 1217, 1263, 1110, 994, 823, 792, 753, 710; **HRMS** (ESI^+) m/z calc. for $C_{10}H_{10}NO$ $[M+H]^+$ 159.0684; compound could not be observed by ESI MS; **m.p.** = 36-37 °C. Spectroscopic data were consistent with the literature data for this compound.[189]

(*RS*, *RS*)-2-(5-Benzyl-2,3,4,4a,5,6-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)-*N*-methoxyacetamide (317):



(*RS*, *RS*)-Ethyl 2-(5-benzyl-2,3,4,4a,5,6-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate **307** (1.49 g, 3.66 mmol, 1.00 equiv.) was dissolved in EtOH (20 mL) with NaOH (1.46 g, 3.66 mmol, 10.0 equiv.) and heated to reflux for 5 h. The mixture was diluted with EtOAc and H_2O, shaken and the layers partitioned. The aqueous layer was extracted twice with EtOAc, then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

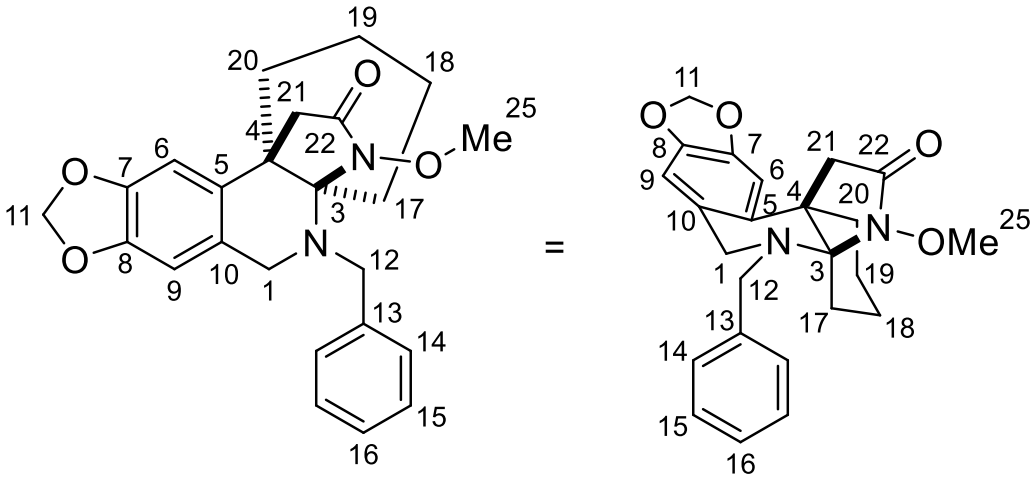
The residue was dissolved in CH_2Cl_2 (20 mL) with EDC HCl (1.55 g, 8.05 mmol, 2.20 equiv.), HOBt H_2O (1.09 g, 8.05 mmol, 2.20 equiv.), methoxyamine HCl (672 mg, 8.05 mmol, 2.20 equiv.) and NEt_3 (2.2 mL, 16 mmol, 4.4 equiv.) and stirred at r.t. overnight. The reaction was then diluted with CH_2Cl_2 and H_2O, shaken and the layers partitioned. The aqueous layer was extracted twice with CH_2Cl_2, then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (10-80% EtOAc in 40-60 pet ether) afforded **317** as an off-white solid (222 mg, 15% over two steps).

Relative stereochemistry assigned by induction assuming retention from compound **307**.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.40 – 7.34 (4H, m, H_{14}, H_{15}), 7.32 (1H, td, *J* = 6.6, 1.9 Hz, H_{16}), 6.80 (1H, s, H_6), 6.29 (1H, s, H_9), 5.84 (2H, dd, *J* = 12.1, 1.4 Hz, H_{11}), 4.31 (1H, d, *J* =

12.1 Hz, H_{12}), 3.61 (1H, d, *J* = 15.1 Hz, H_1), 3.30 – 3.26 (4H, m, H_1', H_{25}), 3.14 – 3.06 (2H, m, H_{12}', H_{21}), 2.53 (1H, d, *J* = 12.3 Hz, H_3), 2.35 (1H, d, *J* = 14.8 Hz, H_{21}'), 2.30 (1H, d, *J* = 7.4 Hz, H_{20}), 2.22 – 2.14 (1H, m, H_{17}), 1.96 (1H, d, *J* = 13.5 Hz, H_{18}), 1.75 – 1.50 (3H, m, H_{17}', H_{19}, H_{19}'), 1.45 – 1.32 (2H, m, H_{18}', H_{20}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 170.1 (C_{22}), 146.7 (C_7), 146.4 (C_8), 138.1 (C_{13}), 133.6 (C_5), 129.4 (C_{15}), 128.9 (C_{14}), 127.8 (C_{16}), 126.4 (C_{10}), 106.2 (C_6), 105.8 (C_9), 101.0 (C_{11}), 68.3 (C_3), 63.7 (C_{25}), 57.5 (C_{12}), 56.9 (C_1), 41.1 (2C, C_4, C_{21}), 38.9 (C_{20}), 25.5 (C_{18}), 24.8 (C_{17}), 20.8 (C_{19}); **IR** (neat) cm^{-1}: 2935, 1654, 1503, 1486, 1453, 1365, 1238, 1040, 935, 912, 732, 701; **HRMS** (ESI^+) m/z calc. for $C_{24}H_{29}N_2O_4$ $[M+H]^+$ 409.2122; found at 409.2130 Δ 1.99 ppm; **m.p.** = 145 °C.

(*RS*, *RS*)-5-Benzyl-14-methoxy-1,2,3,4,5,6-hexahydro-4a,11b-(epiminoethano)[1,3]dioxolo[4,5-j]phenanthridin-13-one (318):



Following a literature procedure by Yu and co-workers:[103] (*RS*, *RS*)-2-(5-Benzyl-2,3,4,4a,5,6-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)-*N*-methoxyacetamide **317** (41 mg, 0.10 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (0.5 mL) with CuF_2 (1.0 mg, 0.010 mmol, 0.10 equiv.), 8-methoxy quinoline (3.0 mg, 0.020 mmol, 0.2 equiv.) and AcOH (45 μL, 0.79 mmol, 7.9 equiv.). The mixture was heated to 125 °C for 2 h, then passed through a short silica plug, eluting with EtOAc. The solution was concentrated *in vacuo*, then purified by flash

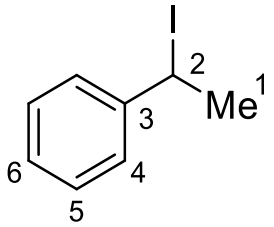
column chromatography (40-80% EtOAc in pentane) to afford **318** as a colourless oil (12 mg, 30%).

Relative stereochemistry assigned by induction assuming retention from compound **317**.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.33 – 7.27 (4H, m, H_{14}, H_{15}), 7.25 – 7.21 (1H, m, H_{16}), 6.68 (1H, s, H_6), 6.33 (1H, s, H_9), 5.91 – 5.85 (2H, m, H_{11}), 4.11 (1H, d, *J* = 14.1 Hz, H_{12}), 4.02 (1H, d, *J* = 14.2 Hz, H_{12}'), 3.96 (3H, s, H_{25}), 3.67 (1H, d, *J* = 15.7 Hz, H_1), 3.59 (1H, d, *J* = 15.7 Hz, H_1'), 2.66 (1H, d, *J* = 16.6 Hz, H_{21}), 2.54 (1H, d, *J* = 16.6 Hz, H_{21}'), 2.39 – 2.31 (1H, m, H_{17}), 2.07 (1H, ddd, *J* = 14.3, 8.9, 3.8 Hz, H_{20}), 1.88 (1H, ddd, *J* = 10.7, 7.8, 3.9 Hz, H_{20}'), 1.86 – 1.79 (1H, m, H_{17}'), 1.66 – 1.47 (3H, m, H_{18}, H_{18}', H_{19}), 1.45 – 1.36 (1H, m, H_{19}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 172.8 (C_{22}), 147.0 (C_7), 146.1 (C_8), 139.9 (C_{13}), 132.8 (C_5), 128.6 (C_{15}), 128.1 (C_{14}), 127.1 (C_{16}), 126.1 (C_{10}), 106.2 (C_6), 105.7 (C_9), 101.0 (C_{11}), 82.1 (C_3), 63.5 (C_{25}), 53.8 (C_{12}), 50.3 (C_1), 42.3 (C_4), 42.2 (C_{21}), 35.6 (C_{20}), 24.8 (C_{17}), 22.2 (C_{19}), 21.4 (C_{18}); **IR** (neat) cm^{-1}: 1716, 1504, 1487, 1232, 1038, 911, 731, 700; **HRMS** (ESI^+) m/z calc. for $C_{24}H_{27}N_2O_4$ $[M+H]^+$ 407.1965; found at 407.1968 Δ 0.65 ppm.

8.7 Experimental data for Chapter 6

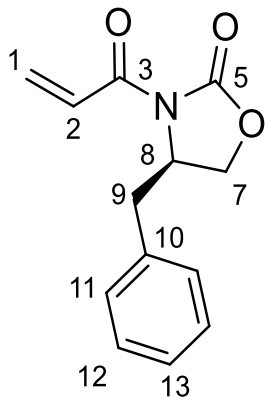
(*RS*)-(1-Iodoethyl)benzene (325):



(1-Bromoethyl)benzene (1.4 mL, 10 mmol, 1.0 equiv.) was dissolved in acetone (20 mL) with NaI (1.8 g, 12 mmol, 1.2 equiv.) and stirred overnight at r.t. in the dark. The reaction was then quenched with H_2O, diluted with EtOAc, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc. The combined organic layers were then washed once each with H_2O and sat. aq. $N_2S_2O_3$, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo* to afford **325** as a pale-brown oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.48 – 7.41 (2H, m, H_4), 7.34 – 7.27 (2H, m, H_5), 7.27 – 7.22 (1H, m, H_6), 5.41 (1H, q, *J* = 7.1 Hz, H_2), 2.22 (1H, d, *J* = 7.2 Hz, H_1); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 145.5 (C_3), 128.8 (C_5), 128.1 (C_6), 126.7 (C_4), 29.1 (C_1), 26.2 (C_2); **IR** (neat) cm^{-1}: 3029, 1494, 1454, 1376, 1206, 1145, 1085, 1047, 1025, 762, 694; **LRMS** (ESI^+) Molecule could not be observed by ESI MS. Spectroscopic data were consistent with the literature data for this compound.[190]

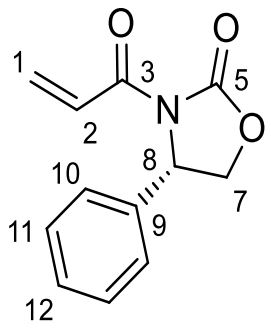
(*R*)-3-Acryloyl-4-benzyloxazolidin-2-one (330):



The title compound was prepared according to **General Procedure F** at the 7.3 mmol scale with (*R*)-4-benzyl oxazolidinone (1.3 g, 7.3 mmol, 1.0 equiv.) as the chiral auxiliary. Purification by flash column chromatography (10-40% EtOAc in pentane) afforded **330** as an off white solid (827 mg, 49%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.52 (1H, dd, *J* = 17.0, 10.4 Hz, H_2), 7.34 (2H, dd, *J* = 8.0, 6.4 Hz, H_{12}), 7.31 – 7.25 (1H, m, H_{13}), 7.25 – 7.19 (2H, m, H_{11}), 6.61 (1H, dd, *J* = 16.9, 1.8 Hz, H_1), 5.94 (1H, dd, *J* = 10.5, 1.8 Hz, H_1'), 4.80 – 4.69 (1H, m, H_8), 4.28 – 4.16 (2H, m, H_7), 3.35 (1H, dd, *J* = 13.4, 3.4 Hz, H_9), 2.81 (1H, dd, *J* = 13.5, 9.5 Hz, H_9'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 165.0 (C_5), 153.5 (C_3), 135.4 (C_{10}), 132.1 (C_1), 129.6 (C_{11}), 129.1 (C_{12}), 127.5 (2C, C_2, C_{13}), 66.4 (C_9), 55.5 (C_8), 38.0 (C_7); **IR** (neat) cm^{-1}: 1781, 1687, 1620, 1410, 1391, 1354, 1317, 1250, 1214, 1115, 987, 704; **HRMS** (ESI^+) m/z calc. for $C_{13}H_{14}NO_3$ $[M+H]^+$ 231.0895; molecule could not be observed by ESI MS; **m.p.** = 57-58 °C; $[\alpha]_D^{20}$ = -94.6 (c = 0.01 gmL^{-1}, $CHCl_3$). Spectroscopic data were consistent with the literature data for this compound.[191]

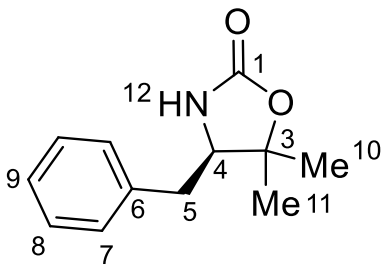
(*S*)-3-Acryloyl-4-phenyloxazolidin-2-one (331):



The title compound was prepared according to **General Procedure F** at the 5.0 mmol scale with (*S*)-4-phenyloxazolidin-2-one (815 mg, 5.00 mmol, 1.00 equiv.) as the chiral auxiliary. Purification by flash column chromatography (15-20% EtOAc in pentane) afforded **331** as an off white solid (482 mg, 44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.52 (1H, dd, *J* = 17.0, 10.5 Hz, H_2), 7.42 – 7.29 (5H, m, H_{10}, H_{11}, H_{12}), 6.49 (1H, dd, *J* = 17.1, 1.7 Hz, H_1), 5.88 (1H, dd, *J* = 10.5, 1.7 Hz, H_1'), 5.49 (1H, dd, *J* = 8.7, 3.9 Hz, H_8), 4.72 (1H, td, *J* = 8.8, 1.7 Hz, H_7), 4.31 (1H, ddd, *J* = 8.8, 3.7, 2.0 Hz, H_7'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 164.6 (C_3), 153.7 (C_5), 139.0 (C_9), 132.3 (C_1), 129.4 (C_{11}), 128.9 (C_{12}), 127.4 (C_2), 126.1 (C_{10}), 70.2 (C_7), 57.9 (C_8); **IR** (neat) cm^{-1}: 1776, 1690, 1409, 1386, 1327, 1248, 1201, 1117, 1071, 1046, 989, 798, 755, 701; **HRMS** (ESI^+) m/z calc. for $C_{12}H_{12}NO_3$ $[M+H]^+$ 218.0812; found at 218.0804 Δ -3.53 ppm; **m.p.** = 66-67 °C, $[\alpha]_D^{20}$ = +145.6 (c = 0.01 gmL^{-1}, $CHCl_3$). Spectroscopic data were consistent with the literature data for this compound.[192]

(*R*)-4-Benzyl-5,5-dimethyloxazolidin-2-one (S332):

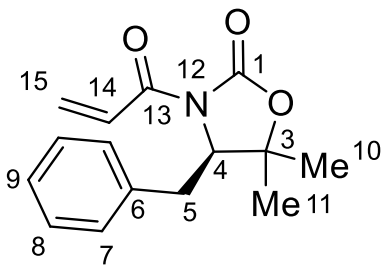


D-Phenyl alanine methyl ester hydrochloride salt (2.16 g, 10.0 mmol, 1.00 equiv.) was dissolved in anhydrous Et_2O (20 mL) and cooled to 0 °C. MeMgBr (22 ml, 65 mmol, 3.0 M in Et_2O, 6.5 equiv.) was added dropwise, then the mixture was heated at reflux for 3 h. After cooling to 0 °C, the reaction was quenched by dropwise addition of sat. aq. NH_4Cl, basified with 2 M aq. NaOH, then diluted with H_2O and Et_2O. The mixture was shaken, the layers partitioned, then the aqueous layer extracted twice more with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

The residue was dissolved in THF (50 mL) with CDI (1.62 g, 10.0 mmol, 1.00 equiv.) and stirred at r.t. overnight. The mixture was then diluted with H_2O and EtOAc, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc, then the combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (20-40% EtOAc in pentane) afforded **S332** as a pale-yellow solid (332 mg, 16% across two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.34 (2H, ddd, *J* = 7.8, 6.5, 1.7 Hz, H_8), 7.30 – 7.26 (1H, m, H_9), 7.22 – 7.15 (2H, m, H_7), 4.84 (1H, br s, H_{12}), 3.69 (1H, dd, *J* = 10.9, 3.7 Hz, H_4), 2.84 (1H, dd, *J* = 13.3, 3.6 Hz, H_5), 2.67 (1H, dd, *J* = 13.3, 10.9 Hz, H_5'), 1.49 (3H, s, $H_{10\text{ or }11}$), 1.46 (3H, s, $H_{10\text{ or }11}$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 158.0 (C_1), 137.0 (C_6), 129.3 (C_8), 129.0 (C_7), 127.4 (C_9), 83.3 (C_3), 63.2 (C_4), 37.3 (C_5), 27.7 ($C_{10\text{ or }11}$), 22.1 ($C_{10\text{ or }11}$); **IR** (neat) cm^{-1}: 1747, 1373, 1301, 996, 744, 701; **HRMS** (ESI^+) m/z calc. for $C_{12}H_{16}NO_2$ $[M+H]^+$ 206.1176; found at 206.1180 Δ 2.16 ppm; **m.p.** = 38-40 °C. Spectroscopic data were consistent with the literature data for this compound.[193]

(*R*)-3-Acryloyl-4-benzyl-5,5-dimethyloxazolidin-2-one (332):

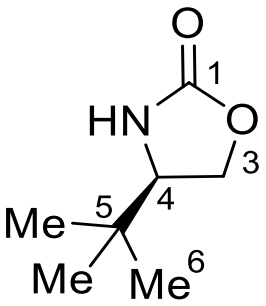


The title compound was prepared according to **General Procedure F** at the 1.62 mmol scale with (*R*)-4-benzyl-5,5-dimethyloxazolidin-2-one **S332** (332 mg, 1.62 mmol, 1.00 equiv.) as the chiral auxiliary. Purification by flash column chromatography (15-20% EtOAc in pentane) afforded **332** as a colourless oil (71 mg, 17%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_C = 7.47 (1H, dd, *J* = 17.0, 10.4 Hz, H_{14}), 7.30 – 7.23 (4H, m, H_7, H_8), 7.19 (1H, td, *J* = 6.3, 2.8 Hz, H_9), 6.49 (1H, dd, *J* = 17.0, 1.8 Hz, H_{15}), 5.85 (1H, dd, *J* = 10.4, 1.8 Hz, H_{15}'), 4.54 (1H, dd, *J* = 9.7, 3.7 Hz, H_4), 3.20 (1H, dd, *J* = 14.4, 3.7 Hz, H_5), 2.87 (1H, dd, *J* = 14.4, 9.7 Hz, H_5'), 1.35 (3H, s, $H_{10 \text{ or } 11}$), 1.33 (3H, s, $H_{10 \text{ or } 11}$); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 165.2 (C_{13}), 152.5 (C_1), 137.0 (C_6), 131.5 (C_{15}), 129.1 (C_7), 128.7 (C_8), 127.8 (C_{14}), 126.8 (C_9), 82.4 (C_3), 63.8 (C_4), 35.2 (C_5), 28.6 ($C_{10 \text{ or } 11}$), 22.4 ($C_{10 \text{ or } 11}$); **IR** (neat) cm^{-1}: 1773, 1685, 1407, 1393, 1356, 1317, 1277, 1248, 1210, 1182, 1160, 1106, 1066, 1031, 1004, 732, 701; **HRMS** (ESI^+) m/z calc. for $C_{15}H_{18}NO_3$ $[M+H]^+$ 260.1281; found at 260.1285 Δ 1.46 ppm; α_D not recorded due to product decomposition.

Stereochemistry of **332** was assigned by induction assuming retention from **S332**.

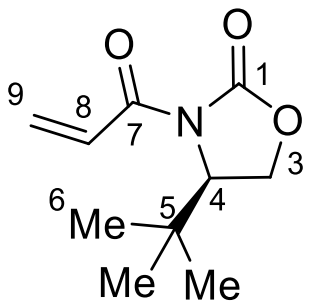
(*R*)-4-(*tert*-Butyl)oxazolidin-2-one (S333):



(*R*)-*tert*-Butyl leucenol (585 mg, 5.00 mmol, 1.00 equiv.) was dissolved in THF (50 mL) and cooled to 0 °C. Ethyl chloroformate (0.6 mL, 6.0 mmol, 1.2 equiv.) was added dropwise, the mixture was stirred for 30 min, then diluted with sat. aq. Na_2CO_3 and EtOAc, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc, then the combined organic layers were dried over Mg_2SO_4, filtered under gravity and concentrated *in vacuo*. The residue was dissolved in anhydrous THF (30 mL), then cooled to 0 °C. NaH (600 mg, 15 mmol, 3.0 equiv.) was added in one portion, the mixture was stirred at 0 °C for 40 min, then at r.t. for a further 3 h. The mixture was quenched with dropwise addition of H_2O, then diluted with further H_2O and EtOAc, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc, then the combined organic layers were dried over Mg_2SO_4, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (30-60% EtOAc in pentane) afforded **S333** as a colourless solid (215 mg, 30%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 4.36 (1H, tt, *J* = 9.1, 1.5 Hz, H_3), 4.18 (1H, ddd, *J* = 9.0, 5.9, 1.5 Hz, H_3'), 3.59 (1H, dd, *J* = 9.0, 5.7 Hz, H_4), 0.90 (9H, s, H); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 160.6 (C_1), 66.7 (C_3), 61.6 (C_4), 33.5 (C_5), 24.9 (C_6); **IR** (neat) cm^{-1}: 3296, 2958, 1742, 1717, 1480, 1402, 1368, 1311, 1238, 1217, 1102, 1052, 1024, 986, 926, 805, 768, 714, 674; **HRMS** (ESI$^+$) m/z calc. for $C_7H_{14}NO_2$ $[M+H]^+$ 144.1019; found at 144.1014 Δ -3.51 ppm; **m.p.** = 92-94 °C. Spectroscopic data were consistent with the literature data for this compound.[194]

(*R*)-3-Acryloyl-4-(tert-butyl)oxazolidin-2-one (333):

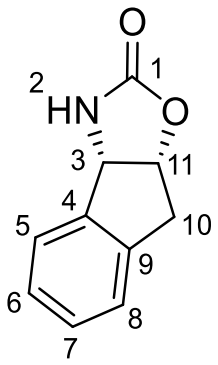


The title compound was prepared according to **General Procedure F** at the 1.5 mmol scale with (*R*)-4-(*tert*-butyl)oxazolidin-2-one **S333** (215 mg, 1.50 mmol, 1.00 equiv.) as the chiral auxiliary. Purification by flash column chromatography (20-40% EtOAc in pentane) afforded **333** as a colourless solid (21.9 mg, 7%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_H = 7.53 (1H, dd, *J* = 16.9, 10.4 Hz, H_8), 6.54 (1H, dd, *J* = 16.9, 1.8 Hz, H_9), 5.90 (1H, dd, *J* = 10.5, 1.8 Hz, H_9), 4.52 (1H, dd, *J* = 7.5, 1.8 Hz, H_4), 4.34 – 4.23 (2H, m, H_3), 0.95 (9H, s, H_6); **^{13}C NMR** (126 MHz, $CDCl_3$): δ_C = 165.4 (C_7), 154.7 (C_1), 131.9 (C_9), 127.6 (C_8), 65.5 (C_3), 61.1 (C_4), 36.1 (C_5), 25.8 (C_6); **IR** (neat) cm^{-1}: 1776, 1693, 1407, 1385, 1326, 1237, 1187, 1115, 1059, 970, 793, 762, 701; **HRMS** (ESI^+) m/z calc. for $C_{10}H_{16}NO_3$ $[M+H]^+$ 198.1125; found at 198.1118 Δ -3.38 ppm; **m.p.** = 35-36 °C; $[\alpha]_D^{20}$ = +82.4 (c = 0.01 gmL^{-1}, $CHCl_3$).

Stereochemistry of **333** was assigned by induction assuming retention from **S333**.

