New catalytic methods for the derivatisation and functionalisation of electron deficient heteroaromatic compounds

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by

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Declaration

The work described in this thesis is entirely my own, except where I have either acknowledged help from a named person or given a reference to a public source. Text taken directly from another source has been enclosed in quotations marks and a reference to that respective source has been given.

Alexandru Grozavu

Oxford, Hilary Term 2019

Contents

Abstract

Introduction

The first part of Chapter 1 provides a brief review on the reactivity of pyridines and quinolines. Additionally, several well-established methods for the derivatisation and functionalisation of these electron-deficient heterocycles are highlighted.

The second part of Chapter 1 introduces the general principles of Transfer Hydrogenation (TH) and highlights how TH and related processes could be used in modern catalysis.

"Interrupted Transfer Hydrogenation" (ITH)

Chapter 2 introduces a novel reactivity mode for quinolinium salts. The first part of the chapter focuses on the initial reaction development. This is followed by a comprehensive substrate scope and attempts to induce enantioselectivity on privileged substrates. Finally, the focus was shifted towards mechanistic investigations that allowed us to propose a mechanism of action for this novel methodology.

Chapter 3 presents how the ITH methodology was extended to encompass electron-deficient pyridines. The substrate scope for pyridiniums that bear an electron-withdrawing group at the 4- position was investigated. Additionally, preliminary attempts to extend the ITH methodology to the less reactive 4-aryl pyridiniums are also highlighted in this chapter. Mechanistic investigations revealed a similar reaction pathway to that of quinoliniums. Additionally, preliminary findings lead to the discovery and development of a new reactivity mode for 4- substituted pyridines.

3,5-Dimethylation of 4-substituted pyridines

Chapter 4 introduces a rhodium catalysed 3,5-dimethylation of 4-substituted pyridines with methanol and formaldehyde. The reaction development, as well as a preliminary substrate scope and detailed mechanistic studies are presented. Additionally, the effect of the simple iodide ion on the catalytic system was also qualitatively assessed.

Experimental details

Chapter 5 contains detailed procedures and spectroscopic characterisation data for the compounds synthesised in this thesis.

Acknowledgements

Firstly, I would like to thank professor Timothy Donohoe for offering me the opportunity to work in his group on novel and exciting chemistry for the past 3 and a half years. Not only that he took a leap of faith and allowed me to work on novel and "unconventional" chemistry, but he knew how to motivate me in order to get the best out of my project.

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During my time in the TJD group I have had the opportunity to work and bounce ideas off great people and chemists. Special thanks deserve to go to the people that helped me conclude the first article on the ITH. More precisely, I would like to thank Dr Hamish H. Hepburn, Phillip J. Smith and last but not least Dr Harish K. Potukuchi. Without their help, our article would have not been as complete and impactful.

I am very grateful to my proof-readers: Hamish, Dr Simon Wubbolt and especially Tim. Without their help, this thesis would have contained many more errors. Additionally, their feedback helped me better explain some of my reasoning during my DPhil, and hopefully made some of the screening and optimisation sections easier to follow.

I am greatly indebted to my family for all their support, their sacrifices and the education they gave me. Without them I would have not been able to study at such a prestigious university for the past 7 years. Moreover, I have been taught that excellence is a habit, and you don't succeed to be admired, but to quench your thirst for knowledge. These life philosophies served me very well in this developing academic system.

Finally, I would like to thank my beautiful Alex (aka kiddo). Without your care and support, it might have been impossible to achieve so much in the last 6 months of my DPhil (doctor Phil) without losing all motivation or collapsing.

Glossary of abbreviations and acronyms

Ac	Acetyl
Add.	Additive
aq.	Aqueous
atm.	Atmosphere
Ar	Aryl/Argon
Bn	Benzyl
br	Broad singlet
cm^{-1}	Wavenumber
cod	1,5-cyclooctadiene
Conc.	Concentration
COSY	Correlated spectroscopy
Cp*	1,2,3,4,5-pentamethylcyclopendadienyl
DCE	Dichloroethane
DCM	Dichloromethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
equiv.	equivalent
ESI	Electrospray ionisation
Et	Ethyl
EWG	Electron-withdrawing group
FCC	Flash column chromatography
g	gram(s)
h	Hour
IR	Infra-red
LUMO	Lowest unoccupied molecular orbital
HMBC	Heteronuclear Multiple Bond Correlation
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
*i*Pr	Isopropyl
M	Molar
m	*meta*
Me	Methyl
mg	Milligram(s)
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
mol%	Molar percent
m.p.	Melting point

m/z	Mass to charge ratio
*n*Bu	*n*Butyl
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
o	*ortho*
p	*para*
Ph	Phenyl
pKa	Logarithmic acid dissociation constant
ppm	Parts per million
RT	Room temperature
SM	Starting material
T	Temperature
TBS	*tert*-Butyldimethylsilyl
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
UV	Ultra-violet
[α]	Specific rotation
Δ	Heated at reflux
δ	Chemical shift
ν_{max}	Infra-red absorption maximum
µ	Micro
°C	Degree Celsius

Chapter 1: Introduction

1.1 Derivatisation and functionalisation of electron deficient heteroaromatic compounds

Aromatic heterocycles that contain basic nitrogen centres, such as pyridines and quinolines, are widely spread in Nature and ubiquitous in pharmaceuticals and molecules of biological interest.[1]

Nicotinic acid **1** along with its amide **2** are examples of simple pyridine alkaloids that are essential to life and belong to the B group of vitamins. The daily requirement of an adult is approximately 20 mg, and deficiency of nicotinic acid can lead to pellagra, a skin disease.[2] Along with nicotine **3**, similar pyridine alkaloids such as nornicotine **4**, anabasine **5** and nicotyrine **6** are examples of natural products isolated from the tobacco metabolites.[3,4]

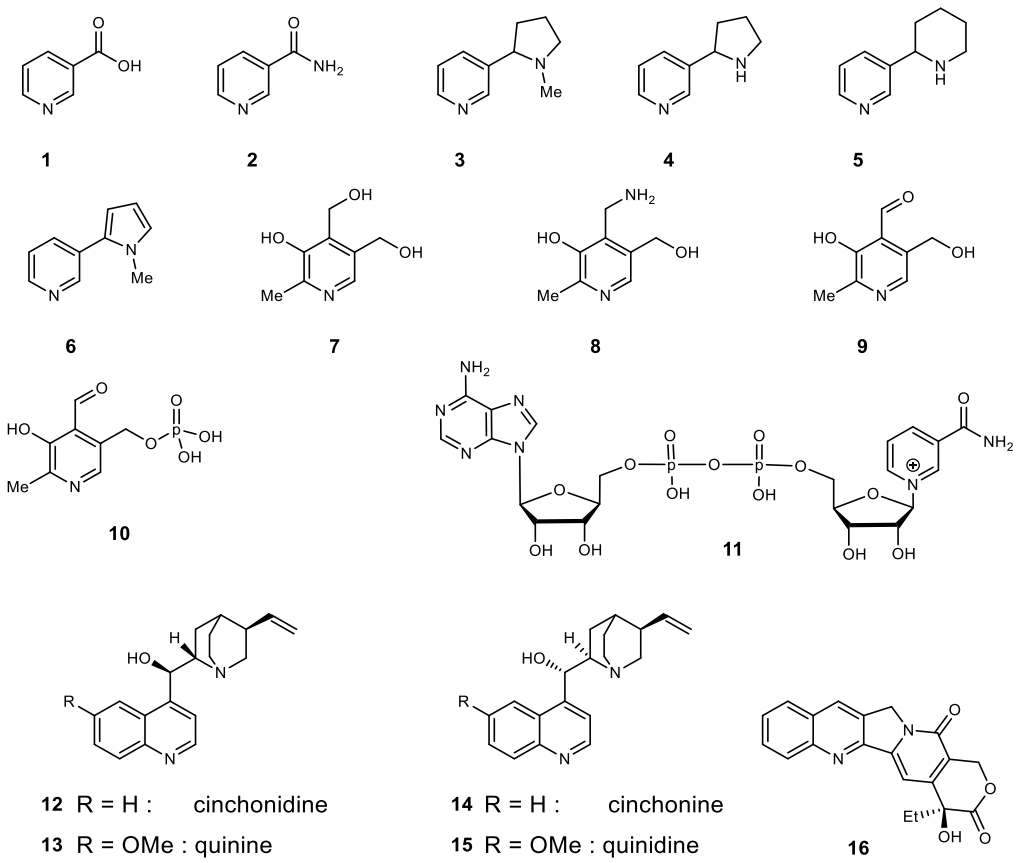


Figure 1.1 Selected pyridine and quinoline motifs found in natural products

Other pyridine derived compounds such as pyridoxol **7**, pyridoxal **8**, pyridoxamine **9** are also part of the B group of vitamins and play important roles in metabolism.[5] For example, pyrodoxal phosphate **10** is a coenzyme involved in the metabolism of amino acids while nicotinamide adenine dinucleotide **11** (NAD^+) and its reduced form NADH are key components of the oxidoreductase enzymes.[6]

The quinoline motif has been found to be privileged in natural products as well. The diastereoisomeric pairs cinchonidine **12** / cinchonine **14** and quinine **13** / quinidine **15,** first isolated from the cinchona bark, [7–9] are very valuable reagents within the chiral pool and have been used by chemists to induce enantioselectivity.[10–13] Another example of a quinoline derived natural product is camptothecin **16,** a highly toxic compound isolated from the stem wood of the Chinese tree Campotheca acuminate.[14]

Pyridine and quinoline derivatives are of high interest both as pharmaceuticals and as compounds with biological activity. Isonicotinic acid derivatives can be used as anticoagulants and vasodilators. Compounds **17** and **18** are used as tuberculostatic agents, while compound **19** is used as an antihistamine. [1,15] 1,4-Dihydropyridines such as Nifedipine **20** are used as antihypertensive agents that target calcium channels.[16] Sulphonamide **21** was one of the first antibacterial agents. [1,17] The penta-substituted pyridine Cerivastatin **22** is a powerful HMG-CoA reductase inhibitor. [18]

Among quinoline derivatives, many have been found to show biological activity. Relatively simple compounds such as 8-hydroxyquinoline exhibit antiseptic properties.[19] Chloroquine **23** remains an important antimalarial drug, despite its being one of the oldest drugs of the class.[20] 4-Quionolone derivatives such as Nalidixic acid **24,** Ciprofloxacin **25** and Moxifloxacin **26** are antibacterial agents.[21] The quinoline derivative Quinmerac **27** is used as a herbicide for broad

level weeds.[22] Methoxatin (pyrroloquinoline quinone) **28** is a redox cofactor that is found in breastmilk.[23]

Isoquinolines are another widely spread class of heteroaromatics that contain one basic nitrogen centre. There are more than 600 reported natural products that contain the isoquinoline motif.[24,25]

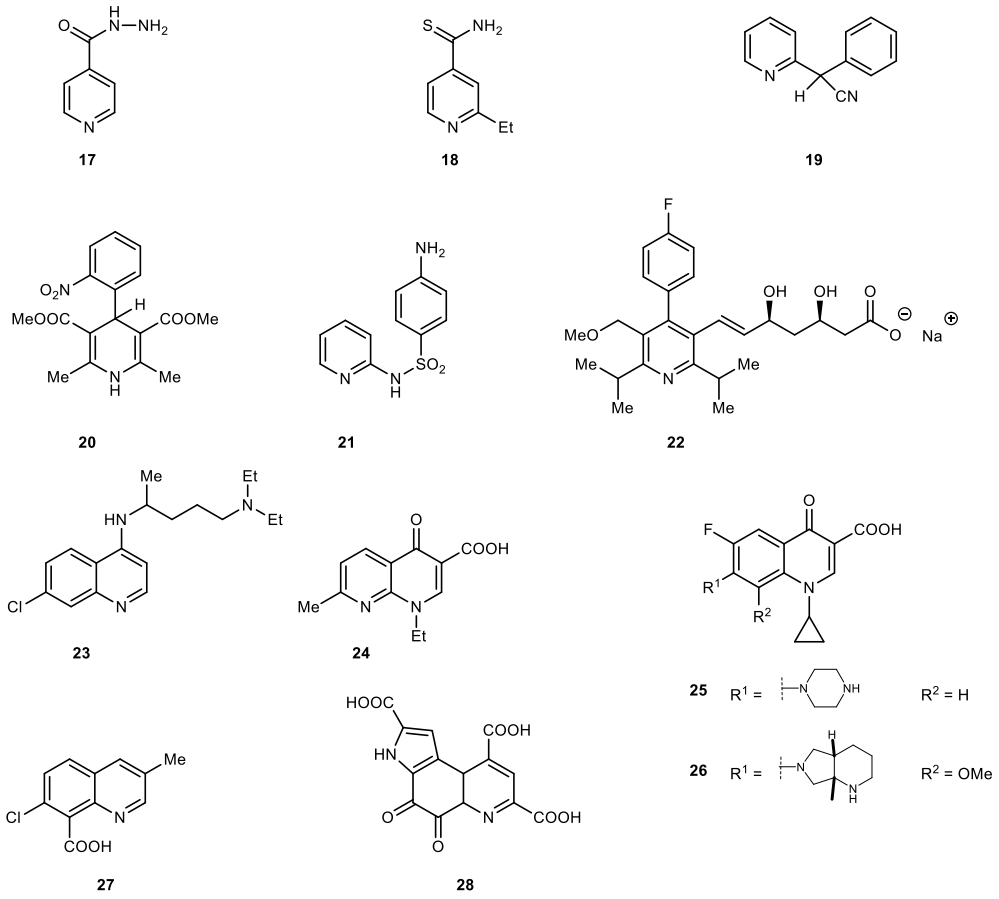


Figure 1.2 Selected pyridine and quinoline motifs found in biologically active compounds

1.1.1 Derivatisation and functionalisation of azaarenes that conserves aromaticity

An aromatic compound is a flat cyclic molecule with a ring of conjugated and delocalised bonds which exhibits higher stability than a hypothetical localised structure. The most common aromatic compounds are benzene derivatives. Nevertheless, other classes of compounds exhibit aromaticity, and a large class of compounds in this category are heteroaromatic compounds, in particular azaarenes.

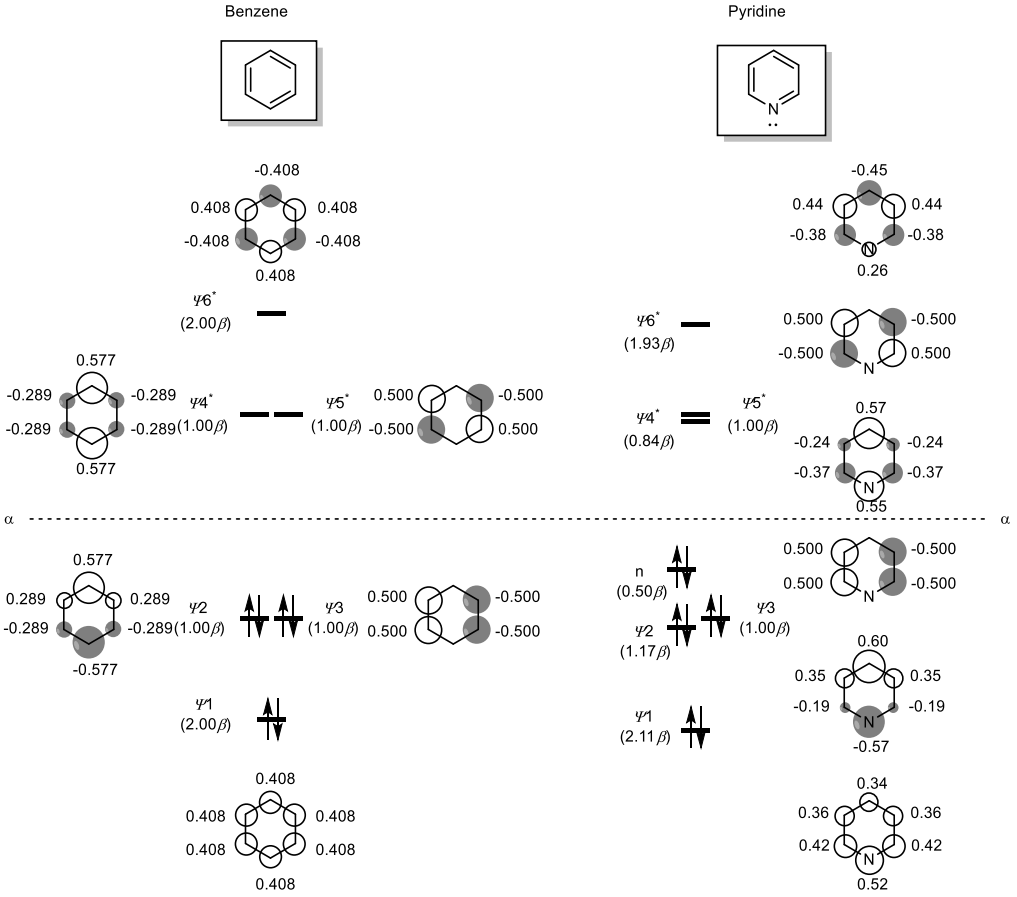


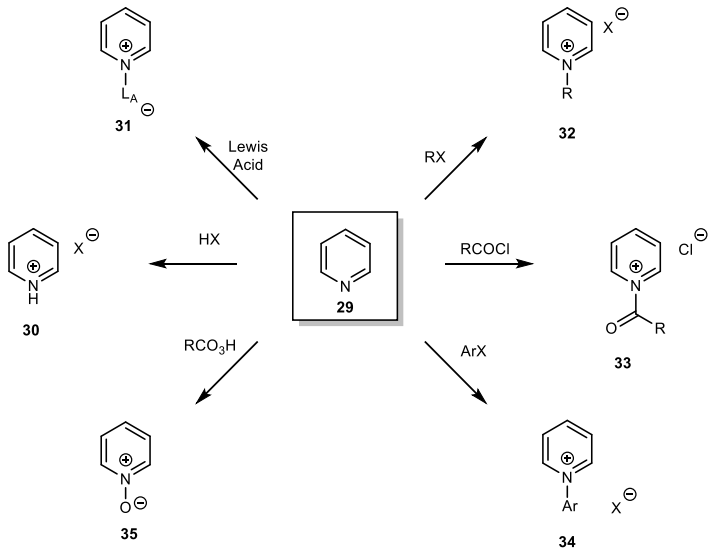
Figure 1.3 Frontier orbitals for benzene and pyridine calculated with the Hückel method[26]

Benzene and pyridine are very similar in some respects, the latter being derived from benzene by replacing one CH unit with one nitrogen atom. This renders the 2-, 3- and 4- positions of the pyridine ring non-equivalent. As a consequence, the 6 π-molecular orbitals are no longer degenerate (**Figure 1.3**). In the pyridine system the empirical resonance is $\Delta E_\pi = 134$ kJ mol^{-1}, while for benzene $\Delta E_\pi = 150$ kJ mol^{-1}. [1] This suggests that pyridine is slightly less aromatic than benzene. However, both pyridine and benzene tend to maintain this aromatic stabilisation, hence addition reactions are usually followed by elimination in order to restore aromaticity.

In addition, pyridine is found to have a permanent dipole moment of 2.22 D with its negative end pointing towards the nitrogen atom.[1] The lone pair on the nitrogen is located in a sp^2 hybridised orbital which is in the plane of the aromatic ring, and it is the highest in energy,

making it the HOMO of pyridine. In contrast to benzene, pyridine can exhibit electrophilic reactions on this nitrogen lone pair.

1.1.1.1 Electrophilic reactions on nitrogen



Scheme 1.1 Electrophilic reactions on nitrogen

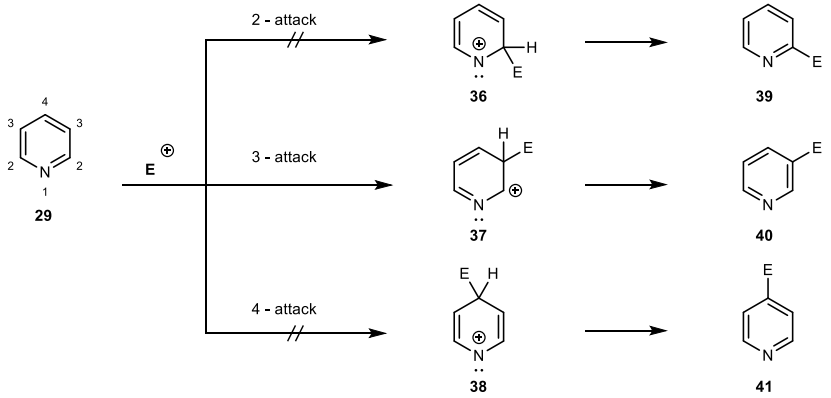
Due to the lone pair on nitrogen, pyridine (**29**) is a Lewis base as well as a weak Brønsted base with a pKa of 5.2.[27] It reacts with strong inorganic acids to give salts **30** that are soluble in water, making its removal from organic mixtures easier.[28,29] It also reacts with Lewis acids to form N-adducts of type **31**.[30] The SO_3 adduct can be used as a sulfonating reagent, while chromate pyridium complexes can be used as oxidizing reagents. [31,32]

Reaction of pyridine with alkyl halides leads to pyridinium quaternary salts **32**.[33] Acid chlorides and carboxylic acid anhydrides can also react with pyridines on the nitrogen. The resulting *N*-acyl pyridinium salts **33** are very reactive and susceptible to hydrolysis.[34] Pyridines can also be added to very reactive aryl chlorides such as 1-chloro-2,4-dinitrobenzene to form aryl quaternary salts **34**. These compounds can undergo Zincke reactions, opening the pyridine ring in the presence of suitable nucleophiles. [35]

Heteroatoms can also be connected to the pyridine nitrogen. For example, treatment of pyridine with peroxy-acids leads to the formation of pyridine *N*-oxide **35**.[36] This reaction has been used to temporarily activate pyridines for electrophilic substitution, as the oxygen atom pushes electron density into the aromatic ring.

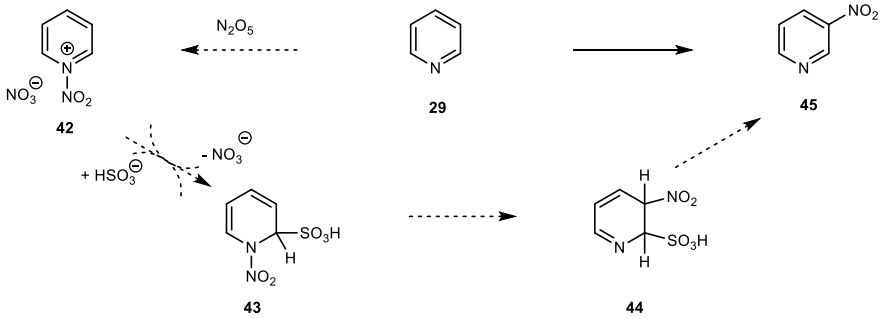
1.1.1.2 Electrophilic substitution reactions

Electrophilic substitution proceeds extremely slowly on pyridine in comparison with benzene, the reactivity of pyridine being comparable to that of nitro-benzene (~10^{-7} relative to benzene).[37,38] Electrophilic attack happens predominantly at the 3- position (**37**), as attack at either the 2- or 4- position will lead to a very unstable intermediate (**36** and **38**) with a positive charge on the nitrogen atom (**Scheme 1.2**). Moreover, the lone pair on the nitrogen can coordinate Lewis and Brønsted acids normally required for S_EAr catalysis, deactivating the aromatic ring even more.



Scheme 1.2 S_EAr pathway for pyridine

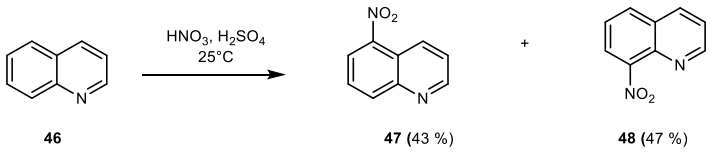
Nitration of pyridine is possible, but it proceeds under extremely forcing conditions (ca. 300°C) and yields modest amounts of 3-nitropyridine **45** (15%).[1] However, a good yield (70%) can be obtained if pyridine is reacted with N_2O_5 in SO_2. A mechanism involving intermediate **42** and a sequence of addition/elimination of SO_2 or SO_3H^- (formed by traces of water) was proposed (**Scheme 1.3**).[39]



Scheme 1.3 Nitration of pyridine in the presence of SO_3H^-

In order to activate pyridines for nitration, more than one methyl group is required. 2,6-Lutidine and 2,4,6-collidine undergo nitration at the 3- position more readily.[40] Stronger activating groups such as hydroxy or amino groups exhibit special features. For example, 3-hydroxypyridine undergoes nitration exclusively at the 2- position. [1,41] Amino groups activate and direct in a similar way, nitration occurring first on the amino group, which is then followed by a Bamberger-Hughes-Ingold rearrangement of the nitro group onto the aromatic ring.[42]

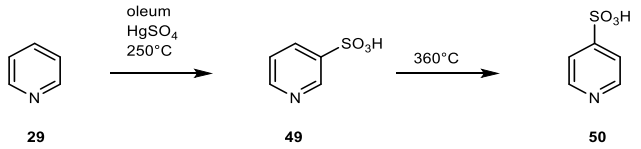
In comparison to pyridines, nitration of quinoline (**46)** requires much milder conditions, occurring at room temperature with a mixture of HNO_3/H_2SO_4.[43,44] The strongly acidic conditions fully protonate the quinoline, strongly deactivating the heterocyclic ring and directing the nitration exclusively at the 5- (**47**) and 8- (**48**) positions in a ratio of almost 1:1 (**Scheme1.4**).



Scheme1.4 Nitration of quinoline

Similar to the nitration of pyridines, sulfonation can be achieved under forcing conditions (250°C) in the presence of oleum and Hg (II) salts. The mercury salt is believed to reduce protonation of the nitrogen which will result in higher deactivation in comparison with mercury coordination. If the sulfonation is performed at 360°C or the 3- substituted isomer **49** is heated

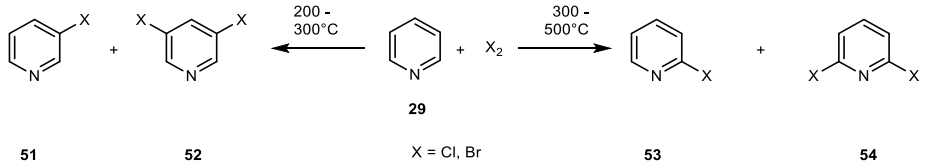
at the same temperature, the 4-substituted product **50** is obtained, indicating thermodynamic control (**Scheme 1.5**).[45]



Scheme1.5 Sulfonation of pyridine

Sulfonation of picolines always produces the 5-sulfonic acid, suggesting that a single methyl group is not enough to activate the ring and significantly change its electronics, which are mainly governed by the presence of the protonated nitrogen group in the ring. [46]

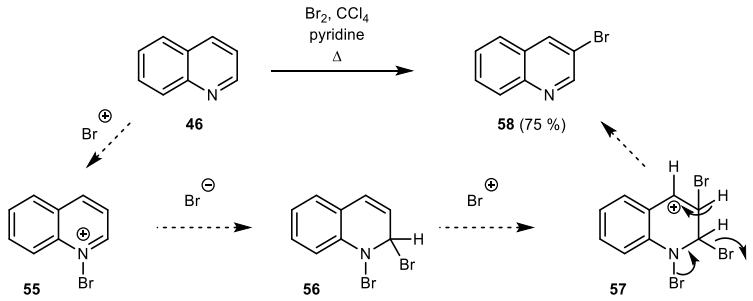
Halogenation of pyridines can occur with elemental halogen at high temperatures (~300°C) via a S_EAr mechanism and furnishes a mixture of 3-halo **51** and 3,5-dihalopyridines **52**. (**Scheme 1.6**) At temperatures above 300°C, a radical pathway is believed to account for the formation of the 2-halo **53** and 2,6-dihalopyridines **54**. [47]



Scheme 1.6 Halogenation of pyridine

The halogenation of quinolines can proceed through different mechanisms to achieve different products. The bromination of the carbocyclic ring is normally achieved with standard S_EAr conditions.[48]

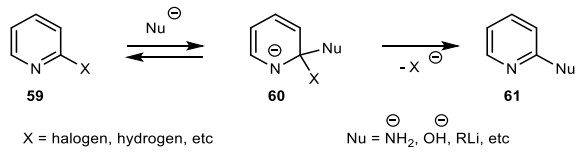
If the quinoline is reacted with Br_2 in carbon tetrachloride and in the presence of pyridine, bromination at the 3 position is achieved instead and compound **58** is the main product of the reaction. The mechanism is believed to involve a sequence of additions and eliminations initiated by a 1,2 addition of bromine (**Scheme 1.7**).[1,49]



Scheme 1.7 Bromination of the heterocyclic ring of quinoline[1,49]

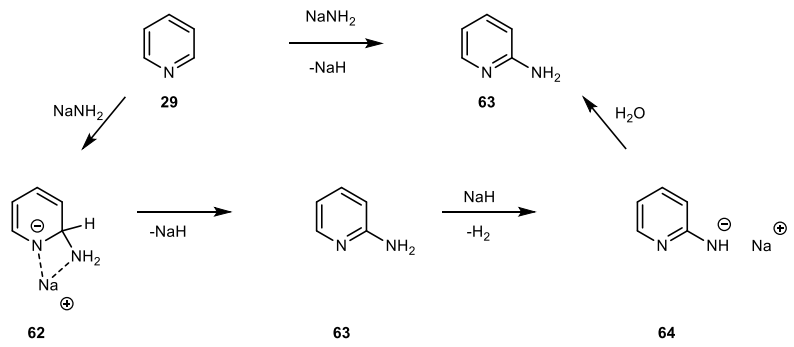
1.1.1.3 Nucleophilic substitution reactions

Due to their electron deficient nature, pyridines and quinolines are ideally suited for S_NAr reactions. The regiochemistry of nucleophilic addition is inverted to that of electrophilic substitution. The most stable Meisenheimer intermediates (**60**) are formed when the nucleophile adds into the ring at the 2- or 4- position, as these intermediates can delocalise the negative charge onto the nitrogen. The nucleophilic addition step could then be followed by elimination of a suitable leaving group to restore aromaticity. (**Scheme 1.8**).[1]



Scheme 1.8 Aromatic nucleophilic substitution pathway

Even though the hydride anion is classically a poor leaving group, strong nucleophiles such as amides or organolithium can react with unsubstituted pyridines at higher temperatures via a S_NAr pathway. For example, the Chichibabin reaction is the first S_NAr reaction known for pyridines.[50]



Scheme 1.9 Proposed mechanism for the Chichibabin reaction[1,50]

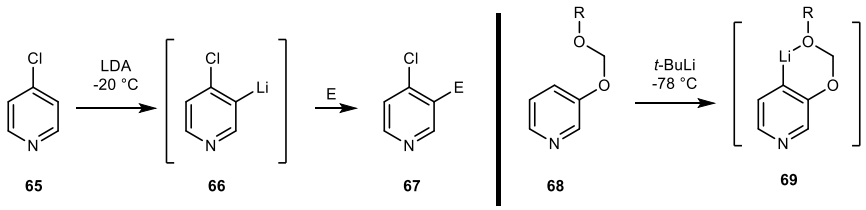
The mechanism of the reaction is believed to be more complex, but the simplified version suggests that coordination of sodium amide to the pyridine directs the addition to the 2- position to form intermediate **62**. This intermediate loses sodium hydride to form the product **63**. The driving force of the reaction is believed to be the irreversible deprotonation of the product to generate the sodium amide **64** and hydrogen. After aqueous work-up, product **63** is isolated (**Scheme 1.9**).

S_NAr reactions proceed faster for quinolines in comparison with pyridines, as the penalty for temporarily losing aromaticity is smaller for the former due to benzannulation. The Chichibabin reaction for quinolines produces a mixture of the 2- and 4- amines.[51] If the 2-position is blocked as in the case of 2-phenylquinoline, the 4-amino compound is produced.

Alkyl- or aryllithiums can also react with pyridine, substitution being favoured at the 2 position. [1,52] Pyridines show peculiar reactivity with Grignard reagents, the outcome being dependent on the nature of the Grignard but also the reaction solvent and temperature.[53] A shift in preference for 4 addition can be observed.

Organometallic reagents can also react with pyridine through metalation. The C-H lithiation can be facilitated by negative inductive effects (e.g. 4-chloropyridine **65**), in which case lithiation takes place *ortho* to the electron-withdrawing group (**Scheme 1.10**).[54] The resulting intermediate **66** is normally trapped with different electrophiles to yield derivatised pyridines

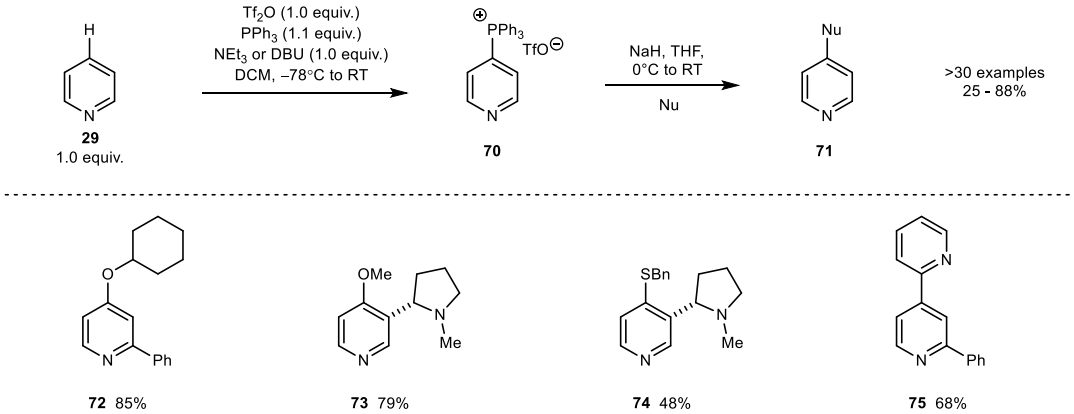
67. [55] Some lithiation can be assisted by directing groups.[56] These can stabilise the metal intermediate **69** through chelation. The lithiation of pyridines and related heterocycles can also be achieved through the well-established metal halogen exchange.[57]



Scheme 1.10 Pyridine metalation with organolithium reagents[54,55,56]

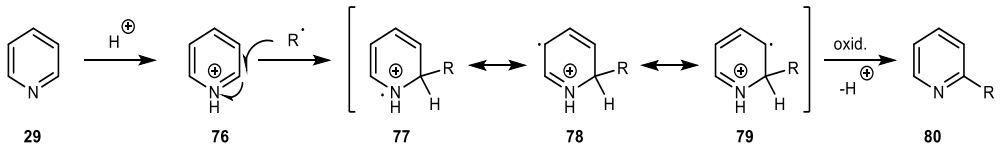
More recently, transition metal catalysed coupling reactions and C-H activations reactions have been extensively developed and preferred due their advantages over the use of stoichiometric organometallic reagents. These recent methodologies have also been employed in order to access functionalised pyridines and quinolines.[58]

McNally and co-workers have reported a method that allows the functionalisation of a unsubstituted pyridine in a two-step procedure.[59] The first step involves the formation of a phosphonium salt **70** from the unsubstituted pyridine in the presence of triflic anhydride and triphenyl phosphine. This step is followed by substitution of the phosphonium salt with different nucleophiles to yield different 4- substituted pyridines **71-75**. (**Scheme 1.11**)



Scheme **1.11** Functionalisation of pyridines via heterocyclic phosphonium salts[59]

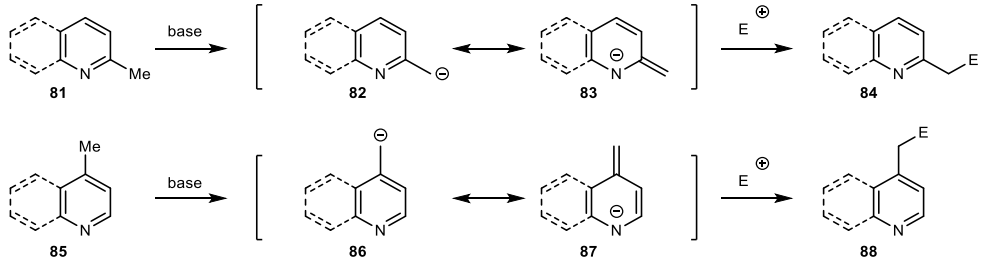
Another valuable method through which unsubstituted pyridines and quinolines are functionalised is the Minisci reaction,[60–63] where radicals are added to protonated pyridines (or quinolines), which subsequently rearomatize to furnish 2- and 4- substituted pyridines **80** (**Scheme 1.12**). The regiochemistry of the reaction can depend on sterics, electronics, as well as on the reversibility of the radical addition (kinetic and thermodynamic factors). The reaction was first pioneered by Minisci in the 60s,[59] but it has gained much attention recently due to advances in the ease of generating radicals through photo-redox catalysis.[64,65]



Scheme 1.12 Nucleophilic radical addition to a protonated pyridinium ion – the Minisci reaction

1.1.1.4 Side-chain reactions

Benzylic protons at the 2- or 4- positions of pyridines and quinolines are significantly more acidic due to the presence of the heterocyclic ring. Deprotonation in these cases leads to stable intermediates where the negative charge is partly delocalised on the nitrogen atom (**Scheme 1.13**). These deprotonated species resemble carbonyl enolates and can be reacted with electrophiles (alkyl halides,[66] alcohols (hydrogen borrowing: *vide infra*),[67,68] ketones,[69] esters,[70] etc) to functionalise the benzylic position.



Scheme 1.13 Reactivity of acidic benzylic positions of pyridines and quinolines[1]

Side alkyl groups can also be oxidised through various methods to furnish pyridine carboxylic acids. When more than one alkyl group is present, selective oxidation can be achieved. For

example, oxidation of 3,4-lutidine will yield as the major product the 4-carboxylic acid (*vide infra* **Scheme 3.6**).[71]

1.1.2 Derivatisation and functionalisation of azaarenes that removes aromaticity

The piperidine motif occupies a privileged position in natural products and compounds of biological relevance (**Figure 1.4**).[72–74] Heterocyclic compounds with different degrees of complexity, saturation and substitution have been found to show promising potential in clinical studies, hence much effort has been put in developing new methods to access such compounds.[75–77]

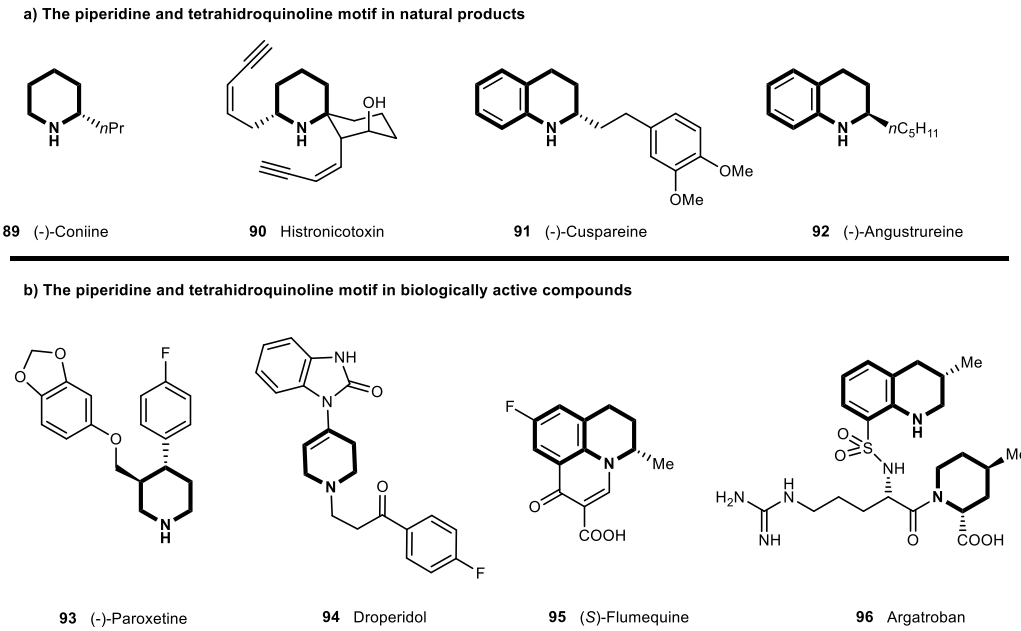


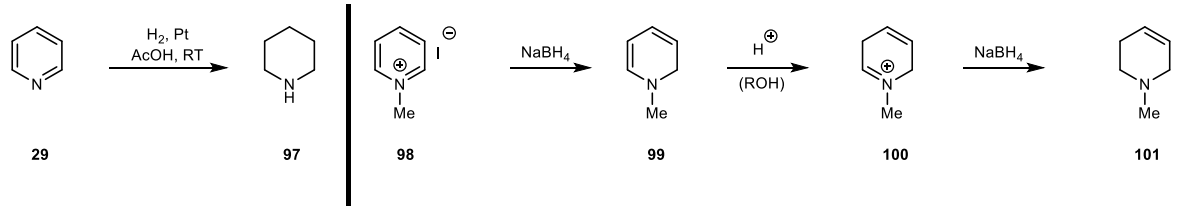
Figure 1.4 The piperidine and tetrahydroquinoline motif in compounds of interest

Heteroaromatic compounds offer pre-functionalised scaffolds that can be quickly derivatised into structurally complex 3-dimensional molecules. It is not surprising that many well-established methods to access heterocyclic compounds with different degrees of saturation take advantage of this abundant feedstock of heteroaromatic compounds.

The main ways to dearomatize an electron deficient aromatic compound are reduction and nucleophilic addition into the ring. These functionalisation modes use the normal reactivity of the electrophilic ring.

1.1.2.1 Reductive dearomatisation of pyridines and quinolines

Reduction of pyridine under heterogeneous conditions (Pt/H_2) proceeds with relative ease at room temperature to yield the fully hydrogenated piperidine **97** (**Scheme 1.14**).[1] This exhaustive hydrogenation proceeds under much milder conditions in comparison with benzene which requires high pressures and temperatures. Piperidine can also be obtained from pyridine with lithium triethylborohydride (Super-Hydride).[78] Interestingly, $LiAlH_4$ does not exhaustively reduce the pyridine,[79] while $NaBH_4$ does not react at all with pyridine.[1]

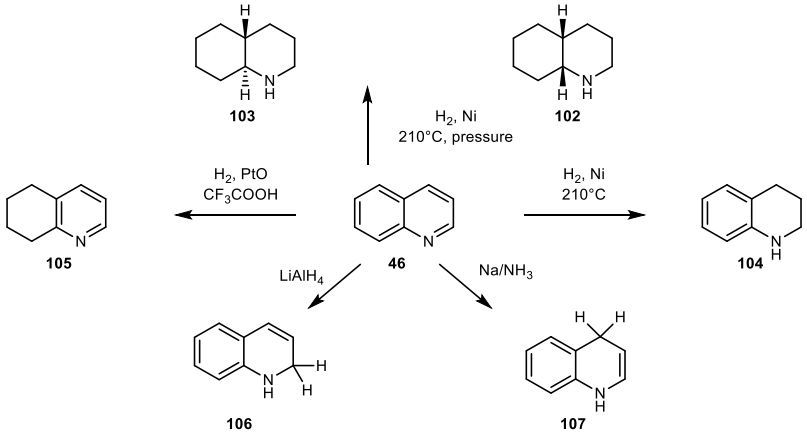


Scheme 1.14 Reduction of pyridine and pyridinium salts

Pyridines and quinolines are often made more electrophilic through protonation or quaternisation. In contrast to pyridine, *N*-methylpyridinium iodide **98** reacts with $NaBH_4$ to produce the tetrahydropyridine **101**.[80]

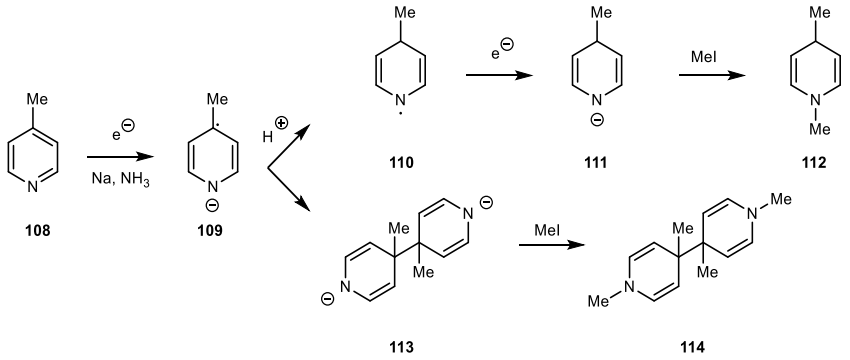
Similar to naphthalene, quinoline can be reduced partially or exhaustively. Exhaustive reduction occurs at high pressures and temperature with Raney nickel to give the decahydro-quinoline as a mixture of cis **102** and trans **103**.[81] Reducing the pressure to atmospheric levels reduces only the heterocyclic ring to yield tetrahydroquinoline **104**. Selective reduction of the carbocyclic ring to yield **105** can be achieved in CF_3COOH with PtO_2 and hydrogen gas (**Scheme 1.15**). [82]

The heterocyclic ring can also be reduced with nucleophilic hydrides such as $LiAlH_4$ or diethyl aluminium hydride to yield the 1,2-dihydroquinoline **106**.[83] Similar reactivity is observed for alkyl quinolinium salts which will produce the *N*-substituted 1,2 dihydroquinoline.[84] The 1,4-dihydroquinoline **107** can be obtained from quinoline if the reduction is carried out with alkali metals in liquid ammonia (*vide infra*) (**Scheme 1.15**).[85] Both dihydroquinolines **106** and **107** are air sensitive and will slowly re-oxidise.



Scheme 1.15 Reduction of quinoline

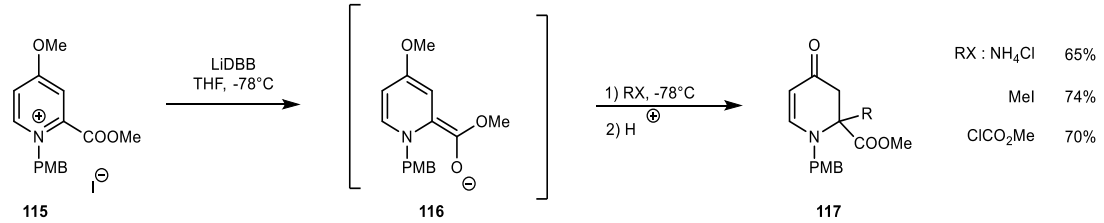
Another well-established method to reduce arenes is the Birch reaction.[86] Traditionally, single electrons from alkali metals dissolved in liquid ammonia are transferred to the aromatic ring. Depending on the nature of the reaction medium (protic or aprotic), different pathways are followed. For example, upon addition of an electron to pyridine **108**, the radical anion **109** is formed. If the reaction is done in the presence of EtOH (protic medium), the intermediate protonates to form the radical **110**, which subsequently adds another electron to form the anion **111**. If methyl iodide is added to the reaction, the anion is quenched to from the 1,4-dihydropyridne **112**. If the reaction is done in the absence of a protic reagent, the dimeric dianion **113** is formed and subsequent quenching with methyl iodide yields compound **114**.[87]



Scheme 1.16 The Birch reduction of 4-methylpyridine

The traditional Birch reduction of pyridines rarely has clean reaction profiles, and the products tend to be unstable and degrade. Given its synthetical relevance, many groups (e.g. Comins, Donohoe) have contributed to developing and advancing this field. For example, in order to stabilise some of the intermediate anions, the pyridine ring can be decorated with electron withdrawing groups. This, in conjunction with ammonia free conditions (lithium and 4,4'-di-*tert*-butylbiphenyl), allows for the trapping of stabilised anions with different electrophiles.[88–90]

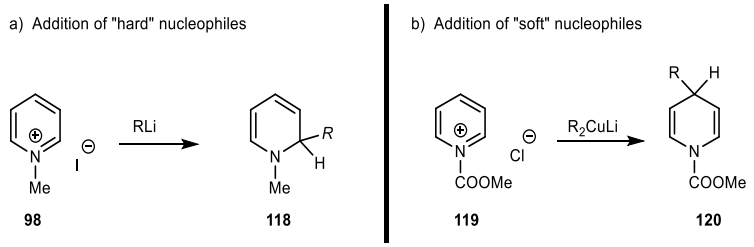
Dihydro-pyridines are air sensitive compounds and slowly degrade over time. One strategy to overcome this is to convert the products into more stable compounds. For example, the 4-methoxypyridine **115** can be reduced under ammonia-free Birch conditions to give the stabilized intermediate **116**. After electrophilic trapping, the intermediate vinyl ether can be hydrolysed *in situ* to the corresponding ketone **117** (**Scheme 1.17**). These products are not only more stable, but they also have more synthetical relevance due to the importance of the carbonyl group.[91–95]



Scheme 1.17 Birch reduction followed by functional group interconversion[91–93]

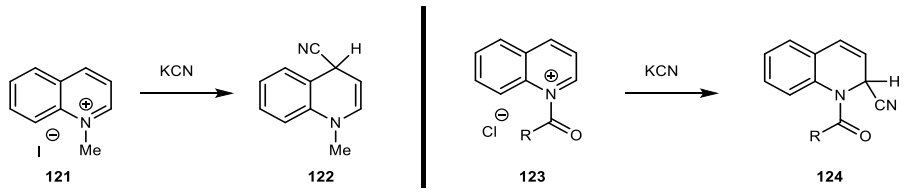
1.1.2.2 Nucleophilic dearomatisation of pyridines and quinolines

The pyridine ring is electrophilic, with the LUMO lying around 3.45 eV, which upon protonation is lowered to – 3.05 eV.[63] Nucleophilic addition into the ring happens more readily with activated pyridines, taking place at the 2- and 4- position. The 2- position, which is in close proximity to the charge, shows a preference for "hard" nucleophiles,[52,96] while "soft" nucleophiles will preferentially be added at the 4- position (**Scheme 1.18**).[97] This is by no means a general rule and normally additions will produce a mixture of regioisomers.



Scheme 1.18 Regiochemistry of nucleophilic addition to activated pyridines

Nucleophilic addition occurs readily for quaternised quinolines. The group chosen for activation can drastically change the regioselectivity of the addition. For example, a non-chelating softer quinolinium **121** will add cyanide preferentially at the 4- position to form product **122** (**Scheme 1.19**).[98] If the quinoline is activated with acyl chloride, the intermediate quinolinium **123** adds cyanide at the 2- position (knows as the Reissert reaction[96]) to form the dihydroquinoline **124**.[97] Addition of cyanide can also be made enantioselective by employing a binaphthyl based catalyst.[101]

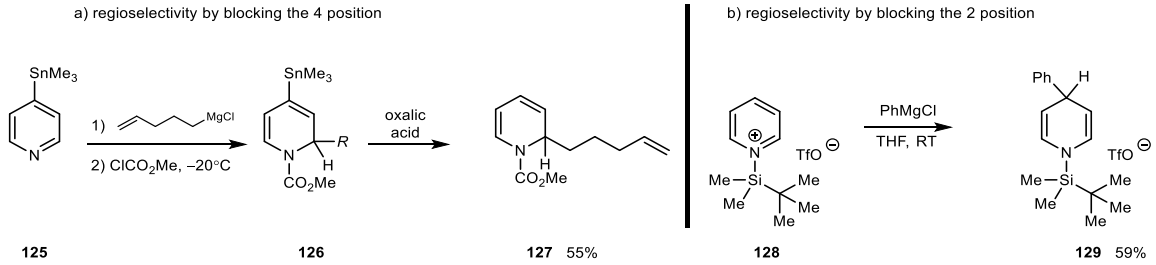


Scheme 1.19 Addition of cyanide to "hard" and "soft" quinoliniums

Attempts to control the regioselectivity of addition to pyridines might include blocking certain positions on the ring, using chelating groups to direct the addition or using bulky groups that

block access to nearby positions. For example, the 4-trimethyltin substituted pyridine **125** has been used by Comins and co-workers to block 4-addition (**Scheme 1.20 a**).[102,103] The intermediate dihydroquinoline **126** can be deprotected of the blocking group with oxalic acid to yield the desired product **127** over two steps.

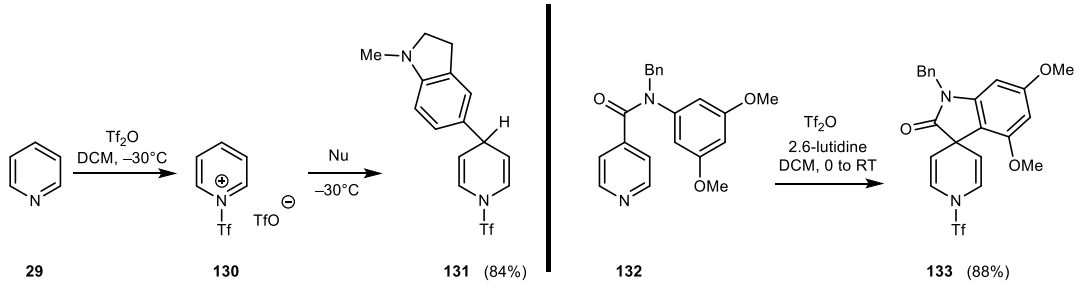
A similar approach was employed by Akiba and co-worker in order to selectively add Grignard reagents at the 4- position.[104] Rather than directly blocking the 2-positions of the pyridine, a bulky group on the nitrogen was used to activate the ring (**Scheme 1.20 b**). Subsequent Grignard addition proceeded away from the bulky TBS group of **128** to yield the 4-addition product **129** with good regioselectivity.



Scheme 1.20 Strategies to control the regioselectivity of nucleophilic addition to activated pyridines

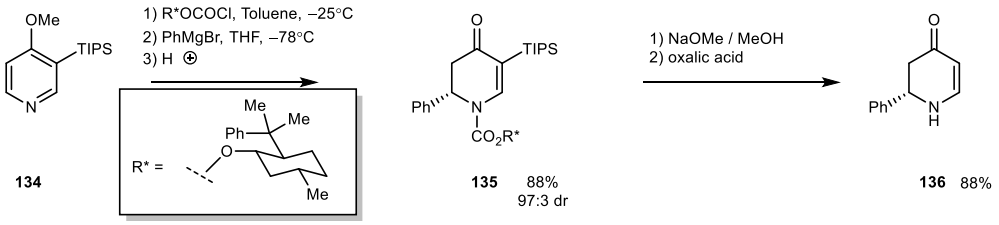
Most examples of nucleophilic addition into activated pyridines highlighted so far involved very reactive nucleophiles such as organometallic reagents. Less reactive nucleophiles can react with pyridines if these are made extremely electron deficient. Corey has shown that pyridines activated with triflic anhydride **130** can be attacked by electron rich aromatics to yield 1,4-dihydropyridines **131** (**Scheme 1.21**).[105] The stereoselectivity can be accounted by pi stacking interactions between the substrates and the bulky nature of the nucleophile.

Clayden and co-workers have implemented this methodology to form spirocyclic dihydropyridines **133** from pyridines that have attached a pendant amide (**132)**.[106]



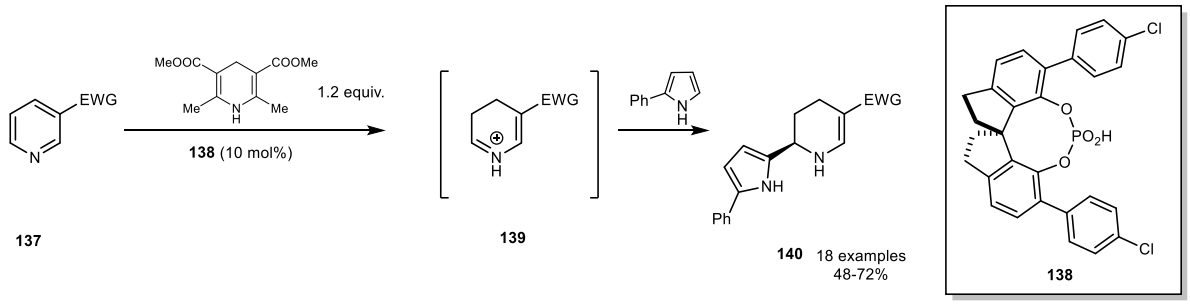
Scheme 1.21 Addition of less reactive nucleophiles into strongly activated pyridines

The activating group of the pyridine can also induce diastereoselectivity when a chiral auxiliary is used. For example, Comins and co-workers have used a menthol derivative in conjunction with a 3-TIPS substituted pyridine **134** in order to add Grignard reagents with high selectivity and regioselectivity (**Scheme 1.22**).[107] The intermediate **135** was treated with sodium methoxide to remove the chiral auxiliary, and then (one pot) with oxalic acid to remove the TIPS group and afford the enantioenriched product **136**.



Scheme 1.22 The use of chiral auxiliary to achieve enantioselective nucleophilic dearomatisation of pyridines

Most of the aforementioned transformations form piperidine derivatives starting from aromatic precursors by forming either new carbon-hydrogen bonds or new carbon-carbon bonds. A very interesting transformation that forms both new carbon-hydrogen and carbon-carbon bonds in one synthetic operation has been reported by You and co-workers.[108] In this transformation, a pyridine substituted with electron withdrawing groups at the 3- position **137** is reduced with Hantzsch ester in the presence of a chiral phosphoric acid **138** (**Scheme 1.23**).[109] The resulting intermediate **139** engages in a Friedel-Crafts alkylation with pyrroles to form the product **140**.

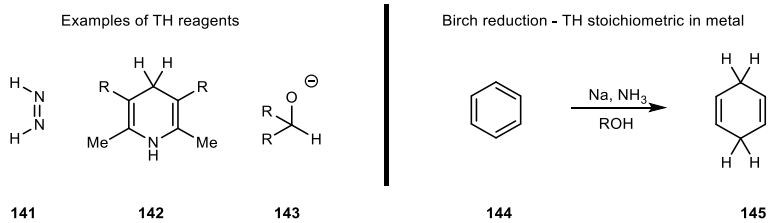


Scheme 1.23 Enantioselective reductive nucleophilic dearomatisation of pyridines

1.2 General principles of Transfer Hydrogenation and related transition metal catalysed methodologies

Transfer Hydrogenation (TH) is the addition of hydrogen to a molecule from a source other than elemental hydrogen. This can offer some advantages over elemental hydrogen, as the latter is a gas which is hard to handle and requires heterogeneous catalysis and special equipment.

There are different ways in which hydrogen can be transferred from one molecule to another. The most common way to gain or lose a hydrogen atom is through protonation/deprotonation. This, in conjunction with addition of electrons, can lead to a net reduction (a representative example is the Birch reduction – **Scheme 1.24**). Hydrogen can also be transferred through a homolytic (hydrogen radical) pathway. For example, diazine **141** can transfer hydrogen to alkenes, with the reaction being driven by the formation of nitrogen.[110]

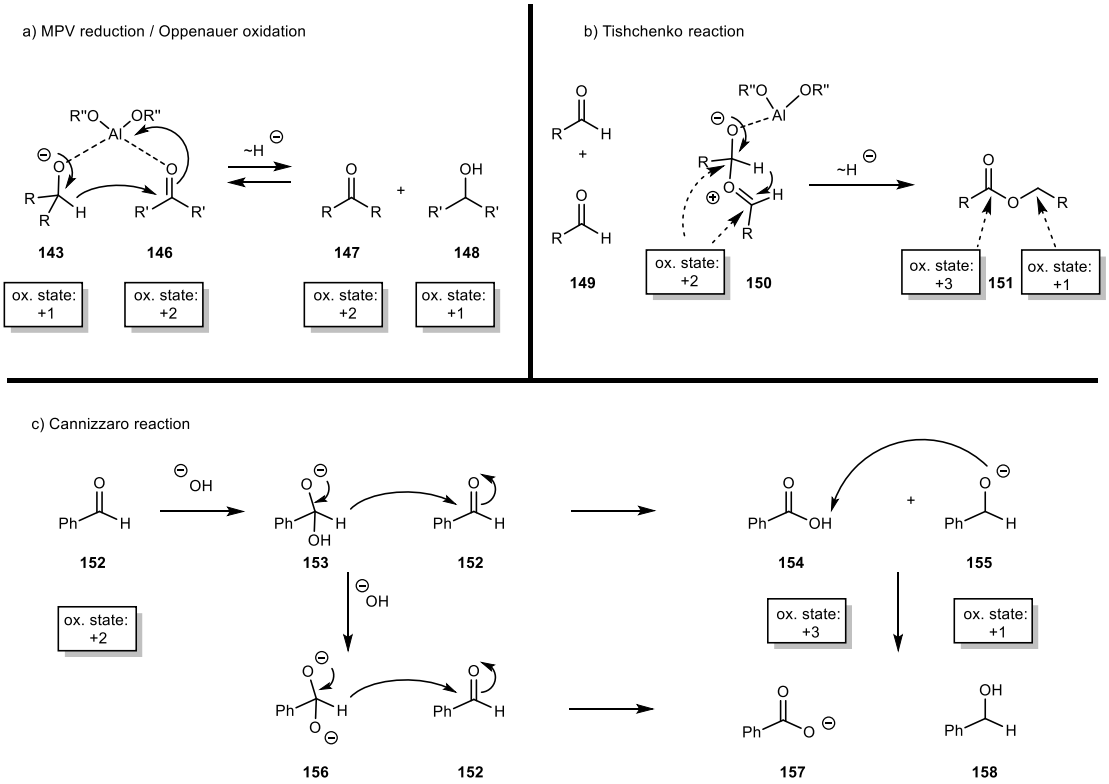


Scheme 1.24 Examples of Transfer Hydrogenation reagents

Finally, hydrogen can be transferred from one molecule to another as a hydride. Traditional hydride donors are normally derived from the group III elements (e.g. $NaBH_4$, $LiAlH_4$, etc). Organic molecules can also act as hydride donors, but this normally requires specific

circumstances as the C-H bond is relatively strong and not normally polarised towards the hydrogen. For example, 1,4-dihydropyridines (Hantzsch ester **142**) [111] can donate a hydride to a suitable acceptor, with the driving force being a gain of aromaticity.

Hydrogen transfer processes have been known for alkoxides **143** as early as 1925, when Meerwein, Ponndorf and Verley have discovered that ketones can be reduced by aluminium isopropoxide (**Scheme 1.25 a**).[110] In 1930 Oppenauer made use of the same principle to oxidise alcohols to ketones in the presence of an excess sacrificial ketone.[112] This heterolytic transfer of hydride results in formal oxidation of the donor and formal reduction of the acceptor (formal redox process).

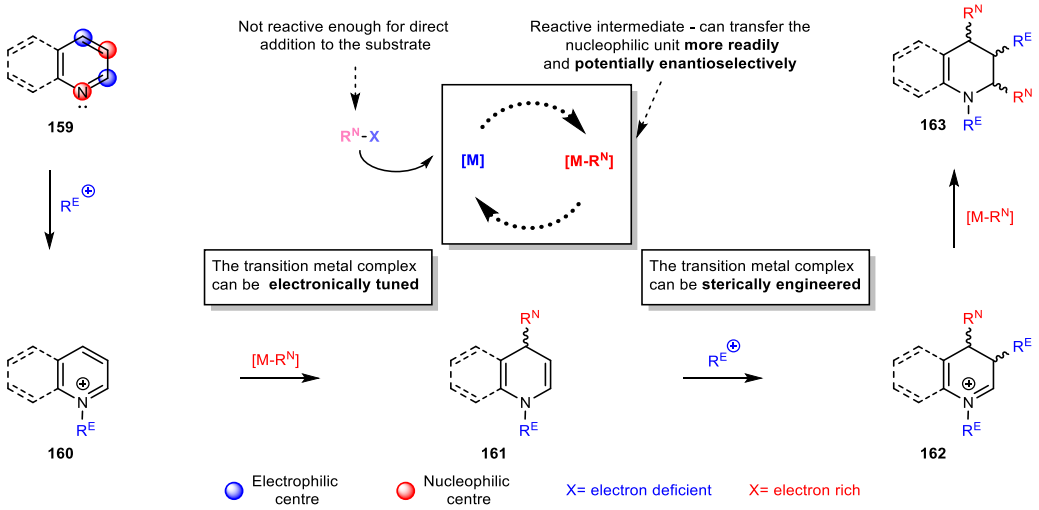


Scheme 1.25 Early examples of Transfer Hydrogenation

Similar hydride transfers have been observed for aldehydes since the 19th century. For example, in the Tishchenko reaction[113] a non-enolizable aldehyde **149** disproportionates to a carboxylic ester **151** via an intramolecular hydride shift (**Scheme 1.25 b**). This process is normally catalysed by aluminium alkoxides and has a very similar transition state with the MPV

reduction. Similarly, in the Cannizzaro reaction[114], non-enolizable aldehydes **152** can disproportionate intermolecularly to form the corresponding carboxylic acid **154** (carboxylate **157** as the reaction conditions are extremely basic) and alcohol **158** or alkoxide **155** (**Scheme 1.25 c**). The Cannizzaro reaction is catalysed by strong base (KOH), and a significant rate acceleration is observed at higher concentrations of base. This is due to the di-anionic tetrahedral intermediate **156** which is a very good hydride donor.[115]

Transition metals have found a very important place in organic chemistry as they act as both homogeneous and heterogeneous catalysts for a multitude of transformations.[116–118] Besides being able to adopt many oxidations states, transition metals can be electronically tuned and sterically engineered with the use of ligands. Methodologies that utilise transition metal catalysts can offer advantages such as milder conditions, use of greener and easier to handle reagents and, most importantly, enantioselective transformations when chiral catalysts are employed. For example, a transition metal could be used to facilitate the transfer of a nucleophilic unit from the reagent (employed stoichiometrically) to the substrate when direct transfer is not energetically favourable (**Scheme 1.26**).



Scheme 1.26 Transition metal catalysed additions to the pyridine/quinoline ring

If the nucleophilic unit is hydride (**Scheme 1.26**: R=H), full or partial reductions of different substrates can be achieved. There are numerous reports in the literature that utilize transition metal catalysed transfer hydrogenations to achieve greener and milder reductions of alkenes,[119] ketones,[120–122] imines[123,124] and electron-deficient azaarenes such as pyridines and quinolines (**159**).[125–129] More importantly, in some of the cases the reductions could be performed in an enantioselective way, by employing only catalytic amounts of chiral transition metal complexes.[130–136]

The nucleophilic unit transferred by the transition metal to the substrate could also be an alky or an aryl (**Scheme 1.26**: R= alkyl or aryl). Organometallic nucleophiles have been reported to be added to activated pyridines and quinolines (**160**) using a range of transition metals (Ni[137–141], Rh[142,143]).

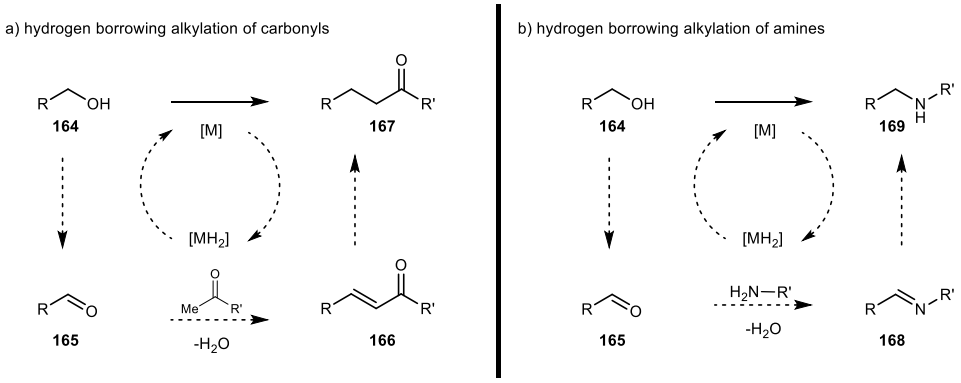
1.2.1 Hydrogen borrowing alkylation of carbonyl derivatives and amines

Significant emphasis has been directed to developing green-chemistry processes that minimise the energy required (e.g. atom, step and redox efficiency) for a desired transformation and reduce the amount of waste produced in the process.

Hydrogen transfer processes allow for the reversible activation/deactivation of unreactive substrates through the means of dehydrogenation/hydrogenation (hydrogen borrowing). Not only is this process atom economical as only one hydrogen is removed/added to achieve desired reactivity, but it also allows for multiple steps to be done in only one synthetic operation.

Most of the reactions employing hydrogen borrowing revolve around alkylation of electron rich substrates (carbonyl derivatives[144–148] and amines[149]) with alcohols (**Scheme 1.27**).[150–152] In this catalytic cycle a transition metal (Ir, Rh, Ru, etc) is used to oxidise the alcohol **164** (normally under basic conditions) to the corresponding aldehyde/ketone **165**, while also forming a metal hydride species. The aldehyde then condenses with the electron rich substrate

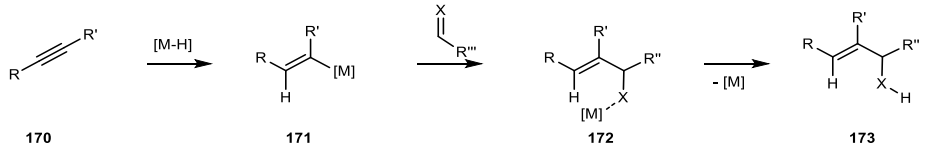
to form a reactive intermediate (**166** or **168**) through loss of water. A final reduction of the reactive intermediate with the metal hydride previously formed completes the catalytic cycle and delivers the alkylated product (**167** or **169**). This methodology allows unreactive and relatively non-toxic alcohols to be used as alkylating reagents, while forming water as the only by-product.



Scheme 1.27 Hydrogen borrowing alkylation of electron-rich substrates with alcohols

1.2.2 Related methodologies that use transition metal catalysed Transfer Hydrogenation

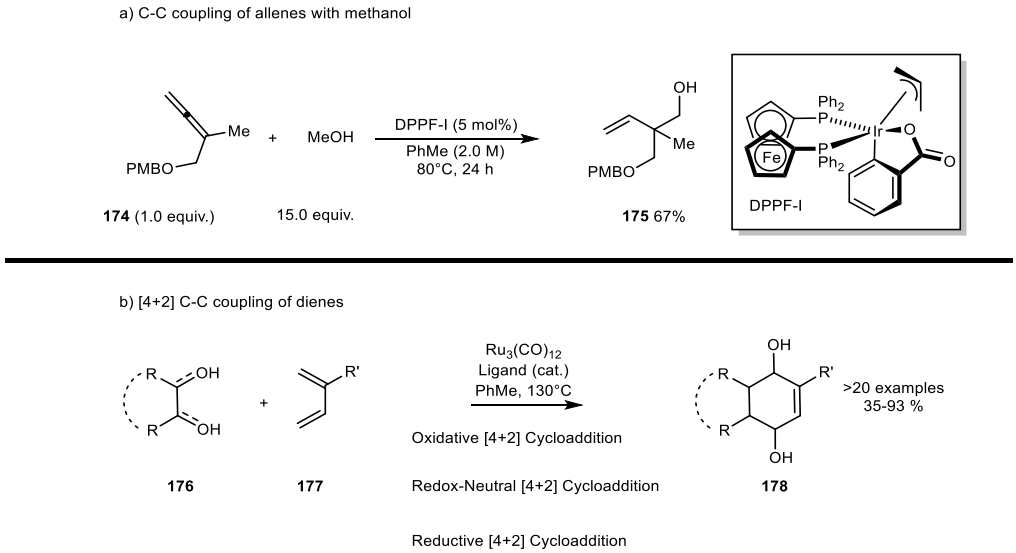
Metal hydrides can also insert into unsaturated systems **170** to produce nucleophilic organometallic intermediates **171**. These nucleophilic intermediates can then be trapped with different electrophiles and subsequently release the metal which can return to the catalytic cycle (**Scheme 1.28**).[153] This methodology offers some advantages over traditional organometallics (organolithiums, Grignard, etc.), as it is economically more efficient and does not result in stoichiometric waste.



Scheme 1.28 General pathway for hydrometallation of unsaturated systems followed by electrophilic trapping

The group of Krische has reported considerable work in this area.[154–156] Two illustrative examples are shown below. In the first example (**Scheme 1.29 a**), an iridium catalyst is used to oxidise methanol to formaldehyde while forming an iridium hydride species.[154] The metal

hydride subsequently adds into the starting allene **174** to generate a nucleophilic intermediate that reacts with the formaldehyde. The release of the metal turns over the catalytic cycle and yields the hydroxymethylated product **175**.

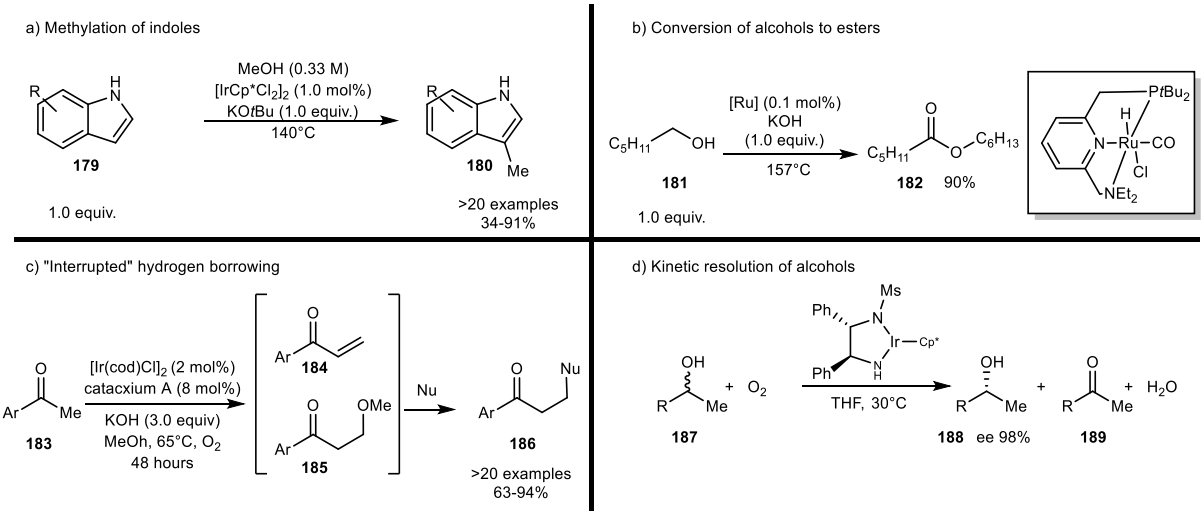


Scheme 1.29 Krische metal catalysed couplings involving hydrogen transfer

In the second example, a diene **177** is coupled a 1,2 dioxygenated compound **176** (**Scheme 1.29 b**).[155] An interesting aspect of this reaction is that it could work with reagents in different oxidation states, but it always yields the same product **178**. For example, if the 1,2 diol **176** is used, the reaction is an oxidative [4+2] cycloaddition and excess diene is used as a hydrogen acceptor. If the hydroxy aldehyde **176** is used, then the reaction is redox neutral. When the 1,2 dicarbonyl compound **176** is used**,** the cycloaddition is reductive in nature and stoichiometric formic acid is used as a reducing agent.

Methodologies that utilise transition metal catalysed hydrogen transfer processes have also been developed and applied on electron-rich aromatic compounds. For example, alkylation using alcohols is possible for indoles **179** [157], phenols[158] and other electron-rich aromatic compounds (**Scheme 1.30 a**).[159]

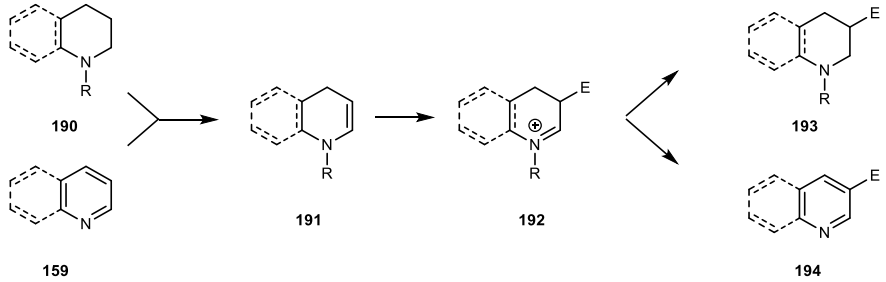
Milstein and co-workers have developed a method that converts alcohols **181** to the corresponding esters **182** through selective dehydrogenation (**Scheme 1.30 b**) .[160] On a similar note where hydrogen is not returned to the system, Donohoe and co-workers have developed conditions that allow coupling of a ketone **183** with methanol to form an enone (**184**, **185**), which is then reacted with different nucleophiles *in situ* (**Scheme 1.30 c**).[161]



Scheme 1.30 Examples of related methodologies that use hydrogen transfer

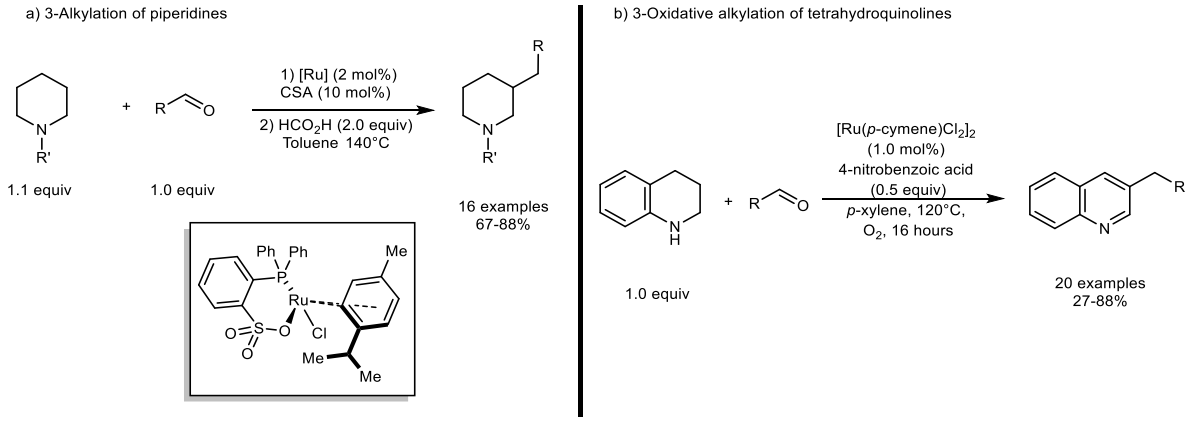
The kinetic resolution of alcohols has also made use of hydrogen transfer processes.[162] For example, a secondary alcohol **187** can be enantioenriched via the enantioselective reduction of the intermediate ketone **189** (**Scheme 1.30 d)**.[163] Similarly, primary allylic alcohols can be isomerised to the corresponding aldehyde.[164]

Similar to alcohols, piperidine and tetrahydroquinoline **190** can be oxidised with transition metals to the corresponding imine, which in turn can tautomerize to the corresponding enamine **191**. This intermediate is nucleophilic and can be trapped with electrophiles to give the imine/iminium intermediate **192**. Depending on the substrate and the reaction conditions, this intermediate can either reduce to yield the 3-substituted piperidine/tetrahydroquinoline **193**, or it can oxidise to the aromatic 3-substituted pyridine/quinoline **194** (**Scheme1.31**).



Scheme 1.31 Potential pathways for hydrogen transfer processes on 6 membered-heterocycles containing nitrogen

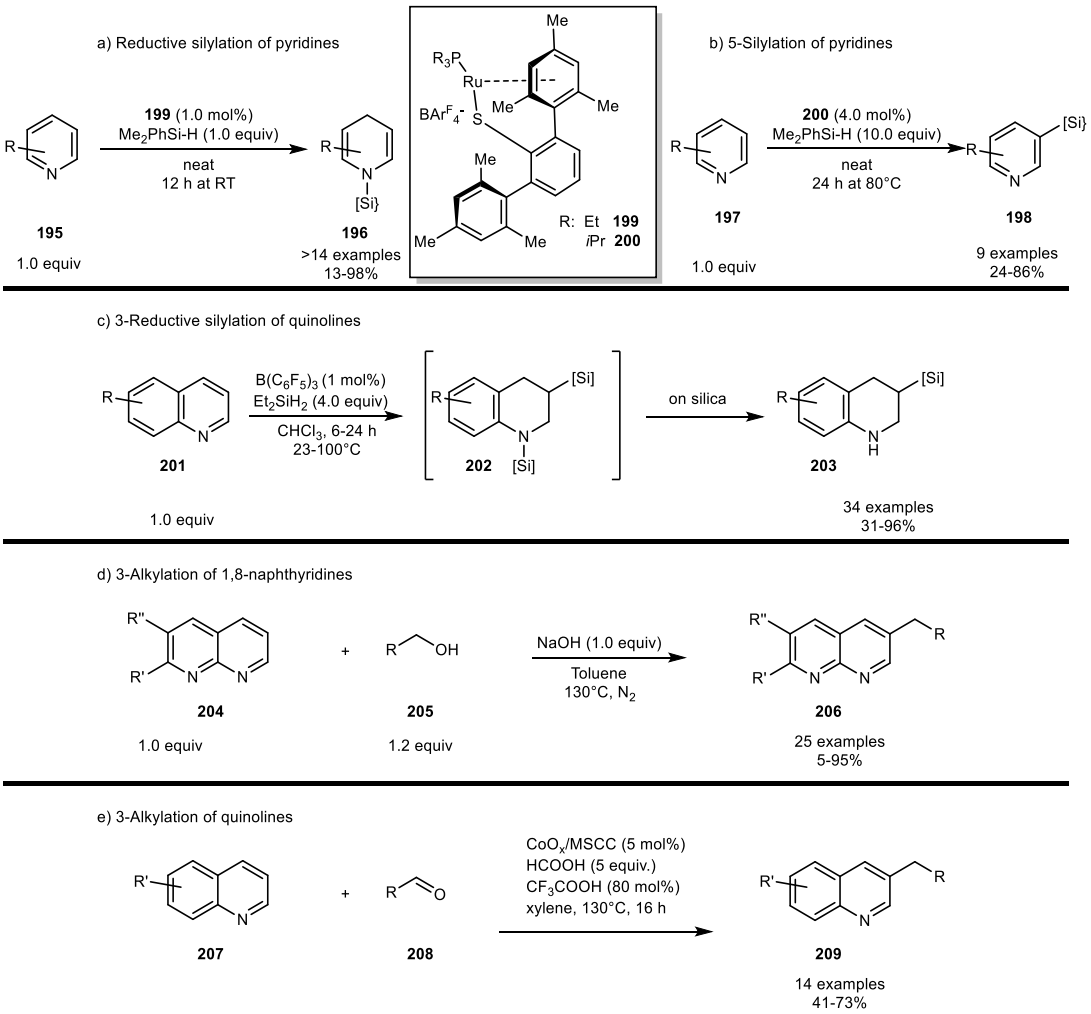
Bruneau and co-workers have reported a functionalisation of *N*-alkylated piperidines with different aldehydes under ruthenium catalysis to yield 3-alkylated piperidines (**Scheme 1.32 a**).[165,166] Similarly, Zhang and co-workers have reported an oxidative functionalization of tetrahydroquinolines to the 3-alkylated quinolines with different benzaldehydes under ruthenium catalysis (**Scheme 1.32b**).[167]



Scheme 1.32 Examples of hydrogen transfer mediated functionalisation of piperidines and tetrahydroquinolines

Although there are plenty of reports in the literature that utilise hydrogen transfer to functionalise and derivatise electron-rich substrates, few examples of such methodologies have been reported for electron-deficient systems such as pyridines or quinolines **159** (**Scheme 1.31**). Most reports on electron-deficient aromatic compounds use transfer hydrogenation to simply achieve the reduction of the ring, forming only new C-H bonds in the process (**Scheme 1.26:** $R^N = R^E = H$). Nevertheless, there are few examples of methodologies employing hydrogen transfer on pyridines and quinolines (**159)** to yield reduced functionalised products **193** or functionalised products that maintain aromaticity **194** (**Scheme1.31**).