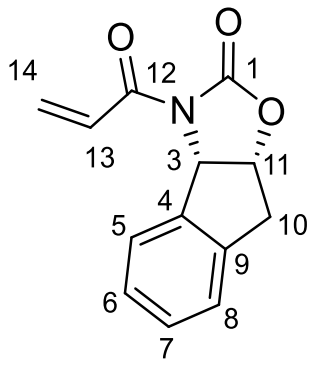
(3a*S*,8a*R*)-3,3a,8,8a-Tetrahydro-2H-indeno[1,2-d]oxazol-2-one (S334):



(1*S*, 2*R*)-*Cis*-1-amino-2-indanol (746 mg, 5.00 mmol, 1.00 equiv.) was dissolved in THF (50 mL) with CDI (811 mg, 5.00 mmol, 1.00 equiv.) and heated at reflux for 2 h. The reaction was cooled to r.t., diluted with EtOAc and sat. aq. Na_2CO_3, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc, then the combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (80-100% EtOAc in pentane) afforded **S334** as a colourless solid (592 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.35 – 7.27 (4H, m, H_5, H_6, H_7, H_8), 6.20 (1H, br s, H_2), 5.42 (1H, ddd, *J* = 8.1, 6.3, 2.1 Hz, H_{11}), 5.18 (1H, d, *J* = 7.3 Hz, H_3), 3.42 (1H, dd, *J* = 18.0, 6.2 Hz, H_{10}), 3.35 (1H, dd, *J* = 17.9, 2.0 Hz, H_{10}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 159.4 (C_1), 140.3 (C_4), 140.0 (C_9), 129.6 (C_7), 128.1 (C_6), 125.8 (C_8), 124.8 (C_5), 80.7 (C_{11}), 61.3 (C_3), 39.0 (C_{10}); **IR** (neat) cm^{-1}: 3522, 1743, 1705, 1394, 1233, 1204, 1182, 1107, 1081, 1052, 1034, 961, 751, 694; **HRMS** (ESI^+) m/z calc. for $C_{10}H_{10}NO_2$ $[M+H]^+$ 176.0706; found at 176.0709 Δ 1.67 ppm; **m.p.** = 175-176 °C. Spectroscopic data were consistent with the literature data for this compound.[195]

(3a*S*,8a*R*)-3-Acryloyl-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazol-2-one (334):

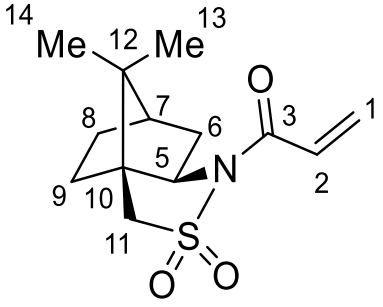


The title compound was prepared according to **General Procedure F** at the 3.38 mmol scale with (3a*S*,8a*R*)-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazol-2-one **S334** (592 mg, 3.38 mmol, 1.00 equiv.) as the chiral auxiliary. Purification by flash column chromatography (15-20% EtOAc in pentane) afforded **334** as an off white solid (280 mg, 36%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.68 (1H, d, *J* = 7.5 Hz, H_5), 7.51 (1H, dd, *J* = 17.0, 10.4 Hz, H_{13}), 7.35 (1H, t, *J* = 7.4 Hz, H_7), 7.32 – 7.23 (2H, m, H_6, H_8), 6.63 (1H, dd, *J* = 17.0, 1.8 Hz, H_{14}), 6.01 (1H, d, *J* = 6.9 Hz, H_3), 5.93 (1H, dd, *J* = 10.5, 1.8 Hz, H_{14}'), 5.32 (1H, ddd, *J* = 7.1, 4.4, 2.8 Hz, H_{11}), 3.47 – 3.35 (2H, m, H_{10}, H_{10}'); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 165.4 (C_{12}), 153.0 (C_1), 139.6 (C_9), 139.1 (C_4), 132.0 (C_{14}), 130.1 (C_7), 128.3 (C_6), 127.6 (C_{13}), 127.5 (C_5), 125.3 (C_8), 78.4 (C_{11}), 63.3 (C_3), 38.1 (C_{10}); **IR** (neat) cm^{-1}: 1776, 1686, 1407, 1362, 1325, 1274, 1252, 1187, 1126, 1089, 1064, 1042, 1004, 794, 756, 725, 690; **HRMS** (ESI^+) m/z calc. for $C_{13}H_{12}NO_3$ $[M+H]^+$ 230.0812; found at 230.0812 Δ 0.13 ppm; **m.p.** = 110-111 °C; $[\alpha]_D^{20}$ = +427 (c = 0.01 gmL^{-1}, $CHCl_3$). Spectroscopic data were consistent with the literature data for this compound.[196]

Stereochemistry of **334** was assigned by induction assuming retention from **S334**.

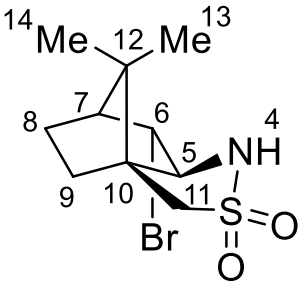
1-((3a*S*,6*R*,7a*R*)-8,8-Dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)prop-2-en-1-one (335):



The title compound was prepared according to **General Procedure F** at the 5.0 mmol scale with (1*S*)-(-)-2,10-camphorsultam (1.08 g, 5.00 mmol, 1.00 equiv.) as the chiral auxiliary. Purification by flash column chromatography (15-20% EtOAc in pentane) afforded **335** as an off white solid (581 mg, 43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 6.87 (1H, dd, *J* = 16.7, 10.4 Hz, H_2), 6.50 (1H, dd, *J* = 16.6, 1.5 Hz, H_1), 5.86 (1H, dd, *J* = 10.4, 1.6 Hz, H_1'), 3.94 (1H, dd, *J* = 7.6, 5.1 Hz, H_5), 3.52 (1H, d, *J* = 13.8 Hz, H_{11}), 3.45 (1H, d, *J* = 13.8 Hz, H_{11}'), 2.22 – 2.06 (2H, m, H_6, H_6'), 2.00 – 1.83 (3H, m, H_7, H_8, H_9), 1.48 – 1.32 (2H, m, H_8', H_9'), 1.18 (3H, s, $H_{13\text{ or }14}$), 0.98 (3H, s, $H_{13\text{ or }14}$); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 164.0 (C_3), 131.5 (C_1), 127.9 (C_2), 65.3 (C_5), 53.3 (C_{11}), 48.7 (C_{12}), 48.0 (C_{10}), 44.8 (C_7), 38.6 (C_6), 33.0 (C_9), 26.6 (C_8), 21.0 ($C_{13\text{ or }14}$), 20.0 ($C_{13\text{ or }14}$); **IR** (neat) cm^{-1}: 1674, 1415, 1330, 1317, 1280, 1280, 1239, 1224, 1166, 1133, 1115, 1061, 1034, 990, 978, 802, 771, 735; **HRMS** (ESI^+) m/z calc. for $C_{13}H_{20}NO_3S$ $[M+H]^+$ 270.1158; found at 270.1159 Δ 0.21 ppm; **m.p.** = 165-168 °C; $[\alpha]_D^{20}$ = -55.6 (c = 0.00493 gmL^{-1}, $CHCl_3$).

(3a*S*,6*S*,7*S*,7a*S*)-7-Bromo-8,8-dimethylhexahydro-3H-3a,6-methanobenzo[c]isothiazole 2,2-dioxide (S336):

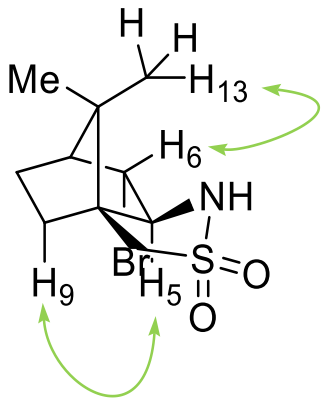


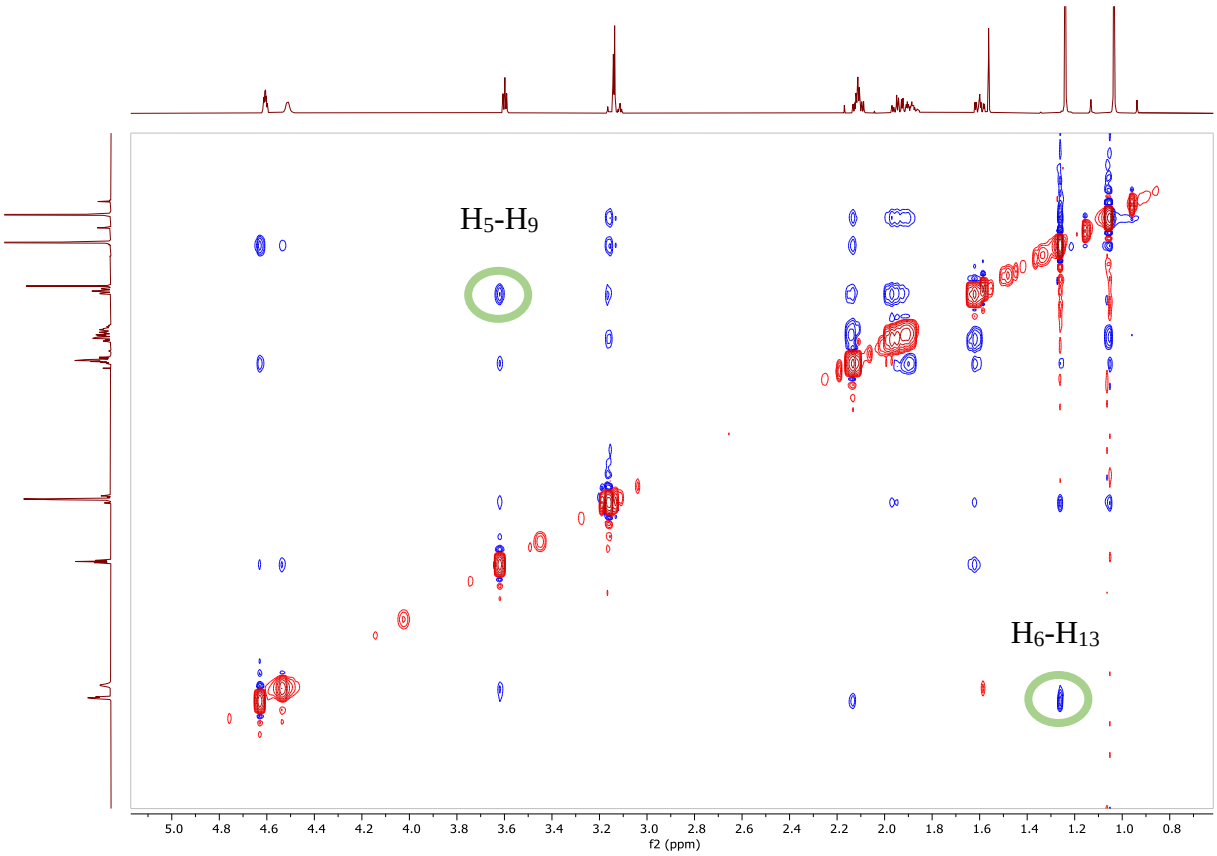
According to a literature procedure published by Chen and co-workers:[197] Camphorsulfonylimine (4.26 g, 20.0 mmol, 1.00 equiv.) was dissolved in anhydrous THF (140 mL) and cooled to 0 °C. NaHMDS (22 mL, 44 mmol, 2 M in THF, 2.2 equiv.) was added dropwise, then the mixture was stirred for 15 min. The solution was then transferred by cannula to a second flask at 0 °C containing NBS (9.0 g, 50 mmol, 2.5 equiv.) with vigorous stirring. The mixture was stirred for a further 1 h, quenched by dilution with H_2O and allowed to warm to r.t. after which it was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 then washed once with 2 M HCl, thrice with H_2O and once with brine. The organic phase was then dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*.

The residue was dissolved in anhydrous THF (40 mL) and added dropwise to a suspension of $LiAlH_4$ (760 mg, 20 mmol, 1.0 equiv.) in anhydrous THF (10 mL) under a nitrogen atmosphere. The suspension was refluxed overnight, then cooled to 0 °C and quenched by dropwise addition of 2M aq. HCl. The mixture was then diluted with EtOAc, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc, then the combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (15% EtOAc in pentane) afforded **S336** as a colourless solid as a single diastereomer (584 mg, 10%).

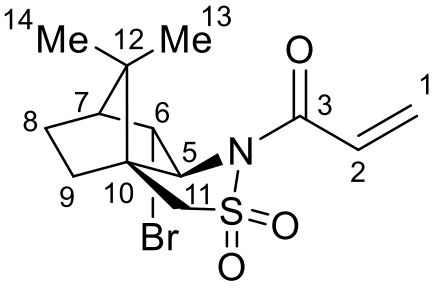
^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 4.61 (1H, td, *J* = 4.0, 2.2 Hz, H_6), 4.51 (1H, br s, H_4), 3.60 (1H, t, *J* = 4.6 Hz, H_5), 3.19 – 3.09 (2H, m, H_{11}, H_{11}'), 2.15 – 2.07 (2H, m, H_7, H_8), 1.95 (1H, td, *J* = 11.6, 4.4 Hz, H_9), 1.92 – 1.84 (1H, m, H_8), 1.60 (1H, ddd, *J* = 11.8, 9.2, 3.0 Hz, H_9), 1.24 (3H, s, H_{13}), 1.04 (3H, s, H_{14}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 72.0 (C_5), 55.8 (C_6), 54.3 (C_{10}), 52.6 (C_7), 50.0 (C_{11}), 47.9 (C_{12}), 32.5 (C_9), 22.6 (C_8), 21.2 (C_{14}), 20.4 (C_{13}); **IR** (neat) cm^{-1}: 3231, 2969, 1344, 1309, 1260, 1236, 1218, 1148, 1125, 1075, 913, 851, 810, 771, 743; **HRMS** (ESI^+) m/z calc. for $C_{10}H_{17}{}^{79}BrNO_2S$ $[M+H]^+$ 294.1058, found at 294.0154 Δ -1.39 ppm; **m.p.** = 120-121 °C.

Stereochemistry was assigned by NOESY, which showed correlations between H_5 and H_9, confirming the down stereochemistry of H_5, and between H_6 and H_{13}, confirming the up stereochemistry of H_6.





1-((3a*S*,6*S*,7*S*,7a*S*)-7-Bromo-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)prop-2-en-1-one (336):



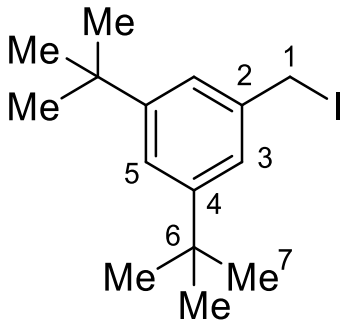
(3a*S*,6*S*,7*S*,7a*S*)-7-Bromo-8,8-dimethylhexahydro-3H-3a,6-methanobenzo[c]isothiazole 2,2-dioxide **S336** (584 mg, 1.99 mmol, 1.00 equiv.) was dissolved in PhMe (2.0 mL) with NaH (119 mg, 2.98 mmol, 1.50 equiv.) under a nitrogen atmosphere, and stirred at r.t. for 30 min. Acryloyl chloride (0.33 mL, 4.0 mmol, 2.0 equiv.) was added dropwise, then the mixture stirred for a further 2 h, after which it was cooled to 0 °C and quenched by dropwise addition of H_2O. The suspension was then diluted further with H_2O and EtOAc, shaken and the layers

partitioned. The aqueous layer was extracted twice more with EtOAc, then the combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (15-30% EtOAc in pentane) afforded **336** as a colourless solid as a single diastereomer (253 mg, 36%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 6.89 (1H, dd, *J* = 16.6, 10.4 Hz, H_1), 6.60 (1H, dd, *J* = 16.6, 1.5 Hz, H_2), 5.91 (1H, dd, *J* = 10.4, 1.5 Hz, H_2'), 4.73 (1H, td, *J* = 3.9, 2.2 Hz, H_6), 4.02 (1H, d, *J* = 3.8 Hz, H_5), 3.49 (1H, d, *J* = 13.8 Hz, H_{11}), 3.43 (1H, d, *J* = 13.9 Hz, H_{11}'), 2.29 (1H, ddd, *J* = 13.7, 9.3, 4.3 Hz, H_8), 2.15 (1H, t, *J* = 4.3 Hz, H_7), 1.98 (1H, td, *J* = 12.1, 4.4 Hz, H_9), 1.91 (1H, tddd, *J* = 12.0, 6.9, 3.9, 2.2 Hz, H_8'), 1.57 (1H, ddd, *J* = 12.5, 9.3, 3.8 Hz, H_9'), 1.24 (3H, s, H_{13}), 1.09 (3H, s, H_{14}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 164.0 (C_3), 132.5 (C_2), 127.4 (C_1), 73.9 (C_5), 56.3 (C_6), 52.9 (C_7), 52.3 (C_{11}), 49.9 (C_{12}), 48.0 (C_{10}), 32.6 (C_9), 23.0 (C_8), 20.8 (C_{13}), 20.8 (C_{14}); **IR** (neat) cm^{-1}: 2981, 1683, 1625, 1411, 1328, 1280, 1268, 1250, 1237, 1215, 1178, 1142, 1091, 1058, 1046, 978, 932, 913, 856, 816, 785, 739; **HRMS** (ESI^+) m/z calc. for $C_{13}H_{19}{}^{79}BrNO_3S$ $[M+H]^+$ 348.0264; found at 348.0247 Δ -4.75 ppm; **m.p.** = 164-166 °C; α_D not recorded due to product decomposition.

Stereochemistry of **336** was assigned by induction assuming retention from **S336**.

1,3-Di-tert-butyl-5-(iodomethyl)benzene (S343):

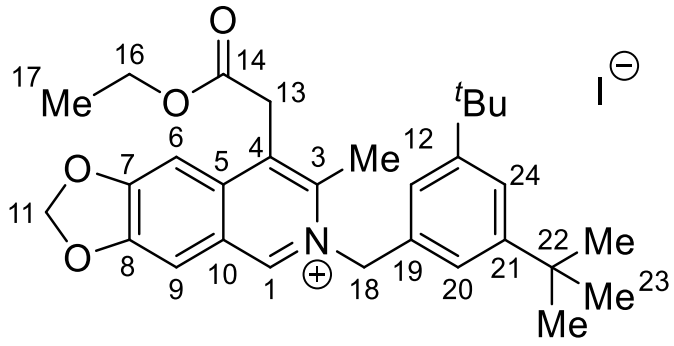


Di-*tert*-butyl benzyl bromide (1.13 g, 4.00 mmol, 1.00 equiv.) was dissolved in acetone (20 mL) with NaI (1.2 g, 8.0 mmol, 2.0 equiv.) and stirred for 18 h in the dark. The mixture

was then diluted with EtOAc and H_2O, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc, then the combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo* to afford S**343** as an orange solid (1.09 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.31 (1H, t, *J* = 1.9 Hz, H_5), 7.22 (2H, d, *J* = 1.8 Hz, H_3), 4.48 (2H, s, H_1), 1.32 (18H, s, H_7); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 151.4 (C_4), 138.3 (C_2), 123.2 (C_3), 122.3 (C_5), 35.0 (C_6), 31.5 (C_7), 7.5 (C_1); **IR** (neat) cm^{-1}: 2963, 1699, 1598, 1477, 1393, 1363, 1249, 1203, 1159, 900, 875, 707; **HRMS** (ESI$^+$) m/z calc. for $C_{15}H_{24}I$ $[M+H]^+$ 330.0844, molecule could not be observed by ESI MS; **m.p.** = 34 °C. Spectroscopic data were consistent with the literature data for this compound.[198]

6-(3,5-Di-tert-butylbenzyl)-8-(2-ethoxy-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide (343):

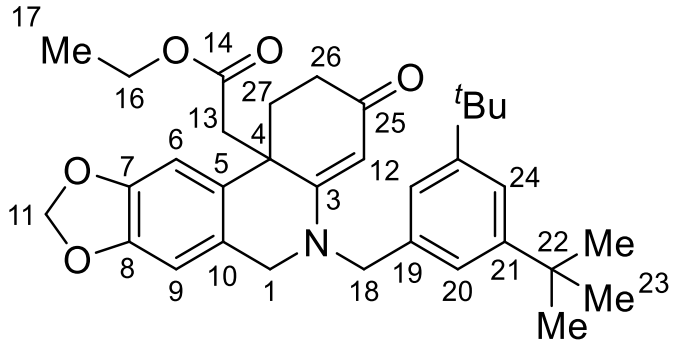


The title compound was synthesised according to **General Procedure G** with 1,3-di-tert-butyl-5-(iodomethyl)benzene **S343** (1.09 g, 3.30 mmol, 1.65 equiv.) to afford **343** as a pale-brown solid (654 mg, 54%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 10.58 (1H, s, H_1), 7.92 (1H, s, H_9), 7.38 (1H, t, *J* = 1.8 Hz, H_{24}), 7.37 (1H, s, H_6), 6.98 (2H, d, *J* = 1.7 Hz, H_{20}), 6.29 (2H, s, H_{11}), 6.13 (2H, s, H_{18}), 4.16 (2H, q, *J* = 7.1 Hz, H_{16}), 4.07 (2H, s, H_{13}), 2.78 (3H, s, H_{12}), 1.24 (18H, s, H_{23}), 1.25 – 1.20 (3H, m, H_{17}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 168.7 (C_{14}), 157.7 (C_7), 152.5 (C_{21}), 150.8

(C_8), 147.4 (C_1), 142.6 (C_3), 138.5 (C_5), 132.0 (C_{19}), 128.0 (C_4), 124.6 (C_{10}), 123.2 (C_{24}), 121.3 (C_{20}), 106.2 (C_9), 103.9 (C_{11}), 100.3 (C_6), 62.8 (C_{18}), 62.2 (C_{16}), 35.4 (C_{22}), 35.1 (C_{13}), 31.5 (C_{23}), 17.3 (C_{12}), 14.3 (C_{17}); **IR** (neat) cm^{-1}: 2965, 1733, 1465, 1289, 1250, 1214, 1033, 917, 731; **HRMS** (ESI^+) m/z calc. for $C_{30}H_{38}NO_4$ $[M]^+$ 476.2795; found at 476.2809 Δ 2.87 ppm; **m.p.** = 106-108 °C

(*RS*)-Ethyl 2-(5-(3,5-di-tert-butylbenzyl)-3-oxo-2,3,5,6-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate (346):

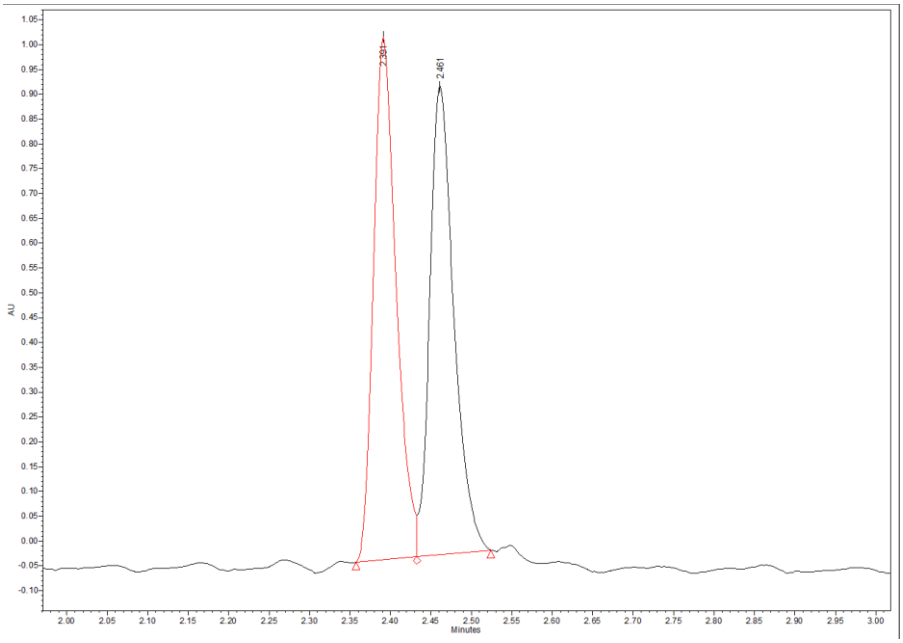


The title compound was synthesised according to **General Procedure I** with 6-(3,5-di-tert-butylbenzyl)-8-(2-ethoxy-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **343** (151 mg, 0.25 mmol, 1.0 equiv.). Purification by flash column chromatography (3-5% EtOH in EtOAc) afforded **346** as a colourless solid (95 mg, 72%).

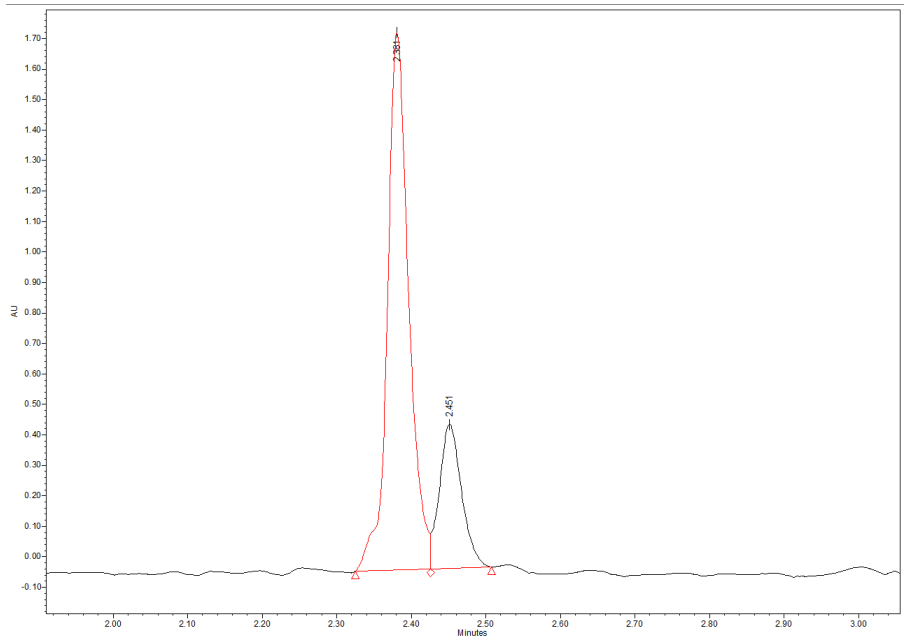
The title compound was synthesised according to **General Procedure J** with 6-(3,5-di-tert-butylbenzyl)-8-(2-ethoxy-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **343** (151 mg, 0.25 mmol, 1.0 equiv.) Purification by flash column chromatography (3-5% EtOH in EtOAc) afforded **346** as a colourless solid (95 mg, 72%, 78:22 e.r.).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.30 (1H, d, *J* = 1.8 Hz, H_{24}), 6.91 (1H, s, H_6), 6.88 (2H, d, *J* = 1.8 Hz, H_{20}), 6.56 (1H, s, H_9), 5.97 (1H, d, *J* = 1.5 Hz, H_{11}), 5.95 (1H, d, *J* = 1.5 Hz, H_{11}'), 5.34 (1H, s, H_{12}), 4.69 – 4.55 (3H, m, H_1, H_{18}, H_{18}'), 4.24 (1H, d, *J* = 16.3 Hz, H_1'), 3.95 (2H, q, *J* = 7.1 Hz, H_{16}), 3.02 (1H, ddd, *J* = 13.2, 5.0, 2.3 Hz, H_{27}), 2.82 (1H, d, *J* = 13.6 Hz, H_{13}),

2.75 – 2.64 (2H, m, H_{13}', H_{26}), 2.53 (1H, ddd, J = 17.8, 4.9, 2.3 Hz, H_{26}'), 2.25 – 2.17 (1H, m, H_{27}'), 1.23 (18H, s, H_{23}), 1.08 (3H, t, J = 7.2 Hz, H_{17}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 195.4 (C_{25}), 169.5 (C_{14}), 165.6 (C_3), 151.7 (C_{21}), 147.8 (C_7), 146.9 (C_8), 133.7 (C_{19}), 130.6 (C_5), 125.9 (C_{10}), 121.8 (C_{24}), 120.5 (C_{20}), 106.3 (C_6), 105.6 (C_9), 101.5 (C_{11}), 98.3 (C_{12}), 60.8 (C_{16}), 56.1 (C_{18}), 52.3 (C_1), 40.9 (C_4), 38.9 (C_{13}), 34.9 (C_{22}), 32.2 (C_{26}), 31.5 (C_{23}), 30.2 (C_{27}), 14.2 (C_{17}); **IR** (neat) cm^{-1}: 2964, 1730, 1603, 1556, 1487, 1325, 1247, 1150, 1038, 927, 813, 732; **HRMS** (ESI^+) m/z calc. for $C_{33}H_{42}NO_5$ $[M+H]^+$ 532.3058; found at 532.3056 Δ -0.28 ppm; **m.p.** = 147-148 °C; **SFC** Chiralpak IA; 1500 psi; 30 °C; flow 1.5 mL/min; from 0% to 50% ^{i}PrOH in 7 min; 56% e.e. (major enantiomer t_R = 2.39 min; minor enantiomer t_R = 2.46 min); $[\alpha]_D^{20}$ = -2.60 (c = 0.01 gmL^{-1}, $CHCl_3$).