Silanes can be catalytically added to activated pyridines.[168,169] For example, the Oestreich group has reported a ruthenium catalysed 1,4-hydrosilylation of pyridines, quinolines and related compounds that utilises a hydrosilane and a ruthenium catalyst to partially reduce the aromatic system and form a new N-Si bond (**Scheme 1.33 a**).[170] Subsequently, the same group developed a method based on similar conditions that achieves a 5-silylation (**198**) of 2- and 3-substituted pyridines (**197**) through a dearomatization/rearomatization sequence (**Scheme 1.33 b**).[171]



Scheme 1.33 Examples of hydrogen transfer mediated functionalisation on electron-deficient heteroaromatics

A boron-catalysed reductive 3-silylation of quinolines **201** has been reported by the group of Chang from South Korea. After 1,4-hydrosilylation, the resulting intermediate is trapped at the

3- position by the silane reagent and subsequently reduced at the 2- position to form the product (**Scheme 1.33 c**).[172]

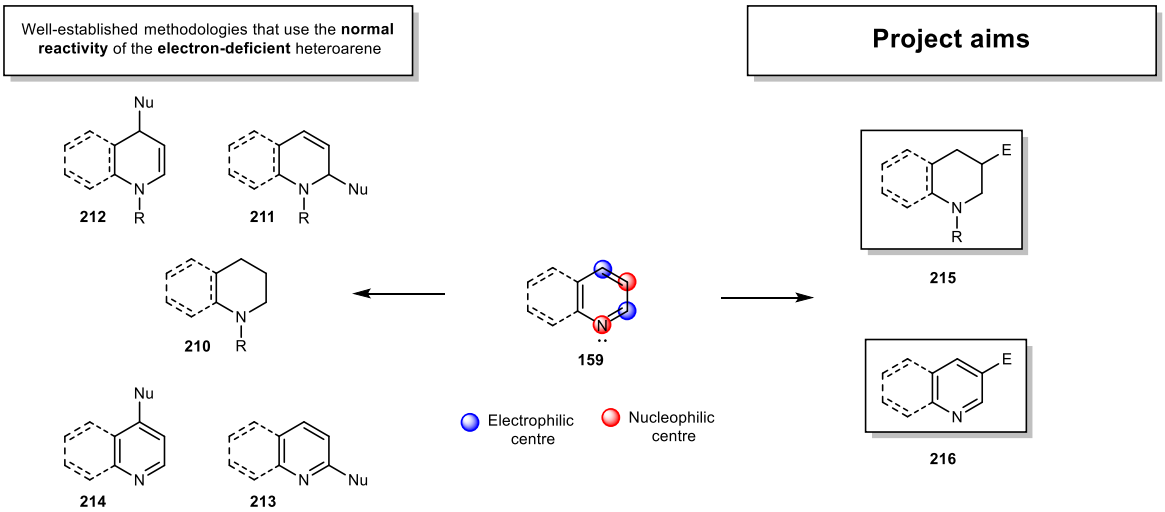
Zhang and co-workers have recently reported a metal free hydrogen transfer mediated 3-alkylation of 1,8-naphthyridines **204** with alcohols **205** under basic conditions at 130°C (**Scheme 1.33 d**). [173] To facilitate hydride transfer from the alkoxide to the substrate, the latter is very electron-deficient. Also, for regioselectivity purposes, one of the rings of the substrate is blocked by substituents. The same group has later reported a method that achieves the 3-alkylation of quinolines **207** with aldehydes **208** in the presence of a cobalt oxide catalyst bound on nanoparticles (**Scheme 1.33 e**).[174]

1.3 Project Aims

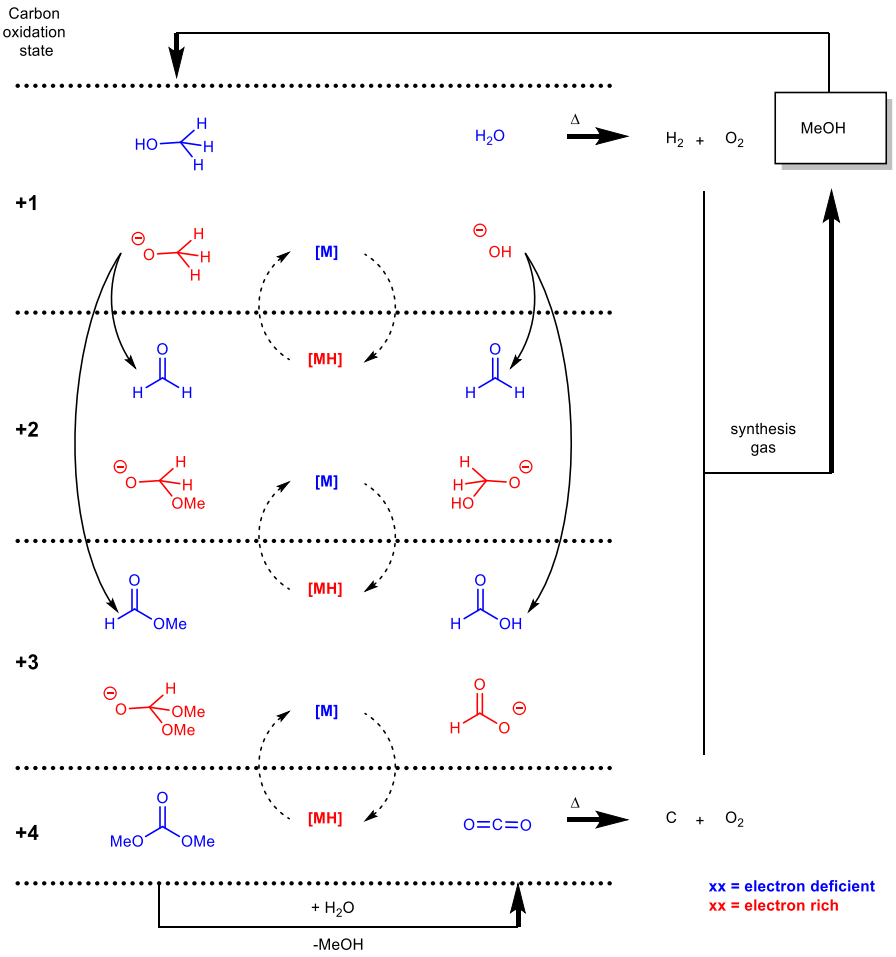
Pyridines, quinolines and their derivatives are chemicals of interest in the pharmaceutical, agrochemical and other industries as highlighted by the large number of compounds that contain these motifs in natural products and compounds with biological activity. It is also clear that there are numerous ways which utilise the normal reactivity of these electron deficient heteroaromatics to derivatise and functionalise them (**Scheme 1.34**).

Hydrogen transfer processes have gained much attention recently, mainly due to their eco-compatibility. In addition, these methodologies allow new connectivity modes that would be hardly accessible otherwise (for example, access to the 3- position of heterocycles containing nitrogen - **Scheme 1.31**).

Therefore, the aim of this project was to develop new catalytic methods that employ the principles of transition metal catalysed transfer hydrogenation (**Scheme 1.26**: R=H) and apply them on electron-deficient heterocyclic aromatic compounds in order to get access to the 3-position with electrophilic species (**Scheme 1.31**). This mode of reactivity would be complementary to the normal reactivity mode of such heteroaromatics (**Scheme 1.34**).



Scheme 1.34 Examples of functionalisation and derivatisation of electron-deficient heteroaromatics



Scheme 1.35 The C^1 building block and its potential use in transfer hydrogenation

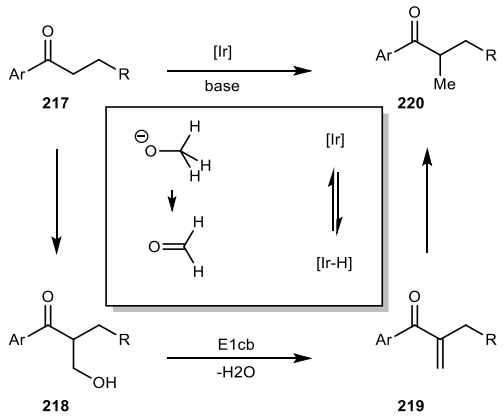
We envisioned that the best transfer hydrogenation reagent would be derived from methanol (**Scheme 1.35**). Firstly, in theory methanol could provide a renewable feedstock of reagents as it is widely available, and the most accessible alcohol derived from inorganic sources of carbon (easily produced from synthesis gas). Also, the oxidation of methanol with different transition metals all the way to carbon dioxide has been well studied.[175]

Secondly, arguably the most valuable homologation is to be able to add one extra carbon unit. In nature, complex systems are formed from less complex substructures through iterations. For example, proteins are formed by adding one amino acid at a time. Similarly, DNA strands are built from monomeric nucleotides that are linked together one at a time, and the list of examples continues.

Chapter 2: The reductive C^3 hydroxymethylation of quinolinium salts

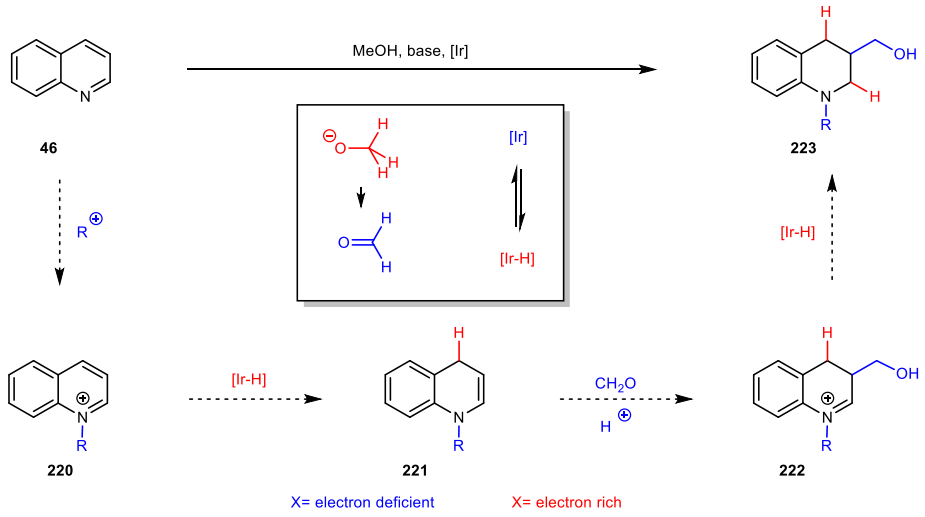
2.1 Introduction

The Donohoe group has recently been focused on developing methodologies that utilise methanol and higher chain alcohols to alkylate aryl ketones **217** through means of hydrogen borrowing catalysis (**Scheme 2.1**).



Scheme 2.1 Hydrogen borrowing methylation of aromatic ketones

As previously mentioned, our aim was to extend the principles of hydrogen borrowing and use them to achieve functionalisation of electron-deficient heteroaromatics, particularly pyridines and quinolines. We envisioned that quinoline **46** would be the most suitable substrate as it would suffer a lower penalty when it loses aromaticity due to benzannulation and offers fewer regioselectivity issues as compared to pyridine. The desired pathway would involve initial reduction by a metal hydride species of an activated quinoline **220** at the 4- position in order to generate the intermediate enamine **221** *in situ* (**Scheme 2.2**). Subsequent trapping of this enamine with formaldehyde would lead to the iminium ion **222**. A final reduction of this iminium ion with a second metal hydride species would furnish the 3- functionalised tetrahydroquinoline **223**. We envisioned that methanol oxidation by the iridium catalyst would furnish both the metal hydride and the formaldehyde required for the reaction.[158] The reaction pathway would be very similar to a transfer hydrogenation of the heterocyclic ring, with the difference that one protonation step has been replaced (interrupted) with electrophilic trapping.



Scheme 2.2 Proposed Interrupted Transfer Hydrogenation of quinolines

2.2 Initial reaction development

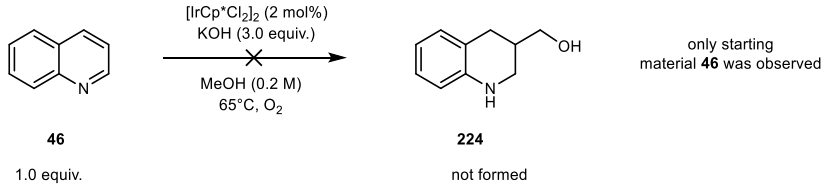
Typical reaction conditions for the alkylation of ketones involves heating of the starting ketone **217** (1 equiv.) in excess alcohol with a significant amount of base (KOH, 3.0 equiv.) and catalytic amounts of $[IrCp^*Cl_2]_2$ (2 mol%).[145] Hydrogen borrowing reactions for higher chain alcohols were found to work best at temperatures in the range of 85 to 105°C under an atmosphere of argon, while alkylations with methanol were found to work optimally at 65°C under an atmosphere of oxygen.[161,176]

There are more theories reported in literature as to why oxygen might have a beneficial effect on similar catalytic cycles. For example, Gabrieslsson and co-workers have proposed that during the catalytic cycle a reductive elimination from an Ir (III) species could lead to an inactive Ir (I) species.[177] The oxygen was believed to regenerate the catalytically inactive Ir (I) species by oxidising it back to Ir (III).

Although advanced mechanistic investigations are beyond our group's current expertise and technical possibilities, several qualitative investigations have been previously conducted on the alkylation of aryl ketones with methanol under an atmosphere of oxygen. The main finding was that oxygen accelerates the overall reaction rate. Also, it was found that carbon monoxide

(which can be formed through reductive elimination of hydrogen from formaldehyde) completely inhibits the reaction.[178–180]

Taking this previous knowledge into consideration, we decided to subject quinoline (0.3 mmol) under the conditions optimised for the methylation of ketones, which at the time were 2 mol% of $[IrCp^*Cl_2]_2$, 3 equivalents of KOH in 1.5 mL of methanol (0.2 M) stirred at 65° C under an oxygen balloon for 16 hours. Unfortunately, the unactivated quinoline **46** did not react and only starting material was observed (**Scheme 2.3**).



Scheme 2.3 Attempts on quinoline using conditions developed for the methylation of ketones

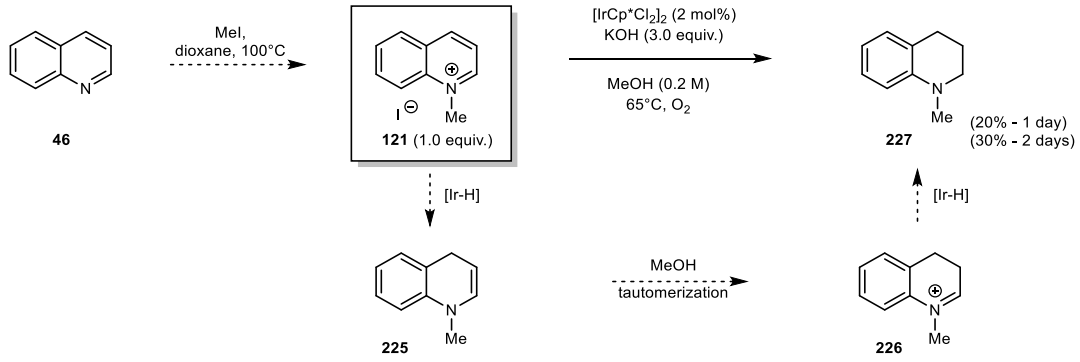
Knowing that both iridium hydride and formaldehyde are being formed under these conditions, we concluded that in order to enhance the reactivity of the quinoline, it had to be activated towards reduction.

2.2.1 Activation of the quinoline ring for initial reduction

The quinoline ring can be made more electrophilic through either protonation, complexation with a Lewis acid or quaternisation. The catalytic oxidation of methanol requires basic conditions, meaning that the protonation of the ring with a Brønsted acid was not feasible for this reaction. We decided to first attempt complexation with Lewis acids, as this mode of activation could potentially be made catalytic.

Using the conditions mentioned above ($[IrCp^*Cl_2]_2$, KOH, 65°C, O_2, 16 hours), we screened a selection of Lewis acids: $MgBr_2•(OEt_2)$, $Mg(OMe)_2$, MgI_2 and Ag_2O. These were employed separately as additives in stoichiometric amounts (1.0 equiv.), but unfortunately the quinoline still remained unreacted in all cases.

As the activation modes that we tried proved to be unsuccessful, our attention was shifted towards quaternisation of the nitrogen with methyl iodide (**Scheme 2.4**). Subjecting the *N*-methylquinolinium iodide salt **121** (0.3 mmol) to the set of conditions previously mentioned ($[IrCp^*Cl_2]_2$, KOH, 65°C, O_2, 16 hours), led to complete consumption of the starting material. The only identifiable product from the reaction was the *N*-methyl tetrahydroquinoline **227**, formed in about 20 % yield and contaminated by unidentified impurities (**Scheme 2.4**). The formation of this product suggests that the quinolinium salt **121** is electrophilic enough to be reduced by the iridium hydride species formed *in situ*. However, the resulting enamine **225** does not trap formaldehyde, but instead becomes protonated by methanol to tautomerize to the iminium ion **226**. A final reduction of this iminium ion provides the product **227**.

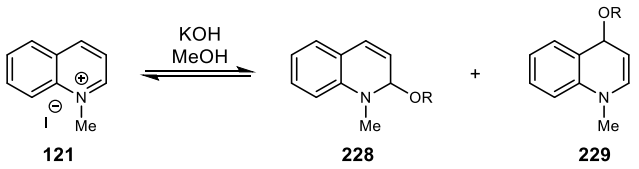


Scheme 2.4 Reduction of the *N*-methylquinolinium salt to the *N*-methyltetrahydroquinoline

As previously mentioned, product **227** was obtained in low yield and was contaminated with different quinoline-related impurities. As about 80% of the mass balance for this reaction could not be clearly accounted for, we decided to examine what happened to the starting material **121** under the strongly basic conditions.

Simply subjecting the starting quinolinium iodide **121** (1.0 equiv.) to basic (KOH, 3.0 equiv.) methanol (0.2 M) at room temperatures leads co complete consumption of starting material. It is documented that the 1,2- base adducts (formed predominantly) **228** and the 1,4- base adducts

(the minor component) **229** are being formed reversibly (**Scheme 2.5**).[181] This equilibrium is very hard to deconvolute in an NMR experiment and an exact ratio could not be assessed.



121 **228** **229**

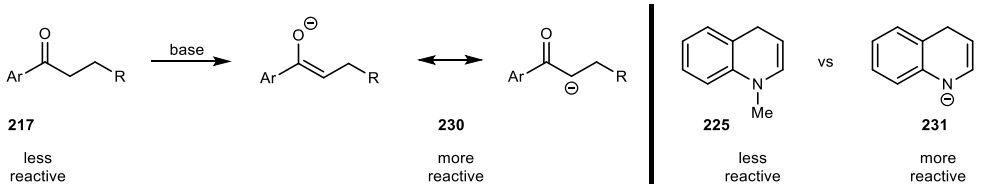
Scheme 2.5 Base adducts of the starting quinolinium salt

To test the reversibility of this background reaction, we ran the reaction conditions on substrate **121** for two days (**Scheme 2.4**). The yield of **227** increased from 20% to about 30 %, with the product still being contaminated by small impurities, which at this point were assumed to be different base adducts and related degradation by-products. The reason why the separation of these impurities was difficult at the time will be discussed further in this chapter. The yield of **227** increasing with a longer reaction time suggested that the base addition into the activated quinolinium **121** was indeed reversible, and slowly more starting material was funnelled towards the fully reduced product **227**.

These experiments suggested that quaternisation was a viable activation mode, but, unfortunately, the resulting enamine **225** was not being trapped by the formaldehyde formed *in situ*.

2.2.2 Trapping of the in situ generated enamine intermediate

In the methylation of ketones through means of hydrogen borrowing, ketone **217** is deprotonated under the strongly basic conditions, thus providing a reactive nucleophilic enolate **230** that is reactive enough to trap the formaldehyde formed *in situ* (**Scheme 2.6**).[146] A nucleophile with similar reactivity would be the deprotonated enamine **231**, but unfortunately such a deprotonated intermediate is not achievable from a quaternary quinolinium salt.



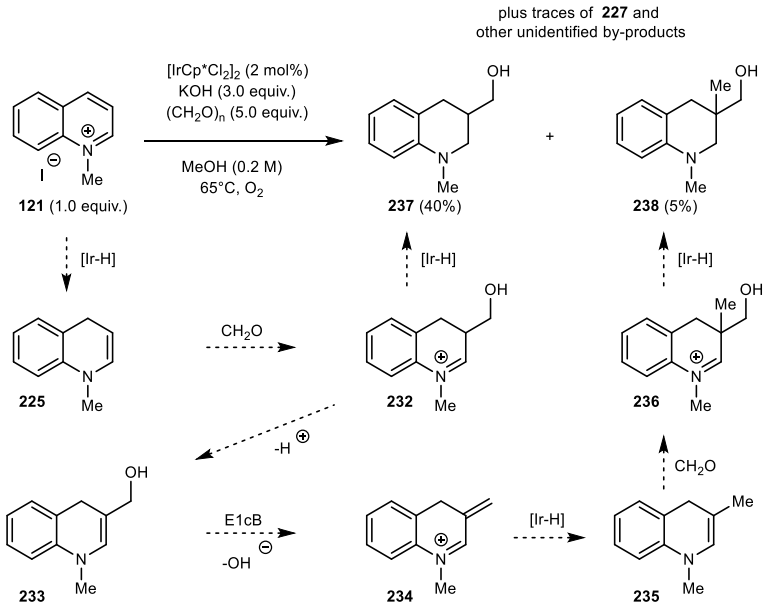
Scheme 2.6 Difference in reactivity of the intermediate nucleophiles

As we previously concluded that quaternisation was required to activate the quinoline towards reduction in order to initiate the reaction, we wanted to investigate if the less nucleophilic intermediate enamine **225** could be trapped by formaldehyde if the latter is provided in excess. We subjected the quinolinium salt **121** to the conditions previously used ($[IrCp^*Cl_2]_2$, KOH, 65°C, O_2, 16 hours), but with an additional 5.0 equivalents of paraformaldehyde added to the reaction (**Scheme 2.7**).

Pleasingly, we discovered that the enamine **225** did trap formaldehyde (when this is employed in excess) to form the intermediate iminium ion **232,** which was subsequently reduced to the desired product **237**. The hydroxymethylated tetrahydroquinoline **237** was isolated in 40% yield, but it was contaminated with impurities that we could not separate efficiently (*vide supra*). Repeated chromatography on this dark brown impure product eventually removed most impurities as well as the dark colour. However, at this stage we decided to focus on improving the reaction before finding a reliable way to isolate the products with reasonable purity and efficiency.

Besides the desired product **237**, the reaction also produced traces of the reduced untrapped product **227** and, interestingly, 5 % of **238** was isolated. This unexpected product is formed when the intermediate iminium ion **232** is not reduced by iridium hydride but is instead deprotonated to form the enamine **233**. This enamine can then form the conjugated iminium **234** through E1cB type elimination of hydroxide. 1,4-Reduction then leads to the methylated enamine **235**. Interestingly, this hindered enamine can trap formaldehyde to generate the

iminium ion **236** that contains a quaternary centre at the 3- position of the ring, which upon a final reduction leads to **238**.



Scheme 2.7 Successful trapping of the *N*-methyl enamine with excess formaldehyde

Hence the addition of excess formaldehyde proved to be beneficial and made trapping of the less reactive *N*-substituted **225** enamine possible. The resulting iminium ion **232** can be either reduced to **237** (desired pathway), or it can be deprotonated leading to alternative pathways. Interestingly, compound **238** highlights the potential for this methodology to produce quaternary centres.

Understanding that formaldehyde is a required reagent for this transformation, we moved on to optimising the reaction for the formation of **237**. In order to achieve this, we concluded that the intermediate **232** (trapped) has to be preferentially formed over **226** (untrapped). Moreover, the formation of this trapped iminium then has to be followed by reduction, as alternative degradation pathways are possible.

2.3 Optimisation for the C3 reductive hydromethylation of quinolinium salts

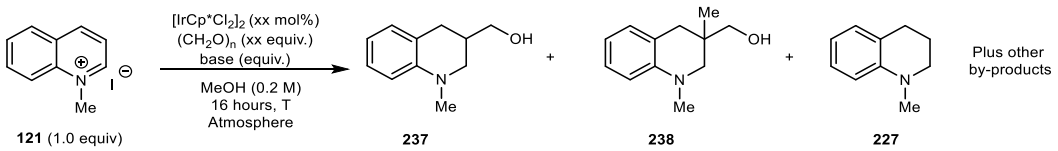
As the starting material is involved in a reversible equilibrium with the base, monitoring the reaction by assessing its consumption was not possible. Hence, we decided to use 1,3,5-trimethoxybenzene as an internal standard to account for the NMR yield of the reaction during optimisation.

We ran the reaction of quinolinium **121** with additional paraformaldehyde under an oxygen atmosphere (**Table 2.1**: Entry 1) in two different batches: one with 0.33 equivalents of 1,3,5-trimethoxybenzene added from the beginning of the reaction, and one where the same amount of internal standard was added before the work-up. Both reactions had the same profile, with NMR yields (measured in d_4-methanol) for **237** and **238** relatively close to the average isolated values (*vide supra*).

Running these reactions under an atmosphere of oxygen would be a high fire risk, especially on larger scales. We wanted to check whether oxygen was still required given the newer conditions where additional formaldehyde was added. Running the reaction under an atmosphere of argon seemed to be significantly worse, as the desired product **237** was formed in only 20% by NMR (**Table 2.1**: Entry 2). It seems that overall less efficient reduction takes place, suggesting that the catalyst loses activity or is less active to begin with.

However, if the amount of paraformaldehyde added at the beginning of the reaction is increased to 10 equivalents and the reaction is run under argon, the NMR yield of the desired product **237** increases to 42% (**Table 2.1**: Entry 3). The increased loadings of paraformaldehyde (10 equiv.) together with an oxygen atmosphere seemed to be beneficial for the reaction (**Table 2.1**: Entry 4), so we kept these variables fixed and moved on to iterate different variables.

The paraformaldehyde added is in significant excess, but the monomeric species is the one that needs to get trapped. Monomeric formaldehyde is released from the polymer in the presence of base as a very volatile compound with a boiling point of –20°C. We wanted to see if the reaction might produce more **237** at lower temperatures, as the solubility of the monomer in solution might be higher. Running the reaction at 40°C led to small improvement in the yield of **237**, while it also formed slightly less **238** (**Table 2.1**: Entry 5).



121 (1.0 equiv) **237** **238** **227**

No.	T (°C)	[Ir] (mol%)	Atmosphere	Base (equiv.)	CH_2O equiv.	Yield of 237 (^{1}H NMR)	Yield of 238 (^{1}H NMR)
1	65	2.0	Oxygen	KOH (3.0)	5	45	7
2	65	2.0	Argon	KOH (3.0)	5	20	8
3	65	2.0	Argon	KOH (3.0)	10	42	12
4	65	2.0	Oxygen	KOH (3.0)	10	55	8
5	40	2.0	Oxygen	KOH (3.0)	10	60	5
6	40	2.0	Oxygen	KOH (0.5)	10	Incomplete conversion	-
7	40	2.0	Oxygen	KOH (1.0)	10	Incomplete conversion	-
8	40	2.0	Oxygen	KOH (1.5)	10	70 (65 isolated)	5
9	40	2.0	Oxygen	KOH (5.0)	10	Severe degradation	-
10	40	1.0	Oxygen	KOH (1.5)	10	70	5
11	40	0.5	Oxygen	KOH (1.5)	10	55	8

Table 2.1. Reaction optimisation on the *N*-methyl quinolinium salt

The screening reactions were run on 0.3 mmol of substrate in 10 mL sealed microwave vials. The isolated yield was obtained from a 0.5 mmol scale reaction.

Next, we examined several bases. Sodium hydroxide and sodium methoxide showed very similar reactivity to potassium hydroxide. However, we decided to use potassium hydroxide due to its higher solubility in methanol. The next variable investigated was the stoichiometry of the base. When under one equivalent of base was used, the reaction did not go to completion (**Table 2.1**: Entries 6 and 7). Moreover, the starting material **121** could be identified in the crude NMR, highlighting that some of the base was consumed as the reaction progressed. The optimum amount of base seemed to be 1.5 equivalents, as this reaction yielded 70% of the desired product **237** (**Table 2.1**: Entry 8). Excessive amounts of base lead to complete degradation and no desired product was identified (**Table 2.1**: Entry 9).

After obtaining a relatively good NMR yield, we wanted to further optimise the reaction with regard to the iridium complex . The catalyst loading could be lowered to only 1 mol % of the iridium dimer, however going lower than this seemed to be detrimental for the reaction (**Table 2.1**: Entries 10 and 11). If no catalyst was used, the reaction produced no product at all.

One recurring problem was to find a practical way to purify the product because, as previously mentioned, simple FCC of the crude mixture would always lead to a brown oil that was contaminated by minor amounts of by-products. We assumed that the residual transition metal was responsible for both the dark colour and the presence of other impurities. Often, transition metal complexes are soluble in the solvent employed for extraction (CH_2Cl_2 in our case) and concentration of the organic layer can cause multiple species to chelate on the same metallic centre.[182]

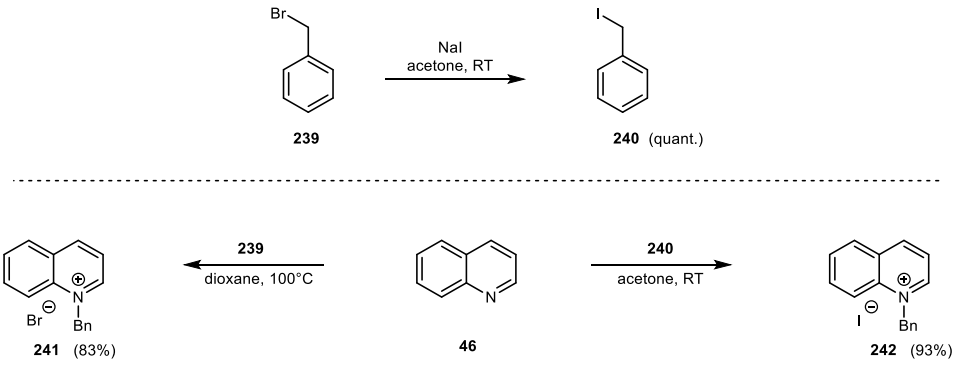
To solve this problem, we focused on different ways to scavenge the iridium complex prior to subjecting the crude product to FCC. Saturated solutions of tartaric acid (Rochelle salts) and EDTA salts have been used in the aqueous work-up, however they proved to be ineffective at removing the dark colour and did not achieve the desired purity.

Commercial products used to remove transition metals would normally consist of a multidentate ligand that is bound on silica. Often, sulfur containing ligands such as thiourea or cysteine derivatives are used. After employing a saturated solution of thiourea in the work-up, the dark colour of the organic layer diminished and a significant improvement in purity was noticed after a single FCC. Better results were obtained when 50 mg of thiourea were added at the end of the reaction (0.3 mmol scale) and the resulting mixture was heated for an additional 30 minutes. Adding thiourea to the reaction caused effervescence and a quick drop in colour from dark-red towards yellow. The effervescence could be explained by release of hydrogen

gas from deprotonation of the metal hydride, while the colour change suggests complexation of the thiourea to the metal.

This new work-up based on thiourea allowed us to consistently isolate the desired product **237** with high purity as a yellow oil. Moreover, the isolated yield of the reactions with the best conditions was within close proximity to the NMR yield calculated against internal standard (**Table 2.1**: Entries 8 and 10).

After obtaining a relatively good yield on *N*-methyl quinolinium iodide salt **121**, we moved on to the *N*-benzyl quinolinium bromide salt **241** (**Scheme 2.8**). We envisioned that having a benzyl group on the nitrogen is more advantageous, as this can be easily deprotected afterwards through well-established hydrogenation reactions.[183]

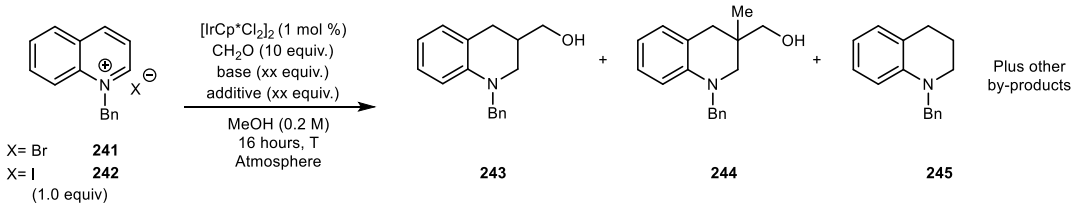


Scheme 2.8 Synthesis of *N*-benzyl quinolinium salts

Unfortunately, employing the best set of conditions (so far) developed for **121** lead to only 15% of the desired product **243** by NMR (**Table 2.2**: Entry 1). Increasing the temperature of the reaction to 65°C increased the yield of product **243** to 27 %, while also producing about 3 % of the by-product **244** (**Table 2.2**: Entry 2). Similar to the *N*-methyl quinolinium iodide salt **121**, running the reaction under argon seemed to have a detrimental effect (**Table 2.2**: Entry 3). As before, more by-product **244** was formed under argon, suggesting a less efficient reduction of the trapped iminium ion. This difference between argon and oxygen seemed to be more pronounced for the *N*-benzyl quinolinium bromide salt **241**.

Two variables were changed when moving from salt **121** to salt **241**: the alkyl group on the nitrogen and the counterion. Literature reports suggested that iodide can have beneficial effects on certain reductions of pyridines and quinolines that employ $[RhCp^*Cl_2]_2$ as a catalyst. [128,129] In order to assess if the lack of iodide from **241** was responsible for the significant difference in reactivity, one equivalent of potassium iodide was added as additive.

Interestingly, the yield of **243** increased from 27 to 40 % in the presence of one equivalent of iodide (**Table 2.2**: Entry 4). However, the reaction presented a significant amount of insoluble inorganic salts after completion. Removing the bromide counterion and using the *N*-benzyl quinolinium iodide salt **242** (**Scheme 2.8**) instead seemed to bring a slight improvement (**Table 2.2**: Entry 5). The yield of **243** increased to 44%, while the amount of insoluble salts present at the end of the reaction decreased.



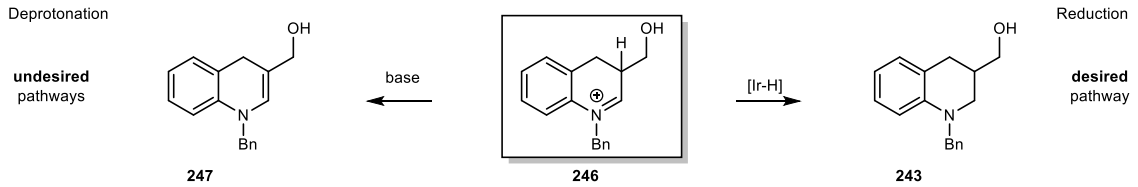
No.	X	T (°C)	Atm.	Base (equiv.)	Additive (equiv.)	Total iodide conc. (M)	Yield of 243 (^{1}H NMR)	Yield of 244 (^{1}H NMR)
1	Br	40	Oxygen	KOH (1.5)	-	x	15	traces
2	Br	65	Oxygen	KOH (1.5)	-	x	27	3
3	Br	65	Argon	KOH (1.5)	-	x	17	10
4	Br	65	Oxygen	KOH (1.5)	KI (1.0)	0.2	40	5
5	I	65	Oxygen	KOH (1.5)	-	0.2	44	4
6	I	65	Oxygen	$Mg(OMe)_2$ (0.75)	-	0.2	70	4
7	I	65	Oxygen	$Mg(OMe)_2$ (0.75)	KI (1.0)	0.4	80	4
8	I	65	Oxygen	$Mg(OMe)_2$ (0.75)	KI (2.0)	0.6	88	3
9	I	65	Oxygen	$Mg(OMe)_2$ (0.75)	MgI_2 (1.0)	0.6	80	3
10	I	50	Oxygen	$Mg(OMe)_2$ (0.75)	KI (2.0)	0.6	81 (87 in 2 days)	3
11	I	65	Argon	$Mg(OMe)_2$ (0.75)	KI (2.0)	0.6	87	3
12	I	65	Air	$Mg(OMe)_2$ (0.75)	KI (2.0)	0.6	88 (84 isolated)	3

Table 2.2 Reaction optimisation on the *N*-benzyl quinolinium salt

The screening reactions were run on 0.3 mmol of substrate in 10 mL sealed microwave vials. The isolated yield was obtained from a 0.5 mmol scale reaction.

Most of the missing mass of the reaction could not be reliably identified. The untrapped reduced tetrahydroquinoline **245** was always observed in these reactions, but most of the time this by-

product would not be higher than 10-15%. We concluded that most of the degradation by-products were formed because the trapped intermediate iminium ion **246** was deprotonated faster than it was reduced (**Scheme 2.9**).



Scheme 2.9 Potential pathways for the trapped iminium ion

Based on our understanding, one equivalent of iridium hydride is produced by consuming one equivalent of base. When the intermediate enamine **221** traps formaldehyde and then abstracts one proton from methanol to form **246** (**222**), one equivalent of base is regenerated (**Scheme 2.2**). However, a final iridium hydride is required for product **243** (**223**) to be formed, making the reaction overall stoichiometric in consumption of base. As lowering the amount of base even more in order to avoid degradation of **246** was not feasible (**Table 2.1**: Entries 6 and 7), we considered changing the base.

Magnesium methoxide seemed like a suitable candidate as it has a more Lewis acidic counterion and could potentially be less basic and nucleophilic. Pleasingly, replacing potassium hydroxide with magnesium methoxide had a beneficial effect. This resulted in less degradation when the *N*-benzyl quinolinium iodide salt **242** was employed and yielded 70% of the desired product **243** (**Table 2.2**: Entry 6). As a side note, if the bromide salt **241** is used, the reaction leads to severe degradation and a significant amount of insoluble salts (probably $MgBr_2$). We concluded that magnesium methoxide employed on the iodide salt **242** was optimal for this transformation.

Using the iodide quinolinium salt **242** in conjunction with one additional equivalent of potassium iodide lead to an increase in the yield of **243** to 80%, suggesting more efficient

reduction of the intermediate iminium ion **222** (**Table 2.2**: Entry 7). Increasing the amount of potassium iodide to 2 equivalents seemed to benefit the reaction even more, delivering the product **243** in 84 % isolated yield (**Table 2.2**: Entry 8). More than two equivalents (3 and 4 have been tested) of potassium iodide could be used without changing the reaction profile. We concluded that two additional equivalents of iodide (amounting to a total concentration of 0.6 M iodide) is the optimal amount. Similar effects where iodide has an influence on a catalytic system based on rhodium have been reported by Xiao and co-workers (more details in **Chapter 4.4**).[129] They have proposed that the iodide binds to the metal, making the resulting hydride more reactive.

Although we are not entirely certain on how the iodide influences the catalytic system, we noticed that the iridium catalyst has a significantly greater preference for reducing the iminium ion **222** at higher iodide concentrations. This change in the electronic properties of the catalyst can be partly accounted for by the *pi* donating capacity of the iodide ligands - Iodide has filled 5p and 4d orbitals that are energetically close to the 6p and 5d orbitals of iridium. Mixing of these orbitals could result in higher HOMO for the metal (**Figure 2.1**). This "softer" metallic centre might be better matched energetically to interact with the iminium ion **246** LUMO.

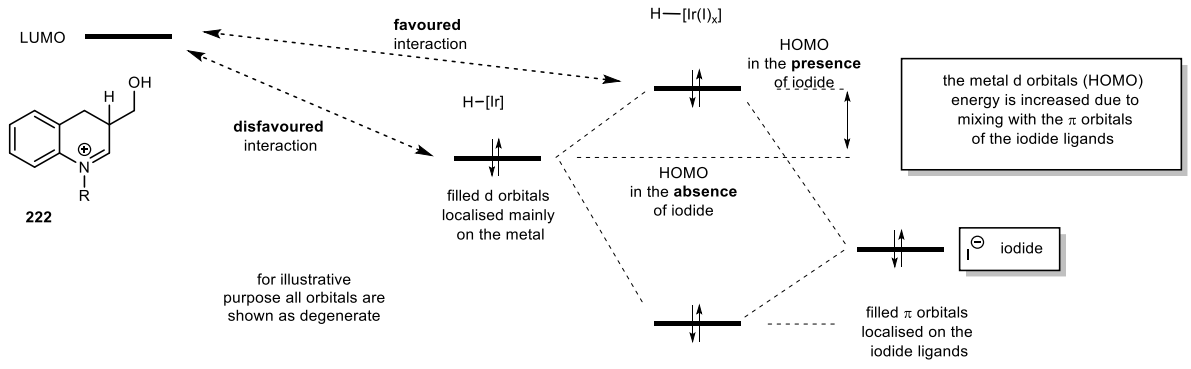


Figure 2.1 Illustrative Molecular Orbital Diagram - iodide *pi* donation to the transition metal.

If one equivalent of magnesium iodide is used instead of the two equivalents of potassium iodide, the reaction furnishes the desired product **243** in a slightly lower yield (80 % by NMR),

while also forming significant amounts (15-20%) of the untrapped reduced tetrahydroquinoline **245** (**Table 2.2**: Entry 9). Lowering the reaction temperature from 65 to 50°C produced less product **243** in 16 hours, however it delivered the same amount of product if left for two days (**Table 2.2**: Entry 10).

We noticed that the ability of the catalyst to reduce the iminium ion **222** improved significantly as increasing amounts of iodide were added to the reaction. We further investigated the requirement of an oxygen atmosphere in the presence of high concentration of iodide. Pleasingly, we found that at high concentration of iodide (0.6 M) the reaction performed equally well under an atmosphere of argon, air or oxygen.

We wanted to see if these conditions ($[IrCp^*Cl_2]_2$ (1.0 mol%) , $Mg(OMe)_2$ (0.75 equiv.), $(CH_2O)_n$ (10.0 equiv.), KI (2.0 equiv.), MeOH (0.2 M), 65°C, 16 hours) would perform well with the *N*-methyl quinolinium iodide salt **121**. The product **237** was obtained in 72% isolated yield. The crude NMR of the reaction also revealed about 21 % of **227**.

This difference in reactivity between the *N*-methyl and *N*-benzyl salts noticed throughout the optimisation process can be partially rationalised through different electronics of the ring. In quinoline the NMR shifts (d_4-MeOD) for the 2- and 4- protons are at 8.83 and 8.36 respectively.

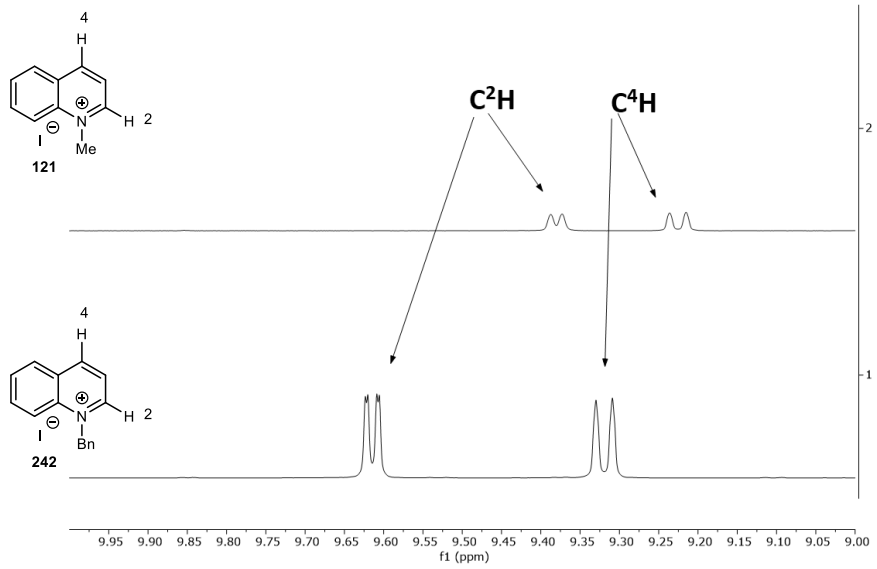
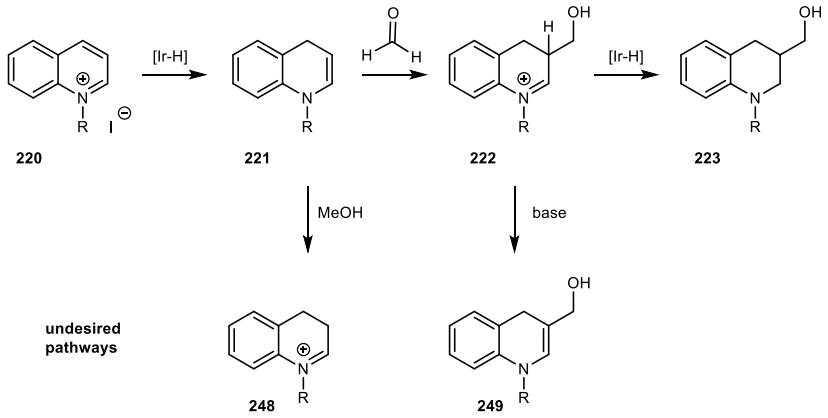


Figure 2.2 Electronic effects on the quinoline ring of different activating groups

The 2- and 4- positions are shifted to 9.38 and 9.22 respectively in *N*-methyl quinolinium, while in *N*-benzyl quinolinium they are shifted to 9.61 and 9.32 (**Figure 2.2**). Clearly, in both cases the aromatic ring becomes more electron-deficient upon quaternarization (resulting in the formation of a quinolinium salt), however the effect is more pronounced for the *N*-benzyl quinolinium. Although anisotropic effects may play a minor role in deshielding the 2- proton of the quinoline, these are non-existent at the 4- position.

Besides altering the electronics of the starting quinolinium ring **220**, the alkylating groups will also change the reactivity of intermediates throughout the reaction pathway towards the desired product **223** (**Scheme 2.10**). For example, enamine **221** could either be protonated or trapped by the more electrophilic formaldehyde.



Scheme 2.10 Difference in reactivity of intermediates dependent on the alkylating group

A less reactive enamine will have an increased preference for trapping formaldehyde, while a more reactive one will discriminate less between protonation (methanol) and formaldehyde trapping. Under reaction conditions optimised for the *N*-benzyl salt **242** (**Table 2.2**: Entry 12) the *N*-methyl salt **121** produces more reduced untrapped tetrahydroquinoline , suggesting that the *N*-methyl enamine is indeed more reactive than the *N*-benzyl.

Once successful trapping of enamine **221** followed by protonation is achieved in order to form intermediate **222**, two major pathways can be followed: desired irreversible reduction to the

functionalised product **223** or deprotonation (**249**), which will eventually lead to a variety of degradation by-products.

The lifetime of this iminium ion **222** depends on multiple factors, such as the reduction rate, the concentration and strength of the base, as well as the nature of the substituent on the nitrogen. A more electron-withdrawing group on the nitrogen will favour deprotonation over reduction, as the base in this system is in excess in comparison with the active hydride species. This could explain why the *N*-benzyl quinolinium salt **242** shows significantly more degradation compared with the *N*-methyl salt **121** under KOH conditions.

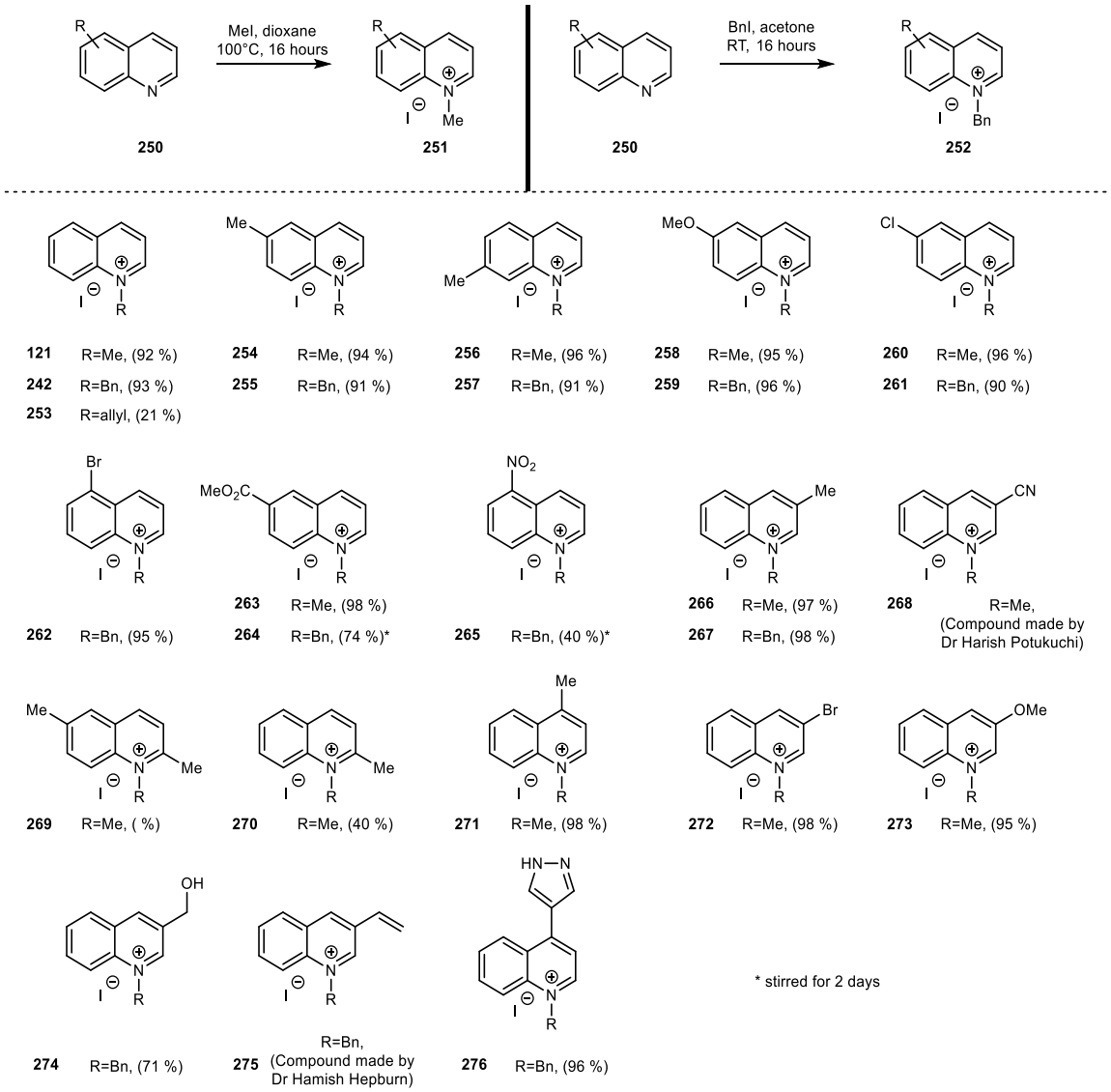
Before moving on to expanding the reaction scope to other quinolines, we attempted to improve the reaction conditions for the *N*-methyl salt **121**. In order to accomplish this, we considered using a more nucleophilic base for this less electron-deficient substrate, as under magnesium methoxide a significant amount of protonation (**248**) took place. Pleasingly, using 1.5 equivalents of KOH in conjunction with 2 equivalents of KI as additive delivered the desired product **237** in 81% isolated yield (**Scheme 2.12**).

2.4 Initial substrate scope

During the optimisation stage we found that the *N*-methyl quinolinium iodide **121** worked best under the following conditions: $[IrCp^*Cl_2]_2$ (1.0 mol%) , **KOH** (1.5 equiv.), $(CH_2O)_n$ (10.0 equiv.), KI (2.0 equiv.), MeOH (0.2 M), 65°C, 16 hours (**General procedure C**). On the other hand, the *N*-benzyl quinolinium iodide **242** works best under: $[IrCp^*Cl_2]_2$ (1.0 mol%) , **$Mg(OMe)_2$** (0.75 equiv.), $(CH_2O)_n$ (10.0 equiv.), KI (2.0 equiv.), MeOH (0.2 M), 65°C, 16 hours (**General procedure D**).

Using these two sets of conditions, we moved on to investigate the reaction scope. Initially, we assessed a selection of quinolines that were commercially available. The synthesis of the *N*-

methyl and *N*-benzyl quinolinium salts and is discussed in detail in the **Chapter 5** (**General Procedure A** and **General Procedure B**) (**Scheme 2.11**).

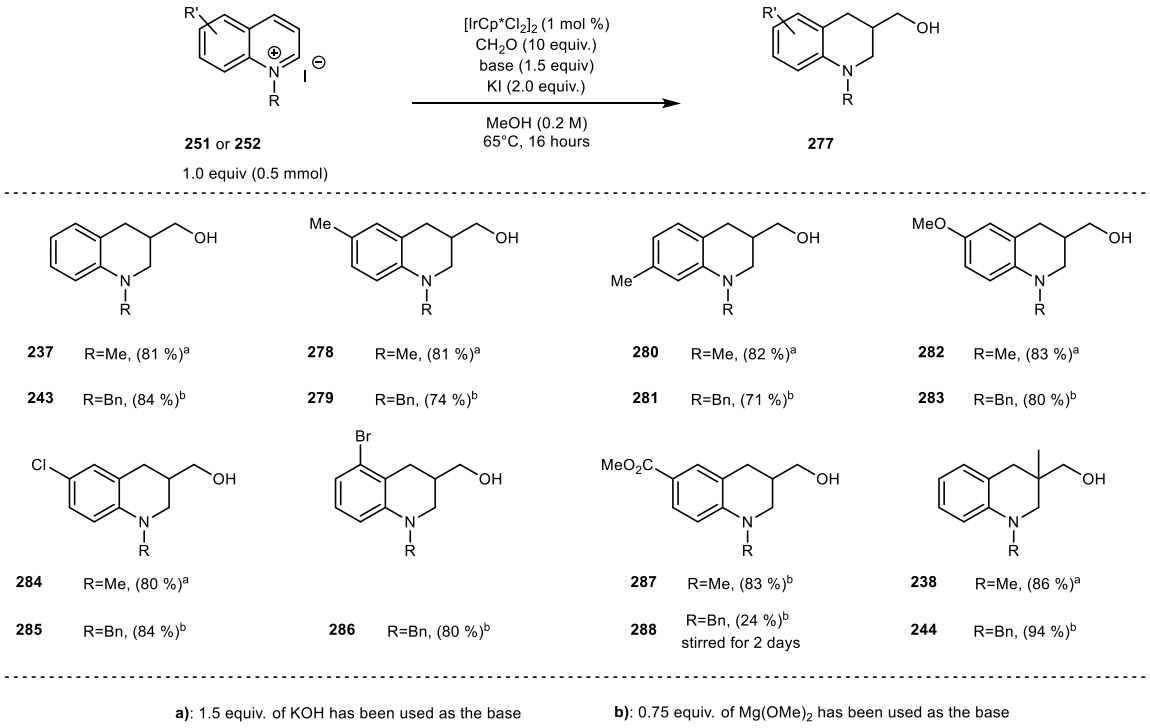


Scheme 2.11 Synthesis of quinolinium iodide salts

As a general rule, we employed the KOH set of conditions for the *N*-methyl salts, while the N-benzyl salts were run under the magnesium methoxide conditions.

Substitution of the carbocyclic ring was well tolerated at the 5-, 6- and 7- positions. Quaternisation attempts on the 8-bromoquinoline failed due to steric reasons. Methyl groups were well tolerated at the 6- and 7- positions, for both the *N*-methyl and the *N*-benzyl salts,

providing the corresponding 3-hydroximethylated tetrahydroquinolines in over 70% yields (**Scheme 2.12: 278-281**).



Scheme 2.12 Substrate scope for *N*-methyl and *N*-benzyl quinolinium salts

The electron donating methoxide and the mild electron-withdrawing chlorine are also well tolerated at the 6- position of the ring (**Scheme 2.12: 282-285**).

Similarly, the mildly electron-withdrawing bromine is well tolerated at the 5- position. The *N*-benzyl hydroxymethylated tetrahydroquinoline **286** was isolated in 80% yield. On the other hand, the strongly deactivated *N*-benzyl-5-nitroquinolinium iodide **265** did not generate any product at all, probably due to the very unreactive electron-deficient enamine produced *in situ*.

Interestingly, despite bearing an *N*-methyl group, the 6-(methoxycarbonyl)-*N*-methylquinolinium iodide **263** worked optimally with the $Mg(OMe)_2$ conditions delivering **287** in 83% isolated yield. Substrate **263** exhibited noticeable degradation under the KOH conditions, similar to that observed for the *N*-benzyl quinolinium salts (*vide supra*). When the

6-(methoxycarbonyl)-*N*-benzylquinolinium iodide **264** was used with $Mg(OMe)_2$ conditions, the corresponding product **284** was isolated in low yield (24%) after two days, while under KOH only severe degradation was observed.

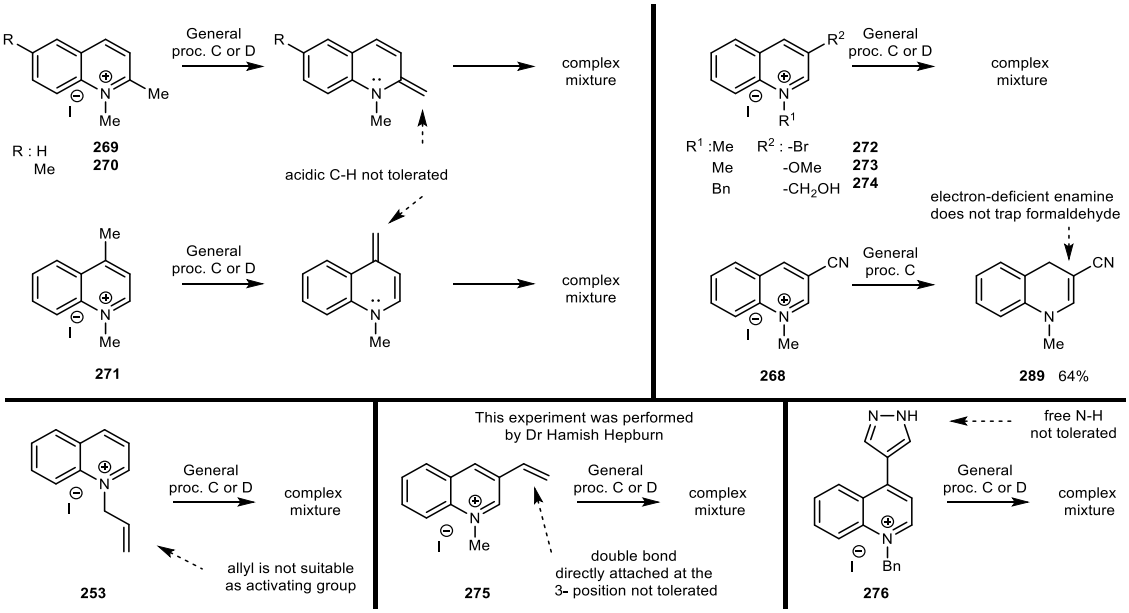
It seems that the reaction requires the substrates to fit within certain electronic requirements. The **substrate** needs to be **electron-deficient** enough to engage in the initial reduction, and subsequently the corresponding **enamines** need to be sufficiently **electron-rich** to trap formaldehyde. Small adjustments of the conditions could be made in order to minimise the amount of untrapped product (normally observed for more electron-rich substrates) or to minimise the base catalysed degradation (normally observed for more electron-deficient substrates).

Before moving to examine more challenging substrates, we wanted to know if the by-products **238** and **244** discovered during the optimisation phase could be produced from the corresponding 3-methylated quinoliniums **266** and **267**. Pleasingly, the tetrahydroquinolines bearing a quaternary centre at the 3- position were obtained in good yields (**Scheme 2.12: 238, 244**). Although 3-substituted tetrahydroquinolines can be obtained from pre-functionalised quinolines through hydrogenation, compounds bearing a quaternary centre at the 3- position could not be accessed in a similar way.[184] Giving this significant advantage of the developed methodology to access the 3- position of tetrahydroquinolines, we continued our scope investigations on more challenging substrates, with variations on the heterocyclic ring.

2.5 Extending the methodology to hindered quinolines – Formation of quaternary centres

Knowing that a methyl group was well tolerated at the 3- position, we wanted to investigate what other functional groups might be allowed on the heterocyclic ring.

When the methyl group is present at either the 2- position (**269**, **270**) or the 4- position (**271**), the reaction produces a complex mixture. Presumably under the reaction conditions, the acidified CH_3 can be deprotonated to form exocyclic enamines which lead to multiple related products.[67]



Scheme 2.13 Investigation of the heterocyclic ring variation – non-tolerated functional groups

Replacing the methyl group at the 3-position with either bromine or methoxy was not tolerated. The corresponding compounds **272** and **273** produced complex reactions mixtures when subjected to the reaction conditions (**Scheme 2.13**). Similarly, a -CH_2OH group at the 3-position was not tolerated either. 1,4-Reduction of **274** leads to formation of an enamine **247** (**Scheme 2.9**) which can eliminate hydroxide to form a conjugated iminium (similar to **Scheme 2.7**).

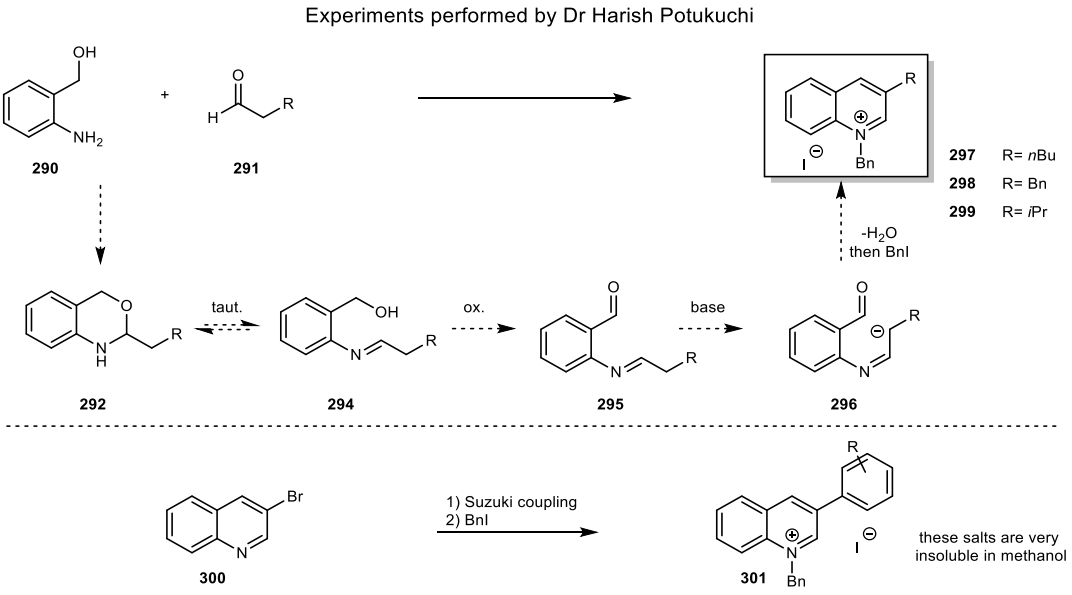
When an electron-withdrawing group is present at the 3- position, such as cyanide (**268**), the resulting enamine **289** is not reactive enough to trap formaldehyde. Moreover, the enamine (assignment based on ^{1}H NMR and NOESY) can be isolated in 64% yield.

N-Allylquinolinium iodide **253** (prepared from quinoline and allyl iodide) was not tolerated either. The reaction produced a very complex mixture. Similarly, alkenes, as determined by Dr

Hamish B. Hepburn, are not tolerated at the 3- position. The reaction of **275** produced a complex mixture similar in aspect (dark blue gum) with the one obtained from **253.**

The quinolinium **276** that presents a free N-H in a pyrazole ring was not tolerated by this methodology. The reaction produced a polymer that could not be dissolved in traditional organic solvents (CH_2Cl_2, Et_2O, MeOH, DMSO) suggesting that N-H units have been bridged together by formaldehyde.

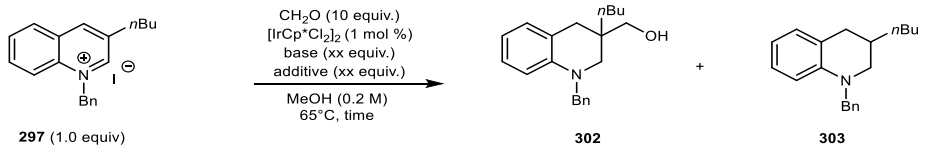
Knowing that a methyl group was well tolerated at the 3-position, we moved on to investigate what other alkyl or aryl groups that might allow the formation of a quaternary centre. Dr Harish K. Potukuchi synthesised and kindly provided a range of 3-substituted quinolinium salts for this purpose: *N*-benzyl-3-butylquinolinium iodide **297**, *N*,3-dibenzylquinolinium iodide **298**, *N*-benzyl-3-isopropylquinolinium iodide **299** and several 3-aryl quinoliniums **301**. Unfortunately, the 3-aryl quinolinium salts **301** were extremely insoluble (even acquiring NMR spectra was difficult) and we did not proceed any further with these substrates (**Scheme 2.14**).



Scheme 2.14 Synthesis of 3-substituted quinoliniums by Dr. Harish Potukuchi

We continued to examine the scope of the reaction with 3-alkyl quinoliniums. Subjecting **297** to the optimised set of conditions for *N*-benzyl salts (**General Procedure D**) produced the

desired product **302** in 52 % yield (**Table 2.3**: Entry 1). The rest of the mass consisted of starting material and untrapped product **303**. Increasing the reaction time from 16 to 40 hours lead to more product (**Table 2.3**: Entry 2). Replacing the two equivalents of KI with one equivalent of MgI_2 resulted in a faster reaction, but also more untrapped by-product **303** (**Table 2.3**: Entry 3).



297 (1.0 equiv) **302** **303**

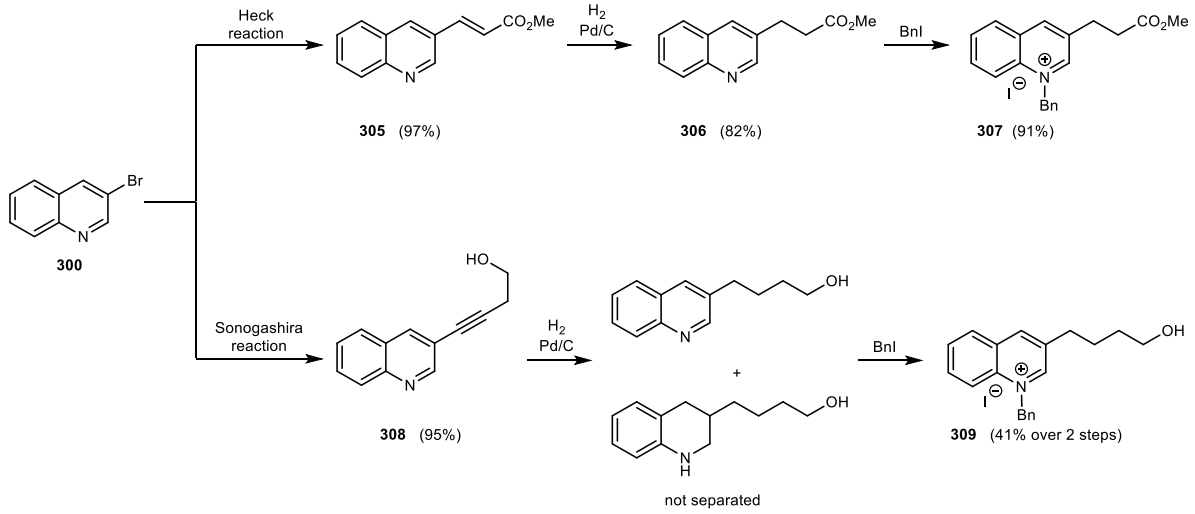
No.	Base (equiv.)	Additive (equiv.)	Reaction time	Yield of 302	Yield of 303 (^{1}H NMR)
1	$Mg(OMe)_2$ (0.75)	KI (2.0)	16 hours	52	18
2	$Mg(OMe)_2$ (0.75)	KI (2.0)	40 hours	75	21
3	$Mg(OMe)_2$ (0.75)	MgI_2 (1.0)	16 hours	54	35
4	KOH (1.5)	KI (2.0)	16 hours	48	15
5	KOH (2.0)	KI (2.0)	16 hours	51	9
6	KOH (2.0)	MgI_2 (1.0)	16 hours	89	5

Table 2.3 Optimisation for substrates leading to quaternary centres
The reactions were run on 0.5 mmol of substrate in 10 mL sealed microwave vials.

When the conditions for the *N*-methyl salts (**General Procedure C**) were used, the reaction produced only 48% of **302**, however the amount of untrapped by-product **303** was significantly reduced (**Table 2.3**: Entry 4). Increasing the amount of KOH from 1.5 to 2.0 equivalents led to a small increase in the yield of desired product **302**, while lowering the amount of untrapped by-product **303** (**Table 2.3**: Entry 5). Using 2.0 equivalents of KOH in conjunction with 1.0 equivalent of MgI_2 proved to be the best set of conditions (**General Procedure E**) for these hindered substrates, as the desired product **302** was isolated in 89% yield (**Table 2.3**: Entry 6).

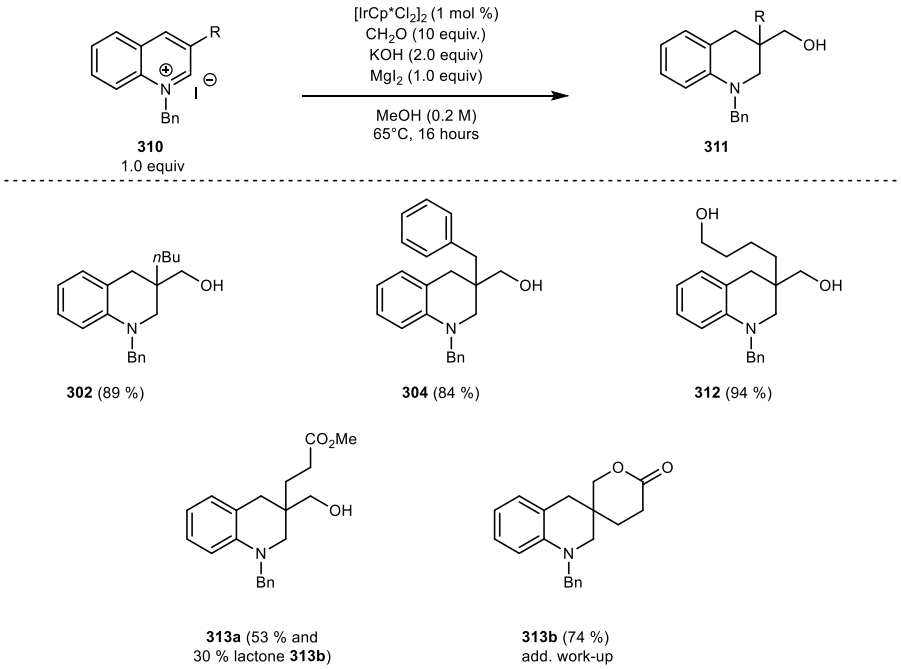
Using the**se** conditions on **298** yielded 84% of the desired product **304** (**Scheme 2.16**). However, substrate **299** (bearing an isopropyl at the 3- position) produced only trace amounts of trapped product under all the conditions developed so far (**General Procedure C, D and E**), suggesting that quaternary centres adjacent to a secondary carbon could not be easily formed through this methodology.

After concluding that linear alkyl substituents are tolerated at the 3- position, we decided to synthesise substrates that have additional functional groups attached to the alkyl chain. Starting from 3-bromoquinoline **300**, palladium catalysed couplings lead to the intermediate quinolines **307** and **309** (**Scheme 2.15**). The hydrogenation of **305** proceeded smoothly, delivering **306** in good isolated yield, which subsequently produced **307** in 91% yield. However, hydrogenation of the triple bond of **308** was slightly more problematic. Incomplete reductions led to mixture of the alkyne, alkene and alkane, which were very hard to separate by FCC. It was more convenient to over-run the reduction and subject the mixture of the alkane and tetrahydroquinoline to quaternisation, as the salt **309** precipitated out and the tetrahydroquinoline could be washed away with ether (**Scheme 2.15**).



Scheme 2.15 Synthesis of 3- substituted quinolines with pendant functional groups on the alkyl chain

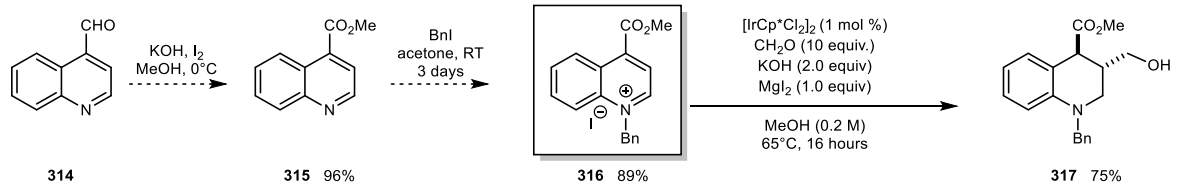
Pleasingly, subjecting quinoliniums **307** and **309** to the conditions developed for hindered substrates (**General Procedure E**) produced the desired products in good yields. The 1,6- diol **312** was isolated in 94% yield as a white solid (**Scheme 2.16**). Interestingly, the product **313** that presented a pendent ester on the side chain was found to partly lactonize under the reaction conditions. However, all of the open alcohol **313a** could be converted to the closed lactone **313b** when an additional acidic workup (10% *p*TSA in toluene) was employed on the crude product.



Scheme 2.17 Substrate scope for 3-substituted *N*-benzylquinoliniums

2.6 Attempts at enantioselective reduction of 4-substituted quinolines

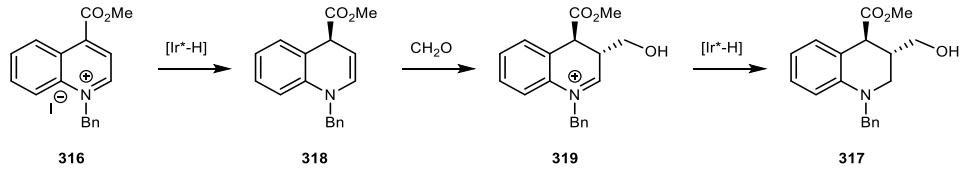
In addition to the 3-substituted quinolines, we also investigated *N*-benzyl-4-(methoxycarbonyl)quinolinium iodide **316** (**Scheme 2.17**). We reasoned that the ester group at the 4- position could be tolerated for several reasons: Firstly, S_NAr would be unlikely on this substrate. Secondly, the enamine **318** formed through 1,4-reduction would not be electronically influenced by the electron-withdrawing group (**Scheme 2.18**).



Scheme 2.17 4-Substituted quinoline tolerated by the methodology

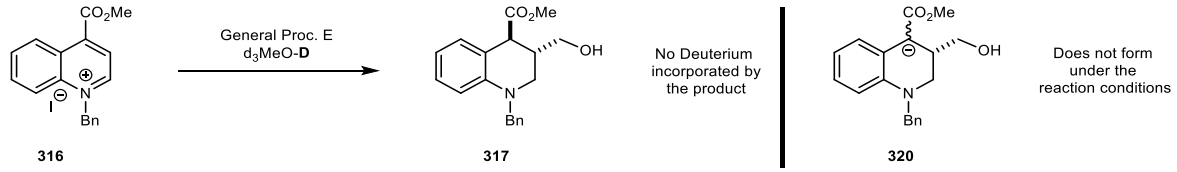
Surprisingly, subjecting **316** to the conditions developed for hindered quinolines (**General Procedure E**) produced **317** in 75% yield. Product **317** was formed exclusively as the *anti* diastereoisomer (racemic) as assigned by NOESY. This revealed that formaldehyde trapping of the enamine **318** happened exclusively from the opposite face of the 4-ester group to form

the trans iminium ion **319**. At this point, we envisioned that an enantioselective reduction of **316** would result in the formation of only one enantiomer (**Scheme 2.18**).



Scheme 2.18 4-Substituted quinolines as potential candidates for enantioselectivity

Before moving on to screen chiral iridium complexes, we ran an experiment with deuterated methanol to rule out epimerisation at the 4- position due to enolate deprotonation/reprotonation (**Scheme 2.19**). The product **317** did not incorporate any deuterium, highlighting that epimerisation (**320**) would not racemise a potentially enantioenriched product **317**.

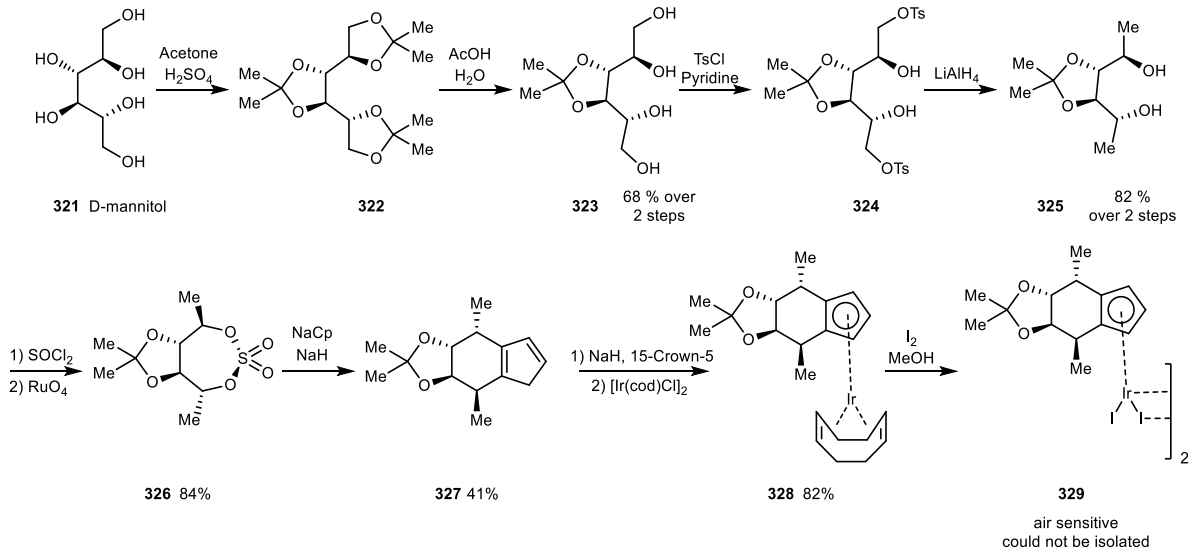


Scheme 2.19 Preliminary test for base catalysed epimerisation

Cramer and co-workers have recently reported rhodium and iridium chiral complexes that were based on a chiral cyclopentadiene **327** derived from D-mannitol (**Scheme 2.20**).[185] The detailed synthesis of **327** is covered in **Chapter 5**. Attempts to synthesise the Ir (III) complex **329** directly from **327** failed due to the Diels-Alder dimerization of the unhindered cyclopentadiene.

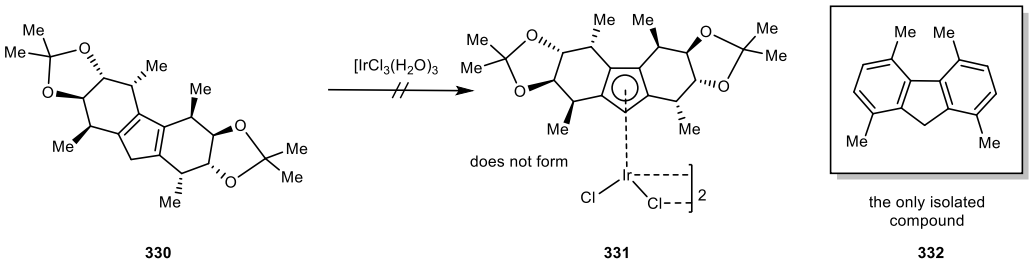
The literature reports on coupling the chiral cyclopentadiene **327** with Ir (I) complexes involved thallium ethoxide as a key reagent. Due to the high toxicity of thallium salts, we investigated alternative methods and discovered that good yields (82%) of **328** can be obtained if sodium hydride and 15-Crown-5 are used to deprotonate the chiral cyclopentadiene **327**. The intermediate anion was subsequently quenched with $[Ir(cod)Cl]_2$. Attempts to obtain the Ir(III) complex **329** from the oxidation of **328** with iodide failed due to the instability of the Ir(III)

complex.[186] We concluded that the non-hindered cyclopentadiene was responsible for the instability of the complex **329**.



Scheme 2.20 Synthesis of a chiral cyclopentadiene based iridium complex

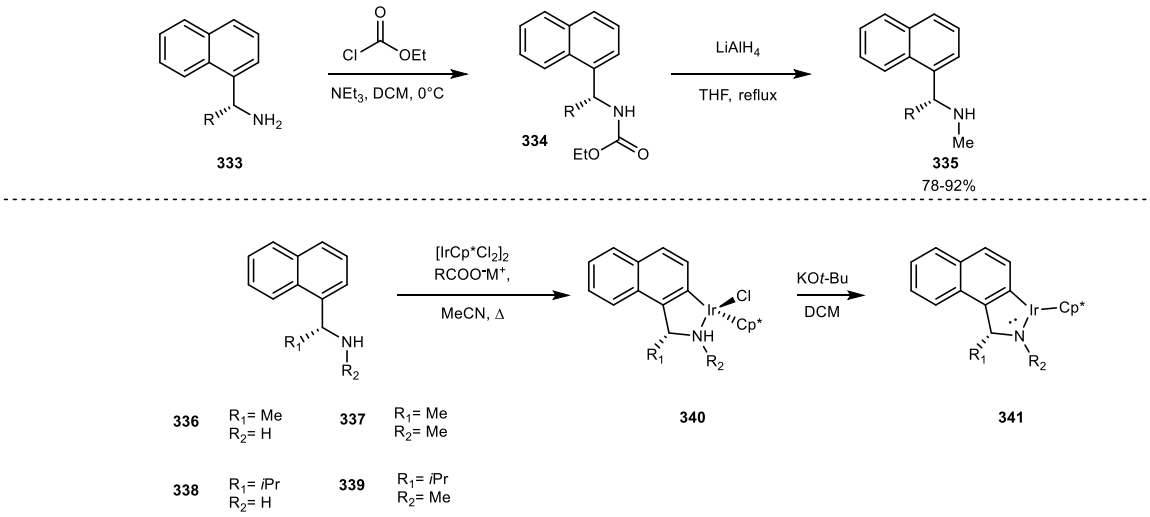
During preparation of the chiral cyclopentadiene **327**, the dimeric by-product **330** was also isolated (**Scheme 2.21**). We considered that this hindered C_2 symmetric cyclopentadiene would produce a more stable Ir (III) complex. However, the formation of the desired iridium complex **331** did not occur, and instead the aromatic compound **332** was isolated. Attempts to couple **330** with $[Ir(cod)Cl]_2$ also failed and we decided to abandon this route.



Scheme 2.21 Attempts to synthesise a more hindered iridium complex derived from a chiral cyclopentadiene

Another class of iridium complexes that came to our attention were derived from $[IrCp^*Cl_2]_2$ and chiral amines **336-339** (**Scheme 2.22**). The detailed synthesis of these complexes is discussed in the experimental chapter. The procedure reported in literature employed sodium acetate in acetonitrile at 60°C to couple benzylic amines with $[IrCp^*Cl_2]_2$.[187] We found that

more hindered amines did not react so readily under these conditions. Attempts to increase the reaction temperature lead to by-products formed from self-condensation of sodium acetate. Replacing sodium acetate with cesium pivalate allowed the reaction mixture to be heated to reflux without any additional side reactions.

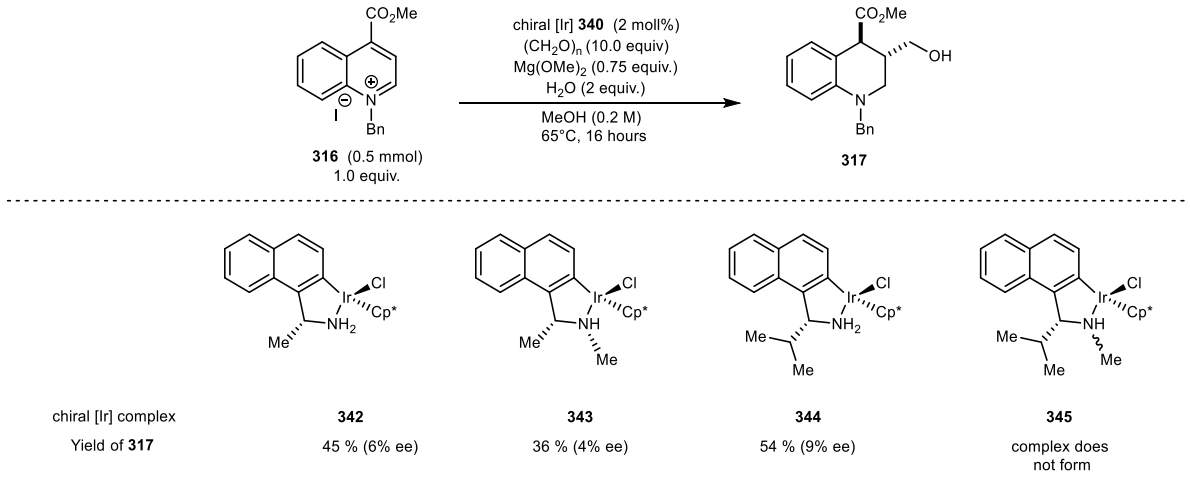


Scheme 2.22 Iridium complexes based on chiral amines

The isolated tetrahedral iridium complexes **342-344** (17-41%, details in **Chapter 5**) are monomeric and reach 18 electrons through a coordinative bond from the nitrogen lone pair to the metal. The stereochemistry at the iridium centre has been determined in literature for **342** (X-Ray and NMR spectroscopy) and further confirmed by X-Ray spectroscopy of complex **343** (X-Ray data attached in the appendix).

As these complexes have only one available catalytic site (in the case of **340** loss of chlorine is required) we investigated conditions that remove the addition of excess iodide. We found that using 0.75 equivalents of magnesium methoxide with 2.0 equivalents of H_2O worked reasonably well and allowed us to test their performance in inducing enantiomeric enrichment. In all cases, the isolated yield of product **317** was lower (38-54%) than the racemic version (75%) of the reaction and the enantio-enrichment was always towards the same isomer of which absolute stereochemistry was not determined (**Scheme 2.23**). The enantiomeric

enrichment determination was performed on an automated HPLC system (Agilent 1260 infinity II) using a Chiralcel OD column.



Scheme 2.23 The performance of several iridium complexes in inducing enantioselectivity

The orange complexes **340** can be deprotonated with KO*t*Bu in DCM at room temperature to form the purple trigonal iridium complexes **341** (**Scheme 2.22**). [187] Unfortunately, we could not isolate these trigonal complexes **341** due to their air sensitivity, although their formation could be assessed by ^{1}H NMR if the deprotonation was carried out in $CDCl_3$ and the sample submitted for NMR spectroscopy (**Figure 2.3**).

All 3 complexes **342-344** were tested under two different set-ups. In one set-up, the complex (2 mol%) would be used in the tetrahedral form **340**, while in the other one, the complex would be previously deprotonated *in situ* to the trigonal form **341** with 1.2 equivalents of KO*t*Bu in 1.0 mL DCM (removed under vacuum at the end) for two hours.

For complexes derived from **342** and **344** that feature a primary amine attached to the iridium center, prior deprotonation made no difference in either yield or ee. It seems that these compounds re-protonate on nitrogen in presence of methanol.

However, for the *N*-methylated iridium complex **343** prior deprotonation seemed to increase both the yield (from 36% to 65%) and ee (from 4% to 7%), which suggests that the *N*-methyl complex **346** does not re-protonate in methanol as readily (**Figure 2.3**).

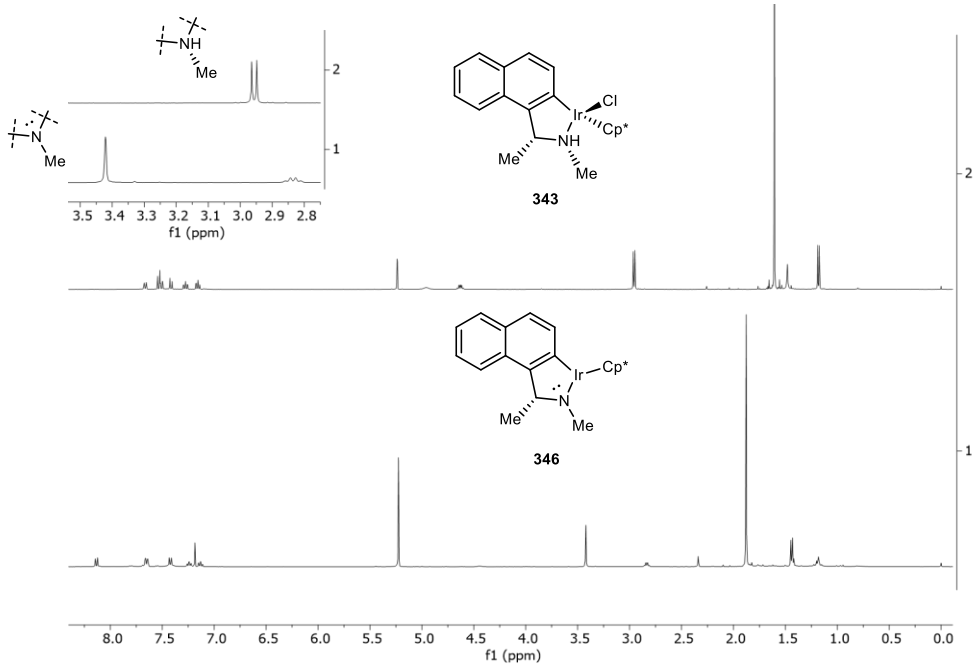
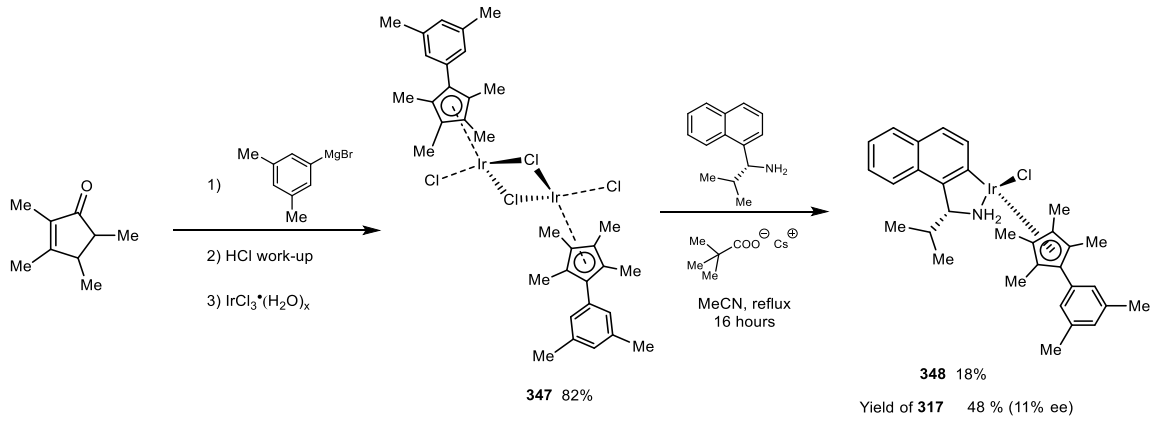


Figure 2.3 NMR confirmation for the formation of trigonal iridium complex **341**

An isopropyl group at the benzylic position seems to be superior to the methyl in terms of both reactivity and ee (**342** vs **344**). This increase in steric bulk could potentially restrict rotation around the C-aryl bond, which in turn forces the nitrogen to be in proximity to the metal center (**Figure 2.4**). Unfortunately, the presence of this bulkier group does not allow for the *N*-methyl complex **345** to form (**Scheme 2.24**). On the other hand, the cyclopentadiene of the starting iridium complex could be modified (**Scheme 2.24**).

The hindered iridium complex **348** was obtained (18%) from the coupling of the iridium complex **347** with the chiral amine **338** by employing cesium pivalate in refluxing acetonitrile. The reaction of quinolinium **316** with 2 mol% of complex **348** produced less product **317** (48%) in comparison to the reaction where **344** was employed (54%). However, the ee of the reaction

increased from 9% to 11% (**Scheme 2.24**). Lowering the temperature from 65° C to 50° C lead to an increase in ee up to 13%, however it had a detrimental effect on the yield (34%).



Scheme 2.24 Synthesis of iridium complexes with a modified cyclopentadiene

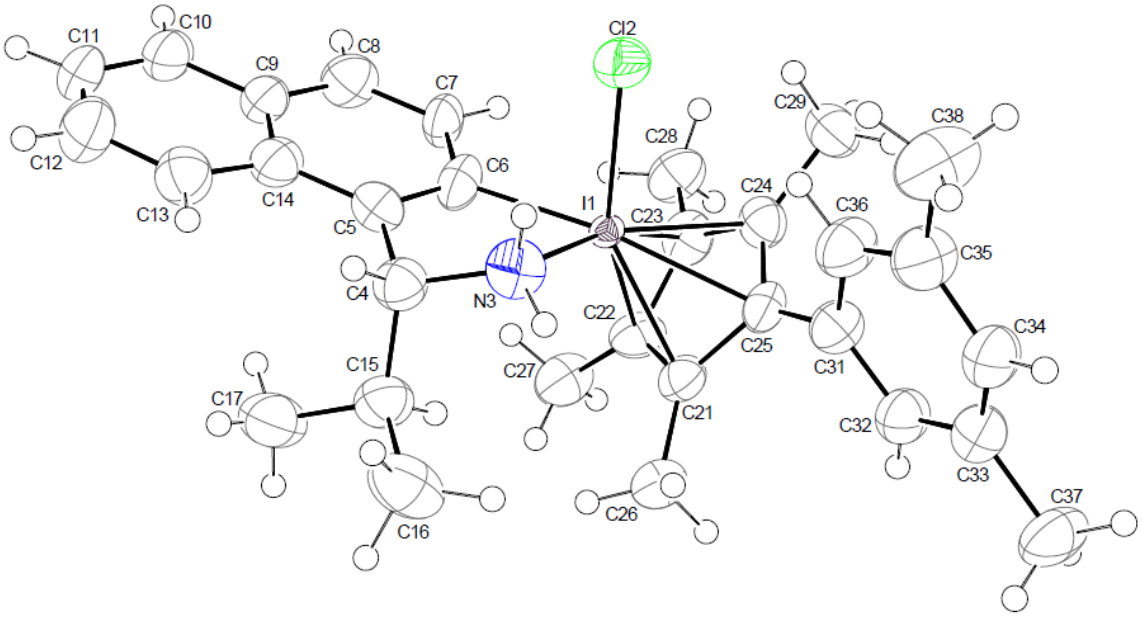


Figure 2.4 X-Ray structure of iridium complex **348**

Low ee values and further findings during our mechanistic studies (uncatalyzed hydride shift from the 1,2 dihydroquinoline to the starting quinolinium **- Scheme 2.30**) have discouraged us to continue work in this direction.

2.7 Mechanistic studies

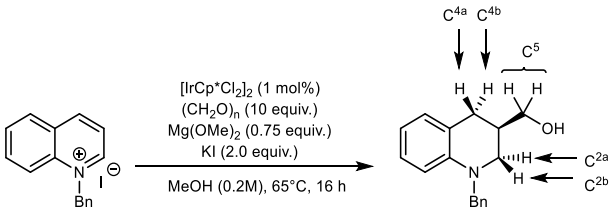
Having developed a comprehensive substrate scope, we wanted to investigate the reaction from a mechanistic perspective. Given the complexity of the pathway followed by the substrate, a quantitative kinetic study was not possible within our laboratory facilities. However, monitoring the reaction via NMR by removing an aliquot every hour revealed a complex mixture that slowly converged towards the desired product. This suggests a reversible series of events that eventually funnels through the product.

Even though quantitative aspects of the reaction were hard to assess, we considered that valuable qualitative information could be obtained through deuterium labelling. This would allow us to identify the hydride source of this reaction, as well as an assessment of how much methanol gets oxidised to formaldehyde.

2.7.1 Deuterium labelling

Performing the reaction with deuterated methanol led to no deuterium incorporation at either the 2- or 4- positions, nor the installed CH_2OH group (**Table 2.4**: Entry 1). Additionally, d_3-methyl formate could be observed in the reaction crude NMR spectra. This suggested that the hydride added to the ring must have come from formaldehyde oxidation to methyl formate **350** via the hemiacetal **349**. Running the reaction with deuterated formaldehyde confirmed this hypothesis (**Table 2.4**: Entry 2). Unsurprisingly, the deuterium incorporation at the CH_2OH moiety of the product **243** revealed that all the formaldehyde trapped by the enamine is the one added in the beginning of the reaction (**Table 2.4**: Entry 2).

Interestingly, no methanol was oxidised to formaldehyde in the presence of magnesium methoxide and at an iodide concentration of 0.6 M. The more reactive formaldehyde adduct **349** was found to be exclusively the hydride source of the reaction (**Scheme 2.25**).



No.	CH_3OH or CD_3OD	$(CH_2O)_n$ or $(CD_2O)_n$	C^{2a}	C^{2b}	C^{4a}	C^{4b}	C^5
1	D	H	0	0	0	0	0
2	H	D	0.75	0.5	0.35	0.35	2.00
3	D	D	0.75	0.5	0.35	0.35	2.00

Table 2.4 Summary of deuterium labelling experiments

The reactions were run on 0.5 mmol of substrate in 10 mL sealed microwave vials. The deuterated version of the reagent was used were specified in the table.

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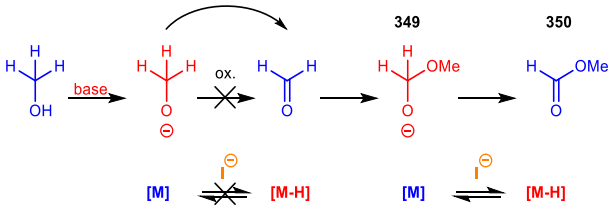
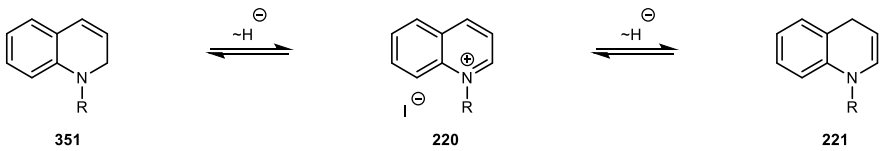


Scheme 2.25 The formal-redox catalytic system of the reaction at high iodide concentration

On the other hand, the deuterium incorporation on the ring presented some peculiar features: more than one deuterium atom has been added at the 2- position, while less than 1 atom was added at the 4- position. Performing the reaction with both deuterated methanol and formaldehyde produced exactly the same pattern of deuterium incorporation (**Table 2.4**: Entry 3), suggesting that the uneven distribution of deuterium may be better explained by some reversible hydride additions, rather than residual methanol oxidation due to primary kinetic isotopic effect (**Scheme 2.26**).

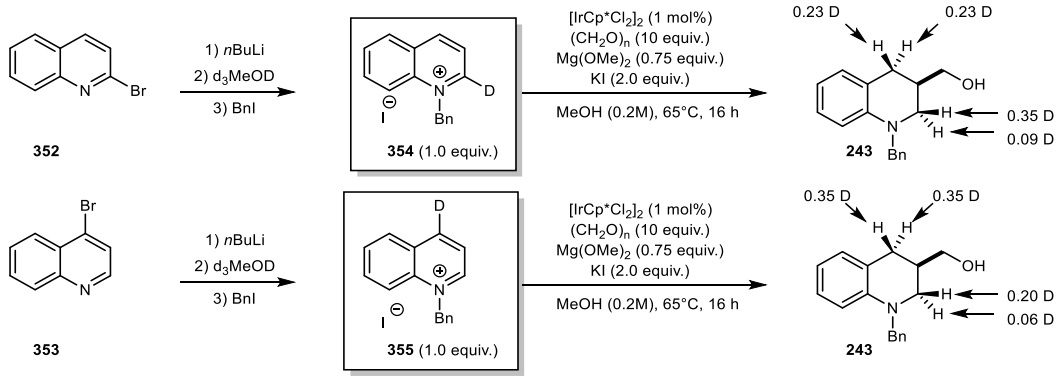


Scheme 2.26 Potential reversible formal-redox for the starting quinolinium

In order to test the reversibility of the hydride addition, the 2- and 4- deuterated quinolines **354** and **355** were prepared (**Scheme 2.27**) . Running reactions with these deuterated substrates led to products **243** that had deuterium present at both the 2- and 4- positions. Giving that the only

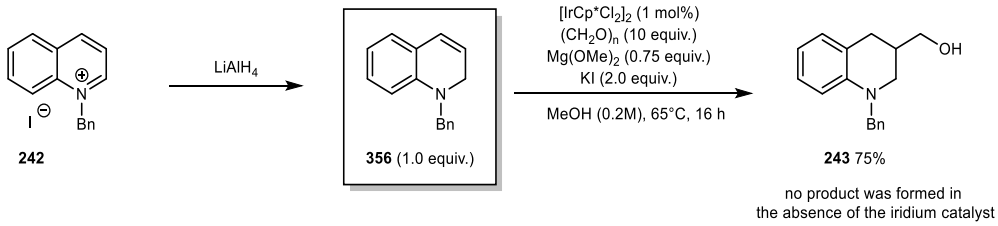
source of deuterium in this reaction were the starting quinoliniums **354** and **355**, the scrambling of deuterium suggests indeed that reduction at both positions is reversible.

In all of these deuterium labelling reactions, the ratio between the diastereotopic protons at the 2- position of **243** was different from 1, while at the 4- position it was always 1. This suggests that reduction at the 4- position is, as expected, non-facially selective, since hydride is added to a flat symmetrical molecule, while addition at the 2- position seems to be happening preferentially opposite to the CH_2OH moiety.



Scheme 2.27 Evidence of reversible hydride reduction at the 2- and 4- positions

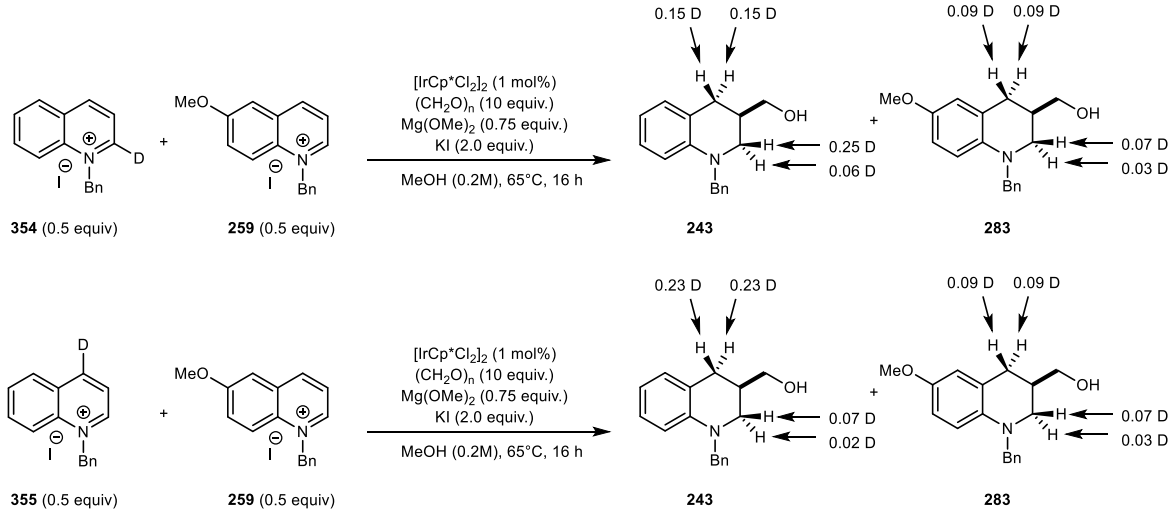
In order to prove that reduction at the 2- position is reversible, we prepared the *N*-benzyl dihydroquinoline **356** separately and subjected it to the reaction conditions (**Scheme 2.28**). This produced **243** in high yield (75% isolated), suggesting that the dihydroquinoline **351** can indeed convert to the reactive enamine **221**, probably through re-oxidation to the quinolinium salt followed by 1,4- reduction (**Scheme 2.26**). Subjecting the same dihydroquinoline under the reaction conditions in absence of the iridium catalyst led to no product (*vide infra*).



Scheme 2.28 Evidence that 1,2-dihydroquinoline is an intermediate of the reaction pathway

2.7.2 Cross-over experiments

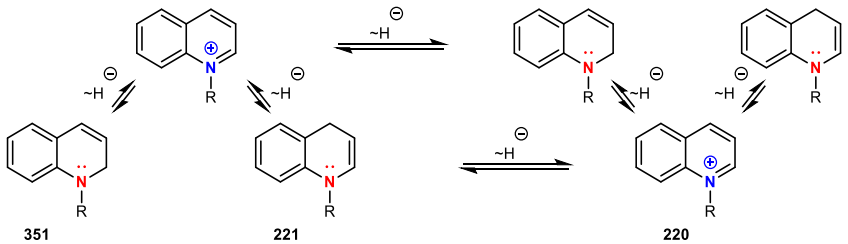
In order to differentiate between an intramolecular and an intermolecular hydride shift, we subjected the deuterated quinoliniums **354** and **355** to the reaction conditions in conjunction with one equivalent of a distinct non-deuterated quinolinium **259** (**Scheme 2.29**). The presence of deuterium in **283** confirmed an intermolecular hydride pathway, suggesting that the 1,4- (**221**) and 1,2- dihydroquinolines (**351**) re-oxidize back to the quinolinium salts through a formal-redox process.



Scheme 2.29 Cross-over experiments summary

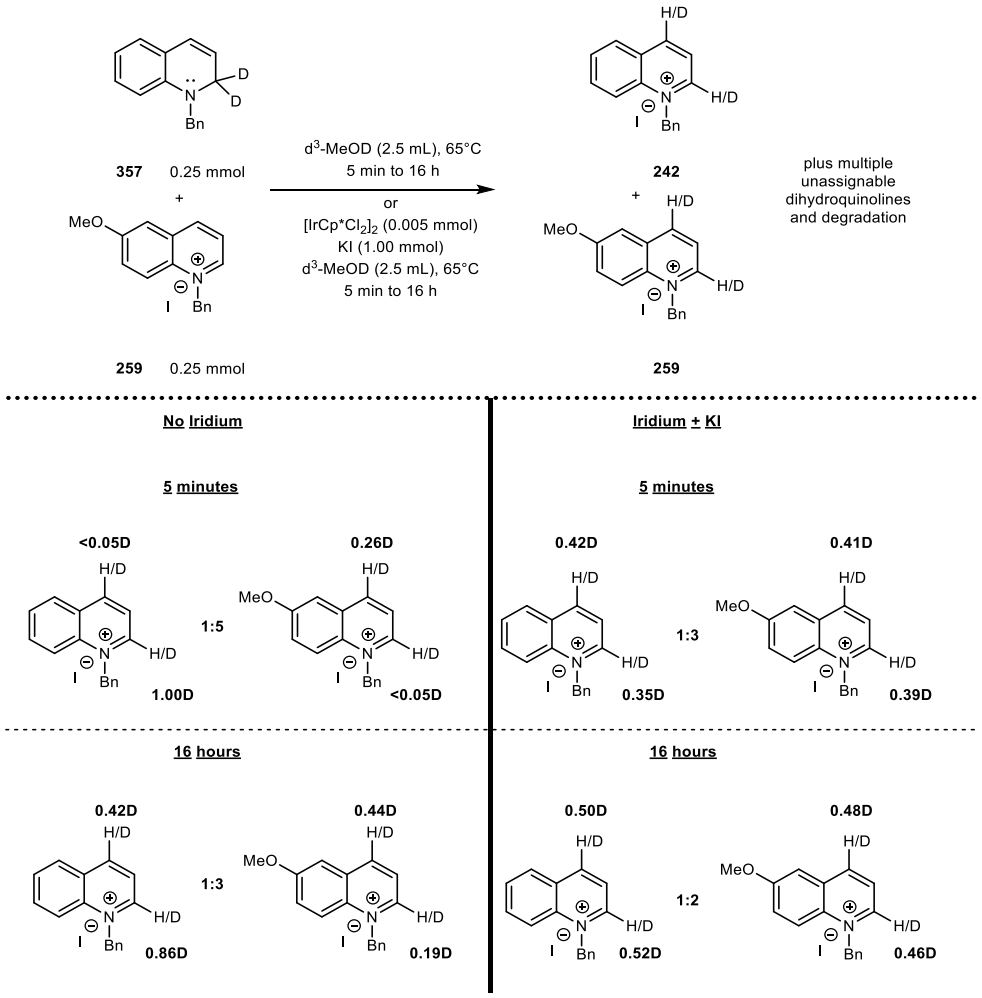
2.7.3 Investigation of the role of the iridium catalyst

The previous experiments have shown that the quinolinium ion can be reversibly converted to either the 1,2- or 1,4- dihydroquinoline through an intermolecular reversible hydride addition (**Scheme 2.30**). This hydride shift could theoretically follow either a direct pathway or a catalysed pathway with the formation of an intermediate iridium-hydride species.



Scheme 2.30 Reversible formal-redox process through hydride shift

In order to qualitatively assess the influence of the iridium catalyst on the formal-redox process, we designed a series of experiments and synthesised (synthesis similar to **356**) the double-deuterated dihydroquinoline **357** (**Scheme 3.31**).



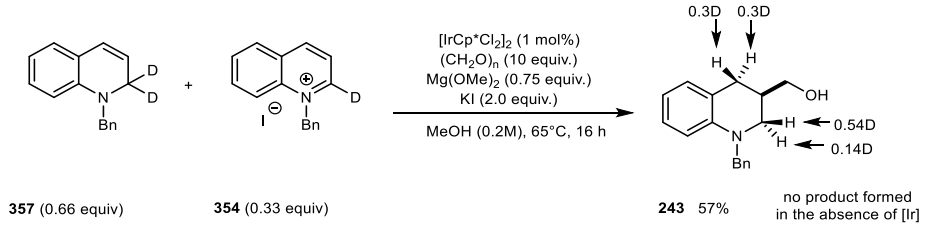
Scheme 2.31 Cross-over experiments in the presence and absence of iridium

A 1:1 mixture of this dihydroquinoline **357** and the corresponding quinolinium **259** previously used in the cross-over experiments were heated to 65° C in deuterated methanol (0.2 M). One experiment was performed in the absence of iridium, while the other was carried out with 1.0 M % of iridium and 2.0 equivalents KI, replicating the reaction iridium loading and iodide concentration (**Scheme 2.31**). An aliquot of each reaction was taken after 5 minutes and 16 hours respectively. The ^{1}H NMR revealed a complex mixture of dihydroquinolines that were difficult to assign. However, the quinolinium salts could be easily quantified.

In the absence of iridium, after 5 minutes of reaction time a mixture of quinoliniums **242** and **259** could be observed in a 1 to 5 ratio. It appears that compound **357** could transfer a hydride (deuterium) to the quinolinium **259** and had a preference for the 4- position. After 16 hours, the ratio between **242** and **259** progressed from 1:5 to 1:3 and the deuterium scrambled across all four positions, but with an increased preference for the 4- position in both quinoliniums.

In the presence of iridium, the ratio between **242** and **259** was 1:3 after only 5 minutes, suggesting significantly faster hydride shifts, with no strong preference for any position. After 16 hours, no significant differences were apparent, and the deuterium was distributed almost statistically across all four possible positions.

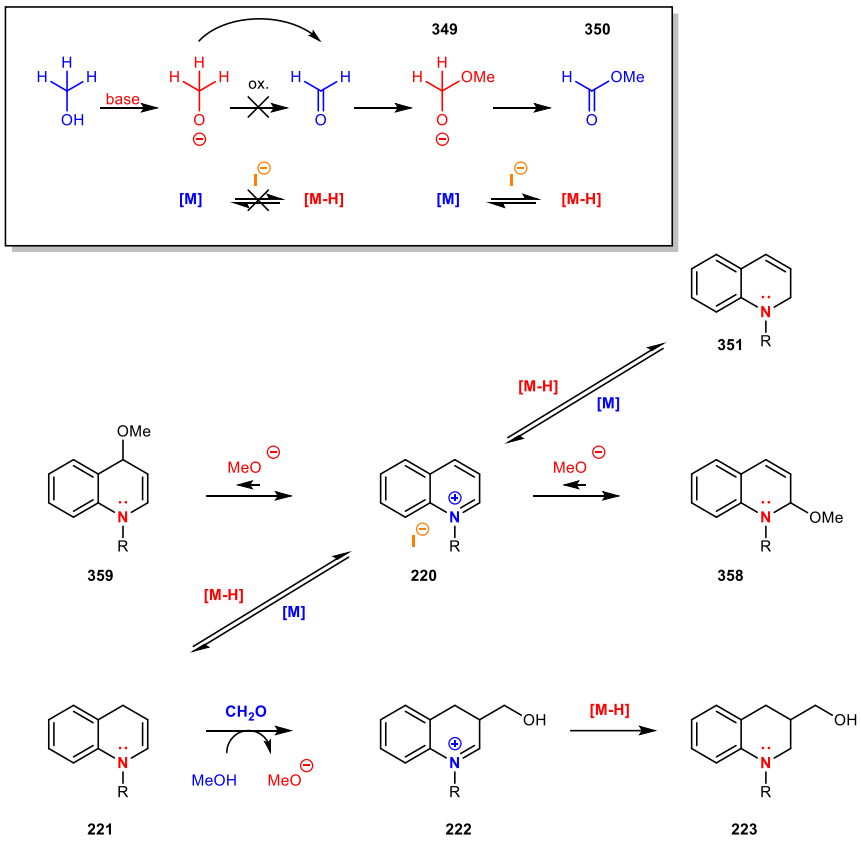
In summary, these experiments highlight that a dihydroquinoline mixed with a quinolinium can eventually produce the enamine required for trapping formaldehyde in the absence of iridium, although the process is significantly slower. Next, we wanted to investigate whether the dihydroquinoline would be a suitable hydride source for reducing the trapped iminium ion.



Scheme 2.32 Investigating the potential of dihydroquinoline to reduce the iminium ion

Subjecting a 2:1 mixture of **357** and **354** to the reaction conditions in the absence of iridium led to no product. This proves that the dihydroquinoline is not a suitable reducing reagent for the last reaction step. When iridium is employed, desired product **243** is obtained in 57% yield, with 1.28 deuterium incorporation (**Scheme 2.32**). This degree of deuterium incorporation (more than 1, but less than 2) suggests that both **357** and **354** were converged towards the product. This proves that iridium is a required reagent for achieving the final reduction of the iminium ion.

The overall proposed mechanism for this transformation is highlighted below (**Scheme 2.33**).



Scheme 2.33 Proposed mechanism for the C^3 reductive hydroxymethylation of quinolinium salts

2.8 Conclusions

In conclusion, we have successfully developed the C^3 hydroxymethylation of quinolinium salts.[188] This method allows access to 3- functionalised tetrahydroquinolines from simple quinolines. Moreover, when pre-functionalized quinolines are employed, formation of quaternary centres at the 3- position is possible.

Mechanistic investigations revealed that the ultimate hydride source, as well as the electrophile for this reaction is the added paraformaldehyde.

The lost ability of the transition metal to oxidise methanol to formaldehyde might be a consequence of the iodide employed in the catalytic system. However, iodide led to an overall better interaction of the metal species with the substrate and the resulting intermediates.

Additionally, the requirement for oxygen was also removed by employing iodide, potentially making this transformation viable on an industrial scale.

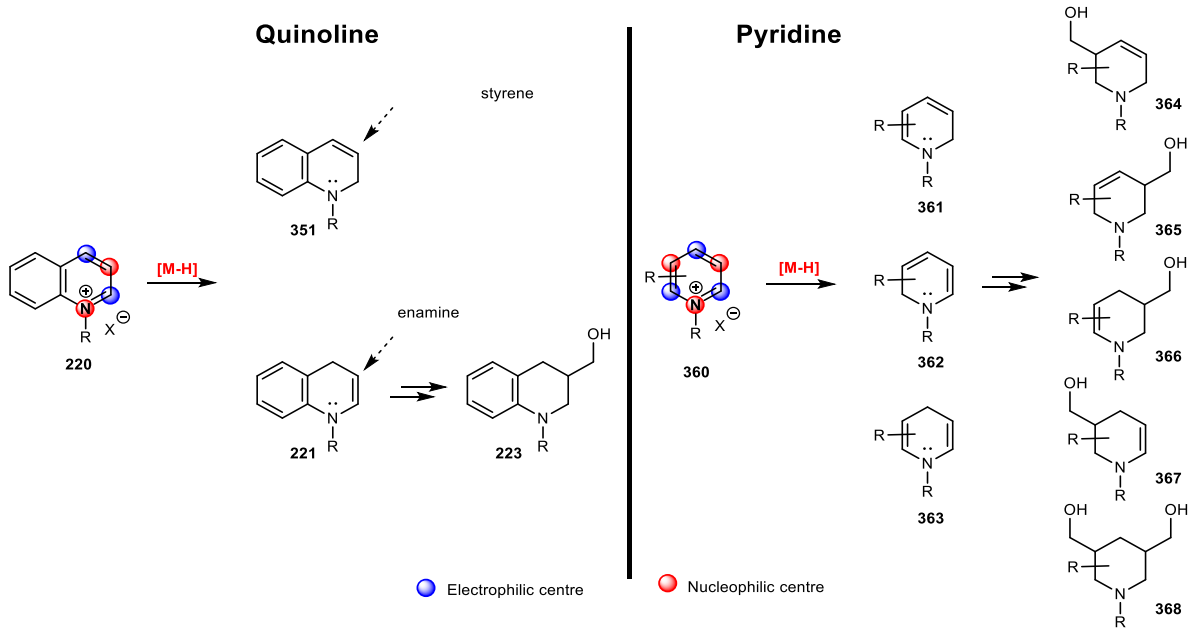
During our mechanistic investigations we have also shown that the iridium complex interacts reversibly with the substrate. Due to these reversible pathways, unproductive intermediates are eventually funnelled through towards the desired product.

Chapter 3: Extending the reductive hydroxymethylation methodology to pyridines

3.1 Introduction

After we successfully developed the reductive hydroxymethylation of quinolinium salts **220** through an iridium catalysed "Interrupted Transfer Hydrogenation", we wanted to extend this methodology to pyridines.

Pyridine is similar to quinoline as both heteroarenes are electron-deficient and present alternating nucleophilic and electrophilic centres (**Scheme 3.1**). However, there are some key differences between these azaarenes.



Scheme 3.1 Potential products for ITH on quinolines and pyridines

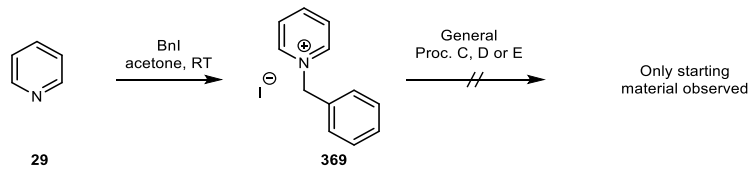
In quinoline the heterocyclic ring is 5,6- fused to a benzene ring. This lowers the energy penalty for removing aromaticity of the heterocyclic ring, making the quinoline more reactive towards nucleophilic addition. Additionally, the resulting intermediates formed from nucleophilic addition at either the 2- or 4- position of the quinolinium **220** would present different connectivity with the nitrogen lone pair. Addition at the 4- position leads to an enamine **221**, while addition at the 2- position would lead to a styrene **351**.

Similar to quinoline, the 2- and 4- positions of pyridine are electrophilic. Additionally, due to the lack of a fused ring, the 6- position of pyridine is also electrophilic. Depending on the substituents present on the pyridinium ring **360**, reduction at either 2-, 4- or 6- position would lead to formation of up to three different enamines **361**-**363** (**Scheme 3.1**). These enamines are nucleophilic at the 3- and 5- positions, and reaction with electrophiles can potentially form multiple distinct products **364**-**368**.

3.2 Preliminary screening of the reductive hydroxymethylation methodology on pyridines

The synthesis of the pyridinium salts employed in the following experiments is discussed in detail in **Chapter 5**. As a general procedure, the corresponding pyridine was stirred overnight with a slight excess of the alkylating reagents, then the resulting precipitate (yields varying from 40 to 99%) was filtered and washed with ether.

We began our screening reactions on the simplest possible substrate, the *N*-benzylpyridinium iodide salt **369** (**Scheme 3.2**), by employing all three sets of conditions developed so far for quinoliniums (**General Procedures C**, **D** and **E**).



Scheme 3.2 Attempts of ITH on *N*-benzylpyridinium iodide salt

Unfortunately, only starting material was observed in all cases. These findings suggested that a simple pyridinium salt would not be electrophilic enough to be reduced under the previously developed catalytic system.

A common way to further activate pyridines towards nucleophilic addition involves attaching electron-withdrawing groups on the ring, which results in an energetically lower LUMO (**Figure 3.1**).[63]

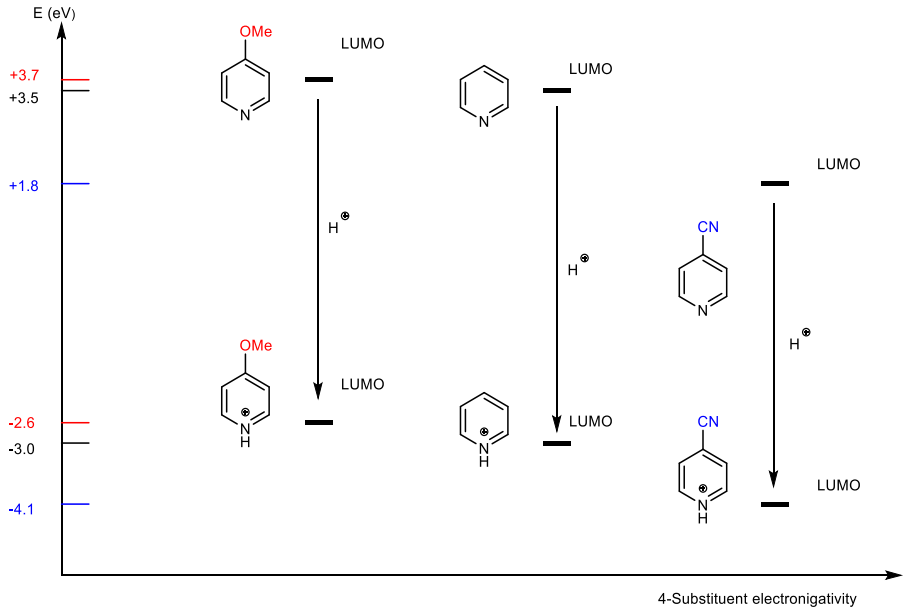
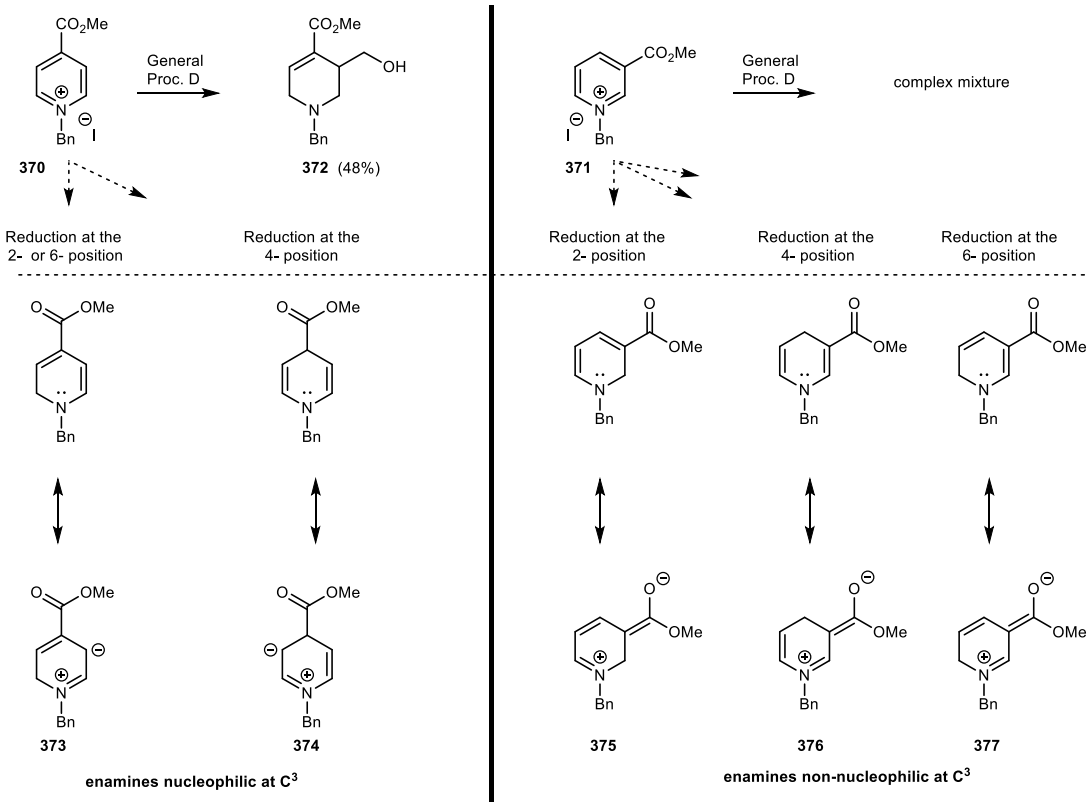


Figure 3.1 Electronic properties of pyridines as a function of substituents and protonation state [63]

Since our prior investigations showed that a methyl ester group was tolerated under the reaction conditions (see **Chapter 2.6**), the introduction of this group our first modification. Attempts at quaternising methyl picolinate (ester at the 2- position) with benzyl iodide failed due to low conversion and difficulties in isolating the product, however both methyl isonicotinate (4-position) as well as methyl nicotinate (3- position) produced the desired benzyl iodide salts **370** and **371** in 99% and 92% yields respectively (Similar to **Scheme 3.2**).

Subjecting **370** and **371** to the reaction conditions resulted in the full consumption of the starting material, highlighting that electron-deficient pyridinium salts are indeed electrophilic enough to engage in reduction. Compound **371** led to a complex mixture, while ester **370** produced, among other by-products, the C^3 hydroxymethylated tetrahydropyridine **372** in 48% yield (**Scheme 3.3**).

Although an additional electron-withdrawing group was required in order to allow the reaction to initiate for pyridines, the placement of this group also seemed to be crucial. For example, when placed at the 2- position, quaternisation becomes unfavourable. When located at the 3-position, the resulting enamines become less reactive due to the conjugation of the nitrogen lone pair with the electron-withdrawing group (**Scheme 3.3**). The optimal placement seemed to be at the 4- position, as these substrates are both electrophilic enough for the initial reduction and nucleophilic enough for the subsequent formaldehyde trapping step.



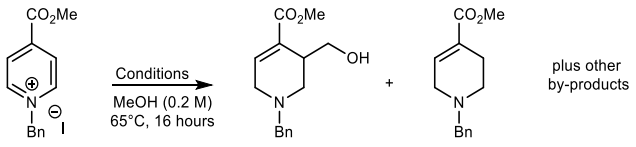
Scheme 3.3 Putative intermediates formed from hydride addition to electron-deficient pyridiniums

3.3 Optimisation for the C^3 reductive hydromethylation of 4-substituted pyridinium salts

Preliminary experiments on the pyridinium salt **370** under **General Procedure D** conditions produced the desired product **372** in 48% yield along with the untrapped tetrahydropyridine **378** as the main by-product (**Table 3.1**: Entry 1 and **Scheme 3.3**).

Using the conditions with KOH as the base developed for quinolines (**General Procedures C** and **E**) led to hydrolysis of the methyl ester to its corresponding carboxylate (**Table 3.1**: Entry 2). When sodium methoxide was employed instead (to avoid hydrolysis) the yield of the desired product was significantly lower (**Table 3.1**: Entry 3). The optimal base for this reaction was found to be the less nucleophilic magnesium methoxide. Using magnesium methoxide and increasing the loadings of paraformaldehyde to 20 equivalents led to an increase in the yield of the desired product **372** and a decrease in the amount of untrapped by-product (**Table 3.1**: Entry 4). Removing the additional potassium iodide from the reaction resulted in a lower yield of **372** and a larger amount of unidentified degradation by-products (**Table 3.1**: Entry 5), suggesting that a high iodide concentration is a requirement for this reaction. Lowering the reaction temperature from 65°C to 45°C seemed to have a beneficial effect, as the yield of **372** noticeably increased, while the amount of degradation by-products decreased (**Table 3.1**: Entry 6).

Lowering the reaction temperature to room temperature had a detrimental effect on the reaction progress (**Table 3.1**: Entry 7), however this could be overcome with an increase in additional potassium iodide loadings to 4 equivalents (**Table 3.1**: Entry 8).



370 (1.0 equiv.) **372** **378**

No.	$(CH_2O)_n$ equiv.	Base (equiv.)	KI equiv.	Total iodide conc. (M)	T (°C)	Conversion	Yield of 372	Yield of 378 (^{1}H NMR)
1	10	$Mg(OMe)_2$ (0.75)	2	0.6	65	>95	48	12
2	10	KOH (1.5)	2	0.6	65	>95	hydrolyses to the carboxylate	
3	10	NaOMe (1.5)	2	0.6	65	>95	15	2
4	20	$Mg(OMe)_2$ (0.75)	2	0.6	65	>95	68	5
5	20	$Mg(OMe)_2$ (0.75)	0	0.2	65	>95	56	4
6	20	$Mg(OMe)_2$ (0.75)	2	0.6	45	>95	75	3
7	20	$Mg(OMe)_2$ (0.75)	2	0.6	22	~80	55	2
8	20	$Mg(OMe)_2$ (0.75)	4	1.0	22	>95	90	3

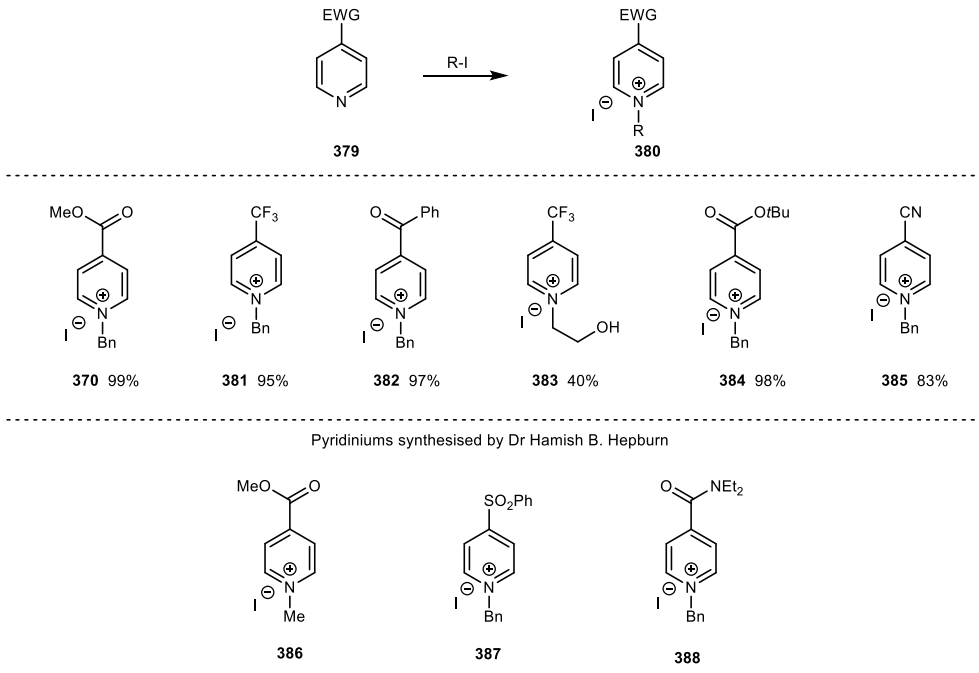
Table 3.1 Reaction optimisation on 1-benzyl-4-(methoxycarbonyl)pyridinium
The reactions were run on 0.5 mmol of substrate in 10 mL sealed microwave vials.

Thus, the final reaction conditions were set to: $[IrCp^*Cl_2]_2$ (1.0 mol%), $Mg(OMe)_2$ (0.75 equiv.), $(CH_2O)_n$ (20.0 equiv.), KI (4.0 equiv.), MeOH (0.2 M), 22°C, 16 hours (**General Procedure G**), which resulted in a 90% yield of desired product **372**.

Performing the reaction on a 3.0 mmol scale (approximately 1 gram) yielded 85% of the desired product **372**, highlighting the potential of this methodology to be used on a preparative scale.

3.4 Substrate Scope for 4-substituted pyridinium salts

The required pyridinium salts for investigating the substrate scope were synthesised by mixing the starting pyridine with 1.5 equivalents of the corresponding alkylating reagent in a suitable solvent (detailed procedure in **Chapter 5**). The pyridinium salts **386-388** were synthesised and provided by Dr Hamish B. Hepburn (**Scheme 3.4**).

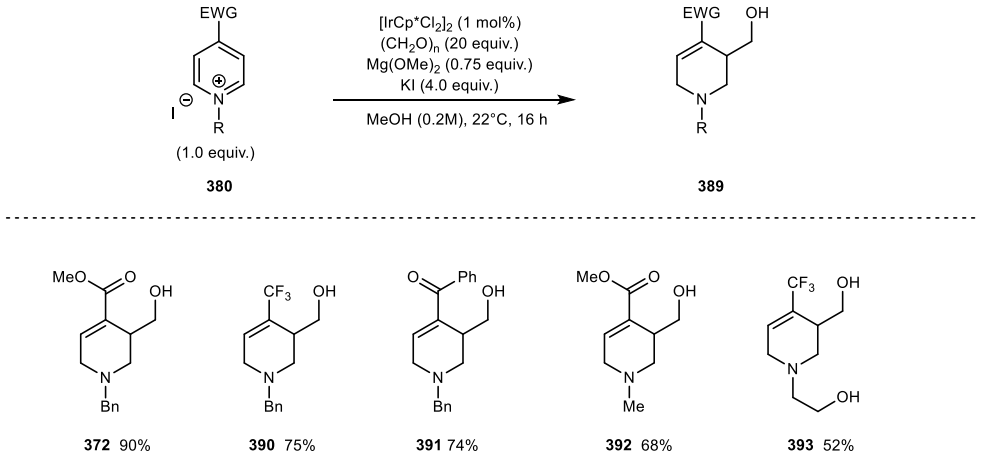


Scheme 3.4 Synthesis of benzyl iodide pyridinium salts bearing electron-withdrawing groups at the 4- position

First, we investigated what other electron-withdrawing groups were tolerated at the 4- position besides a methyl ester. A trifluoromethyl group (**381**) as well as aryl ketones (**382**) were found to be compatible (**Scheme 3.4**), as these produced the desired products **390** and **391** in 75% and 74% yield respectively. On the other hand, a tertbutyl ester (**384)** was found to partly trans-

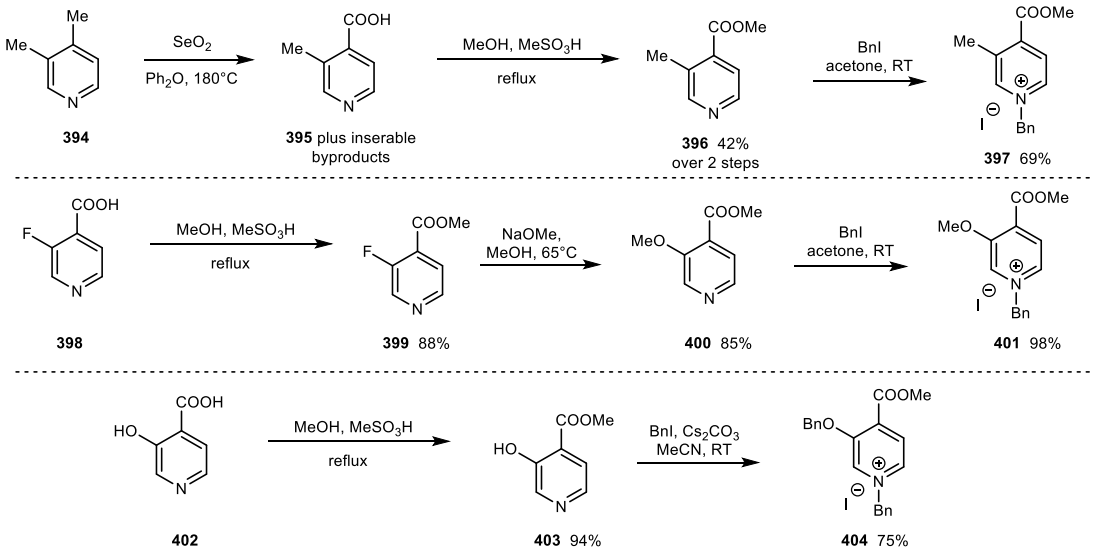
esterify under the reaction conditions, while a nitrile group (**385**) lead to a complex mixture. The compounds **387** and **388**, bearing a sulfone and hindered amide at the 4- position respectively were also found to not be tolerated under the reaction conditions, probably due to S_NAr reactivity or partial hydrolysis.

Next, we moved on to study the variation of the alkyl group on the nitrogen. Besides the benzyl group, a methyl (**392**) or an alkyl chain that presents a free alcohol (**393**) performed well under the reaction conditions (**Scheme 3.5**). Additional examples of tolerated aryl ketones at the 4-position and *N*-alkyl groups were investigated by Dr Hamish B. Hepburn.[188]



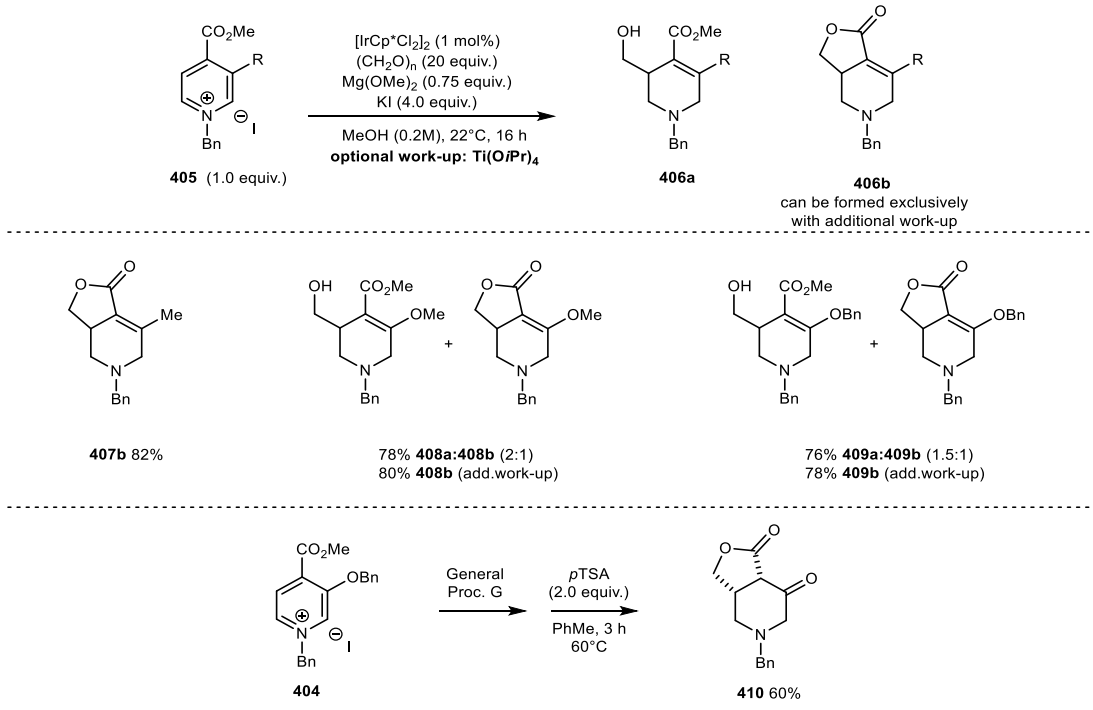
Scheme 3.5 Substrate scope for 4-substituted pyridiniums salts: electron-withdrawing group and *N*-alkyl variation

Philip J. Smith and Dr Hamish Hepburn had previously discovered that the 3-substituted pyridinium salt **397** could undergo reductive hydroxymethylation at the 5- position producing the lactone **407b**. Giving this preliminary result and the recently optimised conditions for pyridines, we went on to synthesise a selection of 3,4- substituted pyridines in order to test and expand the reaction scope to this class of substrates (**Scheme 3.6**). Additional examples of 3,4-substituted pyridines tolerated by the methodology have been synthesised and tested by Philip J. Smith and Dr Hamish Hepburn.[188]



Scheme 3.6 Preparation of 3,4-substituted pyridiniums salts

Interestingly, the pyridines that presented a methyl ester group at the 4- position and an additional substituent at the 3- position (**397**, **401** and **404**) were found to react with formaldehyde exclusively at the 5- position, giving products **407**-**409** in over 75% yield (**Scheme 3.7**). This was shown by a lack of an alkene C-H peak in the ^{1}H NMR spectra of the crude reactions.



Scheme 3.7 Substrate scope for 3,4-substituted pyridiniums salts

Additionally, product **407** was found to lactonize completely under the reaction conditions to the corresponding [6,5-] bicycle **406b** completely, while products **408** and **409** formed a mixture of the open **406a** and lactonized product **406b**. If required, an additional work-up involving $Ti(OiPr)_4$ could be employed to convert all the open product **406a** to the lactonized form **406b** (further details in the Experimental chapter).

The products obtained through this methodology contain a multitude of functional groups: amine, electron-deficient alkene, ester and primary alcohol. In addition, the compound bearing an enol ether at the 3- position **409** contains a protected ketone, which can be unmasked under treatment of the crude product with *p*TSA. The formation of **410** (relative stereochemistry determined by NOESY) further highlighting the complexity of potential compounds attainable by this interrupted transfer hydrogenation reaction.

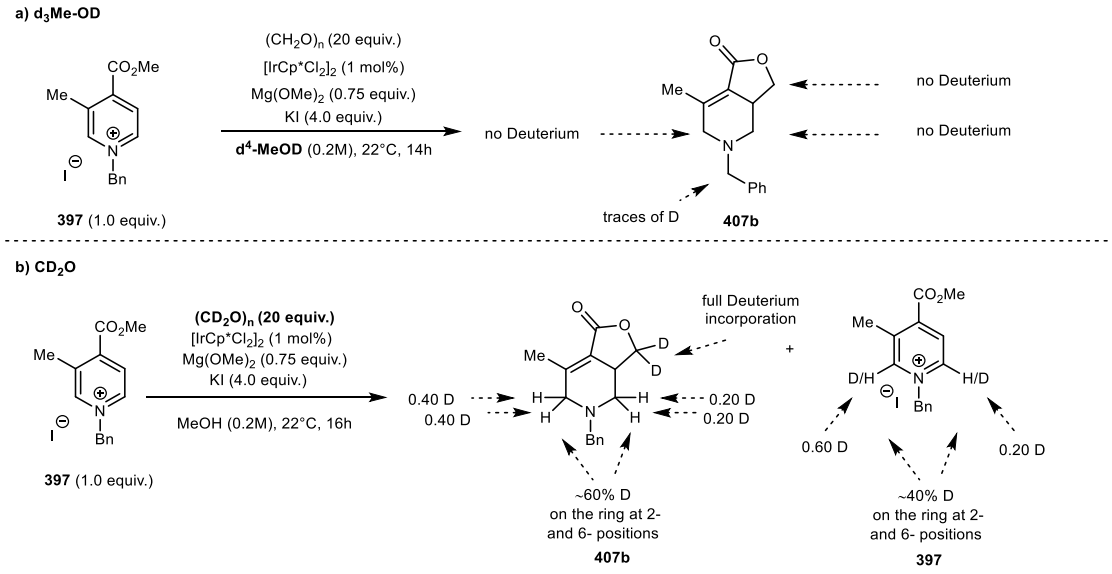
3.5 Mechanistic studies

After developing a comprehensive substrate scope for electron-deficient pyridines, we conducted mechanistic investigations similar to those shown for quinolines (**Chapter 2.7**). Moreover, we questioned the nature of the regioselectivity for the asymmetrical 3,4- substituted pyridines, as these substrates seemed to exclusively react with formaldehyde at the 5- position.

For practical reasons, we considered that substrate **397** was the most suitable for these investigations, as it produced only the lactonized product **406b** without additional work-up.

Similar to quinolines, performing the reaction in deuterated methanol resulted in no deuterium incorporation on the ring or at the CH_2OH handle (**Scheme 3.8a**). Additionally, d_3-methyl formate could be observed in the crude ^1H NMR spectra. However, traces of deuterium were noticed at the benzylic position of the product **407b**. This epimerisation did not occur if **407b** was subjected to the same reaction conditions, suggesting that the starting pyridinium **397** was

responsible for the deuterium incorporated in the product **407b**. Performing the reaction with deuterated formaldehyde instead, resulted in full deuterium (2 out of 2) incorporation at the CH_2OH moiety, 0.8 (out of 2) incorporation at the 2- position and 0.4 (out of 2) incorporation at 6- position (**Scheme 3.8b)**.



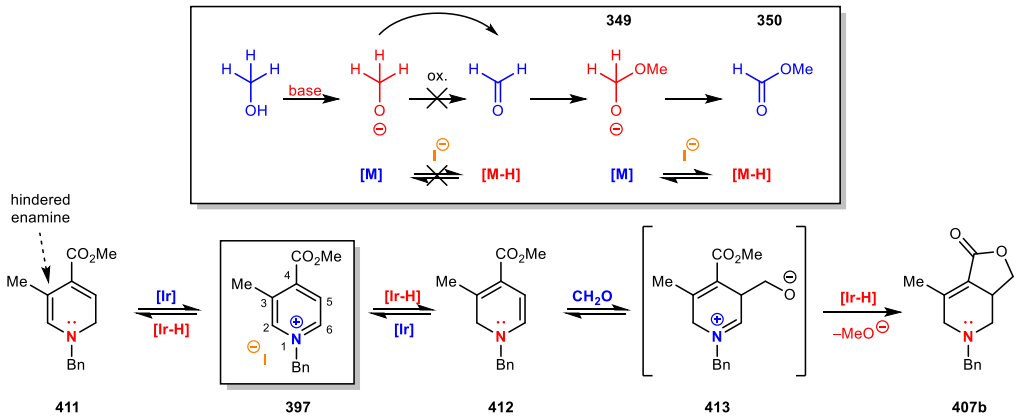
Scheme 3.8 Deuterium labelling experiment on an asymmetrical pyridinium

The deuterium incorporation on the ring was significantly lower (1.2) than expected (2 for full conversion), suggesting either that methanol provided the hydride through oxidation to formaldehyde or that another hydride source was present. The low conversion (less than 50%) of the reaction determined us to analyse the unreacted starting material. Running the reaction a second time allowed us to isolate the starting material, where we found significant deuterium incorporation had taken place (approximately 0.8 D had been incorporated – 0.6 D at the 2-position and 0.2 D at the 6- position). This pattern of incorporation suggests that reduction occurs predominantly at the 2- position, which, is consistent with the deuterium incorporation pattern in the product **407b** from the same reaction. Similar as for quinolines, these experiments also showed that Ir-H/D addition to the pyridinium salts is reversible.

The reaction with both deuterated methanol and deuterated formaldehyde at room temperature progressed extremely slowly, so we attempted it at 45°C. Under these conditions, the deuterium incorporation presented a very similar pattern to that obtained by running the reaction in deuterated formaldehyde and normal methanol at room temperature (2 out of 2 at the CH_2OH moiety and 1.2 out of 2 on the ring – see appendix).

In conclusion, the deuterium labelling highlighted that formaldehyde is both the hydride source (presumably via a hemiacetal **349**) and the electrophile for this reaction, similar to quinolines (**Scheme 2.25**).

In the case of asymmetrical pyridiniums (such as **397**), reductions at both the 2- and 6- positions are possible, however reduction at the 6- position gives rise to a hindered enamine **411**, which does not readily trap formaldehyde at the 3- position **(Scheme 3.9**).



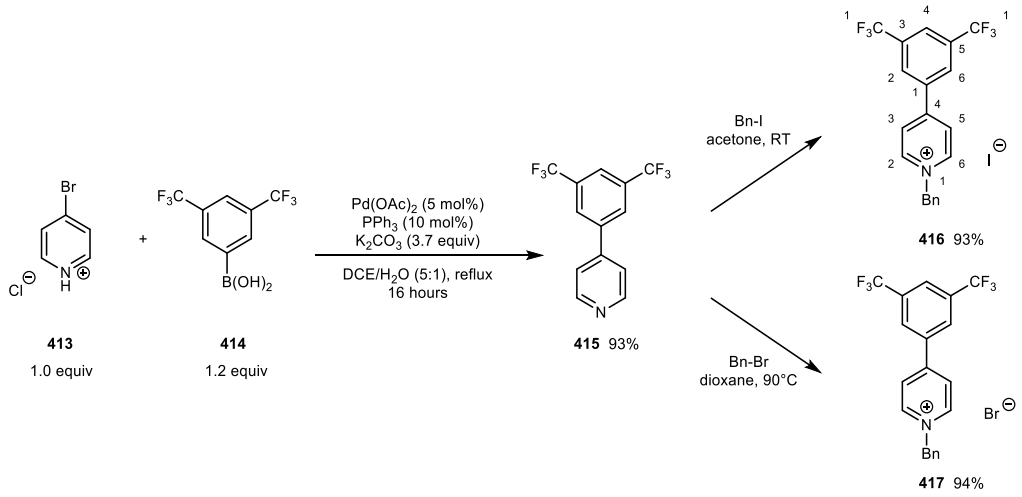
Scheme 3.9 Proposed mechanism and reaction pathway for pyridinium salts

This unproductive enamine can be re-oxidised to the starting material **397**, which eventually will be reduced at the 2- position to form the productive enamine **412** which can subsequently trap formaldehyde at the 5- position to give the iminium ion **413**. This iminium ion probably lactonizes *in situ* and final reduction furnishes the product **407b (Scheme 3.19**).

3.6 Attempts to extend the methodology to less electron deficient pyridines

During our prior investigations, we concluded that an electron-withdrawing group was required at the 4- position of pyridinium salts in order to achieve the desired reactivity necessary for interrupted transfer hydrogenation. Philip J. Smith had carried out preliminary work on applying this methodology to 4-aryl pyridines and observed limited reactivity of these less electron-deficient substrates under the iridium catalysed system.

The 4-aryl pyridine **415** was synthesised from the corresponding boronic acid **413** and the hydrochloric salt of 4-bromopyridine **414** through a Suzuki coupling reaction (**Scheme 3.10**).



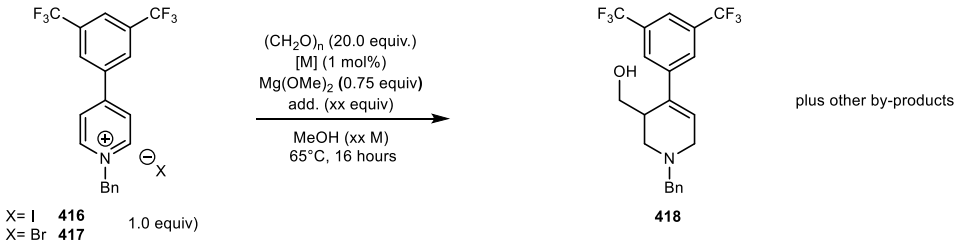
Scheme 3.10 Synthesis of 4-aryl pyridines through a Suzuki coupling

Applying the optimized conditions for the electron-deficient pyridines (**General Procedure G**) on the *N*-benzyl-4-(3,5-bis(trifluoromethyl)phenyl)pyridinium iodide **416** led to modest consumption of starting material. Increasing the temperature to 65° C resulted in about 40% consumption of starting material, but only 32% ^{1}H NMR yield of desired product (**Table 3.2**: Entry 1).

Lowering the amount of iodide seemed to increase both the consumption of starting material and the yield of desired product **418** (**Table 3.2**: Entries 2 and 3). When using the pyridinium

bromide salt **417**, the consumption of starting material was almost complete, however the yield of desired product **418** was significantly decreased to less than 5% (**Table 3.2**: Entry 4).

It seems that the catalytic ability of the iridium hydride species to reduce the starting pyridinium increased inversely proportional to the amount of iodide present in the system (**Table 3.2**: Entries 1-4). However, when no iodide was present in the system, very low amounts of product **418** were formed, suggesting that its formation required iodide (**Table 3.2**: Entry 4). Moreover, at higher iodide concentrations it seemed that more starting pyridinium was converted to **418** with regards to starting material consumption. For example, at an iodide concentration of 1.0 M, about 80% (32/40) of the consumed starting material **416** converged to **418** (**Table 3.2**: Entry 1)**.** These percentages decreased to 78% (35/45 - **Table 3.2**: Entry 2), 64% (39/61 - **Table 3.2**: Entry 3) and <5% (**Table 3.2**: Entry 4) as the iodide concentration was lowered.



No.	X	Metal (1 mol%)	Add. (equiv.)	Total iodide conc. (M)	T (°C)	Substrate concentration (M)	Conversion (^{1}H NMR)	Yield of 418 (^{1}H NMR)
1	I	$[IrCp^*Cl_2]_2$	KI (4.0)	1.0	65	0.2	40	32 (27 isolated)
2	I	$[IrCp^*Cl_2]_2$	KI (2.0)	0.6	65	0.2	45	35
3	I	$[IrCp^*Cl_2]_2$	x	0.2	65	0.2	61	39
4	Br	$[IrCp^*Cl_2]_2$	x	x	65	0.2	>98	<5
5	I	$[RhCp^*Cl_2]_2$	x	0.2	65	0.2	>98	60 (54 isolated)
6	I	$[RhCp^*Cl_2]_2$	KI (2.0)	0.6	65	0.2	>98	45
7	Br	$[RhCp^*Cl_2]_2$	x	x	65	0.2	>98	3
8	I	$[RhCp^*Cl_2]_2$	x	0.2	45	0.2	95	56
9	I	$[RhCp^*Cl_2]_2$	KI (2.0)	0.6	45	0.2	80	42
10	Br	$[RhCp^*Cl_2]_2$	x	0.0	45	0.2	>98	4
11	I	$[Ru(p\text{-cymene})Cl_2]_2$	x	0.2	65	0.2	>98	36
12	I	$[RhCp^*Cl_2]_2$	x	0.2	65	0.1	>98	21

Table 3.2 Use of different transition metals on less electron deficient pyridines

The screening reactions were run on 0.25 mmol of substrate in 10 mL sealed microwave vials. The isolated yield was obtained from a 0.5 mmol scale reaction.

From previous experiments, we were aware that the presence of iodide in the system might result in a better reducing agent for the intermediate iminium ion (see **Chapter 2: Figure 2.1**). On the other hand, in the absence of iodide, a different mechanism may be in play, involving different iridium species, which might interact differently with the starting pyridinium and intermediate iminium ion (**Figure 3.2**).

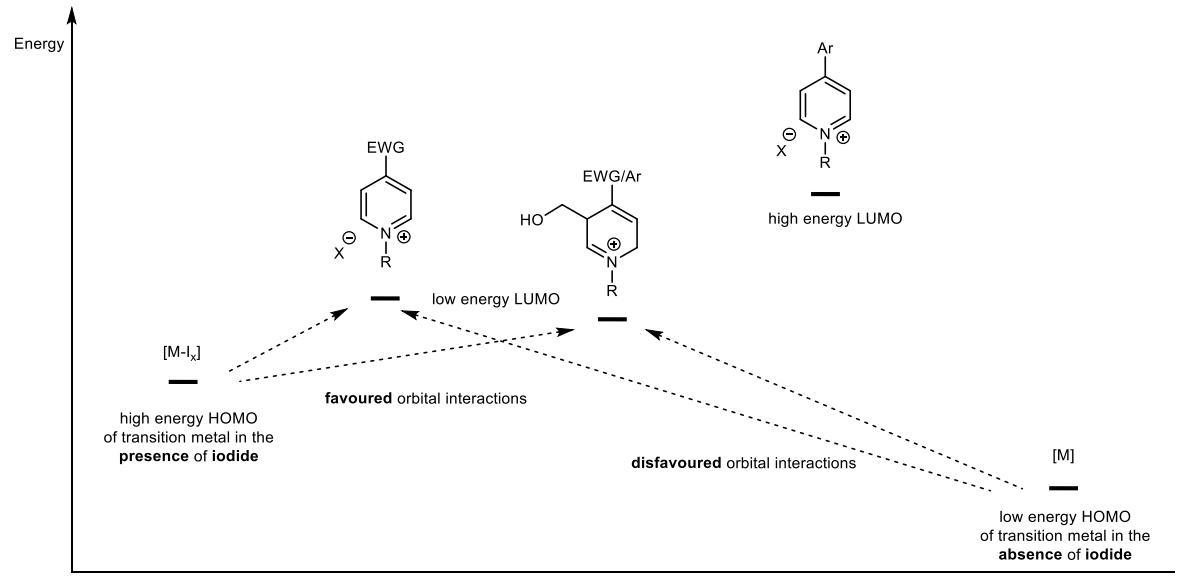


Figure 3.2 Electronic properties of different substrates and intermediates

Literature reports highlighted that electron-neutral and electron-rich pyridinium salts could also be reduced with $[RhCp^*Cl_2]_2$ in the presence of iodide.[128] Replacing iridium with rhodium in the catalytic system resulted in complete consumption of the substrate **416** (the iodide salt), as well as a 54% isolated yield of product **418** (**Table 3.2**: Entry 5). Using 2.0 equivalents of potassium iodide additive in conjunction with rhodium on the pyridinium iodide salt **416** resulted in a lower yield of **418** (**Table 3.2**: Entry 6). The reasoning for this is supposedly the complete depletion of formaldehyde observed in the crude ^{1}H NMR due to altered reactivity of the catalytic system.

When the reaction was run in the absence of iodide using the pyridinium bromide salt **417** , complete consumption of starting material was observed, but only traces of desired product

were formed (**Table 3.2**: Entry 7). This result resembles **Table 3.2**: Entry 4, with iridium as a catalyst, suggesting that iodide is required for the successful reduction of the intermediate iminium ion for the rhodium catalyst as well.

Lowering the temperature to 45° C seemed to have a detrimental effect on the consumption of starting material, which was found to be inversely proportional to the total iodide concentration (**Table 3.2**: Entries 8, 9 and 10). Similar to **Table 3.2**: Entries 1-4 (with the iridium catalyst), the lack of iodide led to low yields of desired product **418**, while increasing the overall iodide concentration affected the consumption of starting material.

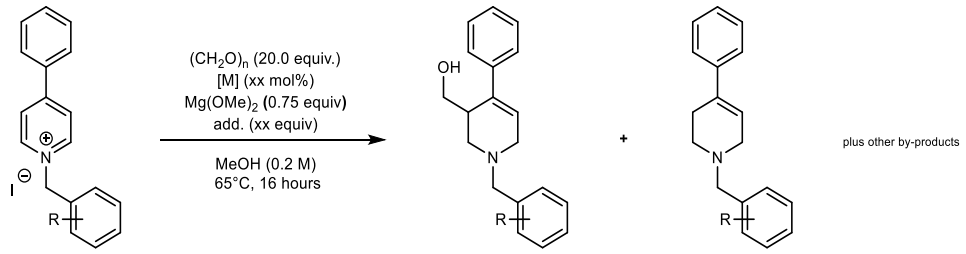
Employing [Ru(*p*-cymene)Cl_2]$_2$ in the catalytic system led to complete consumption of the starting pyridinium iodide **416**, with a 36% yield of desired product (**Table 3.2**: Entry 11). Performing the reaction at a more dilute concentration in the presence of rhodium resulted in less **418** (**Table 3.2**: Entry 12). However, this reaction seemed to favour the formation of the corresponding 3,5-dimethylated pyridinium as a valuable by-product, that will be discussed in detail in **Chapter 4**.

Employing the conditions listed in **Table 3.2**: Entry 5 on the substrates that worked optimally under iridium catalysis (**370**, **381**, **382**) seemed to lead to more degradation by-products. Lowering the temperature and providing 4.0 equivalents of potassium iodide (as in the optimal conditions for iridium) was only slightly beneficial. Significant degradation still occurred under rhodium catalysis for these strongly electron-deficient pyridiniums.

It seems that strongly electron-deficient pyridines (low lying LUMO – **Figure 3.2**) are more suitable for interactions with iridium, while less electron-deficient pyridines (higher lying LUMO) are better matched by rhodium and ruthenium. Depending on the nature of the metal and other factors, the presence of iodide (also depending on its concentration) can potentially increase the HOMO energy levels of the transition metal it binds to through *pi* donation (**Figure**

2.1) and alter the mechanism of action. In the absence of iodide other mechanisms that do not involve a HOMO-LUMO correlation might be at work. Some of these effects are also observed and discussed in **Chapter 4**.

Moving to the even less electron-deficient *N*-benzyl-4-phenylpyridinium iodide **422** (prepared using **General Procedure F** on the commercially available 4-phenylpyridine – **Scheme 3.2**) seemed to perform with difficulty under conditions employed so far (**Table 3.3**: Entries 1, 2 and 3).



419 (1.0 equiv.)
R: H **422**
o-NO_2 **430**

420
R: H **423**
o-NO_2 **431**

421

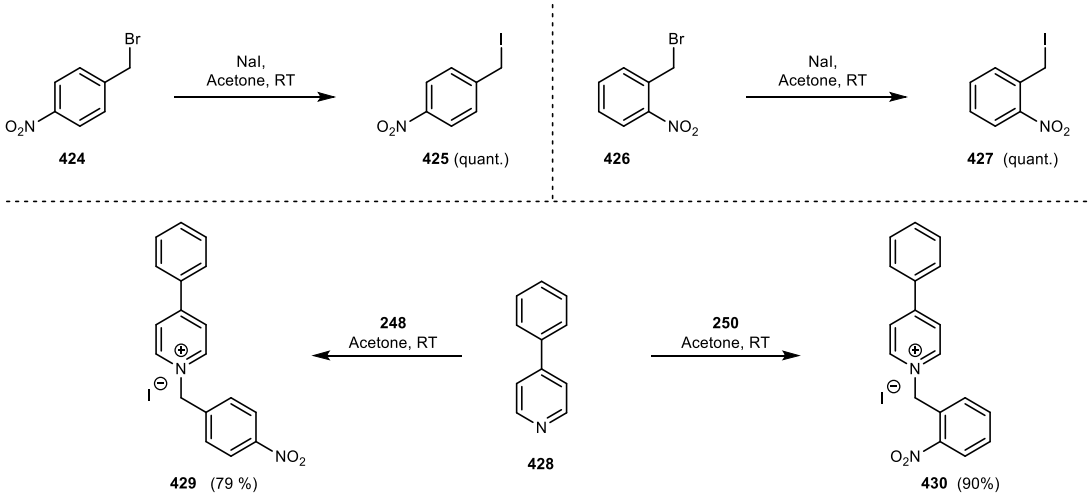
No.	R	Metal	mol%	Add. (equiv.)	Conversion (^{1}H NMR)	Yield of 420 (^{1}H NMR)	Yield of 421 (^{1}H NMR)
1	H	$[IrCp^*Cl_2]_2$	1	x	26	17	traces
2	H	$[RhCp^*Cl_2]_2$	1	x	34	27	3
3	H	$[Ru(p\text{-cymene})Cl_2]_2$	1	x	48	30	12
4	H	$[Ru(p\text{-cymene})Cl_2]_2$	1	KI (4.0)	66	38	22
5	*o*-NO_2	$[Ru(p\text{-cymene})Cl_2]_2$	1	KI (4.0)	72	50	3
6	*o*-NO_2	$[Ru(p\text{-cymene})Cl_2]_2$	2	KI (4.0)	82	66 (62 isolated)	12
7	*o*-NO_2	$[Ru(p\text{-cymene})Cl_2]_2$	5	KI (4.0)	79	43	29

Table 3.3 Use of different alkyl groups to activate less reactive substrates
The screening reactions were run on 0.25 mmol of substrate in 10 mL sealed microwave vials. The isolated yield was obtained from a 0.5 mmol scale reaction.

Using iridium resulted in low consumption of starting material **422** and an even lower yield of **423** (**Table 3.3**: Entry 1). Under rhodium catalysis a noticeable improvement was observed (**Table 3.3**: Entry 2). Interestingly, when $[Ru(p\text{-cymene})Cl_2]_2$ was used, the consumption of starting material **422** increased even more, along with the yield of desired product **423** (**Table 3.3**: Entry 3).

We were interested to investigate the effect of increasing the overall iodide concentration in the presence of [Ru(*p*-cymene)Cl_2]$_2$. Pleasingly, both the consumption of starting material and the yield of desired product increased when 4.0 equivalents of potassium iodide were employed (**Table 3.3**: Entry 4).

We envisioned that the reactivity of the 4-phenylpyridine **428** could be increased if quaternised with an electron-deficient benzyl group. First, we attempted to synthesise the *para*-nitrobenzyl pyridinium iodide salt **429**. Although successful, the process was cumbersome (required recrystallisation) and produced a salt with very limited solubility in methanol, which made it unfit for our reaction conditions. However, the *ortho*-nitrobenzyl pyridinium **430** could be easily obtained from 4-phenylpyridine **428** and *ortho*-nitrobenzyl iodide **427** (**Scheme 3.11**).



Scheme 3.11 Synthesis of pyridiniums quaternised with electron-deficient benzyl group

Pleasingly, replacing the benzyl with the more electron-deficient *ortho*-nitrobenzyl group had beneficial effects, improving both the consumption of starting material **430** and the yield of desired product **431** (**Table 3.3**: Entry 5).

Increasing the ruthenium loading from 1.0 mol% to 2.0 mol% resulted in an increase in the consumption of starting material **430**, as well as an isolated yield of 62% desired product **431** (**Table 3.3**: Entry 6). However, a further increase in the ruthenium concentration up to 5.0

mol% resulted in a similar consumption of starting material **430** and a lower yield of product **431**, while also depleting the paraformaldehyde as observed in the crude ^{1}H NMR spectra (**Table 3.3**: Entry 7). Although the conversion of this reaction was comparable with the previous entry, the amount of untrapped by-product **421** was significantly higher when more catalyst was employed (**Table 3.3**: Entries 6 and 7).

This result bears similarity with the reaction highlighted in **Table 3.2**: Entry 6. In both cases the paraformaldehyde added at the beginning of the reaction was depleted. These results highlight that the rate at which the starting material is consumed and the rate of the background Cannizzaro reaction depend on the catalytic system (loading and iodide concentration) and the reactivity of the starting pyridinium (4-substituent and *N*-alkyl group). If the paraformaldehyde is consumed before the starting material, the desired trapped product does not form in significant amounts. These findings suggest that unreactive pyridiniums are not suitable substrates for this interrupted transfer hydrogenation methodology.

At this point, time constraint meant that we were unable to optimise the system beyond the 54% and 62% isolated yields of **418** and **431** respectively as shown above. Our focus shifted exclusively to developing the 3,5-dimethylation of 4-subtituted pyridines (**Chapter 4**).

3.7 Conclusions

We have successfully extended the reductive hydroxymethylation methodology to encompass electron-deficient pyridinium salts. In comparison with quinolines, we found that pyridines require an additional degree of activation complementary to quaternisation, such as the presence of an electron-withdrawing group at the 4- position.

Strongly electron-deficient pyridines were found to work best under iridium catalysis at room temperature, while less electron-deficient pyridines seemed to be better matched by rhodium

and ruthenium catalysts. Electron-deficient benzyl groups could also be employed to enhance the reactivity of the latter.

Although we are not entirely certain of how iodide operates in the presence of the transition metals we employed, we noticed it can drastically influence the reactivity of these catalytic systems and possibly the mechanism of action.

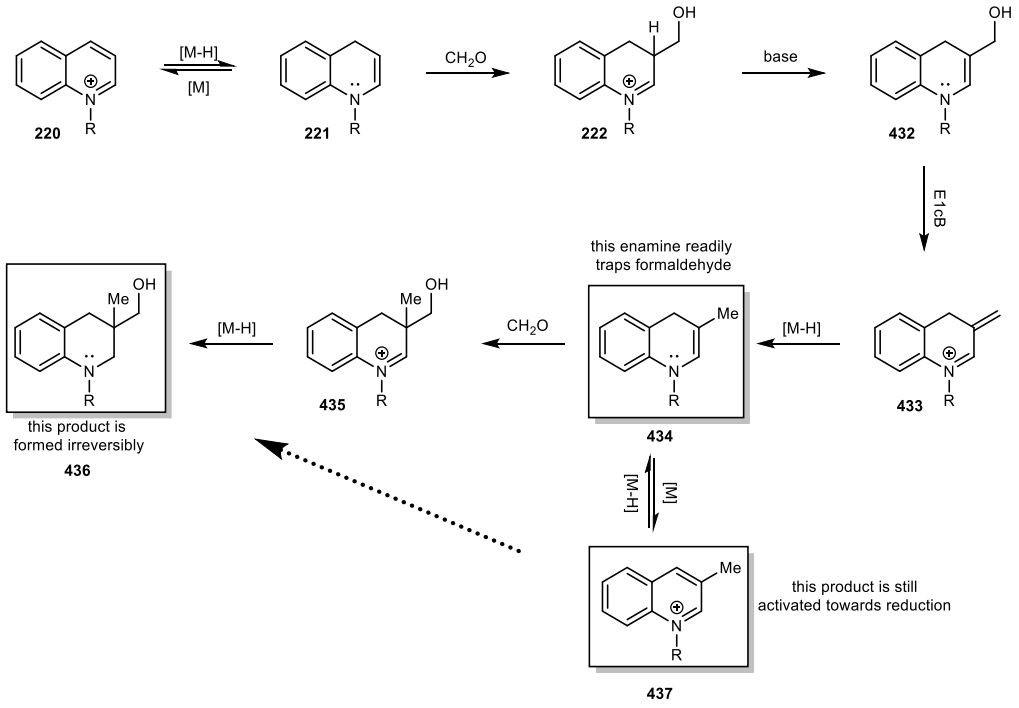
Further work that focuses on extending the scope of this reaction to less electron-deficient pyridines (4-aryl pyridines) is currently undertaken by other members of the group in more detail.

Chapter 4: 3,5-Dimethylation of 4-substituted pyridines

4.1 Introduction

Following the development of the reductive hydroxymethylation of quinolinium and pyridinium salts, we decided to focus on developing a related transformation that utilises electrophiles to functionalise the 3- position of a pyridine but maintains the aromaticity of the starting azaarene.

In theory, for quinoliniums **220** this can be achieved if intermediate **222** is diverged from the reductive pathway through deprotonation. Subsequent E1cB like elimination of hydroxide followed by reduction would lead to the methylated enamine **434** (**Scheme 4.1**). Formal-oxidation (loss of hydride) of this enamine would form the corresponding methylated quinolinium **437**.