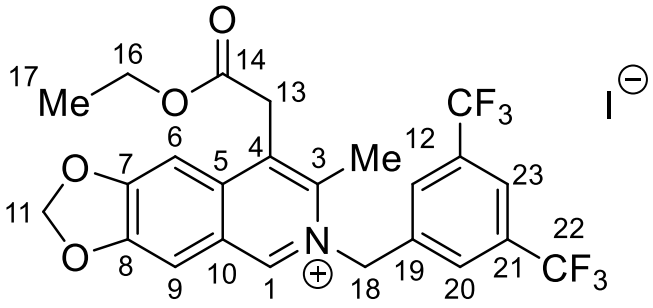


Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area
2.391							2044428	51.25
2.461							1945086	48.75



Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (μV*sec)	% Area
2.381							3507231	78.17
2.451							979389	21.83

6-(3,5-Bis(trifluoromethyl)benzyl)-8-(2-ethoxy-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide (344):

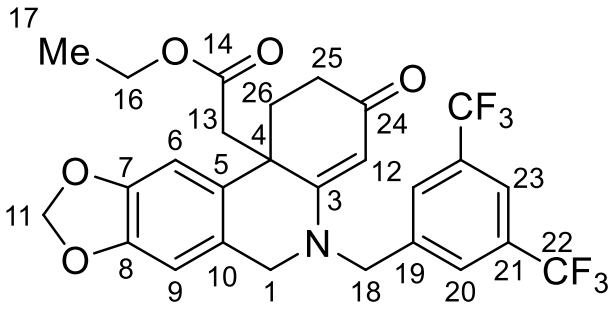


The title compound was synthesised according to **General Procedure G** with 1-(iodomethyl)-3,5-bis(trifluoromethyl)benzene (1.06 g, 3.00 mmol, 1.50 equiv.) to afford **344** as a pale-brown solid (168 mg, 13%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 10.80 (1H, s, H_1), 7.89 (1H, s, H_{23}), 7.85 (1H, s, H_9), 7.63 (2H, s, H_{20}), 7.43 (1H, s, H_6), 6.57 (2H, s, H_{18}), 6.34 (2H, s, H_{11}), 4.18 (2H, q, J = 7.2 Hz, H_{16}),

4.10 (2H, s, H_{13}), 2.74 (3H, s, H_{12}), 1.23 (3H, t, J = 7.1 Hz, H_{17}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 168.4 (C_{14}), 158.4 (C_7), 151.4 (C_8), 148.4 (C_1), 142.1 (C_3), 139.0 (C_5), 136.2 (C_{19}), 133.1 (q, J = 34.1 Hz, C_{21}), 128.8 (C_4), 127.1 (d, J = 4.0 Hz, C_{20}), 125.1 (C_{10}), 123.5 – 123.2 (m, C_{23}), 121.9 (q, J = 273.6 Hz, C_{22}), 106.5 (C_9), 104.1 (C_{11}), 100.6 (C_6), 62.4 (C_{16}), 61.2 (C_{18}), 35.6 (C_{13}), 17.5 (C_{12}), 14.2 (C_{17}); **^{19}F NMR** (565 MHz, $CDCl_3$): δ_F = -62.86; **IR** (neat) cm^{-1}: 1731, 1617, 1467, 1379, 1281, 1217, 1176, 1136, 1034, 934; **HRMS** (ESI^+) m/z calc. for $C_{24}H_{20}F_6NO_4$ $[M]^+$ 500.1291; found at 500.1273 Δ -3.61 ppm; **m.p.** = 174-176 °C.

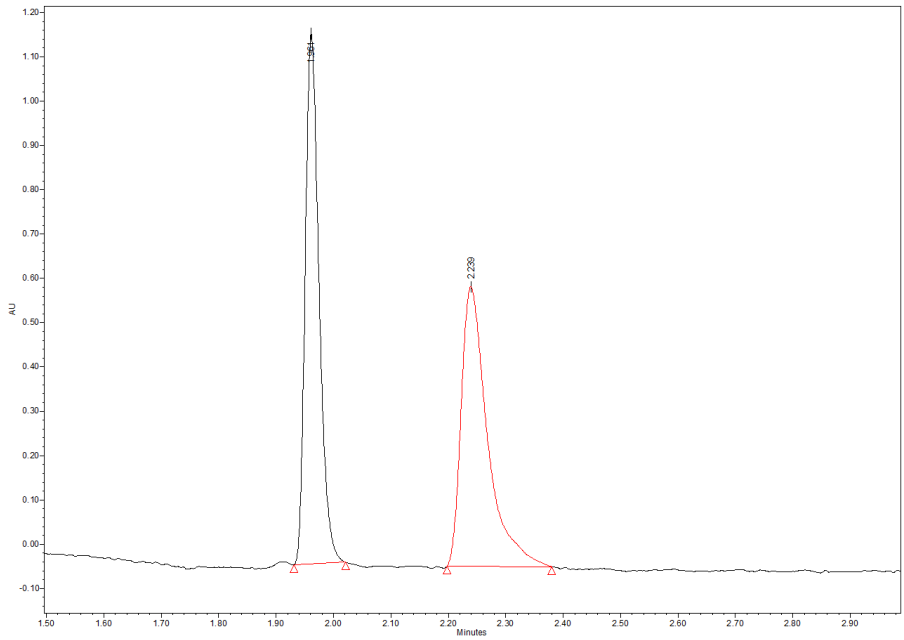
(*RS*)-Ethyl 2-(5-(3,5-bis(trifluoromethyl)benzyl)-3-oxo-2,3,5,6-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate (347):



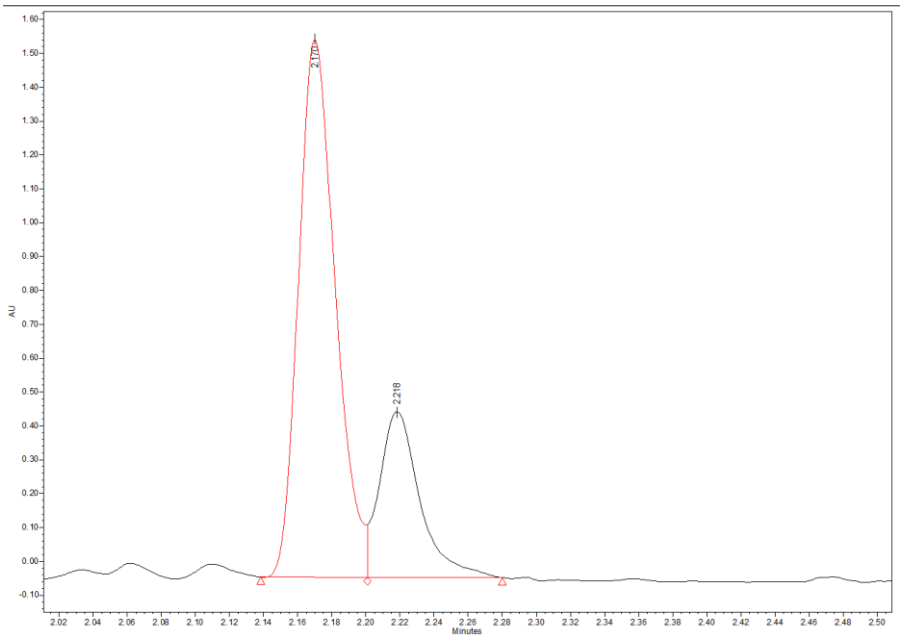
The title compound was synthesised according to **General Procedure I** with 6-(3,5-bis(trifluoromethyl)benzyl)-8-(2-ethoxy-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **344** (63 mg, 0.10 mmol, 1.0 equiv.). Purification by flash column chromatography (3-5% EtOH in EtOAc) afforded **347** as an orange oil (39 mg, 69%).

The title compound was synthesised according to **General Procedure J** with 6-(3,5-bis(trifluoromethyl)benzyl)-8-(2-ethoxy-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **344** (63 mg, 0.10 mmol, 1.0 equiv.). Purification by flash column chromatography (3-5% EtOH in EtOAc) afforded **347** as an orange oil (11 mg, 20%, 75:25 e.r.).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.78 (1H, s, H_{23}), 7.54 (2H, d, *J* = 1.7 Hz, H_{20}), 6.90 (1H, s, H_6), 6.57 (1H, s, H_9), 5.98 (1H, d, *J* = 1.4 Hz, H_{11}), 5.96 (1H, d, *J* = 1.4 Hz, H_{11}'), 5.12 (1H, s, H_{12}), 4.77 (1H, d, *J* = 15.9 Hz, H_1), 4.71 (2H, s, H_{18}), 4.21 (1H, d, *J* = 16.0 Hz, H_1'), 3.95 (2H, qd, *J* = 7.1, 1.1 Hz, H_{16}), 2.99 (1H, ddd, *J* = 13.3, 5.1, 2.3 Hz, H_{26}), 2.79 (1H, d, *J* = 13.6 Hz, H_{13}), 2.71 (1H, dd, *J* = 13.7, 1.2 Hz, H_{13}'), 2.66 (1H, ddd, *J* = 17.9, 14.1, 5.0 Hz, H_{25}), 2.51 (1H, ddd, *J* = 18.0, 5.0, 2.3 Hz, H_{25}'), 2.28 – 2.18 (1H, m, H_{26}'), 1.07 (3H, t, *J* = 7.2 Hz, H_{17}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 195.8 (C_{24}), 169.4 (C_{14}), 165.0 (C_3), 148.1 (C_7), 147.1 (C_8), 138.1 (C_{19}), 132.6 (q, *J* = 33.5 Hz, C_{21}), 130.2 (C_5), 126.4 (t, *J* = 3.8 Hz, C_{20}), 124.9 (C_{10}), 123.1 (q, *J* = 272.8 Hz, C_{22}), 122.0 (q, *J* = 3.8 Hz, C_{23}), 106.2 (C_6), 105.6 (C_9), 101.6 (C_{11}), 99.0 (C_{12}), 60.9 (C_{16}), 55.3 (C_{18}), 52.7 (C_1), 40.8 (C_4), 39.9 (C_{13}), 32.4 (C_{25}), 30.5 (C_{26}), 14.1 (C_{17}); **^{19}F NMR** (565 MHz, $CDCl_3$): δ_F = -62.95; **IR** (neat) cm^{-1}: 1729, 1619, 1558, 1488, 1377, 1327, 1279, 1247, 1173, 1133, 1039, 732, 683; **HRMS** (ESI^+) m/z calc. for $C_{27}H_{24}F_6NO_5$ $[M]^+$ 556.1553; found at 556.1551 Δ -0.39 ppm; **SFC** Chiralpak IA; 1500 psi; 30 °C; flow 1.5 mL/min; from 0% to 50% ^{i}PrOH in 7 min; 50% e.e. (major enantiomer t_R = 1.96 min; minor enantiomer t_R = 2.23 min); $[\alpha]_D^{20}$ = -29.8 (c = 0.01 gmL^{-1}, $CHCl_3$).

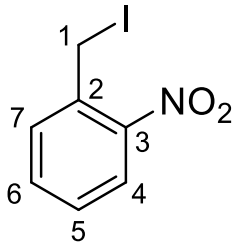


Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area
1.961							2001429	49.97
2.239							2003535	50.03



Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area
2.170							2383480	74.82
2.218							802187	25.18

1-(Iodomethyl)-2-nitrobenzene (S345):

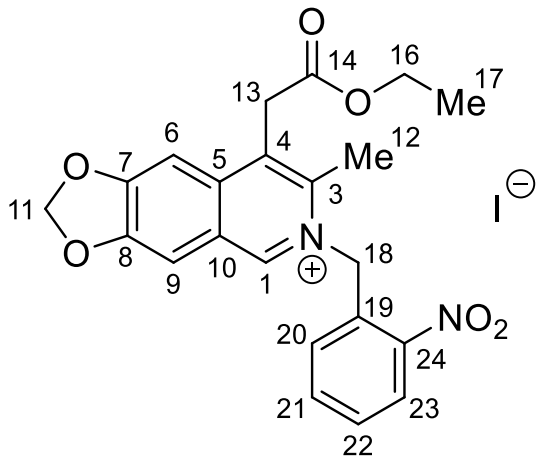


2-Nitrobenzyl bromide (864 mg, 4.00 mmol, 1.00 equiv.) was dissolved in acetone (20 mL) with NaI (1.2 g, 8.0 mmol, 2.0 equiv.) and stirred for 18 h in the dark. The mixture was then diluted with EtOAc and H_2O, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc, then the combined organic layers were dried over $MgSO_4$,

filtered under gravity and concentrated *in vacuo* to afford **S345** as a brown solid (932 mg, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 8.04 (1H, dd, *J* = 8.1, 1.4 Hz, H_4), 7.57 (1H, dd, *J* = 7.6, 1.3 Hz, H_6), 7.52 (1H, td, *J* = 8.2, 1.5 Hz, H_7), 7.44 (1H, ddd, *J* = 8.6, 7.1, 1.7 Hz, H_5), 4.79 (2H, s, H_1); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 147.6 (C_3), 135.1 (C_2), 133.9 (C_6), 132.4 (C_7), 129.2 (C_5), 125.9 (C_4), -0.1 (C_1); **IR** (neat) cm^{-1}: 1520, 133, 1169, 867, 793, 748, 696. Spectroscopic data were consistent with the literature data for this compound.[199]

8-(2-Ethoxy-2-oxoethyl)-7-methyl-6-(2-nitrobenzyl)-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide (345):

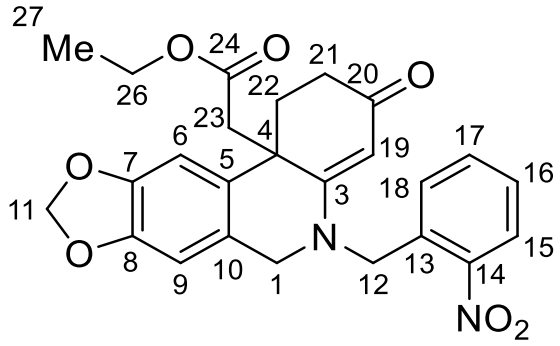


The title compound was synthesised according to **General Procedure G** with 1-(iodomethyl)-2-nitrobenzene **S345** (932 mg, 3.54 mmol, 1.77 equiv.) to afford **345** as a yellow solid (383 mg, 36%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 10.11 (1H, s, H_1), 8.26 – 8.17 (1H, m, H_{23}), 7.74 (1H, s, H_9), 7.72 (1H, td, *J* = 7.6, 1.4 Hz, H_{21}), 7.64 – 7.60 (1H, m, H_{22}), 7.41 (1H, s, H_6), 7.28 – 7.25 (1H, m, H_{20}), 6.52 (2H, s, H_{18}, H_{18}'), 6.30 (2H, s, H_{11}), 4.39 – 4.01 (4H, m, H_{13}, H_{13}', H_{16}), 2.79 (3H, s, H_{12}), 1.30 – 1.23 (3H, m, H_{17}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 168.8 (C_{14}), 158.0 (C_7), 151.0 (C_8), 147.1 (C_{19}), 146.4 (C_1), 142.7 (C_3), 138.9 (C_5), 135.7 (C_{21}), 130.8 (C_{22}), 130.6

(C_{20}), 128.6 (C_4), 128.2 (C_{24}), 126.4 (C_{23}), 124.8 (C_{10}), 106.0 (C_9), 104.1 (C_{11}), 100.6 (C_6), 62.3 (C_{16}), 58.9 (C_{18}), 35.8 (C_{13}), 17.4 (C_{12}), 14.3 (C_{17}); **IR** (neat) cm^{-1}: 1731, 1614, 1530, 1466, 1341, 1218, 1033, 731; **HRMS** (ESI^+) m/z calc. for $C_{22}H_{21}N_2O_6$ $[M]^+$ 409.1394; found at 409.1397 Δ 0.70 ppm; **m.p.** = 138-140 °C.

(*RS*)-Ethyl 2-(5-(2-nitrobenzyl)-3-oxo-2,3,5,6-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate (348):

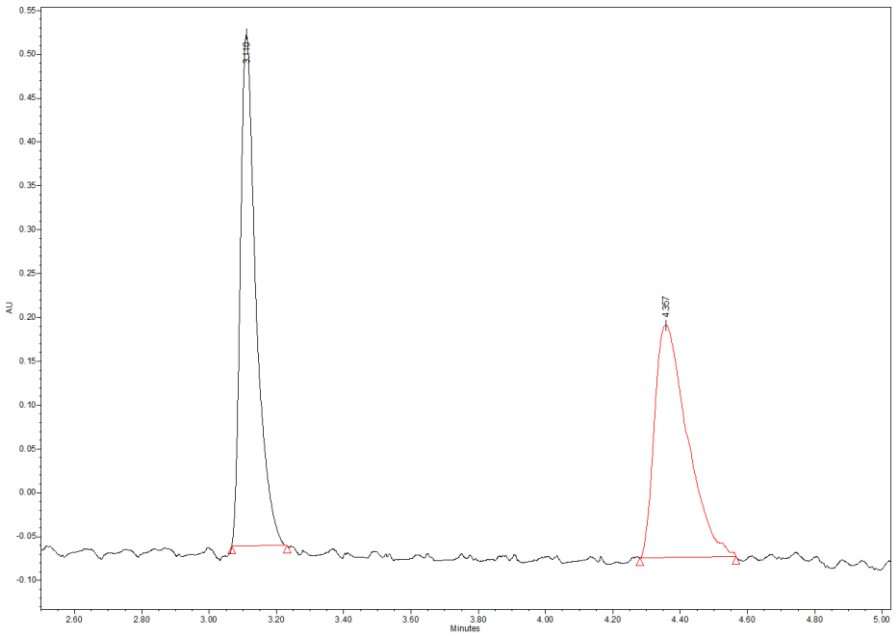


The title compound was synthesised according to **General Procedure I** with 8-(2-ethoxy-2-oxoethyl)-7-methyl-6-(2-nitrobenzyl)-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **345** (54 mg, 0.10 mmol, 1.0 equiv.). Purification by flash column chromatography (0-5% EtOH in EtOAc) afforded **348** as an orange oil (27 mg, 53%).

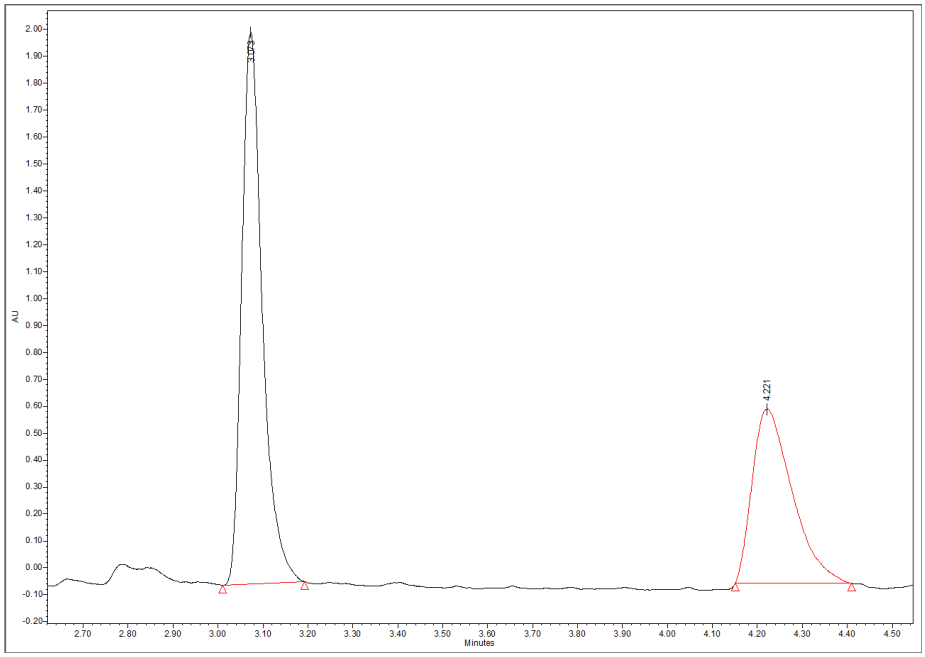
The title compound was synthesised according to **General Procedure J** with 6-benzyl-8-(2-(benzyloxy)-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **345** (54 mg, 0.10 mmol, 1.0 equiv.). Purification by flash column chromatography (0-5% EtOH in EtOAc) afforded **348** as an orange oil (9.5 mg, 20%, 62:38 er).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.19 (1H, dd, *J* = 8.2, 1.3 Hz, H_{15}), 7.51 (1H, td, *J* = 7.5, 1.4 Hz, H_{17}), 7.44 (1H, td, *J* = 7.7, 1.3 Hz, H_{16}), 7.00 (1H, dd, *J* = 7.7, 1.4 Hz, H_{18}), 6.92 (1H, s, H_6), 6.58 (1H, s, H_9), 5.98 (1H, d, *J* = 1.4 Hz, H_{11}), 5.96 (1H, d, *J* = 1.4 Hz, H_{11}'), 5.06 (1H, d, *J* = 18.4 Hz, H_{12}), 4.96 (1H, s, H_{19}), 4.93 (1H, d, *J* = 18.5 Hz, H_{12}'), 4.78 (1H, d, *J* = 16.1 Hz, H_1), 4.22 (1H, d, *J* = 16.3 Hz, H_1'), 3.95 (2H, q, *J* = 7.1 Hz, H_{26}), 3.02 (1H, ddd, *J* = 13.4, 5.0,

2.3 Hz, H_{22}), 2.82 (1H, d, *J* = 13.5 Hz, H_{23}), 2.72 (1H, dd, *J* = 13.6, 1.3 Hz, H_{23}'), 2.64 (1H, ddd, *J* = 17.4, 14.0, 4.7 Hz, H_{21}), 2.48 (1H, ddd, *J* = 17.8, 5.0, 2.7 Hz, H_{21}'), 2.26 – 2.18 (1H, m, H_{22}'), 1.08 (3H, t, *J* = 7.2 Hz, H_{27}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 195.7 (C_{20}), 169.4 (C_{24}), 165.0 (C_3), 148.0 (C_7), 147.7 (C_{14}), 147.0 (C_8), 134.6 (C_{17}), 131.0 (C_{13}), 130.6 (C_5), 128.7 (C_{16}), 127.2 (C_{18}), 126.2 (C_{15}), 125.1 (C_{10}), 106.2 (C_6), 105.7 (C_9), 101.6 (C_{11}), 99.0 (C_{19}), 60.9 (C_{26}), 54.9 (C_{12}), 52.3 (C_1), 40.8 (C_4), 39.4 (C_{23}), 32.4 (C_{21}), 30.2 (C_{22}), 14.1 (C_{27}); **IR** (neat) cm^{-1}: 1727, 1615, 1559, 1525, 1487, 1328, 1248, 1115, 1038, 728; **HRMS** (ESI^+) m/z calc. for $C_{25}H_{25}N_2O_7$ $[M+H]^+$ 465.1656; found at 465.1655 Δ -0.28 ppm; **SFC** Chiralpak IA; 1500 psi; 30 °C; flow 1.5 mL/min; from 0% to 50% ^{i}PrOH in 7 min; 24% e.e. (major enantiomer t_R = 3.11 min; minor enantiomer t_R = 4.36 min); $[\alpha]_D^{20}$ = -15.7 (c = 0.00280 gmL^{-1}, $CHCl_3$).