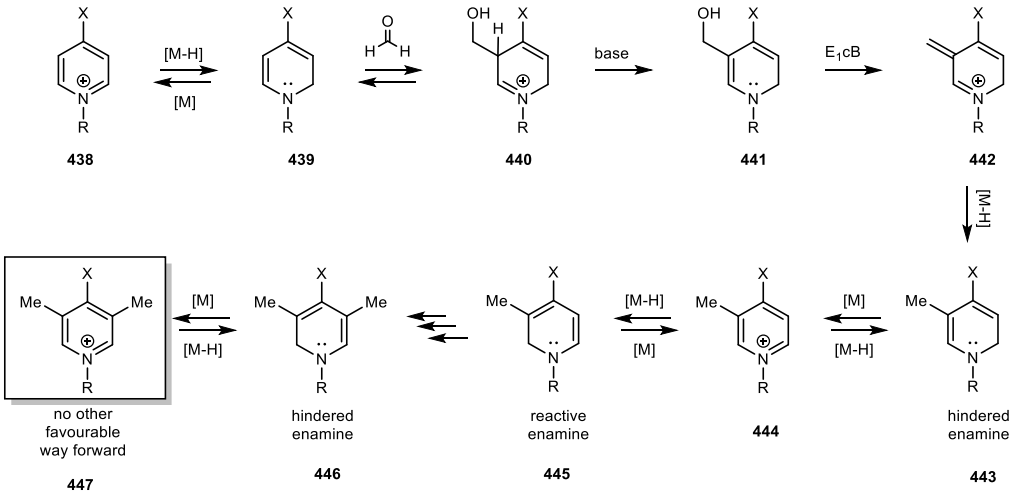
Scheme 4.1 Desired pathway for 3-methylation of quinolinium salts and potential limitations

However, due to the fact that the "Interrupted Transfer Hydrogenation" methodology requires base catalysis, we found that the starting quinolines had to be covalently activated through quaternisation in order to obtain desired reactivity. As a consequence, the 3-methylated

quinolinium **437** would still be activated towards reduction, thus being in an equilibrium with the 3-methylated enamine **434**. As this enamine can follow an additional irreversible reductive pathway towards tetrahydroquinoline **436**, this will eventually lead to the consumption of the desired 3-methylated aromatic compound **437**. This was also highlighted in **Chapter 2.4**, where the corresponding tetrahydroquinoline **238** (*N*-Me) and **244** (*N*-Bn) are formed in yields higher than 80% when starting from the corresponding 3-methylated quinoliniums **266** and **267**.

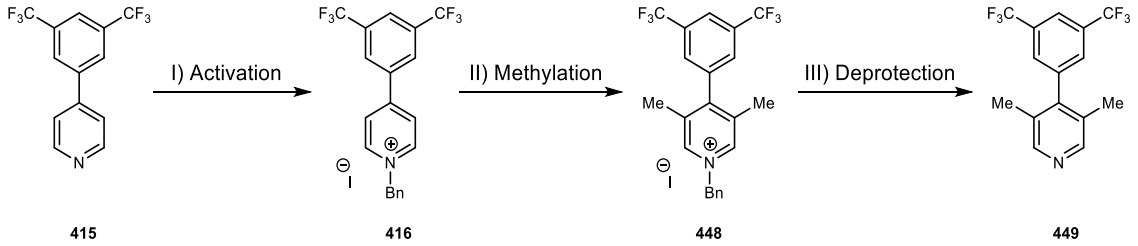
We concluded that achieving an aromatic methylation for quinolinium salts would be extremely difficult, as both enamines **221** and **434** could react readily with formaldehyde (**Scheme 4.1**). For these substrates the tetrahydroquinolines are irreversibly formed as the thermodynamic products.

During our work on developing the reductive hydroxymethylation of 4-substituted pyridiniums **438** and **444**, we observed that substituted enamines such as **443** do not readily trap formaldehyde to form a quaternary centre. By analogy, enamine **446** would also be slow to trap electrophiles, thus making the isolation of the 3,5-dimethylated pyridinium **447** feasible, as there is no favourable pathway for further consumption of this 3,4,5-subtituted pyridium salt (**Scheme 4.2**).



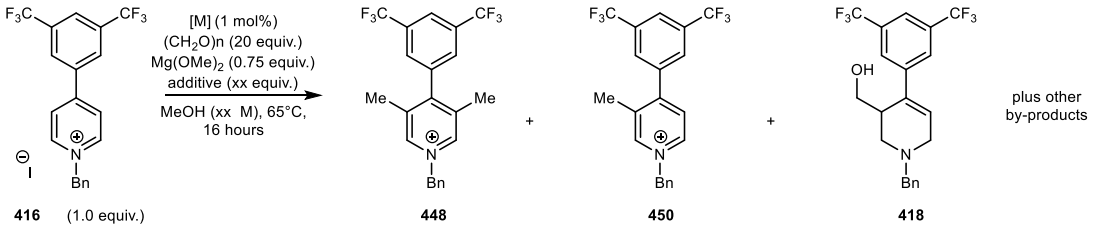
Scheme 4.2 Desired pathway for 3,5-dimethylation of 4-substitued pyridinium salts

Taking into account preliminary results and knowledge obtained during the development of the reductive hydroxymethylation of quinolinium and pyridinium salts, we concluded that it could in theory be possible to achieve a 3,5-dimethylation of 4-subsituted pyridines (**Scheme 4.3**).



Scheme 4.3 Reaction design for the 3,5-dimethylation of 4-substitued pyridines

Encouragingly, the 3,5-dimethylated benzyl salt **448** has been previously observed by ^{1}H NMR spectroscopy during the screening and optimisation of the reductive hydroxymethylation (with rhodium and ruthenium – **Chapter 3.6**) of the benzyl iodide salt **416** (**Table 4.1** Entries 1-4). Having observed **448** and the fact that ^{19}F NMR offers a complementary mode of assessing the reaction, led us to choose this particular pyridine **415** as the model substrate for future optimisation.



No.	Metal (1 mol%)	add. (equiv.)	Total iodide conc. (M)	Substrate conc. (M)	Conversion[a]	Yield of 448[a]	Yield of 450[a]	Yield of 418[a]
1	$[RhCp^*Cl_2]_2$	x	0.2	0.2	>98	14	traces	60
2	$[RhCp^*Cl_2]_2$	KI (2.00)	0.6	0.2	>98	6	12	45
3	[Ru(*p*-cymene)Cl_2]	x	0.2	0.2	>98	5	5	36
4	$[RhCp^*Cl_2]_2$	x	0.1	0.1	>98	40	traces	21

Table 4.1 Initial screening on model substrate benzyl iodide salt

The screening reactions were run on 0.25 mmol of substrate in a 10 mL sealed microwave vial.

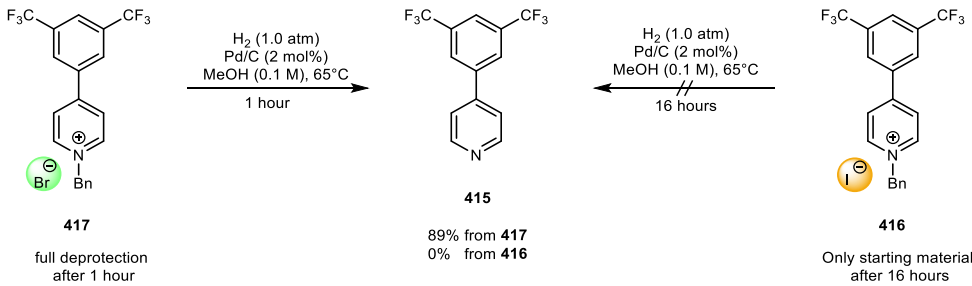
[a] ^{1}H NMR Yield

4.2 Reaction optimisation

4.2.1 Reaction optimisation for the model substrate

During optimisation of the reductive hydroxymethylation of **416** with rhodium we observed that performing the reaction at a more dilute concentration (0.1 M instead of 0.2 M) led to a significant amount of **448** (**Table 4.1**: Entry 4). However, attempts to deprotect the benzyl group of **448** from the crude reaction mixture through heterogeneous palladium catalysed hydrogenation failed (2 mol% Pd, 1 atm. of H_2 at 65°C, 2 hours).

Before proceeding to optimise the 3,5-dimethylation reaction, we wanted to develop a reliable deprotection method that could cleave the benzyl group required for the activation of substrate **415**, ideally from the crude reaction mixture and allow us to isolate the desired product **449** (**Scheme 4.3**). We proceeded to investigate if the counterion of the starting salt could have any effects on the hydrogenation reaction with palladium (**Scheme 4.4**). Hydrogenolysis of the benzyl bromide salt **417** with 2.0 mol% Pd/C under one atmosphere of hydrogen at 65°C in methanol (0.1 M) proceeded smoothly, delivering the deprotected pyridine **415** in 89% yield after only one hour. Interestingly, subjecting the benzyl iodide salt **416** to the same hydrogenation conditions led to no conversion, even after 16 hours.



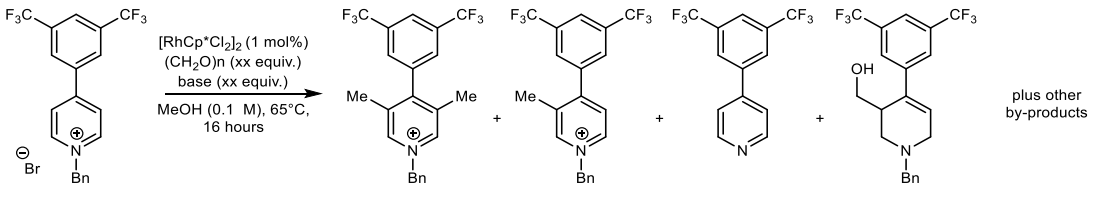
Scheme 4.4 Attempts to deprotect pyridinium salts through heterogonous catalysis

It appeared that the iodide anion was able to "poison" the palladium catalyst, which explains why deprotection of the reaction previously mentioned (**Table 4.1**: Entry 4) failed under these

conditions. Similar systems where the catalytic ability of palladium can be poisoned by the presence of iodide have been reported in the literature.[189]

We decided to employ the benzyl bromide salt **417** in our following optimisation reactions, as this substrate could be easily deprotected under heterogenous hydrogenation conditions. However, when subjecting **417** to the conditions previously developed for di-methylation of the iodide salt **416**, significantly less desired product **448** was observed. Additionally, in the absence of iodide a noticeable amount of premature debenzylation (**415**) took place (**Table 4.2**: Entry 1). When less formaldehyde was added to the reaction, the consumption of starting material decreased, while the amount of premature debenzylation increased (**Table 4.2**: Entry 2).

Increasing the loadings of paraformaldehyde to 30 equivalents seemed to be beneficial for the reaction as both the consumption of starting material and the yield of the desired product **448** increased **Table 4.2**: Entry 3). Deprotection of the benzyl group could be achieved from the crude reaction mixture (2 mol% Pd, 1 atm. of H_2 at 65°C, 2 hours), however the separation of the non-methylated pyridine (**415**), mono-methylated pyridine (**451**) and di-methylated pyridine (**449**) could not be achieved by traditional chromatography (**Scheme 4.5**).



417 (1.0 equiv.) **448** **450** **415** **418**

No.	CH_2O equiv.	Base (equiv.)	Conversion[a]	Yield of 448[a]	Yield of 450[a]	Yield of 415[a]	Yield of 418[a]
1	20	$Mg(OMe)_2$ (0.75)	90	9	9	28	<2
2	10	$Mg(OMe)_2$ (0.75)	80	6	7	38	<2
3	30	$Mg(OMe)_2$ (0.75)	>98	36	15	8	<2
4	30	KOH (1.5)	95	7	30	2	<2

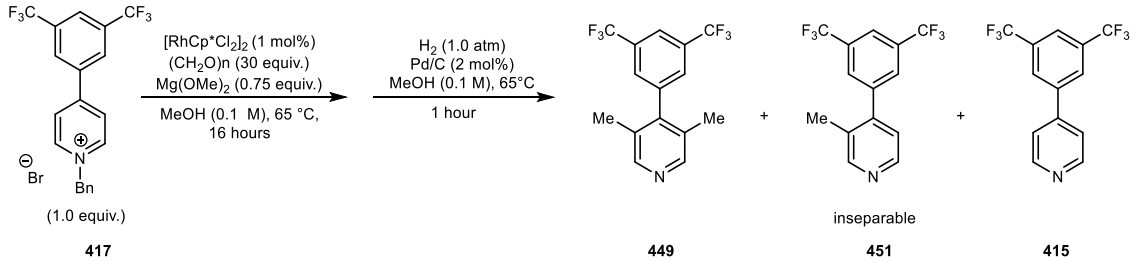
Table 4.2 Initial screening on model substrate benzyl bromide salt

The screening reactions were run on 0.25 mmol of substrate in 10 mL sealed microwave vials.

[a] ^{1}H NMR Yield

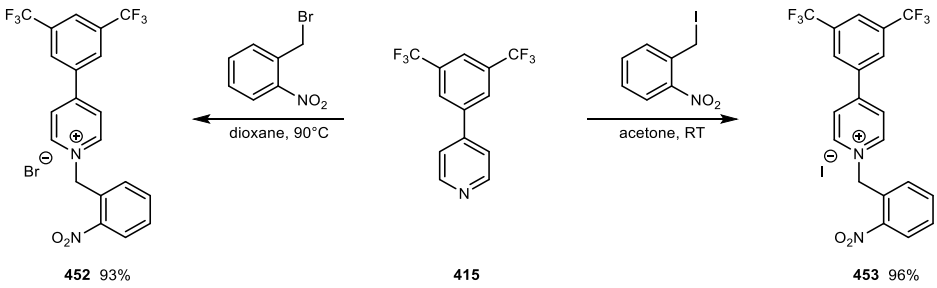
Replacing magnesium methoxide with the more nucleophilic potassium hydroxide resulted in less debenzylation, a significant amount of mono-methylated pyridinium **450** and less desired di-methylated product **448**. The crude ^{1}H NMR spectrum revealed that the added paraformaldehyde was depleted (**Table 4.2**: Entry 4).

Interestingly, the lack of iodide and the increased dilution prevented the reaction from forming the reduced hydroxymethylated compound **418** in significant amounts (**Table 4.2**: Entries 1-4). The bromide salt **417** also allowed for a subsequent one pot hydrogenation of the benzyl group. However, in the absence of iodide, significant premature debenzylation took place, which made substrate **417** unfit for the reaction, as the separation of the non-methylated pyridine, mono-methylated pyridine and di-methylated pyridine could not be achieved by traditional chromatography (**Scheme 4.5**).



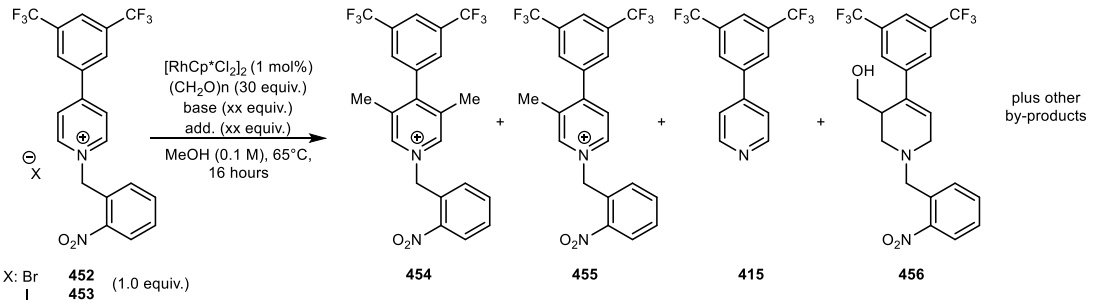
Scheme 4.5 One pot deprotection of the benzyl group through hydrogenation in the absence of iodide

We then moved to investigate the *ortho*-nitrobenzyl group as an alternative for activating the pyridine. The salts **452** and **453** were synthesised in high yield from pyridine **415** and the corresponding *ortho*-nitrobenzyl halide (**Scheme 4.6**).



Scheme 4.6 Preparation of *ortho*-nitrobenzyl 4-(3,5-bis(trifluoromethyl)phenyl)pyridinium salts

When the pyridinium bromide salt **452** was subjected to the conditions previously determined for the salt **417** (30 equivalents of paraformaldehyde, 1 mol% of $[RhCp^*Cl_2]_2$, 0.75 equivalents of $Mg(OMe)_2$ in MeOH (0.1 M) at 65°C for 16 hours), a similar yield of di-methylated product **454** was obtained (**Table 4.3**: Entry 1). However, noticeable amounts of non-methylated pyridine **415** and mono-methylated pyridinium salt **455** were still observed in the crude ^1H NMR spectrum of the reaction. Deprotection of the crude mixture (2 mol% Pd, 1 atm. of H_2 at 65°C, 2 hours) proceeded smoothly, but unfortunately the product was still contaminated by the non-methylated (**415**) and mono-methylated (**451**) pyridines (similar to **Scheme 4.5**).



No.	X	add. (equiv.)	Total iodide conc. (M)	Base (equiv.)	Conversion[a]	Yield of 454[a]	Yield of 455[a]	Yield of 415[a]	Yield of 456[a]
1	Br	x	x	$Mg(OMe)_2$ (0.75)	>98	38	5	6	<2
2	Br	x	x	$Mg(OMe)_2$ (0.5)	>98	43	3	6	<2
3	Br	x	x	$Mg(OMe)_2$ (1.0)	>98	37	6	6	<2
4	Br	x	x	KOH (1.0)	>98	x	x	x	x
5	Br	NaI (0.25)	0.025	$Mg(OMe)_2$ (0.5)	>98	28	3	3	9
6	Br	NaI (0.50)	0.050	$Mg(OMe)_2$ (0.5)	>98	19	3	3	15
7	I	x	0.100	$Mg(OMe)_2$ (0.5)	95	14	3	2	21

Table 4.3 Screening on the model substrate *ortho*-nitrobenzyl salts

The screening reactions were run on 0.25 mmol of substrate in 10 mL sealed microwave vials.

[a] NMR Yield

Reducing the amount of magnesium methoxide to 0.5 equivalents led to a slight increase in the yield of di-methylated product **454** (**Table 4.3**: Entry 2). On the other hand, increasing the amount of base to 1.0 equivalent of magnesium methoxide showed little difference in the

reaction profile (**Table 4.3**: Entry 3). Both these reactions still presented the inseparable by-products **415** and **455** (**451** after deprotection).

The use of a nucleophilic base seemed to decrease the amount of premature debenzylation for the *N*-benzyl bromide salt **417** employed earlier (**Table 4.2**: Entry 4). When a nucleophilic base such as potassium hydroxide was used in conjunction with substrate **452** complete degradation took place (**Table 4.3**: Entry 4).We tested separately the stability of the *ortho*-nitrobenzyl salt **452** in the presence of magnesium methoxide and potassium hydroxide (**Figure 4.1**).

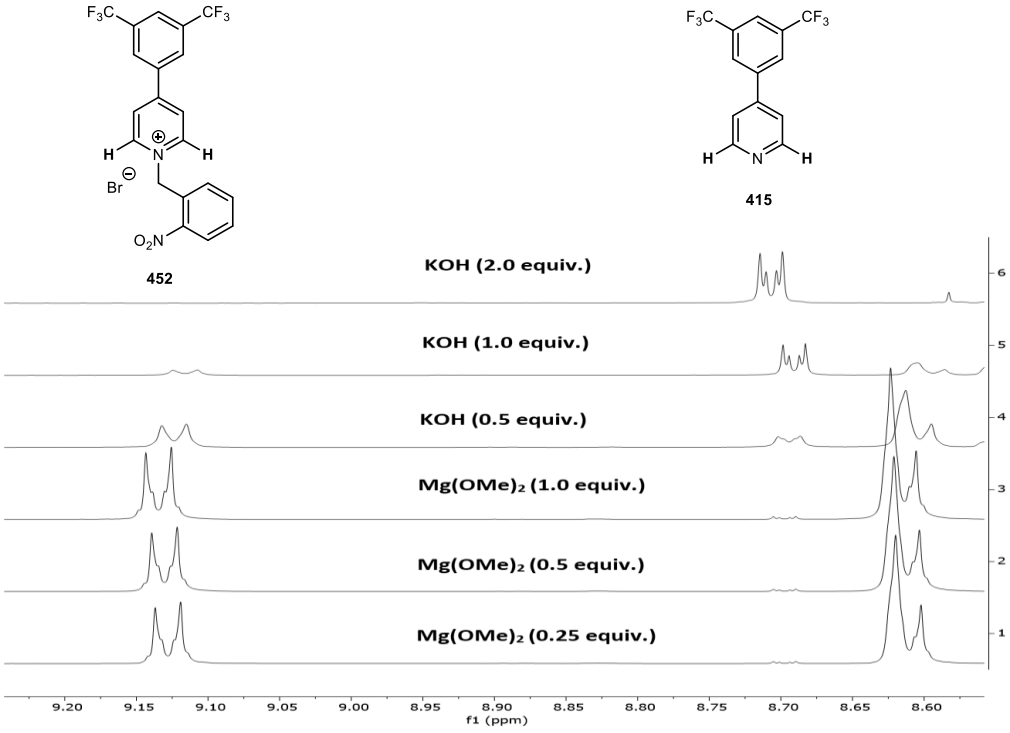


Figure 4.1 Stability of *ortho*-nitrobenzyl salt **452** with different bases

Regardless of the concentration of magnesium methoxide used, the substrate appeared relatively stable towards this non-nucleophilic base (less than 5% debenzylation to **415** was observed). On the other hand, the nucleophilic potassium hydroxide seemed to irreversibly react with the *ortho*-nitrobenzyl group in an almost stoichiometric fashion (complete conversion was observed when 2.0 equivalents of KOH were employed). The results are

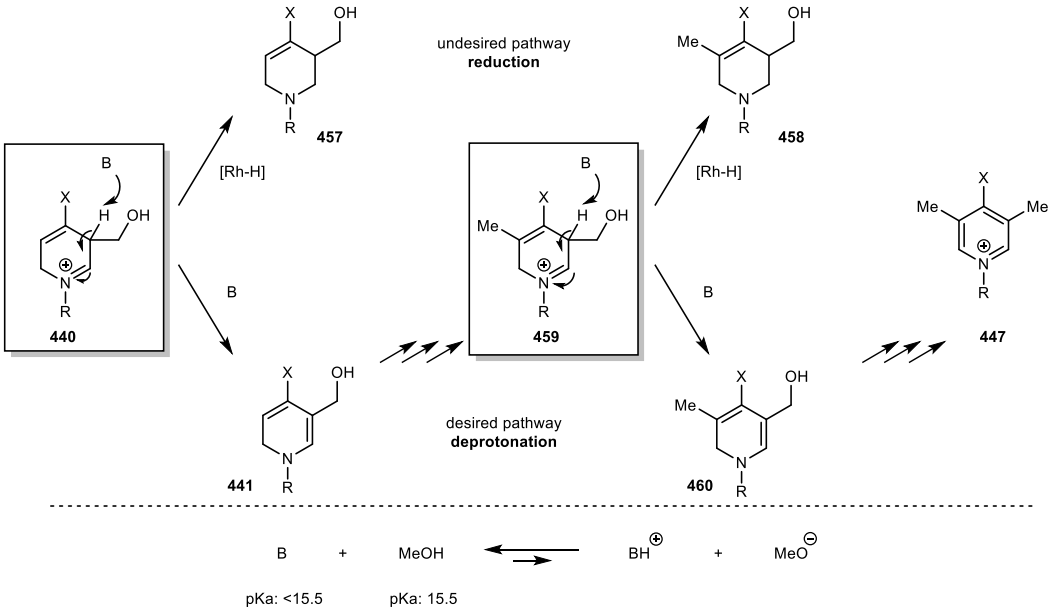
depicted in **Figure 4.1** and revealed different potential modes of deprotection which involve S_N2 displacement of the pyridinium by a suitable nucleophile (**Scheme 4.8**).

This deprotection mode would be independent of the nature of the counterion, which led us to believe that we were not constrained to using bromide salts, especially as for this particular pyridine **415** it invariably produced an inseparable mixture of non-methylated, mono-methylated and di-methylated products.

Taking into account the data from **Table 4.1** showing the beneficial effect of iodide on supressing the amount of debenzylation (formation of **415**) for the *N*-benzyl salt **416**, we proceeded to assess its effects on the *ortho*-nitrobenzyl salts **452** and **453** (**Table 4.3**: Entries 5-7). Although causing a decrease in the amount of by-products **455** and **415**, employing iodide also had a detrimental effect on the yield of desired product **454**. Additionally, the amount of by-product **456** increased as a direct function of the iodide concentration, suggesting that the intermediate iminium ion leading to its formation was not deprotonated efficiently enough, but reduced instead.

It seemed that the reduction of the iminium ion **440** (**Scheme 4.2** and **Scheme 4.7**) and was favoured in the presence of iodide, findings which were consistent with results from the previous chapter. Moreover, the iodide ion has been found to completely inhibit a potential subsequent heterogenous hydrogenation catalysed by palladium. However, previous finding suggested that alternative deprotection modes could theoretically be employed (**Figure 4.1** and **Scheme 4.8**). On the other hand, completely removing iodide from the system resulted in unidentified degradation and loss of the benzyl group through a rhodium-catalysed hydrogenolysis, suggesting that a different mechanism of action and rhodium species might be at play.

We concluded that iodide might be required in order to supress degradation for the model substrate **415** and moved on to investigate potential solutions to overcome the undesired reduction of intermediates **440** and **459**, while favouring their deprotonation instead (**Scheme 4.7**).

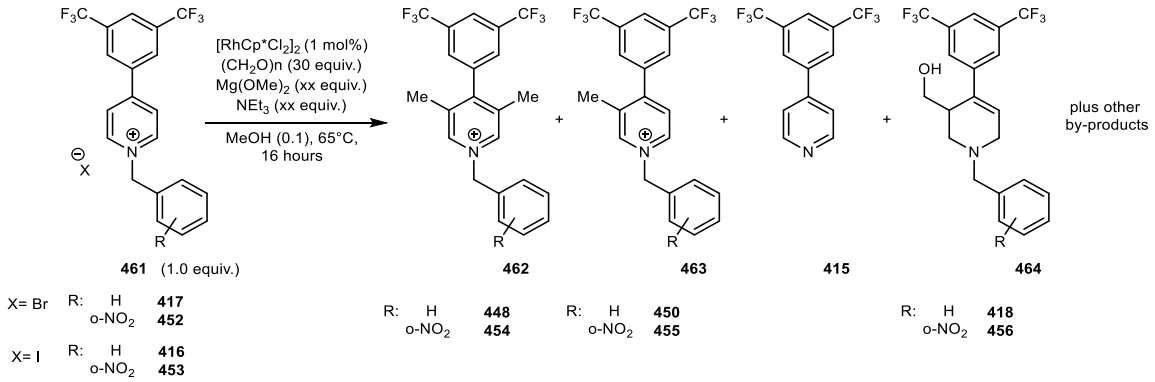


Scheme 4.7 Potential solution in the use of a complementary base

The overall concentration of methoxide, as well as its nucleophilicity (this is a function of the counterion), influences the amount of formaldehyde released from the polymer as well as the amount of the hemiacetal adduct. Previous attempts to use different methoxide bases in different stoichiometries have been proven to be detrimental and did not achieve the desired deprotonation of the iminium ions **440** and **459**.

We reasoned that a non-nucleophilic base with a pKa lower than methanol (15.5) might be a suitable choice if used in conjunction with magnesium methoxide. The nature and the amount of methoxide added initially would not change significantly in the presence of the additional base, which could therefore be employed in super-stoichiometric amounts. Triethylamine is non-nucleophilic base with a pKa of 10.6 and a boiling point of 89°C. These properties make it suitable as a complementary base to magnesium methoxide.

We tested the effect of using NEt_3 as a complementary base in conjunction with the previously developed conditions (30 equivalents of paraformaldehyde, 1 mol% of $[RhCp^*Cl_2]_2$, 0.50 equivalents of $Mg(OMe)_2$ in MeOH (0.1 M) at 65°C for 16 hours) on the pyridinium salts **461** (**Table 4.4**).



No.	X	R	NEt_3 equiv.	$Mg(OMe)_2$ equiv.	Conversion[a]	Yield of 462[a]	Yield of 463[a]	Yield of 415[a]	Yield of 464[a]
1	I	H	1	0.5	>98	46	traces	x	23
2	I	H	2	0.5	>98	55	traces	x	14
3	I	*o*-NO_2	2	0.5	>98	15	21	3	11
4	I	H	2	0.3	>98	56	traces	x	14
5	Br	H	2	0.3	>98	36	13	30	<2
6	I	H	3	0.3	>98	61	x	x	11
7	I	H	3	x	>98	45	traces	x	12
8	I	H	5	0.3	>98	61	x	x	8
9	I	H	10	0.3	>98	63	x	x	7
10	I	H	20	0.3	>98	63	x	x	6

Table 4.4 The effects of NEt_3 on the reaction

The screening reactions were run on 0.25 mmol of substrate in 10 mL sealed microwave vials.

[a] NMR Yield.

When one equivalent of NEt_3 was used on the pyridinium iodide salt **416**, the reaction produced 46% of the desired di-methylated pyridinium **448** and 23% tetrahydropyridine **418** (**Table 4.4**: Entry 1). Increasing the amount of NEt_3 seemed to favour the formation of desired di-methylated product **448**, while also decreasing the yield of **418** (**Table 4.4**: Entry 2). However, the *ortho*-nitrobenzyl salt **453** seemed to be an unfit substrate under the same conditions (**Table 4.4**: Entry 3).

The amount of magnesium methoxide could be lowered to 0.3 equivalents without any noticeable changes to the reaction profile (**Table 4.4**: Entry 4). However, removing magnesium methoxide completely had a detrimental effect on the reaction progression (**Table 4.4**: Entry 7).

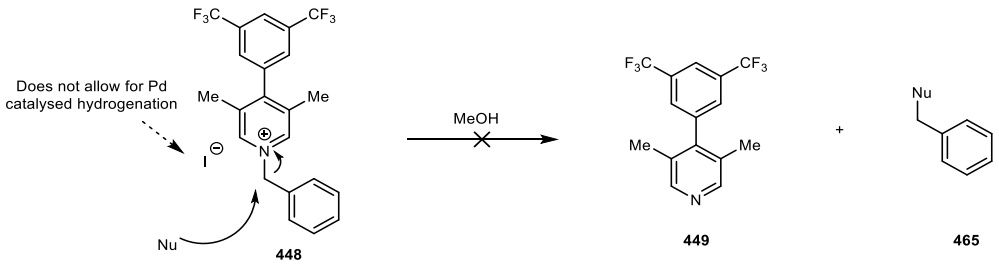
Removing iodide from the system by employing the bromide salt **417** resulted in significant premature debenzylation (**415**) and degradation (**Table 4.4**: Entry 5). In all reactions performed so far different degrees of degradation could be observed. Although the crude reaction mixtures were very complex, the use of ^{19}F NMR allowed us to asses to some degree this unidentified consumption of the starting material. As a general rule, the reactions without any iodide would present a more complex pattern, and so we concluded that iodide was required for this reaction in order to minimize as yet unidentified pathways.

Increasing the amount of NEt_3 up to 20 equivalents proved to be beneficial for the reaction as the amount of by-product **418** decreased to only 6%, while the desired product **448** was formed in 63 % NMR yield (**Table 4.4** Entries 6, 8-10). For this particular substrate, less NEt_3 could be used without altering the reaction outcome, however we found it more beneficial for other substrates to use 20 equivalents. For consistency, we decided to set the amount to 20 equivalents of NEt_3 in our future experiments.

After we obtained a relatively good yield (assessed by NMR) for the 3,5-dimethylation of the model substrate pyridinium **416** , we decided to develop a practical and reliable method to isolate the 3,5-dimethylpyridine product **449**. From previous experiments, we knew that potassium hydroxide (or methoxide) can displace the starting pyridine **415** from its *ortho*-nitrobenzyl salt (**452** and **453**) via SN_2 attack (**Figure 4.1**).

However, when the crude reaction mixture (**Table 4.4**: Entry 10) containing the benzylated di-methylated pyridine **448** was subjected to similar conditions (2.0 equivalents of KOH in MeOH

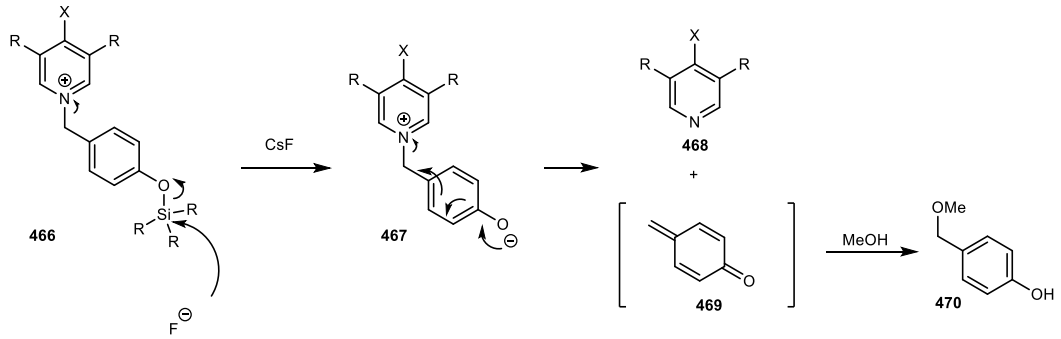
(0.1 M) at 65°C for 16 hours) a very complex mixture and no desired pyridine **449** was observed. Similarly, using 2.0 equivalents of imidazole did not achieve debenzylation either (**Scheme 4.8**).



Scheme 4.8 Attempts at SN_2 displacement of pyridine with a suitable nucleophile as a deprotection method

We wanted to perform the deprotection at the end of the reaction because the isolation of the di-methylated pyridinium salt **448** was extremely challenging. S_N2 reactions are normally unfavourable in protic solvents, so we decided to abandon this approach.

Inspired by the formation and reactivity of quinone methides **469**, [190] we reasoned that a benzyl group containing an electron-donating group at either the 2- or 4- position (**467**) could allow for an intramolecular fragmentation, that in turn would release the pyridine **468** (**Scheme 4.9**).

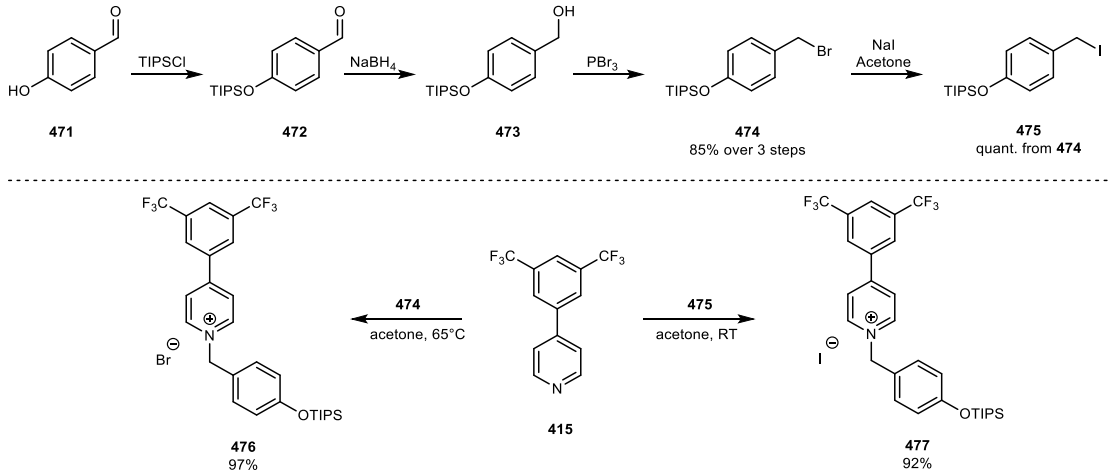


Scheme 4.9 Design of a removable benzyl group

In order to test this hypothesis, we synthesised the benzyl halides **474** and **475** (**Scheme 4.10**). These benzyl groups present a pendent TIPS protected phenol at the 4- position, which after O-Si bond cleavage could undergo a fragmentation reaction that releases the pyridine and forms the 4-quinone methide intermediate (**469**) which subsequently traps methanol. We chose TIPS

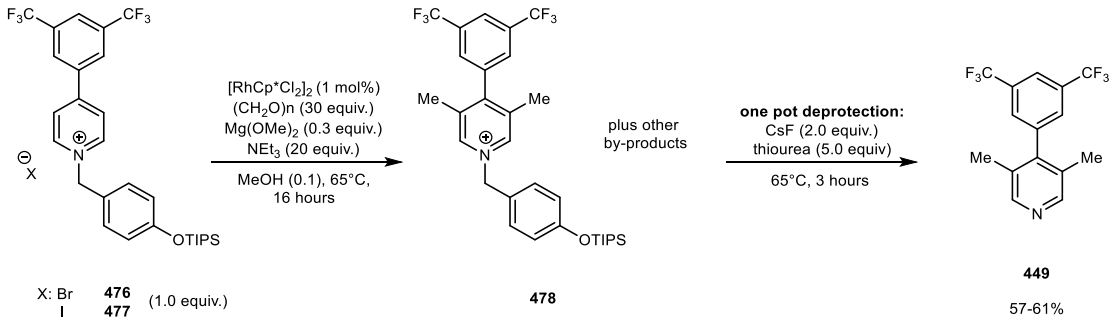
as the protecting group for the 4-phenol, as this silyl group is relatively stable towards bases and can be easily deprotected with fluoride sources.

The corresponding bromide (**476**) and iodide (**477**) salts were synthesised in good yields from the corresponding benzyl halide and **415** (**Scheme 4.10**).



Scheme 4.10 Synthesis of pyridiniums with cleavable benzyl group

Subjecting these salts to the previously developed reaction conditions (30 equivalents of paraformaldehyde, 1 mol% of $[RhCp^*Cl_2]_2$, 0.30 equivalents of $Mg(OMe)_2$, 20 equivalents of NEt_3 in MeOH (0.1 M) at 65°C for 16 hours) with subsequent addition of cesium fluoride and thiourea produced a satisfactory (57-61%) yield of the desired product **449** (**Scheme 4.11**).

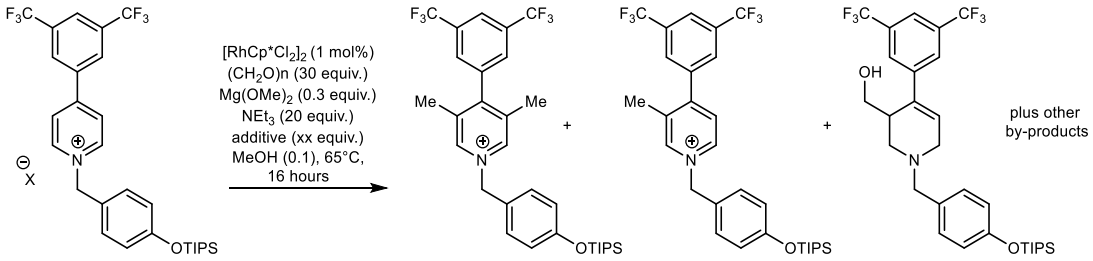


Scheme 4.11 One pot deprotection of the removable benzyl group

Some of the di-methylenated pyridinium salt **478** had already deprotected to the desired pyridine **449** (ratio could vary between 0 to 50%). This was not a problem as the deprotection seemed to occur towards the end of the reaction (no other pyridine intermediates were present

at the end). Addition of 2.0 equivalents of cesium fluoride at the end of the reaction followed by further heating for 3 hours led to complete deprotection of **478** to the desired 3,5-dimethylated pyridine **449** which was isolated in good yields as a white solid (**Scheme 4.11**).

Surprisingly, the absence of iodide seemed to not be such a significant problem for this electron rich benzyl protecting group, although minor degradation still occurred (**Table 4.5:** Entries 1). The lack of iodide would still prove to be significant problem for more electron-deficient pyridines (*vide infra*).



No.	X	add. (equiv.)	Total iodide conc. (M)	Conversion[a]	Yield of 478[a,b]	Yield of 479[a]	Yield of 480[a]
1[c]	Br	x	x	>98	62 (57% isolated yield of **449**)	traces	2
2	Br	NaI (0.33)	0.033	>98	65	x	4
3	Br	NaI (0.66)	0.066	>98	65	x	6
4[c]	Br	NaI (1.00)	0.100	>98	65 (60% isolated yield of **449**)	x	7
5[c]	I	x	0.100	>98	65 (61% isolated yield of **449**)	x	7
6[d]	I	x	0.100	>98	44	12	7
7[e]	I	x	0.100	>98	49	7	9

Table 4.5 Screening on the model substrate *para*-OTIPS-benzyl salts

The screening reactions were run on 0.25 mmol of substrate in 10 mL sealed microwave vials. The isolated yield was obtained from a 0.5 mmol scale reaction

[a] NMR Yield. [b] For the p-OTIPS salts the NMR yield is calculated as the sum of the protected and deprotected product (some product deprotects under the reaction conditions). [c] To the reaction was added CsF and thiourea at the end. [d] Reaction run with 0.5 mol% of rhodium catalyst. [e] Reaction ran at 50°C for 16 hours.

Interestingly, if the bromide salt **476** is used with additional sodium iodide (a more soluble alternative to potassium iodide), the reaction profile becomes extremely similar with that of pyridinium iodide salt **477** (**Table 4.5:** Entries 2-5). This could offer a practical advantage, as

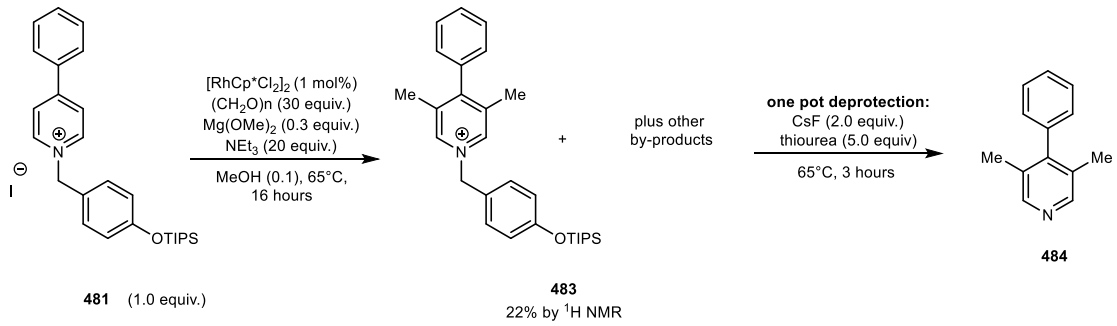
one can synthesise the more readily available bromide salt and reach the required iodide concentration by employing sodium iodide as an additive.

Lowering the reaction temperature from 65 to 50°C had a detrimental effect on the reaction progress. Similarly, a decrease in the rhodium loading from 1 to 0.5 mol% resulted in a slower reaction (**Table 4.5:** Entries 6 and 7).

4.2.2 Extending the methodology to less electron deficient substrates

The pyridinium salts **481** and **482** have been synthesized from 4-phenylpyridine **250** and the corresponding benzyl halides **270** and **271** (further details in **Chapter 5**).

Employing the previously developed conditions for the model substrate **415** (30 equivalents of paraformaldehyde, 1 mol% of $[RhCp^*Cl_2]_2$, 0.30 equivalents of $Mg(OMe)_2$, 20 equivalents of NEt_3 in MeOH (0.1 M) at 65°C for 16 hours) on the less electron-deficient iodide salt **481** proceeded with low yields of desired product **483** (**484** after deprotection), while producing the reduced by-product **488** in significant amounts (**Scheme 4.12** and **Table 4.6**: Entry 1).

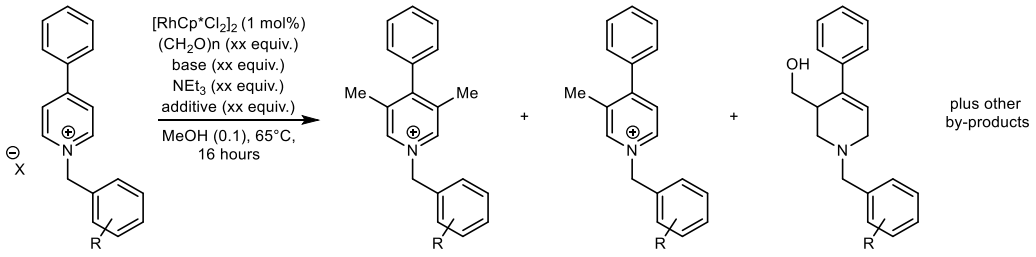


Scheme 4.12 Attempts of the 3,5-dimethylation on less electron-deficient pyridiniums

Similar results were obtained when benzyl iodide salt **422** was employed (**Table 4.6**: Entry 2). On the other hand, the pyridinium iodide salt **430** bearing a more electron-withdrawing benzyl group seemed to be even more detrimental for the desired transformation (**Table 4.6**: Entry 3).

We were aware from previous experiments that absence of iodide from the system led to smaller amounts of reduced by-product **418**, while it also favoured premature debenzylation of

the pyridinium salt **417** (**Table 4.4**: Entry 5). We decided to investigate if any of these observations were also valid for a less electron-deficient pyridinium quaternised with a benzyl group. Interestingly, for this less reactive benzyl bromide salt **489**, no premature debenzylation occurred, while a suppression in the formation of the reduced by-product **423** was observed (**Table 4.6**: Entry 4). Increasing the amount of NEt_3 used in aiming to further decrease the amount of by-product **423** led to no significant improvement (**Table 4.6**: Entry 5).



No.	X	R	NEt_3 equiv.	Base (equiv.)	Conversion[a]	Yield of 483[a,b]	Yield of 486[a]	Yield of 487[a]
1	I	*p*-OTIPS	20	$Mg(OMe)_2$ (0.3)	>98	22	8	30
2	I	H	20	$Mg(OMe)_2$ (0.3)	>98	28	8	30
3	I	*o*-NO_2	20	$Mg(OMe)_2$ (0.3)	>98	8	traces	37
4	Br	H	20	$Mg(OMe)_2$ (0.3)	>98	41	x	17
5	Br	H	30	$Mg(OMe)_2$ (0.3)	>98	40	x	16
6[c]	Br	*p*-OTIPS	20	$Mg(OMe)_2$ (0.3)	>98	41 (38% isolated yield of **484**)	traces	15
7	Br	*p*-OTIPS	x	Na_2CO_3 (1.0)	>98	<25	5	14
8	Br	*p*-OTIPS	x	K_2CO_3 (1.0)	>98	<15	6	12
9	Br	*p*-OTIPS	x	K_3PO_4 (1.0)	>98	<15	6	x 13

Table 4.6 Screening on a less electron-deficient substrate

The screening reactions were run on 0.25 mmol of substrate in 10 mL sealed microwave vials. The isolated yield was obtained from a 0.5 mmol scale reaction

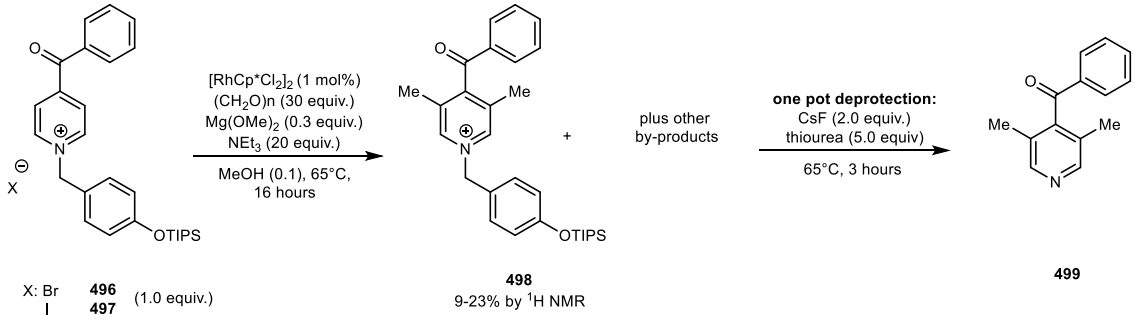
[a] NMR Yield. [b] For the p-OTIPS salts the NMR yield is calculated as the sum of the protected and deprotected product (some product deprotects under the reaction conditions). [c] To the reaction was added CsF and thiourea at the end.

In order to facilitate the isolation step (through the one pot deprotection highlighted in **Scheme 4.12**), we employed *para*-OTIPS as the protecting group in our further screening experiments. Using the optimised conditions on the bromide salt **482** led to 38% isolated product **484** as a white solid (**Table 4.6**: Entry 6 and **Scheme 4.12**).

Attempts to further improve the yield of desired product led us to screen for different bases with pKa values similar to NEt_3 (below 15.5). Several bases were employed on the bromide salt **482**, however none had beneficial effects on the reaction (**Table 4.6**: Entries 7-9).

4.2.3 Extending the methodology to more electron deficient substrates

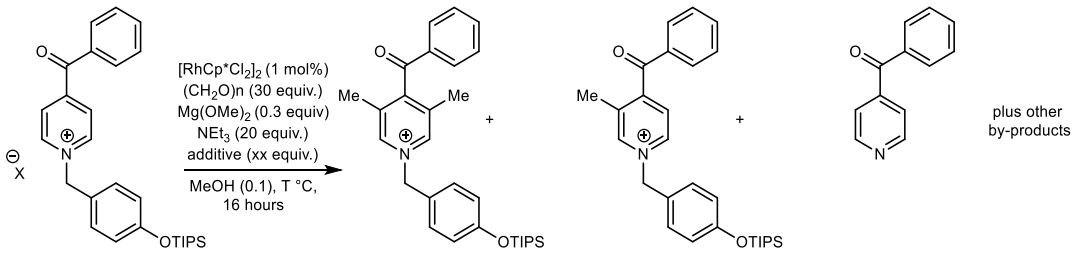
Next, we moved on to test the methodology on more electron-deficient pyridines compared to the model substrate **415**. The *para*-OTIPS benzyl salts **496** and **497** were prepared from phenyl(pyridin-4-yl)methanone and the corresponding benzyl halides (**Scheme 4.13**). The pyridinium bromide salt **496** presented 3% unidentified pyridinium-based impurity. However, it was further used in our screening phase without additional purification.



Scheme 4.13 Attempts of the 3,5-dimethylation on more electron-deficient pyridiniums

Employing the conditions optimised beforehand (30 equivalents of paraformaldehyde, 1 mol% of $[RhCp^*Cl_2]_2$, 0.30 equivalents of $Mg(OMe)_2$, 20 equivalents of NEt_3 in MeOH (0.1 M) at 65°C for 16 hours) on the bromide salt **496** only resulted in 9% yield of desired product **498** (**499** after deprotection) and significant degradation (**Table 4.7**: Entry 1). When the same conditions were employed on the iodide salt **497**, modest improvements were obtained in terms of yield of **498** and unidentified degradation by-products (**Table 4.7**: Entry 2).

Increasing the overall iodide concentration by using the iodide salt **497** with an additional one equivalent of sodium iodide reduced the amount of degradation even more and yielded 26% desired product (**Table 4.7**: Entry 3).



X: Br, I — **496**, **497** (1.0 equiv.) — **498** — **500** — **501**

No.	X	add. (equiv.)	Total iodide conc. (M)	T (°C)	Conversion[a]	Yield of 498[a,b]	Yield of 500[a]	Yield of 501[a]
1	Br	x	x	65	>98	9	8	5
2	I	x	0.1	65	>98	23	5	x
3	I	NaI (1.0)	0.2	65	>98	26	3	x
4	Br	x	x	40	>98	12	4	4
5	Br	NaI (1.0)	0.1	40	>98	37	traces	x
6	Br	NaI (2.0)	0.2	40	>98	44	x	x
7	Br	NaI (4.0)	0.4	40	>98	39	traces	x
8	Br	NaI (2.0)	0.2	22	>98	9	20	x
9	I	x	0.1	40	>98	36	traces	x
10[c]	I	NaI (1.0)	0.2	40	>98	44 (41 % isolated yield of **499**)	x	x

Table 4.7 Screening on a more electron-deficient substrate

The screening reactions were run on 0.25 mmol of substrate in 10 mL sealed microwave vials. The isolated yield was obtained from a 0.5 mmol scale reaction

[a] NMR Yield. [b] For the p-OTIPS salts the NMR yield is calculated as the sum of the protected and deprotected product (some product deprotects under the reaction conditions). [c] To the reaction was added CsF and thiourea at the end.

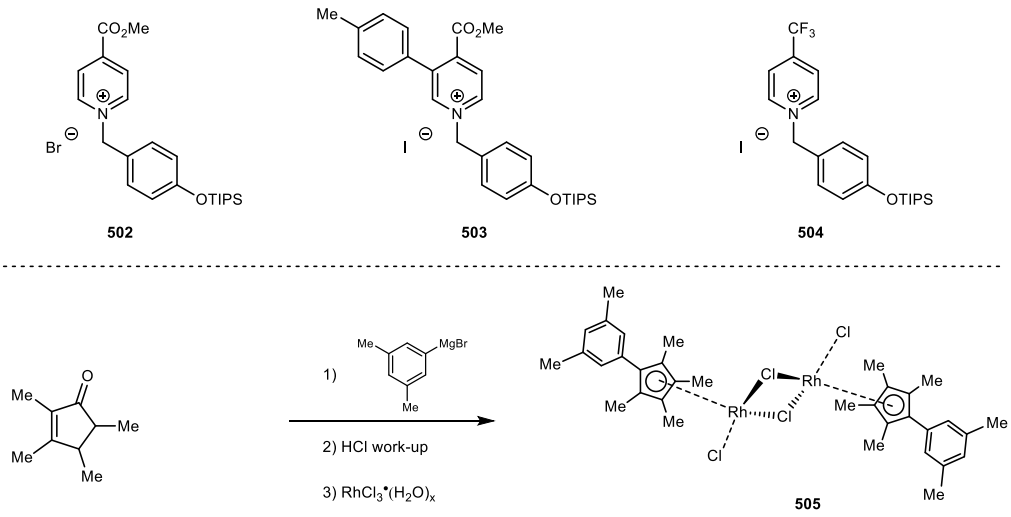
In order to supress unidentified degradation pathways, we reduced the reaction temperature to 40° C. The reaction outcome seemed to be dependent on the iodide concentration, with beneficial effects up to 0.2 M (**Table 4.7**: Entries 4-6). However, increasing the amount of iodide beyond this concentration seemed to have detrimental effects (**Table 4.7**: Entry 7). Lowering the temperature even more, down to room temperature, resulted in a significantly

higher amount of mono-methylated product **500**, suggesting a slower reaction (**Table 4.7**: Entry 8).

Similar reaction profiles could also be obtained starting from the iodide salt **497** and adding the corresponding equivalents of sodium iodide (**Table 4.7**: Entries 5,6 and 9,10).

The best conditions for this particular substrate were thus obtained at 40°C, using the iodide salt as the starting material with one additional equivalent of sodium iodide employed as additive. The best yield (41%) for di-methylated pyridinium **499** was isolated as a white solid from the reaction mentioned in **Table 4.7**: Entry 10 (**Scheme 4.13**).

Further preliminary attempts to extend this methodology to even more electron-deficient substrates such as trifluoromethyl (**504**) or esters (**502** and **503**) have been unsuccessful (**Scheme 4.14**). The pyridine required to form salt **503** was synthesised and provided by Dr Hamish B. Hepburn.[188] The detailed synthesis of the corresponding *para*-OTIPS benzyl salts **502** (the iodide salt is hygroscopic for this pyridine and the bromide salt was made instead)**,** **503** and **504** is discussed in detail in **Chapter 5**.

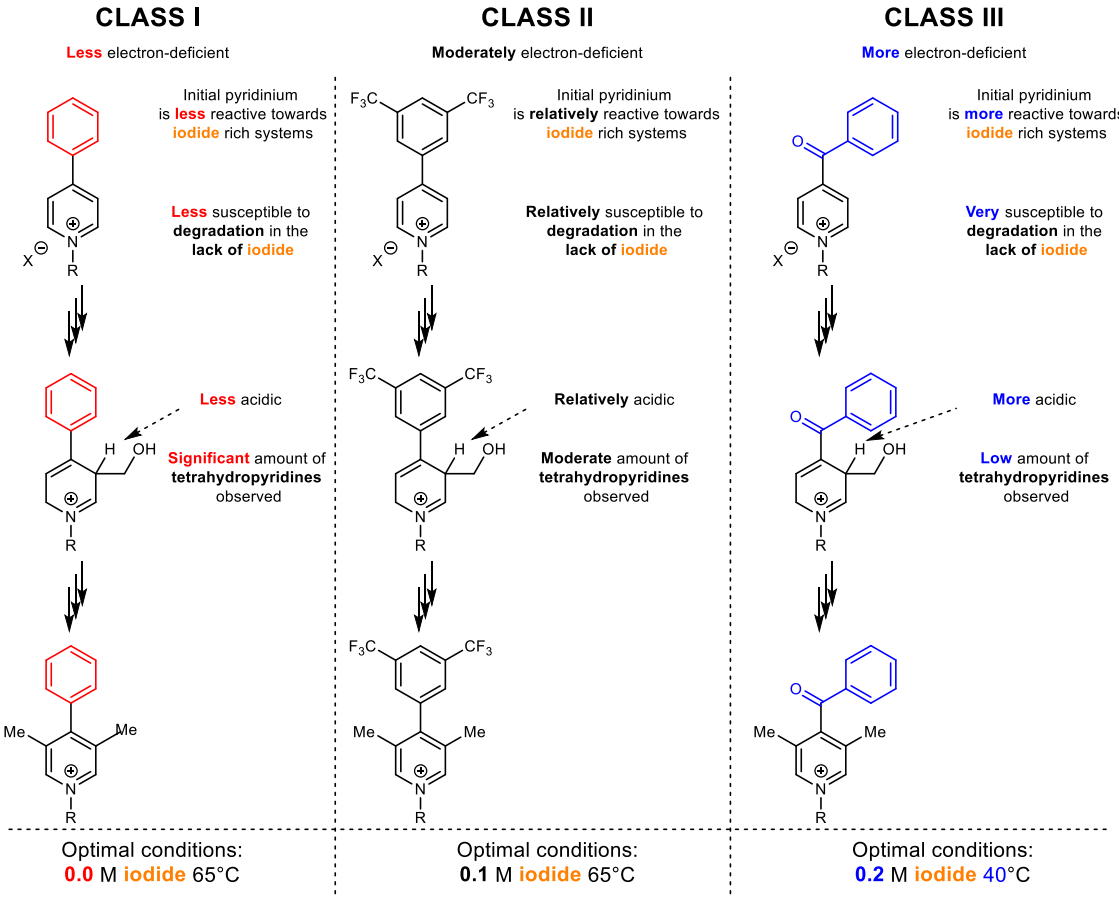


Scheme 4.14 Attempts to extend the methodology to very electron-deficient pyridines

All three set of conditions developed so far have led to very complex reaction mixtures when employed on the pyridiniums **502-504**. Attempts to reduce the reaction temperature down to

room temperature were also unsuccessful in delivering any significant amount of the desired 3,5-dimethylated pyridines. Higher concentration of iodide as well as the use of a bulkier rhodium catalyst **505** seemed to not bring any significant improvements (**Scheme 4.14**). In all cases only severe degradation took place, which discouraged us from carrying on in this direction.

4.2.4 Classification in reactivity classes for the 3,5 di-methylation of 4-substituted pyridines depending on electronics



Scheme 4.15 Different reactivity patterns of pyridiniums depending on electronics

During the screening and optimisation phase we noticed some reactivity patterns that could be corelated to the nature of the substituent present at the 4- position of the pyridine (**Scheme 4.15**). We have classified the pyridines compatible with this methodology in three classes:

Class I: These pyridines have a weakly withdrawing group or weakly donating at the 4-position (e.g. phenyl or moderate electron-deficient phenyls). They are less susceptible to degradation by a catalytic system that does not employ any iodide. On the other hand, they are less reactive if iodide is employed due to an electronic miss-match (*vide supra*). The intermediate iminium ions **440** and **459** (**Scheme 4.7**) are less acidic due to the weak electron-withdrawing group attached to the ring. For this class of pyridines, the corresponding tetrahydropyridines are the main by-products.

The optimal set of conditions developed for this class are: 30 equivalents of paraformaldehyde, 1 mol% of $[RhCp^*Cl_2]_2$, 0.30 equivalents of $Mg(OMe)_2$, 20 equivalents of NEt_3 in MeOH (0.1 M) at **65°C and 0.0 M iodide**.

Class II: These pyridines have a moderately electron-withdrawing group at the 4- position (e.g. significantly electron-deficient phenyls). They are more reactive towards a catalytic system that employs iodide and also more susceptible to degradation towards one that does not. The intermediate iminium ions **440** and **459** (**Scheme 4.7**) are moderately acidic, and modest amounts of tetrahydropyridines are observed, while the rest of the mass balance consists of unidentified by-products.

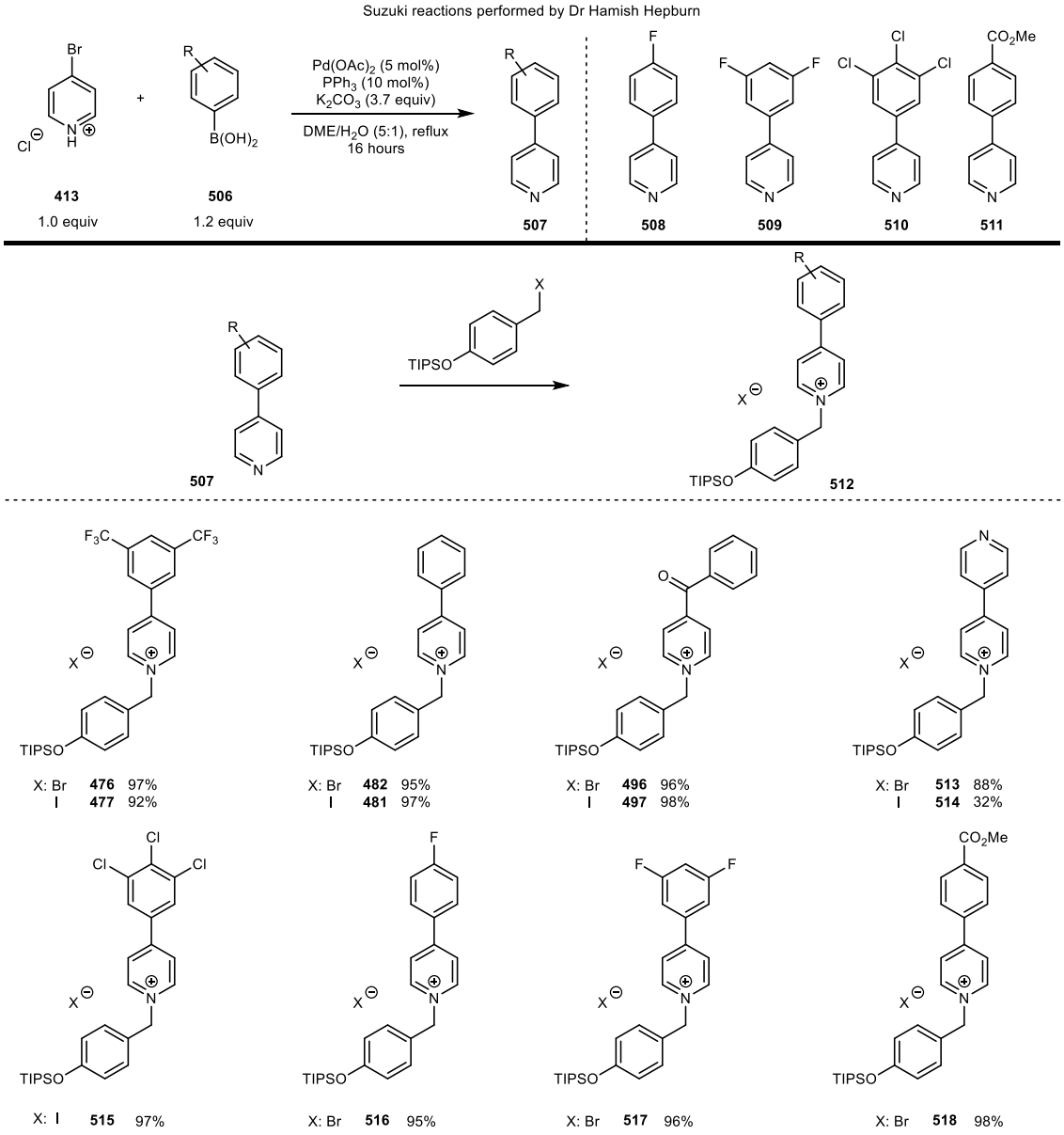
The optimal set of conditions developed for this class are: 30 equivalents of paraformaldehyde, 1 mol% of $[RhCp^*Cl_2]_2$, 0.30 equivalents of $Mg(OMe)_2$, 20 equivalents of NEt_3 in MeOH (0.1 M) at **65°C and 0.1 M iodide**.

Class III: These pyridines have a stronger electron-withdrawing group at the 4- position (e.g. aromatic ketones). They are very reactive towards a catalytic system that employs iodide and also very susceptible to degradation towards one that does not. Reduced temperatures are also required to minimise the amount of degradation. The intermediate iminium ions **440** and **459** (**Scheme 4.7**) are fully deprotonated under the reaction conditions. No tetrahydropyridines are

observed for this reaction, while the rest of the mass balance (more than 50%) is comprised of unidentified by-products. The optimal set of conditions developed for this class are: 30 equivalents of paraformaldehyde, 1 mol% of $[RhCp^*Cl_2]_2$, 0.30 equivalents of $Mg(OMe)_2$, 20 equivalents of NEt_3 in MeOH (0.1 M) at **40°C and 0.2 M iodide**.

4.3 Substrate scope for the 3,5 di-methylation of 4-substituted pyridines

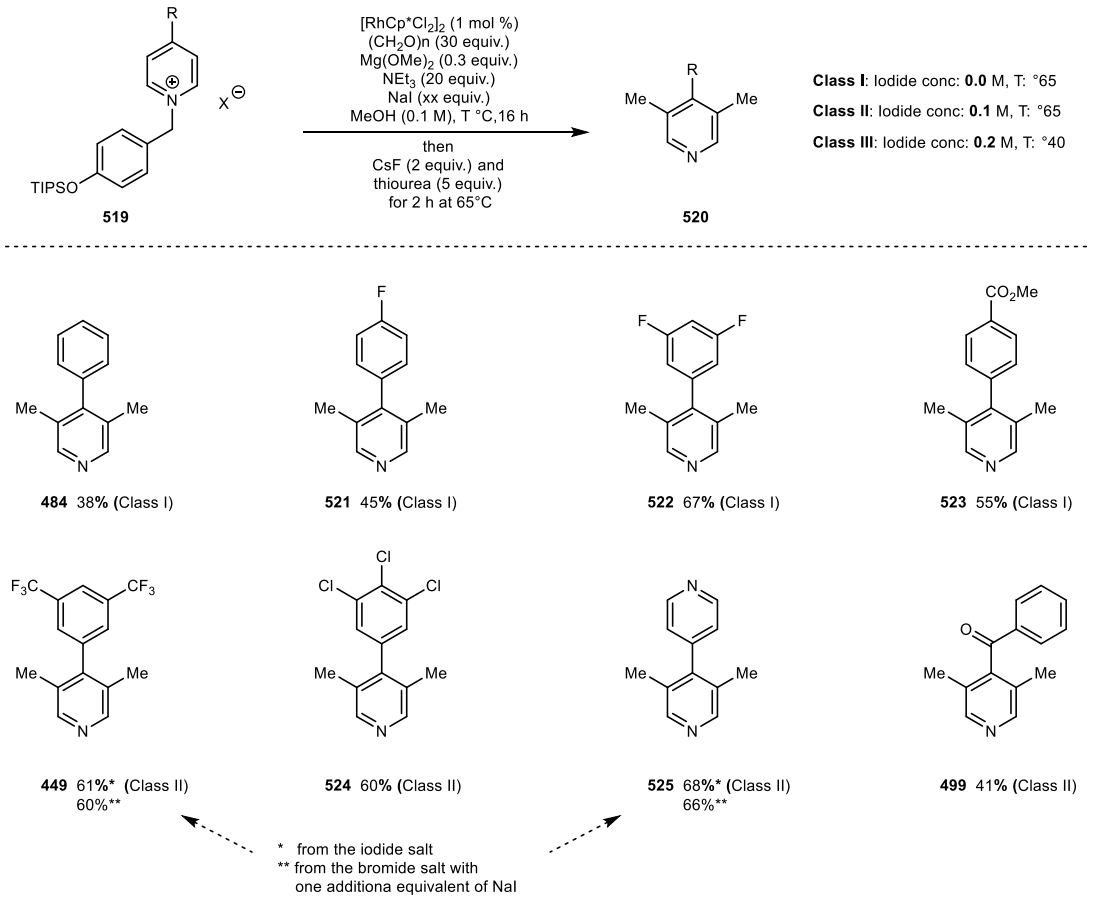
The additional *para*-OTIPS benzyl salts **513-518** required for investigating the substrate scope were made from the corresponding pyridines and the appropriate benzyl halide (**Scheme 4.16**).



Scheme 4.16 Synthesis of 4-subtituted pyridinium salts bearing the *para*-OTIPS benzyl group

Pyridines **508-511** were made and provided by Dr Hamish B. Hepburn through Suzuki coupling of the corresponding boronic acids with 4-bromopyridine hydrogen chloride salt (**Scheme 4.16**).

The 3,5-dimethylated pyridines **484** and **521-523** were obtained in modest to good yields from the corresponding bromide salts **482** and **516-518** under Class I conditions (**Scheme 4.17**). Attempts to react these pyridiniums under Class II conditions resulted in lower yields of desired di-methylated pyridine and increased amount of tetrahydropyridines by-products (assessed by NMR).



Scheme 4.17 Attempts to extend the methodology to very electron-deficient pyridines

The pyridiniums suitable for Class II conditions could be subjected to the desired transformation both as the iodide salts (**477**, **514** and **515**) or alternatively, as the bromide (**476** and **513**) salts with one additional equivalent of sodium iodide. In both cases comparable yields

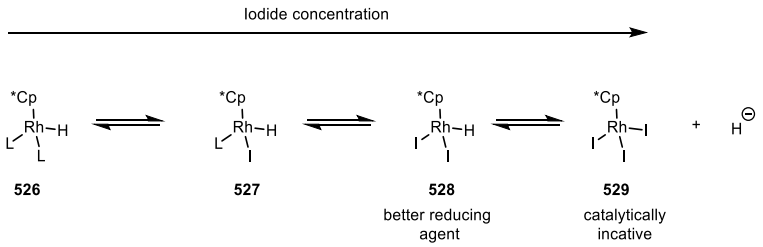
of the di-methylated pyridines were isolated (**Scheme 4.17**). When the bromide salt **513** was subjected to the Class I conditions, the yield of desired product **525** dropped from 72 (68% isolated) to 55% as assessed by NMR spectroscopy. This result was similar and consistent to the one observed for the model substrate **449** during optimisation.

4.4 Mechanistic studies

Similar to the reductive hydroxymethylation reaction developed previously, the reaction pathway is complex, meaning that assessing quantitative mechanistic aspects of the reaction was beyond our expertise and technological facilities.

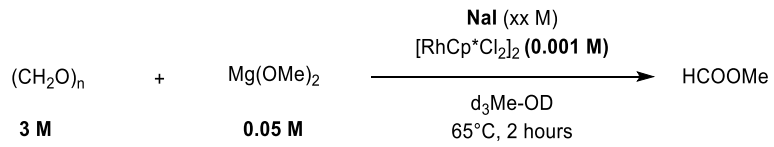
4.4.1 Qualitative analysis of the effect of iodide on the background Cannizzaro reaction

It appeared that even at relatively low concentrations such as 0.1 M, iodide has a significant effect on the rhodium based catalytic system. Similar effects were also observed and reported in the literature, Xiao and co-workers have conducted a study where they assessed the reducing capacity of $[RhCp^*Cl_2]_2$ on quinolines in the presence of potassium iodide and formic acid/ triethylamine azeotrope as the hydride source.[129] They found that the reducing ability of rhodium increased as a function of iodide up to a point, and then suddenly dropped at higher concentrations. They suggested that more iodide ligated to the metal resulted in a better reducing hydride species, while at higher concentrations of iodide the saturation of the catalytic sites with iodide (**529**) rendered the metal inactive (**Scheme 4.18**).



Scheme 4.18 Potential rhodium hydride species in the presence of iodide[129]

Methyl formate (b.p.: 32°C) and monomeric formaldehyde (b.p.: –19°C) are very volatile compounds. We reasoned that a qualitative analysis could be achieved by monitoring the consumption of paraformaldehyde from a rhodium catalysed background reaction (Cannizzaro Reaction). A stock solution of $[RhCp^*Cl_2]_2$ (0.002 M) and $Mg(OMe)_2$ (0.1 M) in deuterated methanol was prepared and loaded (0.5 mL) into two different 10 mL microwave vials that were previously charged with equal amounts of paraformaldehyde (90 mg). To one of the vials was then added 0.5 mL of deuterated methanol, while to the other one was added 0.5 mL of a sodium iodide solution (0.2 M) in deuterated methanol. The concentration of the involved reagents was scaled to mimic the background reaction of the methylation reaction (**Scheme 4.19**).



Scheme 4.19 Qualitative analysis of the iodide influence of the rhodium catalysed Cannizzaro Reaction.

The vials were sealed and left to stir at 65 °C in an oil bath for 2 hours. The reactions were allowed to cool down to room temperature, then 0.6 mL of the reaction mixture was collected with a syringe and added to an NMR tube which was submitted for spectroscopy. The methanol peak from the initially added magnesium methoxide was used as an internal standard to determine the reaction progress.

The reaction without iodide (0.0 M) showed a significant amount of paraformaldehyde left, along with traces of methyl formate and other unidentified products. On the other hand, the reaction with a 0.1 M concentration of iodide presented a completely different profile. Most of the paraformaldehyde initially added was consumed, while a significant amount of methyl formate has formed. These experiments clearly highlighted that even at 0.1 M, iodide had a noticeable influence on the catalytic system (**Figure 4.2**).

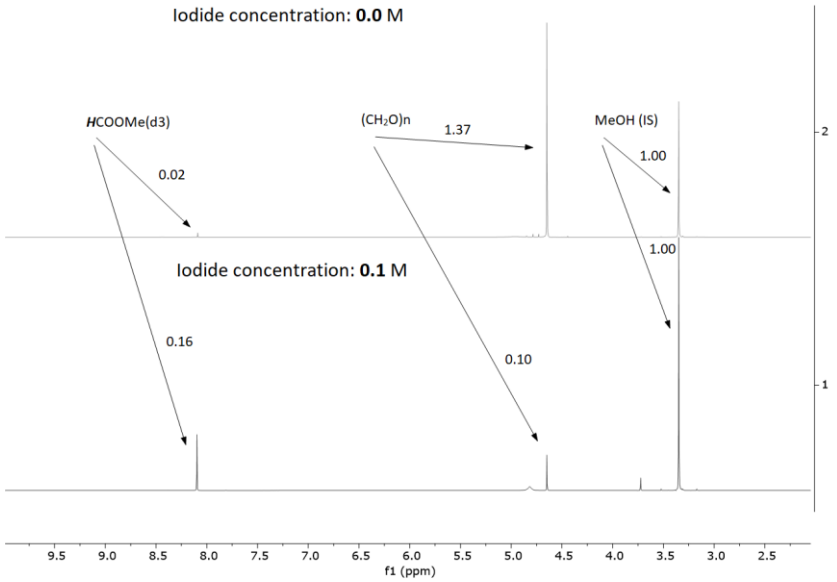


Figure 4.2 Oxidation preference of rhodium as a function of iodide concentration

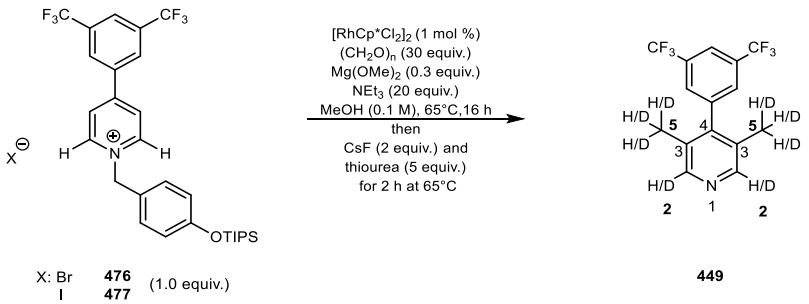
Similar to the iridium based catalytic cycle (**Chapters 2** and **3**), the iodide ion appeared to also change the oxidative ability of the rhodium complex. We proposed that due to the *pi* donating effect of iodide, the transition metal energy levels were raised in energy (**Figure 2.1** and **Figure 3.2**). Additionally, when iodide was present in the catalytic system, we proposed that a frontier orbital interaction between energetically matched levels was favoured ("soft" interactions: high HOMO and low LUMO). A "softer" metallic centre might be less suited to oxidize methoxide ("hard" hydride source) to formaldehyde, and instead could have a preference to oxidise the more reactive ("softer") hemiacetal adduct **349** (**Scheme 2.25**). Some of these qualitative effects are further highlighted below.

4.4.2 Deuterium labelling

Similar to the reductive hydroxymethylation, we conducted deuterium labelling experiments in order to find qualitative aspects of the reaction mechanism. The summary of these experiments is shown in **Table 4.8**, while the corresponding ^{1}H and ^{2}H NMR spectra are attached in the appendix.

We have employed both the bromide salt **476** (Class I conditions) and the iodide salt **477** (Class II conditions) in order to assess if there are any significant differences in the pattern of deuterium incorporation in the absence and presence of iodide.

Interestingly, the reactions run under Class I conditions (0.0 M iodide) presented a mixture of the di-methylated, mono-methylated and non-methylated pyridines (**Table 4.8**: Entries 1-3). On the other hand, the reactions run under Class II conditions (0.1 M iodide) delivered only the di-methylated pyridine (**Table 4.8**: Entries 4-6). These findings can be easily seen in the ^{19}F NMR spectra attached in the appendix.



No.	X	CH_3OH or CD_3OD	$(CH_2O)_n$ or $(CD_2O)_n$	D at 2 (%)	D at 5 (%)	Total D incorporated (%)
1	Br	D	H	1.49 (75%)	1.71 (29%)	3.20 (40%)
2	Br	D	D	1.90 (95%)	5.61 (94%)	7.51 (94%)
3	Br	H	D	1.3 (65%)	3.96 (66%)	5.26 (66%)
4	I	D	H	0.76 (38%)	1.50 (25%)	2.26 (28%)
5	I	D	D	1.91 (96%)	5.62 (94%)	7.53 (94%)
6	I	H	D	1.58 (79%)	4.02 (67%)	5.6 (70%)

Table 4.8 Summary of Deuterium labelling

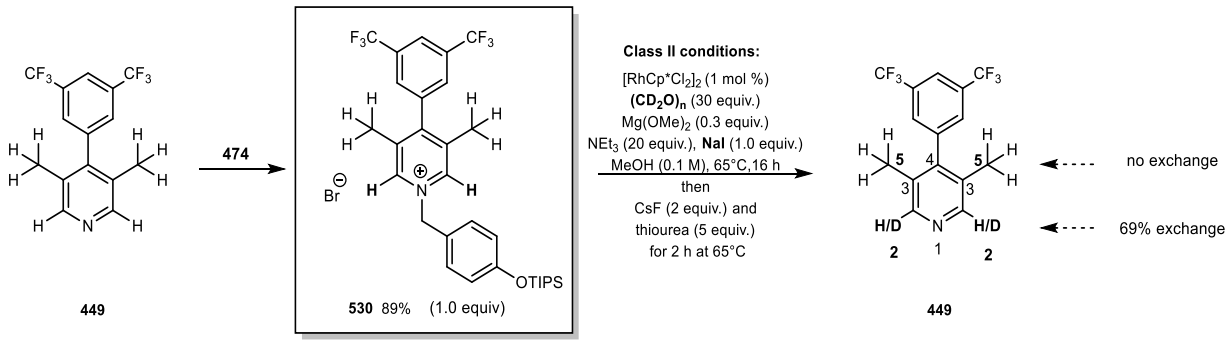
The reactions were run on 0.15 mmol of substrate in 10 mL sealed microwave vials with the appropriate deuterated reagent where specified.

The deuterium incorporated in the molecule is found exclusively at the 2- and 5- positions. All labelling reactions reveal that both methanol and formaldehyde (via the hemiacetal **349**) are oxidised by the metal to form rhodium hydride species, however the formaldehyde added at the beginning of the reactions is the one predominantly trapped (found at the 5- position). It seems that under Class I conditions the rhodium catalyst has a higher preference to oxidise

methanol. On the other hand, under Class II conditions, this preference is shifted by the presence of iodide towards oxidising formaldehyde to methyl formate. This is also consistent with the qualitative analysis of the background reaction (*vide supra*).

The scrambling of hydrogen/deuterium from the 2- position suggest a reversible formal-redox process at this position (**Table 4.8**: Entries 2 and 5). This is not unexpected, as it has been observed before under iridium catalysis (**Chapter 3.5**).

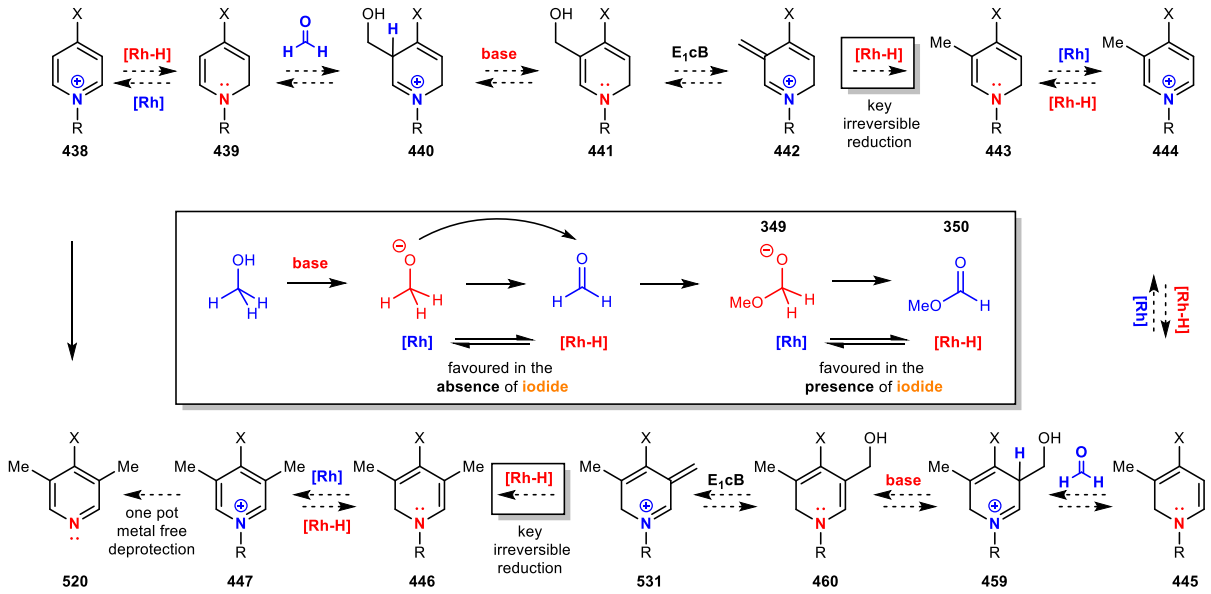
In order to determine whether the reduction at the 5- position is also reversible we prepared the 3,5-dimethylated pyridinium salt **530** and subjected it to Class II conditions with deuterated formaldehyde (**Scheme 4.20**). We employed deuterated formaldehyde to also rule out a protonation/deprotonation pathway that might result in deuterium exchange. Due to practical reasons we used the bromide salt **530 (**0.15 mmol**)** with one equivalent of sodium iodide.



Scheme 4.20 Deuterium labelling on the 3,5-dimethylated pyridinium salt

After 16 hours the mixture turned dark blue, while a normal reaction of a non-methylated pyridinium **477** (or **476** with 1.0 equiv. of NaI) stirred for 16 hours presented colours in the range of yellow to red. After opening the reaction vial to air the colour of the mixture turned orange-red as for normal reactions. The ^{19}F NMR spectrum of the crude product revealed about 30 % degradation. The ^{1}H NMR and the ^{2}H NMR spectra of the isolated pure product revealed 1.38 deuterium incorporated at the **2-** position (69 % of the hydrogen got exchanged) and no deuterium at the **5-** position (NMR spectra attached in the appendix).

These findings confirmed that the reduction of the pyridinium is **reversible** at the **2**- position but **irreversible** at the **5**- position. Taking into consideration the supposedly reversible nature of most reaction steps, this may provide an explanation regarding the driving force of the reaction (**Scheme 4.21**). Additionally, the reaction seemed to slowly degrade over time, suggesting that the equilibrium between **446** and **447** was slowly diverged towards irreversible by-products. The proposed optimal pathway for this di-methylation is shown below, however other reversibly formed intermediates are probably involved. Irreversible deviation from the desired pathway leads to the different unidentified degradation by-products observed during our screening and optimisation.



Scheme 4.21 Proposed reaction pathway and mechanism

4.5 Conclusions

In conclusion, we have developed a hydrogen transfer rhodium catalysed 3,5-dimethylation of 4-substituted pyridinium salts that utilises methanol and formaldehyde as the only stoichiometric reagents. Deuterium labelling studies have allowed us to understand the pathway of the reaction and propose a mechanism for the overall transformation.

Our early findings highlighted that in the presence of iodide, the well-established Pd catalysed hydrogenolysis was not a viable method to deprotect benzyl pyridinium salts. This led us to develop a cleavable benzyl group that could be easily deprotected in one pot and was independent of the nature of the counterion.

The effect of iodide on the transfer hydrogenation catalytic system has also been qualitatively assessed. A *pi* donating effect could probably account for most of the observed outcomes throughout this thesis. When ligated to the metal, electron density from the iodide (orbitals energetically and symmetrically matched to those on the metal) could lead to an increase in the HOMO energy levels of the metal hydride species. This favours frontier orbital interactions with substrates that present a low lying LUMO (quinolines, electron-deficient pyridines, iminium ions). On the other hand, the "softer" metallic centre has a lower tendency to formally oxidise methoxide to formaldehyde, which is a less suitable hydride source in comparison with the deprotonated formaldehyde hemiacetal.

Chapter 5: Experimental

General Experimental Techniques

Chemicals and solvents

Unless stated otherwise, all chemicals were purchased from commercial suppliers (Sigma-Aldrich, Fluorochem, Alfa Aesar) and used without further purification. The magnesium methoxide was purchased from Sigma Aldrich or Alfa Aesar as a 6-10% w/w solution in methanol and was titrated using EDTA in the presence of Eriochrome Black T as an indicator.

The following chemicals were synthesised and kindly provided by Dr Harish Potukuchi: 3-cyano-*N*-methylquinolinium iodide (**268**), *N*-benzyl-3-n-butylquinolinium iodide (**297)**, *N*,3-dibenzylquinolinium iodide **(298)**, and *N*-benzyl-3-isopropylquinolinium iodide (**299)**.

The following chemicals were synthesised and kindly provided by Dr Hamish B. Hepburn: (R)-2-methyl-1-(naphthalen-1-yl)propan-1-aminium chloride **(338)**, 4-(methoxycarbonyl)-*N*-methylpyridinium iodide **(386)**, N-benzyl-4-(phenylsulfonyl)pyridinium iodide (**387**), *N*-benzyl-4-(diethylcarbamoyl)pyridinium iodide (**388**), 4-(4-fluorophenyl)pyridine **(508)**, 4-(3,5-difluorophenyl)pyridine **(509)**, 4-(3,4,5-trichlorophenyl)pyridine **(510)**, methyl 4-(pyridin-4-yl)benzoate **(511)** and methyl 3-(p-tolyl)isonicotinate.

Glassware and reaction conditions

Reactions were carried out in sealed oven-dried microwave vials under an atmosphere of air unless otherwise stated.

Analytical techniques

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVIII400 Spectrometer (400 MHz and 100 MHz respectively) or a Bruker AVII500 (^{1}H: 500 MHz and ^{13}C: 126 MHz) in $CDCl_3$, CD_3-OD or DMSO-d_6, and referenced to residual solvent peaks. ^{19}F NMR spectra were recorded on a Bruker AVIII400 Spectrometer (377 MHz) and are unreferenced. Chemical shifts δ are

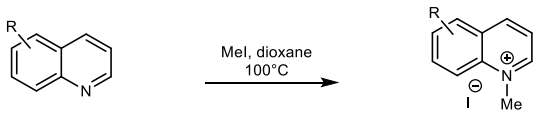
quoted in parts per million (ppm) to the nearest 0.01 for ^{1}H and ^{19}F and 0.1 for ^{13}C, coupling constants J are quoted in Hz to the nearest 0.1 and splitting are recorded as singlet (s), doublet (d), triplet (t), quartet (q), doublet of a doublet (dd), etc, and multiplet (m). Assignments were based upon COSY, HSQC and HMBC experiments. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer fitted with an Attenuated Total Reflectance (ATR) sampling accessory. Absorption maxima are quoted in wavenumbers (cm^{-1}). High resolution mass spectra were recorded on a Bruker MicroTof (resolution = 10000 FWHM). The Δ value was not reported if lower than ±5 ppm. Melting points (m.p.) were obtained using a Lecia VMGT heated-stage microscope and are uncorrected.

Chromatography

Analytical thin layer chromatography was performed on pre-coated silica gel aluminium sheets from Merck (TLC Silica Gel 60 F254s). Spots were visualized either by the quenching of UV fluorescence or by staining with phosphomolybdic acid solution. Preparative flash column chromatography was carried out using Geduran Silica Gel 60 (40 μm – 63 μm) from Merck.

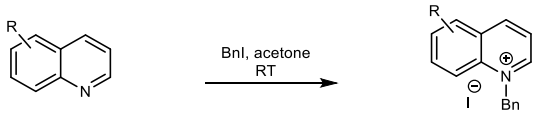
General Procedures

General Procedure A: Preparation of methyl quinolinium iodide salts



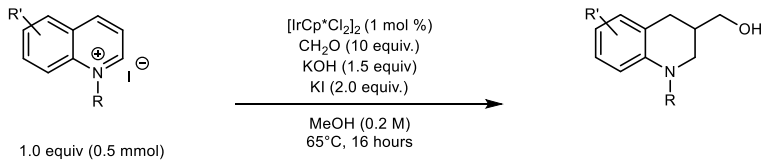
A mixture of the corresponding quinoline **xx** (1 equiv.) and iodomethane (5 equiv.) in 1,4-dioxane (0.4 M) was heated in a sealed pressure resistant flask at 90°C for 16 hours. The mixture was allowed to cool to room temperature, the solid was collected by filtration, washed with diethyl ether and dried under vacuum for one hour to give the *N*-methyl quinolinium iodide salt as powdery solids.

General Procedure B: Preparation of benzyl quinolinium iodide salts



A mixture of the corresponding quinoline **xx** (1.00 equiv.) and benzyl iodide (2.00 equiv.) in acetone (0.5 M) was stirred in the dark at room temperature for 20 hours. The solvent was removed under reduced pressure, followed by addition of diethyl ether (10 mL/mol of substrate). The resulting solid was collected by filtration, washed with diethyl ether and dried under vacuum for one hour to give the benzyl quinolinium iodide salts as powdery solids.

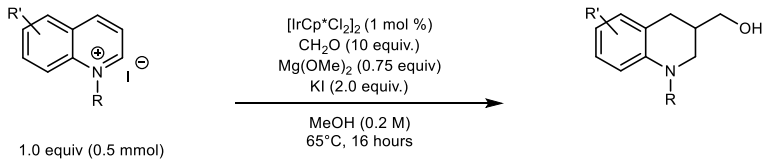
General Procedure C: Preparation of tetrahydro-quinolines [KOH + KI at 65°C]



A 5 µM stock solution of iridium catalyst was prepared by dissolving $[IrCp^*Cl_2]_2$ (20.0 mg, 25.0 µmol) in 5 mL of dichloromethane in a volumetric flask. 1.00 mL of this stock solution was added to a 10 mL microwave vial and the solvent was removed under reduced pressure. The vial was then equipped with a stirring bar and to the reaction were added: Quinolinium salt **5** (0.50 mmol), $(CH_2O)_n$ (5.00 mmol, 150 mg, 10.0 equiv.), KI (1.00 mmol, 166 mg, 2.00 equiv.), KOH (0.750 mmol, 42.0 mg, 1.50 equiv.) and 2.50 mL of methanol. The microwave vial was sealed, and the reaction was left to stir at 65°C in an oil bath for 16 hours. Thiourea (50.0 mg) was added and the reaction mixture was stirred at 65°C for an additional 30 minutes. The reaction was allowed to cool to room temperature and then partitioned between brine (50.0 mL), water (50.0 mL) and dichloromethane (25.0 mL). The aqueous layer was extracted with additional dichloromethane (2 x 25 mL). The combined organic layers were dried over

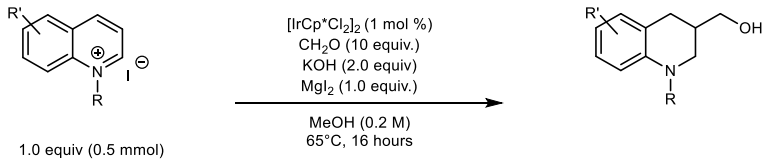
anhydrous Na_2SO_4, concentrated and the crude material was purified by silica gel flash chromatography.

General Procedure D: Preparation of tetrahydro-quinolines [$Mg(OMe)_2$ + KI at 65°C]



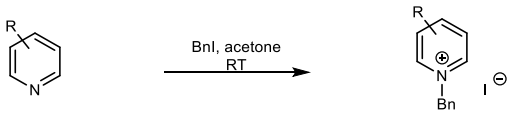
A 5 µM stock solution of iridium catalyst was prepared by dissolving $[IrCp^*Cl_2]_2$ (20.0 mg, 25.0 µmol) in 5 mL of dichloromethane in a volumetric flask. 1.00 mL (1 mol%) of this stock solution was added to a 10 mL microwave vial and the solvent was removed under reduced pressure. The vial was then equipped with a stirring bar and to the reaction were added: Quinolinium salt **XX** (0.50 mmol), $(CH_2O)_n$ (5.00 mmol, 150 mg, 10.0 equiv.), KI (1.00 mmol, 166 mg, 2.00 equiv.), $Mg(OMe)_2$ (0.50 mL 0.75M sol. in methanol, 0.375 mmol, 0.75 equiv.) and 2.00 mL of methanol. The microwave vial was sealed, and the reaction was left to stir at 65°C in an oil bath for 16 hours. Thiourea (50.0 mg) was added and the reaction mixture was stirred at 65°C for an additional 30 minutes. The reaction was allowed to cool to room temperature and then partitioned between brine (50.0 mL), water (50.0 mL) and dichloromethane (25.0 mL). The aqueous layer was extracted with additional dichloromethane (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and the crude material was purified by silica gel flash chromatography.

General Procedure E: Preparation of tetrahydro-quinolines [KOH + MgI_2 at 65°C]



A 5 µM stock solution of iridium catalyst was prepared by dissolving $[IrCp^*Cl_2]_2$ (20.0 mg, 25.0 µmol) in 5 mL of dichloromethane in a volumetric flask. 1.00 mL (1 mol%) of this stock solution was added to a 10 mL microwave vial and the solvent was removed under reduced pressure. The vial was then equipped with a stirring bar and to the reaction were added: Quinolinium salt **XX** (0.50 mmol), $(CH_2O)_n$ (5.00 mmol, 150 mg, 10.0 equiv.), MgI_2 (0.50 mmol, 140 mg, 1.00 equiv.), KOH (56.0 mg, 1.00 mmol, 2.00 equiv.) and 2.50 mL of methanol. The microwave vial was sealed, and the reaction was left to stir at 65°C in an oil bath for 16 hours. Thiourea (50.0 mg) was added and the reaction mixture was stirred at 65°C for an additional 30 minutes. The reaction was allowed to cool to room temperature and then partitioned between brine (50.0 mL), water (50.0 mL) and dichloromethane (25.0 mL). The aqueous layer was extracted with additional dichloromethane (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and the crude material was purified by silica gel flash chromatography.

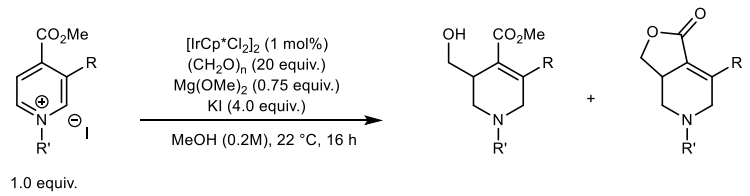
General Procedure F: Preparation of benzyl pyridinium iodide salts



A mixture of the corresponding pyridine (1.00 equiv.) and benzyl iodide (2.00 equiv.) in acetone (0.5 M) was stirred in the dark at room temperature for 16 hours. The solvent was removed under reduced pressure, followed by addition of acetone (1 mL/mol) and diethyl ether (20 mL/mol of substrate). The resulting suspension was sonicated (5 min) then filtered. The

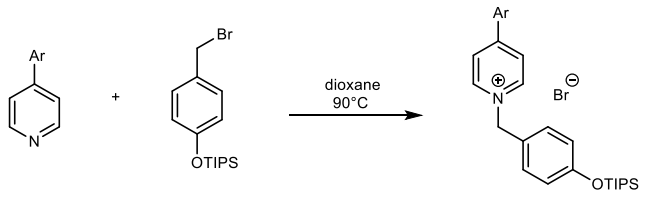
resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the benzyl pyridinium iodide salts as powdery solids.

General Procedure G: Preparation of tetrahydro-pyridines [$Mg(OMe)_2$ + KI at RT]



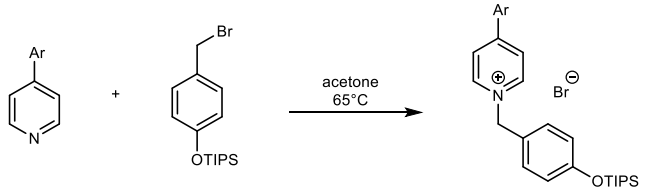
A 5 µM stock solution of iridium catalyst was prepared by dissolving $[IrCp^*Cl_2]_2$ (20.0 mg, 25.0 µmol) in 5 mL of dichloromethane in a volumetric flask. 1.00 mL (1 mol%) of this stock solution was added to a 10 mL microwave vial and the solvent was removed under reduced pressure. The vial was then equipped with a stirring bar and to the reaction were added: pyridinium salt **XX** (0.50 mmol), $(CH_2O)_n$ (10.00 mmol, 300 mg, 20.0 equiv.), KI (2.00 mmol, 332 mg, 4.00 equiv.), $Mg(OMe)_2$ (0.50 mL 0.75M sol. in methanol, 0.375 mmol, 0.75 equiv.) and 2.00 mL of methanol. The microwave vial was sealed, and the reaction was left to stir at room temperature for 16 hours. Thiourea (50.0 mg) was added and the reaction mixture was stirred at 45°C for an additional 30 minutes. The reaction was allowed to cool to room temperature and then partitioned between brine (50.0 mL), water (50.0 mL) and dichloromethane (25.0 mL). The aqueous layer was extracted with additional dichloromethane (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and the crude material was purified by silica gel flash chromatography.

General Procedure H: Preparation of 4-((triisopropylsilyl)oxy)benzyl) pyridinium bromide salts (dioxane at 90°C)



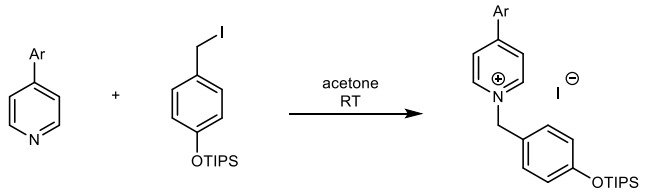
A mixture of the corresponding pyridine (1.0 equiv.) and (4-(bromomethyl)phenoxy)triisopropylsilane (1.5 equiv.) in dioxane (0.3 M) was stirred at 90°C for 16 hours. The mixture was allowed to cool to room temperature, then the solvent was removed under reduced pressure, followed by addition of diethyl ether (15 mL/mmol of substrate). The resulting suspension was sonicated (5 min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium bromide salt.

General Procedure I: Preparation of 4-((triisopropylsilyl)oxy)benzyl) pyridinium bromide salts (acetone at 65°C)



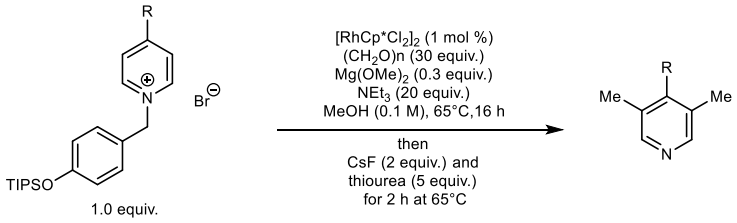
A mixture of the corresponding pyridine (1.0 equiv.) and (4-(bromomethyl)phenoxy)triisopropylsilane (1.5 equiv.) in acetone (0.3 M) was stirred at 65°C for 16 hours. The mixture was allowed to cool to room temperature, then the solvent was removed under reduced pressure, followed by addition of diethyl ether (15 mL/mmol of substrate). The resulting suspension was sonicated (5 min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium bromide salt.

General Procedure J: Preparation of 4-((triisopropylsilyl)oxy)benzyl) pyridinium iodide salts



A mixture of the corresponding pyridine (1.0 equiv.) and (4-(iodomethyl)phenoxy)triisopropylsilane (1.5 equiv.) in acetone (0.3 M) was stirred at room temperature for 16 hours in the dark. The solvent was removed under reduced pressure, followed by addition of diethyl ether (15 mL/mmol of substrate). The resulting suspension was sonicated (5 min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium iodide salt.

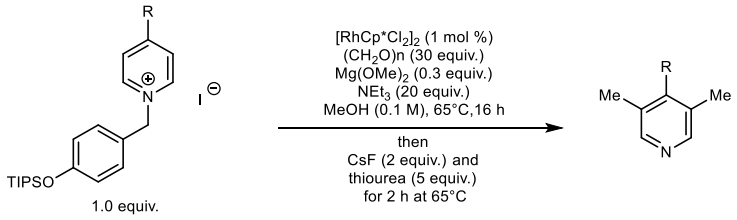
General Procedure K: Preparation of 3,5-dimethyl pyridines - **Class I** (0 M iodide at 65°C)



A 5 µM stock solution of iridium catalyst was prepared by dissolving $[RhCp^*Cl_2]_2$ (15.5 mg, 25.0 µmol) in 5 mL of dichloromethane in a volumetric flask. 1.00 mL (1 mol%) of this stock solution was added to a 20 mL microwave vial and the solvent was removed under reduced pressure. The vial was then equipped with a stirring bar and to the reaction were added: pyridinium bromide salt **XX** (0.50 mmol), $(CH_2O)_n$ (15.0 mmol, 450 mg, 30 equiv.), $Mg(OMe)_2$ (166 µL of 0.9 M sol. in methanol, 0.15 mmol, 0.3 equiv.) NEt_3 (1.40 mL, 10.0 mmol, 20 equiv.) and 3.43 mL of methanol (total reaction volume 5 mL). The microwave vial was sealed, and the reaction was left to stir at 65°C in an oil bath for 16 hours. Thiourea (100.0 mg) and CsF (151.9 mg, 1.00 mmol, 2.0 equiv.) were added and the reaction mixture was

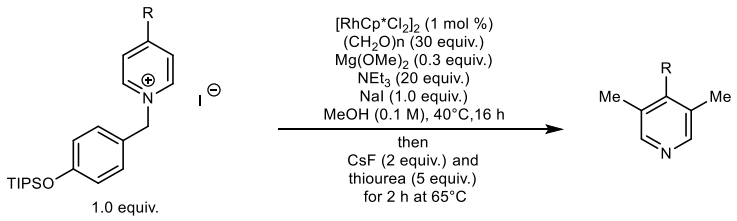
stirred at 65°C for an additional 3 hours. The reaction was allowed to cool to room temperature and then partitioned between brine (50.0 mL), water (50.0 mL) and dichloromethane (25.0 mL). The aqueous layer was extracted with additional dichloromethane (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and the crude material was purified by silica gel flash chromatography.

General Procedure L: Preparation of 3,5-dimethyl pyridines - **Class II** (0.1 M iodide at 65°C)



A 5 µM stock solution of iridium catalyst was prepared by dissolving $[RhCp^*Cl_2]_2$ (15.5 mg, 25.0 µmol) in 5 mL of dichloromethane in a volumetric flask. 1.00 mL (1 mol%) of this stock solution was added to a 20 mL microwave vial and the solvent was removed under reduced pressure. The vial was then equipped with a stirring bar and to the reaction were added: pyridinium iodide salt **XX** (0.50 mmol), $(CH_2O)_n$ (15.0 mmol, 450 mg, 30 equiv.), $Mg(OMe)_2$ (166 µL of 0.9 M sol. in methanol, 0.15 mmol, 0.3 equiv.) NEt_3 (1.40 mL, 10.0 mmol, 20 equiv.) and 3.43 mL of methanol (total reaction volume 5 mL). The microwave vial was sealed, and the reaction was left to stir at 65°C in an oil bath for 16 hours. Thiourea (100.0 mg) and CsF (151.9 mg, 1.00 mmol, 2.0 equiv.) were added and the reaction mixture was stirred at 65°C for an additional 3 hours. The reaction was allowed to cool to room temperature and then partitioned between brine (50.0 mL), water (50.0 mL) and dichloromethane (25.0 mL). The aqueous layer was extracted with additional dichloromethane (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and the crude material was purified by silica gel flash chromatography.

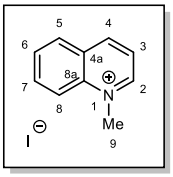
General Procedure M: Preparation of 3,5-dimethyl pyridines - **Class III** (0.2 M iodide at 40°C)



A 5 µM stock solution of iridium catalyst was prepared by dissolving $[RhCp^*Cl_2]_2$ (15.5 mg, 25.0 µmol) in 5 mL of dichloromethane in a volumetric flask. 1.00 mL (1 mol%) of this stock solution was added to a 20 mL microwave vial and the solvent was removed under reduced pressure. The vial was then equipped with a stirring bar and to the reaction were added: pyridinium iodide salt **XX** (0.50 mmol), NaI (75.0 mg, 0.5 mmol, 1.0 equiv.), $(CH_2O)_n$ (15.0 mmol, 450 mg, 30 equiv.), $Mg(OMe)_2$ (166 µL of 0.9 M sol. in methanol, 0.15 mmol, 0.3 equiv.) NEt_3 (1.40 mL, 10.0 mmol, 20 equiv.) and 3.43 mL of methanol (total reaction volume 5 mL). The microwave vial was sealed, and the reaction was left to stir at 40°C in an oil bath for 16 hours. Thiourea (100.0 mg) and CsF (151.9 mg, 1.00 mmol, 2.0 equiv.) were added and the reaction mixture was stirred at 65°C for an additional 3 hours. The reaction was allowed to cool to room temperature and then partitioned between brine (50.0 mL), water (50.0 mL) and dichloromethane (25.0 mL). The aqueous layer was extracted with additional dichloromethane (2 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and the crude material was purified by silica gel flash chromatography.

Experimental details

N-Methylquinolinium Iodide (121)



The title compound was obtained according to **General Procedure A** using quinoline (505 mg, 4.0 mmol) to give *salt* **121** (1.02 g, 92%) as a yellow-orange solid.

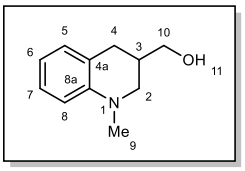
m.p.: 131-133°C;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (d, J = 5.8 Hz, 1H, C^{2}**H**), 9.29 (d, J = 8.4 Hz, 1H, C^{4}**H**), 8.54 – 8.48 (m, 2H, C^{5}**H** + C^{8}**H**), 8.30 (ddd, J = 8.8, 7.0, 1.5 Hz, 1H, C^{7}**H**), 8.18 (dd, J = 8.4, 5.8 Hz, 1H, C^{3}**H**), 8.07 (ddd, J = 8.1, 7.0, 0.9 Hz, 1H, C^{6}**H**), 4.64 (s, 3H, C^{9}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 150.8 (**C**^{2}H), 147.7 (**C**^{4}H), 138.9 (**C**^{8a}), 136.1 (**C**^{7}H), 130.9 (**C**^{5}H), 130.6 (**C**^{6}H), 129.8 (**C**^{4a}), 122.6 (**C**^{3}H), 119.8 (**C**^{8}H), 46.0 (**C**^{9}H$_3$).

Spectroscopic data was consistent with that reported in the literature. [191]

3-(Hydroxymethyl)-*N*-methyl-1,2,3,4-tetrahydroquinoline (237)



The title compound was prepared according to **General Procedure C** using *quinolinium* **121** (136 mg, 0.5 mmol). The crude material was purified by FCC (95:5 CH_2Cl_2:acetone) to give *amine* **237** (72 mg, 81%) as a pale-yellow oil.

HRMS (ESI): Exact mass calculated for $C_{11}H_{16}NO$ $[M+H]^+$ m/z: 178.1226, found: 178.1226;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, J = 7.9 Hz, 1H, C^{7}**H**), 7.00 (d, J = 7.4 Hz, 1H, C^{5}**H**), 6.68 – 6.62 (m, 2H, C^{6}**H** + C^{8}**H**), 3.69 (dd, J = 10.6, 5.8 Hz, 1H, C^{10}**H**$_2$), 3.59 (dd, J = 10.7, 7.5 Hz, 1H, C^{10}**H**$_2$), 3.33 (ddd, J = 11.1, 3.9, 1.6 Hz, 1H, C^{2}**H**$_2$), 3.04 (dd, J = 11.1, 8.3 Hz, 1H,

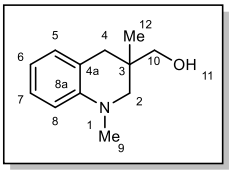
$C^2\mathbf{H}_2$), 2.91 (s, 3H, $C^9\mathbf{H}_3$), 2.89 – 2.82 (m, 1H, $C^4\mathbf{H}_2$), 2.56 (dd, *J* = 15.9, 8.9 Hz, 1H, $C^4\mathbf{H}_2$), 2.30 – 2.20 (m, 1H, $C^3\mathbf{H}$), 2.02 (bs, 1H, $O^{11}\mathbf{H}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3 ($\mathbf{C}^8$), 128.9 ($\mathbf{C}^5$H), 126.9 ($\mathbf{C}^7$H), 121.4 ($\mathbf{C}^{4a}$), 116.4 ($\mathbf{C}^6$H), 110.8 ($\mathbf{C}^8$H), 65.1 ($\mathbf{C}^{10}H_2$), 53.3 ($\mathbf{C}^2H_2$), 39.0 ($\mathbf{C}^9H_3$), 35.0 ($\mathbf{C}^3$H), 30.0 ($\mathbf{C}^4H_2$);

IR (neat) (cm^{-1}): 3332, 2918, 2830, 1885, 1602, 1576, 1502, 1433, 1291, 1029, 746.

All spectroscopic data were consistent with the ones previously mentioned. [192]

(*N*,3-Dimethyl-3-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline (238)



The title compound was prepared according to **General Procedure C** using *quinolinium* **266** (143 mg, 0.5 mmol). The crude material was purified by FCC (95:5 CH_2Cl_2:acetone) to give *amine* **238** (82 mg, 86%) as a pale-yellow oil.

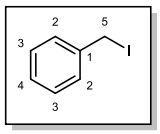
HRMS (ESI): Exact mass calculated for $C_{12}H_{18}NO$ $[M+H]^+$ m/z: 192.1383, found: 192.1383;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.09 (m, 1H, $C^7\mathbf{H}$), 7.01 – 6.98 (m, 1H, $C^5\mathbf{H}$), 6.69 – 6.63 (m, 2H, $C^6\mathbf{H}$ + $C^8\mathbf{H}$), 3.51 (d, *J* = 10.8 Hz, 1H, $C^{10}\mathbf{H}_2$), 3.44 (d, *J* = 10.8 Hz, 1H, $C^{10}\mathbf{H}_2$), 3.08 (dd, *J* = 11.2, 1.7 Hz, 1H, $C^2\mathbf{H}_2$), 2.92 (dd, *J* = 11.2, 1.1 Hz, 1H, $C^2\mathbf{H}_2$), 2.92 (s, 3H, $C^9\mathbf{H}_3$), 2.65 (d, *J* = 16.4 Hz, 1H, $C^4\mathbf{H}_2$), 2.55 (d, *J* = 16.4 Hz, 1H, $C^4\mathbf{H}_2$), 2.10 (bs, 1H, $O^{11}\mathbf{H}$), 1.04 (s, 3H, $C^{12}\mathbf{H}_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8 ($\mathbf{C}^{8a}$), 129.6 ($\mathbf{C}^5$H), 127.1 ($\mathbf{C}^7$H), 121.4 ($\mathbf{C}^{4a}$), 116.9 ($\mathbf{C}^6$), 111.1 ($\mathbf{C}^8$H), 69.3 ($\mathbf{C}^{10}H_2$), 58.6 ($\mathbf{C}^4H_2$), 39.4 ($\mathbf{C}^9H_3$), 37.0 ($\mathbf{C}^2H_2$), 33.8 ($\mathbf{C}^3$H), 22.3 ($\mathbf{C}^{12}H_3$);

IR (neat) (cm^{-1}): 3360, 2922, 2868, 2833, 1603, 1577, 1503, 1452, 1316, 1278, 1222, 1045, 746.

Benzyl iodide (240)



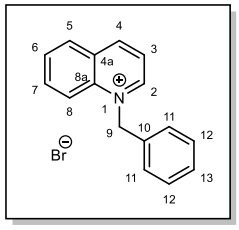
Sodium iodide (18.0 g, 120.0 mmol, 2.0 equiv.) was dissolved in 80 mL of acetone at 0°C. To the reaction was added slowly benzyl bromide (7.2 mL, 60.0 mmol, 1.0 equiv.) and the reaction was left to stir at room temperature overnight in the dark. To the reaction was added 150 mL of brine and extracted with 2 x 100 mL of diethyl ether. The combined organics were dried over $MgSO_4$ and concentrated under vacuum to give the product **240** as a brown oil in quantitative yield. This brown oil contains traces of iodine. This can be removed by doing a silica filtration with pentane: ether (95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.21 (m, 5H, Ar-C**H**), 4.47 (s, 2H, C^5**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1 (**C**^{1}), 128.6 (2 x C, Ar-**C**H), 128.5 (Ar-**C**H), 127.7 (2 x C, Ar-**C**H), 5.58 (**C**^{5}H$_2$).

Spectroscopic data was consistent with that reported in the literature.[193]

***N*-Benzylquinolinium Bromide (241)**



A mixture of quinoline (505 mg, 4.0 mmol, 1.0 equiv.) and benzyl bromide (0.95 mL, 8.0 mmol, 2.0 eq.) in 1,4-dioxane (10.0 mL) was heated at 100°C in a sealed flask for 16 hours. The mixture was allowed to cool to room temperature, the solid was collected by filtration, washed with diethyl ether and dried under vacuum for one hour to give the benzyl quinolinium bromide **241** (1.00 g, 83%) as a white powdery solid.

m.p.: 199-201°C;

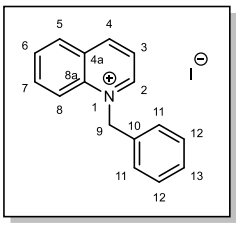
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (dd, *J* = 5.9, 1.5 Hz, 1H, C^2**H**), 9.40 (d, *J* = 8.4 Hz, 1H, C^4**H**), 8.53 – 8.51 (m, 2H, C^5**H** + C^8**H**), 8.31 (dd, *J* = 8.4, 5.8 Hz, 1H, C^3**H**), 8.22 (ddd, *J* = 8.8,

7.0, 1.5 Hz, 1H, C^{7}**H**), 8.03 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H, C^{6}**H**), 7.42 – 7.33 (m, 5H, C$^{11\text{-}13}$**H**), 6.39 (s, 2H, C^{9}**H**$_2$);

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 149.8 (**C**^{2}H), 147.6 (**C**^{4}H), 136.9 (**C**^{8a}), 135.2 (**C**^{7}H), 133.3 (**C**^{10}), 130.3 (**C**^{5}H), 129.4 (**C**^{6}H), 129.3 (**C**^{4a}), 128.5 (2xC, Ar-**C**H), 128.2 (Ar-**C**H), 126.7 (2xC, Ar-**C**H), 121.9 (**C**^{3}H), 118.7 (**C**^{8}H), 59.3 (**C**^{9}H$_2$).

Spectroscopic data was consistent with that reported in the literature.[194]

N-Benzylquinolinium Iodide (242)



The title compound was prepared in accordance with **General Procedure B** using quinoline (505 mg, 4.0 mmol) to give *salt* **242** (1.29 g, 3.72 mmol) as a yellow solid in 93% yield.

m.p.: 155-157°C;

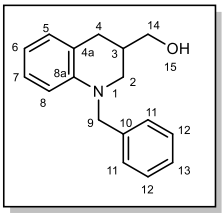
HRMS (ESI): Exact mass calculated for $C_{16}H_{14}N$ [M^+] m/z: 220.1121, found: 220.1122;

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.77 (dd, *J* = 5.9, 1.5 Hz, 1H, C^{2}**H**), 9.40 (d, *J* = 8.4 Hz, 1H, C^{4}**H**), 8.54 – 8.50 (m, 2H, C^{5}**H** + C^{8}**H**), 8.32 (dd, *J* = 8.4, 5.8 Hz, 1H, C^{3}**H**), 8.22 (ddd, *J* = 8.8, 7.0, 1.5 Hz, 1H, C^{7}**H**), 8.03 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H, C^{6}**H**), 7.42 – 7.33 (m, 5H, C$^{11\text{-}13}$**H**), 6.40 (s, 2H, C^{9}**H**$_2$);

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 150.8 (**C**^{2}H), 148.6 (**C**^{4}H), 137.9 (**C**^{8a}), 136.2 (**C**^{7}H), 134.3 (**C**^{10}), 131.3 (**C**^{5}H), 130.4 (**C**^{6}H), 130.3 (**C**^{4a}), 129.5 (2xC, Ar-**C**H), 129.2 (Ar-**C**H), 127.7 (2xC, Ar-**C**H), 122.9 (**C**^{3}H), 119.7 (**C**^{8}H), 60.3 (**C**^{9}H$_2$);

IR (neat) (cm^{-1}): 2926, 2868, 1587, 1528, 1367, 1031, 846, 824, 799, 774, 722, 692.

***N*-Benzyl-3-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline (243)**



The title compound was prepared according to **General Procedure D** using *quinolinium* **242** (174 mg, 0.5 mmol). The crude material was purified by FCC (98:2 CH_2Cl_2:acetone) to give *amine* **243** (106 mg, 84%) as a pale-yellow solid.

m.p.: 60-62°C;

HRMS (ESI): exact mass calculated for $C_{17}H_{20}NO$ $[M+H]^+$ m/z: 254.1539, found: 254.1539;

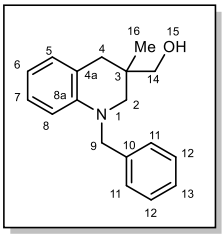
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H, $C^{11\text{-}13}$**H**), 7.05 (m, 2H, C^5**H** + C^7**H**), 6.66 (td, *J* = 7.3, 1.1 Hz, 1H, C^6**H**), 6.60 (dd, *J* = 8.7, 1.1 Hz, 1H, C^8**H**), 4.53 (m, 2H, C^9**H**$_2$), 3.71 (dd, *J* = 10.7, 5.9 Hz, 1H, C^{14}**H**$_2$), 3.62 (dd, *J* = 10.7, 7.4 Hz, 1H, C^{14}**H**$_2$), 3.49 (ddd, *J* = 11.4, 3.9, 1.8 Hz, 1H, C^2**H**$_2$), 3.22 (dd, *J* = 11.3, 8.4 Hz, 1H, C^2**H**$_2$), 2.93 (dd, *J* = 15.9, 5.0 Hz, 1H, C^4**H**$_2$), 2.64 (dd, *J* = 15.8, 9.1 Hz, 1H, C^4**H**), 2.36 – 2.26 (m, 1H, C^3**H**), 1.91 (bs, 1H, O^{15}**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1 (Ar-**C**), 138.6 (Ar-**C**), 129.2 (Ar-**C**H), 128.4 (Ar-**C**), 127.0 (Ar-**C**H), 126.6 (2 x C, Ar-**C**H), 126.4 (Ar-**C**H), 120.6 (2 x C, Ar-**C**H), 116.0 (**C**^{6}H), 110.8 (**C**^{8}H), 64.8 (**C**^{14}H$_2$), 55.0 (**C**^{9}H$_2$), 51.6 (**C**^{2}H$_2$), 34.8 (**C**^{3}H), 30.4 (**C**^{4}H$_2$);

IR (neat) (cm^{-1}): 3345, 3062, 3027, 2918, 2836, 2360, 1601, 1503, 1451, 1353, 1295, 1244, 1170, 1030, 743.

Spectroscopic data was consistent with that reported in the literature. [195]

***N*-Benzyl-3-(hydroxymethyl)-3'-methyl-1,2,3,4-tetrahydroquinoline (244)**



The title compound was prepared according to **General Procedure D** using *quinolinium* **267** (181 mg, 0.5 mmol). The crude material was purified by FCC (99:1 CH_2Cl_2:acetone) to give *amine* **244** (126 mg, 94%) as a pale-yellow oil.

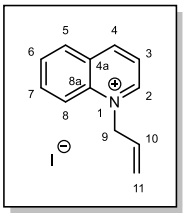
HRMS (ESI): Exact mass calculated for $C_{18}H_{22}NO$ $[M+H]^+$ m/z: 268.1696, found: 268.1694;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H, $C^{11\text{-}13}$**H**), 7.09 – 7.03 (m, 2H, C^{5}**H** + C^{7}**H**), 6.69 – 6.62 (m, 2H, C^{6}**H** + C^{8}**H**), 4.59 – 4.47 (m, 2H, C^{9}**H**$_2$), 3.55 (d, *J* = 10.8 Hz, 1H, C^{14}**H**$_2$), 3.48 (d, *J* = 10.8 Hz, 1H, C^{14}**H**$_2$), 3.24 (dd, *J* = 11.5, 1.7 Hz, 1H, C^{2}**H**$_2$), 3.10 (d, *J* = 11.5 Hz, 1H, C^{2}**H**$_2$), 2.72 (d, *J* = 16.1 Hz, 1H, C^{4}**H**$_2$), 2.62 (d, *J* = 16.1 Hz, 1H, C^{4}**H**$_2$), 1.74 (bs, 1H, O^{15}**H**), 1.09 (s, 3H, C^{16}**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1 (Ar-**C**), 139.5 (Ar-**C**), 130.2 (Ar-**C**H), 129.0 (Ar-**C**), 127.5 (Ar-**C**H), 127.3 (2 x C, Ar-**C**H), 127.0 (Ar-**C**H), 120.8 (2 x C, Ar-**C**H), 116.0 (**C**^{6}H), 111.3 (**C**^{8}H), 69.2 (**C**^{14}H$_2$), 57.0 (**C**^{2}H$_2$), 55.7 (**C**^{9}H$_2$), 37.4 (**C**^{4}H$_2$), 34.1 (**C**^{3}), 22.3 (**C**^{16}H$_3$);

IR (neat) (cm^{-1}): 3375, 3063, 3027, 2920, 2837, 1601, 1501, 1451, 1245, 1029, 740, 696.

N-Allylquinolinium Iodide (253)



A mixture of quinoline (0.48 mL, 5.0 mmol, 1.0 equiv.) and ally iodide (1.2 mL, 15.0 mmol, 3.0 equiv.) were stirred in 10 mL of acetone at room temperature overnight in the dark. The solvent was removed under reduced pressure, followed by the addition of 25 mL of Et_2O. The resulting solid was filtered and washed with more Et_2O to give the product **253** (319 mg, 21 % yield) as a yellow solid.

m.p.: 179-181°C;

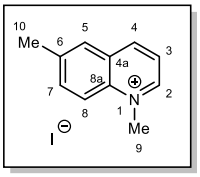
HRMS (ESI): Exact mass calculated for $C_{12}H_{12}N$ [M^+] m/z: 170.09643, found: 170.09659;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (dd, J = 5.8, 1.5 Hz, 1H, C^{2}**H**), 9.34 (d, J = 8.3 Hz, 1H, C^{4}**H**), 8.53 (t, J = 8.8 Hz, 2H, C^{8}**H** + C^{5}**H**), 8.36 – 8.22 (m, 2H, C^{3}**H** + C^{7}**H**), 8.06 (t, J = 7.6 Hz, 1H, C^{6}**H**), 6.34 – 6.11 (m, 1H, C^{10}**H**), 5.75 (dt, J = 5.6, 1.7 Hz, 2H, C^{9}**H**$_2$), 5.41 (d, J = 10.3 Hz, 1H, C^{11}**H**$_2$), 5.32 (d, J = 17.2 Hz, 1H, C^{11}**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 149.9 (**C**^{2}H), 147.8 (**C**^{4}H), 137.6 (**C**^{8a}), 135.6 (**C**^{7}H), 131.3 (**C**^{10}H), 130.7 (**C**^{5}H), 130.0 (**C**^{6}H), 129.7 (**C**^{4a}), 122.4 (**C**^{3}H), 120.4 (**C**^{11}H$_2$), 119.2 (**C**^{8}H), 59.1 (**C**^{9}H$_2$);

IR (neat) (cm^{-1}): 2980, 1590, 1523, 1373, 1362, 1161, 1007, 981, 948, 917, 798, 772, 736, 666, 611.

N,6-Dimethylquinolinium Iodide (254)



The title compound was obtained according to **General Procedure A** using 6-methylquinoline (573 mg, 4.0 mmol) to give *salt* **254** (1.07 g, 94%) as a yellow solid.

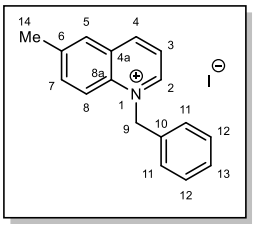
m.p.: 216-218°C;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (d, J = 5.8 Hz, 1H, C^{2}**H**), 9.16 (d, J = 8.4 Hz, 1H, **C**^{4}H), 8.43 (d, J = 9.0 Hz, 1H, **C**^{8}H), 8.25 (s, 1H, **C**^{5}H), 8.16 – 8.11 (m, 2H, **C**^{3}H + **C**^{7}H), 4.62 (s, 3H, **C**^{9}H$_3$), 2.63 (s, 3H, **C**^{10}H$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 148.7 (**C**^{2}H), 145.8 (**C**^{4}H), 139.9 (**C**^{6}), 136.9 (**C**^{7}H), 136.4 (**C**^{8a}), 128.9 (**C**^{5}H), 128.3 (**C**^{4a}), 121.6 (**C**^{3}H), 118.5 (**C**^{8}H), 44.9 (**C**^{9}H$_3$), 20.4 (**C**^{10}H$_3$).

Spectroscopic data was consistent with that reported in the literature.[196]

N-Benzyl-6-methylquinolinium Iodide (255)



The title compound was prepared according to **General Procedure B** using 6-methylquinoline (573 g, 4.0 mmol) to give *salt* **255** (1.31 g, 91%) as a yellow solid.

m.p.: 226-228°C;

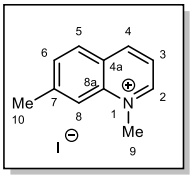
HRMS (ESI): Exact mass calculated for $C_{16}H_{16}N$ [M^+] m/z: 234.12773, found: 234.12773;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.67 (dd, J = 5.8, 1.4 Hz, 1H, C^{2}**H**), 9.26 (d, J = 8.4 Hz, 1H, C^{4}**H**), 8.41 (d, J = 9.1 Hz, 1H, C^{8}**H**), 8.28 – 8.23 (m, 2H, C^{3}**H** + C^{5}**H**), 8.06 (dd, J = 9.1, 2.0 Hz, 1H, C^{7}**H**), 7.42 – 7.32 (m, 5H, C$^{11\text{-}13}$**H**), 6.35 (s, 2H, C^{9}**H**$_2$), 2.57 (s, 3H, C^{14}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 148.7 (**C**^{2}H), 146.7 (**C**^{4}H), 139.8 (**C**^{6}), 137.1 (**C**^{7}H), 135.4 (**C**^{8a}), 133.3 (**C**^{10}), 129.4 (**C**^{4a}), 128.6 (2xC, Ar-**C**H), 128.5 (**C**^{5}H), 128.1 (Ar-**C**H), 126.6 (2xC, Ar-**C**H), 121.8 (**C**^{3}H), 118.4 (**C**^{8}H), 59.2 (**C**^{9}H$_2$), 20.2 (**C**^{14}H$_3$);

IR (neat) (cm^{-1}): 2995, 2929, 1519, 1299, 1237, 824, 806, 771, 721, 700.

N,7-Dimethylquinolinium Iodide (256)



The title compound was obtained according to **General Procedure A** using 7-methylquinoline (573 mg, 4.0 mmol) to give *salt* **256** (1.10 g, 96%) as a yellow solid.

m.p.: 218-220°C;

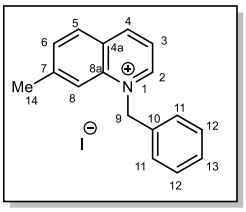
HRMS (ESI): Exact mass calculated for $C_{11}H_{12}N$ [M$^+$] m/z: 158.0964, found: 158.0966;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (d, *J* = 5.7 Hz, 1H, C^{2}**H**), 9.21 (d, *J* = 8.3 Hz, 1H, C^{4}**H**), 8.38 – 8.34 (m, 2H, C^{5}**H** + C^{8}**H**), 8.09 (dd, *J* = 8.3, 5.8 Hz, 1H, C^{3}**H**), 7.92 (dd, *J* = 8.4, 1.4 Hz, 1H, C^{6}**H**), 4.59 (s, 3H, C^{9}**H**$_3$), 2.72 (s, 3H, C^{10}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 149.8 (**C**^{2}H), 147.4 (**C**^{4}H), 146.8 (**C**^{7}), 138.8 (**C**^{8a}), 132.1 (**C**^{6}H), 130.2 (**C**^{5}H), 127.8 (**C**^{4a}), 121.2 (**C**^{3}H), 118.2 (**C**^{8}H), 45.4 (**C**^{9}H$_3$), 22.4 (**C**^{10}H$_3$;

IR (neat) (cm^{-1}): 3035, 1593, 1519, 1369, 846, 750, 628.

N-Benzyl-7-methylquinolinium Iodide (257)



The title compound was prepared according to **General Procedure B** using 7-methylquioline (573 mg, 4.0 mmol) to give *salt* **257** (1.29 g, 91%) as a yellow solid.

m.p.: 222-224°C;

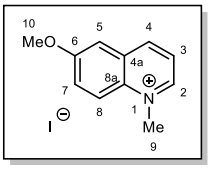
HRMS (ESI): Exact mass calculated for $C_{17}H_{16}N$ [M$^+$] m/z: 234.12773, found: 234.12776;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.67 (dd, *J* = 5.9, 1.5 Hz, 1H, C^{2}**H**), 9.32 (d, *J* = 8.3 Hz, 1H, C^{4}**H**), 8.42 – 8.38 (m, 2H, C^{5}**H** + C^{8}**H**), 8.21 (dd, *J* = 8.3, 5.8 Hz, 1H, C^{3}**H**), 7.87 (dd, *J* = 8.5, 1.3 Hz, 1H, C^{6}**H**), 7.44 – 7.32 (m, 5H, C$^{11\text{-}13}$**H**), 6.36 (s, 2H, C^{9}**H**$_2$), 2.62 (s, 3H, C^{14}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 149.6 (**C**^{2}H), 147.6 (**C**^{7}), 147.6 (**C**^{4}H), 137.9 (**C**^{8a}), 133.9 (**C**^{10}), 132.0 (**C**^{6}H), 130.4 (**C**^{5}H), 129.1 (2xC, Ar-**C**H), 128.8 (Ar-**C**H), 128.2 (**C**^{4a}), 127.4 (2xC, Ar-**C**H), 121.5 (**C**^{3}H), 118.0 (**C**^{8}H), 59.5 (**C**^{9}H$_2$), 22.3 (**C**^{14}H$_3$);

IR (neat) (cm^{-1}): 2967, 1731, 1626, 1521, 1490, 1372, 1289, 1194, 1098, 1041.

6-Methoxy-*N*-methylquinolinium Iodide (258)



The title compound was obtained according to **General Procedure A** using 6-methoxyquinoline (637 mg, 4.0 mmol) to give *salt* **258** (1.14 g, 95%) as a yellow solid.

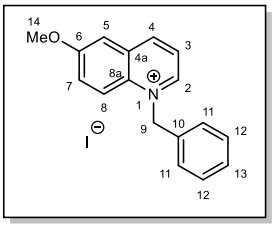
m.p.: 236-238°C;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (d, *J* = 5.7 Hz, 1H, C^{2}**H**), 9.10 (d, *J* = 8.6 Hz, 1H, C^{4}**H**), 8.44 – 8.42 (m, 1H, C^{8}**H**), 8.10 (dd, *J* = 8.6, 5.7 Hz, 1H, C^{3}**H**), 7.93 – 7.89 (m, 2H, C^{5}**H** + C^{7}**H**), 4.60 (s, 3H, C^{9}**H**$_3$), 4.00 (s, 3H, C^{10}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 159.9 (**C**^{6}), 147.8 (**C**^{2}H), 145.8 (**C**^{4}H), 134.7 (**C**^{8a}), 131.8 (**C**^{4a}), 128.0 (**C**^{7}H), 123.0 (**C**^{3}H), 121.5 (**C**^{8}H), 108.5 (**C**^{5}H), 57.0 (**C**^{10}H$_3$), 46.1 (**C**^{9}H$_3$).

Spectroscopic data was consistent with that reported in the literature.[197]

N-Benzyl-6-methoxyquinolinium Iodide (259)



The titled compound was prepared according to **General Procedure B** using 6-methoxyquinoline (637 mg, 4.0 mmol) to give *salt* **259** (1.45 g, 96%) as a yellow solid.

m.p.: 225-227°C;

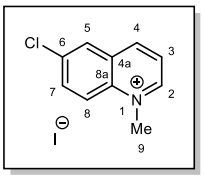
HRMS (ESI): Not found. The molecule fragments during spectroscopy;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (dd, J = 5.8, 1.4 Hz, 1H, C^{2}**H**), 9.20 (d, J = 8.4 Hz, 1H, C^{4}**H**), 8.42 (d, J = 9.8 Hz, 1H, C^{8}**H**), 8.23 (dd, J = 8.4, 5.8 Hz, 1H, C^{3}**H**), 7.93 (d, J = 2.9 Hz, 1H, C^{5}**H**), 7.85 (dd, J = 9.8, 2.9 Hz, 1H, C^{7}**H**), 7.42 – 7.32 (m, 5H, C$^{11\text{-}13}$**H**), 6.34 (s, 2H, C^{9}**H**$_2$), 3.98 (s, 3H, C^{14}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 159.1 (**C**^{6}), 147.3 (**C**^{2}H), 146.1 (**C**^{4}H), 133.9 (**C**^{4a}), 133.2 (**C**^{8a}), 132.0 (**C**^{10}), 129.1 (2xC, Ar-**C**H), 128.7 (Ar-**C**H), 127.7 (**C**^{7}H), 127.1 (2xC, Ar-**C**H), 122.8 (**C**^{3}H), 120.9 (**C**^{8}H), 108. 5(**C**^{5}H), 59.9 (**C**^{9}H$_2$), 56.40 (d, J = 3.4 Hz, **C**^{14}H$_3$);

IR (neat) (cm^{-1}): 2933, 1518, 1299, 1272, 1216, 1166, 1042, 1007, 908, 808, 772, 723, 709, 696.

6-Chloro-*N*-methylquinolinium Iodide (260)



The title compound was obtained according to **General Procedure A** using 6-chloroquinoline (654 mg, 4.0 mmol) to give *salt* **260** (1.17 g, 96%) as a yellow solid.

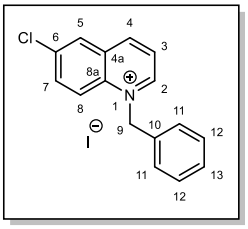
m.p.: 252-254°C;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (d, J = 5.6 Hz, 1H, C^{2}**H**), 9.21 (d, J = 8.5 Hz, 1H, C^{4}**H**), 8.67 (d, J = 2.4 Hz, 1H, C^{5}**H**), 8.56 (d, J = 9.4 Hz, 1H, C^{8}**H**), 8.33 (dd, J = 9.4, 2.4 Hz, 1H, C^{7}**H**), 8.24 (dd, J = 8.5, 5.7 Hz, 1H, C^{3}**H**), 4.64 (s, 3H, C^{9}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 151.1 (**C**^{2}H), 146.6 (**C**^{4}H), 137.5 (**C**^{8a}), 135.7 (**C**^{7}H), 134.8 (**C**^{6}), 130.5 (**C**^{4a}), 129.1 (**C**^{5}H), 123.7 (**C**^{3}H), 122.1 (**C**^{8}H), 46.1 (**C**^{9}H$_3$).

Spectroscopic data was consistent with that reported in the literature.[196]

N-Benzyl-6-chloroquinolinium Iodide (261)



The title compound was prepared according to **General Procedure B** using 6-chloroquinoline (654 mg, 4.0 mmol) to give *salt* **261** (1.37 g, 90%) as an orange solid.

m.p.: 206-208°C;

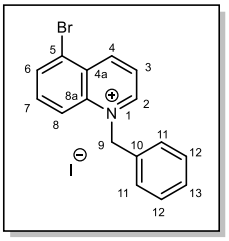
HRMS (ESI): Exact mass calculated for $C_{15}H_{13}NCl$ [M^+] m/z: 254.0731, found: 254.0723;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (dd, *J* = 5.8, 1.4 Hz, 1H, C^{2}**H**), 9.30 (d, *J* = 8.5 Hz, 1H, C^{4}**H**), 8.70 (d, *J* = 2.4 Hz, 1H, C^{5}**H**), 8.54 (d, *J* = 9.5 Hz, 1H, C^{8}**H**), 8.35 (dd, *J* = 8.5, 5.8 Hz, 1H, C^{3}**H**), 8.27 (dd, *J* = 9.5, 2.5 Hz, 1H, C^{7}**H**), 7.44 – 7.34 (m, 5H, C$^{11\text{-}13}$**H**), 6.38 (s, 2H, C^{9}**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 151.6 (**C**^{2}H), 147.9 (**C**^{4}H), 136.9 (**C**^{8a}), 136.3 (**C**^{7}H), 135.2 (**C**^{6}), 134.3 (**C**^{10}), 131.5 (**C**^{4a}), 130.0 (**C**^{5}H), 129.8 (2xC, Ar-**C**H), 129.5 (Ar-**C**H), 128.0 (2xC, Ar-**C**H), 124.4 (**C**^{3}H), 122.3 (**C**^{8}H), 60.8 (**C**^{9}H$_2$);

IR (neat) (cm^{-1}): 3064, 3001, 2934, 1511, 1291, 1221, 1198, 916, 888, 808, 771, 720, 700, 652.

N-Benzyl-5-bromoquinolinium Iodide (262)



The titled compound was prepared according to **General Procedure B** using 5-bromoquinoline (832 mg, 4.0 mmol) to give *salt* **262** (1.62 g, 95%) as a yellow solid.

m.p.: 200–202°C;

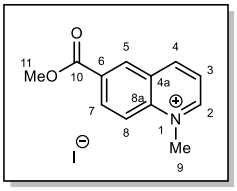
HRMS (ESI): Exact mass calculated for $C_{16}H_{13}N$ [$M]^+$ m/z: 298.0226, found: 298.0225;

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.80 (dd, J = 5.7, 1.3 Hz, 1H, C^{2}**H**), 9.46 (dt, J = 8.7, 1.1 Hz, 1H, C^{4}**H**), 8.53 (d, J = 9.2 Hz, 1H, C^{8}**H**), 8.39 (dd, J = 8.4, 5.8 Hz, 2H, C^{3}**H** + C^{6}**H**), 8.10 (dd, J = 9.0, 7.6 Hz, 1H, C^{7}**H**), 7.43 – 7.35 (m, 5H, C$^{11\text{-}13}$**H**), 6.40 (s, 2H, C^{9}**H**);

^{13}C NMR (126 MHz, DMSO-d_6) δ 151.4 (**C**^{2}H), 146.9 (**C**^{4}H), 138.9 (**C**^{8a}), 135.9 (**C**^{7}H), 134.1 (**C**^{6}H), 133.7 (**C**^{10}), 129.1 (2xC, Ar-**C**H), 128.9 (Ar-**C**H), 128.8 (**C**^{4a}), 127.3 (2xC, Ar-**C**H), 124.1 (**C**^{5}), 123.9 (**C**^{3}H), 119.5 (**C**^{8}H), 60.2 (**C**^{9}H$_2$);

IR (neat) (cm^{-1}): 3083, 3025, 1580, 1510, 1493, 1451, 1358, 1280, 1221, 1148, 1028, 792, 701.

6-(Methoxycarbonyl)-*N*-methylquinolinium Iodide (263)



The title compound was obtained according to **General Procedure A** using methyl quinoline-6-carboxylate (749 mg, 4.0 mmol) to give *salt* **263** (1.29 g, 98%) as a yellow solid.

m.p.: 211-213°C;

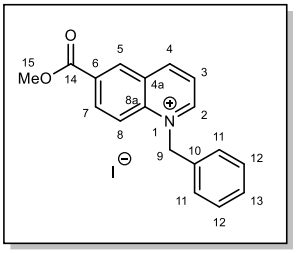
HRMS (ESI): Exact mass calculated for $C_{12}H_{12}O_2N$ [M^+] m/z: 202.0863, found: 202.0864;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.63 (d, J = 5.8 Hz, 1H, C^{2}**H**), 9.47 (d, J = 8.4 Hz, 1H, C^{4}**H**), 9.13 (s, 1H, C^{5}**H**), 8.63 (m, 2H, C^{7}**H** + C^{8}**H**), 8.28 (dd, J = 8.4, 5.8 Hz, 1H, C^{3}**H**), 4.67 (s, 3H, C^{9}**H**$_3$), 3.99 (s, 3H, C^{11}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 164.2 (**C**^{10}), 151.7 (**C**^{2}H), 147.9 (**C**^{4}H), 139.7 (**C**^{8a}), 133.3 (**C**^{7}H), 131.8 (**C**^{5}H), 129.8 (**C**^{4a}), 128.4 (**C**^{6}), 122.6 (**C**^{3}H), 119.8 (**C**^{8}H), 52.6 (**C**^{11}H$_3$), 45.2 (**C**^{9}H$_3$);

IR (neat) (cm^{-1}): 2941, 1709, 1291, 1218, 821, 772.

N-Benzyl-6-(methoxycarbonyl)quinolinium Iodide (264)



The title compound was prepared according to **General Procedure B** (stirred for 2 days) using methyl quinoline-6-carboxylate (748 mg, 4.0 mmol) to give *salt* **264** (1.20 g, 74%) as an orange solid.

m.p.: 192-194°C;

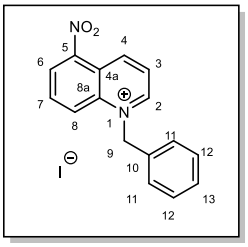
HRMS (ESI): Exact mass calculated for $C_{18}H_{16}O_2N$ [M^+] m/z: 278.11756, found: 278.11646;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (dd, J = 5.9, 1.5 Hz, 1H, C^2**H**), 9.57 (d, J = 8.3 Hz, 1H, C^4**H**), 9.17 (d, J = 1.8 Hz, 1H, C^5**H**), 8.64 – 8.56 (m, 2H, C^7**H** + C^8**H**), 8.40 (dd, J = 8.4, 5.8 Hz, 1H, C^3**H**), 7.44 – 7.33 (m, 5H, C$^{11\text{-}13}$**H**), 6.40 (s, 2H, C^9**H**$_2$), 3.97 (s, 3H, C^{15}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 163.9 (**C**^{14}), 151.7 (**C**^{2}H), 148.9 (**C**^{4}H), 138.8 (**C**^{8a}), 133.6 (**C**^{7}H), 133.0 (**C**^{10}), 132.2 (**C**^{5}H), 129.7 (**C**^{6}), 129.1 (**C**^{4a}), 128.5 (2xC, Ar-**C**H), 128.3 (Ar-**C**H), 126.8 (2xC, Ar-**C**H), 122.9 (**C**^{3}H), 119.6 (**C**^{8}H), 59.6 (**C**^{9}H$_2$), 52.4 (**C**^{15}H$_3$);

IR (neat) (cm^{-1}): 2996, 1719, 1305, 1273, 1218, 975, 820, 775, 719, 702.

N-Benzyl-5-nitroquinolinium Iodide (265)



The title compound was prepared according to **General Procedure B** (stirred for 2 days) using 5-nitroquinoline (522 mg, 3.0 mmol) to give *salt* **265** (471 mg, 40%) as an orange solid.

m.p.: 189–191°C;

HRMS (ESI): Exact mass calculated for $C_{16}H_{13}O_2N_2$ [M^+] m/z: 265.09715, found: 265.09729;

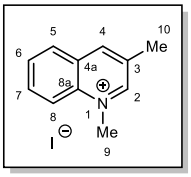
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.94 (dd, J = 5.8, 1.4 Hz, 1H, C^2**H**), 9.61 (dt, J = 9.0, 1.2 Hz, 1H, C^4**H**), 8.92 (d, J = 9.1 Hz, 1H C^8**H**), 8.74 (d, J = 7.7 Hz, 1H, C^6**H**), 8.51 (dd, J = 9.0,

5.7 Hz, 1H, C^{3}**H**), 8.37 (dd, *J* = 9.1, 7.8 Hz, 1H, C^{7}**H**), 7.46 – 7.33 (m, 5H, C$^{11\text{-}13}$**H**), 6.49 (s, 2H, C^{9}**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 152.0 (**C**^{2}H) , 146.6 (Ar-**C**), 143.4 (**C**^{4}H), 137.6 (Ar-**C**), 134.2 (**C**^{7}H), 133.4 (Ar-**C**), 129.1 (2xC, Ar-**C**H), 129.0 (Ar-**C**H), 127.5 (2xC, Ar-**C**H), 127.2 (**C**^{6}H), 125.3 (**C**^{8}H), 125.0 (**C**^{3}H), 122.6 (Ar-**C**), 61.1 (**C**^{9}H$_2$);

IR (neat) (cm^{-1}): 2979, 2887, 1523, 1357, 1162, 1082, 954, 816, 745, 696.

N,3-Dimethylquinolinium Iodide (266)



The title compound was obtained according to **General Procedure A** using 3-methylquinoline (573 mg, 4.0 mmol) to give *salt* **266** (1.10 g, 97%) as a yellow solid.

m.p.: 219-221°C;

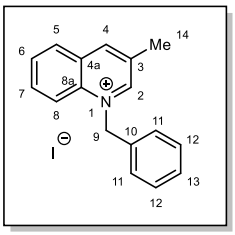
HRMS (ESI): Exact mass calculated for $C_{11}H_{12}N$ [M^+] m/z: 158.0964, found: 158.0965;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H, C^{2}**H**), 9.10 (s, 1H, C^{4}**H**), 8.46 (d, *J* = 8.5 Hz, 1H, C^{8}**H**), 8.36 (d, *J* = 8.0 Hz, 1H, C^{5}**H**), 8.21 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H, C^{7}**H**), 8.02 (ddd, *J* = 8.0, 7, 1.0 Hz, 1H, C^{6}**H**), 4.61 (s, 3H, C^{9}**H**$_3$), 2.64 (s, 3H, C^{10}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 150.8 (**C**^{2}H), 145.2 (**C**^{4}H), 136.3 (**C**^{8a}), 133.9 (**C**^{7}H), 131.6 (**C**^{3}), 129.5 (**C**^{6}H), 129.1 (**C**^{5}H), 128.5 (**C**^{4a}), 118.5 (**C**^{8}H), 44.8 (**C**^{9}H$_3$), 17.5, (**C**^{10}H$_3$);

IR (neat) (cm^{-1}): 2921, 1229, 1042, 1033, 1001, 927, 867, 847, 772, 747.

N-Benzyl-3-methylquinolinium Iodide (267)



The title compound was prepared according to **General Procedure B** using 3-methylquinoline (573 mg, 4.0 mmol) to give *salt* **267** (1.42 g, 98%) as a yellow solid.

m.p.: 196-198°C;

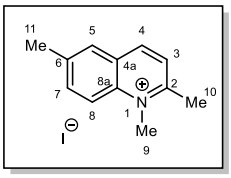
HRMS (ESI): Exact mass calculated for $C_{16}H_{16}N$ [M^+] m/z: 234.12773, found: 234.12798;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 (d, J = 1.9 Hz, 1H, C^2**H**), 9.20 (s, 1H, C^4**H**), 8.43 (d, J = 9.0 Hz, 1H, C^8**H**), 8.38 (dd, J = 8.3, 1.4 Hz, 1H, C^5**H**), 8.12 (ddd, J = 8.8, 7.0, 1.5 Hz, 1H, C^7**H**), 7.97 (ddd, J = 8.0, 7.0, 0.9 Hz, 1H, C^6**H**), 7.43 – 7.32 (m, 5H, C$^{11\text{-}13}$**H**), 6.34 (s, 2H, C^9**H**$_2$), 2.71 (s, 3H, C^{14}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 150.9 (**C**^{2}H), 146.2 (**C**^{4}H), 135.2 (**C**^{8a}), 134.0 (**C**^{7}H), 133.3 (**C**^{10}), 132.0 (**C**^{3}), 129.4 (**C**^{5}H), 129.3 (**C**^{6}H), 129.0 (**C**^{4a}), 128.4 (2xC, Ar-**C**H), 128.1 (Ar-**C**H), 126.6 (2xC, Ar-**C**H), 118.4 (**C**^{8}H), 59.3 (**C**^{9}H$_2$), 17.5 (**C**^{14}H$_3$);

IR (neat) (cm^{-1}): 2936, 2873, 770, 751, 739, 700, 677, 630 cm^{-1}.

N,2,6-Trimethylquinolinium Iodide (269)



The title compound was obtained according to **General Procedure A** using 2,6-dimethylquinoline (629 mg, 4.0 mmol) to give *salt* **269** (1.14 g, 95%) as a green solid.

m.p.: 260-262°C;

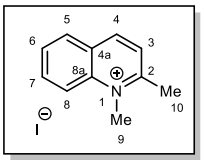
HRMS (ESI): Exact mass calculated for $C_{12}H_{14}N$ [M^+] m/z: 172.1121, found: 172.1121;

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (d, J = 8.5 Hz, 1H, C^4**H**), 8.50 (d, J = 9.0 Hz, 1H, C^8**H**), 8.17 (s, 1H, C^5**H**), 8.08 (m, 2H, C^3**H** + C^7**H**), 4.43 (s, 3H, C^9**H**$_3$), 3.05 (s, 3H, C^{10}**H**$_3$), 2.60 (s, 3H, C^{11}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 160.4 (**C**^{2}), 145.1 (**C**^{4}H), 139.6 (**C**^{6}), 138.1 (**C**^{8a}), 137.3 (**C**^{7}H), 129.3 (**C**^{5}H), 128.3 (**C**^{4a}), 125.5 (**C**^{3}H), 119.2 (**C**^{8}H), 40.0 (**C**^{9}H$_3$), 23.2 (**C**^{10}H$_3$), 21.0 (**C**^{11}H$_3$);

IR (neat) (cm^{-1}): 2938, 1306, 1518, 1356, 1034, 829, 818.

N,2-Dimethylquinolinium Iodide (270)



A mixture of the 2-methylquinoline (573 mg, 4.0 mmol, 1.0 eq.) and iodomethane (1.25 mL, 20.0 mmol, 5.0 equiv.) in 1,4-dioxane (10.0 mL) was heated at 80°C in a sealed flask for 4 hours. The mixture was allowed to cool to room temperature, the solid was collected by filtration, washed with diethyl ether and dried under vacuum for one hour to give *salt* **270** (461 mg, 40%) as a green solid.

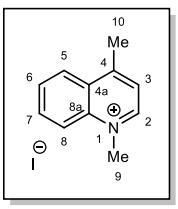
m.p.: 188-190°C;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (d, *J* = 8.5 Hz, 1H, C^{4}**H**), 8.60 (d, *J* = 8.9 Hz, 1H, C^{8}**H**), 8.41 (dd, *J* = 8.1, 1.5 Hz, 1H, C^{5}**H**), 8.23 (ddd, *J* = 8.9, 7.0, 1.6 Hz, 1H, C^{7}**H**), 8.13 (d, *J* = 8.6 Hz, 1H, C^{3}**H**), 8.00 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H, C^{6}**H**), 4.45 (s, 3H, C^{9}**H**$_3$), 3.09 (s, 3H, C^{10}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6 (**C**^{2}H), 145.8 (**C**^{4}H), 139.6 (**C**^{8a}), 135.5 (**C**^{7}H), 130.7 (**C**^{5}H), 129.4 (**C**^{6}H), 128.2 (**C**^{4a}), 125.6 (**C**^{3}H), 119.4 (**C**^{8}H), 40.4 (**C**^{9}H$_3$), 23.6 (**C**^{10}H$_3$).

Spectroscopic data was consistent with that reported in the literature.[198]

N,4-Dimethylquinolinium Iodide (271)



The title compound was obtained according to **General Procedure A** using 4-methylquinoline (573 mg, 4.0 mmol) to give *salt* **271** (1.12 g, 98%) as a yellow solid.

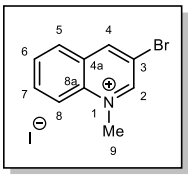
m.p.: 173–175°C;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (d, J = 6.0 Hz, 1H, C^{2}**H**), 8.54 (dd, J = 8.5, 1.3 Hz, 1H, C^{5}**H**), 8.49 (d, J = 8.8 Hz, 1H, C^{8}**H**), 8.27 (ddd, J = 8.8, 7.0, 1.4 Hz, 1H, C^{7}**H**), 8.09 – 8.05 (m, 2H, C^{3}**H** + C^{6}**H**), 4.58 (s, 3H, C^{9}**H**$_3$), 3.01 (s, 3H, C^{10}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 158.8 (**C**^{4}), 149.6 (**C**^{2}H), 138.3 (**C**^{8a}), 135.5 (**C**^{7}H), 130.3 (**C**^{6}H), 129.1 (**C**^{4a}), 127.4 (**C**^{5}H), 123.1 (**C**^{3}H), 120.2 (**C**^{8}H), 45.7 (**C**^{9}H$_3$), 20.3 (**C**^{10}H$_3$).

Spectroscopic data was consistent with that reported in the literature.[199]

3-Bromo-*N*-methylquinolinium Iodide (272)



The title compound was obtained according to **General Procedure A** using 3-bromoquinoline (832 mg, 4.0 mmol) to give *salt* **272** (1.37 g, 98%) as a yellow solid.

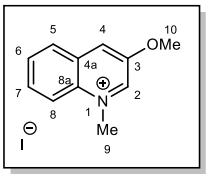
m.p.: 294-296°C;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (d, J = 2.0 Hz, 1H, C^{2}**H**), 9.65 (d, J = 2.0 Hz, 1H, C^{4}**H**), 8.51 (d, J = 8.9 Hz, 1H, C^{8}**H**), 8.40 (dd, J = 8.3, 1.4 Hz, 1H, C^{5}**H**), 8.31 (ddd, J = 8.8, 7.0, 1.5 Hz, 1H, C^{7}**H**), 8.10 (ddd, J = 8.0, 7.0, 0.9 Hz, 1H, C^{6}**H**), 4.63 (s, 3H, C^{9}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 152.0 (**C**^{2}H), 148.7 (**C**^{4}H), 137.8 (**C**^{8a}), 136.2 (**C**^{7}H), 131.4 (**C**^{6}H), 130.2 (**C**^{5}H), 127.1 (**C**^{3}), 119.9 (**C**^{8}H), 115.1 (**C**^{4a}), 46.0 (**C**^{9}H$_3$).

Spectroscopic data was consistent with that reported in the literature.[84]

3-methoxy-*N*-methylquinolinium Iodide (273)



The title compound was obtained according to **General Procedure A** using 3-methoxyquinoline (637 mg, 4.0 mmol) to give *salt* **273** (1.14 g, 95%) as a yellow solid.

m.p.: 210-212°C;

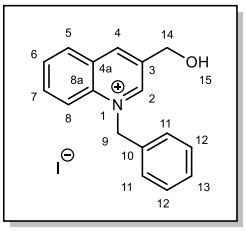
HRMS (ESI): Exact mass calculated for $C_{11}H_{12}ON$ [M^+] m/z: 174.0913, found: 174.0915;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (d, *J* = 2.7 Hz, 1H, C^2**H**), 8.83 (d, *J* = 2.7 Hz, 1H, C^4**H**), 8.41 (d, *J* = 8.9 Hz, 1H, C^8**H**), 8.33 (dd, *J* = 8.1, 1.4 Hz, 1H, C^5**H**), 8.07 (ddd, *J* = 8.7, 7.0, 1.4 Hz, 1H, C^7**H**), 7.98 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H, C^6**H**), 4.62 (s, 3H, C^9**H**$_3$), 4.10 (s, 3H, C^{10}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 152.0 (**C**^{3}), 143.2 (**C**^{2}H), 133.5 (**C**^{8a}), 131.6 (**C**^{7}H), 129.7 (**C**^{6}H), 129.4 (**C**^{5}H), 128.5 (**C**^{4a}), 124.2 (**C**^{4}H), 118.5 (**C**^{8}H), 57.0 (**C**^{10}H$_3$), 45.0 (**C**^{9}H$_3$);

IR (neat) (cm^{-1}): 3032, 2986, 1357, 1236, 1207, 777, 651.

N-Benzyl-3-(hydroxymethyl)quinolinium Iodide (274)



A solution of quinoline-3-carbaldehyde (825 mg, 5.3 mmol, 1.0 equiv.) in 20 mL of methanol was cooled to 0°C in an ice bath. To the reaction was added $NaBH_4$ (400 mg, 10.5 mmol, 2.0 equiv.) portion wise at 0°C. The reaction was left stirring at room temperature for 2 hours, then quenched with water (50 mL) and extracted with ethyl acetate (3x 25 mL). The combined organics were dried over Na_2SO_4 and concentrated under vacuum to give the crude alcohol which was subjected to **General Procedure B** to give *salt* **274** (1,47g, 74% over 2 steps**)** as a pale-yellow solid.

m.p.: 75-77°C;

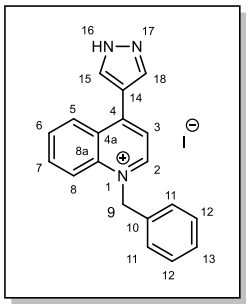
HRMS (ESI): Exact mass calculated for $C_{17}H_{16}ON$ [M^+] m/z: 250.12264, found: 250.12276;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (d, *J* = 1.9 Hz, 1H, C^2**H**), 9.28 (s, 1H, C^4**H**), 8.55 – 8.42 (m, 2H, C^5**H** + C^8**H**), 8.16 (ddd, *J* = 8.8, 7.0, 1.5 Hz, 1H, C^7**H**), 7.99 (ddd, *J* = 8.1, 7.1, 0.9 Hz, 1H, C^6**H**), 7.42 – 7.32 (m, 5H, C$^{11\text{-}13}$**H**), 6.40 (s, 2H, C^9**H**$_2$), 5.98 (t, *J* = 5.4 Hz, 1H, O^{15}**H**), 4.94 (dd, *J* = 5.5, 1.1 Hz, 2H, C^{14}**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 149.9 (**C**^{2}H), 144.8 (**C**^{4}H), 137.7 (Ar-**C**), 137.1 (Ar-**C**), 135.6, (**C**^{7}H) 134.4(Ar-**C**), 131.0 (**C**^{5}H), 130.5 (**C**^{6}H), 130.1 (Ar-**C**), 129.6 (2xC, Ar-**C**H), 129.2 (Ar-**C**H), 127.7 (2xC, Ar-**C**H), 119.7 (**C**^{8}H), 60.5 (**C**^{9}H$_2$), 60.2 (**C**^{14}H$_2$);

IR (neat) (cm^{-1}): 3336, 1630, 1589, 1527, 1455, 1234, 1064, 1043, 1002, 775, 753, 703, 678.

N-Benzyl-4-(1H-pyrazol-4-yl)quinolinium Iodide (276)



The title compound was prepared according to **General Procedure B** using 4-(1H-pyrazol-4-yl)quinoline (976 mg, 5.0 mmol) to give *salt* **276** (1.98 g, 96%) as a yellow solid.

m.p.: 124-126°C;

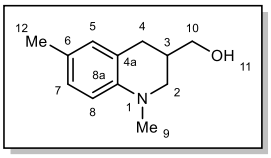
HRMS (ESI): Exact mass calculated for $C_{19}H_{16}N_3$ [M^+] m/z: 286.13387, found: 286.13388;

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.90 (br s, 1H, N^{16}**H**) 9.61 (d, *J* = 6.4 Hz, 1H, C^2**H**), 8.74 (dd, *J* = 8.6, 1.4 Hz, 1H, C^5**H**), 8.61 (br s, 2H, C^{15}**H** + C^{18}**H**), 8.45 (d, *J* = 8.9 Hz, 1H, C^8**H**), 8.32 (d, *J* = 6.3 Hz, 1H, C^3**H**), 8.19 (ddd, *J* = 8.7, 7.0, 1.4 Hz, 1H, C^7**H**), 7.99 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H, C^6**H**), 7.42 – 7.31 (m, 5H, C$^{11\text{-}13}$**H**), 6.30 (s, 2H, C^9**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 150.9 (Ar-**C**), 148.5 (**C**^{2}H), 138.1 (Ar-**C**), 135.2 (**C**^{7}H), 134.3(Ar-**C**), 129.9 (**C**^{6}H), 129.1 (2xC, Ar-**C**H), 128.6 (**C**^{5}H), 128.6, 128.0, 127.1 (2xC, Ar-**C**H), 126.4 (Ar-**C**H), 120.0 (**C**^{3}H), 119.7 (**C**^{8}H), 116.0 (Ar-**C**), 59.2 (**C**^{9}H$_2$); The pyrazole **C**^{15}H and **C**^{18}H are in rapid exchange, making the assignment of the pyrazole atoms difficult;

IR (neat) (cm^{-1}): 3139, 1704, 1603, 1571, 1546, 1532, 1367, 894, 767, 724, 678.

(*N*,6-Dimethyl-3-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline (278)



The title compound was prepared according to **General Procedure C** using *quinolinium* **254** (143 mg, 0.5 mmol). The crude material was purified by FCC (95:5 CH_2Cl_2:acetone) to give *amine* **278** (77 mg, 81%) as a pale-yellow oil.

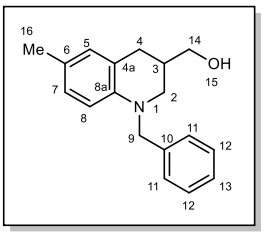
HRMS (ESI): Exact mass calculated for $C_{12}H_{18}NO$ $[M+H]^+$ m/z: 192.1383, found: 192.1384;

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, *J* = 8.2 Hz, 1H, C^7**H**), 6.84 (s, 1H, C^5**H**), 6.58 (d, *J* = 8.2 Hz, 1H, C^8**H**), 3.69 (dd, *J* = 10.7, 5.8 Hz, 1H, C^{10}**H**$_2$), 3.60 (dd, *J* = 10.7, 7.4 Hz, 1H, C^{10}**H**$_2$), 3.29 (ddd, *J* = 11.0, 3.8, 1.5 Hz, 1H, C^2**H**$_2$), 2.99 (dd, *J* = 11.0, 8.1 Hz, 1H, C^2**H**$_2$), 2.88 (s, 3H, C^9**H**$_3$), 2.87 – 2.80 (m, 1H, C^4**H**$_2$), 2.53 (dd, *J* = 16.1, 8.7 Hz, 1H, C^4**H**$_2$), 2.30 – 2.22 (m, 1H, C^3**H**), 2.25 (s, 3H, C^{12}**H**$_3$), 2.09 (bs, 1H, O^{11}**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (**C**^{8a}), 130.3 (**C**^{5}H), 127.9 (**C**^{7}H), 126.4 (**C**^{6}), 122.3 (**C**^{4a}), 111.9 (**C**^{8}H), 65.9 (**C**^{10}H$_2$), 54.1 (**C**^{4}H$_2$), 40.0 (**C**^{9}H$_3$), 35.8 (**C**^{3}H), 30.6 (**C**^{2}H$_2$), 20.7 (**C**^{12}H$_3$);

IR (neat) (cm^{-1}): 3330, 2916, 2860, 1618, 1511, 1462, 1327, 1290, 1208, 1072, 1029, 800, 695.

(*N*-Benzyl-3-(hydroxymethyl)-6-methyl-1,2,3,4-tetrahydroquinoline (279)



The title compound was prepared according to **General Procedure D** using *quinolinium* **255** (181 mg, 0.5 mmol). The crude material was purified by FCC (98:2 CH_2Cl_2: acetone) to give *amine* **279** (99 mg, 74%) as a pale-yellow solid.

m.p.: 68-70°C;

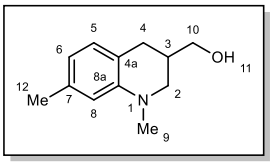
HRMS (ESI): exact mass calculated for $C_{18}H_{22}NO$ $[M+H]^+$ m/z: 268.16959, found: 268.16945;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H, $C^{11\text{-}13}$**H**), 6.93 – 6.87 (m, 2H, C^{5}**H** + C^{7}**H**), 6.56 (d, *J* = 8.2 Hz, 1H, C^{8}**H**), 4.57 – 4.47 (m, 2H, C^{9}**H**$_2$), 3.72 (dd, *J* = 10.7, 5.9 Hz, 1H, C^{14}**H**$_2$), 3.63 (dd, *J* = 10.7, 7.4 Hz, 1H, C^{14}**H**$_2$), 3.48 (ddd, *J* = 11.3, 3.8, 1.7 Hz, 1H, C^{2}**H**$_2$), 3.21 (dd, *J* = 11.3, 8.4 Hz, 1H, C^{2}**H**$_2$), 2.92 (dd, *J* = 16.1, 5.2 Hz, 1H, C^{4}**H**$_2$), 2.64 (dd, *J* = 16.1, 8.9 Hz, 1H, C^{4}**H**$_2$), 2.36 – 2.27 (m, 1H, C^{3}**H**), 2.30 (s, 3H, C^{16}**H**$_3$), 2.16 (bs, 1H, O^{15}**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.9 (Ar-**C**), 138.8 (Ar-**C**), 129.9 (Ar-**C**H), 128.3 (2 x C, Ar-C**H**), 127.4 (Ar-**C**H), 126.5 (Ar-**C**H), 126.4 (2 x C, Ar-**C**H), 125.1 (Ar-**C**), 120.7 (Ar-**C**), 111.0 (**C**^{8}H), 64.8 (**C**^{14}H$_2$), 55.1 (**C**^{9}H$_2$), 51.7 (**C**^{2}H$_2$), 34.9 (**C**^{3}H), 30.3 (**C**^{4}H$_2$), 20.0 (**C**^{16}H$_3$);

IR (neat) (cm^{-1}): 3334, 3026, 2916, 2857, 2360, 1618, 1510, 1451, 1354, 1245, 1028, 799, 730, 695, 650.

(*N*,7-Dimethyl-3-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline (280)



The title compound was prepared according to **General Procedure C** using *quinolinium* **256** (143 mg, 0.5 mmol). The crude material was purified by FCC (95:5 CH_2Cl_2:acetone) to give *amine* **280** (78 mg, 82%) as a pale-yellow oil.

m.p.: 57-59°C;

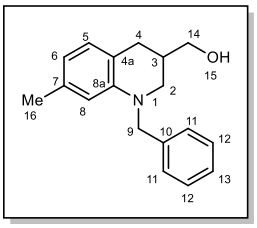
HRMS (ESI): Exact mass calculated for $C_{12}H_{18}NO$ $[M+H]^+$ m/z: 192.1383, found: 192.1383;

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, *J* = 7.4 Hz, 1H, C^{5}**H**), 6.53 – 6.48 (m, 2H, C^{6}**H** + C^{8}**H**), 3.68 (dd, *J* = 10.7, 5.8 Hz, 1H, C^{10}**H**$_2$), 3.59 (dd, *J* = 10.7, 7.5 Hz, 1H, C^{10}**H**$_2$), 3.33 (ddd, *J* = 11.2, 3.8, 1.6 Hz, 1H, C^{2}**H**$_2$), 3.03 (dd, *J* = 11.1, 8.3 Hz, 1H, C^{2}**H**$_2$), 2.92 (s, 3H, C^{9}**H**$_3$), 2.84 (dd, *J* = 15.9, 5.4 Hz, 1H, C^{4}**H**$_2$), 2.52 (dd, *J* = 15.9, 9.0 Hz, 1H, C^{4}**H**$_2$), 2.41 (bs, 1H, O^{11}**H**), 2.34 (s, 3H, C^{12}**H**$_3$), 2.30 – 2.19 (m, 1H, C^{3}**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8 (**C**^{8a}), 137.0 (**C**^{7}), 129.4 (**C**^{5}H), 119.1 (**C**^{4a}), 117.9 (**C**^{6}H), 112.3 (**C**^{8}H), 65.7 (**C**^{10}H_2), 54.0 (**C**^{2}H_2), 39.7 (**C**^{9}H_3), 35.7 (**C**^{3}H), 30.3 (**C**^{2}H_2), 22.0 (**C**^{12}H_3);

IR (neat) (cm^{-1}): 3334, 3022, 2915, 1612, 1574, 1482, 1291, 1170, 1089, 1070, 838, 795.

(*N*-Benzyl-3-(hydroxymethyl)-7-methyl-1,2,3,4-tetrahydroquinoline (281)



The title compound was prepared according to **General Procedure D** using *quinolinium* **257** (181 mg, 0.5 mmol). The crude material was purified by FCC (98:2 CH_2Cl_2:acetone) to give *amine* **281** (95 mg, 71%) as a pale-yellow solid.

m.p.: 79-81°C;

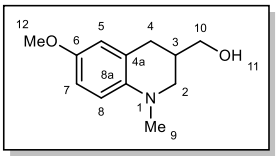
HRMS (ESI): exact mass calculated for $C_{18}H_{22}NO$ $[M+H]^+$ m/z: 268.16959, found: 268.16944;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 5H, C$^{11\text{-}13}$**H**), 6.93 (d, *J* = 7.4 Hz, 1H, C^{5}**H**), 6.50 – 6.42 (m, 2H, C^{6}**H** + C^{8}**H**), 3.70 (dd, *J* = 10.7, 6.0 Hz, 1H, C^{14}**H**$_2$), 3.61 (dd, *J* = 10.7, 7.4 Hz, 1H, C^{16}**H**$_2$), 3.44 (ddd, *J* = 11.4, 3.9, 1.7 Hz, 1H, C^{2}**H**$_2$), 3.17 (dd, *J* = 11.4, 8.3 Hz, 1H, C^{2}**H**$_2$), 2.88 (dd, *J* = 15.7, 4.9 Hz, 1H, C^{4}**H**$_2$), 2.59 (dd, *J* = 15.7, 9.0 Hz, 1H, C^{4}**H**$_2$), 2.32 – 2.24 (m, 1H, C^{3}**H**), 2.23 (s, 3H, C^{16}**H**$_3$), 1.63 (bs, 1H, O^{15}**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4 (Ar-**C**), 139.1 (Ar-**C**), 137.0 (**C**^{7}), 129.4 (**C**^{5}H), 128.7 (2 x C, Ar-**C**H), 126.9 (Ar-**C**H), 126.8 (2 x C, Ar-**C**H), 118.0 (Ar-**C**), 117.2 (**C**^{6}H), 111.7 (**C**^{8}H), 65.2 (**C**^{14}H_2), 55.2 (**C**^{9}H_2), 51.8 (**C**^{2}H_2), 35.3 (**C**^{3}H), 30.4 (**C**^{4}H_2), 21.7 (**C**^{16}H_3);

IR (neat) (cm^{-1}): 3385, 2918, 1977, 1572, 1509. 1451, 1427, 1205, 1184, 1018.