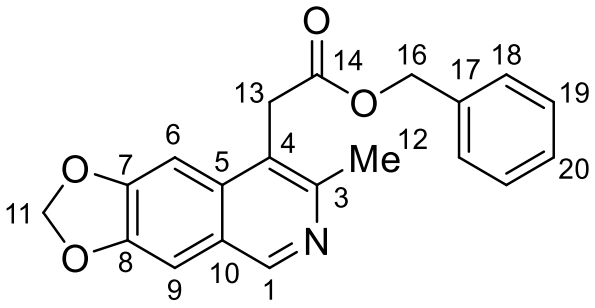


Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area
3.110							1889060	51.33
4.357							1791491	48.67



Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (μV*sec)	% Area
3.073							6543406	62.05
4.221							4002044	37.95

Benzyl 2-(7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate (S337):

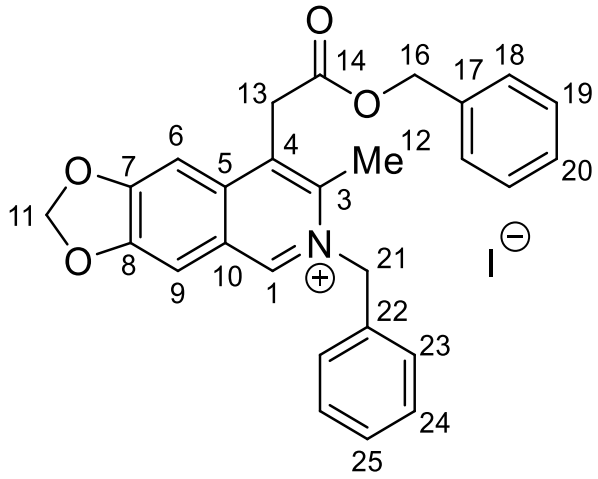


The title compound was synthesised according to **General Procedure H** with benzyl alcohol (2.1 ml, 20 mmol, 10 equiv.). Purification by flash column chromatography (80-100% EtOAc in pentane) afforded S**337** as a pale brown solid (119 mg, 18%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.85 (1H, s, H_1), 7.34 – 7.29 (3H, m, H_{19}, H_{20}), 7.27 – 7.25 (2H, m, H_{18}), 7.24 (1H, s, H_6), 7.17 (1H, s, H_9), 6.10 (2H, s, H_{11}), 5.13 (2H, s, H_{16}), 4.01 (2H, s, H_{13}), 2.71 (3H, s, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 170.6 (C_{14}), 152.2 (C_8), 149.3

(C_3), 148.4 (C_1), 147.9 (C_7), 135.7 (C_{17}), 134.7 (C_5), 128.7 (C_{19}), 128.5 (C_{20}), 128.2 (C_{18}), 124.7 (C_{10}), 121.4 (C_4), 103.7 (C_9), 101.9 (C_{11}), 99.6 (C_6), 67.1 (C_{16}), 34.8 (C_{13}), 22.3 (C_{12}); **IR** (neat) cm^{-1}: 1731, 1495, 1465, 1254, 1230, 1154, 1038, 943, 838, 739, 700; **HRMS** (ESI^+) m/z calc. for $C_{20}H_{18}NO_4$ $[M+H]^+$ 336.1230; found at 336.1226 Δ -1.30 ppm; **m.p.** = 100-101 °C.

6-Benzyl-8-(2-(benzyloxy)-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide (337):

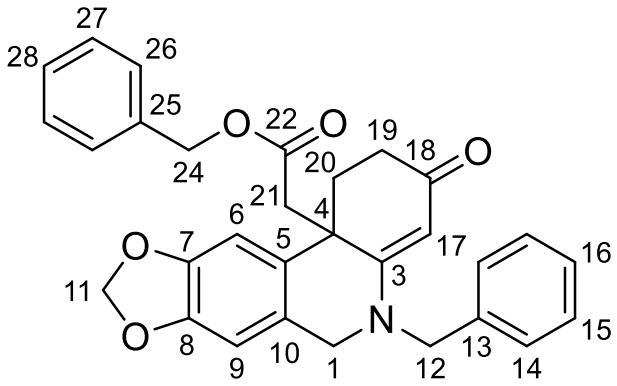


The title compound was synthesised according to **General Procedure E** with benzyl 2-(7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate **S337** (119 mg, 0.360 mmol, 1.00 equiv.) to afford **337** as a pale brown solid (121 mg, 61%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 10.58 (1H, s, H_1), 7.90 (1H, s, H_9), 7.39 – 7.29 (7H, m, H_6, H_{19}, H_{20}, H_{24}, H_{25}), 7.25 – 7.22 (2H, m, H_{18}), 7.22 – 7.16 (2H, m, H_{23}), 6.29 (2H, s, H_{11}), 6.16 (2H, s, H_{21}), 5.13 (2H, s, H_{16}), 4.10 (2H, s, H_{13}), 2.71 (3H, s, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 168.5 (C_{14}), 157.8 (C_7), 150.9 (C_8), 147.8 (C_1), 142.5 (C_3), 138.5 (C_5), 135.0 (C_{17}), 132.8 (C_{22}), 129.7 (C_{24}), 129.3 (C_{25}), 128.9 (2C, C_{19}, C_{20}), 128.6 (C_{18}), 128.0 (C_4), 127.4 (C_{23}), 124.8 (C_{10}), 106.3 (C_9), 103.9 (C_{11}), 100.3 (C_6), 68.0 (C_{16}), 62.3 (C_{21}), 35.5 (C_{13}), 17.3 (C_{12}); **IR** (neat) cm^{-1}: 1733, 1616, 1496, 1465, 1290, 1217, 1034, 935, 733, 701, 649, 627;

HRMS (ESI$^+$) m/z calc. for $C_{27}H_{24}NO_4$ $[M]^+$ 426.1700; found at 426.1704 Δ 0.97 ppm; **m.p.** = 164-165 °C.

(*RS*)-Benzyl 2-(5-benzyl-3-oxo-2,3,5,6-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate (340):

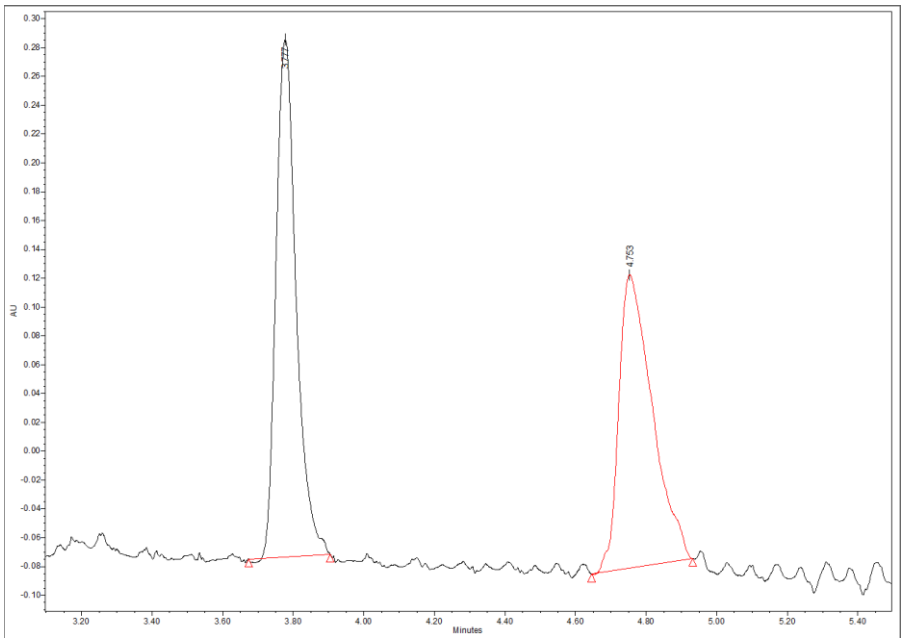


The title compound was synthesised according to **General Procedure I** with 6-benzyl-8-(2-(benzyloxy)-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **337** (55 mg, 0.10 mmol, 1.0 equiv.). Purification by flash column chromatography (0-5% EtOH in EtOAc) afforded **340** as an orange oil (44 mg, 91%).

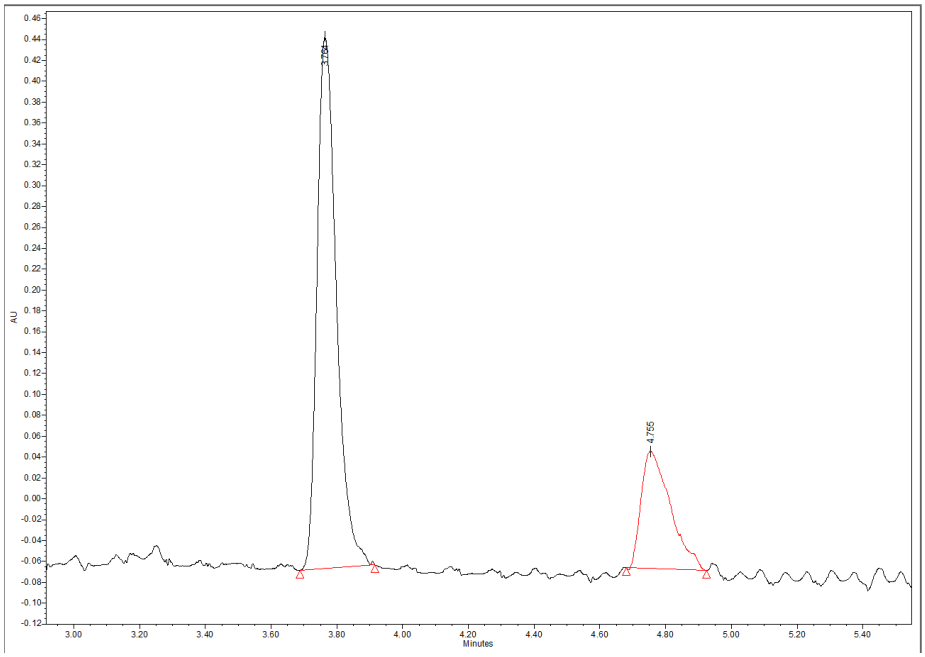
The title compound was synthesised according to **General Procedure J** with 6-benzyl-8-(2-(benzyloxy)-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **337** (55 mg, 0.10 mmol, 1.0 equiv.). Purification by flash column chromatography (0-5% EtOH in EtOAc) afforded **340** as an orange oil (14 mg, 30%, 75:25 e.r.).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.32 – 7.29 (3H, m, H_{27}, H_{28}), 7.29 – 7.26 (2H, m, H_{15}), 7.26 – 7.21 (1H, m, H_{16}), 7.16 – 7.10 (2H, m, H_{26}), 7.09 – 7.05 (2H, m, H_{14}), 6.80 (1H, s, H_6), 6.52 (1H, s, H_9), 5.93 (1H, t, *J* = 1.7 Hz, H_{11}), 5.90 (1H, t, *J* = 1.7 Hz, H_{11}'), 5.27 (1H, s, H_{17}), 4.96 – 4.85 (2H, m, H_{24}), 4.61 (1H, d, *J* = 16.2 Hz, H_1), 4.58 – 4.50 (2H, m, H_{12}), 4.21 (1H, d, *J* = 16.3 Hz, H_1'), 2.95 (1H, ddd, *J* = 13.4, 5.0, 2.3 Hz, H_{20}), 2.85 (1H, d, *J* = 13.6 Hz, H_{21}), 2.72 (1H, dd, *J* = 13.5, 1.3 Hz, H_{21}'), 2.65 (1H, ddd, *J* = 18.5, 14.1, 4.9 Hz, H_{19}), 2.47 (1H, ddd,

J = 17.8, 5.1, 2.2 Hz, H_{19}'), 2.20 – 2.11 (1H, m, H_{20}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 195.4 (C_{18}), 169.2 (C_{22}), 165.1 (C_3), 147.8 (C_7), 146.9 (C_8), 135.3 (C_{25}), 134.9 (C_{13}), 130.3 (C_5), 129.1 (C_{15}), 128.6 (C_{27}), 128.4 (C_{28}), 128.3 (C_{26}), 127.8 (C_{16}), 126.5 (C_{14}), 125.4 (C_{10}), 106.0 (C_6), 105.6 (C_9), 101.4 (C_{11}), 98.4 (C_{17}), 66.6 (C_{24}), 55.7 (C_{12}), 52.0 (C_1), 40.8 (C_4), 39.2 (C_{21}), 32.3 (C_{19}), 30.0 (C_{20}); **IR** (neat) cm^{-1}: 1730, 1613, 1556, 1487, 1326, 1245, 1148, 1039, 730, 697; **HRMS** (ESI^+) m/z calc. for $C_{30}H_{28}NO_5$ $[M+H]^+$ 482.1962; found at 482.1961 Δ -0.21 ppm; **SFC** Chiralpak IA; 1500 psi; 30 °C; flow 1.5 mL/min; from 0% to 50% ^{i}PrOH in 7 min; 50% e.e. (major enantiomer t_R = 3.78 min; minor enantiomer t_R = 4.75 min); $[\alpha]_D^{20}$ = -65.5 (c = 0.00586 gmL^{-1}, $CHCl_3$).

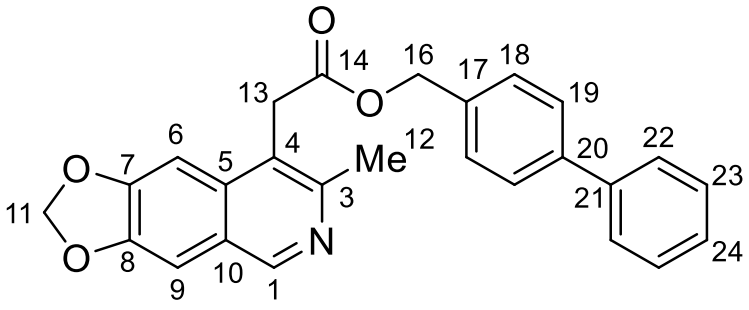


Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area
3.777							1428099	51.60
4.753							1339760	48.40



Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area
3.764							2081917	74.96
4.755							695446	25.04

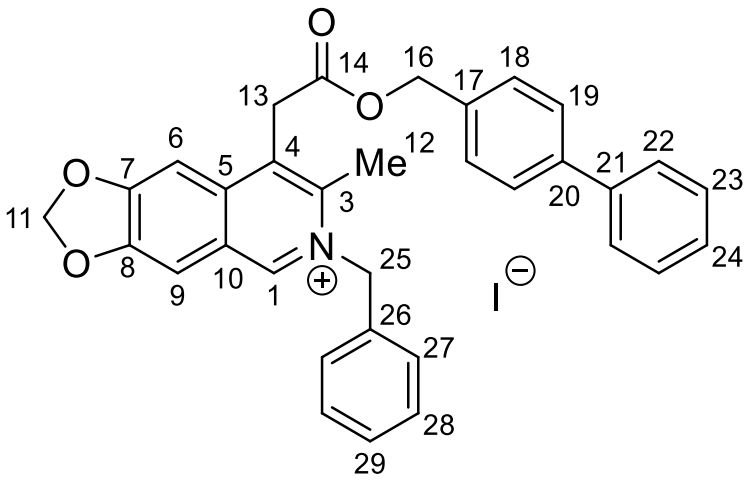
Ethyl 2-(5-(2-nitrobenzyl)-3-oxo-2,3,5,6-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-[1,1'-Biphenyl]-4-ylmethyl 2-(7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate (S338):



The title compound was synthesised according to **General Procedure H** with biphenyl-4-methanol (3.7 g, 20 mmol, 10 equiv.). Purification by flash column chromatography (40-80% EtOAc in pentane) afforded **S338** as a colourless solid (148 mg, 18%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.86 (1H, s, H_1), 7.60 – 7.56 (2H, m, H_{22}), 7.56 – 7.53 (2H, m, H_{19}), 7.44 (2H, t, *J* = 7.7 Hz, H_{23}), 7.38 – 7.34 (1H, m, H_{24}), 7.33 (2H, d, *J* = 8.0 Hz, H_{18}), 7.23 (1H, s, H_6), 7.17 (1H, s, H_9), 6.06 (2H, s, H_{11}), 5.17 (2H, s, H_{16}), 4.02 (2H, s, H_{13}), 2.74 (3H, s, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 170.6 (C_{14}), 152.3 (C_8), 149.2 (C_3), 148.4 (C_1), 147.9 (C_7), 141.4 (C_{20}), 140.7 (C_{21}), 134.8 (C_5), 134.7 (C_{17}), 129.0 (C_{23}), 128.8 (C_{18}), 127.7 (C_{24}), 127.4 (C_{19}), 127.2 (C_{22}), 124.7 (C_{10}), 121.4 (C_4), 103.8 (C_9), 101.9 (C_{11}), 99.6 (C_6), 66.8 (C_{16}), 34.9 (C_{13}), 22.3 (C_{12}); **IR** (neat) cm^{-1}: 1730, 1491, 1464, 1253, 1230, 1153, 1039, 945, 836, 763, 735, 699, 624; **HRMS** (ESI^+) m/z calc. for $C_{26}H_{22}NO_4$ $[M+H]^+$ 412.1543; found at 412.1557 Δ -4.21 ppm; **m.p.** = 138-139 °C.

8-(2-([1,1'-Biphenyl]-4-ylmethoxy)-2-oxoethyl)-6-benzyl-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide (338):

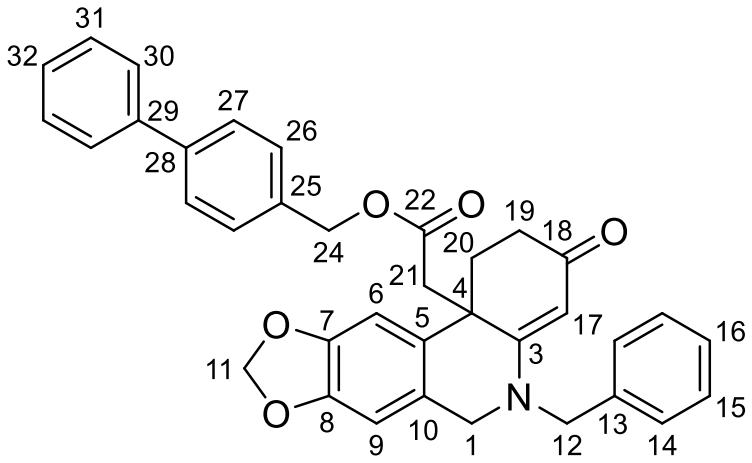


The title compound was synthesised according to **General Procedure E** with [1,1'-biphenyl]-4-ylmethyl 2-(7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate **S338** (148 mg, 0.360 mmol, 1.00 equiv.) to afford **338** as a pale brown solid (132 mg, 58%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 10.61 (1H, s, H_1), 7.90 (1H, s, H_9), 7.58 – 7.55 (2H, m, H_{22}), 7.54 (2H, d, *J* = 8.1 Hz, H_{19}), 7.45 (2H, dd, *J* = 8.4, 7.0 Hz, H_{23}), 7.39 – 7.35 (1H, m, H_{24}), 7.34 – 7.29 (6H, m, H_6, H_{18}, H_{28}, H_{29}), 7.22 – 7.17 (2H, m, H_{27}), 6.21 (2H, s, H_{11}), 6.16

(2H, s, H_{25}), 5.16 (2H, s, H_{16}), 4.11 (2H, s, H_{13}), 2.74 (3H, s, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 168.6 (C_{14}), 157.8 (C_7), 150.8 (C_8), 147.5 (C_1), 142.6 (C_3), 141.7 (C_{20}), 140.4 (C_{21}), 138.5 (C_5), 133.9 (C_{17}), 132.7 (C_{26}), 129.6 (C_{28}), 129.2 (C_{29}), 129.1 (C_{18}), 129.0 (C_{23}), 128.0 (C_4), 127.8 (C_{24}), 127.5 (C_{19}), 127.4 (C_{27}), 127.2 (C_{22}), 124.7 (C_{10}), 106.1 (C_9), 103.9 (C_{11}), 100.3 (C_6), 67.7 (C_{16}), 62.2 (C_{25}), 35.5 (C_{13}), 17.4 (C_{12}); **IR** (neat) cm^{-1}: 1733, 1614, 1465, 1290, 1217, 1035, 732; **HRMS** (ESI^+) m/z calc. for $C_{33}H_{28}NO_4$ $[M]^+$ 502.2013; molecule could not be observed by ESI MS; **m.p.** = 124-126 °C.

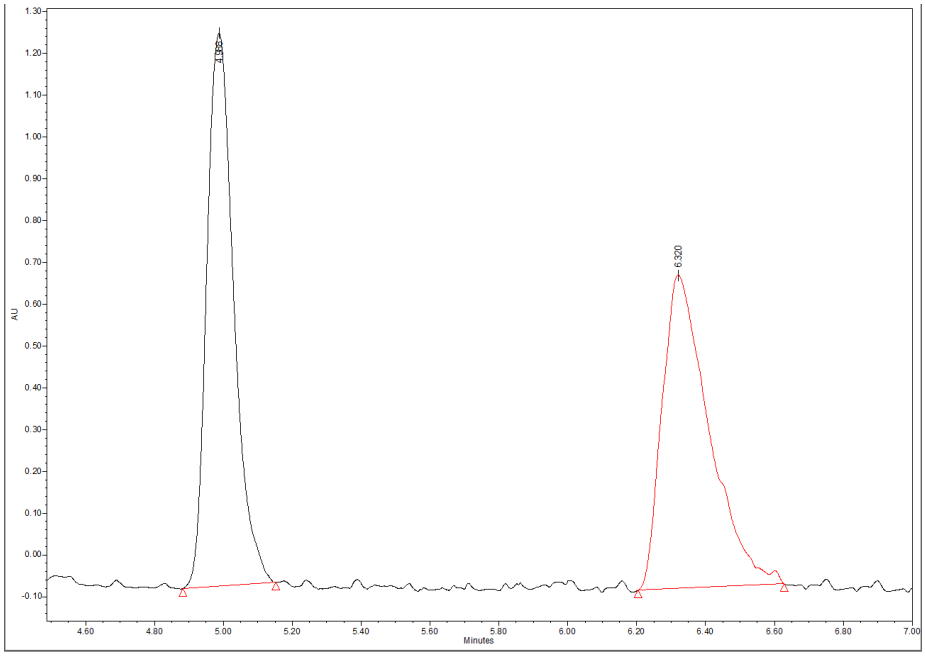
(*RS*)-[1,1'-Biphenyl]-4-ylmethyl 2-(5-benzyl-3-oxo-2,3,5,6-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate (341):



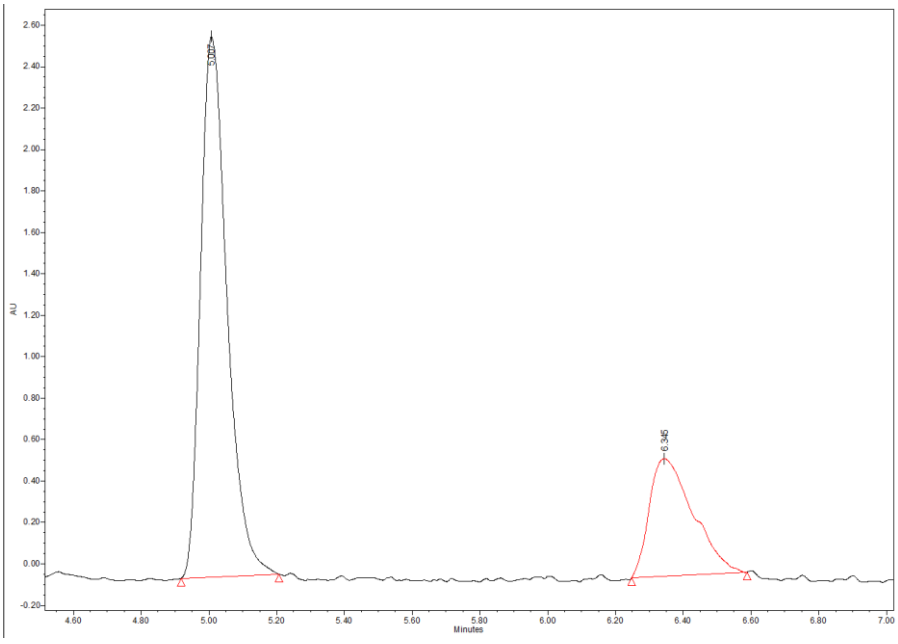
The title compound was synthesised according to **General Procedure I** with 8-(2-([1,1'-biphenyl]-4-ylmethoxy)-2-oxoethyl)-6-benzyl-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **338** (63 mg, 0.10 mmol, 1.0 equiv.). Purification by flash column chromatography (0-5% EtOH in EtOAc) afforded **341** as a pale-yellow solid (39 mg, 69%).