(3-(Hydroxymethyl)-6-methoxy-*N*-methyl-1,2,3,4-tetrahydroquinoline (282)



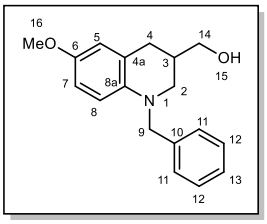
The title compound was prepared according to **General Procedure C** using *quinolinium* **258** (151 mg, 0.5 mmol). The crude material was purified by FCC (85:15 CH_2Cl_2:acetone) to give *amine* **282** (86 mg, 83%) as a pale-yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (dd, *J* = 8.8, 3.0 Hz, 1H, C^7**H**), 6.63 – 6.58 (m, 2H, C^5**H** + C^8**H**), 3.74 (s, 3H, C^{12}**H**$_3$), 3.67 (dd, *J* = 10.7, 5.8 Hz, 1H, C^{10}**H**$_2$), 3.59 (dd, *J* = 10.6, 7.3 Hz, 1H, C^{10}**H**$_2$), 3.23 (ddd, *J* = 11.0, 3.8, 1.5 Hz, 1H, C^2**H**$_2$), 2.93 (dd, *J* = 11.0, 8.1 Hz, 1H, C^2**H**$_2$), 2.87 – 2.81 (m, 1H, C^4**H**$_2$), 2.84 (s, 3H, C^9**H**$_3$), 2.54 (dd, *J* = 16.3, 8.7 Hz, 1H, C^4**H**$_2$), 2.29 – 2.18 (m, 2H, C^3**H** + O^{11}**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3 (**C**^{6}), 141.1 (**C**^{8a}), 123.4 (**C**^{4a}), 115.0 (**C**^{5}H), 112.3 (**C**^{8}H), 112.1 (**C**^{7}H), 65.3 (**C**^{10}H$_2$), 55.5 (**C**^{12}H$_3$), 53.8 (**C**^{4}H$_2$), 39.8 (**C**^{9}H$_3$), 35.2 (**C**^{3}H), 30.2 (**C**^{2}H$_2$).

Spectroscopic data was consistent with that reported in the literature.[200]

***N*-Benzyl-3-(hydroxymethyl)-6-methoxy-1,2,3,4-tetrahydroquinoline (283)**



The title compound was prepared according to **General Procedure D** using *quinolinium* **259** (189 mg, 0.5 mmol). The crude material was purified by FCC (97:3 CH_2Cl_2:acetone) to give *amine* **283** (113 mg, 80%) as a pale-yellow solid.

m.p.: 92-94°C;

HRMS (ESI): exact mass calculated for $C_{18}H_{22}NO_2$ $[M+H]^+$ m/z: 284.1645, found: 284.1641;

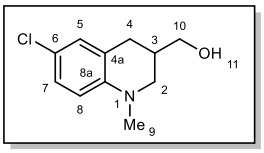
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.22 (m, 5H, C$^{11\text{-}13}$**H**), 6.70 – 6.59 (m, 2H, C^5**H** + C^7**H**), 6.52 (d, *J* = 8.8 Hz, 1H, C^8**H**), 4.50 – 4.39 (m, 2H, C^9**H**$_2$), 3.75 (s, 3H, C^{16}**H**$_3$), 3.69 (dd, *J* = 10.7, 6.0 Hz, 1H, C^{14}**H**$_2$), 3.61 (dd, *J* = 10.6, 7.3 Hz, 1H, C^{14}**H**$_2$), 3.41 (ddd, *J* = 11.2, 3.7, 1.6

Hz, 1H, $C^2\mathbf{H}_2$), 3.13 (dd, *J* = 11.2, 8.3 Hz, 1H, $C^2\mathbf{H}_2$), 2.90 (dd, *J* = 16.1, 5.1 Hz, 1H, $C^4\mathbf{H}_2$), 2.62 (dd, *J* = 16.1, 8.8 Hz, 1H, $C^4\mathbf{H}_2$), 2.33 – 2.24 (m, 1H, $C^3\mathbf{H}$), 2.00 (bs, 1H, $O^{15}\mathbf{H}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4 (Ar-**C**), 140.4 (Ar-**C**), 139.6 (Ar-**C**), 129.0 (Ar-**C**), 127.2 (2 x C, Ar-**C**H), 127.2 (Ar-**C**H), 122.9 (2 x C, Ar-**C**H), 115.9 ($\mathbf{C}^5$H), 112.8 ($\mathbf{C}^7$H), 112.7 ($\mathbf{C}^8$H), 65.5 ($\mathbf{C}^{14}H_2$), 56.3 ($\mathbf{C}^{16}H_3$), 56.1 ($\mathbf{C}^9H_2$), 52.4 ($\mathbf{C}^4H_2$), 35.7 ($\mathbf{C}^3$H), 31.2 ($\mathbf{C}^2H_2$);

IR (neat) (cm^{-1}): 3375, 3028, 2915, 2830, 1506, 1451, 1239, 1049, 1027, 796, 731, 695.

(6-Chloro-3-(hydroxymethyl)-*N*-methyl-1,2,3,4-tetrahydroquinoline (284)



The title compound was prepared according to **General Procedure C** using *quinolinium* **260** (153 mg, 0.5 mmol). The crude material was purified by FCC (95:5 CH_2Cl_2:acetone) to give *amine* **284** (85 mg, 80%) as a pale-yellow oil.

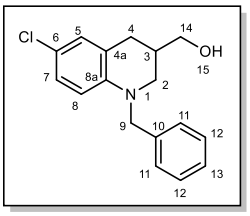
HRMS (ESI): Exact mass calculated for $C_{11}H_{15}ClNO$ $[M+H]^+$ m/z: 212.0837, found: 212.0839

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (dd, *J* = 8.7, 2.6 Hz, 1H, $C^7\mathbf{H}$), 6.94 – 6.91 (m, 1H, $C^5\mathbf{H}$), 6.49 (d, *J* = 8.8 Hz, 1H, $C^8\mathbf{H}$), 3.64 (dd, *J* = 10.7, 5.9 Hz, 1H, $C^{10}\mathbf{H}_2$), 3.58 – 3.51 (m, 1H, $C^{10}\mathbf{H}_2$), 3.29 (ddd, *J* = 11.3, 3.9, 1.6 Hz, 1H, $C^2\mathbf{H}_2$), 3.01 (dd, *J* = 11.2, 8.1 Hz, 1H, $C^2\mathbf{H}_2$), 2.86 (s, 3H, $C^9\mathbf{H}_3$), 2.78 (dd, *J* = 16.1, 5.4 Hz, 1H, $C^4\mathbf{H}_2$), 2.49 (dd, *J* = 16.1, 8.8 Hz, 1H, $C^4\mathbf{H}_2$), 2.24 – 2.15 (m, 2H, $C^3\mathbf{H}$ + $O^{11}\mathbf{H}$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 ($\mathbf{C}^{8a}$), 128.4 ($\mathbf{C}^5$H), 126.5 ($\mathbf{C}^7$H), 123.0 ($\mathbf{C}^{4a}$), 120.7 ($\mathbf{C}^6$H), 111.8 ($\mathbf{C}^8$H), 64.8 ($\mathbf{C}^{10}H_2$), 53.0 ($\mathbf{C}^4H_2$), 39.0 ($\mathbf{C}^9H_3$), 34.7 ($\mathbf{C}^3$H), 29.9 ($\mathbf{C}^2H_2$);

IR (neat) (cm^{-1}): 3329, 2919, 2826, 1597, 1501, 1461, 1434, 1327, 1287, 1219, 1111, 1026, 856, 798, 622.

***N*-Benzyl-6-chloro-3-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline (285)**



The title compound was prepared according to **General Procedure D** using *quinolinium* **261** (191 mg, 0.5 mmol). The crude material was purified by FCC (92:2 CH_2Cl_2:acetone) to give *amine* **285** (121 mg, 84%) as a pale-yellow solid.

m.p.: 74-75°C;

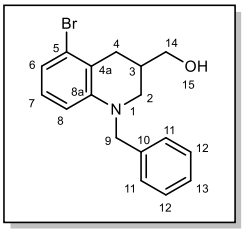
HRMS (ESI): exact mass calculated for $C_{17}H_{19}ClNO$ $[M+H]^+$ m/z: 288.1150, found: 288.1149;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 5H, $C^{11\text{-}13}$**H**), 7.00 – 6.92 (m, 2H, C^5**H** + C^7**H**), 6.46 (d, *J* = 8.8 Hz, 1H, C^8**H**), 4.53 – 4.43 (m, 2H, C^9**H**$_2$), 3.68 (dd, *J* = 10.7, 5.9 Hz, 1H, C^{14}**H**$_2$), 3.59 (dd, *J* = 10.7, 7.4 Hz, 1H, C^{14}**H**$_2$), 3.46 (ddd, *J* = 11.5, 3.9, 1.7 Hz, 1H, C^2**H**$_2$), 3.21 (dd, *J* = 11.5, 8.3 Hz, 1H, C^2**H**$_2$), 2.85 (dd, *J* = 16.1, 5.0 Hz, 1H, C^4**H**$_2$), 2.58 (dd, *J* = 16.1, 9.0 Hz, 1H, C^4**H**$_2$), 2.31 – 2.21 (m, 1H, C^3**H**), 2.02 (s, 1H, O^{15}**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (Ar-**C**), 138.7 (Ar-**C**), 129.3 (Ar-**C**H), 129.1 (2 x C, Ar-**C**H), 127.4 (Ar-**C**H), 127.3 (Ar-**C**H), 126.9 (2 x C, Ar-**C**H), 122.8 (Ar-**C**), 120.9 (Ar-**C**), 112.5 (**C**^{8}H), 65.2 (**C**^{14}H$_2$), 55.6 (**C**^{9}H$_2$), 52.2 (**C**^{4}H$_2$), 35.2 (**C**^{3}H), 30.8 (**C**^{2}H$_2$);

IR (neat) (cm^{-1}): 3335, 3029, 2920, 2839, 1499, 1468, 1245, 1028, 797, 727, 696.

***N*-Benzyl-3-(hydroxymethyl)-5-bromo-1,2,3,4-tetrahydroquinoline (286)**



The title compound was prepared according to **General Procedure D** using *quinolinium* **262** (212 mg, 0.5 mmol). The crude material was purified by FCC (97:3 CH_2Cl_2:acetone) to give *amine* **286** (132 mg, 80%) as a pale-yellow solid.

m.p.: 74-76°C;

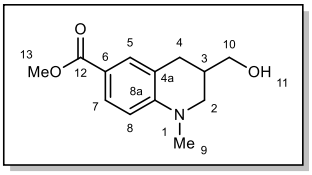
HRMS (ESI): exact mass calculated for $C_{17}H_{19}NOBr$ $[M+H]^+$ m/z: 332.06500 found: 332.06436;

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.22 (m, 5H, $C^{11\text{-}13}$**H**), 6.89 – 6.79 (m, 2H, C^{6}**H** + C^{7}**H**), 6.49 (dd, *J* = 8.2, 1.1 Hz, 1H, C^{8}**H**), 4.56 – 4.44 (m, 2H, C^{9}**H**$_2$), 3.75 (dd, *J* = 10.7, 5.5 Hz, 1H, C^{14}**H**$_2$), 3.61 (dd, *J* = 10.7, 7.7 Hz, 1H, C^{14}**H**$_2$), 3.47 (ddd, *J* = 11.5, 3.7, 1.7 Hz, 1H, C^{2}**H**$_2$), 3.22 (dd, *J* = 11.5, 8.6 Hz, 1H, C^{2}**H**$_2$), 3.02 (ddd, *J* = 16.7, 5.4, 1.7 Hz, 1H, C^{4}**H**$_2$), 2.54 (dd, *J* = 16.7, 9.0 Hz, 1H, C^{4}**H**$_2$), 2.33 – 2.25 (m, 1H, C^{3}**H**), 1.59 (bs, 1H, O^{15}**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7 (Ar-**C**), 138.0 (Ar-**C**), 128.5 (2 x C, Ar-**C**H) , 127.6 (**C**^{7}H), 127.6 (Ar-**C**H), 126.8 (2 x C Ar-**C**H), 126.3 (**C**^{6}H), 125.6 (**C**^{5}), 120.0 (2 x C, **C**^{7}H + Ar-**C**), 110.1 (**C**^{8}H), 64.6 (**C**^{14}H$_2$), 55.4 (**C**^{9}H$_2$), 51.5 (**C**^{2}H$_2$), 34.7 (**C**^{3}H), 31.0 (**C**^{4}H$_2$);

IR (neat) (cm^{-1}): 3334, 2916, 1586, 1558, 1462, 1355, 1245, 1187, 1028, 827.

3-(Hydroxymethyl)-6-(methoxycarbonyl)-*N*-methyl-1,2,3,4-tetrahydroquinoline (287)



The title compound was prepared according to **General Procedure D** using *quinolinium* **263** (165 mg, 0.5 mmol). The crude material was purified by FCC (90:10 CH_2Cl_2:acetone) to give *amine* **287** (98 mg, 83%) as a pale-yellow oil.

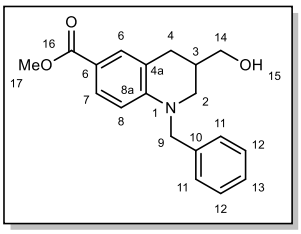
HRMS (ESI): Exact mass calculated for $C_{13}H_{18}NO_3$ $[M+H]^+$ m/z: 236.1281, found: 236.1281;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.7, 2.2 Hz, 1H, C^{7}**H**), 7.61 (dd, *J* = 2.2, 1.1 Hz, 1H, C^{5}**H**), 6.49 (d, *J* = 8.7 Hz, 1H, C^{8}**H**), 3.82 (s, 3H, C^{13}**H**$_3$), 3.69 – 3.63 (m, 1H, C^{10}**H**$_2$), 3.56 – 3.50 (m, 1H, C^{10}**H**$_2$), 3.41 (ddd, *J* = 11.6, 4.2, 1.8 Hz, 1H, C^{2}**H**$_2$), 3.16 (dd, *J* = 11.6, 8.5 Hz, 1H, C^{2}**H**$_2$), 2.95 (s, 3H, C^{9}**H**$_3$), 2.80 (dd, *J* = 15.7, 4.9 Hz, 1H, C^{4}**H**$_2$), 2.51 (dd, *J* = 15.7, 9.6 Hz, 1H, C^{4}**H**$_2$), 2.29 (bs, 1H, O^{11}**H**), 2.24 – 2.14 (m, 1H, C^{3}**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (**C**^{12}), 150.1 (**C**^{8a}), 130.9 (**C**^{5}H), 130.1 (**C**^{7}H), 120.6 (**C**^{4a}), 117.0 (**C**^{6}), 109.6 (**C**^{8}H), 65.1 (**C**^{10}H$_2$), 53.6 (**C**^{4}H$_2$), 51.9 (**C**^{13}H$_3$), 39.2 (**C**^{9}H$_3$), 35.0 (**C**^{3}H), 30.6 (**C**^{2}H$_2$);

IR (neat) (cm^{-1}): 3430, 2920, 2838, 1680, 1604, 1522, 1439, 1283, 1209, 1133, 1113, 1029, 918, 768.

Methyl *N*-benzyl-3-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline-6-carboxylate (288)



The title compound was prepared according to **General Procedure E** (stirred for 2 days) using *quinolinium* **264** (203 mg, 0.5 mmol). The crude material was purified by FCC (95:5 CH_2Cl_2:acetone) to give *amine* **288** (65 mg, 42%) as an orange solid .

m.p.: 94-96°C;

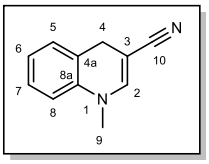
HRMS (ESI): exact mass calculated for $C_{19}H_{22}NO_3$ $[M+H]^+$ m/z: 312.15942, found: 312.15938;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.65 (d, *J* = 7.8 Hz, 2H, C^6**H** + C^7**H**), 7.37 – 7.14 (m, 5H, $C^{11\text{-}13}$**H**), 6.50 (d, *J* = 9.0 Hz, 1H, C^8**H**), 4.56 (d, *J* = 2.4 Hz, 2H, C^9**H**$_2$), 3.82 (s, 3H, C^{17}**H**$_3$), 3.71 (dd, *J* = 10.7, 5.7 Hz, 1H, C^{14}**H**$_2$), 3.63 – 3.47 (m, 2H, C^{14}**H**$_2$ + C^2**H**$_2$), 3.29 (dd, *J* = 11.7, 8.5 Hz, 1H, C^2**H**$_2$), 2.89 (ddd, *J* = 15.8, 4.6, 1.7 Hz, 1H, C^4**H**$_2$), 2.61 (dd, *J* = 15.6, 9.3 Hz, 1H, C^4**H**$_2$), 2.27 (qd, *J* = 8.6, 4.1 Hz, 1H, C^3**H**), 1.76 (bs, 1H, O^{17}**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6 (**C**^{16}), 149.1 (Ar-**C**), 137.7 (Ar-**C**), 131.1 (Ar-**C**H), 129.8 (Ar-**C**H), 128.9 (2 x C, Ar-**C**H), 127.3 (Ar-**C**H), 126.5 (2 x C, Ar-**C**H), 120.0 (Ar-**C**), 117.1 (Ar-**C**), 109.9 (Ar-**C**H), 64.8 (**C**^{14}H$_2$), 54.9 (**C**^{9}H$_2$), 52.0 (**C**^{2}H$_2$), 51.6 (d, *J* = 3.4 Hz, **C**^{17}H$_3$), 34.7 (**C**^{3}H), 30.5 (**C**^{4}H$_2$);

IR (neat) (cm^{-1}): 3390, 2921, 1702, 1608, 1523, 1441, 1298, 1269, 1238, 1191, 1136, 1074, 1012, 766, 740, 726, 693.

1-Methyl-1,4-dihydroquinoline-3-carbonitrile (289)



The title compound was prepared according to **General Procedure C** using 3-cyano-1-methylquinolinium iodide (148 mg, 0.5 mmol). The crude material was purified by FCC (98:2 CH_2Cl_2: acetone) to give compound **289** (55 mg, 64%) as a pale-yellow solid. The double bond assignment was done using NOESY.

m.p.: 89-91°C;

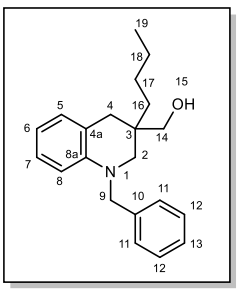
HRMS (ESI): Exact mass calculated for $C_{11}H_{11}N_2$ $[M+H]^+$: 171.09167, found: 171.09164;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.14 (m, 1H, Ar-C**H**), 7.01 – 6.95 (m, 2H, Ar-C**H**), 6.76 – 6.68 (m, 2H, Ar-C**H** + C^2**H**), 3.74 (s, 2H, C^4**H**$_2$), 3.19 (s, 3H, C^9**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.2 (Ar-**C**H), 145.2(Ar-**C**), 138.4(Ar-**C**), 129.4 (Ar-**C**H), 127.9 (Ar-**C**H), 123.8 (Ar-**C**H), 121.4 (Ar-**C**), 120.4 (Ar-**C**), 112.9 (Ar-**C**H), 39.0 (**C**^{9}H$_3$), 27.5 (**C**^{4}H$_2$);

IR (neat) (cm^{-1}): 3065, 2917, 2848, 2191, 1683, 1645, 1602, 1575, 1521, 1494, 1483, 1104, 754, 734, 692.

***N*-Benzyl-3-*n*-butyl-3-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline (302)**



The title compound was prepared according to **General Procedure E** using *quinolinium* **297** (202 mg, 0.5 mmol). The crude material was purified by FCC (99:1 CH_2Cl_2:acetone) to give *amine* **302** (137 mg, 89%) as a yellow oil.

HRMS ESI): Exact mass calculated for $C_{21}H_{29}NO$ $[M+H]^+$ m/z calculated: 310.2165, found: 310.2163;

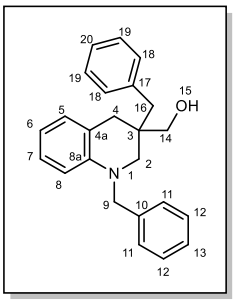
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5H, C$^{11\text{-}13}$**H**), 7.05 – 7.01 (m, 2H, C^5**H** + C^7**H**), 6.66 – 6.59 (m, 2H, C^6**H** + C^8**H**), 4.49 (m, 2H, C^9**H**$_2$), 3.56 (d, *J* = 11.0 Hz, 1H, C^{14}**H**$_2$), 3.51

(d, *J* = 11.0 Hz, 1H, C^{14}**H**$_2$), 3.18 (d, *J* = 11.6 Hz, 1H, C^{2}**H**$_2$), 3.09 (d, *J* = 11.6 Hz, 1H, C^{2}**H**$_2$), 2.66 (d, *J* = 3.6 Hz, 2H, C^{4}**H**$_2$), 1.63 (bs, 1H, O^{15}**H**), 1.51 – 1.25 (m, 6H, C$^{16\text{-}18}$**H**$_2$), 0.96 – 0.88 (m, 3H, C^{19}**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8 (Ar-**C**), 138.9 (Ar-**C**), 129.6 (Ar-**C**H), 128.5 (2 x C, Ar-**C**H), 126.9 (Ar-**C**H), 126.7 (Ar-**C**H), 126.5 (2 x C, Ar-**C**H), 120.3 (Ar-**C**), 116.3 (Ar-**C**H), 110.7 (Ar-**C**H), 65.5 (**C**^{14}H$_2$), 55.2 (**C**^{9}H$_2$), 55.1 (**C**^{2}H$_2$), 35.8 (**C**^{3}), 35.3 (**C**^{4}H$_2$), 34.2 (**C**$^{n\text{Bu}}$H$_2$), 25.1 (**C**$^{n\text{Bu}}$H$_2$), 23.4 (**C**$^{n\text{Bu}}$H$_2$), 14.0 (**C**^{19}H$_3$);

IR (neat) (cm^{-1}): 3401, 3028, 2928, 2858, 1660, 1601, 1504, 1452, 1353, 1283, 1248, 1203, 1152, 1050, 1030, 743, 697.

(*N*,3-Dibenzyl-3-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline (304)



The title compound was prepared according to **General Procedure E** using *quinolinium* **298** (219 mg, 0.5 mmol). The crude material was purified by FCC (99:1 CH_2Cl_2:acetone) to give *amine* **304** (144 mg, 84%) as a pale-yellow oil.

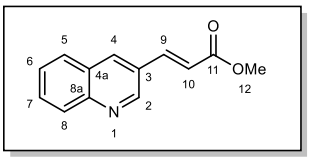
HRMS (ESI): exact mass calculated for $C_{24}H_{26}NO$ $[M+H]^+$ m/z calculated: 344.2009, found: 344.2007;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 10H, Ar-C**H**), 7.15 – 7.07 (m, 2H, C^{5}**H** + C^{7}**H**), 6.76 – 6.69 (m, 2H, C^{6}**H** + C^{8}**H**), 4.69 – 4.50 (m, 2H, C^{9}**H**$_2$), 3.53 – 3.47 (m, 2H, C^{16}**H**$_2$), 3.33 (dd, *J* = 11.6, 1.7 Hz, 1H, C^{14}**H**$_2$), 3.25 (d, *J* = 11.6 Hz, 1H, C^{14}**H**$_2$), 2.90 – 2.76 (m, 3H, 2 x C^{2}**H**$_2$ + C^{4}**H**$_2$), 2.61 (d, *J* = 16.0 Hz, 1H, C^{4}**H**$_2$), 1.69 (bs, 1H, O^{15}**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1 (Ar-**C**), 139.4 (Ar-**C**), 138.0 (Ar-**C**), 130.9 (2 x C, Ar-**C**H), 130.3 (Ar-**C**H), 129.1 (2 x C, Ar-**C**H), 128.5 (2 x C, Ar-**C**H), 127.6 (Ar-**C**H), 127.3 (Ar-**C**H), 127.1 (2 x C, Ar-**C**H), 126.7 (Ar-**C**H), 120.3 (Ar-**C**), 116.9 (Ar-**C**H), 111.3 (Ar-**C**H), 65.4 (**C**^{14}H$_2$), 55.9 (**C**^{9}H$_2$), 55.7 (**C**^{16}H$_2$), 40.3 (**C**^{4}H$_2$), 37.6 (**C**^{3}), 35.1 (**C**^{2}H$_2$);

IR (neat) (cm^{-1}): 3407, 3062, 3027, 2921, 2839, 2360, 1601, 1496, 1451, 1353, 1320, 1173, 1030, 908, 730, 701.

(*E*)-3-(Quinolin-3-yl)acrylic acid methyl ester (305)



A mixture of 3-bromoquinoline (1.40 mL, 10.3 mmol), methyl acrylate (1.10 mL, 12.5 mmol, 1.2 equiv.), $Pd(OAc)_2$ (24 mg, 0.1 mmol, 1 mol%) and P(*o*-tolyl)$_3$ (122 mg, 0.4 mmol, 4 mol%) in Et_3N (5.0 mL) was stirred at 100°C for 16 hours. The cooled reaction mixture was partitioned between DCM (100 mL) and water (50 mL) and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over Na2SO4, filtered and concentrated. Silica gel flash column-chromatography using DCM/Acetone (95:5) yielded **305** (2.13 g, 97 % yield) as a white solid.

m.p.: 116–118°C;

HRMS (ESI): Exact mass calculated for $C_{13}H_{12}O_2N$ $[M+H]^+$ m/z: 214.08626, found 214.08630;

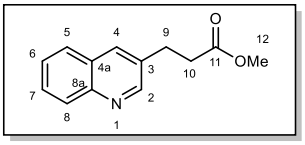
^{1}H-NMR (500 MHz, DMSO-d_6) δ = 9.09 (d, J = 2.2 Hz, 1H, C^2**H**), 8.24 (d, J = 2.2 Hz, 1H, C^4**H**), 8.11 (dd, J = 8.5, 0.9 Hz, 1H, C^5**H**), 7.89 – 7.82 (m, 1H, C^8**H**), 7.86 (d, J = 16.0 Hz, 1H, C^9**H**), 7.76 (ddd, J = 8.5, 6.9, 1.4 Hz, 1H, C^7**H**), 7.59 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H, C^6**H**), 6.67 (d, J = 16.0 Hz, 1H, C^{10}**H**), 3.85 (s, 3H, C^{12}**H**$_3$);

^{13}C NMR (126 MHz, DMSO-d_6) δ = 167.0 (**C**^{11}), 149.4 (**C**^{2}H), 148.8 (**C**^{8a}), 141.6 (**C**^{9}H), 135.6 (**C**^{4}H), 130.8 (**C**^{6}H), 129.6 (**C**^{5}H), 128.5 (**C**^{8}H), 127.8 (**C**^{4a}), 127.6 (**C**^{7}H), 127.5 (**C**^{3}H), 119.9 (**C**^{10}H), 52.1 (**C**^{12}H$_3$);

IR (neat) (cm^{-1}): 2943, 1713, 1633, 1612, 1570, 1433, 1316, 1259, 1169, 982, 862, 759.

Spectroscopic data was consistent with that reported in the literature. [201]

Methyl 3-(quinolin-3-yl)propanoate (306)



To a solution of*(E)*-3-(Quinolin-3-yl)acrylic acid methyl ester **305** (1.81 g, 8.5 mmol) in 50 mL of dioxane was added 10% Pd/C (362 mg, 20 wt.%). The reaction mixture was purged with hydrogen several times and left stirring under a balloon of hydrogen for 14 hours at room temperature. The reaction mixture was filtered through a pad of celite, washed with EtOAc and concentrated. Silica gel flash column-chromatography using DCM/Acetone (95:5) yielded **306** (1.50 g, 82 % yield) as a white solid.

m.p.: 44–46°C;

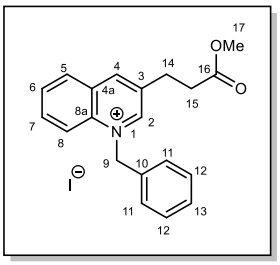
HRMS (ESI): Exact mass calculated for $C_{13}H_{14}O_2N$ $[M+H]^+$ m/z: 216.10191, found 216.10187;

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.80 (d, J = 2.2 Hz, 1H, C^2**H**), 8.07 (dd, J = 8.5, 1.0 Hz, 1H, C^8**H**), 7.98 – 7.86 (m, 1H, C^4**H**), 7.76 (dd, J = 8.2, 1.3 Hz, 1H, C^5**H**), 7.66 (ddd, J = 8.3, 6.9, 1.5 Hz, 1H, C^7**H**), 7.52 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H, C^6**H**), 3.67 (s, 3H, C^{12}**H**$_3$), 3.14 (t, J = 7.6 Hz, 2H, C^9**H**$_2$), 2.75 (t, J = 7.6 Hz, 2H, C^{10}**H**$_2$);

^{13}C NMR (126 MHz, $CDCl_3$) δ = 172.9 (**C**^{11}), 151.8 (**C**^{2}H), 147.2 (**C**^{8a}), 134.6 (**C**^{4}H), 133.3 (**C**^{3}H), 129.3 (**C**^{8}H), 129.0 (**C**^{7}H), 128.2 (**C**^{4a}), 127.5 (**C**^{5}H), 126.9 (**C**^{6}H), 51.9 (**C**^{12}H$_3$), 35.3 (**C**^{10}H$_2$), 28.3 (**C**^{9}H$_2$);

IR (neat) (cm^{-1}): 3046, 2945, 1723, 1639, 1624, 1521, 1434, 1383, 1323, 1169, 979, 772, 701. Spectroscopic data was consistent with that reported in the literature. [202]

N-Benzyl-3-(3-methoxy-3-oxopropyl)quinolinium Iodide (307)



The title compound was prepared according to **General Procedure B** using the corresponding quinoline **306** (538 mg, 2.5 mmol) to give *salt* **307** (983 mg, 91%) as a yellow solid.

m.p.: 191–193°C;

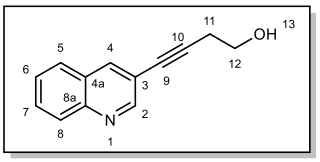
HRMS (ESI): Exact mass calculated for $C_{20}H_{20}O_2N$ [M^+] m/z: 306.1489, found: 306.1485;

^{1}H NMR (500 MHz, DMSO-d_6) δ = 9.83 (d, *J* = 1.8 Hz, 1H, C^2**H**) 9.27 (s, 1H, C^4**H**), 8.45 (d, *J* = 9.0 Hz, 1H, C^8**H**), 8.39 (dd, *J* = 8.3, 1.4 Hz, 1H, C^5**H**), 8.14 (ddd, *J* = 8.7, 7.0, 1.5 Hz, 1H, C^7**H**), 7.98 (ddd, *J* = 8.1, 7.0, 0.9 Hz, 1H, C^6**H**), 7.44 – 7.31 (m, 5H, C$^{11\text{-}13}$**H**), 6.34 (s, 2H, C^9**H**$_2$), 3.61 (s, 3H, C^{17}**H**$_3$), 3.28 (t, *J* = 7.4 Hz, 2H, C^{14}**H**$_2$), 2.98 (t, *J* = 7.4 Hz, 2H, C^{15}**H**$_2$);

^{13}C NMR (126 MHz, DMSO-d_6) δ = 172.3 (**C**^{16}), 151.4 (**C**^{2}H), 146.7 (**C**^{4}H), 136.1 (**C**^{8a}), 135.3 (**C**^{3}), 135.0 (**C**^{7}H), 133.9 (**C**^{10}), 130.3 (**C**^{5}H), 130.0 (**C**^{6}H), 129.6 (**C**^{4a}), 129.0 (2xC, Ar-**C**H), 128.8 (Ar-**C**H), 127.2 (2xC, Ar-**C**H), 119.1 (**C**^{8}H), 60.0 (**C**^{9}H), 51.6 (**C**^{17}H$_3$), 33.3 (**C**^{15}H$_2$), 27.1 (**C**^{14}H$_2$);

IR (neat) (cm^{-1}): 3046, 2945, 1723, 1639, 1624, 1521, 1434, 1383, 1323, 1169, 979, 772, 701.

3-(but-3-yn-1-ol) quinoline (308)



To a 20 mL vial was added 3-bromoquinoline (1.4 mL, 10.3 mmol, 1.0 equiv.), followed by triethylamine (4.0 mL, 29.0 mmol, 2.8 equiv.) and 7.5 mL of DCM. The solution is purged with argon for 15 minutes, then bis(triphenylphosphine)palladium (70 mg, 0.10 mmol, 0.01 equiv.) and cuprous iodide (1.3 mg, 0.007 mmol, catalytic) are added. The vial is purged with argon, then stirred at 50°C for 12 hours. The reaction is allowed to cool to room temperature, then partitioned between DCM (25 mL) and water (50 mL). The aqueous layer is extracted with 2 x 25 mL DCM. The combined organics are dried over Na_2SO_4 and concentrated under vacuum

to give the crude material. The crude material was purified by FCC (20:80 acetone:DCM) to give *quinoline* **308** (1.93 g, 95%) as a yellow solid.

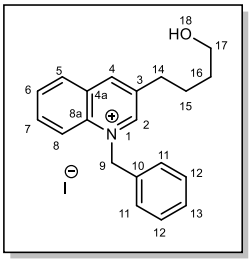
m.p.: 92-94°C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, *J* = 2.1 Hz, 1H, C^{2}**H**), 8.20 – 8.01 (m, 2H, C^{4}**H** + Ar-C**H**), 7.78 – 7.64 (m, 2H, Ar-C**H**), 7.63 – 7.50 (m, 1H, Ar-C**H**), 3.89 (t, *J* = 6.2 Hz, 2H, C^{12}**H**$_2$), 2.76 (t, *J* = 6.2 Hz, 2H, C^{11}**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4 (**C**^{2}H), 146.7 (Ar-**C**), 138.5 (**C**^{4}H), 130.1 (Ar-**C**H), 129.3(2xC, Ar-**C**H + Ar-**C**), 127.6 (Ar-**C**H), 127.4 (Ar-**C**H), 117.7 (Ar-**C**), 90.6 (**C**^{10}), 79.6 (**C**^{9}), 61.1 (**C**^{12}H$_2$), 24.1 (**C**^{11}H$_2$).

Spectroscopic data was consistent with that reported in the literature. [203]

***N*-Benzyl-3-(*n*-4-butan-1-ol)quinolinium Iodide (309)**



3-(But-3-yn-1-ol) quinoline **308** (1.7 g, 8.6 mmol) is dissolved in 40 mL of ethanol. To this solution was added 200 mg of 10% palladium on carbon. The reaction mixture was purged with hydrogen several times and left stirring under a balloon of hydrogen for 14 hours at room temperature. The reaction mixture was filtered through a pad of Celite, concentrated, and the crude product was subjected to **General Procedure B** to give *salt* **309** (1.51 g, 42%) as a yellow solid over two steps.

m.p.: 172-174°C;

HRMS (ESI): Exact mass calculated for $C_{20}H_{22}NO$ [M^+] m/z: 292.16959, found: 292.16962;

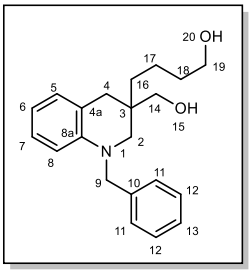
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (d, *J* = 1.9 Hz, 1H, C^{2}**H**), 9.26 (s, 1H, C^{4}**H**), 8.46 – 8.39 (m, 2H, C^{5}**H** + C^{8}**H**), 8.13 (ddd, *J* = 8.8, 7.0, 1.5 Hz, 1H, C^{7}**H**), 7.97 (ddd, *J* = 8.0, 7.0, 0.8 Hz, 1H, C^{6}**H**), 7.42 – 7.31 (m, 5H, $C^{11\text{-}13}$**H**), 6.35 (s, 2H, C^{9}**H**$_2$), 4.48 (t, *J* = 5.0 Hz, 1H,

O[18]**H**), 3.48 (td, *J* = 6.3, 4.9 Hz, 2H, C[17]**H**$_2$), 3.03 (t, *J* = 7.7 Hz, 1H, C[14]**H**$_2$), 1.90 – 1.81 (m, 2H, C[15]**H**$_2$), 1.59 – 1.51 (m, 2H, C[16]**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 151.1 (**C**[2]H), 146.3 (**C**[4]H), 137.0 (**C**[8a]), 136.1 (**C**[3]), 134.8 (**C**[7]H), 134.0 (**C**[10]), 130.2 (**C**[5]H), 129.9 (**C**[6]H), 129.8 (**C**[4a]), 129.1(2xC, Ar-**C**H), 128.7 (Ar-**C**H), 127.1 (2xC, Ar-**C**H), 119.1 (**C**[8]H), 60.3 (**C**[17]H$_2$), 60.0 (**C**[9]H$_2$), 31.7 (**C**[14]H$_2$ + **C**[16]H$_2$), 26.5 (**C**[15]H$_2$);

IR (neat) (cm^{-1}): 3436, 2927, 1953, 1583, 1489, 1364, 1185, 1141, 1067, 955.

4-(*N*-Benzyl-3-(hydroxymethyl)-1,2,3,4-tetrahydroquinolin-3-yl)butan-1-ol (312)



The title compound was prepared according to **General Procedure E** using *quinolinium* **309** (210 mg, 0.5 mmol). The crude material was purified by FCC (85:15 CH_2Cl_2:acetone) to give *amine* **312** (153 mg, 94%) as a grey solid.

m.p.: 115-117°C;

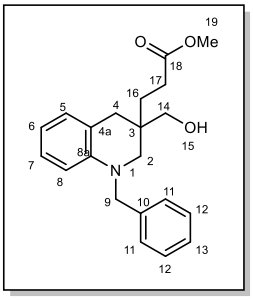
HRMS (ESI): exact mass calculated for $C_{21}H_{28}NO_2$ $[M+H]^+$ m/z: 326.21146, found: 326.21133;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.21 (m, 5H, C[11-13]**H**), 7.04 – 6.96 (m, 2H, C[5]**H**, C[7]**H**), 6.65 – 6.55 (m, 2H, C[6]**H** + C[8]**H**), 4.55 – 4.39 (m, 2H, C[9]**H**$_2$), 3.64 (t, *J* = 6.2 Hz, 2H, C[19]**H**$_2$), 3.57 – 3.47 (m, 2H, C[14]**H**$_2$), 3.17 (dd, *J* = 11.6, 1.3 Hz, 1H, C[2]**H**$_2$), 3.08 (d, *J* = 11.5 Hz, 1H, C[2]**H**$_2$), 2.70 – 2.62 (m, 2H, C[4]**H**$_2$), 1.85 (bs, 1H, O[15]**H**), 1.70 (bs, 1H, O[20]**H**), 1.59 – 1.31 (m, 6H, C[16-18]**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1 (Ar-**C**), 139.2 (Ar-**C**), 130.0 (Ar-**C**H), 128.8 (2 x C, Ar-**C**H), 127.2 (Ar-**C**H), 127.1 (Ar-**C**H), 126.8 (2 x C, Ar-**C**H), 120.4 (Ar-**C**), 116.6 (**C**[6]H), 111.0 (**C**[8]H), 65.6 (**C**[14]H$_2$), 62.5 (**C**[19]H$_2$), 55.7 (**C**[2]H$_2$), 55.4 (**C**[9]H$_2$), 36.2 (**C**[3]), 35.6 (**C**[4]H$_2$), 33.8, 33.1, 19.2 (**C**[16-18]H$_2$);

IR (neat) (cm^{-1}): 3265, 2936, 1602, 1574, 1449, 1291, 1277, 1213, 1050, 1013.

Methyl 3-(*N*-benzyl-3-(hydroxymethyl)-1,2,3,4-tetrahydroquinolin-3-yl)propanoate (313a)



The standard reaction of *quinolinium* **307** under **General Procedure E** showed an isolated yield of 53% of the *open product* **313a** and 30% of *lactone* **313b**, purified by FCC (99.5:0.5 CH_2Cl_2:acetone to 95:5 CH_2Cl_2:acetone).

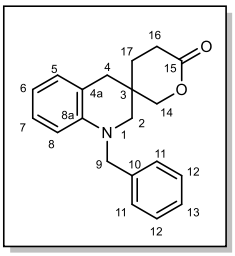
HRMS (ESI): exact mass calculated for $C_{21}H_{26}NO_3$ $[M+H]^+$ m/z: 340.19072, found: 340.19062;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.22 (m, 5H, $C^{11\text{-}13}$**H**), 7.04 – 6.96 (m, 2H, C^5**H** + C^7**H**), 6.65 – 6.55 (m, 2H, C^6**H** + C^8**H**), 4.55 – 4.43 (m, 2H, C^9**H**$_2$), 3.68 (s, 3H, C^{19}**H**$_3$), 3.50 – 3.37 (m, 2H, C^{14}**H**$_2$), 3.21 (d, *J* = 11.8 Hz, 1H, C^2**H**$_2$), 3.09 (d, *J* = 11.6 Hz, 1H, C^2**H**$_2$), 2.61 (s, 2H, C^4**H**$_2$), 2.40 (t, *J* = 7.5 Hz, 2H, C^{17}**H**$_2$), 2.22 (bs, 1H, O^{15}**H**), 1.89 – 1.81 (m, 1H, C^{16}**H**$_2$), 1.74 – 1.66 (m, 1H, C^{16}**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3 (**C**^{18}), 145.0 (Ar-**C**), 139.0 (Ar-**C**), 130.0 (Ar-**C**H), 128.8 (2 x C, Ar-**C**H), 127.4 (Ar-**C**H), 127.1 (Ar-**C**H), 126.8 (2 x C, Ar-**C**H), 119.8 (Ar-**C**), 116.7 (Ar-**C**H), 111.2 (Ar-**C**H), 65.4 (**C**^{14}H$_2$), 55.6 (**C**^{2}H$_2$), 55.5 (**C**^{9}H$_2$), 52.1 (**C**^{19}H$_3$), 36.2 (**C**^{3}), 35.3 (**C**^{4}H$_2$), 28.4 (**C**^{16}H$_2$), 28.3 (**C**^{17}H$_2$);

IR (neat) (cm^{-1}): 3431, 3063, 1734, 1602, 1576, 1504, 1451, 1354, 1286, 1200.

***N*-benzyl-1',4,4',5-tetrahydro-2H,2'H,6H-spiro[pyran-3,3'-quinolin]-6-one (313b)**



The title compound was prepared according to **General Procedure E** with an additional work-up using *quinolinium* **307** (217 mg, 0.5 mmol). The crude material was dissolved in PhMe (10 mL) and pTSA (0.1 equiv.) was added and the solution was heated in an open flask for 3 hours at 80°C then concentrated *in* vacuo. The crude material was purified by FCC (99:1 CH_2Cl_2:acetone) to give *amine* **313b** (114 mg, 74%) as a yellow oil.

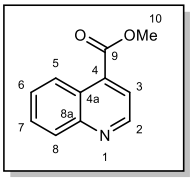
HRMS (ESI): exact mass calculated for $C_{20}H_{22}NO_2$ $[M+H]^+$ m/z: 308.16451, found: 308.16448;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 5H, $C^{11\text{-}13}$**H**), 7.09 – 6.99 (m, 2H, C^5**H** + C^7**H**), 6.70 – 6.62 (m, 2H, C^6**H** + C^8**H**), 4.59 – 4.44 (m, 2H, C^9**H**$_2$), 4.19 – 4.11 (m, 2H, C^{14}**H**$_2$), 3.26 – 3.17 (m, 2H, C^2**H**$_2$), 2.82 – 2.69 (m, 2H, C^4**H**$_2$), 2.67 – 2.48 (m, 2H, C^{16}**H**$_2$), 1.80 (td, *J* = 7.3, 1.7 Hz, 2H, C^{17}**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (**C**^{15}), 144.5 (Ar-**C**), 138.5 (Ar-**C**), 130.2 (Ar-**C**H), 128.9 (2 x C, Ar-**C**H), 127.9 (Ar-**C**H), 127.3 (Ar-**C**H), 126.8 (2 x C, Ar-**C**H), 118.7 (Ar-**C**), 117.2 (Ar-**C**H), 111.6 (Ar-**C**H), 74.1 (**C**$^{14}H_2$), 56.2 (**C**$^2H_2$), 55.4 (**C**$^9H_2$), 37.0 (**C**$^4H_2$), 31.2 (**C**^{3}), 28.9 (**C**$^{17}H_2$), 27.1 (**C**$^{16}H_2$);

IR (neat) (cm^{-1}): 3062, 1738, 1602, 1575, 1500, 1452, 1354, 1325, 1287, 1248.

Methyl quinoline-4-carboxylate (315)



To a solution of quinoline-4-carbaldehyde (5.0 g, 31.8 mmol, 1.0 equiv.) in 100 mL of MeOH was added KOH (4.5 g, 80.0 mmol, 2.5 equiv.) at 0°C in an ice bath. To the reaction was added I_2 (9.7 g, 38.6 mmol, 1.2 equiv.) and then it was stirred at 0°C for one hour. The ice bath was removed, and to the reaction was added $Na_2S_2O_3$ x 5 H_20 (8.0 g, 32.0 mmol, 1 equiv.) and stirred for one hour at room temperature.

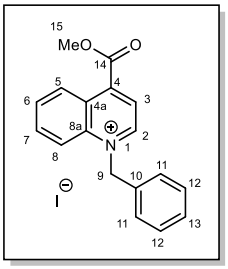
The solvent was removed under vacuum. The reaction was partitioned between water (200 mL) and DCM (100 mL), and the aqueous layer was extracted with 2 x 50 mL DCM. The combined organics were dried over Na_2SO_4 and concentrated under vacuum to give the product **315 (**5.68 g**,** 96 % yield**)** as a pale pink oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, *J* = 4.4 Hz, 1H, C^2**H**), 8.76 (d, *J* = 7.9 Hz, 1H, C^5**H**), 8.17 (d, *J* = 8.5 Hz, 1H, C^8**H**), 7.90 (d, *J* = 4.4 Hz, 1H, C^3**H**), 7.77 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H, C^7**H**), 7.65 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H, C^6**H**), 4.03 (s, 3H, C^{10}**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7 (**C**^{9}), 149.9 (**C**^{2}H), 149.2 (Ar-**C**), 134.9 (Ar-**C**), 130.2 (**C**^{8}H), 129.9 (**C**^{7}H), 128.3 (**C**^{6}H), 125.7 (**C**^{5}H), 125.2 (Ar-**C**), 122.4 (**C**^{3}H), 52.9 (**C**^{10}H$_3$).

Spectroscopic data was consistent with that reported in the literature.[204]

N-Benzyl-4-(methoxycarbonyl)quinolinium Iodide (316)



The title compound was prepared according to **General Procedure B** (stirred for 3 days) using methyl quinoline-4-carboxylate **315** (748 mg, 4.0 mmol) to give *salt* **316** (1.44 g, 89%) as a red solid.

m.p.: 145-147°C;

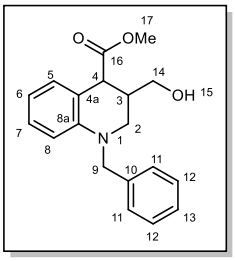
HRMS (ESI): Exact mass calculated for $C_{18}H_{16}O_2N$ [M^+] m/z: 278.11756, found: 278.11759;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (d, *J* = 6.0 Hz, 1H, C^2**H**), 8.79 (dd, *J* = 8.6, 1.3 Hz, 1H, C^5**H**), 8.61 (dd, *J* = 7.5, 4.5 Hz, 2H, C^3**H** + C^8**H**), 8.27 (ddd, *J* = 8.8, 7.0, 1.5 Hz, 1H, C^7**H**), 8.14 – 8.08 (m, 1H, C^6**H**), 7.46 – 7.34 (m, 5H, C$^{11\text{-}13}$**H**), 6.46 (s, 2H, C^9**H**$_2$), 4.11 (s, 3H, C^{15}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 164.1 (**C**^{14}), 151.1 (**C**^{2}H), 145.0 (**C**^{4}), 138.3 (**C**^{8a}), 135.8 (**C**^{7}H), 133.5 (**C**^{10}), 131.1 (**C**^{6}H), 129.1 (2xC, Ar-**C**H), 128.9 (Ar-**C**H), 127.8 (**C**^{5}H), 127.5 (2xC, Ar-**C**H), 126.5 (**C**^{4a}), 122.9 (**C**^{3}H), 120.0 (**C**^{8}H), 60.8 (**C**^{9}H$_2$), 54.2 (**C**^{15}H$_3$);

IR (neat) (cm^{-1}): 2988, 2946, 1729, 1431, 1311, 1267, 1207, 1135, 790, 764, 697.

Methyl *N*-benzyl-3-(hydroxymethyl)-1,2,3,4-tetrahydroquinoline-4-carboxylate (317)



The title compound was prepared according to **General Procedure E** using *quinolinium* **316** (203 mg, 0.5 mmol). The crude material was purified according to FCC (95:5 CH_2Cl_2:acetone) to give *amine* **317** (117 mg, 75%) as a yellow oil. The compound was found to be only the anti diastereoisomer, as confirmed by NOESY (run in methanol).

HRMS (ESI): exact mass calculated for $C_{19}H_{22}NO_3$ $[M+H]^+$ m/z: 312.15942, found: 312.15925;

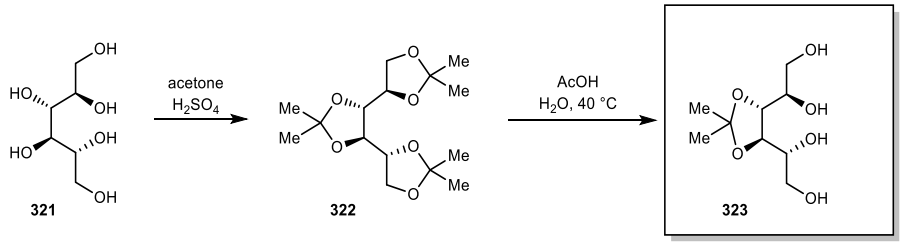
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.22 (m, 5H, $C^{11\text{-}13}$**H**), 7.15 – 7.03 (m, 2H, C^5**H** + C^7**H**), 6.68 – 6.57 (m, 2H, C^6**H** + C^8**H**), 4.59 – 4.42 (m, 2H, C^9**H**$_2$), 3.77 (d, *J* = 4.2 Hz, 1H, C^4**H**), 3.74 (s, 3H, C^{17}**H**$_3$), 3.68 – 3.57 (m, 3H, 2 x C^{14}**H**$_2$ + C^2**H**$_2$), 3.24 (ddd, *J* = 12.0, 4.7, 1.4 Hz, 1H, C^2**H**$_2$), 2.58 – 2.50 (m, 1H, C^3**H**), 1.68 (bs, 1H, O^{15}**H**);

^{1}H NMR (500 MHz, CD_3OD) δ 7.30 – 7.16 (m, 5H, $C^{11\text{-}13}$**H**), 7.03 (dt, *J* = 7.4, 1.1 Hz, 1H, C^5**H**), 6.95 (ddd, *J* = 8.6, 7.2, 1.7 Hz, 1H, C^7**H**), 6.58 – 6.52 (m, 2H, C^6**H** + C^8**H**), 4.54 (d, *J* = 16.9 Hz, 1H, C^9**H**$_2$), 4.42 (d, *J* = 16.9 Hz, 1H, C^9**H**$_2$), 3.77 (d, *J* = 4.2 Hz, 1H, C^4**H**), 3.69 (s, 3H, C^{17}**H**$_3$), 3.62 (dd, *J* = 11.9, 3.8 Hz, 1H, C^2**H**$_2$), 3.53 – 3.44 (m, 2H, C^{14}**H**$_2$), 3.20 (ddd, *J* = 12.0, 4.7, 1.4 Hz, 1H, C^2**H**$_2$), 2.47 – 2.41 (m, 1H, C^3**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7 (**C**^{16}), 144.9 (Ar-**C**), 138.7 (Ar-**C**), 130.6 (Ar-**C**H), 128.8 (2 x C, Ar-**C**H), 128.6 (Ar-**C**H), 127.1 (Ar-**C**H), 126.7 (2 x C, Ar-**C**H), 116.6 (2 x C, Ar-**C**, Ar-**C**H), 111.8 (Ar-**C**H), 63.7 (**C**^{14}H$_2$), 55.3 (**C**^{9}H$_2$), 52.4 (**C**^{17}H$_3$), 48.1 (**C**^{2}H$_2$), 44.9 (**C**^{4}H), 36.9 (**C**^{3}H);

IR (neat) (cm^{-1}): 3435, 3062, 2949, 1727, 1601, 1503, 1451, 1434, 1341, 1195, 744, 697.

(1*R*,1'*R*)-1,1'-((4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(ethane-1,2-diol) (323)



To a 1 litre flask was added D-mannitol **321** (20.0 g, 109 mmol, 1.0 equiv.), followed by 250 mL of anhydrous acetone (freshly distilled over $CaSO_4$) and 2 mL of concentrated H_2SO_4 at room temperature. The reaction was left stirring overnight under an atmosphere of argon. The sulfuric acid was neutralised with 3.9 g of anhydrous sodium carbonate and the acetone was evaporated under vacuum. The resulting oil was partitioned between 500 mL of water and 250 mL of Et_2O. The organic layer was collected, and the aqueous layer was extracted twice more. The combined organics were collected and dried over $MgSO_4$ then concentrated under vacuum. The resulting white solid **322** was dissolved in 250 mL of 70 % (by volume) aqueous acetic acid and the resulting solution was stirred at 40°C for 2 hours. The solvent is evaporated under vacuum (co-evaporating with toluene for 3 times). The residue was dissolved in acetone, leaving some crystals undissolved. The acetone filtrate was concentrated to a white gum. Recrystallisation from toluene of this gum yields pure white crystals **323** (16. 5 g, 68 % over 2 steps).

m.p.: 84-86°C;

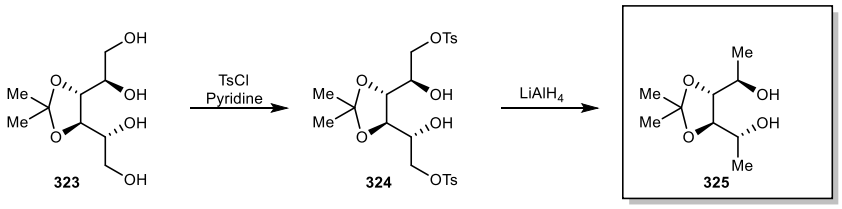
^{1}H NMR (400 MHz, DMSO-d_6) δ 5.09 (d, J = 3.5 Hz, 2H, 2 x -CH_2O**H**), 4.47 (t, J = 5.6 Hz, 2H, 2 x -CHO**H**), 3.94 – 3.77 (m, 2H, 2 x -C**H**), 3.59 – 3.43 (m, 4H, 2 x -C**H** + -C**H**$_2$), 3.38 – 3.32 (m, 2H, -C**H**$_2$), 1.28 (s, 6H, 2 x -C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 108.3 (-**C(**CH_3)$_2$), 79.1 (2 x C, -**C**H), 72.9 (2 x C, -**C**H), 63.0 (2 x C, -**C**H_2), 27.3 (2 x C, -**C**H_3);

[α]$_D^{25°C}$ = + 28.4 (c=0.82, MeOH).

Spectroscopic data was consistent with that reported in the literature.[205]

(1*R*,1'*R*)-1,1'-((4*R*,5*R*)-2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(ethan-1-ol) (325)



The monoacetonide **323** (11.1 g, 50.0 mmol, 1.0 equiv.) dissolved in pyridine (160 mL) was stirred at 0 ºC in an ice bath for 5 minutes. Tosyl chloride (19.5 g, 102.5 mmol, 2.1 equiv.) was slowly added and the reaction was stirred at 0º C for 4 hours, then poured into a cold mixture of hydrochloric acid (6N, 320 mL) and extracted with 150 mL of Et_2O twice. The ether extract was washed with an aqueous solution of sodium bicarbonate (3%, 200 mL), dried over $MgSO_4$ and concentrated under vacuum to a syrup which was used without further purification. The intermediate tosylate **324** was dissolved in 100 mL of anhydrous THF and was stirred at 0 ºC in an ice bath for 5 minutes. To the reaction was slowly added lithium aluminium hydride (6.0 g, 120.0 mmol, 3.0 equiv.) and the reaction was left stirring at room temperature overnight. The reaction was then slowly quenched with 6.0 mL of water and stirred for an additional 10 minutes at 0 ºC in an ice bath. To the reaction was added 6.0 mL of 15 % sodium hydroxide solution and stirred at room temperature for an additional 10 minutes. To the reaction was added 18.0 mL of water and the reaction was stirred for 10 minutes. Finally, $MgSO_4$ (ca. 5 g) was added and the reaction was stirred for another 5 minutes. The resulting suspension was filtered with diethyl ether and then concentrated under vacuum to give an oil which was then purified by FCC (pentane/ EtOAc, 1:1) to give product **325** (8.1 g, 85 % over 2 steps) as a white solid.

m.p.: 89-91°C;

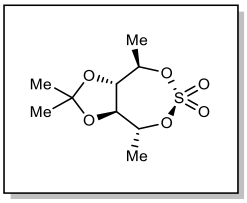
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 – 3.72 (m, 2H, 2 x -C**H**), 3.67 – 3.58 (m, 2H, 2 x -C**H**), 3.29 (d, *J* = 3.0 Hz, 2H, 2 x -O**H**), 1.37 (s, 6H, 2 x -C**H**$_3$), 1.31 (d, *J* = 6.2 Hz, 6H, 2 x -C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 108.9 (-**C(**$CH_3)_2$), 84.2 (2 x C, -**C**H), 69.4 (2 x C, -**C**H), 27.0 (2 x C, -**C**H_3), 20.6 (2 x C, -**C**H_3);

[α]$_D^{25°C}$ = –10.4 (c= 0.96, $CHCl_3$).

Spectroscopic data was consistent with that reported in the literature.[206]

(3a*R*,4*R*,8*R*,8a*S*)-2,2,4,8-Tetramethyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxathiepine 6,6-dioxide (326)



The diol **325** (0.95 g, 5.0 mmol, 1.0 equiv.) and Et_3N (1.4 mL, 10.0 mmol, 2.0 equiv.) in DCM (30 mL) was stirred at 0°C in an ice bath for 5 minutes. To the reaction was added dropwise a solution of $SOCl_2$ (0.5 mL, 6.0 mmol, 1.2 equiv.) in DCM (10 mL) at 0°C and was stirred for one hour under an atmosphere of argon. The reaction mixture was quenched with 30 mL of brine. The separated aqueous layer was then extracted with 3 × 30 mL of DCM. The combined organics were dried over Na_2SO_4, concentrated under vacuum, then dried under high vacuum for 30 min. The intermediate sulfoxide was dissolved in 20 mL of CCl_4, 20 mL of CH_3CN, and 30 mL of water. $RuCl_3$*xH_2O (25 mg, catalytic) and $NaIO_4$ (1.33 g, 6.0 mmol, 1.2 equiv.) were added at 0°C, and the mixture was stirred for 30 min. Brine (50 mL) was added, and the aqueous solution was extracted with 3 × 50 mL of diethyl ether. The combined organics were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by FCC (pentane/ EtOAc, 9:1) to give product **326** (1.03 g, 82 % over 2 steps) as a white solid.

m.p.: 68-70°C;

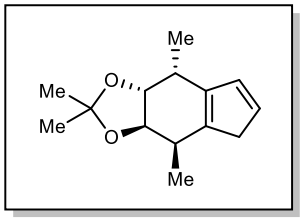
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (td, *J* = 6.4, 2.4 Hz, 2H, 2 x -C**H**), 3.99 (dd, *J* = 6.5, 2.4 Hz, 2H, 2 x -C**H**), 1.53 (d, *J* = 6.5 Hz, 6H, 2 x -C**H**$_3$), 1.37 (s, 6H, 2 x -C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 110.7 (-**C**$(CH_3)_2$), 81.2 (2 x C, -**C**H), 80.5 (2 x C, -**C**H), 26.7 (2 x C, -**C**H_3), 18.4 (2 x C, -**C**H_3);

[α]$_D^{25°C}$ = + 10.2 (c= 0.94, $CHCl_3$).

Spectroscopic data was consistent with that reported in the literature.[207]

(3a*R*,4*R*,8*R*,8a*R*)-2,2,4,8-Tetramethyl-3a,5,8,8a-tetrahydro-4H-indeno[5,6-d][1,3]dioxole (327)



To a flamed dried two-necked flask equipped with a water reflux condenser was added sodium hydride (442 mg, 18.4 mmol, 2.20 equiv.) under a flow of argon. The flask was evacuated and backfilled with argon 3 times. To the flask was added a solution of sodium cyclopentadienylide (8.8 mL, 8.8 mmol, 1.0 M in THF, 1.1 equiv.) at 0°C, followed by a solution of **326** (2.1 g, 8.4 mmol, 1.0 equiv.) in 65 mL of THF. Finally, 15-crown- 5 (3.4 mL, 16.8 mmol, 2.0 equiv.) was added at 0°C, then the reaction was refluxed overnight under an atmosphere of argon. The reaction was cooled down to 0°C, then slowly quenched with 100 mL of water. The product was extracted with 3 x 75 mL Et_2O. The combined organics were dried over Na_2SO_4 and concentrated under vacuum. The crude material was purified by FCC (pentane/Et_2O, 9:1) to give the product **327** (815 mg, 42 % yield) as a yellow solid.

m.p.: 72-74°C;

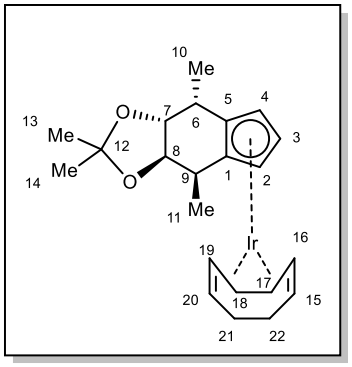
^{1}H NMR (400 MHz, C_6D_6) δ 6.22 – 6.16 (m, 2H, cp-C**H** + cp-C**H**), 4.03 (dd, *J* = 3.8, 1.8 Hz, 2H, cp-C**H**$_2$), 2.91 – 2.68 (m, 3H, 3 x -C**H**), 2.39 (dd, *J* = 23.4, 1.2 Hz, 1H, -C**H**), 1.47 (d, *J* = 2.2 Hz, 6H, 2 x -C**H**$_3$), 1.17 (d, *J* = 7.1 Hz, 3H, -C**H**$_3$), 1.09 (d, *J* = 7.1 Hz, 3H, -C**H**$_3$);

^{13}C NMR (101 MHz, C_6D_6) δ 142.2 (cp-**C**), 142.1 (cp-**C**), 133.3 (cp-**C**H), 132.6 (cp-**C**H), 109.7 (-**C**(CH$_3$)$_2$), 75.1 (-**C**H), 75.0 (-**C**H), 41.7 (cp-**C**H$_2$), 33.7 (-**C**H), 32.9 (-**C**H), 27.4 (-**C**H$_3$), 27.4 (-**C**H$_3$), 14.9 (-**C**H$_3$), 13.8 (-**C**H$_3$);

[α]$_D$ $^{25°C}$ = –192.5 (c= 0.54, CH_2Cl_2).

Spectroscopic data was consistent with that reported in the literature.[208]

Chiral iridium complex (328)



To a Schlenk flask was added (3a*R*,4*R*,8*R*,8a*R*)-2,2,4,8-Tetramethyl-3a,5,8,8a-tetrahydro-4H-indeno[5,6-d][1,3]dioxole **327** (220 mg, 1.0 mmol, 1.0 equiv.) and sodium hydride (26 mg, 1.1 mmol, 1.1 equiv.) under a flow of argon. The flask was evacuated and backfilled with argon 3 times. To the flask was added 10 mL of degassed (freeze-pump-thaw) THF under a flow of argon at room temperature. To the reaction was added 15-crown-5 (220 µL, 1.1 mmol, 1.1 equiv.), and the reaction was stirred at room temperature for 4 hours under an atmosphere of argon. During this time the reaction turned dark blue. To the flask was added [Ir(cod)Cl$_2$]$_2$ (403 mg, 0.6 mmol, 0.6 equiv.) under a flow of argon at room temperature and the reaction was stirred at room temperature overnight under argon. The reaction was filtered through a pad of silica with Et$_2$O and concentrated under vacuum. The crude material was purified by FCC (toluene) to yield the product **328** (426 mg, 82 % yield) as a white solid.

m.p.: 114-116°C;

HRMS (ESI): Exact mass calculated for $C_{22}H_{32}O_2{}^{193}Ir$ [M+H]$^+$: 521.20261; found: 521.20283;

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (s, 1H, cp-Ar-C**H**), 5.06 (dd, *J* = 2.6, 1.5 Hz, 1H, cp-Ar-C**H**), 4.51 (t, *J* = 1.9 Hz, 1H, cp-Ar-C**H**), 4.08 (dd, *J* = 10.1, 5.8 Hz, 1H, cp-C**H**OC(CH$_3$)$_2$),

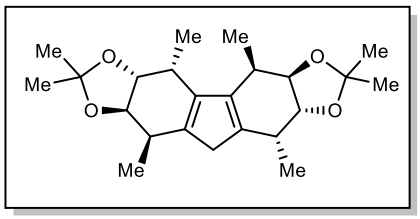
3.99 (dd, *J* = 10.1, 6.7 Hz, 1H, cp-C**H**OC(CH_3)$_2$), 3.71 (td, *J* = 7.7, 2.6 Hz, 2H, cod-C**H**Ir), 3.30 (td, *J* = 7.7, 2.6 Hz, 2H, cod-C**H**Ir), 3.00 (p, *J* = 6.9 Hz, 1H, cp-C**H**CH_3), 2.54 (p, *J* = 6.9 Hz, 1H, cp-C**H**CH_3), 2.06 (td, *J* = 9.5, 8.4, 5.5 Hz, 4H, cod-C**H**$_2$), 1.80 (dddd, *J* = 19.3, 14.6, 11.7, 3.5 Hz, 4H, cod-C**H**$_2$), 1.48 (s, 3H, cp-C(C**H**$_3$)$_2$), 1.44 (s, 3H, cp-C(C**H**$_3$)$_2$)), 1.42 (d, *J* = 7.0 Hz, 3H, cp-CHC**H**$_3$), 1.21 (d, *J* = 7.1 Hz, 3H, cp-CHC**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 110.4 (-**C**(CH_3)$_2$), 105.2 (cp-**C**), 101.6 (cp-**C**), 81.7 (cp-**C**H**)**, 80.0 (cp-**C**H**)**, 77.8 (cp-**C**H**)**, 74.7 (-**C**HOC(CH_3)$_2$), 74.2 (-**C**HOC(CH_3)$_2$), 50.6 (2 x C, cod-**C**HIr), 47.3 (2 x C, cod-**C**HIr), 34.1 (2 x C, cod-**C**H_2), 33.9 (2 x C, cod-**C**H_2), 30.0 (-**C**HCH_3), 29.9 (-**C**HCH_3), 27.2 (-CHOC(**C**H_3)$_2$), 27.1 (-CHOC(**C**H_3)$_2$), 21.5 (-CH**C**H_3), 16.2 (-CH**C**H_3);

IR (neat) (cm^{-1}): 2965, 2928, 2883, 2828, 1377, 1232, 1174, 1113, 1077, 1044, 908, 860, 805, 793;

[*α*]$_D^{25°C}$ = –71.2 (c= 0.96, $CHCl_3$).

(3a*R*,4*R*,5*R*,5a*R*,8a*R*,9*R*,11*R*,11a*R*)-2,2,4,5,7,7,9,11-Octamethyl-3a,5,5a,8a,9,10,11,11a-octahydro-4H-fluoreno[2,3-d:6,7-d']bis([1,3]dioxole) (330)



The title compound was isolated as a by-product during the preparation of compound **327** and was purified by FCC (pentane/Et_2O, 8:2) to give the product **330** (365 mg, 11% yield) as a yellow solid.

m.p.: 142-144°C;

HRMS (ESI): Exact mass calculated for $C_{23}H_{35}O_4$ $[M+H]^+$: 375.25299, found: 375.25223;

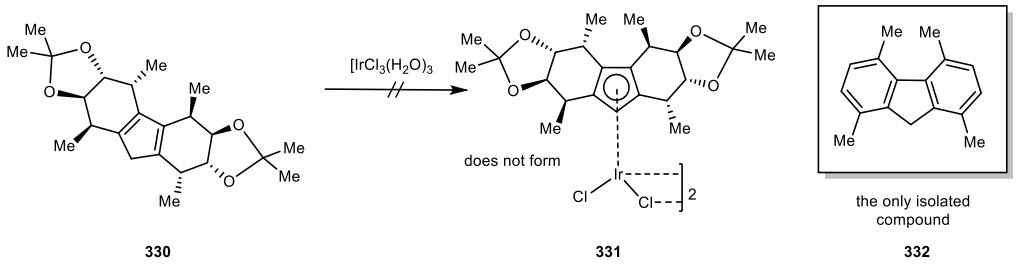
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 – 3.89 (m, 4H,4 x -C**H**OC(CH_3)$_2$), 3.03 – 2.85 (m, 4H, 4 x -C**H**CH_3), 2.73 (s, 2H, cp-C**H**$_2$), 1.42 (s, 12H, 4 x -CHOC(C**H**$_3$)$_2$), 1.09 (dd, *J* = 7.1, 4.6 Hz, 12H, 4 x -CHC**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1 (2 x C, cp-**C**), 140.3 (2 x C, cp-**C**), 109 (2 x C, -**C**$(CH_3)_2$).6, 74.7 (2 x C, -**C**HOC$(CH_3)_2$), 74.3 (2 x C, -**C**HOC$(CH_3)_2$), 40.6 (cp-**C**H_2), 33.6 (2 x C, -**C**HCH_3), 31.3 (2 x C, -**C**HCH_3), 27.1 (2 x C, -C(**C**$H_3)_2$), 27.1 (2 x C, -C(**C**$H_3)_2$), 14.9 (2 x C, -CH**C**H_3), 13.4 (2 x C, -CH**C**H_3);

IR (neat) (cm^{-1}): 2980, 1453, 1378, 1234, 1182, 1107, 1079, 1002, 857;

[α]$_D^{25°C}$ = –17.23 (c = 0.8, $CHCl_3$).

1,4,5,8-Tetramethyl-9H-fluorene (332)



The title compound **332** was obtained as an undesired product when trying to obtain the iridium complex **331**.

To a 10 mL microwave vial was added $IrCl_3$*$3H_2O$ (56 mg, 0.15 mmol, 1.00 equiv.), chiral cyclopentadiene **330** (120 mg, 0.32 mmol, 2.00 equiv.) and 5 mL of degassed methanol. The vialed was sealed and heated at 80°C for 16 hours. The reaction was allowed to cool to room temperature, then cooled to –30°C (freezer) for 3 hours. The resulting precipitate was filtered and washed with 10 mL of cold methanol to give the side product **332** as a white solid (30 mg, 42% yield).

m.p.: 98-100°C;

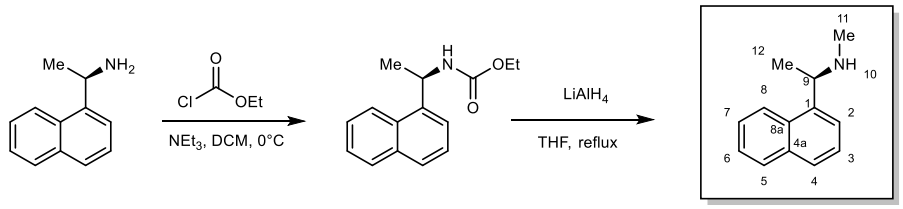
HRMS (ESI): Exact mass calculated for $C_{17}H_{19}$ $[M+H]^+$: 223.14813, found: 223.14831;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 7.6 Hz, 2H, Ar-C**H**), 7.05 (d, *J* = 7.6 Hz, 2H, Ar-C**H**), 3.62 (s, 2H, -C**H**$_2$), 2.72 (s, 6H, 2 x -C**H**$_3$), 2.41 (s, 6H, 2 x -C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (2 x C, Ar-**C**), 141.6 (2 x C, Ar-**C**), 131.0 (2 x C, Ar-**C**), 130.9 (2 x C, Ar-**C**H), 129.7 (2 x C, Ar-**C**), 127.5 (2 x C, Ar-**C**H), 35.7 (-**C**H$_2$), 25.3 (2 x C, -**C**H$_3$), 18.8 (2 x C, -**C**H$_3$);

IR (neat) (cm^{-1}): 2969, 2917, 1259, 1088, 1017, 801.

(*R*)-N-methyl-1-(naphthalen-1-yl)ethan-1-amine (337)



336 337

To a stirred solution of amine **336** (171 mg, 1.0 mmol, 1.0 equiv.) in 5 mL DCM was added triethylamine (0.16 mL, 1.1 mmol, 1.1 equiv.) at 0°C. To the reaction was added slowly ethyl chloroformate (0.11 mL, 1.1 mmol, 1.1 equiv.) at 0°C and the left to stir overnight at room temperature. The reaction was poured into 10 mL 0.1 M HCl and then extracted with 2 x 20 mL DCM. The organic layer was washed with a saturated solution of $NaHCO_3$ and then with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The resulting crude carbamate was dissolved in 5 mL anhydrous THF and stirred at 0°C for 5 minutes. To the reaction was added slowly $LiAlH_4$ (190 mg, 5 mmol, 5 equiv.) and then the reaction was refluxed for 4 hours. The reaction was cooled to 0°C, then slowly quenched with 0.2 mL of water and stirred for 10 minutes. To the reaction was added 0.2 mL 15 % w/w NaOH solution and stirred for an additional 10 minutes. To the reaction was added 0.6 mL of water and stirred for an additional 10 minutes. To the reaction was added anhydrous $MgSO_4$ (ca. 1 g) and after stirring for 10 minutes. The resulting suspension was filtered and washed with Et_2O. The

organic layer was concentrated then purified by FCC eluting with DCM/IPA (1:1) and 1% NEt_3 to give the amine **337** (144 mg, 78 % yield) as a light-yellow oil.

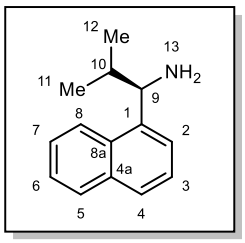
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 1H, Ar-C**H**), 7.89 (d, *J* = 7.9 Hz, 1H, Ar-C**H**), 7.76 (d, *J* = 8.1 Hz, 1H, Ar-C**H**), 7.64 (d, *J* = 7.1 Hz, 1H, Ar-C**H**), 7.56 – 7.45 (m, 3H, Ar-C**H**), 4.54 (q, *J* = 6.6 Hz, 1H, C^9**H**), 2.43 (s, 3H, C^{11}**H**$_3$), 1.62 (bs, 1H, N^{10}**H**), 1.52 (d, *J* = 6.6 Hz, 3H, C^{12}**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0 (Ar-**C**), 134.1 (Ar-**C**), 131.5 (Ar-**C**), 129.1, (Ar-**C**H), 127.3 (Ar-**C**H), 125.9 (Ar-**C**H), 125.8 (Ar-**C**H), 125.4 (Ar-**C**H), 123.0 (Ar-**C**H), 122.6 (Ar-**C**H), 55.5 (**C**^{9}H), 34.8 (**C**^{11}H$_3$), 23.3 (**C**^{12}H$_3$);

[α]$_D^{25°C}$ = +72.5 (c= 0.98, $CHCl_3$).

Spectroscopic data was consistent with that reported in the literature.[209]

(*R*)-2-Methyl-1-(naphthalen-1-yl)propan-1-amine (338)



The chiral amine **338** was synthesised by Dr Hamish B. Hepburn and was provided as the HCl salt. Free basing was achieved with a saturated solution of potassium carbonate and the amine was extracted with DCM.

HRMS (ESI): Exact mass calculated for $C_{14}H_{18}N$ $[M+H]^+$: 200.14338, found: 200.14363;

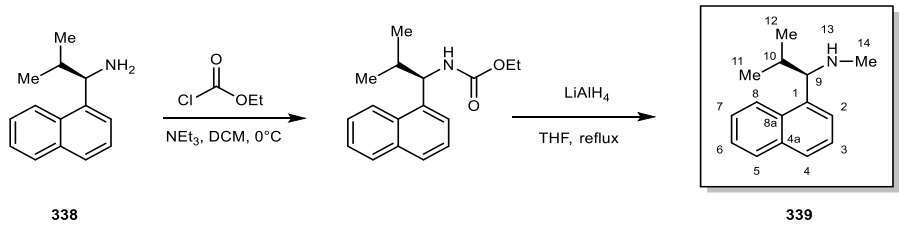
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.6 Hz, 1H, Ar-C**H**), 7.88 (dd, *J* = 8.1, 1.6 Hz, 1H, Ar-C**H**), 7.76 (dt, *J* = 8.2, 1.1 Hz, 1H, Ar-C**H**), 7.60 (dd, *J* = 7.2, 1.3 Hz, 1H, Ar-C**H**), 7.55 – 7.45 (m, 3H, Ar-C**H**), 4.55 (d, *J* = 6.4 Hz, 1H, C^9**H**), 2.24 – 2.11 (m, *J* = 6.7 Hz, 1H, C^{10}**H**), 1.58 (bs, 2H, N^{13}**H**$_2$), 1.00 (d, *J* = 6.6 Hz, 3H, -C**H**$_3$), 0.94 (d, *J* = 6.8 Hz, 3H, -C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (Ar-**C**), 134.0 (Ar-**C**), 131.4 (Ar-**C**), 129.1 (Ar-**C**H), 127.2 (Ar-**C**H), 125.8 (Ar-**C**H), 125.5 (Ar-**C**H), 125.4 (Ar-**C**H), 123.5 (Ar-**C**H), 123.4 (Ar-**C**H), 57.1 (**C**^{9}H), 34.7 (**C**^{10}H), 20.8 (-**C**H_3), 18.0 (-**C**H_3);

IR (neat) (cm^{-1}): 3046, 2957, 2868, 1595, 1509, 1465, 1383, 1365, 860, 776, 731, 650, 627;

[α]$_D^{25°C}$ = + 25.6 (c= 0.68, $CHCl_3$).

(*R*)-*N*,2-Dimethyl-1-(naphthalen-1-yl)propan-1-amine (339)



338 **339**

To a stirred solution of amine **338** (199 mg, 1.0 mmol, 1.0 equiv.) in 5 mL DCM was added triethylamine (0.16 mL, 1.1 mmol, 1.1 equiv.) at 0°C. To the reaction was added slowly ethyl chloroformate (0.11 mL, 1.1 mmol, 1.1 equiv.) at 0°C and the left to stir overnight at room temperature. The reaction was poured into 10 mL 0.1 M HCl and then extracted with 2 x 20 mL DCM. The organic layer was washed with a saturated solution of $NaHCO_3$ and then with brine. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The resulting crude carbamate was dissolved in 5 mL anhydrous THF and stirred at 0°C for 5 minutes. To the reaction was added slowly $LiAlH_4$ (190 mg, 5 mmol, 5 equiv.) and then the reaction was refluxed for 4 hours. The reaction was cooled to 0°C, then slowly quenched with 0.2 mL of water and stirred for 10 minutes. To the reaction was added 0.2 mL 15 % w/w NaOH solution and stirred for an additional 10 minutes. To the reaction was added 0.6 mL of water and stirred for an additional 10 minutes. To the reaction was added anhydrous $MgSO_4$ (ca. 1 g) and after stirring for 10 minutes. The resulting suspension was filtered and washed with Et_2O. The

organic layer was concentrated then purified by FCC eluting with Et_2O to give the amine **339** (196 mg, 92 % yield) as a light-yellow oil.

HRMS (ESI): Exact mass calculated for $C_{15}H_{20}N$ $[M+H]^+$: 214.15903, found: 214.15912;

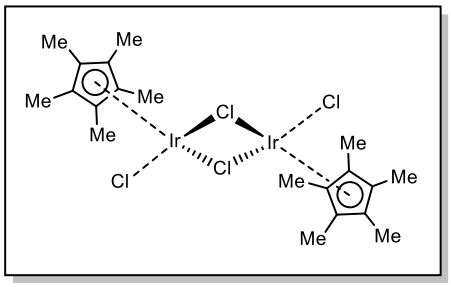
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.1 Hz, 1H, Ar-C**H**), 7.90 – 7.85 (m, 1H, Ar-C**H**), 7.76 (d, *J* = 7.9 Hz, 1H, Ar-C**H**), 7.61 – 7.37 (m, 4H, Ar-C**H**), 4.14 (d, *J* = 6.4 Hz, 1H, C^9**H**), 2.26 (s, 3H, C^{14}**H**$_3$), 2.14 (h, *J* = 6.8 Hz, 1H, C^{10}**H**), 1.67 (bs, 1H, N^{13}**H**), 1.00 (d, *J* = 6.7 Hz, 3H, -C**H**$_3$), 0.88 (d, *J* = 6.8 Hz, 3H, -C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0 (Ar-**C**), 134.1 (Ar-**C**), 132.7 (Ar-**C**), 129.1 (Ar-**C**H), 127.2 (Ar-**C**H), 125.7 (Ar-**C**H), 125.5 (Ar-**C**H), 125.3 (Ar-**C**H), 124.4 (Ar-**C**H), 123.6 (Ar-**C**H), 35.1 (-**C**H), 35.1 (-**C**H$_3$), 34.3 (-**C**H), 20.7 (-**C**H$_3$), 18.9 (-**C**H$_3$);

IR (neat) (cm^{-1}): 3047, 2956, 2869, 2789, 1509, 1467, 1383, 1132, 1098, 861, 793, 775, 732, 699, 646, 624;

[α]$_D^{25°C}$ = + 64.9 (c= 0.45, $CHCl_3$).

[Ir(Cp*)Cl$_2$]$_2$



To a 20 mL microwave vial was added $IrCl_3$*$3H_2O$ (352 mg, 1.0 mmol, 1.0 equiv.), pentamethylcyclopentadiene (0.3 mL, 2.0 mmol, 2.0 equiv.) and 10 mL of degassed methanol. The vialed was sealed and heated at 80°C for 40 hours. The reaction was allowed to cool to room temperature, then cooled to –30°C (freezer) for 3 hours. The resulting precipitate was filtered and washed with 20 mL of cold methanol, and then 100 mL of ether to give the product as an orange powder (288 mg, 72% yield).

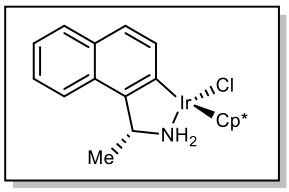
m.p.: Decomposes above 300°C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 30H, Cp*-C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 86.4 (Cp*-**C**), 9.5 (Cp*-**C**H_3).

Spectroscopic data was consistent with that reported in the literature.[210]

Cp*IrCl[k^2(*N*,*C*)-(*R*)-{NH$_2$CH(CH$_3$)-2-C$_{10}$H$_6$}] (342)



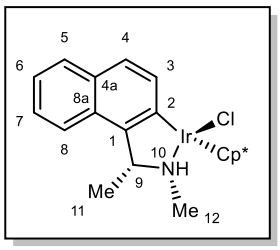
The title compound **342** was prepared according to literature reports in 17 % yield on 0.063 mmol of $[IrCp^*Cl_2]_2$ and was contaminated with small amounts of the chiral amine **336**. [187]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 1H, Ar-C**H**), 7.70 (d, *J* = 8.3 Hz, 1H, Ar-C**H**), 7.53 (d, *J* = 8.2 Hz, 2H, Ar-C**H**), 7.37 – 7.11 (m, 2H, Ar-C**H**), 5.13 – 5.03 (m, 1H, C**H**CH_3NH_2), 4.85 (bs, 1H, N**H**$_2$), 3.66 (d, *J* = 10.4 Hz, 1H, N**H**$_2$), 1.76 (s, 15H, Cp*-C**H**$_3$), 1.37 (d, *J* = 6.5 Hz, 3H, CHC**H**$_3$NH$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3 (Ar-**C**), 145.2 (Ar-**C**), 135.9 (Ar-**C**H), 131.4 (Ar-**C**H), 128.7 (Ar-**C**H), 128.3 (Ar-**C**H), 126.7 (Ar-**C**H), 125.4 (Ar-**C**H), 123.5 (Ar-**C**H), 122.7 (Ar-**C**H), 87.0 (Cp*-**C**), 59.6 (**C**HCH$_3$NH$_2$), 22.7 (CH**C**H$_3$NH$_2$), 9.2 (Cp*-**C**H$_3$).