The title compound was synthesised according to **General Procedure J** with 8-(2-([1,1'-biphenyl]-4-ylmethoxy)-2-oxoethyl)-6-benzyl-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **338** (63 mg, 0.10 mmol, 1.0 equiv.). Purification by flash column chromatography (0-5% EtOH in EtOAc) afforded **341** as a pale-yellow solid (18 mg, 31%, 74:26 e.r.).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.60 – 7.57 (2H, m, H_{30}), 7.57 – 7.53 (2H, m, H_{27}), 7.45 (2H, dd, *J* = 8.4, 7.0 Hz, H_{31}), 7.40 – 7.34 (1H, m, H_{32}), 7.30 (2H, dd, *J* = 8.2, 6.4 Hz, H_{15}), 7.28 – 7.23 (1H, m, H_{16}), 7.23 – 7.19 (2H, m, H_{26}), 7.11 – 7.06 (2H, m, H_{14}), 6.82 (1H, s, H_6), 6.54 (1H, s, H_9), 5.90 (1H, d, *J* = 1.5 Hz, H_{11}), 5.84 (1H, d, *J* = 1.5 Hz, H_{11}'), 5.32 (1H, s, H_{17}), 4.97 (2H, s, H_{24}), 4.64 (1H, d, *J* = 16.2 Hz, H_1), 4.61 – 4.53 (2H, m, H_{12}), 4.23 (1H, d, *J* = 16.3 Hz, H_1'), 2.99 (1H, ddd, *J* = 13.2, 5.0, 2.3 Hz, H_{20}), 2.87 (1H, d, *J* = 13.5 Hz, H_{21}), 2.75 (1H, dd, *J* = 13.6, 1.3 Hz, H_{21}'), 2.68 (1H, ddd, *J* = 18.6, 14.1, 5.0 Hz, H_{19}), 2.51 (1H, ddd, *J* = 17.7, 4.9, 2.3 Hz, H_{19}'), 2.24 – 2.14 (1H, m, H_{20}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 195.4 (C_{18}), 169.3 (C_{22}), 165.3 (C_3), 147.9 (C_7), 147.0 (C_8), 141.4 (C_{28}), 140.6 (C_{29}), 134.9 (C_{13}), 134.3 (C_{25}), 130.3 (C_5), 129.2 (C_{15}), 129.0 (C_{31}), 128.9 (C_{26}), 127.9 (C_{16}), 127.7 (C_{32}), 127.3 (C_{27}), 127.2 (C_{30}), 126.6 (C_{14}), 125.4 (C_{10}), 106.1 (C_6), 105.7 (C_9), 101.5 (C_{11}), 98.4 (C_{17}), 66.5 (C_{24}), 55.9 (C_{12}), 52.2 (C_1), 40.9 (C_4), 39.3 (C_{21}), 32.3 (C_{19}), 30.1 (C_{20}); **IR** (neat) cm^{-1}: 1730, 1613, 1556, 1487, 1326, 1245, 1148, 1039, 763, 731, 698; **HRMS** (ESI^+) m/z calc. for $C_{36}H_{32}NO_5$ $[M+H]^+$ 558.2275; found at 558.2288 Δ 2.33 ppm; **m.p.** = 73-75 °C; **SFC** Chiralpak IA; 1500 psi; 30 °C; flow 1.5 mL/min; from 0% to 50% ^{i}PrOH in 7 min; 48% e.e. (major enantiomer t_R = 4.99 min; minor enantiomer t_R = 6.32 min; $[\alpha]_D^{20}$ = -63.2 (c = 0.00586 gmL^{-1}, $CHCl_3$).

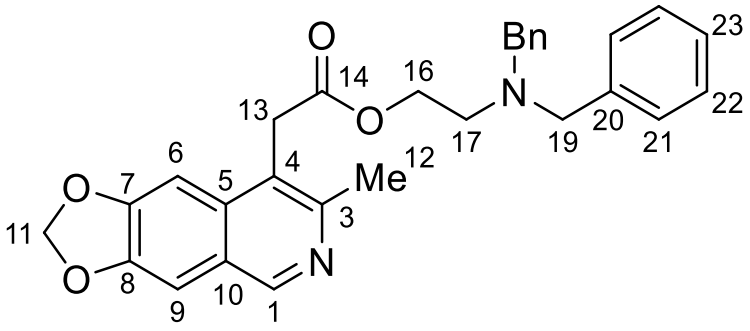


Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area
4.988							7203456	50.35
6.320							7102936	49.65



Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area
5.007							14196267	73.76
6.345							5050844	26.24

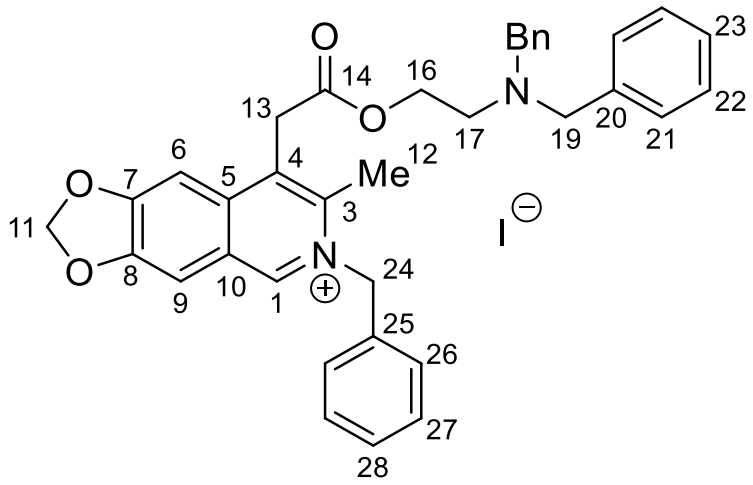
2-(Dibenzylamino)ethyl 2-(7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate (S339):



The title compound was synthesised according to **General Procedure H** with *N*, *N*-dibenzyl amino ethanol (4.5 mL, 20 mmol, 10 equiv.). Purification by flash column chromatography (40-80% EtOAc in pentane) afforded **S339** as a dark-orange oil (333 mg, 36%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.82 (1H, s, H_1), 7.31 – 7.24 (8H, m, H_{21}, H_{22}), 7.24 – 7.20 (3H, m, H_6, H_{23}), 7.12 (1H, s, H_9), 6.05 (2H, s, H_{11}), 4.21 – 4.12 (2H, m, H_{16}), 3.92 (2H, s, H_{13}), 3.51 (4H, s, H_{19}), 2.76 – 2.64 (5H, m, H_{12}, H_{17}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 170.7 (C_{14}), 152.1 (C_7), 149.5 (C_3), 148.6 (C_1), 147.7 (C_8), 139.3 (C_{20}), 134.6 (C_5), 128.8 (C_{21}), 128.4 (C_{22}), 127.1 (C_{23}), 124.7 (C_{10}), 121.3 (C_4), 103.7 (C_9), 101.9 (C_{11}), 99.5 (C_6), 63.5 (C_{16}), 58.7 (C_{19}), 52.0 (C_{17}), 34.9 (C_{13}), 22.5 (C_{12}); **IR** (neat) cm^{-1}: 1731, 1494, 1464, 1252, 1230, 1038, 945, 846, 836, 747, 700; **HRMS** (ESI^+) m/z calc. for $C_{29}H_{29}N_2O_4$ $[M+H]^+$ 469.2122; found at 469.2114 Δ -1.67 ppm.

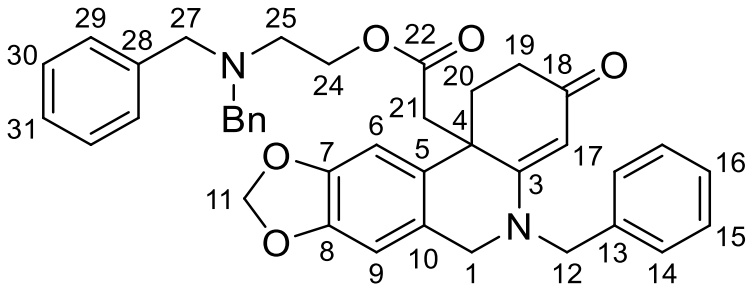
6-Benzyl-8-(2-(2-(dibenzylamino)ethoxy)-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide (339):



The title compound was synthesised according to **General Procedure E** with 2-(dibenzylamino)ethyl 2-(7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate (333 mg, 0.710 mmol, 1.00 equiv.) to afford **339** as a pale-yellow solid (370 mg, 76%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 10.65 (1H, s, H_1), 7.90 (1H, s, H_9), 7.36 – 7.32 (3H, m, H_{27}, H_{28}), 7.30 – 7.27 (8H, m, H_{21}, H_{22}), 7.26 (1H, s, H_6), 7.26 – 7.22 (2H, m, H_{23}), 7.22 – 7.19 (1H, m, H_{26}), 6.24 (2H, s, H_{11}), 6.15 (2H, s, H_{24}), 4.18 (2H, t, *J* = 5.6 Hz, H_{16}), 3.97 (2H, s, H_{13}), 3.55 (4H, s, H_{19}), 2.69 (2H, t, *J* = 5.7 Hz, H_{17}), 2.67 (3H, s, H_{12}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 168.6 (C_{14}), 157.7 (C_7), 150.8 (C_8), 147.6 (C_1), 142.5 (C_3), 139.2 (C_{20}), 138.5 (C_5), 132.8 (C_{25}), 129.7 (C_{27}), 129.3 (C_{28}), 128.9 (C_{21}), 128.5 (C_{22}), 128.0 (C_4), 127.5 (C_{26}), 127.3 (C_{23}), 124.7 (C_{10}), 106.3 (C_9), 103.9 (C_{11}), 100.2 (C_6), 64.4 (C_{16}), 62.1 (C_{24}), 59.0 (C_{19}), 52.1 (C_{17}), 35.3 (C_{13}), 17.2 (C_{12}); **IR** (neat) cm^{-1}: 1733, 1497, 1465, 1291, 1217, 1033, 732, 700; **HRMS** (ESI^+) m/z calc. for $C_{36}H_{34}N_2O_4$ $[M]^+$ 559.2591; found at 559.2596 Δ 0.83 ppm; **m.p.** = 95-98 °C.

(*RS*)-2-(Dibenzylamino)ethyl 2-(5-benzyl-3-oxo-2,3,5,6-tetrahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate (342):

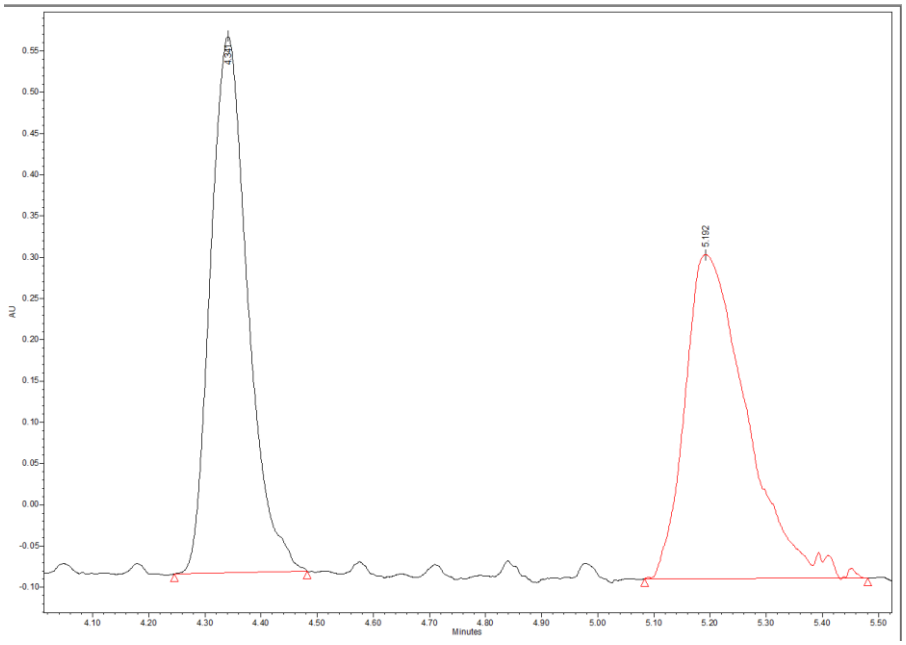


The title compound was synthesised according to **General Procedure I** with 6-benzyl-8-(2-(2-(dibenzylamino)ethoxy)-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **339** (69 mg, 0.10 mmol, 1.0 equiv.). Purification by flash column chromatography (0-5% EtOH in EtOAc) afforded **342** as a yellow oil (41 mg, 66%).

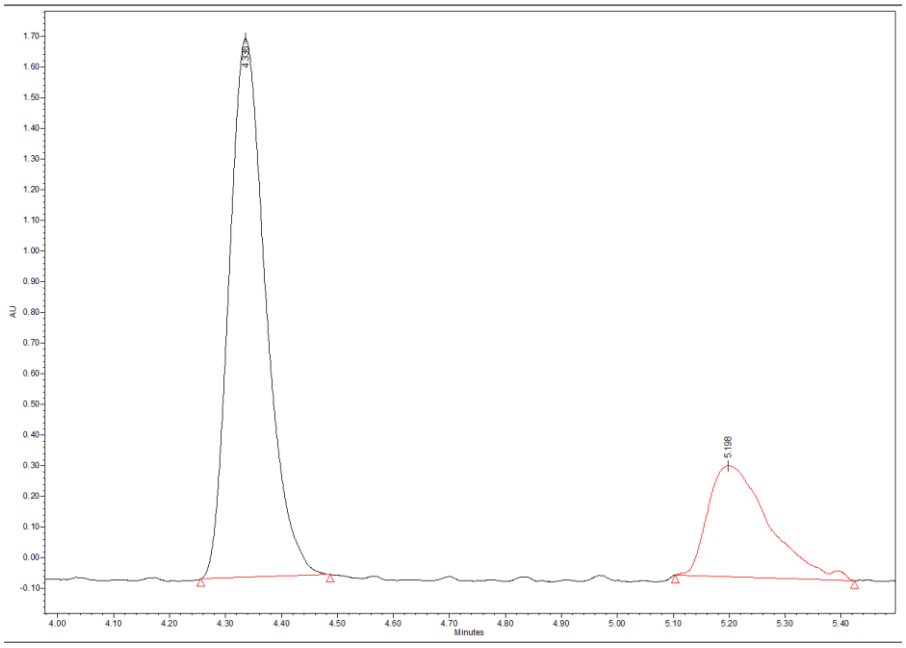
The title compound was synthesised according to **General Procedure J** with 6-benzyl-8-(2-(2-(dibenzylamino)ethoxy)-2-oxoethyl)-7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **339** (69 mg, 0.10 mmol, 1.0 equiv.). Purification by flash column chromatography (0-5% EtOH in EtOAc) afforded **342** as a yellow oil (18 mg, 29%, 75:25 e.r.).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.33 – 7.27 (11H, m, H_{15}, H_{16}, H_{29}, H_{30}), 7.25 – 7.22 (2H, m, H_{31}), 7.09 (2H, dd, *J* = 7.1, 1.8 Hz, H_{14}), 6.86 (1H, s, H_6), 6.49 (1H, s, H_9), 5.93 (1H, d, *J* = 1.4 Hz, H_{11}), 5.88 (1H, d, *J* = 1.4 Hz, H_{11}'), 5.28 (1H, s, H_{17}), 4.65 – 4.50 (3H, m, H_1, H_{12}, H_{12}'), 4.19 (1H, d, *J* = 16.3 Hz, H_1'), 4.01 (1H, dt, *J* = 11.9, 6.0 Hz, H_{24}), 3.91 (1H, dt, *J* = 11.6, 6.0 Hz, H_{24}'), 3.54 (4H, s, H_{27}), 2.98 (1H, ddd, *J* = 13.3, 5.0, 2.4 Hz, H_{20}), 2.78 (1H, d, *J* = 13.7 Hz, H_{21}), 2.66 – 2.44 (5H, m, H_{19}, H_{19}', H_{21}', H_{25}, H_{25}'), 2.20 – 2.11 (1H, m, H_{20}'); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 195.6 (C_{18}), 169.3 (C_{22}), 165.0 (C_3), 147.8 (C_7), 146.8 (C_8), 139.2 (C_{28}), 135.0 (C_{13}), 130.4 (C_5), 129.1 (C_{15}), 128.8 (C_{29}), 128.4 (C_{30}), 127.8 (C_{16}), 127.2 (C_{31}), 126.5 (C_{14}), 125.5 (C_{10}), 106.1 (C_6), 105.7 (C_9), 101.4 (C_{11}), 98.4 (C_{17}), 62.8 (C_{24}), 58.7 (C_{27}), 55.8 (C_{12}), 52.1 (C_1), 51.6 (C_{25}), 40.8 (C_4), 39.0 (C_{21}), 32.3 (C_{19}), 30.0 (C_{20}); **IR** (neat)

cm^{-1}: 1729, 1614, 1557, 1487, 1326, 1245, 1149, 1039, 911, 732, 699; **HRMS** (ESI^+) m/z calc. for $C_{39}H_{38}N_2O_5$ $[M+H]^+$ 615.2853; found at 615.2851 Δ -0.41 ppm; **SFC** Chiralpak IA; 1500 psi; 30 °C; flow 1.5 mL/min; from 0% to 50% ^{i}PrOH in 7 min; 50% e.e. (major enantiomer t_R = 4.34 min; minor enantiomer t_R = 5.19 min); $[\alpha]_D^{20}$ = -49.9 (c = 0.00806 gmL^{-1}, $CHCl_3$).

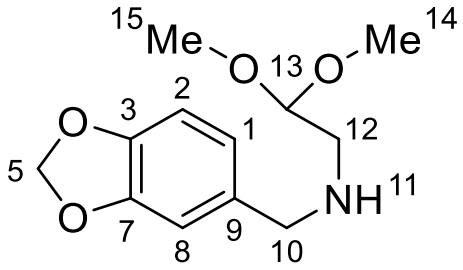


Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (μV*sec)	% Area
4.341							2998533	49.90
5.192							3010301	50.10



Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area
4.336							7982424	74.54
5.198							2726920	25.46

***N*-(Benzo[d][1,3]dioxol-5-ylmethyl)-2,2-dimethoxyethan-1-amine (365):**

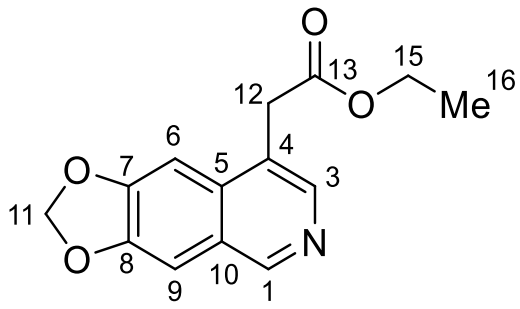


Piperonyl amine (5.0 mL, 40 mmol, 1.0 equiv.) was dissolved in EtOH (150 mL) with 2,2-dimethoxyacetaldehyde (6.9 g, 40 mmol, 60 wt% in H_2O, 1.0 equiv.) and Na_2SO_4 (22.0 g, 154 mmol, 3.9 equiv.), then stirred at r.t. overnight. The solution was filtered under gravity, and cooled to 0 °C then $NaBH_4$ was added portionwise (1.5 g, 40 mmol, 1.0 equiv.) and the mixture stirred for 1 h. The reaction was then quenched with H_2O, diluted with EtOAc, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc, then the combined organic layers were dried over $MgSO_4$, filtered under gravity and concentrated *in*

vacuo. Purification by flash column chromatography (0-20% EtOH in EtOAc) afforded **365** as a pale orange oil (2.94 g, 28%).

^{1}H NMR (200 MHz, $CDCl_3$): δ_H = 6.78 (1H, d, *J* = 1.1 Hz, H_8), 6.73 – 6.64 (2H, m, H_1, H_2), 5.87 (2H, s, H_5), 4.43 (1H, t, *J* = 5.5 Hz, H_{13}), 3.65 (2H, s, H_{10}), 3.32 (6H, s, H_{14}, H_{15}), 2.67 (2H, d, *J* = 5.5 Hz, H_{12}); **^{13}C NMR** (101 MHz, $CDCl_3$): δ_C = 147.7 (C_7), 146.5 (C_3), 134.1 (C_9), 121.2 (C_1), 108.6 (C_8), 108.0 (C_2), 103.9 (C_{13}), 100.8 (C_5), 53.9 (2C, C_{14}, C_{15}), 53.6 (C_{10}), 50.3 (C_{12}); **IR** (neat) cm^{-1}: 1503, 1489, 1442, 1247, 1191, 1130, 1068, 1039, 966, 927, 861, 809, 775, 732; **HRMS** (ESI^+) m/z calc. for $C_{12}H_{18}NO_4$ $[M+H]^+$ 240.1230, found at 240.1219 Δ -4.73 ppm. Spectroscopic data were consistent with the literature data for this compound.[200]

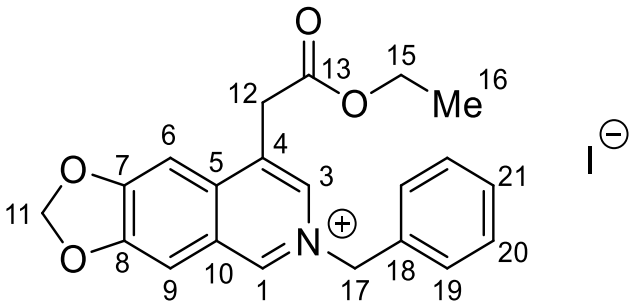
Ethyl 2-([1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate (S349):



N-(Benzo[d][1,3]dioxol-5-ylmethyl)-2,2-dimethoxyethan-1-amine **365** (2.94 g, 11.4 mmol, 1.00 equiv.) was dissolved in EtOH (30 mL) with 12 M HCl (30 mL) and ethyl glyoxylate solution (4.70 g, 22.8 mmol, 50 wt% in PhMe, 2.0 equiv.), then heated to 100 °C for 2 h. The mixture was cooled to 0 °C, diluted with H_2O, basified by slow addition of solid K_2CO_3, then diluted with EtOAc, shaken and the layers partitioned. The aqueous layer was extracted twice more with EtOAc, then the combined organic extracts were dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (100% EtOAc) afforded **S349** as a pale brown solid (730 mg, 24%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 8.92 (1H, s, H_1), 8.28 (1H, s, H_3), 7.23 (1H, s, H_6), 7.20 (1H, s, H_9), 6.10 (2H, s, H_{11}), 4.15 (2H, q, *J* = 7.1 Hz, H_{15}), 3.89 (2H, s, H_{12}), 1.23 (3H, t, *J* = 7.1 Hz, H_{16}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 171.0 (C_{13}), 151.6 (C_7), 150.4 (C_1), 148.4 (C_8), 143.7 (C_3), 133.5 (C_5), 126.1 (C_{10}), 124.0 (C_4), 103.8 (C_9), 101.7 (C_{11}), 99.8 (C_6), 61.4 (C_{15}), 36.9 (C_{12}), 14.3 (C_{16}); **IR** (neat) cm^{-1}: 1731, 1501, 1468, 1430, 1245, 1036, 952, 935, 900, 879, 846, 832; **HRMS** (ESI^+) m/z calc. for $C_{14}H_{14}NO_4$ $[M+H]^+$ 260.0917; found at 260.0906 Δ -4.37 ppm; **m.p.** = 65-67 °C.

6-Benzyl-8-(2-ethoxy-2-oxoethyl)-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide (349):

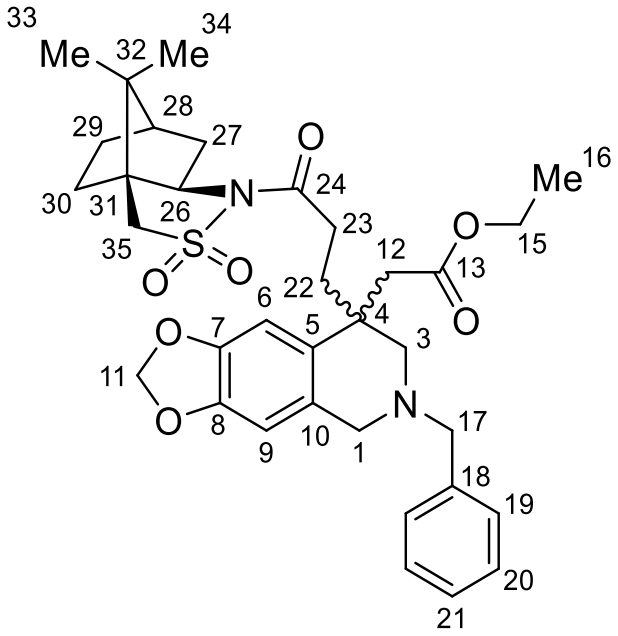


Ethyl 2-([1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate **S349** (1.10 g, 4.24 mmol, 1.00 equiv.) was dissolved in acetone (20 mL) with BnI (1.1 g, 5.1 mmol, 1.2 equiv.) and stirred at r.t. for 60 h. The solution was triturated with Et_2O and the resultant precipitate filtered under reduced pressure. The solid was washed with Et_2O and dried *in vacuo* to afford **349** as a yellow solid (885 mg, 44%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 10.51 (1H, d, *J* = 1.5 Hz, H_1), 8.73 (1H, d, *J* = 1.5 Hz, H_3), 7.84 (1H, s, H_9), 7.72 – 7.66 (2H, m, H_{19}), 7.37 – 7.29 (3H, m, H_{20}, H_{21}), 7.24 (1H, s, H_6), 6.29 (2H, s, H_{11}), 6.02 (2H, s, H_{17}), 4.11 (2H, q, *J* = 7.1 Hz, H_{15}), 4.07 (2H, s, H_{12}), 1.19 (3H, t, *J* = 7.1 Hz, H_{16}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 168.9 (C_{13}), 157.3 (C_7), 151.4 (C_8), 145.0 (C_1), 137.7 (C_5), 134.1 (C_3), 133.1 (C_{18}), 129.9 (C_{21}), 129.6 (C_{19}), 129.6 (C_{20}), 129.5, (C_4) 126.1 (C_{10}), 106.3 (C_9), 104.1 (C_{11}), 100.5 (C_6), 63.0 (C_{17}), 62.1 (C_{15}), 36.1 (C_{12}), 14.2 (C_{16}); **IR**

(neat) cm^{-1}: 1731, 1467, 1285, 1222, 1032, 920, 726; **HRMS** (ESI^+) m/z calc. for $C_{21}H_{20}NO_4$ $[M]^+$ 350.1387; found at 350.1393 Δ 1.76 ppm; **m.p.** 152-153 °C.