Spectroscopic data was consistent with that reported in the literature.

Cp*IrCl[k^2(*N*,*C*)-(*R*)-{NH(CH$_3$)CH(CH$_3$)-2-C$_{10}$H$_6$}] (343)

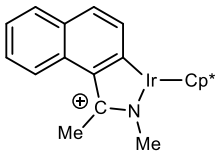


To a 20 mL microwave vial was added chiral amine **337** (58 mg, 0.31 mmol, 1.2 equiv.), sodium acetate (27 mg, 0.33 mmol, 1.5 equiv.), $[IrCp^*Cl_2]_2$ (100 mg, 0.13 mmol, 0.5 equiv.) and 5 mL of degassed (argon purge) acetonitrile. The reaction was sealed and left stirring at 65°C for 20 hours. The reaction was allowed to cool down to room temperature, then the

solvent was removed under vacuum. The residue was filtered through filter paper with toluene, then concentrated under vacuum. The crude product was recrystalised from toluene/pentane to afford the product **343** (50 mg, 35 % yield) as purple crystals suitable for X-Ray crystallography.

m.p.: 220-222°C;

HRMS (ESI): The compound loses HCl and H^- during mass spectroscopy:



Exact mass calculated for $C_{23}H_{27}{}^{193}IrN$ $[M - HCl - H^-]^+$: 510.17673; found : 510.17685 ;

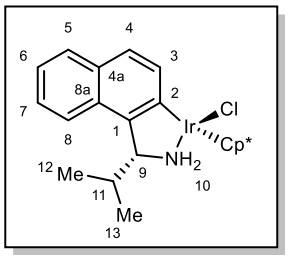
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.75 (ddt, *J* = 8.2, 1.2, 0.6 Hz, 1H, Ar-C**H**), 7.64 – 7.57 (m, 2H, Ar-C**H**), 7.50 (dd, *J* = 8.3, 0.8 Hz, 1H, Ar-C**H**), 7.36 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H, Ar-C**H**), 7.24 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1H, Ar-C**H**), 5.04 (s, 1H, N^{10}**H**), 4.71 (qd, *J* = 6.5, 4.1 Hz, 1H, C^9**H**), 3.04 (d, *J* = 6.4 Hz, 3H, C^{12}**H**$_3$), 1.69 (s, 15H, cp*-C**H**$_3$), 1.26 (d, *J* = 6.5 Hz, 3H, C^{11}**H**$_3$);

^{13}C NMR (101 MHz, CD_2Cl_2) δ 153.6 (Ar-**C**), 145.1 (Ar-**C**), 136.5 (Ar-**C**H), 131.5 (Ar-**C**), 128.8 (Ar-**C**H), 128.4 (Ar-**C**), 126.5 (Ar-**C**H), 125.9 (Ar-**C**H), 123.9 (Ar-**C**H), 123.1 (Ar-**C**H), 87.8 (Cp*-**C**), 67.3 (**C**^{9}H), 40.1 (**C**^{12}H$_3$), 17.9 (**C**^{11}H$_3$), 9.8 (Cp*-**C**H$_3$);

IR (neat) (cm^{-1}) = 3215, 3043, 2972, 2910, 1613, 1574, 1500, 1454, 1420, 1377, 1204, 813, 781, 745;

$[\alpha]_D^{25°C}$ = - 76.5 (c= 0.49, $CHCl_3$)

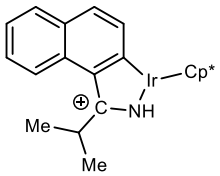
Cp*IrCl[k^2(*N*,*C*)-(*R*)-{NH(CH$_3$)CH(CH(CH$_3$)$_2$)-2-C$_{10}$H$_6$}] (344)



To a 10 mL microwave vial was added chiral amine **338** (28 mg, 0.140 mmol, 1.2 equiv.), sodium acetate (14 mg, 0.160 mmol, 1.5 equiv.), [IrCp*Cl$_2$]$_2$ (50 mg, 0.063 mmol, 0.5 equiv.) and 2.5 mL of degassed (argon purge) acetonitrile. The reaction was sealed and left stirring at 70°C for 20 hours. The reaction was allowed to cool down to room temperature, then the solvent was removed under vacuum. The residue was filtered through filter paper with toluene, then concentrated under vacuum. The crude product was recrystalised from toluene/pentane to afford the product **344** (28 mg, 41 % yield) as yellow crystals.

m.p.: 238-240°C;

HRMS (ESI): The compound loses HCl and H$^-$ during mass spectroscopy:



Exact mass calculated for $C_{24}H_{29}N^{193}Ir$ [M – HCl – H$^-$]$^+$: 524.19238; found: 524.19241;

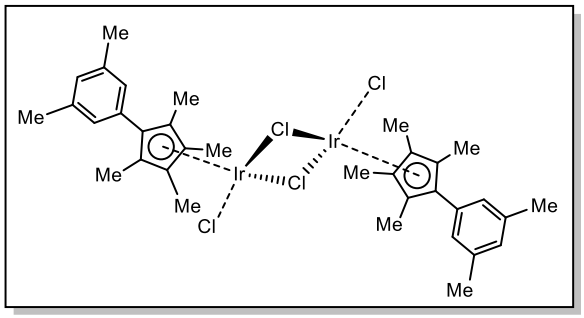
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (t, *J* = 8.5 Hz, 2H, Ar-C**H**), 7.60 (d, *J* = 8.5 Hz, 1H, Ar-C**H**), 7.53 (d, *J* = 8.2 Hz, 1H, Ar-C**H**), 7.31 – 7.27 (m, 1H, Ar-C**H**), 7.18 (ddd, *J* = 8.0, 6.7, 1.1 Hz, 1H, Ar-C**H**), 4.55 (d, *J* = 8.5 Hz, 2H, C^9**H** + N^{10}**H**$_2$), 4.16 (s, 1H, N^{10}**H**$_2$), 1.77 (s, 16H, Cp*-C**H**$_3$ + C^{11}**H**), 1.21 (d, *J* = 6.6 Hz, 3H, -C**H**$_3$), 0.88 (d, *J* = 7.1 Hz, 3H, -C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0 (Ar-**C**), 142.9 (Ar-**C**), 136.0 (Ar-**C**H), 131.2 (Ar-**C**), 130.3 (Ar-**C**), 128.3 (Ar-**C**H), 126.7 (Ar-**C**H), 125.1 (Ar-**C**H), 124.7 (Ar-**C**H), 122.4 (Ar-**C**H), 87.0 (Cp*-**C**), 69.0 (**C**^{9}H), 34.2 (**C**^{11}H), 20.9 (-**C**H$_3$), 20.6 (-**C**H$_3$), 9.6 (Cp*-**C**H$_3$);

IR (neat) (cm^{-1}): 3337, 3252, 2912, 1574, 1132, 1102, 1077, 1027, 813, 782, 750, 697;

[α]$_D^{25°C}$ = - 44.7 (c= 0.44, $CHCl_3$).

Iridium complex (347)



A solution of 2,3,4,5-tetramethylcyclopent-2-en-1-one (0.45 mL, 3.0 mmol, 3.0 equiv.) in 10 mL of THF was stirred at 0°C in an ice bath for 5 minutes. A solution of 0.5 M (3,5-dimethylphenyl)magnesium bromide in 2-MeTHF (18 mL, 9.0 mmol, 9.0 equiv.) was added to the reaction at 0°C, and then the mixture was stirred at room temperature for 4 hours. The reaction was slowly quenched with 5 mL of 2 N HCl at room temperature, and the aqueous layer was extracted with 3 x 25 mL of Et_2O. The combined organics were dried over $MgSO_4$, then filtered through a silica plug, washing with additional Et_2O. The filtrate was concentrated under vacuum, and the crude cyclopentadiene was dissolved in 5 mL degassed methanol and transferred to a 20 mL microwave vial. To the vial was added $IrCl_3*3H_2O$ (353 mg, 1.0 mmol, 1.0 equiv.). The vial was sealed, and the reaction was heated at 80°C for 3 days. The reaction was allowed to cool to room temperature, then cooled to –30°C (freezer) for 3 hours. The resulting precipitate was filtered and washed with 20 mL of cold methanol, and then 100 mL of ether to give the product **347** as an orange powder (400 mg, 82% yield).

m.p.: Decomposes above 300°C;

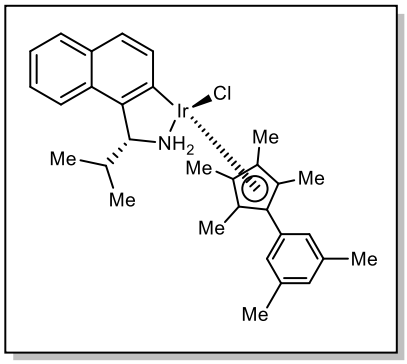
HRMS (ESI): Not found. The complex exchanges chlorides with methanol and shows a very complex spectrum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 4H, Ar-C**H**), 6.97 (s, 2H, Ar-C**H**), 2.32 (s, 12H, Ar-C**H**$_3$), 1.70 (s, 12H, Cp-C**H**$_3$), 1.62 (s, 12H, Cp-C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (Ar-**C**), 130.3 (Ar-**C**H), 129.7 (Ar-**C**), 128.0 (Ar-**C**H), 92.7 (Cp-**C**), 85.6 (Cp-**C**), 83.0 (Cp-**C**), 21.4 (Ar-**C**H$_3$), 10.6 (Cp-**C**H$_3$), 9.7 (Cp-**C**H$_3$);

IR (neat) (cm^{-1}): 2912, 1601, 1450, 1379, 1035, 858, 704.

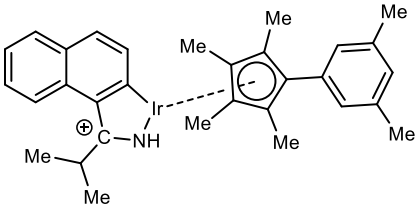
Chiral iridium complex (348)



To a 10 mL microwave vial was added (*R*)-2-methyl-1-(naphthalen-1-yl)propan-1-amine **338** (28 mg, 0.140 mmol, 1.2 equiv.), cesium pivalate (36 mg, 0.160 mmol, 1.5 equiv.), iridium complex **347** (61 mg, 0.063 mmol, 0.5 equiv.) and 2.5 mL of degassed (argon purge) acetonitrile. The reaction was sealed and left stirring at 80°C for 20 hours. The reaction was allowed to cool down to room temperature, then the solvent was removed under vacuum. The residue was portioned between water and DCM, the organic layer was collected, and the aqueous layers was extracted with DCM twice more. The combined organics were dried over Na_2SO_4, and then concentrated under vacuum. The crude product was purified by FCC (DCM/acetone 98:2) and then recrystalised from toluene/pentane to afford the product **348** (35 mg, 18 % yield) as yellow crystals that were suitable for X-Ray crystallography.

m.p.: 228-232°C;

HRMS (ESI): The compound loses HCl and H^- during mass spectroscopy:



Exact mass calculated for $C_{31}H_{35}N^{193}Ir$ $[M - HCl - H^-]^+$: 614.23933; found: 614.23990;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H, Ar-C**H**), 7.59 (d, *J* = 8.5 Hz, 1H, Ar-C**H**), 7.54 (d, *J* = 8.2 Hz, 1H, Ar-C**H**), 7.31 – 7.26 (m, 1H, Ar-C**H**), 7.20 (ddd, *J* = 7.9, 6.7, 1.1 Hz, 1H, Ar-C**H**), 7.01 (s, 2H, Ar-C**H**), 6.97 (s, 1H, Ar-C**H**), 4.73 (dd, *J* = 10.0, 4.9 Hz, 1H, $N^{10}\mathbf{H}_2$), 4.50 (dd, *J* = 9.3, 4.8 Hz, 1H, $C^9\mathbf{H}$), 4.14 (d, *J* = 10.2 Hz, 1H, $N^{10}\mathbf{H}_2$), 2.31 (s, 6H, Ar-

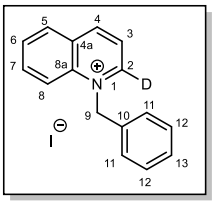
C**H**$_3$), 1.92 (s, 3H, Cp-C**H**$_3$), 1.87 (s, 3H, Cp-C**H**$_3$), 1.83 (s, 3H, Cp-C**H**$_3$), 1.69 (s, 3H, Cp-C**H**$_3$), 1.66 – 1.57 (m, 1H, C^{11}**H**), 0.92 (d, *J* = 6.5 Hz, 3H, -C**H**$_3$), 0.78 (d, *J* = 7.0 Hz, 3H, -C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4 (Ar-**C**), 143.2 (Ar-**C**), 138.1 (2x C, Ar-**C**), 135.7 (Ar-**C**H), 132.1 (Ar-**C**), 131.3 (Ar-**C**), 130.5 (Ar-**C**), 129.4 (Ar-**C**H), 128.3 (Ar-**C**H), 128.3 (2 x C, Ar-**C**H), 126.8 (Ar-**C**H), 125.2 (Ar-**C**H), 124.7 (Ar-**C**H), 122.5 (Ar-**C**H), 98.4 (Cp-**C**), 92.6 (Cp-**C**), 89.8 (Cp-**C**), 82.8 (Cp-**C**), 79.5 (Cp-**C**), 69.0 (**C**^{9}H), 34.0 (**C**^{11}H), 21.4 (2 x C, Ar-**C**H$_3$), 20.6 (-**C**H$_3$), 20.5 (-**C**H$_3$), 11.2 (Cp-**C**H$_3$), 10.1 (Cp-**C**H$_3$), 9.7 (Cp-**C**H$_3$), 9.2 (Cp-**C**H$_3$);

IR (neat) (cm^{-1}): 3347, 3243, 2958, 2919, 1599, 1575, 1643, 1369, 1123, 1094, 1073, 1035, 853, 831, 809, 780, 741, 705, 660, 644;

[*α*]$_D^{25°C}$ = - 94.5 (c= 0.52, $CHCl_3$).

N-Benzylquinolinium-2-d Iodide (354)



A solution of 2-bromoquinoline (208 mg, 1.0 mmol, 1.0 equiv.) in 10 mL anhydrous diethyl ether was cooled to −78°C using a dry ice/acetone bath. To the solution was added slowly *n*BuLi 2.5 M solution in hexanes (0.6 mL, 1.5 mmol, 1.5 equiv.) and the reaction mixture was allowed to stir for 2 hours at −78°C. To the reaction was added 0.7 mL of d4-MeOD at −78°C, then allowing the reaction to warm up to room temperature over 30 min while stirring. The reaction mixture was partitioned between 50 mL of brine and 50 mL of dichloromethane. The organic layer was collected, and the aqueous layer was extracted with dichloromethane (2 x 25 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*, and the resulting crude product was dissolved in 3 mL of acetone. To this solution was added benzyl iodide (436 mg, 2.0 mmol, 2.0 equiv.) and the reaction was allowed to stir at room temperature in the dark overnight. The solvent was

removed *in vacuo*, 25 mL of diethyl ether was added to the crude product and the resulting yellow solid **354** (261 mg, 0.75 mmol, 75% yield) was filtrated and washed with diethyl ether and dried under vacuum for 1 hour.

m.p.: 160-162°C;

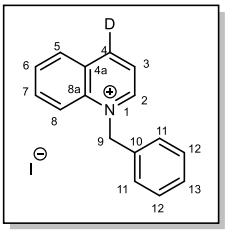
HRMS (ESI): Exact mass calculated for $C_{16}H_{13}D_1N$ $[M]^+$ m/z: 221.11835, found: 221.11837;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (d, *J* = 8.4 Hz, 1H, C^4**H**), 8.54 – 8.48 (m, 2H, C^5**H** + C^8**H**), 8.30 (d, *J* = 8.4 Hz, 1H, C^3**H**), 8.22 (ddd, *J* = 8.9, 7.0, 1.5 Hz, 1H, C^7**H**), 8.03 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H, C^6**H**), 7.43 – 7.33 (m, 5H, C$^{11\text{-}13}$**H**), 6.37 (s, 2H, C^9**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 150.0 (t, *J* = 28.4 Hz, **C**^{2}D), 148.1 (**C**^{4}H), 137.4 (**C**^{8a}), 135.7 (**C**^{7}H), 133.8 (**C**^{10}), 130.8 (**C**^{5}H), 129.9 (**C**^{6}H), 129.8 (**C**^{4a}), 129.1 (2 x C, Ar-**C**H), 128.8 (Ar-**C**H), 127.3 (2 x C, Ar-**C**H), 122.3 (**C**^{3}H), 119.2 (**C**^{8}H), 59.8 (**C**^{9}H$_2$);

IR (neat) (cm^{-1}): 3042, 1621, 1516, 1480, 1438, 1305, 1208, 1132, 1030, 969.

***N*-Benzylquinolinium-4-d Iodide (355)**



A solution of 4-bromoquinoline (208 mg, 1.0 mmol, 1.0 equiv.) in 10 mL anhydrous diethyl ether was cooled to −78°C using a dry ice/acetone bath. To the solution was added slowly *n*BuLi 2.5 M solution in hexanes (0.6 mL, 1.5 mmol, 1.5 equiv.) and the reaction mixture was allowed to stir for 2 hours at −78°C. To the reaction was added 0.7 mL of d4-MeOD at −78°C, then allowing the reaction to warm up to room temperature over 30 min while stirring. The reaction mixture was partitioned between 50 mL of brine and 50 mL of dichloromethane. The organic layer was collected, and the aqueous layer was extracted with dichloromethane (2 x 25 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*, and the resulting crude product was dissolved in 3 mL of acetone. To this solution was added benzyl iodide (436 mg,

2.0 mmol, 2.0 equiv.) and the reaction was allowed to stir at room temperature in the dark overnight. The solvent was removed *in vacuo*, 25 mL of diethyl ether was added to the crude product and the resulting yellow solid **355** (236 mg, 0.68 mmol, 68% yield) was filtrated and washed with diethyl ether and dried under vacuum for 1 hour.

m.p.: 160-162°C;

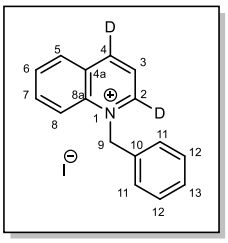
HRMS (ESI): Exact mass calculated for $C_{16}H_{13}D_1N$ $[M]^+$ m/z: 221.11835, found: 221.11843;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.73 (d, *J* = 5.8 Hz, 1H, C^2**H**), 8.54 – 8.48 (m, 2H, C^5**H** + C^8**H**), 8.30 (d, *J* = 5.8 Hz, 1H C^3**H**), 8.22 (ddd, *J* = 8.9, 7.0, 1.5 Hz, 1H, C^7**H**), 8.03 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H, C^6**H**), 7.43 – 7.33 (m, 5H, C$^{11\text{-}13}$**H**), 6.37 (s, 2H, C^9**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 150.4 (**C**^{2}H), 147.7 (t, *J* = 28.4 Hz, **C**^{4}D), 137.5 (**C**^{8a}), 135.7 (**C**^{7}H), 133.8 (**C**^{10}), 130.8 (**C**^{5}H), 130.0 (**C**^{6}H), 129.8 (**C**^{4a}), 129.1 (2 x C, Ar-**C**H), 128.8 (Ar-**C**H), 127.3 (2x C, Ar-**C**H), 122.3 (**C**^{3}H), 119.3 (**C**^{8}H), 59.9 (**C**^{9}H$_2$);

IR (neat) (cm^{-1}): 2924, 2361, 1622, 1597, 1524, 1392, 1376, 1127, 1047, 966.

N-Benzylquinolinium-2,4-d$_2$ Iodide



A solution of 2,4-dibromoquinoline (287 mg, 1.0 mmol, 1 equiv.) in 20 mL anhydrous diethyl ether was cooled to −78°C using a dry ice/acetone bath. To the solution was added slowly *sec*-BuLi 1.4 M solution in hexanes (2.14 mL, 3 mmol, 3 equiv.) and the reaction mixture was allowed to stir for 2 hours at −78°C. To the reaction was added 0.7 mL of d4-MeOD at −78°C, then allowing the reaction to warm up to room temperature over 30 min while stirring. The reaction mixture was partitioned between 50 mL of brine and 50 mL of dichloromethane. The organic layer was collected, and the aqueous layer was extracted with dichloromethane (2 x 25 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*, and the resulting crude

product was dissolved in 3 mL of acetone. To this solution was added benzyl iodide (436 mg, 2.0 mmol, 2. equiv.) and the reaction was allowed to stir at room temperature in the dark overnight. The solvent was removed *in vacuo*, 25 mL of diethyl ether was added to the crude product and the resulting yellow solid (150 mg, 0.44 mmol, 44 % yield) was filtrated and washed with diethyl ether and dried under vacuum for 1 hour.

m.p.: 158-160°C;

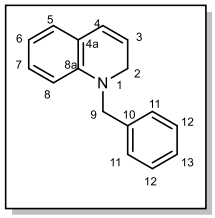
HRMS (ESI): Exact mass calculated for $C_{16}H_{12}D_2N$ [M^+] m/z: 222.12463, found: 222.12489;

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 – 8.48 (m, J = 8.7 Hz, 2H, C^5**H** + C^8**H**), 8.31 (s, 1H, C^3**H**), 8.21 (ddd, J = 8.7, 7.0, 1.6 Hz, 1H, C^7**H**), 8.02 (dd, J = 8.3, 7.0 Hz, 1H, C^6**H**), 7.42 – 7.33 (m, 5H, C$^{11\text{-}13}$**H**), 6.40 (s, 2H, C^9**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 150.1 (t, J = 28.4 Hz, **C**^{2}D), 147.8 (t, J = 28.4 Hz, **C**^{4}D), 137.5 (**C**^{8a}), 135.8 (**C**^{7}H), 133.8 (**C**^{10}), 130.8 (**C**^{5}H), 130.0 (**C**^{6}H), 129.8 (**C**^{4a}), 129.1 (2 x C, Ar-**C**H), 128.8 (Ar-**C**H), 127.3 (2 x C, Ar-**C**H), 122.3 (**C**^{3}H), 119.3 (**C**^{8}H), 59.9 (**C**^{9}H$_2$);

IR (neat) (cm^{-1}): 2941, 1571, 1511, 1375, 945, 762, 744, 712, 693, 633.

***N*-Benzyl-1,2-dihydroquinoline (356)**



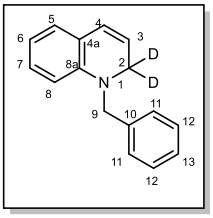
To a suspension of quinolinium benzyl iodide **242** (1.0 g, 3.0 mmol, 1.0 equiv.) in 25 mL of diethyl ether was slowly added lithium aluminium hydride (170 mg, 4.5 mmol, 1.5 equiv.) at room temperature. The reaction was stirred at room temperature for 15 min, then slowly quenched with 0.2 mL of water and stirred for an additional 10 minutes. To the reaction was added 0.2 mL 15 % sodium hydroxide solution and stirred at room temperature for an additional 10 minutes. To the reaction was added 0.6 mL of water and the reaction was stirred for 10 minutes. Finally, $MgSO_4$ (ca. 2 g) was added and the reaction was stirred for another 5 min. the resulting suspension was filtered with diethyl ether through a pad of basic Al_2O_3 (activity IV) then

concentrated to give the unstable crude dihydroquinoline **356** as a yellow oil (498 mg, 75%). This oil was used immediately in our mechanistic investigations. The structure of this compound was assigned by comparison with the literature spectroscopic data for the N-methyl analogue.[84]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.10 (m, 5H, $C^{10\text{-}13}$**H**), 6.96 (ddd, *J* = 8.2, 7.4, 1.7 Hz, 1H, C^{7}**H**), 6.85 (dd, *J* = 7.3, 1.7 Hz, 1H, C^{5}**H**), 6.56 (td, *J* = 7.4, 1.1 Hz, 1H, C^{6}**H**), 6.45 (d, *J* = 8.2 Hz, 1H, C^{8}**H**), 6.33 (dt, *J* = 9.8, 1.8 Hz, 1H, C^{4}**H**), 5.64 (dt, *J* = 9.9, 3.9 Hz, 1H, C^{3}**H**), 4.37 (s, 2H, C^{9}**H**$_2$), 4.19 (dd, *J* = 3.8, 2.0 Hz, 2H, C^{2}**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5 (Ar-**C**), 137.5 (Ar-**C**), 129.2 (Ar-**C**), 128.8 (2 x C, Ar-**C**H), 127.4 (2 x C, Ar-**C**H), 127.2 (Ar-**C**H), 127.1 (Ar-**C**H), 126.7 (Ar-**C**H), 122.0 (Ar-**C**H), 121.9 (Ar-**C**H), 116.9 (Ar-**C**H), 110.2 (Ar-**C**H), 53.8 (**C**^{9}H$_2$), 50.6 (**C**^{2}H$_2$).

N-Benzyl-1,2-dihydroquinoline-2,2-d$_2$ (357)

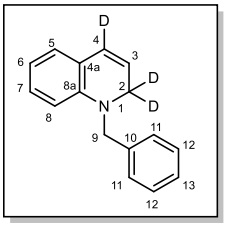


To a suspension of *N*-benzylquinolinium-2-d iodide **354** (1.1 g, 3.0 mmol, 1.0 equiv.) in 25 mL of diethyl ether was slowly added lithium aluminium deuteride (1.0 M in ether, 5.0 mL, 5.0 mmol, 1.7 equiv.) at room temperature. The reaction was stirred at room temperature for 15 min, then slowly quenched with 0.2 mL of water and stirred for an additional 10 minutes. To the reaction was added 0.2 mL 15 % sodium hydroxide solution and stirred at room temperature for an additional 10 minutes. To the reaction was added 0.6 mL of water and the reaction was stirred for 10 minutes. Finally, $MgSO_4$ (ca. 2 g) was added and the reaction was stirred for another 5 min. the resulting suspension was filtered with diethyl ether through a pad of basic Al_2O_3 (activity IV) then concentrated to give the unstable crude dihydroquinoline **357** as a yellow oil (482 mg, 72%). This oil was used immediately in our mechanistic investigations.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.15 (m, 5H, $C^{10\text{-}13}$**H**), 6.90 (ddd, *J* = 8.1, 7.3, 1.7 Hz, 1H, C^{7}**H**), 6.79 (dd, *J* = 7.3, 1.7 Hz, 1H, C^{5}**H**), 6.50 (td, *J* = 7.3, 1.1 Hz, 1H, C^{6}**H**), 6.39 (d, *J* = 8.2 Hz, 1H, C^{8}**H**), 6.27 (dd, *J* = 9.8, 0.8 Hz, 1H, C^{4}**H**), 5.57 (d, *J* = 9.9 Hz, 1H, C^{3}**H**), 4.31 (s, 2H, C^{9}**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5 (Ar-**C**), 137.6 (Ar-**C**), 129.2 (Ar-**C**), 128.8 (2 x C, Ar-**C**H), 127.4 (2 x C, Ar-**C**H), 127.2 (Ar-**C**H), 127.1 (Ar-**C**H), 126.8 (Ar-**C**H), 121.9 (Ar-**C**H), 121.8 (Ar-**C**H), 116.9 (Ar-**C**H), 110.2 (Ar-**C**H), 53.8 (**C**^{9}H$_2$), 49.9 (q, *J* = 20.1 Hz, **C**^{2}D$_2$).

N-Benzyl-1,2-dihydroquinoline-2,2,4-d$_3$

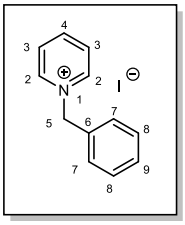


To a suspension of *N*-benzylquinolinium-2,4-d2 iodide (0.35 g, 1.0 mmol) in 15 mL of diethyl ether was slowly added lithium aluminium deuteride (1M in ether, 1.6 mL, 1.6 mmol) at room temperature. The reaction was stirred at room temperature for 15 min, then slowly quenched with 0.1 mL of water and stirred for an additional 10 minutes. To the reaction was added 0.1 mL 15 % sodium hydroxide solution and stirred at room temperature for an additional 10 minutes. To the reaction was added 0.3 mL of water and the reaction was stirred for 10 minutes. Finally, $MgSO_4$ (ca. 2 g) was added and the reaction was stirred for another 5 min. the resulting suspension was filtered with diethyl ether through a pad of basic Al_2O_3 (activity IV) then concentrated to give the unstable crude dihydroquinoline as a yellow oil (66%). This oil was used immediately in our mechanistic investigations.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 5H, $C^{10\text{-}13}$**H**), 6.96 (ddd, *J* = 8.3, 7.4, 1.7 Hz, 1H, C^{7}**H**), 6.86 (dd, *J* = 7.3, 1.7 Hz, 1H, C^{5}**H**), 6.57 (td, *J* = 7.4, 1.1 Hz, 1H, C^{6}**H**), 6.46 (dd, *J* = 8.2, 1.0 Hz, 1H, C^{8}**H**), 5.63 (s, 1H, C^{3}**H**), 4.37 (s, 2H, C^{9}**H**$_2$);

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.5 (Ar-**C**), 137.5 (Ar-**C**), 129.2 (Ar-**C**), 128.8 (2 x C, Ar-**C**H), 127.3 (2 x C, Ar-**C**H), 127.1 (Ar-**C**H), 127.1 (Ar-**C**H), 126.4 (t, *J* = 23.4 Hz, **C**^{4}D), 121.8 (Ar-**C**H), 121.7 (Ar-**C**H), 116.9 (Ar-**C**H), 110.2 (Ar-**C**H), 53.7 (**C**$^9H_2$)., 49.8 (q, *J* = 20.1 Hz, **C**$^2D_2$).

N-Benzylpyridinium iodide (369)



A mixture of pyridine (0.40 mL, 5.0 mmol, 1.0 equiv.) and benzyl iodide (1.25 mL, 10.0 mmol, 2.0 equiv.) in acetone (10.0 mL) was stirred at room temperature for 16 hours in the dark. To the reaction was added 50 mL of water and 50 ml of diethyl ether. The aqueous layer was washed with diethyl ether (2 x 25 mL). Water was then removed under reduced pressure. The resulting solid was then dried in a desiccator over activated silica under high vacuum to give *salt* **369** (1.40 g, 4.7 mmol) as a very hygroscopic white solid in 94% yield.

m.p.: The melting point could not be determined accurately due to the solid being very hygroscopic.

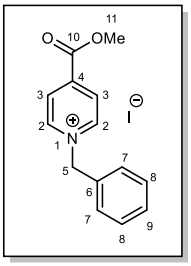
HRMS (ESI): Not found. The molecule fragments during spectroscopy;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (m, 2H, C^{2,}**H**), 8.65 (t, *J* = 7.8 Hz, 1H, C^4**H**), 8.21 (t, *J* = 7.0 Hz, 2H, C^3**H**), 7.60 – 7.52 (m, 2H, Ar-C**H**), 7.49 – 7.41 (m, 3H, Ar-C**H**), 5.90 (s, 2H, C^5**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 146.6 (**C**^{4}H), 145.4 (**C**^{2}H), 134.9 (**C**^{6}), 130.0 (Ar-**C**H), 129.9 (2 x C, Ar-**C**H), 129.4 (2 x C, Ar-**C**H), 129.1 (**C**^{3}H), 63.8 (**C**$^7H_2$);

IR (neat) (cm^{-1}): 3437, 3043, 1625, 1478, 1454, 1206, 1161, 1098, 1050, 1023, 774, 748, 702, 678.

N-(Benzyl)-4-(methoxycarbonyl)pyridinium Iodide (370)



The title compound was prepared according to **General Procedure F** using methyl isonicotinate (0.86 mL, 7.3 mmol) to give *salt* **370** (2.56 g, 99%) as a yellow solid.

m.p.: 170-172°C;

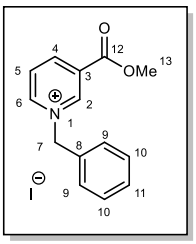
HRMS (ESI): Exact mass calculated for $C_{14}H_{14}O_2N$ $[M]^+$ m/z: 228.10191, found: 228.10208;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (d, J = 6.8 Hz, 2H, C^2**H**), 8.54 (d, J = 6.2 Hz, 2H, C^3**H**), 7.66-7.49 (m, 2H, Ar-**H**), 7.50-7.42 (m, 3H, Ar-**H**), 5.97 (s, 2H, C^5**H**$_2$), 3.97 (s, 3H, C^{11}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.5 (**C**^{10}), 146.3 (**C**^{2}H), 144.1 (**C**^{4}), 133.9 (**C**^{6}), 129.5 (**C**^{3}H), 129.3 (2 x C, Ar-**C**H), 129.0 (2 x C, Ar-**C**H), 127.6 (Ar-**C**H), 63.6 (**C**^{5}H$_2$), 53.9 (**C**^{11}H$_3$);

IR (neat) (cm^{-1}): 1734, 1642, 1452, 1217, 1157, 962, 747, 703, 662, 647.

N-(Benzyl)-3-(methoxycarbonyl)pyridinium Iodide (371)



The title compound was prepared according to **General Procedure F** using methyl nicotinate (0.86 mL, 7.3 mmol) to give *salt* **371** (2.40 g, 92%) as a yellow solid.

m.p.: 87- 89°C;

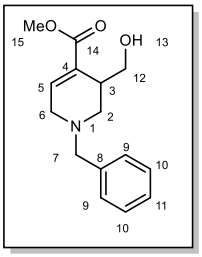
HRMS (ESI): Exact mass calculated for $C_{14}H_{14}O_2N$ $[M]^+$ m/z: 228.10191, found: 228.10196;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H, C^2**H**), 9.37 (dt, J = 6.2, 1.3 Hz, 1H, C^6**H**), 9.01 (dt, J = 8.1, 1.5 Hz, 1H, C^4**H**), 8.31 (dd, J = 8.1, 6.1 Hz, 1H, C^5**H**), 7.60 – 7.41 (m, 5H, C$^{9\text{-}11}$**H**), 5.99 (s, 2H, C^7**H**$_2$), 3.98 (s, 3H, C^{13}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.1 (**C**^{12}), 147.8 (**C**^{4}H), 145.9 (**C**^{2}H), 145.6 (**C**^{6}H), 133.9 (Ar-**C**), 130.2 (Ar-**C**) , 129.5 (Ar-**C**H), 129.2 (2 x C, Ar-**C**H), 128.9 (2 x C, Ar-**C**H), 128.8 (Ar-**C**H), 63.5 (**C**^{7}H$_2$), 53.6 (**C**^{13}H$_3$);

IR (neat) (cm^{-1}): 3029, 2947, 1737, 1636, 1498, 1473, 1444, 1317, 1301, 1131, 740, 677.

Methyl-*N*-benzyl-3-(hydroxymethyl)-1,2,3,6-tetrahydropyridine-4-carboxylate (372)



The title compound was prepared according to **General Procedure G** using *pyridinium* **370** (178 mg, 0.5 mmol). The crude material was purified by FCC (50:50:0.1 pentane:EtOAc:*i*PrOH) to give *amine* **371** (117 mg, 90%) as a yellow oil.

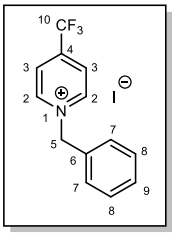
HRMS (ESI): Exact mass calculated for $C_{15}H_{20}O_3N$ $[M+H]^+$ m/z: 262.14377, found: 262.14375;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 5H, $C^{9\text{-}11}$**H**), 7.03 (dd, *J* = 4.6, 2.2 Hz, 1H, C^5**H**), 3.84 (t, *J* = 2.8 Hz, 2H, C^{12}**H**$_2$), 3.73 (s, 3H, C^{15}**H**$_3$), 3.64 – 3.56 (m, 2H, C^7**H**$_2$), 3.43 (dd, *J* = 18.9, 4.5 Hz, 1H, C^6**H**$_2$), 3.07 (dt, *J* = 11.3, 1.4 Hz, 1H, C^2**H**$_2$), 2.80 (dt, *J* = 19.0, 2.4 Hz, 1H, C^6**H**$_2$), 2.73 – 2.69 (m, 1H, C^3**H**), 2.47 (ddd, *J* = 11.3, 3.6, 1.5 Hz, 1H, C^2**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3 (**C**^{14}), 138.7 (**C**^{5}H), 136.8 (**C**^{8}), 129.1 (2 x C, Ar-**C**H), 128.8 (**C**^{4}), 128.7 (2 x C, Ar-**C**H), 127.7 (Ar-**C**H), 66.4 (**C**^{12}H$_2$), 62.5 (**C**^{7}H$_2$), 55.2 (**C**^{2}H$_2$), 52.8 (**C**^{6}H$_2$), 51.8 (**C**^{15}H$_3$), 36.2 (**C**^{3}H);

IR (neat) (cm^{-1}): 3399, 2917, 1711, 1454, 1435, 1254, 1101, 1075, 1054, 1008.

***N*-(Benzyl)-4-(trifluoromethyl)pyridinium Iodide (381)**



The title compound was prepared according to **General Procedure F** using 4-trifluoromethylpyridine (441 mg, 5.0 mmol) to give *salt* **381** (1.75 g, 95%) as a yellow solid.

m.p.: 141-143°C;

HRMS (ESI): Exact mass calculated for $C_{13}H_{11}F_3N$ $[M]^+$ m/z: 238.08381, found: 238.08387;

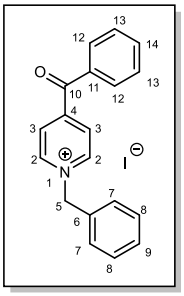
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (d, *J* = 6.4 Hz, 2H, C^2**H**), 8.68 (d, *J* = 6.2 Hz, 2H, C^3**H**), 7.62-7.55 (m, 2H, Ar-C**H**), 7.50-7.45 (m, 3H, Ar-C**H**), 5.98 (s, 2H, C^5**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 147.1 (**C**^{2}H), 143.6 (q, J = 34.0 Hz, **C**^{4}))133.6 (**C**^{6}), 129.6 (Ar-**C**H), 129.2 (2 x C, Ar-**C**H), 129.1 (2 x C, Ar-**C**H), 125.4 (q, J = 3.7 Hz, **C**^{3}H), 121.3 (q, J = 274.9 Hz, **C**^{10}F$_3$), 64.0 (**C**^{5}H$_2$);

^{19}F NMR (377 MHz, DMSO-d_6) δ –63.9

IR (neat) (cm^{-1}): 3105, 3038, 3004, 2961, 1465, 1280, 1076, 701.

N-Benzyl-4-benzoyl-pyridinium Iodide (382)



The title compound was prepared according to **General Procedure F** using 4-benzoylpyridine (917 mg, 5.0 mmol) to give *salt* **382** (1.99 g, 97%) as a yellow solid.

m.p.: 184-186°C;

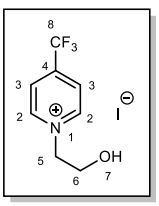
HRMS (ESI): Exact mass calculated for $C_{19}H_{16}ON$ $[M]^+$ m/z: 274.12264, found: 274.12264;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (d, J = 6.8 Hz, 2H, C^{2}**H**), 8.40 (d, J = 6.8 Hz, 2H, C^{3}**H**), 7.89-7.84 (m, 2H, C^{12}**H**), 7.80 (ddt, J = 8.7, 7.2, 1.3 Hz, 1H, C^{14}**H**), 7.66-7.59 (m, 4H, Ar-C**H**), 7.53-7.46 (m, 3H, Ar-C**H**), 5.97 (s, 2H, C^{5}**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 192.0 (**C**^{10}), 151.8 (Ar-**C**), 145.7 (**C**^{2}H), 134.8 (Ar-**C**H), 134.1 (Ar-**C**), 133.9 (Ar-**C**), 130.3 (**C**^{12}H), 129.5 (Ar-**C**H), 129.2 (2 x C, Ar-**C**H), 129.1 (4 x C, Ar-**C**H), 127.4 (**C**^{3}H), 63.5 (**C**^{5}H$_2$);

IR (neat) (cm^{-1}): 1664, 1496, 1451, 1383, 1312, 1071, 998, 937,750, 655.

N-(2-Hydroxyethyl)-4-(trifluoromethyl)pyridinium iodide (383)



4-Trifluoropyridine (588 mg, 4.0 mmol) and 2-iodoethanol (1.03 g, 6 mmol) were heated at 90°C in dioxane (10 mL) for 14 hours. The solution was cooled down and Et$_2$O (20 mL) was added and the resulting suspension was filtered.

The solid was washed with Et_2O and dried under high vacuum for 1 hour to yield *salt* **383** (510 mg, 40%) as a yellow solid.

m.p.: 125-127°C;

HRMS (ESI): Exact mass calculated for $C_8H_9NOF_3$ $[M]^+$ m/z: 192.06308, found: 192.06309;

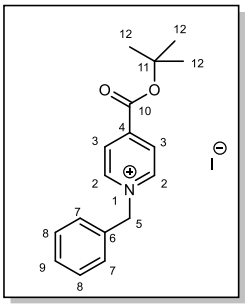
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (d, J = 6.4 Hz, 2H, C^2**H**), 8.70 (d, J = 6.4 Hz, 2H, C^3**H**), 5.24 (t, J = 5.5 Hz, 1H, O^7**H**), 4.79 (t, J = 4.9 Hz, 2H, C^5**H**$_2$), 3.89 (q, J = 5.1 Hz, 2H, C^6**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 147.5 (**C**^{2}H), 142.9 (q, J = 36 Hz, **C**^{4}), 124.5 (q, J = 3.5 Hz, **C**^{3}H), 121.4 (q, J = 275 Hz, **C**^{8}F$_3$), 63.94 (**C**^{5}H$_2$), 59.97 (**C**^{6}H$_2$);

^{19}F NMR (377 MHz, DMSO-d_6) δ –63.85;

IR (neat) (cm^{-1}): 3288, 3017, 1653, 1471, 1444, 1255, 1190, 1120, 1062, 991.

N-Benzyl-4-(tert-butoxycarbonyl)pyridinium iodide (384)



A mixture of methyl isonicotinate (2.5 g, 18.2 mmol, 1.0 equiv.) and Li*O*t*B*u (2.1 g, 26.2 mmol, 1.4 equiv.) was refluxed in 40 mL of THF for 4 hours. The reaction was allowed to cool down, then it was partitioned between 100 mL of water and 100 mL of EtOAc. The organic layer was collected, and the aqueous layer was extracted twice more. The combined organics were dried over $MgSO_4$ and filtered through a silica plug, washing with additional EtOAc. The filtrate was concentrated under vacuum, and the crude pyridine was subjected to **General Procedure F** to give *salt* **384** (7.15 g, 98% over 2 steps) as a yellow solid.

m.p.: 158-160°C;

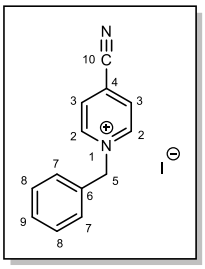
HRMS (ESI): Exact mass calculated for $C_{17}H_{20}O_2N$ $[M]^+$ m/z: 270.14886, found: 270.14890;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (d, J = 6.2 Hz, 2H, C^2**H**), 8.49 (d, J = 6.2 Hz, 2H, C^3**H**), 7.56 – 7.41 (m, 5H, Ar-C**H**), 5.97 (s, 2H, C^5**H**$_2$), 1.58 (s, 9H, C^{12}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 161.3 (**C**^{10}), 146.7 (**C**^{2}H), 146.1 (Ar-**C**), 134.5 (Ar-**C**), 129.9 (Ar-**C**H), 129.7 (2 x C, Ar-**C**H), 129.3 (2 x C, Ar-**C**H), 128.1 (**C**^{3}H), 84.8 (**C**^{11}), 64.0 (**C**^{5}H$_2$), 27.9 (**C**^{12}H$_3$);

IR (neat) (cm^{-1}): 2972, 1723, 1451, 1303, 1158, 1128, 1115, 874, 827, 767, 750, 729, 690.

N-Benzyl-4-cyanopyridinium iodide (385)



The title compound was prepared according to **General Procedure F** using isonicotinonitrile (312 mg, 3.0 mmol) to give *salt* **385** (802 mg, 83%) as a yellow solid.

m.p.: 189-191°C;

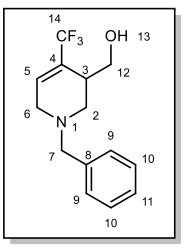
HRMS (ESI): Exact mass calculated for $C_{13}H_{11}N_2$ $[M]^+$ m/z: 195.09167, found: 195.09192;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (d, J = 6.3 Hz, 2H, C^{2}**H**), 8.72 (d, J = 6.2 Hz, 2H, C^{3}**H**), 7.60 – 7.42 (m, 5H, Ar-C**H**), 5.95 (s, 2H, C^{5}**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 146.1 (**C**^{2}H), 133.5 (Ar-**C**), 131.4 (**C**^{3}H), 129.6 (Ar-**C**H), 129.2 (2 x C, Ar-**C**H), 129.1 (2 x C, Ar-**C**H), 127.4 (Ar-**C**), 114.7 (**C**^{10}), 64.2 (**C**^{5}H$_2$);

IR (neat) (cm^{-1}): 2969, 1637, 1454, 1143, 1060, 817, 769, 725, 700.

(*N*-Benzyl-4-(trifluoromethyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (390)



The title compound was prepared according to **General Procedure G** using *pyridinium* **381** (183 mg, 0.5 mmol). The crude material was purified by FCC (95:5 DCM:EtOAc) to give *amine* **390** (102 mg, 75%) as a colourless oil.

HRMS (ESI): Exact mass calculated for $C_{14}H_{17}ONF_3$ $[M+H]^+$ m/z: 272.12521, found: 272.12568;

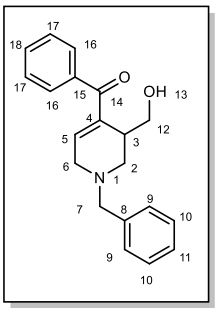
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H, $C^{9\text{-}11}$**H**), 6.49 (dt, *J* = 4.0, 1.9 Hz, 1H, C^{5}**H**), 4.82 (br s, 1H, O^{13}**H**), 3.94-3.81 (m, 2H, C^{12}**H**$_2$), 3.67 (d, *J* = 12.7 Hz, 1H, C^{7}**H**$_2$), 3.61 (d, *J* = 12.7 Hz, 1H, C^{7}**H**$_2$), 3.42 (ddd, *J* = 18.1, 4.4, 2.6 Hz, 1H, C^{6}**H**$_2$), 3.11 (dd, *J* = 11.2, 1.3 Hz, 1H, C^{2}**H**$_2$), 2.79 (dtd, *J* = 18.2, 3.5, 1.7 Hz, 1H, C^{6}**H**$_2$), 2.58-2.48 (m, 2H, C^{3}**H** + C^{2}**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4 (**C**^{8}), 131,2 (q, *J* = 6.1 Hz, **C**^{5}H), 129.0 (2 x C, Ar-**C**H), 128.7 (2 x C, Ar-**C**H), 127.8 (Ar-**C**H), 126.7 (q, *J* = 30.8 Hz, **C**^{4}), 123.5 (q, *J* = 272.6 Hz, **C**$^{14}F_3$), 65.7 (**C**$^{12}H_2$), 62.4 (**C**$^{7}H_2$), 55.2 (**C**$^{2}H_2$), 51.7 (**C**$^{6}H_2$), 35.1 (**C**^{3}H);

^{19}F NMR (377 MHz, $CDCl_3$) δ –66.8□

IR (neat) (cm^{-1}): 2980, 2888, 1383, 1293, 1146, 1111, 983, 956, 728, 699.

(*N*-Benzyl-3-(hydroxymethyl)-1,2,3,6-tetrahydropyridin-4-yl)(phenyl)methanone (391)



The title compound was prepared according to **General Procedure G** using *pyridinium* **382** (201 mg, 0.5 mmol). The crude material was purified by FCC (80:20:0.1 pentane:EtOAc:*i*PrOH) to give *amine* **xx** (114 mg, 74%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{20}H_{22}NO_2$ $[M+H]^+$ m/z: 308.16451, found: 308.16437;

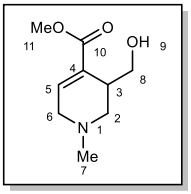
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 2H, Ar-C**H**), 7.53 – 7.27 (m, 8H, Ar-C**H**), 6.53 (dd, *J* = 4.5, 2.2 Hz, 1H, C^{5}**H**), 3.89 (dd, *J* = 10.5, 2.8 Hz, 1H, C^{12}**H**), 3.78 (ddd, *J* = 10.5, 3.1, 2.0 Hz, 1H, C^{12}**H**), 3.69 (d, *J* = 12.8 Hz, 1H, C^{7}**H**), 3.59 (d, *J* = 12.8 Hz, 1H, C^{7}**H**), 3.49 (dd, *J* = 19.1, 4.5 Hz, 1H, C^{6}**H**), 3.17 (dt, *J* = 11.3, 1.4 Hz, 1H, C^{2}**H**), 3.13-3.08 (m, 1H, C^{3}**H**), 2.82 (dt, *J* = 19.1, 2.3 Hz, 1H, C^{6}**H**), 2.56 (ddd, *J* = 11.3, 3.7, 2.0 Hz, 1H, C^{2}**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8 (**C**^{14}), 141.1 (**C**^{5}H), 138.4 (Ar-**C**), 137.1 (Ar-**C**), 136.8 (Ar-**C**), 132.0 (Ar-**C**H), 129.5 (2 x C, Ar-**C**H), 129.2 (2 x C, Ar-**C**H), 128.7 (2 x C, Ar-**C**H),

128.2 (2 x C, Ar-**C**H), 127.7 (Ar-**C**H), 66.4 (**C**^{12}H), 62.6 (**C**^{7}H$_2$), 55.5 (**C**^{2}H$_2$), 52.7 (**C**^{6}H$_2$), 35.8 (**C**^{3}H);

IR (neat) (cm^{-1}): 2981, 2889, 1641, 1597, 1578, 1494, 1447, 1385, 1363, 1303, 1268, 1144, 1068.

Methyl-*N*-methyl-3-(hydroxymethyl)-1,2,3,6-tetrahydropyridine-4-carboxylate (392)



The title compound was prepared according to **General Procedure G** using *pyridinium* **386** (139 mg, 0.5 mmol). The crude material was purified by FCC (100% acetone) to give *amine* **392** (63 mg, 68%) as a yellow oil.

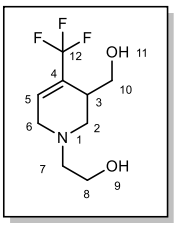
HRMS (ESI): Exact mass calculated for $C_9H_{16}O_3N$ $[M+H]^+$ m/z: 186.11247, found: 186.11237;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (dd, *J* = 4.5, 1.9 Hz, 1H, C^{5}**H**), 3.92 – 3.80 (m, 2H, C^{8}**H**$_2$), 3.72 (s, 3H, C^{11}**H**$_3$), 3.44 (ddd, *J* = 18.1, 4.5, 1.1 Hz, 1H, C^{6}**H**$_2$), 2.95 (dt, *J* = 11.3, 1.4 Hz, 1H, C^{2}**H**$_2$), 2.76 – 2.67 (m, 2H, C^{6}**H**$_2$ + C^{3}**H**), 2.42 (ddd, *J* = 11.2, 3.5, 2.2 Hz, 1H, C^{2}**H**$_2$), 2.33 (s, 3H, C^{7}**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (**C**^{10}), 138.8 (**C**^{5}H), 128.5 (**C**^{4}), 66.6 (**C**^{8}H$_2$), 57.4 (**C**^{2}H$_2$), 54.6 (**C**^{6}H$_2$), 51.8 (**C**^{11}H$_3$), 45.1 (**C**^{7}H$_3$), 36.1 (**C**^{3}H);

IR (neat) (cm^{-1}): 3360, 2949, 1710, 1653, 1436, 1254, 1242, 1134, 1089, 1013.

2-(3-(Hydroxymethyl)-4-(trifluoromethyl)-3,6-dihydropyridin-1(2H)-yl)ethan-1-ol (393)



The title compound was prepared according to **General Procedure G** using *pyridinium* **383** (159 mg, 0.5 mmol). The crude material was purified by FCC (70:20:10 CH_2Cl_2:acetone:*i*PrOH) to give *amine* **393** (59 mg, 52%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_9H_{15}O_2N_2F_3$ $[M+H]^+$ m/z: 226.10494, found: 226.10490;

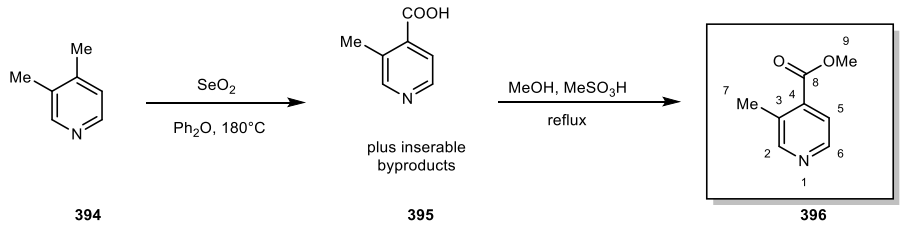
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (dt, *J* = 4.0, 1.9 Hz, 1H, C^5**H**), 3.93-3.82 (m, 2H, C^{10}**H**$_2$), 3.81 – 3.68 (m, 2H, C^8**H**$_2$), 3.52 (ddd, *J* = 18.2, 4.4, 2.5 Hz, 1H, C^6**H**$_2$), 3.19 – 3.12 (m, 1H, C^2**H**$_2$), 2.92 – 2.82 (m, 1H, C^6**H**$_2$), 2.66 (t, *J* = 5.3 Hz, 2H, C^7**H**$_2$), 2.57 – 2.48 (m, 2H, C^2**H**$_2$ +C^3**H**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 131.4 (q, *J* = 6.0 Hz, **C**^{5}H), 126.9 (q, *J* = 30.6 Hz, **C**^{4}), 123.5 (q, *J* = 273 Hz, **C**^{12}) 65.1 (**C**^{10}H$_2$) , 59.0 (2 x C, **C**^{7}H$_2$ + **C**^{8}H$_2$), 54.2 (**C**^{2}H$_2$), 52.1 (**C**^{6}H$_2$), 35.3 (**C**^{3}H);

^{19}F NMR (377 MHz, $CDCl_3$) δ –66.7;

IR (neat) (cm^{-1}): 3345, 2914, 1682, 1392, 1296, 1150, 1111, 1025, 982, 932.

Methyl 3-methylisonicotinate (396)



394 395 396

To a two necked flask equipped with a water condenser that is opened to the atmosphere was added 3,4-dimethylpyridine (5.6 mL, 50.0 mmol, 1.0 equiv.) in 50 mL of Ph_2O and the solution was heated to 120°C. To this hot solution was added SeO_2 (8.88g, 80.0 mmol, 1.6 equiv.) in portions. The reaction was heated to 180°C and left stirring for one hour. The reaction was allowed to cool to room temperature, and then filtered with water through filter paper. The aqueous layer was washed with 2 x 100 mL of $CHCl_3$. and concentrated to afford the crude carboxylic acid **395**, which was dissolved in 50 mL of methanol. To this solution was added methanesulphonic acid (6.0 ml, 90.0 mmol, 1.8 equiv.) and the reaction was refluxed overnight. The reaction was allowed to cool to room temperature, and then poured into 300 mL of cold

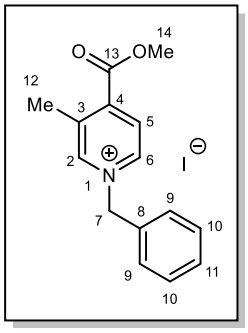
solution of saturated $NaHCO_3$. The aqueous layer was extracted with DCM (3 x 150 mL), the resulting organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude material was purified by flash column chromatography (1-5% Acetone in DCM) to give the product **396** (3.17 g, 42 % yield) as a light green oil.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.56 – 8.51 (m, 2H, C^2**H** + C^6**H**), 7.66 (d, *J* = 5.0 Hz, 1H, C^5**H**), 3.91 (s, 3H, C^9**H$_3$**), 2.54 (s, 3H, C^7**H$_3$**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6 (**C**^{8}), 152.9 (Ar-**C**H), 147.9 (Ar-**C**H), 136.4 (Ar-**C**), 133.5 (Ar-**C**), 123.1 (Ar-**C**H), 52.4 (**C**^{9}H$_3$), 18.2 (**C**^{7}H$_3$).

Spectroscopic data was consistent with that reported in the literature. [211]

***N*-(Benzyl)-3-methyl-4-(methoxycarbonyl)pyridinium Iodide (397)**



The title compound was prepared using **General Procedure F** using methyl 3-methylisonicotinate (560 mg, 3.7 mmol) to give *salt* **397** (938 mg, 69%) as a yellow solid.

m.p.: 170-172°C;

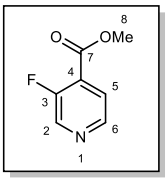
HRMS (ESI): Exact mass calculated for $C_{15}H_{16}O_2N$ $[M]^+$ m/z: 242.11756, found:242.11750;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H, C^2**H**), 9.18 (d, *J* = 6.3 Hz, 1H, C^6**H**), 8.38 (d, *J* = 6.3 Hz, 1H, C^3**H**), 7.67-7.53 (m, 2H, Ar-C**H**), 7.52-7.39 (m, 3H, Ar-C**H**), 5.87 (s, 2H, C^7**H$_2$**), 3.95 (s, 3H, C^{14}**H$_3$**), 2.63 (s, 3H, C^{12}**H$_3$**);

^{13}C NMR (101 MHz, DMSO-d_6) δ 163.6 (**C**^{13}), 147.1 (**C**^{2}H), 144.2 (**C**^{4}), 143.0 (**C**^{6}H), 138.7 (Ar-**C**), 133.8 (Ar-**C**), 129.5 (Ar-**C**H), 129.2 (2 x C, Ar-**C**H), 128.9 (2 x C, Ar-**C**H), 127.8 (**C**^{5}H), 65.5 (**C**^{7}H$_2$), 53.6 (**C**^{14}H$_3$), 17.7 (**C**^{12}H$_3$);

IR (neat) (cm^{-1}): 1721, 1567, 1311, 1282, 1202, 1069, 1024, 972, 767, 704.

Methyl 3-fluoroisonicotinate (399)



To a solution of 3-fluoroisonicotinic acid **398** (635 mg, 4.5 mmol, 1.0 equiv.) in 5 mL of methanol was added methanesulphonic acid (0.6 mL, 9.0 mmol, 2.0 equiv.) and the reaction was refluxed overnight. The reaction was allowed to cool to room temperature, and then poured into 100 mL of cold solution of saturated $NaHCO_3$. The aqueous layer was extracted with DCM (3 x 50 mL), the resulting organic layer was dried over Na_2SO_4, then concentrated under vacuum to give the product **399** (614 mg, 88 % yield) as a light green oil.

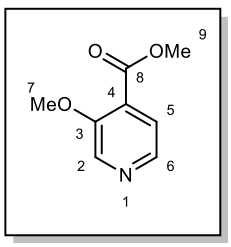
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.3 Hz, 1H, C^{2}**H**), 8.54 (dd, *J* = 4.9, 0.9 Hz, 1H, C^{6}**H**), 7.76 (td, *J* = 5.3, 4.9, 0.8 Hz, 1H, C^{5}**H**), 3.97 (d, *J* = 2.0 Hz, 3H, C^{8}**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5 (d, *J* = 3.0 Hz, **C**^{7}), 157.1 (d, *J* = 269.2 Hz, **C**^{3}F), 146.1 (d, *J* = 5.8 Hz, **C**^{5}H), 140.6 (d, *J* = 25.3 Hz, **C**^{2}H), 125.3 (d, *J* = 8.3 Hz, **C**^{4}), 124.5 (d, *J* = 1.5 Hz, **C**^{6}H), 53.1 (d, *J* = 2.8 Hz, **C**^{8}H$_3$);

^{19}F NMR (377 MHz, $CDCl_3$) δ –124.95 (dd, *J* = 6.3, 2.5 Hz).

Spectroscopic data was consistent with that reported in the literature. [212]

Methyl 3-methoxy-isonicotinate (400)



Methyl 3-fluoroisonicotinate **399** (775 mg, 5.0 mmol, 1.0 equiv.) was dissolved in methanol (10 mL) and at room temperature sodium methoxide (405 mg, 7.5 mmol, 1.5 equiv.) was added. The solution was heated at 65°C for 3 hours then cooled to room temperature and concentrated. The crude material was partitioned between water (50 mL) and CH_2Cl_2 (50 mL) and separated. The aqueous layer was extracted twice more (CH_2Cl_2 2 x 50 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give *pyridine* **400** (710 mg, 85%) as a white solid.

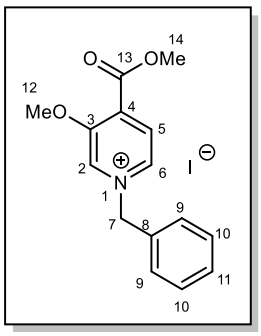
m.p.: 54-56°C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H, C^{2}**H**), 8.33 (d, *J* = 4.9 Hz, 1H, C^{6}**H**), 7.57 (dd, *J* = 4.8, 0.6 Hz, 1H, C^{5}**H**), 4.01 (s, 3H, C^{7}**H**$_3$), 3.92 (s, 3H, C^{9}**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4 (**C**^{8}), 153.6 (Ar-**C**), 142.6 (Ar-**C**H), 136.0 (Ar-**C**H), 126.9 (Ar-**C**), 123.9 (Ar-**C**H), 56.9 (**C**^{7}H$_3$), 52.7 (**C**^{9}H$_3$).

Spectroscopic data was consistent with that reported in the literature.[213]

***N*-(Benzyl)-3-methoxy-4-(methoxycarbonyl)pyridinium Iodide (401)**



The title compound was a prepared by **General Procedure F** using pyridine **400** (668 mg, 4.0 mmol) to give *salt* **401** (1.51 g, 98%) as a yellow solid.

m.p.: 160-162°C;

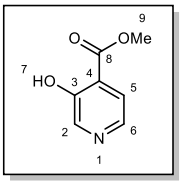
HRMS (ESI): Exact mass calculated for $C_{15}H_{16}O_3N$ $[M]^+$ m/z: 258.11247, found: 258.11251;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (d, *J* = 1.3 Hz, 1H, C^{2}**H**), 8.88 (dd, *J* = 6.2, 1.3 Hz, 1H, C^{6}**H**), 8.29 (d, *J* = 6.1 Hz, 1H, C^{5}**H**), 7.62-7.57 (m, 2H, Ar-C**H**), 7.48-7.43 (m, 3H, Ar-C**H**), 5.89 (s, 2H, C^{7}**H**$_2$), 4.11 (s, 3H, C^{12}**H**$_3$), 3.92 (s, 3H, C^{14}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.5 (**C**^{13}), 155.5 (**C**^{3}), 137.7 (**C**^{6}H), 134.0 (**C**^{4}), 133.9 (**C**^{8}), 132.7 (**C**^{2}H), 129.4 (Ar-**C**H), 129.1 (2 x C, Ar-**C**H), 128.8 (2 x C, Ar-**C**H), 122.8 (**C**^{5}H), 64.0 (**C**^{7}H$_2$), 58.5 (**C**^{12}H$_3$), 53.6 (**C**^{14}H$_3$);

IR (neat) (cm^{-1}): 1738, 1475, 1459, 1341, 1313, 1204, 1090, 893, 819, 705.

Methyl 3-hydroxyisonicotinate (403)



To a solution of 3-hydroxyisonicotinic acid **402** (626 mg, 4.5 mmol, 1.0 equiv.) in 5 mL of methanol was added methanesulphonic acid (0.6 mL, 9.0 mmol, 2.0 equiv.) and the reaction was refluxed overnight. The reaction was allowed to cool to room temperature, and then poured into 100 mL of cold solution of saturated $NaHCO_3$. The aqueous layer was extracted with DCM (3 x 50 mL), the resulting organic layer was dried over Na_2SO_4, then concentrated under vacuum to give the product **403** (647 mg, 94 % yield) as a light brown solid.

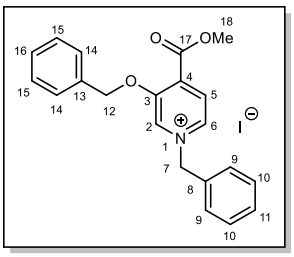
m.p.: 75-77°**C**;

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H, O^7**H**), 8.50 (s, 1H, C^2**H**), 8.21 (d, *J* = 5.1 Hz, 1H, C^6**H**), 7.61 (d, *J* = 5.1 Hz, 1H, C^5**H**), 4.00 (s, 3H, C^9**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4 (**C**^{8}), 155.7 (Ar-**C**), 142.2 (Ar-**C**H), 140.7 (Ar-**C**H), 121.6 (Ar-**C**H), 118.0 (Ar-**C**), 53.1 (**C**^{9}H$_3$).

Spectroscopic data was consistent with that reported in the literature. [214]

***N*-(Benzyl)-3-benzoxy-4-(methoxycarbonyl)pyridinium Iodide (404)**



Methyl 3-hydroxyisonicotinate **403** (765 mg, 5.0 mmol, 1.0 equiv.) was dissolved in MeCN (50 mL) and to the reaction was added cesium carbonate (1.95 g, 6.0 mmol, 1.2 equiv.) and benzyl iodide (3.27 g, 15 mmol, 3.0 equiv.). The reaction was stirred at room temperature for 16 hours in the dark. The suspension was concentrated *in vacuo* and loaded onto a silica plug, eluting with CH_2Cl_2 (300 mL), then eluting with acetone (1 L). The acetone filtrate was concentrated *in vacuo* and the resulting solid was suspended in acetone (50 mL) and diethyl ether (200 mL) and was sonicated and filtered. The resultant solid was washed with

diethyl ether (100 mL) and dried for 1 hour under high vacuum to give *salt* **404** (1.73 g 75%) as an orange solid.

m.p.: 166-168°C;

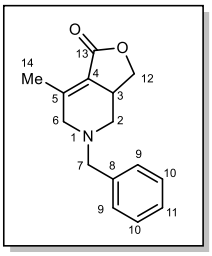
HRMS (ESI): Exact mass calculated for $C_{21}H_{20}O_3N$ $[M]^+$ m/z: 334.14377, found: 334.14357;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 1H, C^2**H**), 8.94 (d, J = 6.2 Hz, 1H, C^6**H**), 8.33 (d, J = 6.1 Hz, 1H, C^5**H**), 7.58-7.52 (m, 2H, Ar-C**H**), 7.50-7.38 (m, 8H, Ar-C**H**), 5.88 (s, 2H, C^7**H**$_2$), 5.49 (s, 2H, C^{12}**H**$_2$), 3.91 (s, 3H, C^{18}**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.4 (**C**^{17}), 154.5 (**C**^{3}), 138.1 (**C**^{6}H), 134.6 (Ar-**C**), 134.4 (Ar-**C**), 133.9 (Ar-**C**), 133.5 (**C**^{2}H), 129.4 (Ar-**C**H), 129.2 (2 x C, Ar-**C**H), 128.74 (2 x C, Ar-**C**H), 128.71 (2 x C, Ar-**C**H), 128.6 (Ar-**C**H), 128.1 (2 x C, Ar-**C**H), 127.6 (**C**^{5}H), 72.1 (**C**^{7}H$_2$), 64.1 (**C**^{12}H$_2$), 53.5 (**C**^{18}H$_3$);

IR (neat) (cm^{-1}): 1741, 1511, 1355, 1313, 1254, 1137, 1086, 1006, 728, 693.

N-Benzyl-7-methyl-3a,4,5,6-tetrahydrofuro[3,4-c]pyridin-1(3H)-one (407b)



The title compound was prepared according to **General Procedure G** using *pyridinium* **397** (185 mg, 0.5 mmol). The crude material was purified by FCC (1-5% acetone in CH_2Cl_2) to give *amine* **407b** (100 mg, 82%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{15}H_{17}O_2N$ $[M+H]^+$ m/z: 244.13321, found: 244.13331;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.12 (m, 5H, $C^{9\text{-}11}$**H**), 4.34 (t, J = 8.5 Hz, 1H, C^{12}**H**$_2$), 3.68 (dd, J = 7.6, 1.3 Hz, 1H, C^{12}**H**$_6$), 3.66 (d, J = 12.9 Hz, 1H, C^7**H**$_2$), 3.55 (d, J = 13.1 Hz, 1H, C^7**H**$_2$), 3.35 (dd, J = 18.7, 3.0 Hz, 1H, C^6**H**$_2$), 3.21 (m, 1H, C^3**H**), 3.07 (dd, J = 10.5, 5.3 Hz, 1H, C^2**H**$_2$), 2.78 (m, 1H, C^6**H**$_2$), 2.02 (d, J = 2.5 Hz, 3H, C^{14}**H**$_3$), 1.93 (t, J = 10.1 Hz, 1H, C^2**H**$_2$);

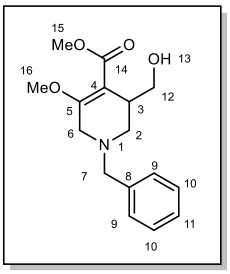
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9 (**C**^{13}), 146.7 (**C**^{5}), 137.7 (Ar-**C**), 129.1 (2 x C, Ar-**C**H), 128.6 (2 x C, Ar-**C**H), 127.6 (Ar-**C**H), 120.4 (**C**^{4}), 69.2 (**C**$^{12}H_2$), 61.8 (**C**$^{7}H_2$), 58.1 (**C**$^{6}H_2$), 52,3 (**C**$^{2}H_2$), 38.2 (**C**^{3}H), 15.8 (**C**$^{14}H_3$);

IR (neat) (cm^{-1}): 2889, 1747, 1688, 1381, 1254, 1151, 968, 770, 682, 636.

Methyl-*N*-benzyl-3-(hydroxymethyl)-5-methoxy-1,2,3,6-tetrahydropyridine-4-carboxylate (408a) and ***N*-Benzyl-7-methoxy-3a,4,5,6-tetrahydrofuro[3,4-c]pyridin-1(3H)-one (408b)**

The title compounds were prepared according to **General Procedure G** using *pyridinium* **401** (193 mg, 0.5 mmol). The crude material was purified by FCC (5-10% acetone in CH_2Cl_2) to give *open amine* **408a** (74 mg, 51%) and *lactone* **408b** (35 mg, 27%). To access exclusively *lactone* **408b**, the crude material was dissolved in PhMe (6 mL) and titanium *iso*propoxide (0.5 mmol, 1.0 equiv.) was added and the solution was stirred at room temperature for 14 hours. The solution was poured into a 5% aqueous solution of EDTA and extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The crude material was purified by FCC (90:10 CH_2Cl_2:acetone) to give *lactone* **408b** (104 mg, 80%) as a colourless oil.

***Open-Product* (408a)**:



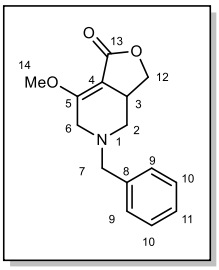
HRMS (ESI): Exact mass calculated for $C_{16}H_{22}O_4N$ $[M+H]^+$ m/z: 292.15433, found: 292.15428;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H, C$^{9\text{-}11}$**H**), 3.78 – 3.75 (m, 2H, C^{12}**H**$_2$), 3.73 (s, 3H, C^{15}**H**$_3$), 3.69 (s, 3H, C^{16}**H**$_3$), 3.62 (q, *J* = 12.8 Hz, 2H, C^{7}**H**$_2$), 3.51 – 3.44 (m, 1H, C^{6}**H**$_2$), 3.03 (dt, *J* = 11.3, 1.4 Hz, 1H, C^{2}**H**$_2$), 2.82 – 2.72 (m, 2H, C^{3}**H** + C^{6}**H**$_2$), 2.47 – 2.40 (m, 1H, C^{2}**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (**C**^{14}), 162.2 (**C**^{5}), 136.5 (**C**^{8}), 129.1 (2 x C, Ar-**C**H), 128.8 (2 x C, Ar-**C**H), 127.9 (Ar-**C**H), 106.3 (**C**^{4}), 66.6 (**C**$^{12}H_2$), 62.5 (**C**$^{7}H_2$), 57.1 (**C**$^{16}H_3$), 54.9 (**C**$^{2}H_2$), 52.6 (**C**$^{6}H_2$), 51.6 (**C**$^{15}H_3$), 36.6 (**C**^{3}H);

IR (neat) (cm^{-1}): 3413, 2922, 1702, 1629, 1454, 1435, 1290, 1271, 1216, 1121.

***Lactone* (408b)**:



HRMS (ESI): Exact mass calculated for $C_{15}H_{18}O_3N$ $[M+H]^+$ m/z: 260.12812, found: 260.12815;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 5H, C$^{9\text{-}11}$**H**), 4.32 (t, *J* = 8.3 Hz, 1H, C^{12}**H**$_2$), 3.94 (s, 3H, C^{14}**H**$_3$), 3.76 – 3.61 (m, 3H, C^{12}**H**$_2$ + 2 x C^{7}**H**$_2$), 3.50 (dd, *J* = 17.3, 2.2 Hz, 1H, C^{6}**H**$_2$), 3.43 – 3.31 (m, 1H, C^{3}**H**), 3.05 (dd, *J* = 10.6, 5.0 Hz, 1H, C^{2}**H**$_2$), 2.95 (dd, *J* = 17.3, 3.5 Hz, 1H, C^{6}**H**$_2$), 1.98 (t, *J* = 10.3 Hz, 1H, C^{2}**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2 (**C**^{13}), 160.7 (**C**^{5}), 137.2 (**C**^{8}), 128.9 (2 x C, Ar-**C**H), 128.6 (2 x C, Ar-**C**H), 127.6 (Ar-**C**H), 99.8 (**C**^{4}), 69.0 (**C**$^{12}H_2$), 61.6 (**C**$^{7}H_2$), 58.4 (**C**$^{14}H_3$), 53.0 (**C**$^{6}H_2$), 52.2 (**C**$^{2}H_2$), 38.1 (**C**^{3}H);

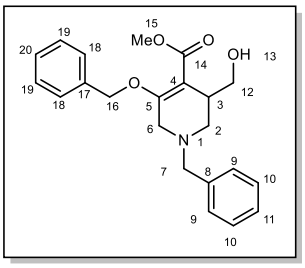
IR (neat) (cm^{-1}): 2919, 1746, 1666, 1454, 1263, 1200, 1163, 1140, 1009, 989.

Methyl-*N*-benzyl-3-(hydroxymethyl)-5-benzloxy-1,2,3,6-tetrahydropyridine-4-carboxylate (409a) and ***N*-Benzyl-7-benzloxy-3a,4,5,6-tetrahydrofuro[3,4-c]pyridin-1(3H)-one (409b)**

The title compounds were prepared according to **General Procedure G** using *pyridinium* **404** (231 mg, 0.5 mmol). The crude material was purified by FCC (3-5% acetone in CH_2Cl_2) to give *open amine* **409a** (84 mg, 46%) and *lactone* **409b** (50 mg, 30%). To access exclusively *lactone* **409b**, the crude material was dissolved in PhMe (6 mL) and titanium *iso*propoxide (0.5 mmol, 1.0 equiv.) was added and the solution was stirred at room temperature for 14 hours. The solution was poured into a 5% aqueous solution of EDTA and extracted with CH_2Cl_2 (3 x

50 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The crude material was purified by FCC (3-5% acetone in CH_2Cl_2) to give *lactone* **409b** (131 mg, 78%) as a colourless oil.

***Open product* (409a)**:



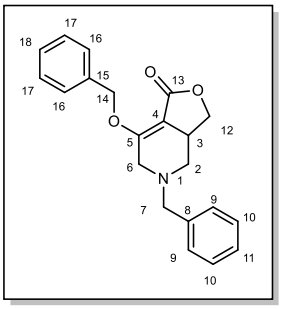
HRMS (ESI): Exact mass calculated for $C_{22}H_{26}O_4N$ $[M+H]^+$ m/z: 368.18563, found: 368.18554;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 10H, $C^{9\text{-}13}\mathbf{H}$ + $C^{18\text{-}20}\mathbf{H}$), 4.96 – 4.89 (m, 2H, $C^{16}C\mathbf{H}_2$), 3.80 – 3.78 (m, 2H, $C^{12}\mathbf{H}_2$), 3.75 (s, 3H, $C^{15}\mathbf{H}_3$), 3.63 (d, *J* = 12.8 Hz, 1H, $C^{7}\mathbf{H}_2$), 3.55 (d, *J* = 12.9 Hz, 1H, $C^{7}\mathbf{H}_2$), 3.46 (d, *J* = 16.8 Hz, 1H, $C^{6}\mathbf{H}_2$), 3.03 (dt, *J* = 11.3, 1.5 Hz, 1H, $C^{2}\mathbf{H}_2$), 2.82 – 2.72 (m, 2H, $C^{3}\mathbf{H}$ + $C^{6}\mathbf{H}_2$), 2.44 (dd, *J* = 11.3, 3.7 Hz, 1H, $C^{2}\mathbf{H}_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 ($\mathbf{C}^{14}$), 161.6 ($\mathbf{C}^{5}$), 136.9 (Ar-**C**), 136.6 (Ar-**C**), 129.1 (2 x C, Ar-**C**H), 128.8 (2 x C, Ar-**C**H), 128.6 (2 x C, Ar-**C**H), 128.2 (Ar-**C**H), 127.9 (Ar-**C**H), 127.4 (2 x C, Ar-**C**H), 108.7 ($\mathbf{C}^{4}$), 72.3 ($\mathbf{C}^{16}H_2$), 66.7 ($\mathbf{C}^{12}H_2$), 62.5 ($\mathbf{C}^{7}H_2$), 55.1 ($\mathbf{C}^{2}H_2$), 53.6 ($\mathbf{C}^{6}H_2$), 51.6 ($\mathbf{C}^{15}H_3$), 36.8 ($\mathbf{C}^{3}$H);

IR (neat) (cm^{-1}): 3418, 3029, 1706, 1633, 1454, 1402, 1288, 1265, 1173, 1118.

***Lactone* (409b)**:



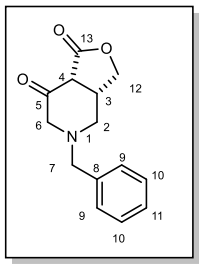
HRMS (ESI): Exact mass calculated for $C_{21}H_{22}O_3N$ $[M+H]^+$ m/z: 336.15942, found: 336.15896;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 10H, $C^{8\text{-}11}\mathbf{H}$ + $C^{16\text{-}18}\mathbf{H}$), 5.45 (d, *J* = 12.3 Hz, 1H, $C^{14}\mathbf{H}_2$), 5.27 (d, *J* = 12.3 Hz, 1H, $C^{14}\mathbf{H}_2$), 4.35 (t, *J* = 8.2 Hz, 1H, $C^{12}\mathbf{H}_2$), 3.73 (dd, *J* = 8.6, 2.1 Hz, 1H, $C^{12}\mathbf{H}_2$), 3.71 – 3.57 (m, 2H, $C^{7}\mathbf{H}_2$), 3.50 – 3.34 (m, 2H, $C^{6}\mathbf{H}_2$ + $C^{3}\mathbf{H}$), 3.05 (dd, *J* = 10.6, 5.0 Hz, 1H, $C^{2}\mathbf{H}_2$), 2.92 (dd, *J* = 17.3, 3.4 Hz, 1H, $C^{6}\mathbf{H}_2$), 1.97 (t, *J* = 10.4 Hz, 1H, $C^{2}\mathbf{H}_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2 (**C**^{13}), 159.9 (**C**^{5}), 137.3 (Ar-**C**), 136.6 (Ar-**C**), 129.0 (2 x C, Ar-**C**H), 128.7 (2 x C, Ar-**C**H), 128.6 (2 x C, Ar-**C**H), 128.3 (Ar-**C**H), 127.8 (2 x C, Ar-**C**H), 127.7 (Ar-**C**H), 101.4 (**C**^{4}), 73.9 (**C**$^{14}H_2$), 69.1 (**C**$^{12}H_2$), 61.6 (**C**$^{7}H_2$), 54.3 (**C**$^{6}H_2$), 52.3 (**C**$^{2}H_2$), 38.5 (**C**^{3}H);

IR (neat) (cm^{-1}): 2894, 1747, 1668, 1122, 1165, 1073, 1009, 988, 743, 698.

5-Benzyltetrahydrofuro[3,4-c]pyridine-1,7(3H,4H)-dione (410)



The title compound was prepared by **General Procedure G** from salt **404** (231 mg, 0.5 mmol) with an additional work-up. The crude material was dissolved in 25 mL of toluene and to the solution was added p-toluenesulfonic acid (190 mg, 1 mmol, 2 equiv.). The reaction was left stirring at 60°C for 3 hours. The reaction mixture was allowed to cool to room temperature, then partitioned between 50 mL saturated solution of NaHCO3 and 50 mL of CH2Cl2. The organic layer was separated, and the aqueous layer was basified to pH 11-12 by adding solid K2CO3 and extracted with CH2Cl2 (2 x 25 mL). The organic layers were combined, dried over Na2SO4, and concentrated in vacuo. The crude material was purified by FCC (70:30:0.1 to 50:50:0.1 pentane:EtOAc:iPrOH) to give beta-ketolactone **410** (73 mg, 60%) as a pale-yellow oil (single sin diastereoisomer confirmed by NOE).

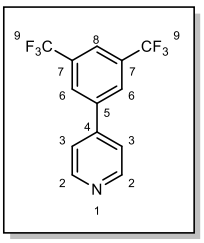
HRMS (ESI): Exact mass calculated for $C_{14}H_{16}NO_3$ $[M+H]^+$ m/z: 246.11247, found: 246.11253;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 5H, C$^{9\text{-}11}$**H**), 4.41 (dd, *J* = 9.2, 6.9 Hz, 1H, C^{12}**H**$_2$), 4.15 (dd, *J* = 9.3, 2.7 Hz, 1H, C^{12}**H**$_2$), 3.66 (d, *J* = 13.1 Hz, 1H, C^{7}**H**$_2$), 3.53 – 3.47 (m, 2H, C^{7}**H** + C^{4}**H**), 3.37 (d, *J* = 17.5 Hz, 1H, C^{6}**H**$_2$), 3.05 – 2.96 (m, 2H, C^{6}**H**$_2$ + C^{3}**H**), 2.65 (d, *J* = 4.7 Hz, 2H, C^{2}**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6 (**C**^{5}), 171.1 (**C**^{13}), 136.9 (**C**^{8}), 128.9 (2 x C, Ar-**C**H), 128.8 (2 x C, Ar-**C**H), 127.9 (Ar-**C**H), 72.7 (**C**$^{12}H_2$), 63.7 (**C**$^{6}H_2$), 61.4 (**C**$^{7}H_2$), 53.9 (**C**$^{2}H_2$), 52.1 (**C**^{4}H), 36.1 (**C**^{3}H);

IR (neat) (cm^{-1}): 2924, 2855, 1773, 1724, 1454, 1377, 1207, 1163, 1028, 750.

3,5-bis(trifluoromethyl)phenylpyridine (415)



4-Bromopyridine hydrochloride **413** (1.94 g, 10 mmol, 1.0 equiv.), 3,5-bis(trifluoromethyl)benzene boronic acid **414** (3.00 g, 12 mmol, 1.2 equiv.), triphenylphosphine (262 mg, 1 mmol, 10 mol%), potassium carbonate (5.1 g, 37 mmol, 3.7 equiv.), DCE (50 mL), and water (10 mL) were added to a two-necked flask with a reflux condenser fitted. The solution was sparged with argon for 10 minutes then palladium (II) acetate (56 mg, 0.25 mmol, 2.5 mol%) was added and the solution was heated at reflux (92°C) under argon for 14 hours. The solution was cooled down and partitioned between water (100 mL) and DCM (100 mL). The aqueous layer was extracted with DCM (2 x 100 mL) and the organic layers were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The crude material was purified by flash column chromatography (1-3% Acetone in DCM) to give *pyridine* **415** (2.7 g, 93%) as a white solid.

m.p.: 123-125°C;

HRMS (ESI): Exact mass calculated for $C_{13}H_8F_6N$ $[M + H]^+$ m/z: 292.05555, found: 292.05551;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.5, 1.6 Hz, 2H, C^{2}**H**), 8.06 (s, 2H, C^{6}**H**), 7.96 (s, 1H, C^{8}**H**), 7.54 (dd, *J* = 4.5, 1.6 Hz, 2H, C^{3}**H**);

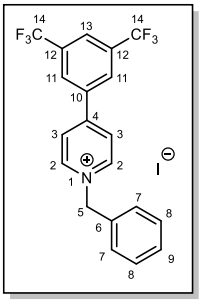
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.0 (**C**^{2}H), 145.5 (Ar-**C**), 140.6 (Ar-**C**), 132.8, (q, *J* = 33.6 Hz, **C**^{7}), 127.4 (q *J* = 3.0 Hz, **C**^{6}), 123.3 (q, *J* = 278.9 Hz, **C**$^{9}F_3$), 122.8 (m, **C**^{8}), 121.7 (**C**^{3}H);

^{19}F NMR (377 MHz, $CDCl_3$) δ –62.9;

IR (neat) (cm^{-1}): 1595, 1379, 1282, 1269, 1163, 1115, 1102, 1072, 1059, 952, 906, 841, 817, 699, 682, 666, 622.