(*RS*)-Ethyl 2-(6-benzyl-8-(3-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-3-oxopropyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate (351):



6-Benzyl-8-(2-ethoxy-2-oxoethyl)-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **349** (119 mg, 0.250 mmol, 1.00 equiv.) was dissolved in 1,4-dioxane (3.75 mL) with 1-((3aS,6R,7aR)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)prop-2-en-1-one **335** (115 mg, 0.500 mmol, 2.00 equiv.) and 5:2 HCO_2H:NEt_3 (0.17 mL, 2.0 mmol, 8.0 equiv.) and an aliquot of a premade solution of $(RhCp^*Cl)_2$ in 1,4-dioxane (0.25 mL, 0.020 mol%, 3.1 mg in 25 mL) was added. The mixture was stirred at 80 °C for 18 h, then cooled, diluted with EtOAc, washed with sat. aq. Na_2CO_3 and the layers partitioned. The aqueous layer was washed twice more with EtOAc, the organic layers combined, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column

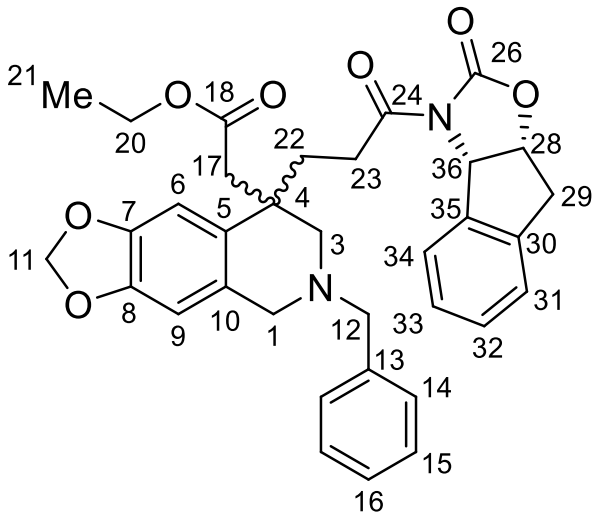
chromatography (20-60% EtOAc in 40-60 pet ether) afforded **351** as a pale-yellow foam as an inseparable mixture of diastereomers in a 66:34 ratio (57 mg, 36%).

Data for both diastereoisomers:

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.39 – 7.35 (4H, m, $H_{19\ major}$, $H_{19\ minor}$), 7.32 – 7.28 (4H, m, $H_{20\ major}$, $H_{20\ minor}$), 7.26 – 7.22 (2H, m, $H_{21\ major}$, $H_{21\ minor}$), 6.72 (1H, s, $H_{6\ major}$), 6.71 (1H, s, $H_{6\ minor}$), 6.39 (1H, s, $H_{9\ minor}$), 6.38 (1H, s, $H_{9\ major}$), 5.88 – 5.85 (4H, m, $H_{11\ major}$, $H_{11\ minor}$), 4.03 – 3.95 (4H, m, $H_{15\ major}$, $H_{15\ minor}$), 3.85 – 3.77 (2H, m, $H_{26\ major}$, $H_{26\ minor}$), 3.65 – 3.58 (4H, m, $H_{17\ major}$, $H_{17\ minor}$), 3.48 – 3.35 (8H, m, $H_{1\ major}$, H_{1}'$_{major}$, $H_{1\ minor}$, H_{1}'$_{minor}$, $H_{35\ major}$, H_{35}'$_{major}$, $H_{35\ minor}$, H_{35}'$_{minor}$), 2.91 – 2.86 (2H, m, $H_{3\ major}$, $H_{3\ minor}$), 2.87 – 2.79 (2H, m, $H_{23\ major}$, $H_{23\ minor}$), 2.79 – 2.72 (2H, m, $H_{12\ major}$, $H_{12\ minor}$), 2.61 – 2.57 (2H, m, H_{3}'$_{major}$, H_{3}'$_{minor}$) 2.57 – 2.54 (2H, m, H_{12}'$_{major}$, H_{12}'$_{minor}$), 2.45 (1H, ddd, *J* = 16.1, 10.7, 5.1 Hz, H_{23}'$_{major}$), 2.37 (1H, ddd, *J* = 15.8, 11.5, 4.5 Hz, H_{23}'$_{minor}$), 2.33 – 2.24 (2H, m, $H_{22\ major}$, $H_{22\ minor}$), 2.11 – 2.00 (6H, m, H_{22}'$_{major}$, H_{22}'$_{minor}$, $H_{27\ major}$, H_{27}'$_{major}$, $H_{27\ minor}$, H_{27}'$_{minor}$), 1.94 – 1.82 (6H, m, $H_{28\ major}$, $H_{28\ minor}$, $H_{29\ major}$, $H_{29\ minor}$, $H_{30\ major}$, $H_{30\ minor}$), 1.40 – 1.36 (2H, m, H_{30}'$_{major}$, H_{30}'$_{minor}$), 1.36 – 1.30 (2H, m, H_{29}'$_{major}$, H_{29}'$_{minor}$), 1.16 – 1.07 (12H, m, $H_{16\ major}$, $H_{16\ minor}$, $H_{33\ major}$, $H_{33\ minor}$), 0.96 (3H, s, $H_{34\ minor}$), 0.95 (3H, s, $H_{34\ major}$); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_c = 172.2 ($C_{24\ minor}$), 172.1 ($C_{24\ major}$), 171.4 ($C_{13\ minor}$), 171.4 ($C_{13\ minor}$), 146.6 ($C_{7\ minor}$), 146.5 ($C_{7\ major}$), 146.0 ($C_{8\ minor}$), 146.0 ($C_{8\ major}$), 138.5 (2C, $C_{18\ major}$, $C_{18\ minor}$), 131.8 ($C_{5\ minor}$), 131.7 ($C_{5\ major}$), 129.3 ($C_{19\ major}$), 129.3 ($C_{19\ minor}$), 129.2 ($C_{10\ major}$), 129.1 ($C_{10\ minor}$), 128.4 ($C_{20\ minor}$), 128.3 ($C_{20\ major}$), 127.2 ($C_{21\ minor}$), 127.2 ($C_{21\ major}$), 106.5 (2C, $C_{9\ major}$, $C_{9\ minor}$), 106.4 ($C_{6\ major}$), 106.2 ($C_{6\ minor}$), 100.9 (2C, $C_{11\ major}$, $C_{11\ minor}$), 65.4 (2C, $C_{26\ major}$, $C_{26\ minor}$), 63.0 ($C_{11\ minor}$), 63.0 ($C_{11\ major}$), 60.2 (2C, $C_{15\ major}$, $C_{15\ minor}$), 59.5 ($C_{3\ major}$), 59.4 ($C_{3\ minor}$), 56.7 ($C_{1\ minor}$), 56.7 ($C_{1\ major}$), 53.1 (2C, $C_{35\ major,}$ $C_{35\ minor}$), 48.5 ($C_{31\ minor}$), 48.5 ($C_{31\ major}$), 47.9 ($C_{32\ minor}$), 47.9 ($C_{32\ major}$), 45.9 ($C_{12\ major}$), 45.8 ($C_{12\ minor}$), 44.8 ($C_{28\ major}$), 44.8 ($C_{28\ minor}$), 41.0 ($C_{4\ major}$), 41.0 ($C_{4\ minor}$), 38.7 (2C, $C_{27\ major}$, $C_{27\ minor}$), 34.6 ($C_{22\ minor}$), 34.1 ($C_{22\ major}$), 33.0 (2C, $C_{30\ major}$, $C_{30\ minor}$), 31.7 ($C_{23\ minor}$), 31.6

($C_{23\ major}$), 26.6 (2C, $C_{29\ major}$, $C_{29\ minor}$), 21.1 ($C_{33\ minor}$), 21.0 ($C_{33\ major}$), 20.0 (2C, $C_{34\ major}$, $C_{34\ minor}$), 14.3 (2C, $C_{16\ major}$, $C_{16\ minor}$); **IR** (neat) cm^{-1}: 1727, 1694, 1505, 1487, 1329, 1237, 1215, 1167, 1134, 1039, 913, 732, 701; **HRMS** (ESI^+) m/z calc. for $C_{34}H_{42}N_2O_7S$ $[M+H]^+$ 623.2786; found at 623.2805 Δ -0.08 ppm; **m.p.** = 49-50 °C; $[\alpha]_D^{20}$ = -38.6 (c = 0.01 gmL^{-1}, $CHCl_3$).

(*RS*)-Ethyl 2-(6-benzyl-8-(3-oxo-3-((3aS,8aR)-2-oxo-8,8a-dihydro-2H-indeno[1,2-d]oxazol-3(3aH)-yl)propyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate (350):



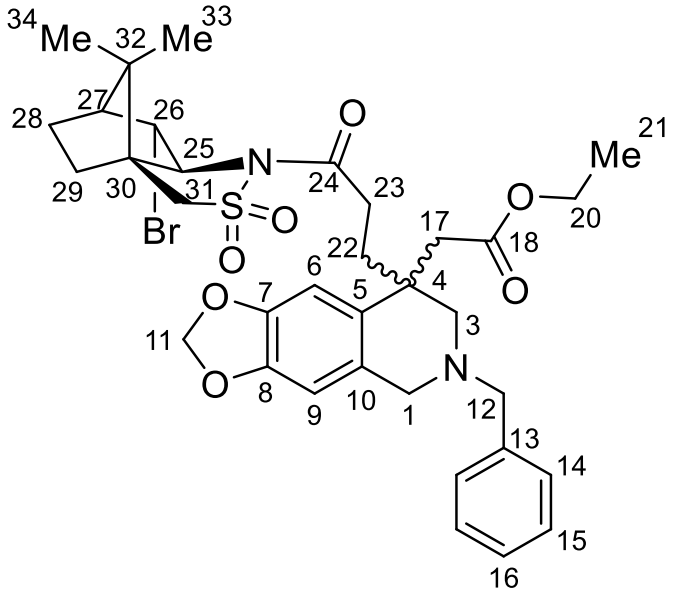
The title compound was synthesised according to **General Procedure J** with 6-benzyl-8-(2-ethoxy-2-oxoethyl)-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **349** (119 mg, 0.25 mmol, 1.0 equiv.). Purification by flash column chromatography (20-40% EtOAc in pentane) afforded **350** as an off-white solid as an inseparable mixture of diastereomers in a 52:48 ratio (52 mg, 36%).

Due to the approximately 1:1 ratio of the two diastereomers in the inseparable mixture, it was impossible to accurately assign peaks as belonging to either diastereomer. Therefore, the two signals corresponding to the same environment have been grouped to minimise ambiguity. Carbons 15 and 33 were insufficiently separated to be able to distinguish between their

environments at the resolution of the 2D spectral data collected and are therefore presented as both possibilities.

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.62 – 7.58 (1H, m, H_{34}), 7.41 – 7.32 (3H, m, H_{14}, H_{32}), 7.31 – 7.24 (4H, m, H_{15}, H_{31}, H_{33}), 7.24 – 7.20 (1H, m, H_{16}), 6.74 and 6.73 (1H, s, H_6), 6.41 and 6.39 (1H, s, H_9), 5.90 – 5.83 (3H, m, H_{11}, H_{28}), 5.21 (1H, m, H_{36}), 4.06 – 3.94 (2H, m, H_{20}), 3.66 – 3.54 (2H, m, H_{12}, H_{12}'), 3.45 (2H, s, H_1, H_1'), 3.35 (1H, s, H_{29}, H_{29}'), 3.11 – 2.98 (1H, m, H_{23}), 2.91 – 2.86 (1H, m, H_3), 2.81 – 2.74 (1H, m, H_{17}), 2.67 – 2.53 (3H, m, H_3', H_{17}', H_{23}'), 2.36 – 2.26 (1H, m, H_{22}), 2.16 – 2.05 (1H, m, H_{22}'), 1.12 (3H, m, H_{21}); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 173.7 and 173.6 (C_{24}), 171.4 and 171.4 (C_{18}), 152.9 and 152.9 (C_{26}), 146.4 and 146.4 (C_7), 145.9 and 145.9 (C_8), 139.6 and 139.5 (C_{30}), 139.3 and 139.3 (C_{35}), 138.4 and 138.4 (C_{13}), 131.9 and 131.9 (C_5), 129.9 (C_{32}) 129.2 and 129.1 (C_{14}), 129.0 (C_{10}), 128.3 and 128.3 ($C_{15 \text{ or } 33}$), 128.2 and 128.2 ($C_{15 \text{ or } 33}$), 127.4 and 127.4 (C_{34}), 127.2 (C_{16}), 125.3 and 125.3 (C_{31}), 106.5 and 106.5 (C_9), 106.1 and 106.1 (C_6), 100.8 (C_{11}), 78.1 and 78.1 (C_{28}), 63.1 and 63.1 (C_{36}), 62.8 and 62.7 (C_{12}), 60.1 and 60.1 (C_{20}), 59.3 and 59.1 (C_3), 56.8 and 56.8 (C_1), 45.6 and 45.5 (C_{17}), 40.9 (C_4), 38.1 and 38.1 (C_{29}), 33.8 and 33.8 (C_{22}), 31.3 and 31.2 (C_{23}); **IR** (neat) cm^{-1}: 1779, 1725, 1700, 1486, 1364, 1191, 1040, 910, 730; **HRMS** (ESI^+) m/z calc. for $C_{34}H_{35}N_2O_7$ $[M+H]^+$ 583.2439; found at 583.2420 Δ -3.22 ppm; **m.p.** = 48-50 °C; $[\alpha]_D^{20}$ = +79.6 (c = 0.01 gmL^{-1}, $CHCl_3$).

(*RS*)-Ethyl 2-(6-benzyl-8-(3-((3aS,6S,7S,7aS)-7-bromo-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)-3-oxopropyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate (352):



6-Benzyl-8-(2-ethoxy-2-oxoethyl)-[1,3]dioxolo[4,5-g]isoquinolin-6-ium iodide **349** (119 mg, 0.25 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (3.75 mL) with 1-((3aS,6S,7S,7aS)-7-bromo-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)prop-2-en-1-one **336** (98 mg, 0.28 mmol, 1.1 equiv.), 5:2 HCO_2H:NEt_3 (0.17 mL, 0.80 mmol, 8.0 equiv.) and an aliquot of a premade solution of $(RhCp^*Cl)_2$ in 1,4-dioxane (0.25 mL, 0.020 mol%, 3.1 mg in 25 mL) was added. The mixture was stirred at 80 °C for 18 h, then cooled, diluted with EtOAc, washed with sat. aq. Na_2CO_3 and the layers partitioned. The aqueous layer was washed twice more with EtOAc, the organic layers combined, dried over $MgSO_4$, filtered under gravity and concentrated *in vacuo*. Purification by flash column chromatography (20-40% EtOAc in pentane) afforded **352** as a pale-yellow oil as an inseparable mixture of diastereomers in a 63:37 ratio (30 mg, 17%).

Data for both diastereoisomers:

^{1}H NMR (600 MHz, $CDCl_3$): δ_H = 7.40 – 7.34 (4H, m, $H_{14\ major}$, $H_{14\ minor}$), 7.33 – 7.28 (4H, m, $H_{15\ major}$, $H_{15\ minor}$), 7.25 – 7.21 (2H, m, $H_{16\ major}$, $H_{16\ minor}$), 6.72 (1H, s, $H_{6\ major}$), 6.70 (1H, s, $H_{6\ minor}$), 6.38 (1H, s, $H_{9\ minor}$), 6.37 (1H, s, $H_{9\ major}$), 5.87 (2H, dd, *J* = 6.5, 1.5 Hz, $H_{11\ minor}$), 5.85 (2H, t, *J* = 1.5 Hz, $H_{11\ major}$), 4.65 (1H, td, *J* = 3.9, 2.1 Hz, $H_{26\ minor}$), 4.59 (1H, td, *J* = 3.8, 2.1 Hz, $H_{26\ major}$), 4.04 – 3.93 (4H, m, $H_{20\ major}$, $H_{20\ minor}$), 3.88 (1H, d, *J* = 3.7 Hz, $H_{25\ minor}$), 3.87 (1H, d, *J* = 3.8 Hz, $H_{25\ major}$), 3.60 (4H, s, $H_{12\ major}$, $H_{12\ minor}$), 3.44 – 3.34 (8H, m, $H_{1\ major}$, H_1'$_{major}$, $H_{1\ minor}$, H_1'$_{minor}$, $H_{31\ major}$, H_{31}'$_{major}$, $H_{31\ minor}$, H_{31}'$_{minor}$), 2.94 – 2.82 (4H, m, $H_{3\ major}$, $H_{3\ minor}$, $H_{23\ major}$, $H_{23\ minor}$), 2.79 – 2.70 (2H, m, $H_{17\ major}$, $H_{17\ minor}$), 2.66 – 2.58 (2H, m, H_3'$_{major}$, H_3'$_{minor}$), 2.58 – 2.53 (2H, m, H_{17}'$_{major}$, H_{17}'$_{minor}$), 2.50 (1H, td, *J* = 10.7, 5.2 Hz, H_{23}'$_{major}$), 2.43 (1H, ddd, *J* = 16.1, 11.7, 4.3 Hz, H_{23}'$_{minor}$), 2.37 – 2.28 (2H, m, $H_{22\ major}$, $H_{22\ minor}$), 2.27 – 2.20 (2H, m, $H_{28\ major}$, $H_{28\ minor}$), 2.14 – 2.05 (4H, m, H_{22}'$_{major}$, H_{22}'$_{minor}$, $H_{27\ major}$, $H_{27\ minor}$), 1.97 – 1.90 (2H, m, $H_{29\ major}$, $H_{29\ minor}$), 1.90 – 1.82 (2H, m, H_{28}'$_{major}$, H_{28}'$_{minor}$), 1.54 – 1.47 (2H, m, H_{29}'$_{major}$, H_{29}'$_{minor}$), 1.20 (3H, s, $H_{33\ minor}$), 1.13 (3H, s, $H_{33\ major}$), 1.13 – 1.08 (6H, m, $H_{21\ major}$, $H_{21\ minor}$), 1.06 (3H, s, $H_{34\ minor}$), 1.05 (3H, s, $H_{34\ major}$); **^{13}C NMR** (151 MHz, $CDCl_3$): δ_C = 172.1 ($C_{24\ minor}$), 172.1 ($C_{24\ major}$), 171.3 ($C_{18\ minor}$), 171.3 ($C_{18\ major}$), 146.6 ($C_{7\ minor}$), 146.4 ($C_{7\ major}$), 146.0 ($C_{8\ minor}$), 146.0 ($C_{8\ major}$), 138.4 (2C, $C_{13\ major}$, $C_{13\ minor}$), 131.6 ($C_{5\ minor}$), 131.5 ($C_{5\ major}$), 129.3 ($C_{14\ major}$), 129.3 ($C_{14\ minor}$), 129.2 ($C_{10\ major}$), 129.1 ($C_{10\ minor}$), 128.3 ($C_{15\ minor}$), 128.3 ($C_{15\ major}$), 127.2 (2C, $C_{16\ major}$, $C_{16\ minor}$), 106.5 (2C, $C_{9\ major}$, $C_{9\ minor}$), 106.3 ($C_{6\ major}$), 106.1 ($C_{6\ minor}$), 100.9 (2C, $C_{11\ major}$, $C_{11\ minor}$), 74.0 ($C_{25\ minor}$), 74.0 ($C_{25\ major}$), 63.0 ($C_{12\ minor}$), 62.9 ($C_{12\ major}$), 60.5 ($C_{20\ minor}$), 60.2 ($C_{20\ major}$), 59.6 ($C_{3\ major}$), 59.5 ($C_{3\ minor}$), 56.6 ($C_{1\ minor}$), 56.6 ($C_{1\ major}$), 56.4 (2C, $C_{26\ major}$, $C_{26\ minor}$), 52.9 ($C_{27\ major}$), 52.8 ($C_{27\ minor}$), 52.1 (2C, $C_{31\ major}$, $C_{31\ minor}$), 49.7 ($C_{32\ minor}$), 49.7 ($C_{32\ major}$), 47.9 ($C_{30\ minor}$), 47.9 ($C_{30\ major}$), 45.9 ($C_{17\ major}$), 45.8 ($C_{17\ minor}$), 40.9 (2C, $C_{4\ major}$, $C_{4\ minor}$), 34.4 ($C_{22\ minor}$), 34.3 ($C_{22\ major}$), 32.5 (2C, $C_{29\ major}$, $C_{29\ minor}$), 31.7 ($C_{23\ minor}$), 31.6 ($C_{23\ major}$), 23.0 (2C, $C_{28\ major}$, $C_{28\ minor}$), 20.8 ($C_{33\ minor}$), 20.8 ($C_{33\ major}$), 20.7 ($C_{34\ minor}$), 20.7 ($C_{34\ major}$), 14.3 ($C_{21\ minor}$), 14.2 ($C_{21\ major}$); **IR** (neat) cm^{-1}: 1724, 1486,

1333, 1235, 1206, 1142, 1039, 912, 731; **HRMS** (ESI^+) m/z calc. for $C_{34}H_{42}{}^{79}BrN_2O_7S$ $[M+H]^+$ 701.1891; found at 701.1906 Δ 2.19 ppm; $[\alpha]_D{}^{20}$ = +17.0 (c = 0.01 gmL^{-1}, $CHCl_3$).

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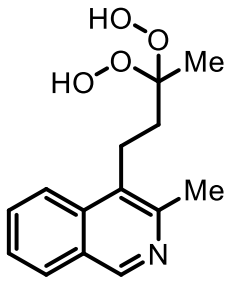
Appendix I – Single crystal X-ray diffraction data

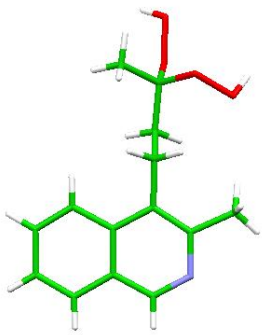
Unless otherwise stated, all single crystal X-ray analysis detailed herein was conducted by T. C. Jenkins.

(*RS*)-4-(3,3-Dihydroperoxybutyl)-3-methylisoquinoline (122):

Single crystal X-ray analysis for this compound was conducted by Dr K. E. Christensen.



122

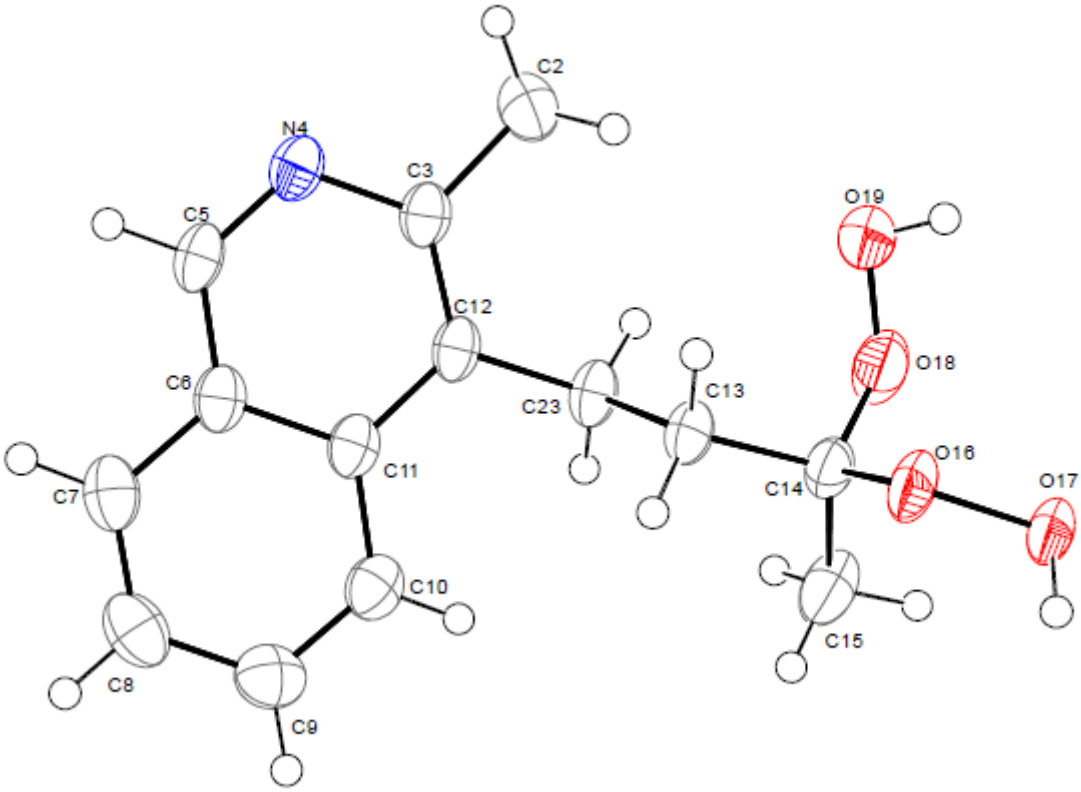


Formula	C14 H17 N1 O4	Recrystallised from	$CDCl_3$ by slow evaporation
Crystal Class	monoclinic	Space Group	C 2/c
a	18.6148(8)	alpha	90
b	8.3647(3)	beta	92.092(4)
c	19.4083(7)	gamma	90
Volume	3020.0(2)	Z	8
Radiation type	Cu K\a	Wavelength	1.541800
Dx	1.158	Mr	263.29
Mu	7.04	Temperature (K)	150
Size	0.10 x 0.15 x 0.20		
Cell from	1120 Reflections	Theta range	4 to 76
Standard Interval	0	Standard Count	0
Diffractometer type	multi-scan	Scan type	OMEGA
Absorption type	multi-scan	Transmission range	0.81 0.93

Reflections measured	10839	Independent reflections	3140
Rint	0.028	Theta max	76.303
Hmin, Hmax	-23 22		
Kmin, Kmax	-7 10		
Lmin, Lmax	-23 24		

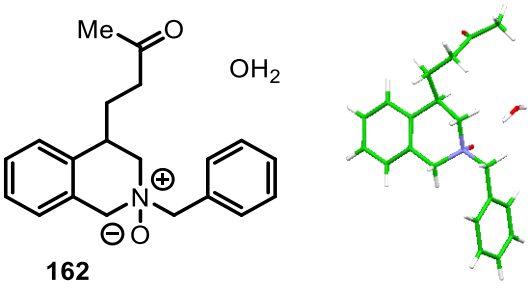
Refinement on Fsqd

R-factor	0.0451	Weighted R-factor	0.1122
Delta Rho min	-0.49	Delta Rho max	0.34
Reflections used	3140	sigma(I) limit	-3.00
Number of parameters	172	Goodness of fit	1.0048



Thermal ellipsoids are drawn at the 50% probability level.

(*RS*)-2-Benzyl-4-(3-oxobutyl)-1,2,3,4-tetrahydroisoquinoline 2-oxide monohydrate (162):

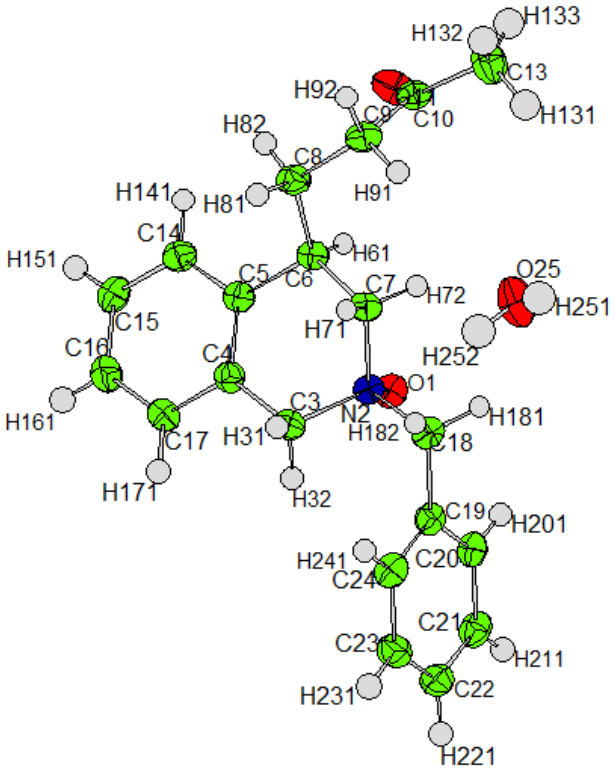


162

Formula	C20 H25 N1 O3	Recrystallised from EtOAc/heptane by slow evaporation	
Crystal Class	orthorhombic	Space Group	P n a 21
a	5.08650(10)	alpha	90
b	25.8569(3)	beta	90
c	13.4629(2)	gamma	90
Volume	1770.66(5)	Z	4
Radiation type	Cu K\a	Wavelength	1.541800
Dx	1.23	Mr	327.42
Mu	0.655	Temperature (K)	150
Size	0.05x 0.05x 0.20		
Colour	clear light colourless	Shape	needle
Cell from	18292 Reflections	Theta range	3 to 76
Standard Interval	0	Standard Count	0
Diffractometer type	multi-scan	Scan type	OMEGA
Absorption type	multi-scan	Transmission range	0.74 0.97
Reflections measured	38018	Independent reflections	3555

Rint	0.0004	Theta max	76.18
Hmin, Hmax	-6 6		
Kmin, Kmax	-32 32		
Lmin, Lmax	-16 13		
Refinement on Fsqd			
R-factor	0.030	Weighted R-factor	0.080
Max shift/su	0.0006		
Delta Rho min	-0.13	Delta Rho max	0.11
Reflections used	3555	sigma(I) limit	-3.00
Number of parameters	225	Goodness of fit	1.021

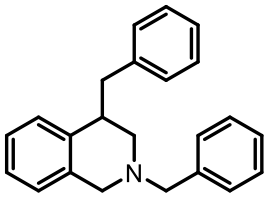
Flack parameter -0.01(6)



Thermal ellipsoids are drawn at the 50% probability level.

(*RS*)-2,4-Dibenzyl-1,2,3,4-tetrahydroisoquinoline (178):

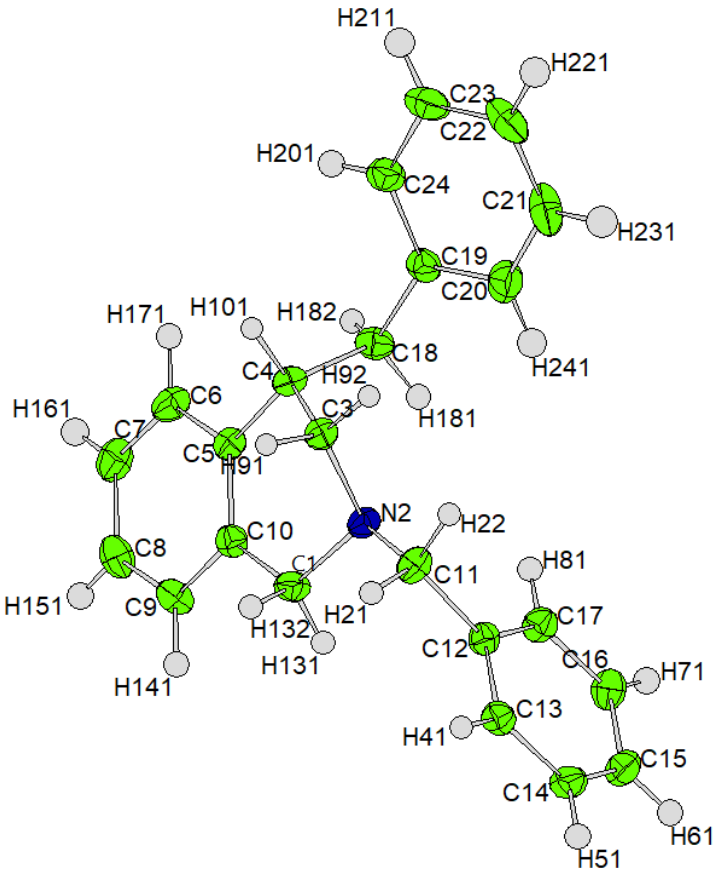
CCDC deposition number 2347994, **178** is a previously reported structure, see Xu, L. Zhu, H. Long, G. Zhao, J. Li, D. Ganguly, R. Li, Y. X, Q. H. Zhang, Q. *J. Mater. Chem.* **2015**, *3*, 9191.



178

Formula C23 H23 N1		Recrystallised from acetone by slow evaporation	
Crystal Class	orthorhombic	Space Group	P c c n
a	24.1315(3)	alpha	90
b	20.9517(2)	beta	90
c	6.92850(10)	gamma	90
Volume	3503.02(7)	Z	8
Radiation type	Cu K\a	Wavelength	1.541840
Dx	1.19	Mr	313.44
Mu	0.515	Temperature (K)	150
Size	0.20x 0.20x 0.20		
Colour	clear pale colourless	Shape	prism
Cell from	18114 Reflections	Theta range	4 to 76
Diffractometer type multi-scan		Scan type	OMEGA
Absorption type multi-scan		Transmission range	0.83 0.90
Reflections measured	36816	Independent reflections	3669
Rint	0.0004	Theta max	76.34

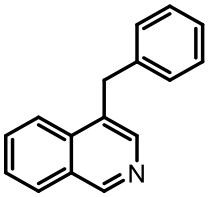
Hmin, Hmax	-30 30		
Kmin, Kmax	-25 18		
Lmin, Lmax	-8 8		
Refinement on Fsqd			
R-factor	0.041	Weighted R-factor	0.100
Max shift/su	0.0127		
Delta Rho min	-0.22	Delta Rho max	0.26
Reflections used	3668	sigma(I) limit	-3.00
Number of parameters	309	Goodness of fit	0.962



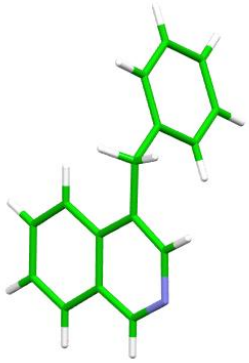
Thermal ellipsoids are drawn at the 50% probability level.

4-Benzylisoquinoline (201):

CCDC deposition number 2347992

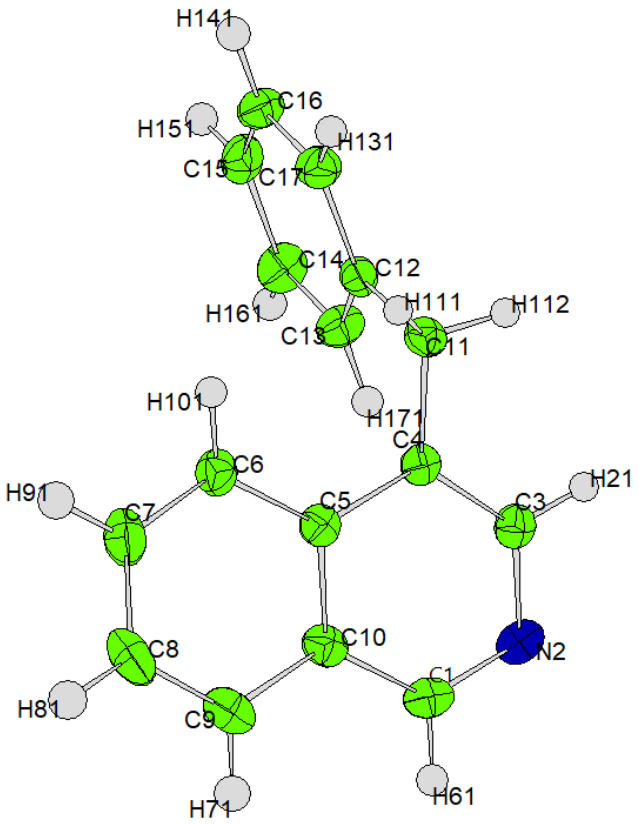


201



Formula C16 H13 N1		Recrystallised from acetone by slow evaporation	
Crystal Class	monoclinic	Space Group	P 21/n
a	6.4852(2)	alpha	90
b	8.1394(2)	beta	92.424(3)
c	21.9972(7)	gamma	90
Volume	1160.10(6)	Z	4
Radiation type	Cu K\a	Wavelength	1.541840
Dx	1.26	Mr	219.29
Mu	0.559	Temperature (K)	150
Size	0.01x 0.20x 0.30		
Colour	clear light colourless	Shape	plate
Cell from	3514 Reflections	Theta range	4 to 76
Diffractometer type multi-scan		Scan type	OMEGA
Absorption type multi-scan		Transmission range	0.92 0.99
Reflections measured	5629	Independent reflections	2389

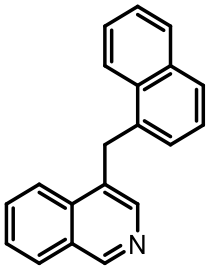
Rint	0.0002	Theta max	76.10
Hmin, Hmax	-6 8		
Kmin, Kmax	-10 9		
Lmin, Lmax	-27 27		
Refinement on Fsqd			
R-factor	0.042	Weighted R-factor	0.104
Max shift/su	0.0104		
Delta Rho min	-0.26	Delta Rho max	0.21
Reflections used	2389	sigma(I) limit	-3.00
Number of parameters	154	Goodness of fit	0.974



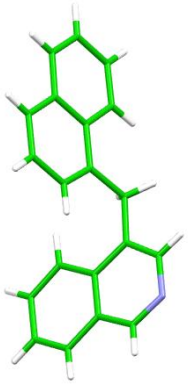
Thermal ellipsoids are drawn at the 50% probability level.

4-(Naphthalen-1-ylmethyl)isoquinoline (202):

CCDC deposition number 2347993

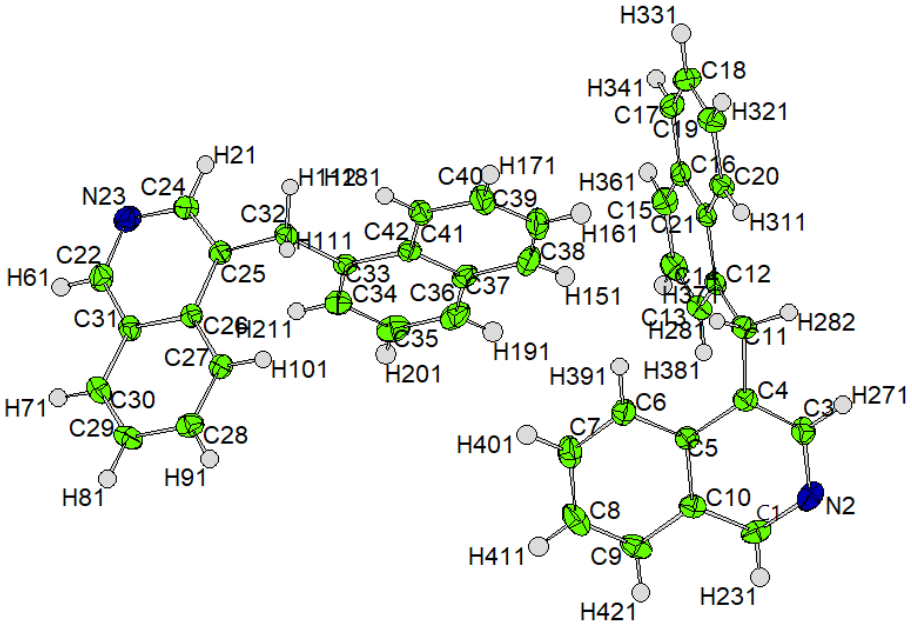


202



Formula C20 H15 N1		Recrystallised from acetone by slow evaporation	
Crystal Class	monoclinic	Space Group	P 21/n
a	15.7726(2)	alpha	90
b	8.89510(10)	beta	109.5290(11)
c	21.2757(2)	gamma	90
Volume	2813.24(6)	Z	8
Radiation type	Cu K\a	Wavelength	1.541840
Dx 1.27		Mr	538.69
Mu	0.563	Temperature (K)	150
Size	0.20x 0.20x 0.20		
Colour	clear colourless	Shape	shapeless
Cell from	32408 Reflections	Theta range	4 to 76
Reflections measured	71442	Independent reflections	5872
Rint	0.0004	Theta max	76.30
Hmin, Hmax	-17 19		

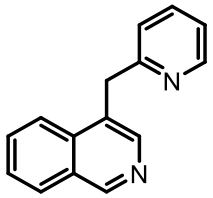
Kmin, Kmax	-11 11		
Lmin, Lmax	-26 26		
Refinement on Fsqd			
R-factor	0.038	Weighted R-factor	0.095
Max shift/su	0.0008		
Delta Rho min	-0.17	Delta Rho max	0.25
Reflections used	5872	sigma(I) limit	-3.00
Number of parameters	379	Goodness of fit	0.970



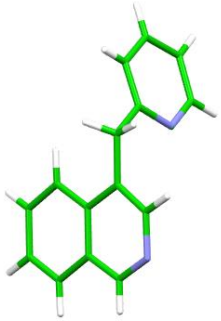
Thermal ellipsoids are drawn at the 50% probability level.

4-(Pyridin-2-ylmethyl)isoquinoline (209):

CCDC deposition number 2347995

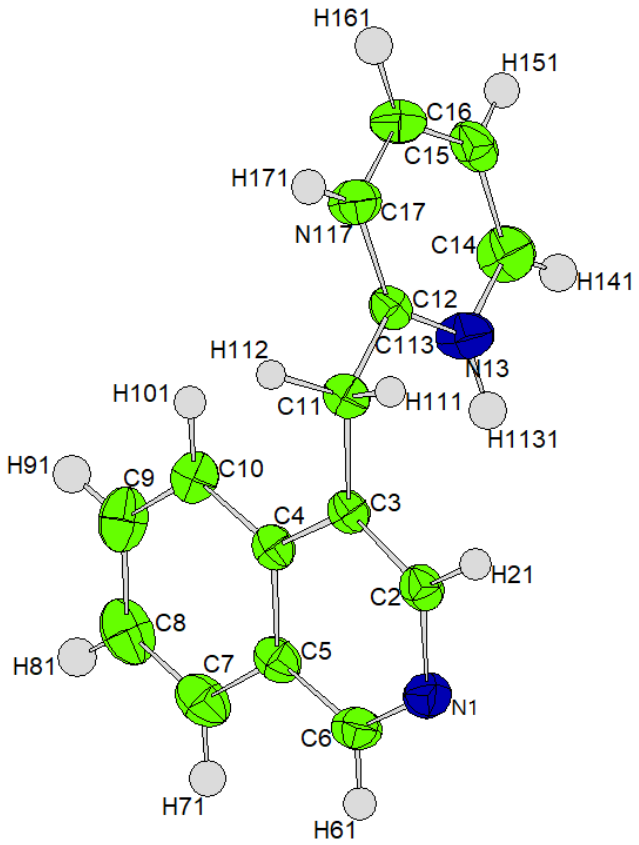


209



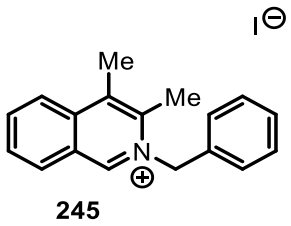
Formula C15 H12 N2		Recrystallised from acetone by slow evaporation	
Crystal Class	monoclinic	Space Group	P 21/n
a	6.4010(2)	alpha	90
b	8.1364(2)	beta	91.842(3)
c	21.7622(7)	gamma	90
Volume	1132.81(6)	Z	4
Radiation type	Cu K\a	Wavelength	1.541840
Dx	1.29	Mr	220.27
Mu	0.601	Temperature (K)	150
Size	0.10x 0.10x 0.20		
Colour	translucent light bronze	Shape	block
Cell from	3969 Reflections	Theta range	4 to 76
Diffractometer type multi-scan		Scan type	OMEGA
Absorption type multi-scan		Transmission range	0.85 0.94
Reflections measured	9273	Independent reflections	2338
Rint	0.0003	Theta max	76.25

Hmin, Hmax	-7 7		
Kmin, Kmax	-7 10		
Lmin, Lmax	-27 27		
Refinement on Fsqd			
R-factor	0.048	Weighted R-factor	0.106
Max shift/su	0.0003		
Delta Rho min	-0.22	Delta Rho max	0.23
Reflections used	2338	sigma(I) limit	-3.00
Number of parameters	155	Goodness of fit	0.994



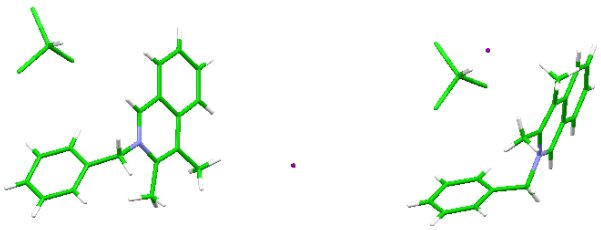
Thermal ellipsoids are drawn at the 50% probability level.

2-Benzyl-3,4-dimethylisoquinolin-2-ium iodide chloroform mono-solvate (245):



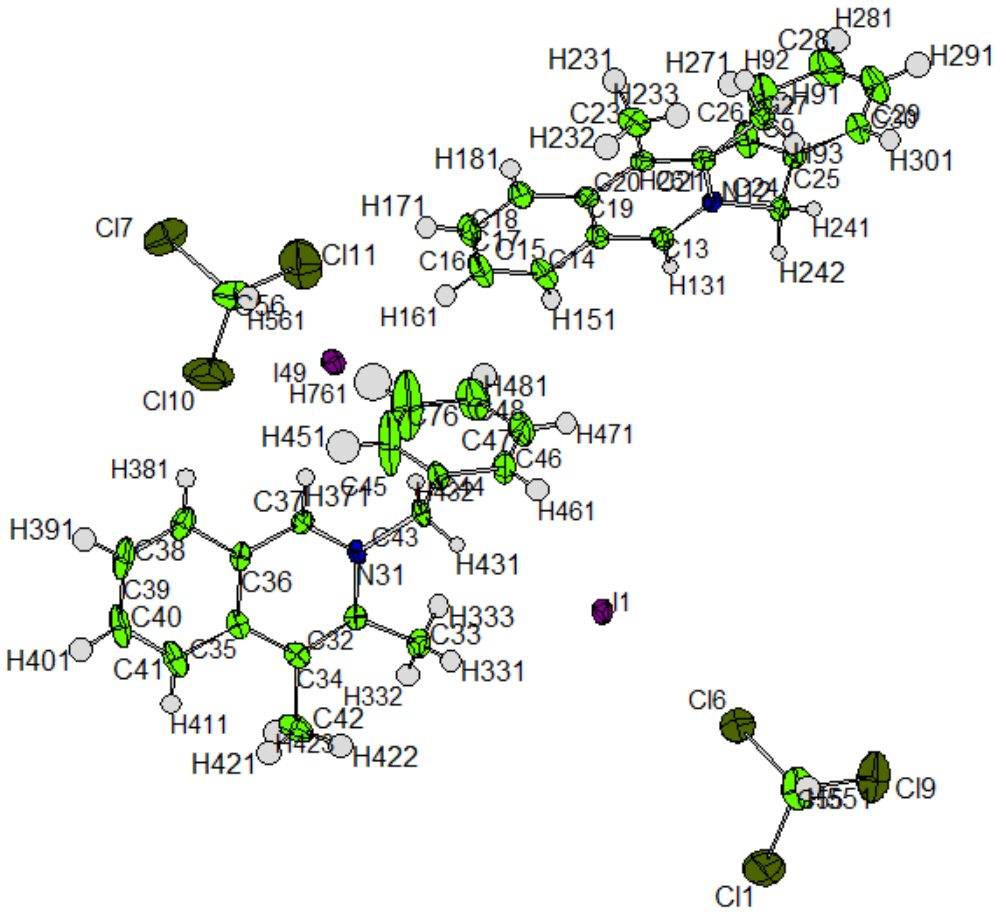
245

$CHCl_3$



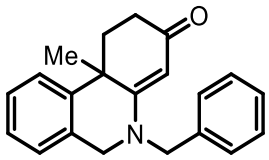
Formula	C19 H19 Cl3 I1 N1	Recrystallised from chloroform by slow evaporation	
Crystal Class	triclinic	Space Group	P -1
a	10.7398(2)	alpha	75.0797(14)
b	11.4511(2)	beta	89.7666(12)
c	17.0842(2)	gamma	82.9145(14)
Volume	2013.88(6)	Z	4
Radiation type	Cu K\a	Wavelength	1.541800
Dx	1.63	Mr	989.26
Mu	16.151	Temperature (K)	150
Size	0.20x 0.20x 0.20		
Colour	clear light colourless	Shape	block
Cell from	30505 Reflections	Theta range	4 to 76
Standard Interval	0	Standard Count	0
Diffractometer type	multi-scan	Scan type	OMEGA
Absorption type	multi-scan	Transmission range	0.02 0.04
Reflections measured	39783	Independent reflections	8367
Rint	0.0005	Theta max	76.30

Hmin, Hmax	-13 13		
Kmin, Kmax	-14 14		
Lmin, Lmax	-20 21		
Refinement on Fsqd			
R-factor	0.032	Weighted R-factor	0.084
Max shift/su	0.0041		
Delta Rho min	-1.17	Delta Rho max	0.98
Reflections used	8367	sigma(I) limit	-3.00
Number of parameters	433	Goodness of fit	1.002

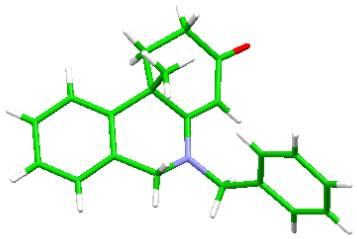


Thermal ellipsoids are drawn at the 50% probability level.

(*RS*)-5-Benzyl-10b-methyl-1,5,6,10b-tetrahydrophenanthridin-3(2H)-one (247):

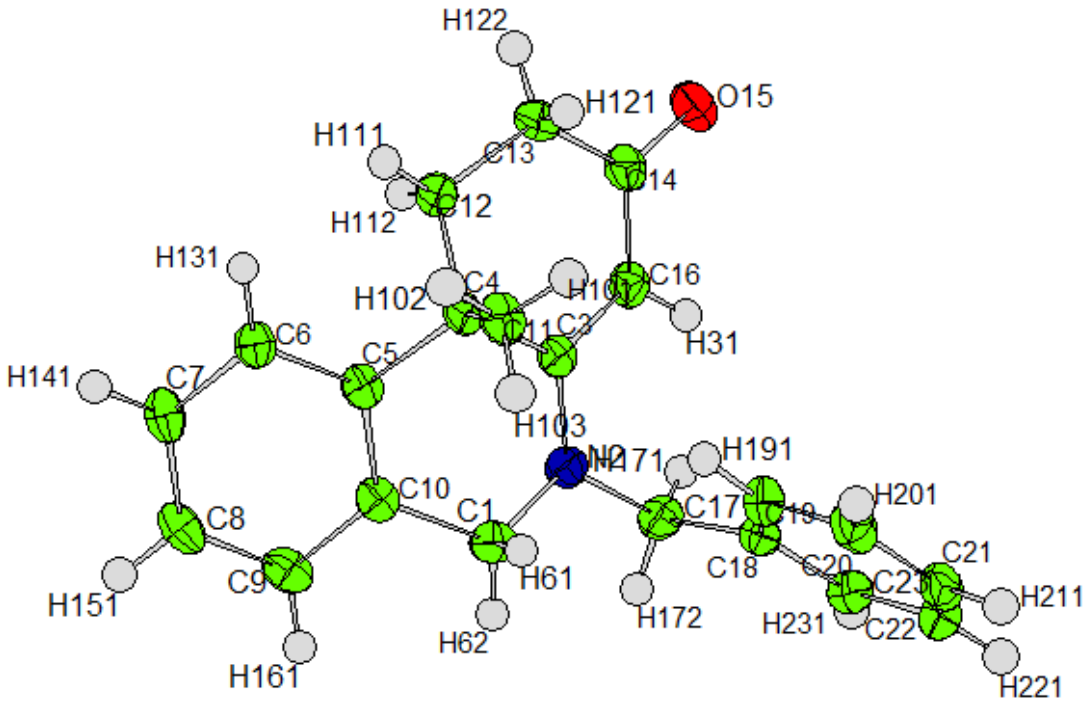


247



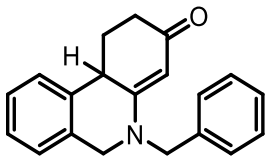
Formula	C21 H21 N1 O1	Recrystallised from acetone by slow evaporation	
Crystal Class	monoclinic	Space Group	I 1 a 1
a	10.5618(4)	alpha	90
b	17.0539(7)	beta	104.178(4)
c	9.044(3)	gamma	90
Volume	1579.42(11)	Z	4
Radiation type	Cu K\a	Wavelength	1.541800
Dx	1.28	Mr	303.40
Mu	6.02	Temperature (K)	150
Size	0.10 x 0.10 x 0.10		
Colour	translucent pale colourless	Shape	prism
Cell from	2391 Reflections	Theta range	5 to 75
Standard Interval	0	Standard Count	0
Diffractometer type	multi-scan	Scan type	OMEGA
Absorption type	multi-scan	Transmission range	0.93 0.94
Reflections measured	4881	Independent reflections	2117
Rint	0.032	Theta max	75.42
Hmin, Hmax	-13 13		

Kmin, Kmax	-21 21		
Lmin, Lmax	-11 8		
Refinement on Fsqd			
R-factor	0.0398	Weighted R-factor	0.0919
Max shift/su	0.0005483		
Delta Rho min	-0.17	Delta Rho max	0.14
Reflections used	2117	sigma(I) limit	-3.00
Number of parameters	209	Goodness of fit	1.0066
Flack parameter	-0. 1(5)		

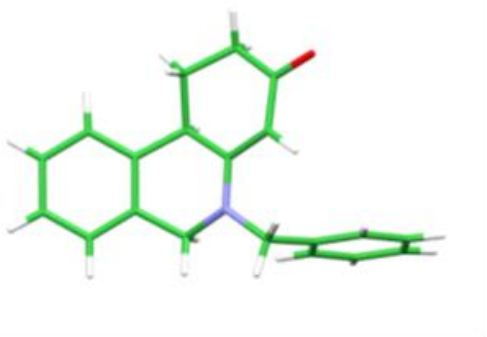


Thermal ellipsoids are drawn at the 50% probability level.

(*RS*)-5-Benzyl-1,5,6,10b-tetrahydrophenanthridin-3(2H)-one (256):

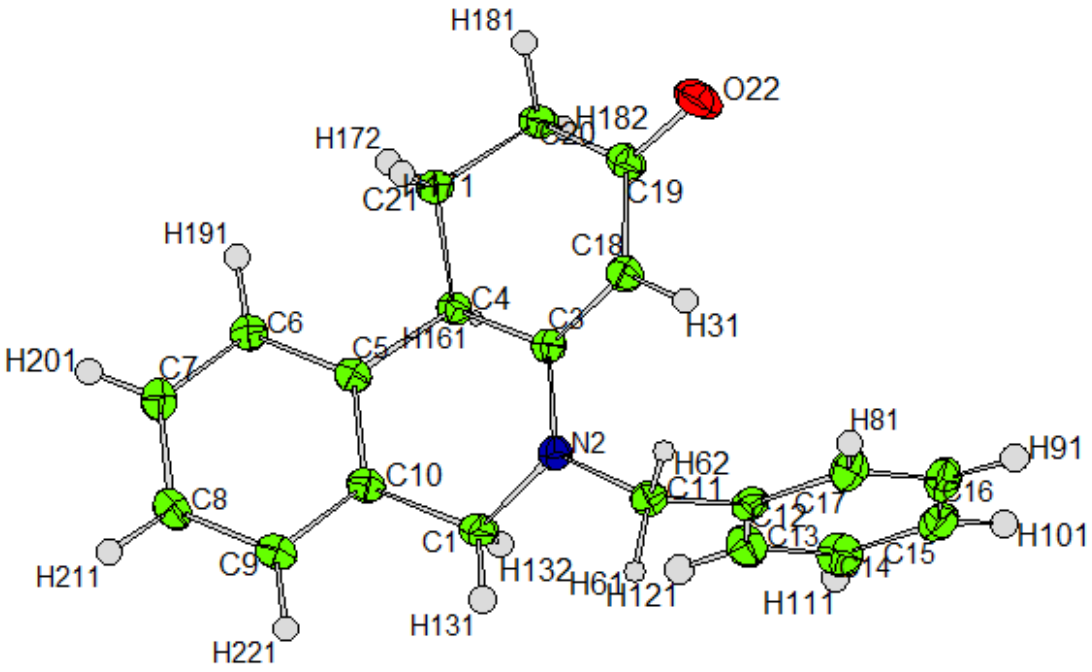


256



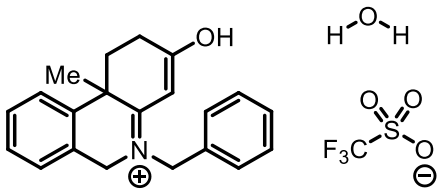
Formula C20 H19 N1 O1	Recrystallised from chloroform by slow evaporation
Crystal Class monoclinic	Space Group P 21/c
a 11.1926(1)	alpha 90
b 13.6162(1)	beta 116.0549(8)
c 11.0720(1)	gamma 90
Volume 1515.90(2)	Z 4
Radiation type Cu K\a	Wavelength 1.54184
Dx 1.27	Mr 289.38
Mu 6.04	Temperature (K) 100
Size 0.05x 0.10x 0.10	
Colour translucent pale colourless	Shape lath
Cell from 41888 Reflections	Theta range 3 to 75
Standard Interval 0	Standard Count 0
Diffractometer type multi-scan	Scan type OMEGA
Absorption type multi-scan	Transmission range 0.91 0.97
Reflections measured 58838	Independent reflections 3107
Rint 0.022	Theta max 75.41

Hmin, Hmax	-14 13		
Kmin, Kmax	-14 16		
Lmin, Lmax	-13 13		
Refinement on Fsqd			
R-factor	0.0385	Weighted R-factor	0.0999
Max shift/su	0.0003425		
Delta Rho min	-0.21	Delta Rho max	0.39
Reflections used	3107	sigma(I) limit	-3.00
Number of parameters	199	Goodness of fit	0.9671

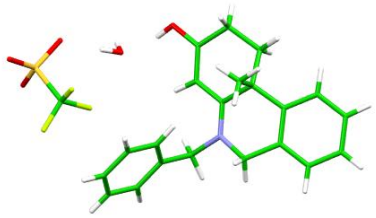


Thermal ellipsoids are drawn at the 50% probability level.

(*RS*)-5-Benzyl-3-hydroxy-10b-methyl-1,2,6,10b-tetrahydrophenanthridin-5-ium trifluoromethanesulfonate monohydrate (258):

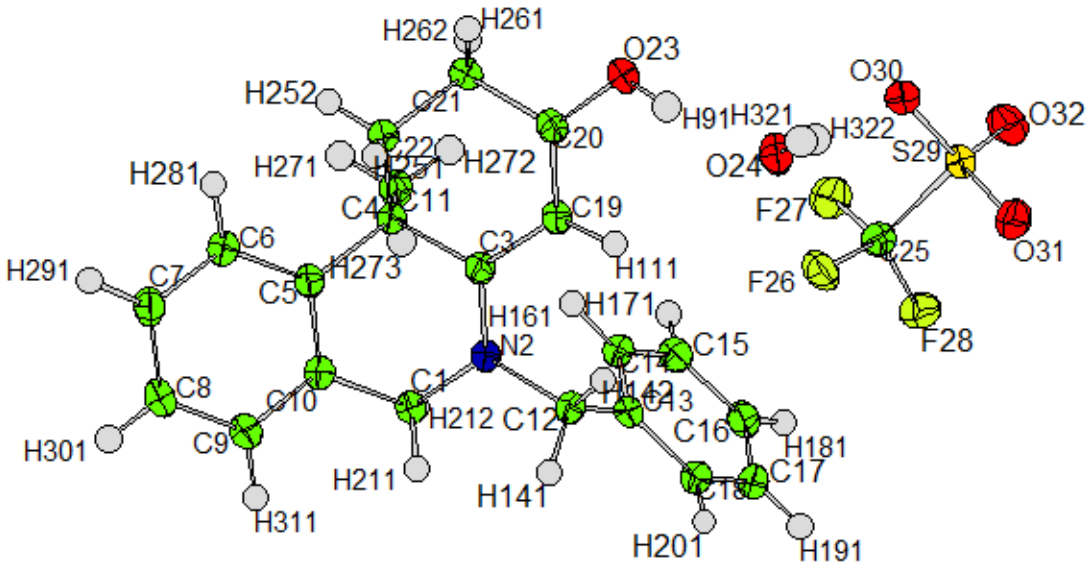


258



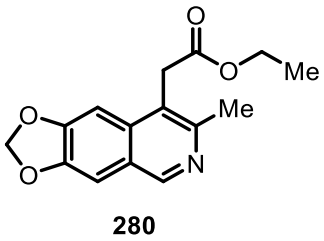
Formula C22 H24 F3 N1 O5 S1	Recrystallised from chloroform by slow evaporation
Crystal Class monoclinic	Space Group P 21/c
a 11.4345(1)	alpha 90
b 16.5127(2)	beta 109.6524(13)
c 11.8761(1)	gamma 90
Volume 2111.76(4)	Z 4
Radiation type Cu K\a	Wavelength 1.541800
Dx 1.48	Mr 471.50
Mu 19.23	Temperature (K) 100
Size 0.02x 0.10x 0.10	
Colour clear pale colourless	Shape plate
Cell from 13022 Reflections	Theta range 5 to 76
Standard Interval 0	Standard Count 0
Diffractometer type multi-scan	Scan type OMEGA
Absorption type multi-scan	Transmission range 0.73 0.96
Reflections measured 23191	Independent reflections 4361

Rint	0.0003	Theta max	75.96
Hmin, Hmax	-14 14		
Kmin, Kmax	-20 20		
Lmin, Lmax	-14 13		
Refinement on Fsqd			
R-factor	0.039	Weighted R-factor	0.103
Max shift/su	0.0006		
Delta Rho min	-0.55	Delta Rho max	0.26
Reflections used	4361	sigma(I) limit	-3.00
Number of parameters	289	Goodness of fit	0.980

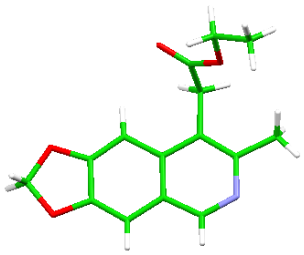


Thermal ellipsoids are drawn at the 50% probability level.

Ethyl 2-(7-methyl-[1,3]dioxolo[4,5-g]isoquinolin-8-yl)acetate (280):

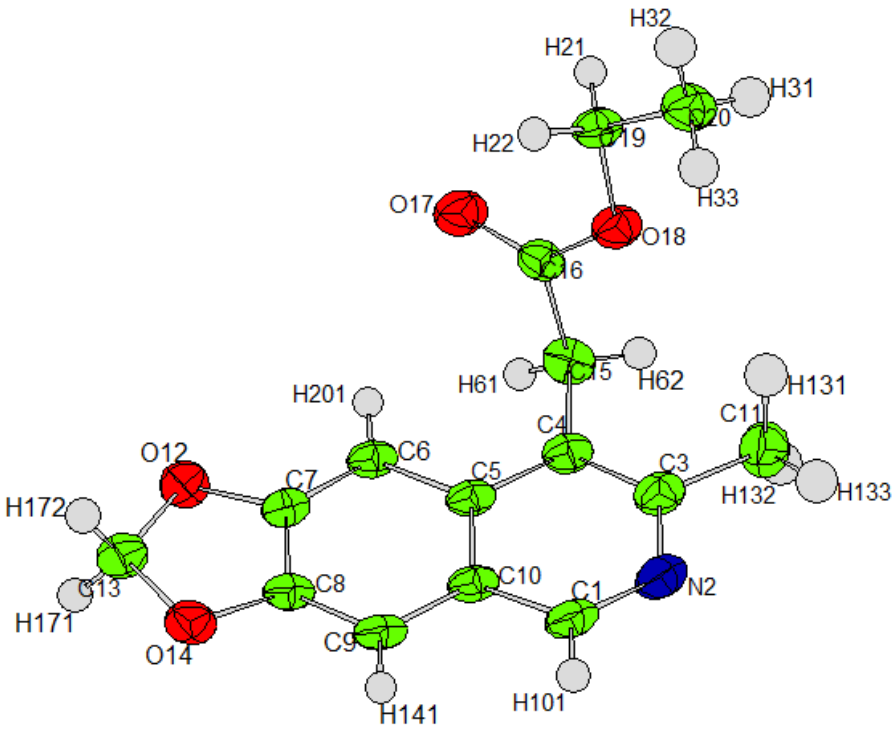


280



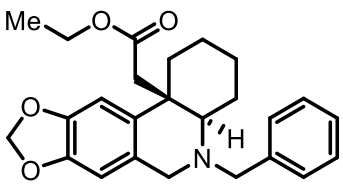
Formula	C15 H15 N1 O4	Recrystallised from acetone by slow evaporation	
Crystal Class	triclinic	Space Group	P -1
a	4.4575(4)	alpha	98.731(8)
b	8.8401(9)	beta	92.383(8)
c	17.1177(15)	gamma	99.394(8)
Volume	656.22(11)	Z	2
Radiation type	Cu K\a	Wavelength	1.54184
Dx	1.38	Mr	273.29
Mu	8.37	Temperature (K)	150
Size	0.01x 0.10x 0.80		
Colour	translucent pale colourless	Shape	lath
Cell from	3161 Reflections	Theta range	5 to 76
Standard Interval	0	Standard Count	0
Diffractometer type	multi-scan	Scan type	OMEGA
Absorption type	multi-scan	Transmission range	0.44 0.99
Reflections measured	9636	Independent reflections	2696
Rint	0.067	Theta max	76.843

Hmin, Hmax	-5 5		
Kmin, Kmax	-9 11		
Lmin, Lmax	-21 21		
Refinement on Fsqd			
R-factor	0.0885	Weighted R-factor	0.2139
Max shift/su	0.0000971		
Delta Rho min	-0.37	Delta Rho max	0.46
Reflections used	2696	sigma(I) limit	-3.00
Number of parameters	181	Goodness of fit	1.0019



Thermal ellipsoids are drawn at the 50% probability level.

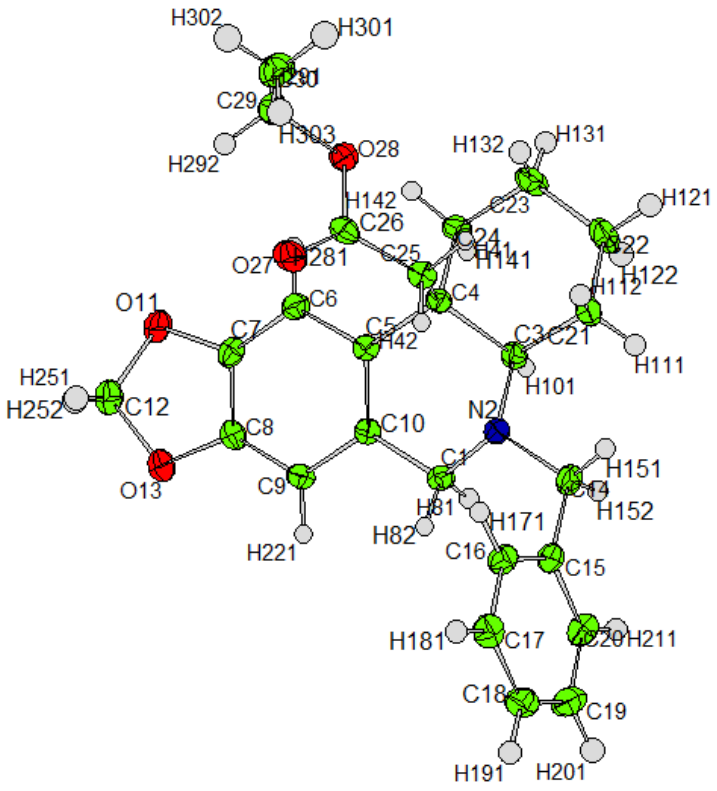
(*RS*, *RS*)-Ethyl 2-(5-benzyl-2,3,4,4a,5,6-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)acetate (307):



307

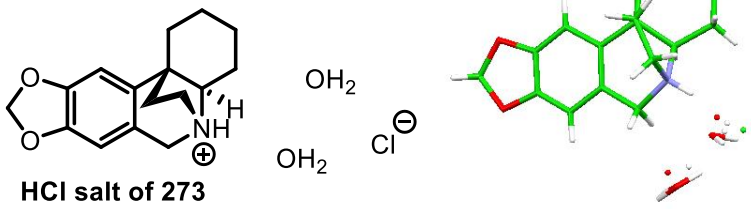
Formula C25 H29 N1 O4	Recrystallised from EtOAc by slow evaporation
Crystal Class triclinic	Space Group P -1
a 7.5106(1)	alpha 104.0095(19)
b 11.9895(2)	beta 105.5155(19)
c 12.2796(3)	gamma 93.0676(16)
Volume 1025.46(4)	Z 2
Radiation type Cu K\a	Wavelength 1.541840
Dx 1.32	Mr 407.51
Mu 0.713	Temperature (K) 150
Size 0.20x 0.30x 0.30	
Colour translucent pale yellow	Shape block
Cell from 14637 Reflections	Theta range 4 to 76
Standard Interval 0	Standard Count 0
Diffractometer type multi-scan	Scan type OMEGA
Absorption type multi-scan	Transmission range 0.78 0.87
Reflections measured 18816	Independent reflections 4261

Rint	0.0002	Theta max	76.23
Hmin, Hmax	-9 9		
Kmin, Kmax	-15 14		
Lmin, Lmax	-15 15		
Refinement on Fsqd			
R-factor	0.035	Weighted R-factor	0.095
Max shift/su	0.0004		
Delta Rho min	-0.25	Delta Rho max	0.25
Reflections used	4261	sigma(I) limit	-3.00
Number of parameters	271	Goodness of fit	0.974



Thermal ellipsoids are drawn at the 50% probability level.

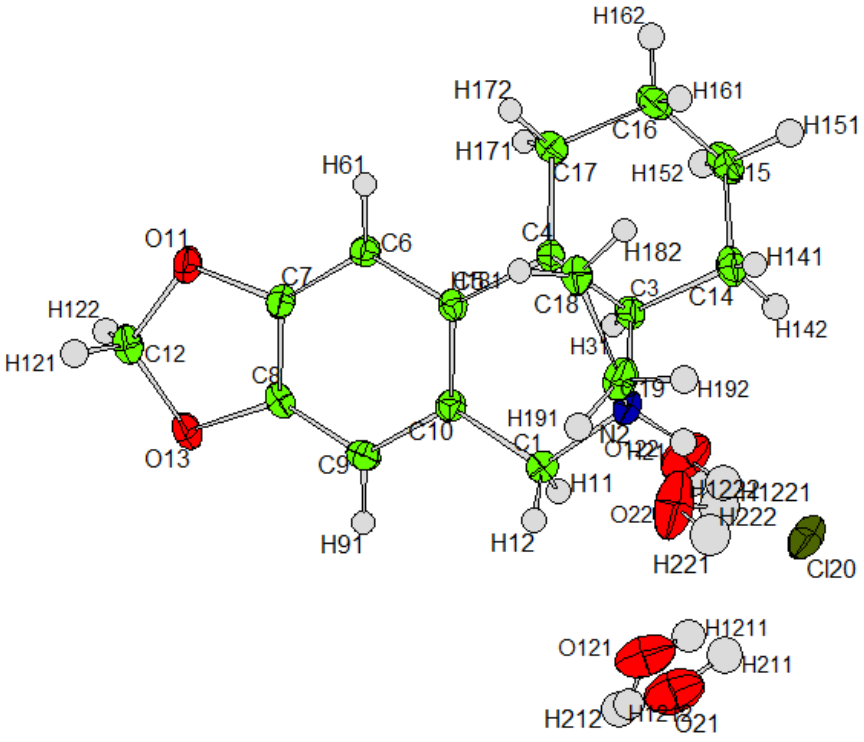
(*RS*, *RS*)-2,3,4,4a,5,6-Hexahydro-1H-5,11b-ethano[1,3]dioxolo[4,5-j]phenanthridin-5-ium chloride dihydrate (273):



HCl salt of 273

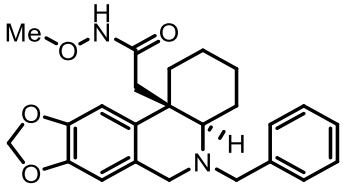
Formula	C16 H23.50 Cl1 N1 O4	Recrystallised from EtOAc/heptane by slow evaporation	
Crystal Class	monoclinic	Space Group	P 21/c
a	10.3738(2)	alpha	90
b	21.7216(4)	beta	91.7695(17)
c	6.9925(1)	gamma	90
Volume	1574.91(5)	Z	4
Radiation type	Cu K\a	Wavelength	1.541800
Dx	1.39	Mr	329.32
Mu	23.07	Temperature (K)	150
Size	0.10 x 0.10 x 0.20		
Colour	translucent pale colourless	Shape	shapeless
Cell from	6716 Reflections	Theta range	4 to 76
Standard Interval	0	Standard Count	0
Diffractometer type	multi-scan	Scan type	OMEGA
Absorption type	multi-scan	Transmission range	0.63 0.79
Reflections measured	12110	Independent reflections	3283

Rint	0.032	Theta max	76.35
Hmin, Hmax	-12 13		
Kmin, Kmax	-27 26		
Lmin, Lmax	-7 8		
Refinement on Fsqd			
R-factor	0.0423	Weighted R-factor	0.0982
Max shift/su	0.0011920		
Delta Rho min	-0.44	Delta Rho max	0.42
Reflections used	3283	sigma(I) limit	-3.00
Number of parameters	219	Goodness of fit	1.0037

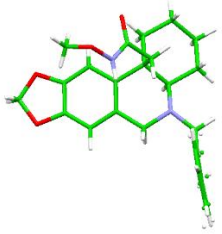


Thermal ellipsoids are drawn at the 50% probability level.

(*RS*, *RS*)-2-(5-benzyl-2,3,4,4a,5,6-hexahydro-[1,3]dioxolo[4,5-j]phenanthridin-11b(1H)-yl)-*N*-methoxyacetamide (317):



317

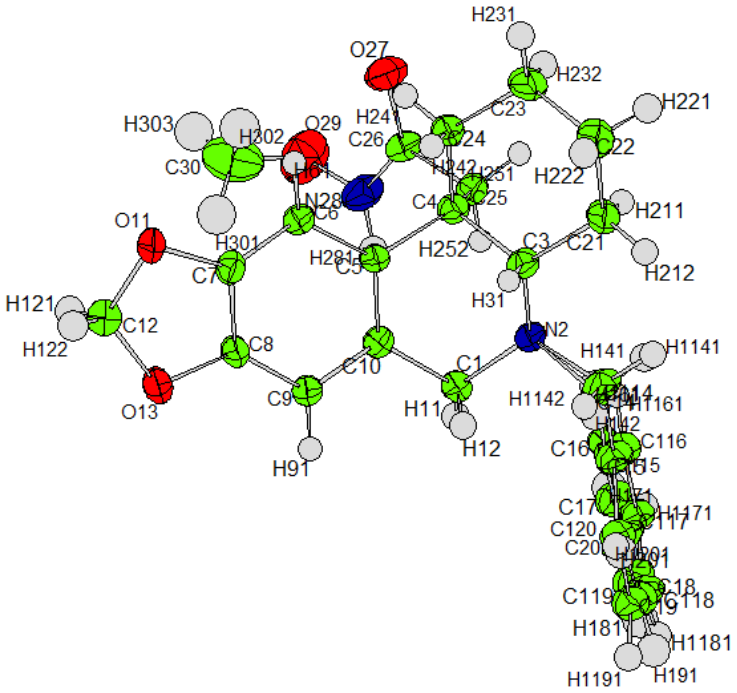


Formula	C21 H21 N1 O1	Recrystallised from	Et_2O/heptane by slow evaporation
Crystal Class	hexagonal	Space Group	P 61
a	16.9860(13)	alpha	90
b	16.9860(13)	beta	90
c	13.2605(8)	gamma	120
Volume	3313.4(5)	Z	6
Radiation type	Cu K\a	Wavelength	1.541800
Dx	1.23	Mr	408.50
Mu	6.77	Temperature (K)	150
Size	0.05 x 0.05 x 0.40		
Colour	translucent pale colourless	Shape	needle
Cell from	2634 Reflections	Theta range	4 to 74
Standard Interval	0	Standard Count	0
Diffractometer type	multi-scan	Scan type	OMEGA
Absorption type	multi-scan	Transmission range	0.08 0.97
Reflections measured	24908	Independent reflections	4510

Rint	0.138	Theta max	73.58
Hmin, Hmax	-21 21		
Kmin, Kmax	-20 21		
Lmin, Lmax	-16 16		

Refinement on Fsqd

R-factor	0.0986	Weighted R-factor	0.1782
Max shift/su	0.0209413		
Delta Rho min	-0.40	Delta Rho max	0.47
Reflections used	4509	sigma(I) limit	-3.00
Number of parameters	336	Goodness of fit	0.9873
Flack parameter	-0. 10(19)		



Thermal ellipsoids are drawn at the 50% probability level.