Spectroscopic data was consistent with that reported in the literature. [215]

N-Benzyl-4-(3,5-bis(trifluoromethyl)phenyl)pyridinium Iodide (416)



The title compound was prepared according to **General Procedure F** using *pyridine* **415** (1.16 g, 4.0 mmol) to give *salt* **416** (1.90 g, 93%) as a yellow solid.

m.p.: 240-242°C;

HRMS (ESI): Exact mass calculated for $C_{20}H_{14}F_6N$ $[M]^+$ m/z: 382.10250, found: 382.10249;

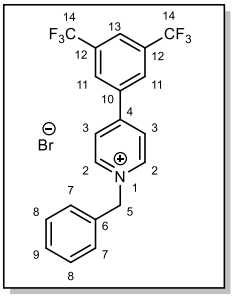
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 (d, J = 7.1 Hz, 2H, C^2**H**), 8.77 (d, J = 7.0 Hz, 2H, C^3**H**), 8.72 (s, 2H, C^{11}**H**), 8.42 (s, 1H, C^{13}**H**), 7.68 – 7.54 (m, 2H, Ar-C**H**), 7.53 – 7.36 (m, 3H, Ar-C**H**), 5.91 (s, 2H, C^5**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 152.3 (**C**^{4}), 145.0 (**C**^{2}H), 136.5 (**C**^{5}), 134.4 (Ar-**C**), 131.3 (q, J = 33.4 Hz, **C**^{12}), 129.4 (m, **C**^{11}H), 129.4 (Ar-**C**H), 129.2 (2 x C, Ar-**C**H), 128.7 (2 x C, Ar-**C**H), 126.5 (**C**^{3}H), 125.1 (m, **C**^{13}H), 123.0 (q, J = 273.3 Hz, **C**^{14}F$_3$), 62.9 (**C**^{5}H$_2$);

^{19}F NMR (377 MHz, DMSO-d_6) δ –61.1;

IR (neat) (cm^{-1}): 1707, 1562, 1382, 1275, 1129, 1089, 1060, 955, 696, 682.

N-Benzyl-4-(3,5-bis(trifluoromethyl)phenyl)pyridinium Bromide (417)



A mixture of 4-(3,5-bis(trifluoromethyl)phenyl)pyridine **415** (582 mg, 2.0 mmol 1.0 equiv.) and benzyl bromide (0.36 mL, 3.0 mmol, 1.5 equiv.) in 5 mL of dioxane was stirred at 90°C for 16 hours. The mixture was allowed to cool to room temperature, then the solvent was removed under reduced pressure and 25 mL of diethyl ether was added. The resulting suspension was sonicated (5 min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium bromide salt **417** (869 mg, 94 % yield) as a white solid.

m.p.: 272-275°C;

HRMS (ESI): Exact mass calculated for $C_{20}H_{14}NF_6$ $[M]^+$ m/z: 382.10250, found: 382.10266;

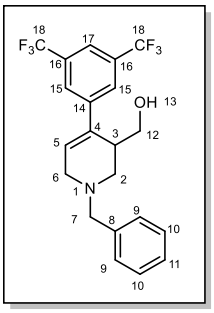
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (d, J = 7.0 Hz, 2H, C^2**H**), 8.80 (d, J = 7.0 Hz, 2H, C^3**H**), 8.73 (s, 2H, C^{11}**H**), 8.37 (s, 1H, C^{13}**H**), 7.65 (dd, J = 7.8, 1.7 Hz, 2H, Ar-C**H**), 7.49 – 7.40 (m, 3H, Ar-C**H**), 6.00 (s, 2H, C^5**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 152.3 (**C**^{4}), 145.0 (**C**^{2}H), 136.6 (**C**^{5}), 134.5 (Ar-**C**), 131.33 (q, J = 33.4 Hz, **C**^{12}), 129.4 (m, **C**^{11}H), 129.3 (Ar-**C**H), 129.2 (2 x C, Ar-**C**H), 128.8 (2 x C, Ar-**C**H), 126.5 (**C**^{3}H), 125.0 (m, **C**^{13}H), 123.01 (d, J = 273.1 Hz, **C**^{14}F$_3$). 62.6 (**C**^{5}H$_2$);

^{19}F NMR (376 MHz, DMSO-d_6) δ –61.2;

IR (neat) (cm^{-1}): 1634, 1378, 1285, 1275, 1192, 1171, 1128, 1058, 911, 868, 847, 819, 746, 735, 713, 695, 684, 633.

(*N*-Benzyl-4-(3,5-bis(trifluoromethyl)phenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (418)



Pyridinium **416** (225 mg, 0.5 mmol), $[Rh(Cp^*)Cl_2]_2$ (1 mol%), and paraformaldehyde (300 mg, 20 equiv.) were added to a vial and $Mg(OMe)_2$ (0.75 equiv. MeOH solution) and methanol (total volume 2.5 mL) were added and the solution was heated at 65°C for 14 hours under an atmosphere of argon. To the reaction was added thiourea (50 mg) and the reaction was stirred for an additional 30 minutes. The solution was partitioned between brine (50 mL) water (50 mL) and CH_2Cl_2 (50 ml) and the aqueous layer was extracted with additional CH_2Cl_2 (2 x 25 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The crude material was purified by FCC (80:20:0.1 pentane:EtOAc:*i*PrOH) to give *amine* **418** (112 mg, 54%).

HRMS (ESI): Exact mass calculated for $C_{21}H_{20}ONF_6$ $[M+H]^+$ m/z: 416.14395, found: 416.14436;

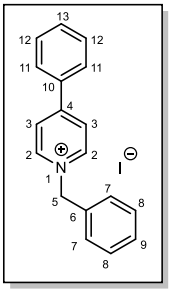
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.77 (m, 3H, 2 x C^{15}**H** + C^{17}**H**), 7.41-7.29 (m, 5H, $C^{9\text{-}11}$**H**), 6.24 (dd, *J* = 4.8, 2.2 Hz, 1H, C^5**H**), 5.02 (br s, 1H, O^{13}**H**), 3.84 (dd, *J* = 10.5, 2.4 Hz, 1H, C^{12}**H**$_2$), 3.72 (d, *J* = 12.8 Hz, 1H, C^7**H**$_2$), 3.64 (d, *J* = 12.8 Hz, 1H, C^7**H**$_2$), 3.58 (ddd, *J* = 10.4, 3.0, 2.2 Hz, 1H, C^{12}**H**$_2$), 3.47 (dd, *J* = 17.6, 4.8 Hz, 1H, C^6**H**$_2$), 3.25 (dt, *J* = 11.3, 1.5 Hz, 1H, C^2**H**$_2$), 2.90 (dt, *J* = 17.6, 2.4 Hz, 1H, C^6**H**$_2$), 2.87-2.83 (m, 1H, C^3**H**), 2.73 (ddd, *J* = 11.2, 3.6, 2.2 Hz, 1H, C^2**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9 (**C**^{14}), 136.8 (**C**^{8}), 134.3 (**C**^{4}), 131.8 (q, *J* = 33.1 Hz, **C**^{16}), 129.0 (2 x C, Ar-**C**H), 128.6 (2 x C, Ar-**C**H), 128.0 (Ar-**C**H), 127.7 (**C**^{5}H), 126.1 (q, *J* = 4.0 Hz, **C**^{15}H), 123.3 (q, *J* = 272.8 Hz, **C**$^{18}F_3$), 121.0 (q, *J* = 3.8 Hz, **C**^{17}H), 65.4 (**C**$^{12}H_2$), 62.6 (**C**$^7H_2$), 55.8 (**C**$^2H_2$), 53.1 (**C**$^6H_2$), 38.3 (**C**^{3}H);

^{19}F NMR (377 MHz, $CDCl_3$) δ –62.9;

IR (neat) (cm^{-1}): 2980, 2888, 1473, 1384, 1275, 1167, 1126, 1072, 955, 682.

N-Benzyl-4-(phenyl)pyridinium Iodide (422)



The title compound was prepared according to **General Procedure F** using 4-phenylpyridine (1.0 g, 6.4 mmol) to give *salt* **422** (2.1 g, 85%) as a yellow solid.

m.p.: 161-163°C;

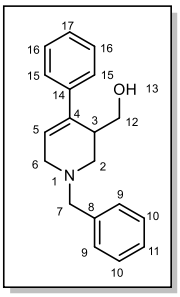
HRMS (ESI): Exact mass calculated for $C_{18}H_{16}N$ $[M]^+$ m/z: 246.12773, found: 246.12792;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, *J* = 7.0 Hz, 2H, C^2**H**), 8.55 (d, *J* = 7.1 Hz, 2H, C^3**H**), 8.07 (dd, *J* = 7.7, 1.9 Hz, 2H, Ar-C**H**), 7.72-7.61 (m, 3H, Ar-C**H**), 7.60-7.56 (m, 2H, Ar-C**H**), 7.50-7.43 (m, 3H, Ar-C**H**), 5.89 (s, 2H, C^5**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 155.6 (**C**^{4}), 145.2 (**C**^{2}H), 134.9 (Ar-**C**), 134.0 (Ar-**C**), 132.7 (Ar-**C**H), 130.2 (2 x C, Ar-**C**H), 129.8 (Ar-**C**H), 129.7 (2 x C, Ar-**C**H), 129.2 (2 x C, Ar-**C**H), 128.7 (2 x C, Ar-**C**H), 125.4 (**C**^{3}H), 63.0 (**C**^{5}H$_2$);

IR (neat) (cm^{-1}): 3512, 3109, 3012, 2982, 2945, 2340, 2287, 2104, 1948, 1635.

(*N*-Benzyl-4-phenyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (423)



Pyridinium **422** (187 mg, 0.5 mmol), $[Ir(Cp^*)Cl_2]_2$ (1 mol%), KI (166 mg, 1.0 mmol) and paraformaldehyde (300 mg, 20 equiv.) were added to a 10 mL vial and $Mg(OMe)_2$ (0.75 equiv. MeOH solution) and methanol (total volume 2.5 mL) were added and the solution was heated at 65°C for 14 hours. To the reaction was added thiourea (50 mg) and the reaction was stirred for an additional 30 minutes. The solution was partitioned between brine (50 mL) water (50 mL) and CH_2Cl_2 (50 ml) and the aqueous layer was extracted with additional CH_2Cl_2 (2 x 25 mL). The

organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The crude material was purified by FCC (80:20:0.1 pentane:EtOAc:*i*PrOH) to give *amine* **423** (21 mg, 15%).

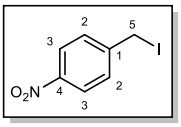
HRMS (ESI): Exact mass calculated for $C_{19}H_{22}ON$ $[M+H]^+$ m/z: 280.16959, found: 280.16953;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.22 (m, 10H, $C^{9\text{-}11}$**H** + $C^{15\text{-}17}$**H**), 6.09 (dd, *J* = 4.7, 1.8 Hz, 1H, C^5**H**), 3.80 (dd, *J* = 10.2, 2.4 Hz, 1H, C^{12}**H**$_2$), 3.68 (d, *J* = 12.7 Hz, 1H, C^{12}**H**$_2$), 3.62 (m, 2H, C^7**H**$_2$), 3.41 (m, 1H, C^6**H**$_2$), 3.20 (dt, *J* = 11.1, 1.4 Hz, 1H, C^2**H**$_2$), 2.85 (m, 2H, C^6**H**$_2$ + C^3**H**), 2.70 (ddd, *J* = 11.1, 3.6, 2.1, 1H, C^2**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9 (Ar-**C**), 137.4 (Ar-**C**), 136.5 (**C**^{4}), 129.4 (2 x C, Ar-**C**H), 128.8 (2 x C, Ar-**C**H), 128.7 (2 x C, Ar-**C**H), 127.8 (Ar-**C**H), 127.6 (Ar-**C**H), 126.3 (2 x C, Ar-**C**H), 124.6 (**C**^{5}H), 66.1 (**C**^{12}H$_2$), 63.0 (**C**^{7}H$_2$), 56.3 (**C**^{2}H$_2$), 53.6 (**C**^{6}H$_2$), 38.5 (**C**^{3}H);

IR (neat) (cm^{-1}): 3733, 1636, 1599, 1495, 1444, 1300, 1204, 1103, 1027.

1-(Iodomethyl)-4-nitrobenzene (425)



To a stirred solution of sodium iodide (9.0 g, 60.0 mmol, 2.0 equiv.) in 40 mL of acetone was added slowly 1-(bromomethyl)-4-nitrobenzene (6.5 g, 30.0 mmol, 1.0 equiv.) at room temperature. The reaction was left stirring at room temperature in the dark for 16 hours. To the reaction was added 50 mL of brine and then extracted with 2 x Et_2O (100 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the product **425** (7.9 g) as a light brown solid in quantitative yield.

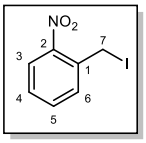
m.p.: 124-126°C;

1H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.13 (m, 2H, C^3**H**), 7.55 – 7.49 (m, 2H, C^2**H**), 4.48 (s, 2H, C^5**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3 (**C**^{4}), 146.9 (**C**^{1}), 129.7 (**C**^{2}H), 124.2 (**C**^{3}H), 2.2 (**C**^{5}H$_2$).

Spectroscopic data was consistent with that reported in the literature.[216]

1-(Iodomethyl)-2-nitrobenzene (427)



To a stirred solution of sodium iodide (9.0 g, 60.0 mmol, 2.0 equiv.) in 40 mL of acetone was added slowly 1-(bromomethyl)-2-nitrobenzene (6.5 g, 30.0 mmol, 1.0 equiv.) at room temperature. The reaction was left stirring at room temperature in the dark for 16 hours. To the reaction was added 50 mL of brine and then extracted with 2 x Et_2O (100 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the product **427** (7.9 g) as a light brown solid in quantitative yield.

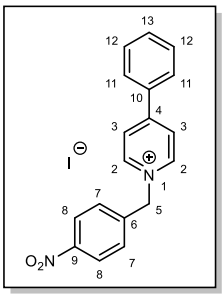
m.p.: 74-76°C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 1H, C^3**H**), 7.60 – 7.47 (m, 2H, Ar-C**H**), 7.43 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H, Ar-C**H**), 4.77 (s, 2H, C^7**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5 (**C**^{2}), 135.0 (**C**^{1}), 133.9 (Ar-**C**H), 132.3 (Ar-**C**H), 129.1 (Ar-**C**H), 125.8 (Ar-**C**H), 0.00 (**C**^{7}H$_2$).

Spectroscopic data was consistent with that reported in the literature.[217]

N-(4-Nitrobenzyl)-4-phenylpyridinium Iodide (429)



A mixture of 4-phenylpyridine (776 mg, 5.0 mmol 1.0 equiv.) and 1-(iodomethyl)-4-nitrobenzene **425** (1.97 g, 7.5 mmol, 1.5 equiv.) in 50 mL of acetone was stirred at room temperature for 16 hours in the dark. The solvent was removed under reduced pressure, then the residue was dissolved in the minimum amount of methanol at 65°C. The solution was cooled in the freezer (-30°C). The resulting yellow crystals (1.30 g) were filtered and collected. To the filtrate was added 50 mL of diethyl ether. The resulting suspension was sonicated (5

min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium iodide salt **425** (0.33 g) as a green powder. Combined yield 79% (1.63 g).

m.p.: 171-173°C;

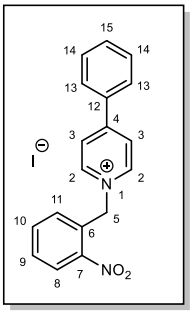
HRMS (ESI): Exact mass calculated for $C_{18}H_{15}O_2N_2$ $[M]^+$ m/z: 291.11280, found: 291.11277;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (d, J = 6.8 Hz, 2H, C^2**H**), 8.60 (d, J = 6.8 Hz, 2H, C^3**H**), 8.30 (d, J = 8.8 Hz, 2H, C^8**H**), 8.11 – 8.07 (m, 2H, Ar-C**H**), 7.84 (d, J = 8.8 Hz, 2H, C^7**H**), 7.69 – 7.62 (m, 3H, Ar-C**H**), 6.06 (s, 2H, C^5**H**$_2$);

^{13}C NMR (101 MHz, DMSO) δ 155.4 (Ar-**C**), 147.8 (Ar-**C**), 145.1 (**C**^{2}H), 141.4 (Ar-**C**), 133.4 (Ar-**C**), 132.3 (Ar-**C**H), 130.0 (**C**^{7}H), 129.7 (2 x C, Ar-**C**H), 128.2 (2 x C, Ar-**C**H), 125.0 (**C**^{3}H), 124.1 (**C**^{8}H), 61.2 (**C**^{5}H$_2$);

IR (neat) (cm^{-1}): 1634, 1536, 1524, 1486, 1439, 1345, 1294, 1159, 858, 846, 820, 805, 769, 757, 725, 709, 691.

N-(2-Nitrobenzyl)-4-phenylpyridinium Iodide (430)



A mixture of 4-phenylpyridine (776 mg, 5.0 mmol 1.0 equiv.) and 1-(iodomethyl)-2-nitrobenzene **427** (1.97 g, 7.5 mmol, 1.5 equiv.) in 15 mL of acetone was stirred at room temperature for 16 hours in the dark. The solvent was removed under reduced pressure, followed by addition of 50 mL of diethyl ether. The resulting suspension was sonicated (5 min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium iodide salt **430** (1.88 g, 90% yield) as a yellow solid.

m.p.: 196-198°C;

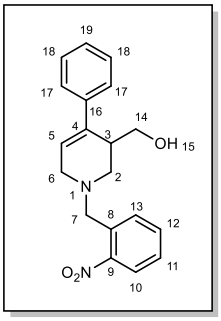
HRMS (ESI): Exact mass calculated for $C_{18}H_{15}O_2N_2$ $[M]^+$ m/z: 291.11280, found: 291.11275;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (d, *J* = 7.1 Hz, 2H, C^2**H**), 8.63 (d, *J* = 7.1 Hz, 2H, C^3**H**), 8.28 (dd, *J* = 8.1, 1.4 Hz, 1H, C^8**H**), 8.15 – 8.10 (m, 2H, Ar-C**H**), 7.89 – 7.59 (m, 5H, Ar-C**H**), 7.22 (dd, *J* = 7.7, 1.4 Hz, 1H, C^{11}**H**), 6.25 (s, 2H, C^5**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 155.5 (Ar-**C**), 147.5 (Ar-**C**), 145.5 (**C**^{2}H), 134.9 (Ar-**C**H), 133.4 (Ar-**C**), 132.4 (Ar-**C**H), 130.4 (Ar-**C**H), 130.1 (**C**^{11}H), 129.7 (2 x C, Ar-**C**H), 129.5 (Ar-**C**), 128.2 (2 x C, Ar-**C**H), 125.6 (**C**^{8}H), 124.8 (**C**^{3}H), 59.8 (**C**^{5}H$_2$);

IR (neat) (cm^{-1}): 1637, 1514, 1440, 1347, 1335, 1200, 861, 790, 772, 747, 729, 720, 693, 676, 626.

(1-(2-Nitrobenzyl)-4-phenyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (431)



Pyridinium **430** (209 mg, 0.5 mmol), [Ru(p-cymene)Cl$_2$]$_2$ (2 mol%), and paraformaldehyde (300 mg, 20 equiv.) were added to a 10 mL vial and Mg(OMe)$_2$ (0.75 equiv. MeOH solution) and methanol (total volume 2.5 mL) were added and the solution was heated at 65°C for 14 hours under an atmosphere of argon. To the reaction was added thiourea (50 mg) and the reaction was stirred for an additional 30 minutes. The solution was partitioned between brine (50 mL) water (50 mL) and CH_2Cl_2 (50 ml) and the aqueous layer was extracted with additional CH_2Cl_2 (2 x 25 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The crude material was purified by FCC (3-5% acetone in CH_2Cl_2) to give *amine* **431** (100 mg, 62%) as a white solid.

m.p.: 124-126°C;

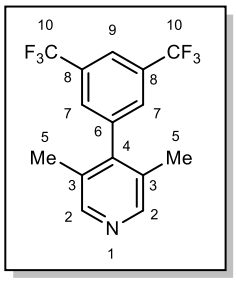
HRMS (ESI): Exact mass calculated for $C_{19}H_{21}O_3N_2$ $[M+H]^+$ m/z: 325.15467, found: 325.15454;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 1H, C^{10}**H**), 7.67 – 7.53 (m, 2H, Ar-C**H**), 7.49 – 7.18 (m, 6H Ar-C**H**), 6.02 (dd, *J* = 4.6, 2.2 Hz, 1H, C^{5}**H**), 4.01 (d, *J* = 14.0 Hz, 1H, C^{7}**H**$_2$), 3.88 (d, *J* = 14.1 Hz, 1H, C^{7}**H**$_2$), 3.77 – 3.58 (m, 3H, C^{14}**H**$_2$ + O^{15}**H**), 3.38 (dd, *J* = 16.9, 4.6 Hz, 1H C^{6}**H**$_2$), 3.18 (dt, *J* = 11.1, 1.5 Hz, 1H, C^{2}**H**$_2$), 2.98 – 2.83 (m, 2H, C^{6}**H**$_2$ + C^{3}**H**), 2.69 (dd, *J* = 11.1, 3.6 Hz, 1H, C^{2}**H**$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8 (Ar-**C**), 139.6 (Ar-**C**), 136.2 (Ar-**C**), 133.0 (Ar-**C**), 132.9 (Ar-**C**H), 131.4 (Ar-**C**H), 128.5 (2 x C, Ar-**C**H), 128.5 (Ar-**C**H), 127.4 (Ar-**C**H), 126.0 (2 x C, Ar-**C**H), 124.8 (Ar-**C**H), 124.0 (**C**^{5}H), 64.7 (**C**^{14}H$_2$), 59.1 (**C**^{7}H$_2$), 54.7 (**C**^{2}H$_2$), 53.7 (**C**^{6}H$_2$), 39.2 (**C**^{3}H);

IR (neat) (cm^{-1}): 3311, 2928, 2852, 2811, 1726, 1523, 1350, 1127, 1071, 991, 788, 763, 736, 699, 667.

4-(3,5-Bis(trifluoromethyl)phenyl)-3,5-dimethylpyridine (449)



The title compound was prepared according to **General Procedure L** using *pyridinium* **477** (341 mg, 0.5 mmol) or according to modified **General Procedure K** using *pyridinium* **476** (317 mg, 0.5 mmol) plus one equivalent of sodium iodide. The crude material was purified by FCC (DCM:EtOAc - 100:0 to 90:10) to give *pyridine* **449** (97 mg, 61 % yield) as a white solid.

m.p.: 75-78°C;

HRMS (ESI): Exact mass calculated for $C_{15}H_{12}NF_6$ $[M+H]^+$ m/z: 320.08685, found: 320.08710;

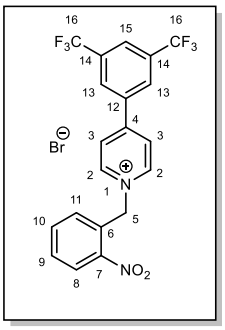
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 2H, C^{2}**H**), 7.93 (s, 1H, C^{9}**H**), 7.63 (s, 2H, C^{7}**H**), 2.02 (s, 6H, C^{5}**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0 (**C**^{2}H), 146.1 (**C**^{4}), 140.3 (**C**^{6}), 132.50 (q, *J* = 33.6 Hz, **C**^{8}), 130.4 (**C**^{3}), 128.70 (q, *J* = 4.0 Hz, **C**^{7}), 123.25 (q, *J* = 272.8 Hz, **C**$^{10}F_3$), 121.9 (h, *J* = 3.8 Hz, **C**^{9}), 17.4 (**C**$^{5}H_3$);

^{19}F NMR (377 MHz, $CDCl_3$) δ –62.9;

IR (neat) (cm^{-1}): 1375, 1278, 1181, 1164, 1112, 1062, 1030, 906, 844, 716, 693, 680.

4-(3,5-bis(trifluoromethyl)phenyl)-*N*-(2-nitrobenzyl)pyridinium Bromide (452)



A mixture of 4-(3,5-bis(trifluoromethyl)phenyl)pyridine **415** (582 mg, 2.0 mmol 1.0 equiv.) and 1-(bromomethyl)-2-nitrobenzene **426** (648 mg, 3.0 mmol, 1.5 equiv.) in 5 mL of dioxane was stirred at 90°C for 16 hours. The mixture was allowed to cool to room temperature, then the solvent was removed under reduced pressure and 25 mL of diethyl ether was added. The resulting suspension was sonicated (5 min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium bromide salt **452** (943 mg, 93 % yield) as a white solid.

m.p.: 266-268°C;

HRMS (ESI): Exact mass calculated for $C_{20}H_{13}O_2N_2F_6$ $[M]^+$ m/z: 427.08757, found: 427.08738;

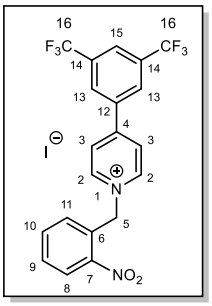
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (d, *J* = 6.9 Hz, 2H, C^{2}**H**), 8.88 (d, *J* = 6.9 Hz, 2H, C^{3}**H**), 8.79 (s, 1H, C^{13}**H**), 8.44 (s, 1H, C^{15}**H**), 8.29 (dd, *J* = 8.0, 1.5 Hz, 1H, C^{8}**H**), 7.78 (dtd, *J* = 26.3, 7.7, 1.5 Hz, 2H, Ar-C**H**), 7.18 (dd, *J* = 7.7, 1.5 Hz, 1H, C^{11}**H**), 6.34 (s, 2H, C^{5}**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 152.7 (Ar-**C**), 147.5 (Ar-**C**), 145.9 (**C**^{2}H), 136.5 (Ar-**C**), 135.0 (Ar-**C**H), 131.4 (q, J = 33.3 Hz, **C**^{14}), 130.5 (Ar-**C**H), 129.9 (**C**^{11}H), 129.6 (Ar-**C**), 129.5 (**C**^{13}H), 126.4 (**C**^{3}H), 125.7 (**C**^{8}H), 125.3 (**C**^{15}H), 123.1 (q, J = 273.2 Hz, **C**$^{16}F_3$), 60.2 (**C**$^{5}H_2$);

^{19}F NMR (377 MHz, DMSO-d_6) δ –61.1;

IR (neat) (cm^{-1}): 1638, 1531, 1382, 1344, 1276, 1189, 1166, 1127, 1063, 906, 858, 838, 796, 731, 719, 702, 682.

4-(3,5-bis(trifluoromethyl)phenyl)-*N*-(2-nitrobenzyl)pyridinium Iodide (453)



A mixture of 4-(3,5-bis(trifluoromethyl)phenyl)pyridine **415** (582 mg, 2.0 mmol 1.0 equiv.) and 1-(iodomethyl)-2-nitrobenzene **427** (789 mg, 3.0 mmol, 1.5 equiv.) in 5 mL of acetone was stirred at room temperature for 16 hours in the dark. The solvent was removed under reduced pressure, followed by addition of 30 mL of diethyl ether. The resulting suspension was sonicated (5 min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium iodide salt **453** (1.06 g, 96% yield) as a yellow solid.

m.p.: 233-235°C;

HRMS (ESI): Exact mass calculated for $C_{20}H_{13}O_2N_2F_6$ $[M]^+$ m/z: 427.08757, found: 427.08731;

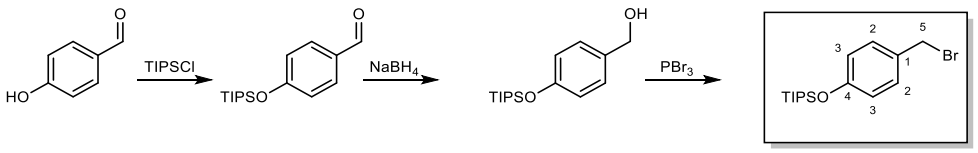
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.30 (d, J = 6.3 Hz, 2H, C^{2}**H**), 8.88 (d, J = 6.3 Hz, 2H, C^{3}**H**), 8.78 (s, 2H, C^{13}**H**), 8.41 (s, 1H, C^{15}**H**), 8.29 (d, J = 8.0 Hz, 1H, C^{8}**H**), 7.80 (dt, J = 28.1, 7.6 Hz, 2H, Ar-C**H**), 7.22 (d, J = 7.7 Hz, 1H, C^{11}**H**), 6.34 (s, 2H, C^{5}**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 152.6 (Ar-**C**), 147.4 (Ar-**C**), 145.8 (**C**^{2}H), 136.4 (Ar-**C**), 134.9 (Ar-**C**H), 131.4 (q, J = 33.5 Hz, **C**^{14}), 130.4 (Ar-**C**H), 130.0 (**C**^{11}H), 129.4 (Ar-**C**), 129.4 (**C**^{13}H), 126.4 (**C**^{3}H), 125.5 (**C**^{8}H), 125.1 (**C**^{15}H), 123.0 (q, J = 273.3 Hz, **C**^{16}F$_3$), 60.2 (**C**^{5}H$_2$);

^{19}F NMR (377 MHz, DMSO-d_6) δ –61.2;

IR (neat) (cm^{-1}): 1643, 1534, 1384, 1339, 1280, 1176, 1164, 1123, 1061, 907, 870, 852, 837, 827, 811, 790, 728, 704, 682, 637, 611.

(4-(Bromomethyl)phenoxy)triisopropylsilane (474)



To a flask was added 4-hydroxybenzaldehyde (6.1 g, 50.0 mmol, 1.0 equiv.), imidazole (5.1 g, 75.0 mmol, 1.5 equiv.), triisopropylsilyl chloride (13.0 mL, 60.0 mmol, 1.2 equiv.) and 150 mL of DCM. The reaction was left stirring at 40°C under an atmosphere of argon for 16 hours. The reaction was allowed to cool to room temperature, then filtered through a pad of silica with DCM. The filtrate was concentrated under vacuum, and the crude product was dissolved in 100 mL of ethanol. To the reaction was added sodium borohydride (3.8 g, 100.0 mmol, 2.0 equiv.) in portions at room temperature. The reaction was left stirring at room temperature for 2-3 hours. To the reaction was added 100 mL of water and then 250 mL of brine and 150 mL of ethyl acetate. The aqueous layer was extracted with ethyl acetate twice more. The combined organics were dried over $MgSO_4$ and concentrated under vacuum. The crude product was dissolved in 500 mL of dry ether and cooled to 0°C using an ice bath. To the reaction was added PBr_3 (5.7 mL, 60.0 mmol, 1.2 equiv.) slowly at 0°C. The reaction was left to stir overnight in the ice bath. The reaction was added to a cold saturated solution of $NaHCO_3$ and extracted with ether. The ether layer was dried over $MgSO_4$, concentrated under vacuum, and

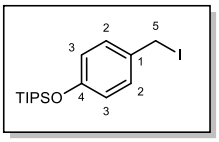
then filtered through a pad of silica with pentane/ether (95:5) to give the product **474** as a colourless oil (14.6 g, 42.5 mmol, 85 % yield over 3 steps) of reasonable purity.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H, C^2**H**), 6.83 (d, *J* = 8.6 Hz, 2H, C^3**H**), 4.49 (s, 2H, C^5**H**$_2$), 1.31 – 1.18 (m, 3H, TIPS-C**H**), 1.09 (d, *J* = 7.3 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4 (Ar-**C**), 130.5 (**C**^{2}H), 130.3 (Ar-**C**), 120.2 (**C**^{3}H), 34.3 (**C**^{5}H$_2$), 18.0 (TIPS-**C**H$_3$), 12.8 (TIPS-**C**H).

Spectroscopic data was consistent with that reported in the literature.[218]

(4-(Iodomethyl)phenoxy)triisopropylsilane (475)



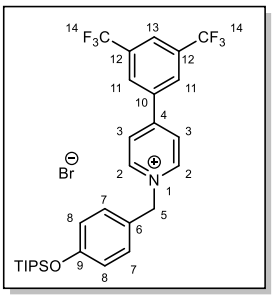
To a stirred solution of sodium iodide (4.5 g, 30.0 mmol, 2.0 equiv.) in 40 mL of acetone was added slowly (4-(Bromomethyl)phenoxy)triisopropylsilane **474** (5.1 g, 15.0 mmol, 1.0 equiv.) at room temperature. The reaction was left stirring at room temperature in the dark. To the reaction was added 50 mL of brine and then extracted with 2 x Et_2O (100 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the product **475** (11.7 g) as a brown liquid in quantitative yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H, C^2**H**), 6.79 (d, *J* = 8.5 Hz, 2H, C^3**H**), 4.46 (s, 2H, C^5**H**$_2$), 1.32 – 1.14 (m, 3H, TIPS-C**H**), 1.09 (d, *J* = 7.3 Hz, 18H, TIPS-C**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9 (Ar-**C**), 131.7 (Ar-**C**), 130.1 (**C**^{2}H), 120.3 (**C**^{3}H), 18.0 (TIPS-**C**H$_3$), 12.8 (TIPS-**C**H), 7.0 (**C**^{5}H$_2$).

Spectroscopic data was consistent with that reported in the literature.[219]

4-(3,5-Bis(trifluoromethyl)phenyl)-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Bromide (476)



The title compound was prepared according to **General Procedure I** using 4-(3,5-bis(trifluoromethyl)phenyl)pyridine **415** (582 mg, 2.0 mmol) to give *salt* **476** (1.85 g, 97% yield) as a white solid.

m.p.: 252-254°C;

HRMS (ESI): Exact mass calculated for $C_{29}H_{34}OF_6N^{28}Si$ $[M]^+$ m/z: 554.23084, found: 554.23114;

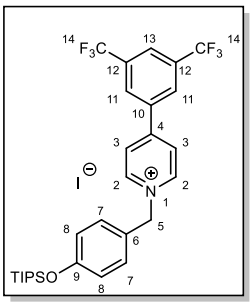
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (d, J = 7.0 Hz, 2H, C^2**H**), 8.79 (d, J = 7.1 Hz, 2H, C^3**H**), 8.73 (s, 2H, C^{11}**H**), 8.41 (s, 1H, C^{13}**H**), 7.56 (d, J = 8.6 Hz, 2H, C^7**H**), 6.93 (d, J = 8.6 Hz, 2H, C^8**H**), 5.87 (s, 2H, C^5**H**$_2$), 1.30 – 1.19 (m, 3H, TIPS-C**H**), 1.04 (d, J = 7.4 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 156.3 (Ar-**C**), 152.1 (Ar-**C**), 144.8 (**C**^{2}H), 136.5 (Ar-**C**), 131.3 (q, J = 33.5 Hz, **C**^{12}), 130.6 (**C**^{7}H), 129.4 (**C**^{11}H), 127.0 (Ar-**C**), 126.4 (**C**^{3}H), 125.0 (**C**^{13}H), 123.0 (d, J = 273.1 Hz, **C**^{14}F$_3$), 120.0 (**C**^{8}H), 62.3 (**C**^{5}H$_2$), 17.7 (6 x C, TIPS-**C**H$_3$), 12.0 (3 x C, TIPS-**C**H);

^{19}F NMR (377 MHz, DMSO-d_6) δ –61.1;

IR (neat) (cm^{-1}): 1509, 1383, 1276, 1173, 1143, 1110, 914, 904, 882, 837, 701, 682.

4-(3,5-Bis(trifluoromethyl)phenyl)-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Iodide (477)



The title compound was prepared according to **General Procedure J** using 4-(3,5-bis(trifluoromethyl)phenyl)pyridine **415** (873 mg, 3.0 mmol) to give *salt* **477** (1.87 g, 92% yield) as a yellow solid.

m.p.: 191-193°C;

HRMS (ESI): Exact mass calculated for $C_{29}H_{34}OF_6N^{28}Si$ $[M]^+$ m/z: 554.23084, found: 554.23041;

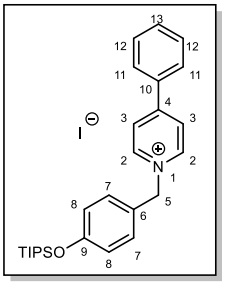
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (d, J = 6.4 Hz, 2H, C^2**H**), 8.79 (d, J = 6.5 Hz, 2H, C^3**H**), 8.74 (s, 2H, C^{11}**H**), 8.40 (s, 1H, C^{13}**H**), 7.55 (d, J = 8.1 Hz, 2H, C^7**H**), 6.93 (d, J = 8.2 Hz, 2H, C^8**H**), 1.31 – 1.18 (m, 3H, TIPS-C**H**), 1.04 (d, J = 7.5 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 156.4 (Ar-**C**), 152.1 (Ar-**C**), 144.8 (**C**^{2}H), 136.5 (Ar-**C**), 131.3 (q, J = 33.5 Hz, **C**^{12}), 130.6 (**C**^{7}H), 129.4 (**C**^{11}H), 127.0 (Ar-**C**), 126.4 (**C**^{3}H), 125.0 (**C**^{13}H), 123.0 (q, J = 273.3 Hz, **C**^{14}F$_3$), 120.1 (**C**^{8}H), 62.4 (**C**^{5}H$_2$), 17.7 (6 x C, TIPS-**C**H$_3$), 12.0 (3 x C, TIPS-**C**H);

^{19}F NMR (377 MHz, DMSO-d_6) δ –61.2;

IR (neat) (cm^{-1}): 2946, 2869, 1508, 1382, 1275, 1174, 1141, 1110, 1061, 904, 882, 841, 682.

4-Phenyl-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Iodide (481)



The title compound was prepared according to **General Procedure J** using 4-phenylpyridine (310 mg, 2.0 mmol) to give *salt* **481** (1.06 g, 97% yield) as a light-yellow solid.

m.p.: 216-218°C;

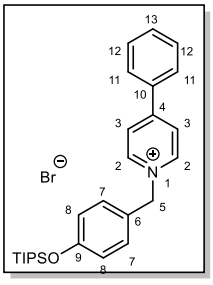
HRMS (ESI): Exact mass calculated for $C_{27}H_{36}ON^{28}Si$ $[M]^+$ m/z: 418.25607, found: 418.25607;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, J = 7.1 Hz, 2H, C^2**H**), 8.55 (d, J = 7.1 Hz, 2H, C^3**H**), 8.07 (dd, J = 7.6, 2.0 Hz, 2H, Ar-C**H**), 7.68 – 7.61 (m, 3H, Ar-C**H**), 7.52 (d, J = 8.6 Hz, 2H, C^7**H**), 6.92 (d, J = 8.6 Hz, 2H, C^8**H**), 5.79 (s, 2H, C^5**H**$_2$), 1.30 – 1.17 (m, 3H, TIPS-C**H**), 1.03 (d, J = 7.5 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 156.3 (Ar-**C**), 155.0 (Ar-**C**), 144.6 (**C**^{2}H), 133.5 (Ar-**C**), 132.2 (Ar-C**H**), 130.7 (**C**^{7}H), 129.7 (2 x C, Ar-**C**H), 128.2 (2 x C, Ar-**C**H), 127.1 (Ar-**C**), 124.9 (**C**^{3}H), 120.1 (**C**^{8}H), 61.9 (**C**^{5}H$_2$), 17.7 (6 x C, TIPS-**C**H$_3$), 12.0 (3 x C, TIPS-**C**H);

IR (neat) (cm^{-1}): 2943, 1635, 1607, 1511, 1489, 1461, 1285, 1159, 990, 915, 884, 811, 775, 749, 705, 688, 673.

4-Phenyl-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Bromide (482)



The title compound was prepared according to **General Procedure H** using 4-phenylpyridine (310 mg, 2.0 mmol) to give *salt* **482** (947 mg, 95% yield) as a white solid.

m.p.: 233-235°C;

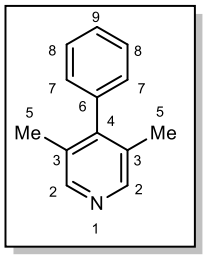
HRMS (ESI): Exact mass calculated for $C_{27}H_{36}ON^{28}Si$ $[M]^+$ m/z: 418.25607, found: 418.25641;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (d, *J* = 6.8 Hz, 2H, C^2**H**), 8.55 (d, *J* = 6.9 Hz, 2H, C^3**H**), 8.07 (dd, *J* = 7.7, 2.0 Hz, 2H, Ar-C**H**), 7.69 – 7.60 (m, 3H, Ar-C**H**), 7.53 (d, *J* = 8.6 Hz, 2H, C^7**H**), 6.92 (d, *J* = 8.6 Hz, 2H, C^8**H**), 5.80 (s, 2H, C^5**H**$_2$), 1.30 – 1.17 (m, 3H, TIPS-C**H**), 1.03 (d, *J* = 7.4 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 156.3 (Ar-**C**), 155.0 (Ar-**C**), 144.6 (**C**^{2}H), 133.5 (Ar-**C**), 132.2 (Ar-**C**H), 130.7 (**C**^{7}H), 129.7 (2 x C, Ar-**C**H), 128.2 (2 x C, Ar-**C**H), 127.1 (Ar-**C**), 124.9 (**C**^{3}H), 120.1 (**C**^{8}H), 61.9 (**C**^{5}H$_2$), 17.7 (6 x C, TIPS-**C**H$_3$), 12.0 (3 x C, TIPS-**C**H);

IR (neat) (cm^{-1}): 1635, 1608, 1511, 1490, 1281, 1157, 993, 914, 885, 865, 812, 773, 749, 705, 685, 660.

3,5-Dimethyl-4-phenylpyridine (484)



The title compound was prepared according to **General Procedure K** using *pyridinium* **482** (249 mg, 0.5 mmol). The crude material was purified by FCC (DCM:EtOAc - 95:5 to 85:15) to give *pyridine* **484** (36 mg, 38 % yield) as a white solid.

m.p.: 70-72°C;

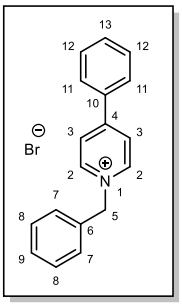
HRMS (ESI): Exact mass calculated for $C_{13}H_{14}N$ $[M+H]^+$ m/z: 184.11208, found: 184.11211;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 2H, C^2**H**), 7.48 – 7.34 (m, 3H, Ar-C**H**), 7.13 – 7.09 (m, 2H, Ar-C**H**), 2.02 (s, 6H, C^5**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.4 (Ar-**C**), 148.5 (**C**^{2}H), 138.2 (Ar-**C**), 130.9 (**C**^{3}), 128.8 (2 x C, Ar-**C**H), 128.1 (2 x C, Ar-**C**H), 127.6 (Ar-**C**H), 17.4 (**C**^{5}H$_3$);

IR (neat) (cm^{-1}): 1584, 1472, 1441, 1409, 1159, 877, 774, 755, 710, 666.

N-Benzyl-4-(phenyl)pyridinium Bromide (489)



A mixture of 4-phenylpyridine (466 mg, 3.0 mmol 1.0 equiv.) and benzyl bromide (0.54 mL, 4.5 mmol, 1.5 equiv.) in 5 mL of dioxane was stirred at 90°C for 16 hours. The mixture was allowed to cool to room temperature, then the solvent was removed under reduced pressure and 30 mL of diethyl ether was added. The resulting suspension was sonicated (5 min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium bromide salt **489** (861 mg, 88 % yield) as a white solid.

m.p.: 226-228°C;

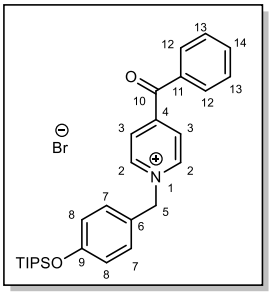
HRMS (ESI): Exact mass calculated for $C_{18}H_{16}N$ $[M]^+$ m/z: 246.12773, found: 246.12779;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (d, J = 7.0 Hz, 2H, C^2**H**), 8.56 (d, J = 7.1 Hz, 2H, C^3**H**), 8.07 (dd, J = 7.8, 1.9 Hz, 2H, Ar-C**H**), 7.66 – 7.60 (m, 5H, Ar-C**H**), 7.51 – 7.39 (m, 3H, Ar-C**H**), 5.95 (s, 2H, C^5**H**$_2$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 155.0 (**C**^{4}), 144.8 (**C**^{2}H), 134.5 (Ar-**C**), 133.5 (Ar-**C**), 132.1(Ar-**C**H), 129.6 (2 x C, Ar-**C**H), 129.3 (Ar-**C**H), 129.2 (2 x C, Ar-**C**H), 128.8 (2 x C, Ar-**C**H), 128.2 (2 x C, Ar-**C**H), 124.9 (**C**^{3}H), 62.1 (**C**^{5}H$_2$);

IR (neat) (cm^{-1}): 1633, 1595, 1557, 1525, 1492, 1454, 1367, 1293, 1201, 1176, 889, 875, 773, 744, 725, 714, 689.

4-Benzoyl-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Bromide (496)

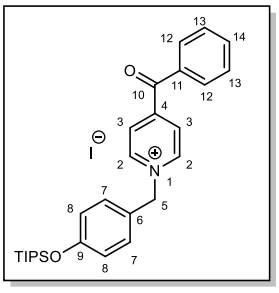


A mixture of (916 mg, 5.0 mmol 1.0 equiv.) and (4-(Bromomethyl)phenoxy)triisopropylsilane (2.58 g, 7.5 mmol, 1.5 equiv.) in 12 mL of acetonitrile was stirred at 80°C for 16 hours. The mixture was allowed to cool to room temperature, then the solvent was removed under reduced pressure and 50 mL of diethyl ether was added. The resulting suspension was sonicated (5 min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium bromide salt **496** (2.53 g, 96 % yield) as a white solid. The product was contaminated by 3 % unknown pyridinium impurity, but it was used in our screening without further purification.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (d, J = 6.8 Hz, 2H, C^{2}**H**), 8.38 (d, J = 6.7 Hz, 2H, C^{3}**H**), 7.88 – 7.83 (m, 2H, C^{12}**H**), 7.83 – 7.77 (m, 1H, C^{14}**H**), 7.63 (t, J = 7.8 Hz, 2H, C^{13}**H**), 7.56 (d, J = 8.6 Hz, 2H, C^{7}**H**), 6.95 (d, J = 8.5 Hz, 2H, C^{8}**H**), 5.91 (s, 2H, C^{5}**H**$_2$), 1.32 – 1.20 (m, 3H, TIPS-C**H**), 1.05 (d, J = 7.4 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 192.1 (**C**^{10}), 156.5 (Ar-**C**), 151.7 (Ar-**C**), 145.6 (**C**^{2}H), 134.9 (**C**^{14}H), 134.1 (Ar-**C**), 131.1 (**C**^{7}H), 130.4 (**C**^{12}H), 129.1 (**C**^{13}H), 127.4 (**C**^{3}H), 126.5 (Ar-**C**), 120.1 (**C**^{8}H), 63.0 (**C**^{5}H$_2$), 17.7 (6 x C, TIPS-**C**H$_3$), 12.0 (3 x C, TIPS-**C**H).

4-Benzoyl-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Iodide (497)



The title compound was prepared according to **General Procedure J** using phenyl(pyridin-4-yl)methanone (916 mg, 5.0 mmol) to give *salt* **497** (2.81 g , 98% yield) as a yellow solid.

m.p.: 125-127°C;

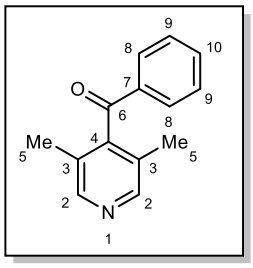
HRMS (ESI): Exact mass calculated for $C_{28}H_{36}O_2N^{28}Si$ $[M]^+$ m/z: 446.25098, found: 446.25128;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (d, *J* = 6.8 Hz, 2H, C^2**H**), 8.38 (d, *J* = 6.7 Hz, 2H, C^3**H**), 7.88 – 7.84 (m, 2H, C^{12}**H**), 7.83 – 7.78 (m, 1H, C^{14}**H**), 7.67 – 7.59 (m, 2H, C^{13}**H**), 7.54 (d, *J* = 8.6 Hz, 2H, C^7**H**), 6.95 (d, *J* = 8.5 Hz, 2H, C^8**H**), 5.88 (s, 2H, C^5**H**$_2$), 1.34 – 1.20 (m, 3H, TIPS-C**H**), 1.05 (d, *J* = 7.5 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 192.1 (**C**^{10}), 156.5 (Ar-**C**), 151.7 (Ar-**C**), 145.6 (**C**^{2}H), 134.9 (**C**^{14}H), 134.1 (Ar-**C**), 131.0 (**C**^{7}H), 130.4 (**C**^{12}H), 129.1 (**C**^{13}H), 127.4 (**C**^{3}H), 126.4 (Ar-**C**), 120.1 (**C**^{8}H), 63.1 (**C**^{5}H$_2$), 17.8 (6 x C, TIPS-**C**H$_3$), 12.1 (3 x C, TIPS-**C**H);

IR (neat) (cm^{-1}): 1669, 1513, 1458, 1288, 1268, 907, 886, 844, 807, 737, 686, 645, 634.

(3,5-Dimethylpyridin-4-yl)(phenyl)methanone (499)



The title compound was prepared according to **General Procedure M** using *pyridinium* **497** (287 mg, 0.5 mmol). The crude material was purified by FCC (DCM:Acetone - 95:5 to 90:10) to give *pyridine* **499** (43 mg, 41 % yield) as a white solid.

m.p.: 54-56°C;

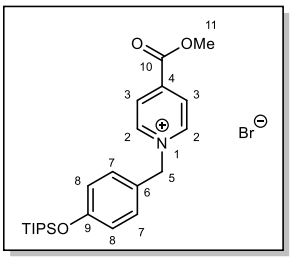
HRMS (ESI): Exact mass calculated for $C_{14}H_{14}ON$ $[M+H]^+$ m/z: 212.10699 , found: 212.10715;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 2H, C^2**H**), 7.80 – 7.74 (m, 2H, C^8**H**), 7.66 – 7.61 (m, 1H, C^{10}**H**), 7.53 – 7.45 (m, 2H, C^9**H**), 2.11 (s, 6H, C^5**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7 (**C**^{6}), 148.8 (**C**^{2}H), 146.9 (Ar-**C**), 135.8 (Ar-**C**), 134.6 (**C**^{10}H), 129.4 (**C**^{8}H), 129.3 (**C**^{9}H), 128.7 (**C**^{3}), 16.3 (**C**^{5}H$_3$);

IR (neat) (cm^{-1}): 1666, 1593, 1579, 1452, 1283, 1261, 929, 874, 802, 774, 709, 685, 676, 617.

4-(Methoxycarbonyl)-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Bromide (502)



A mixture of methyl isonicotinate (411 mg, 3.0 mmol, 1.0 equiv.) and (4-(bromomethyl)phenoxy)triisopropylsilane (1.55 g, 4.5 mmol, 1.5 equiv.) in 6 mL of acetonitrile was stirred at 40°C for 40 hours. The mixture was allowed to cool to room temperature, then the solvent was removed under reduced pressure and 30 mL of diethyl ether was added. The resulting suspension was sonicated (5 min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium bromide salt **502** (1.38 g, 96 % yield) as a white solid.

m.p.: 155-157°C;

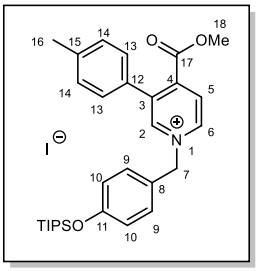
HRMS (ESI): Exact mass calculated for $C_{23}H_{34}O_3N^{28}Si$ $[M]^+$ m/z: 400.23025, found: 400.23056;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (d, J = 6.9 Hz, 2H, C^2**H**), 8.52 (d, J = 6.8 Hz, 2H, C^3**H**), 7.50 (d, J = 8.6 Hz, 2H, C^7**H**), 6.92 (d, J = 8.6 Hz, 2H, C^8**H**), 5.91 (s, 2H, C^5**H**$_2$), 3.97 (s, 3H, C^{11}**H**$_3$), 1.31 – 1.18 (m, 3H, TIPS-C**H**), 1.04 (d, J = 7.5 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.5 (**C**^{10}), 156.5 (Ar-**C**), 146.1 (**C**^{2}H), 144.0 (Ar-**C**), 131.0 (**C**^{7}H), 127.6 (**C**^{3}H), 126.5 (Ar-**C**), 120.2 (**C**^{8}H), 63.1 (**C**^{5}H$_2$), 53.8 (**C**^{11}H$_3$), 17.7 (6 x C, TIPS-**C**H$_3$), 12.0 (3 x C, TIPS-**C**H);

IR (neat) (cm^{-1}): 1736, 1510, 1463, 1291, 1260, 1116, 901, 878, 844, 795, 734, 693, 670.

4-(Methoxycarbonyl)-3-(p-tolyl)-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Iodide (503)



The title compound was prepared according to **General Procedure J** using methyl 3-(p-tolyl)isonicotinate (681.8 mg, 3.0 mmol) to give *salt* **503** (1.82 g, 98% yield) as a yellow solid.

m.p.: 160-162°C;

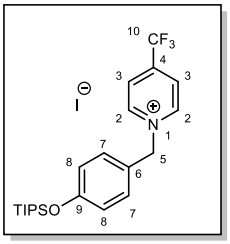
HRMS (ESI): Exact mass calculated for $C_{30}H_{40}O_3N^{28}Si$ $[M]^+$ m/z: 490.27720, found: 490.27761;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (d, *J* = 1.3 Hz, 1H, C^2**H**), 9.22 (dd, *J* = 6.3, 1.3 Hz, 1H, C^6**H**), 8.41 (d, *J* = 6.3 Hz, 1H, C^5**H**), 7.55 (d, *J* = 8.6 Hz, 2H, C^9**H**), 7.40 (s, 4H, Ar-C**H**), 6.93 (d, *J* = 8.5 Hz, 2H, C^{10}**H**), 5.85 (s, 2H, C^7**H**$_2$), 3.77 (s, 3H, C^{18}**H**$_3$), 2.40 (s, 3H, C^{16}**H**$_3$), 1.31 – 1.18 (m, 3H, TIPS-C**H**), 1.04 (d, *J* = 7.4 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 165.3 (**C**^{17}), 156.9 (Ar-**C**), 146.8 (**C**^{2}H), 145.1 (Ar-**C**), 143.8 (**C**^{6}H), 140.3 (Ar-**C**), 139.4 (Ar-**C**), 131.5 (**C**^{9}H), 130.5 (Ar-**C**), 130.1 (2 x C, Ar-**C**H), 129.1 (2 x C, Ar-**C**H), 127.8 (**C**^{5}H), 126.8 (Ar-**C**), 120.6 (**C**^{10}H), 63.7 (**C**^{7}H$_2$), 54.1 (**C**^{18}H$_3$), 21.3 (**C**^{16}H$_3$), 18.2 (6 x C, TIPS-**C**H$_3$), 12.5 (3x C, TIPS-**C**H);

IR (neat) (cm^{-1}): 2943, 2866, 1739, 1636, 1607, 1510, 1459, 1273, 1174, 1154, 1101, 994, 913, 883, 857, 820, 808, 756, 707, 661, 637.

4-(Trifluoromethyl)-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Iodide (504)



The title compound was prepared according to **General Procedure J** using 4-(trifluoromethyl)pyridine (441 mg, 3.0 mmol) to give *salt* **xx** (1.37 g, 85% yield) as a yellow solid.

m.p.: 133-135°C;

HRMS (ESI): Exact mass calculated for $C_{22}H_{31}OF_3N^{28}Si$ $[M]^+$ m/z: 410.21215, found: 410.21207;

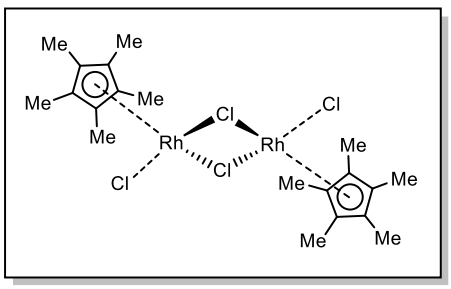
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (d, J = 6.2 Hz, 2H, C^2**H**), 8.68 (d, J = 6.2 Hz, 2H, C^3**H**), 7.53 (d, J = 8.1 Hz, 2H, C^7**H**), 6.92 (d, J = 8.1 Hz, 2H, C^8**H**), 5.93 (s, 2H, C^5**H**$_2$), 1.23 (h, J = 7.6 Hz, 3H, TIPS-C**H**), 1.03 (d, J = 7.5 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 156.5 (Ar-**C**), 146.9 (**C**^{2}H), 143.0 (q, J = 35.2 Hz, **C**^{4}), 131.1 (**C**^{7}H), 126.1 (Ar-**C**) , 125.3 (q, J = 3.4 Hz, **C**^{3}H), 121.3 (q, J = 274.7 Hz, **C**^{10}F$_3$), 120.1 (**C**^{8}H), 63.5 (**C**^{5}H$_2$), 17.7 (6 x C, TIPS-**C**H$_3$), 12.0 (3 x C, TIPS-**C**H);

^{19}F NMR (377 MHz, DMSO-d_6) δ –63.9;

IR (neat) (cm^{-1}): 2945, 2867, 1608, 1512, 1456, 1326, 1273, 1186, 1148, 1078, 996, 911, 882, 843, 813, 762, 726, 681.

[Rh(Cp*)Cl$_2$]$_2$



In a 20 mL microwave vial was added $RhCl_3$*$3H_2O$ (263 mg, 1.0 mmol, 1.0 equiv.), pentamethylcyclopentadiene (0.3 mL, 2.0 mmol, 2.0 equiv.) and 10 mL of degassed methanol. The vialed was sealed and heated at 80°C for 40 hours. The reaction was allowed to cool to room temperature, then cooled to –30°C (freezer)

for 3 hours. The resulting precipitate was filtered and washed with 20 mL of cold methanol, and then 100 mL of ether to give the product as a dark red powder (281 mg, 92% yield).

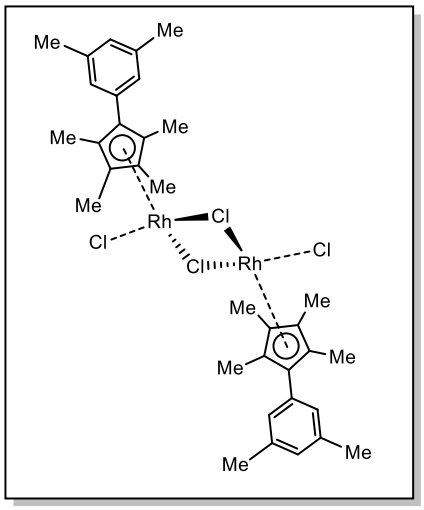
m.p.: Decomposes above 300°C;

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (s, 30H, Cp*-C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 94.3 (d, *J* = 9.7 Hz, Cp*-**C**), 9.5 (Cp*-**C**H_3).

Spectroscopic data was consistent with that reported in the literature.[220]

Rhodium complex (505)



A solution of 2,3,4,5-tetramethylcyclopent-2-en-1-one (0.45 mL, 3.0 mmol, 3.0 equiv.) in 10 mL of THF was stirred at 0°C in an ice bath for 5 minutes. A solution of 0.5 M (3,5-dimethylphenyl)magnesium bromide in 2-MeTHF (18 mL, 9.0 mmol, 9equiv.) was added to the reaction at 0°C, and then the mixture was stirred at room temperature for 4 hours. The reaction was slowly quenched with 5 mL of 2 N HCl at room temperature, and the aqueous layer was extracted with 3 x 25 mL of Et_2O. The combined organics were dried over $MgSO_4$, then filtered through a silica plug, washing with additional Et_2O. The filtrate was concentrated under vacuum, and the crude cyclopentadiene was dissolved in 5 mL degassed methanol and transferred to a 20 mL microwave vial. To the vial was added $RhCl_3$*$3H_2O$ (263 mg, 1.0 mmol, 1.0 equiv.). The vial was sealed, and the reaction was heated at 80°C for 16 hours. The reaction was allowed to cool to room temperature, then cooled to –30°C (freezer) for 3 hours. The resulting precipitate was filtered and washed with 20 mL of cold methanol, and then 100 mL of ether to give the product **505** as a dark red powder (224 mg, 67% yield).

m.p.: Decomposes above 300°C;

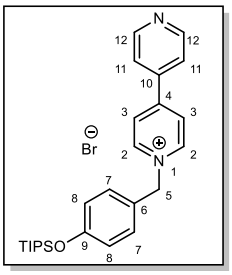
HRMS (ESI): Exact mass calculated for $C_{34}H_{42}N^{35}Cl_3{}^{103}Rh_2$ $[M - Cl]^+$: 761.04567; found: 761.04608;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 4H, Ar-C**H**), 7.01 (s, 2H, Ar-C**H**), 2.34 (s, 12H, Ar-C**H**$_3$), 1.70 (s, 12H, Cp-C**H**$_3$), 1.68 (s, 12H, Cp-C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (Ar-**C**), 130.9 (Ar-**C**H), 128.2 (Ar-**C**), 128.0 (Ar-**C**H), 99.50 (d, J = 8.5 Hz, Cp-**C**), 93.63 (d, J = 9.1 Hz, Cp-**C**), 91.70 (d, J = 10.1 Hz, Cp-**C**), 21.4 (Ar-**C**H$_3$), 10.8 (Cp-**C**H$_3$), 9.7 (Cp-**C**H$_3$);

IR (neat) (cm^{-1}): 1597, 1448, 1377, 1112, 1025, 915, 859, 830, 704, 669, 620.

N-(4-((Triisopropylsilyl)oxy)benzyl)-[4,4'-bipyridin]ium Bromide (513)



To a stirred solution of 4,4'-bipyridine (937 mg, 6.0 mmol, 1.5 equiv.) in 50 mL of dioxane was added (4-(bromomethyl)phenoxy)triisopropylsilane (1.37 g, 4.0 mmol, 1.0 equiv.) at room temperature. The reaction was left stirring at room temperature for 3 days. The solvent was removed under vacuum, and then 100 mL of ether was added. The resulting suspension was sonicated (5 min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium bromide salt **513** (1.76 g, 88% yield) as a white solid.

m.p.: 203-205°C;

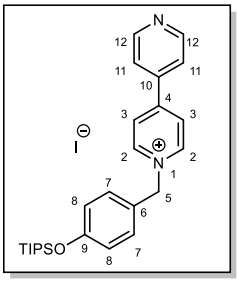
HRMS (ESI): Exact mass calculated for $C_{26}H_{35}ON_2{}^{28}Si$ $[M]^+$ m/z: 419.25132, found: 419.25140;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (d, J = 6.9 Hz, 2H, C^{2}**H**), 8.86 (d, J = 6.2 Hz, 2H, C^{12}**H**), 8.64 (d, J = 7.0 Hz, 2H, C^{3}**H**), 8.02 (d, J = 6.2 Hz, 2H, C^{11}**H**), 7.52 (d, J = 8.6 Hz, 2H, C^{7}**H**), 6.93 (d, J = 8.6 Hz, 2H, C^{8}**H**), 5.82 (s, 2H, C^{5}**H**$_2$), 1.31 – 1.19 (m, 3H, TIPS-C**H**), 1.04 (d, J = 7.5 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 156.4 (Ar-**C**), 152.7 (Ar-**C**), 151.0 (**C**^{12}H), 145.1 (**C**^{2}H), 140.8 (Ar-**C**), 130.7 (**C**^{7}H), 126.8 (Ar-**C**), 125.8 (**C**^{3}H), 122.0 (**C**^{11}H), 120.1 (**C**^{8}H), 62.5 (**C**^{5}H$_2$), 17.7 (6 x C, TIPS-**C**H$_3$), 12.0 (3 x C, TIPS-**C**H);

IR (neat) (cm^{-1}): 1636, 1605, 1509, 1459, 1269, 1154, 909, 882, 820, 806, 757, 709, 677, 636.

N-(4-((Triisopropylsilyl)oxy)benzyl)-[4,4'-bipyridin]ium Iodide (514)



To a stirred solution of 4,4'-bipyridine (937 mg, 6.0 mmol, 1.5 equiv.) in 50 mL of Et$_2$O was added (4-(iodomethyl)phenoxy)triisopropylsilane (1.56 g, 4.0 mmol, 1.0 equiv.) at room temperature. The reaction was left stirring at room temperature for 3 days in the dark. The solvent was removed under vacuum, and the resulting residue was dissolved in the minimum amount of DCM at 40°C. The solution was left to cool down, then 100 mL of ether was added. The resulting suspension was sonicated (5 min) then filtered. The resultant solid was washed with diethyl ether and dried under vacuum for one hour to give the pyridinium iodide salt **514** (710 mg, 32% yield) as a yellow solid.

m.p.: 93-95°C;

HRMS (ESI): Exact mass calculated for $C_{26}H_{35}ON_2{}^{28}Si$ $[M]^+$ m/z: 419.25132, found: 419.25134;

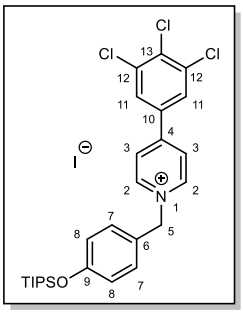
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.33 (d, J = 6.6 Hz, 2H, C^{2}**H**), 8.87 – 8.85 (m, 2H, C^{12}**H**), 8.64 (d, J = 6.5 Hz, 2H, C^{3}**H**), 8.03 – 8.01 (m, 2H, C^{11}**H**), 7.52 (d, J = 8.2 Hz, 2H, C^{7}**H**), 6.95

– 6.91 (m, 2H, C[8]**H**), 5.82 (s, 2H, C[5]**H**$_2$), 1.24 (h, *J* = 7.4 Hz, 3H, TIPS-C**H**), 1.04 (d, *J* = 7.5 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 156.4 (Ar-**C**), 152.6 (Ar-**C**), 151.0 (**C**[12]H), 145.1 (**C**[2]H), 140.8 (Ar-**C**), 130.7 (**C**[7]H), 126.8 (Ar-**C**), 125.8 (**C**[3]H), 121.9 (**C**[11]H), 120.1 (**C**[8]H), 62.5 (**C**[5]H$_2$), 17.7 (6 x C, TIPS-**C**H$_3$), 12.0 (3 x C, TIPS-**C**H);

IR (neat) (cm^{-1}): 2943, 1636, 1605, 1509, 1460, 1270, 1154, 909, 882, 805, 757, 708, 679.

4-(3,4,5-Trichlorophenyl)-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Iodide (515)



The title compound was prepared according to **General Procedure J** using 4-(3,4,5-trichlorophenyl)pyridine **510** (388 mg, 1.5 mmol) to give *salt* **515** (973 mg, 97% yield) as a yellow solid.

m.p.: 222-224°C;

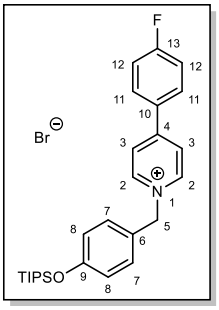
HRMS (ESI): Exact mass calculated for $C_{27}H_{33}ON^{35}Cl_3{}^{28}Si$ $[M]^+$ m/z: 520.13915, found: 520.13971;

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.31 (d, *J* = 7.1 Hz, 2H, C[2]**H**), 8.64 (d, *J* = 7.1 Hz, 2H, C[3]**H**), 8.40 (s, 2H, C[11]**H**), 7.51 (d, *J* = 8.6 Hz, 2H, C[7]**H**), 6.92 (d, *J* = 8.6 Hz, 2H, C[8]**H**), 5.78 (s, 2H, C[5]**H**$_2$), 1.30 – 1.17 (m, 3H, TIPS-C**H**), 1.03 (d, *J* = 7.5 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 156.4 (Ar-**C**), 151.5 (Ar-**C**), 144.8 (**C**[2]H), 134.4 (Ar-**C**), 134.2 (**C**[12]), 133.4 (Ar-**C**), 130.7 (**C**[7]H), 128.8 (**C**[11]H), 126.9 (Ar-**C**), 125.7 (**C**[3]H), 120.1 (**C**[8]H), 62.4 (**C**[5]H$_2$), 17.7 (6 x C, TIPS-**C**H$_3$), 12.0 (3 x C, TIPS-**C**H);

IR (neat) (cm^{-1}): 2945, 1643, 1541, 1511, 1461, 1431, 1278, 1172, 993, 915, 733, 679.

4-(4-Fluorophenyl)-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Bromide (516)



The title compound was prepared according to **General Procedure H** using 4-(4-fluorophenyl)pyridine **508** (346 mg, 2.0 mmol) to give *salt* **516** (981 mg, 95% yield) as a white solid.

m.p.: 223-225°C;

HRMS (ESI): Exact mass calculated for $C_{27}H_{35}OFN^{28}Si$ $[M]^+$ m/z: 436.24665, found: 436.24670;

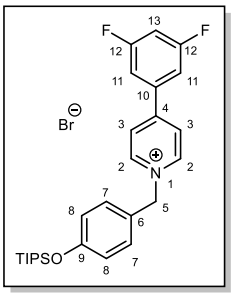
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (d, J = 7.1 Hz, 2H, C^2**H**), 8.55 (d, J = 7.1 Hz, 2H, C^3**H**), 8.21 – 8.15 (m, 2H, C^{11}**H**), 7.55 – 7.48 (m, 4H, C^{12}**H** + C^7**H**), 6.93 (d, J = 8.6 Hz, 2H, C^8**H**), 5.79 (s, 2H, C^5**H**$_2$), 1.30 – 1.18 (m, 3H, TIPS-C**H**), 1.04 (d, J = 7.5 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 165.0 (d, J = 251.4 Hz, **C**^{13}F), 156.8 (Ar-**C**), 154.3 (Ar-**C**), 145.0 (**C**^{2}H), 131.5 (d, J = 9.3 Hz, **C**^{11}H), 131.1 (**C**^{7}H), 130.5 (d, J = 2.9 Hz, **C**^{10}), 127.6 (Ar-**C**), 125.2 (**C**^{3}H), 120.6 (**C**^{8}H), 117.24 (d, J = 21.9 Hz, **C**^{12}H), 62.4 (**C**^{5}H$_2$), 18.2 (6 x C, TIPS-**C**H$_3$), 12.5(3 x C, TIPS-**C**H);

^{19}F NMR (377 MHz, DMSO-d_6) δ –107.8 (ddd, J = 14.3, 9.0, 5.3 Hz);

IR (neat) (cm^{-1}): 1638, 1594, 1495, 1271, 1229, 1149, 990, 907, 838, 746, 675, 647, 633.

4-(3,5-Difluorophenyl)-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Bromide (517)



The title compound was prepared according to **General Procedure H** using 4-(3,5-difluorophenyl)pyridine **509** (382 mg, 2.0 mmol) to give *salt* **517** (1.03 g, 96% yield) as a white solid.

m.p.: 220-222°C;

HRMS (ESI): Exact mass calculated for $C_{27}H_{34}OF_2N^{28}Si$ $[M]^+$ m/z: 454.23722, found: 454.23724;

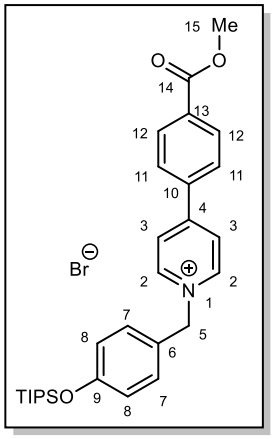
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (d, J = 7.0 Hz, 2H, C^2**H**), 8.62 (d, J = 7.1 Hz, 2H, C^3**H**), 7.92 (dt, J = 7.0, 2.1 Hz, 2H, C^{11}**H**), 7.59 (tt, J = 9.0, 2.1 Hz, 1H, C^{13}**H**), 7.53 (d, J = 8.6 Hz, 2H, C^7**H**), 6.92 (d, J = 8.6 Hz, 2H, C^8**H**), 5.81 (s, 2H, C^5**H**$_2$), 1.28 – 1.18 (m, 3H, TIPS-C**H**), 1.04 (d, J = 7.4 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 163.44 (dd, J = 247.2, 13.4 Hz, **C**^{12}F), 156.8 (Ar-**C**), 152.9 (Ar-**C**), 145.4 (**C**^{2}H), 137.40 (t, J = 10.2 Hz, **C**^{10}), 131.2 (**C**^{7}H), 127.4 (Ar-**C**), 126.0 (**C**^{3}H), 120.6 (**C**^{8}H), 112.3 (m, **C**^{11}H), 107.80 (t, J = 26.2 Hz, **C**^{13}H), 62.7 (**C**^{5}H$_2$), 18.2 (6 x C, TIPS-**C**H$_3$), 12.5 (3 x C, TIPS-**C**H);

^{19}F NMR (377 MHz, DMSO-d_6) δ –107.9 (t, J = 8.5 Hz);

IR (neat) (cm^{-1}): 2942, 1638, 1606, 1510, 1473, 1426, 1337, 1280, 1176, 1154, 1125, 991, 913, 869, 800, 740, 675, 658.

4-(4-(Methoxycarbonyl)phenyl)-*N*-(4-((triisopropylsilyl)oxy)benzyl)pyridinium Bromide (518)



The title compound was prepared according to **General Procedure H** using methyl 4-(pyridin-4-yl)benzoate **511** (426 mg, 2.0 mmol) to give *salt* **518** (1.09 g, 98% yield) as a white solid.

m.p.: 180-182°C;

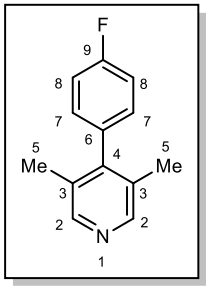
HRMS (ESI): Exact mass calculated for $C_{29}H_{38}O_3N^{28}Si$ $[M]^+$ m/z: 476.26155, found: 476.26208;

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (d, J = 7.1 Hz, 2H, C^{2}**H**), 8.61 (d, J = 7.1 Hz, 2H, C^{3}**H**), 8.24 – 8.14 (m, 4H, Ar-C**H**), 7.54 (d, J = 8.6 Hz, 2H, C^{7}**H**), 6.93 (d, J = 8.6 Hz, 2H, C^{8}**H**), 5.83 (s, 2H, C^{5}**H**$_2$), 3.91 (s, 3H, C^{15}**H**$_3$), 1.31 – 1.18 (m, 3H, TIPS-C**H**), 1.04 (d, J = 7.4 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, DMSO-d_6) δ 165.5 (**C**^{14}), 156.3 (Ar-**C**), 153.7 (Ar-**C**), 144.8 (**C**^{2}H), 137.8 (Ar-**C**), 132.2 (Ar-**C**), 130.7 (**C**^{7}H), 130.1 (2 x C, Ar-**C**H), 128.7 (2 x C, Ar-**C**H), 127.0 (Ar-**C**), 125.6 (**C**^{3}H), 120.1 (**C**^{8}H), 62.1 (**C**^{5}H$_2$), 52.6 (**C**^{15}H$_3$), 17.7 (6 x C, TIPS-**C**H$_3$), 12.0 (3 x C, TIPS-**C**H);

IR (neat) (cm^{-1}): 1727, 1633, 1514, 1458, 1433, 1276, 1179, 1108, 1014, 919, 882, 841, 801, 773, 753, 716, 673.

4-(4-Fluorophenyl)-3,5-dimethylpyridine (521)



The title compound was prepared according to **General Procedure K** using *pyridinium* **516** (258 mg, 0.5 mmol). The crude material was purified by FCC (DCM:EtOAc - 95:5 to 85:15) to give *pyridine* **521** (45 mg, 45 % yield) as a white solid.

m.p.: 47-49°C;

HRMS (ESI): Exact mass calculated for $C_{13}H_{13}NF$ $[M+H]^+$ m/z: 202.10265, found: 202.10269;

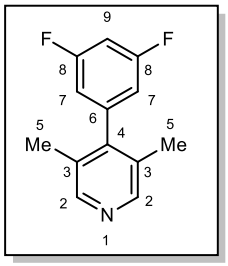
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 2H, C^{2}**H**), 7.17 – 7.05 (m, 4H, Ar-C**H**), 2.01 (s, 6H, C^{5}**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.24 (d, J = 246.7 Hz, **C**^{9}), 148.5 (**C**^{2}H), 148.4 (**C**^{4}), 133.98 (d, J = 3.6 Hz, **C**^{6}), 131.1 (**C**^{3}), 129.86 (d, J = 8.0 Hz, **C**^{7}H), 115.90 (d, J = 21.4 Hz, **C**^{8}H), 17.4 (**C**^{5}H$_3$);

^{19}F NMR (377 MHz, $CDCl_3$) δ –114.55 (tt, *J* = 8.6, 5.4 Hz);

IR (neat) (cm^{-1}): 1601, 1510, 1474, 1379, 1218, 1161, 837, 817, 761, 619.

4-(3,5-Difluorophenyl)-3,5-dimethylpyridine (522)



The title compound was prepared according to **General Procedure K** using *pyridinium* **517** (267 mg, 0.5 mmol). The crude material was purified by FCC (DCM:EtOAc - 95:5 to 85:15) to give *pyridine* **522** (73 mg, 67 % yield) as a white solid.

m.p.: 84-87°C;

HRMS (ESI): Exact mass calculated for $C_{13}H_{12}NF_2$ $[M+H]^+$ m/z: 220.09323, found: 220.09331;

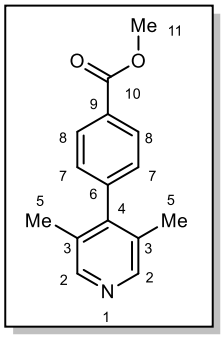
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 2H, C^2**H**), 6.85 (tt, *J* = 9.0, 2.3 Hz, 1H, C^9**H**), 6.70 – 6.63 (m, 2H, C^7**H**), 2.04 (s, 6H, C^5**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4 (dd, *J* = 250.2, 12.8 Hz, **C**^{8}F), 148,7 (**C**^{2}H), 147.1 (m, **C**^{4}), 141.46 (m, **C**^{6}), 130.5 (**C**^{3}) 111.3 (m, **C**^{7}H), 103.34 (t, *J* = 25.1 Hz, **C**^{9}H) 17.2 (**C**^{5}H$_3$);

^{19}F NMR (377 MHz, $CDCl_3$) δ –108.72 (ddd, *J* = 9.6, 6.6, 1.6 Hz);

IR (neat) (cm^{-1}): 1625, 1586, 1462, 1429, 1409, 1380, 1330, 1119, 979, 876, 854, 759, 725, 698, 608.

Methyl 4-(3,5-dimethylpyridin-4-yl)benzoate (523)



The title compound was prepared according to **General Procedure K** using *pyridinium* **518** (278 mg, 0.5 mmol). The crude material was purified by FCC (DCM:EtOAc - 95:5 to 85:15) to give *pyridine* **523** (66 mg, 55 % yield) as a white solid.

m.p.: 100-102°C;

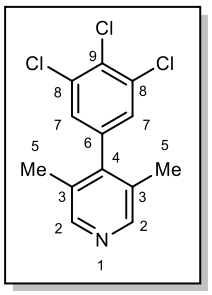
HRMS (ESI): Exact mass calculated for $C_{15}H_{16}O_2N$ $[M+H]^+$ m/z: 242.11756 , found: 224.11742;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 2H, C^2**H**), 8.14 – 8.10 (m, 2H, C^8**H**), 7.22 – 7.17 (m, 2H, C^7**H**), 3.93 (s, 3H, C^{11}**H**$_3$), 1.99 (s, 6H, C^5**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (**C**^{10}), 148.6 (**C**^{2}H), 148.4 (**C**^{4}), 143.0 (**C**^{6}), 130.4 (**C**^{3}), 130.2 (**C**^{8}H), 129.6 (**C**^{9}), 128.3 (**C**^{7}H), 52.3 (**C**^{11}H$_3$), 17.3 (**C**^{5}H$_3$);

IR (neat) (cm^{-1}): 1717, 1584, 1438, 1315, 1288, 1181, 1160, 1115, 1103, 862, 774, 760, 710.

3,5-Dimethyl-4-(3,4,5-trichlorophenyl)pyridine (524)



The title compound was prepared according to **General Procedure L** using *pyridinium* **515** (325 mg, 0.5 mmol). The crude material was purified by FCC (DCM:EtOAc - 100:0 to 90:10) to give *pyridine* **524** (86 mg, 60 % yield) as a white solid.

m.p.: 146-148°C;

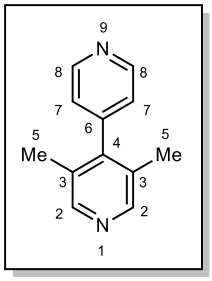
HRMS (ESI): Exact mass calculated for $C_{13}H_{11}N^{35}Cl_3$ $[M+H]^+$ m/z: 285.99516, found: 285.99509;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 2H, C^2**H**), 7.17 (s, 2H C^7**H**), 2.04 (s, 6H, C^5**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.8 (**C**^{2}H), 145.8 (Ar-**C**), 138.2 (Ar-**C**), 134.9 (Ar-**C**), 131.1 (Ar-**C**), 130.5 (**C**^{3}), 128.5 (**C**^{7}H), 17.3 (**C**$^5H_3$);

IR (neat) (cm^{-1}): 1578, 1538, 1436, 1420, 1377, 1203, 1163, 877, 814, 756, 727, 705, 606.

3,5-Dimethyl-4,4'-bipyridine (525)



The title compound was prepared according to **General Procedure L** using *pyridinium* **513** (273 mg, 0.5 mmol) or according to modified **General Procedure K** using *pyridinium* **514** (250 mg, 0.5 mmol) plus one equivalent of sodium iodide. The crude material was purified by FCC (EtOAc:Pyridine - 100:0 to 95:5) to give *pyridine* **525** (63 mg, 68 % yield) as a white solid.

m.p.: 133-135°C;

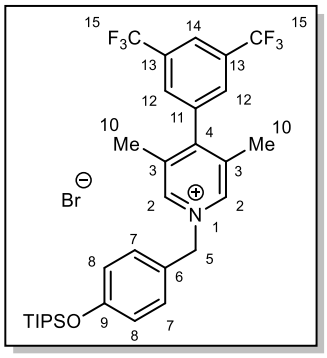
HRMS (ESI): Exact mass calculated for $C_{12}H_{13}N_2$ $[M+H]^+$ m/z: 185.10732, found: 185.10744;

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 – 8.67 (m, 2H, C^8**H**), 8.33 (s, 2H, C^2**H**), 7.07 – 7.05 (m, 2H, C^7**H**), 1.99 (s, 6H, C^5**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4 (**C**^{8}H), 148.6 (**C**^{2}H), 146.4 (Ar-**C**), 146.3 (Ar-**C**), 129.9 (**C**^{3}), 123.3 (**C**^{7}H), 17.2 (**C**$^5H_3$);

IR (neat) (cm^{-1}): 1585, 1411, 1379, 987, 878, 838, 759, 670.

4-(3,5-bis(Trifluoromethyl)phenyl)-3,5-dimethyl-*N*-(4-(triisopropylsilyl)oxy)benzyl)pyridinium Bromide (530)



The title compound was prepared according to **General Procedure I** using 4-(3,5-bis(trifluoromethyl)phenyl)-3,5-dimethylpyridine **449** (319 mg, 1.0 mmol) to give *salt* **530** (590 mg, 89%) as a white solid.

m.p.: 249-251°C;

HRMS (ESI): Exact mass calculated for $C_{31}H_{38}OF_6N^{28}Si$ $[M]^+$ m/z: 582.26214, found: 582.26190;

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 2H, C^2**H**), 8.01 (s, 1H, C^{14}**H**), 7.69 (d, *J* = 8.4 Hz, 2H, C^7**H**), 7.64 (s, 2H, C^{12}**H**), 6.88 (d, *J* = 7.5 Hz, 2H, C^8**H**), 6.21 (s, 2H, C^5**H**$_2$), 2.22 (s, 6H, C^{10}**H**$_3$), 1.26 – 1.14 (m, 3H, TIPS-C**H**), 1.04 (d, *J* = 7.4 Hz, 18H, TIPS-C**H**$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (Ar-**C**), 154.8 (Ar-**C**), 142.9 (**C**^{2}H), 137.4 (**C**^{3}), 136.6 (Ar-**C**), 133.3 (q, *J* = 34.0 Hz, **C**^{13}), 131.6 (**C**^{7}H), 127.7 (**C**^{12}H), 125.3 (Ar-**C**), 123.6 (**C**^{14}H), 122.8 (d, *J* = 273.4 Hz, **C**$^{15}F_3$), 121.0 (**C**^{8}H), 63.4 (**C**$^5H_2$), 18.2 (**C**$^{10}H_3$), 17.9 (6 x C, TIPS-**C**H_3), 12.7 (3 x C, TIPS-**C**H);

^{19}F NMR (377 MHz, $CDCl_3$) δ –62.9;

IR (neat) (cm^{-1}): 1509, 1375, 1277, 1258, 1165, 1153, 1139, 1108, 902, 885, 845, 714, 700, 681, 647.

Appendix

Appendix 1: References

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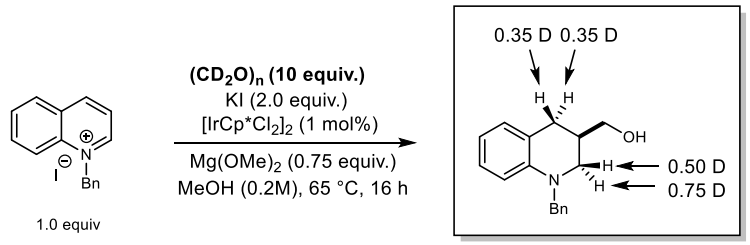
Appendix 2: Mechanistic NMR spectra for Chapter 2



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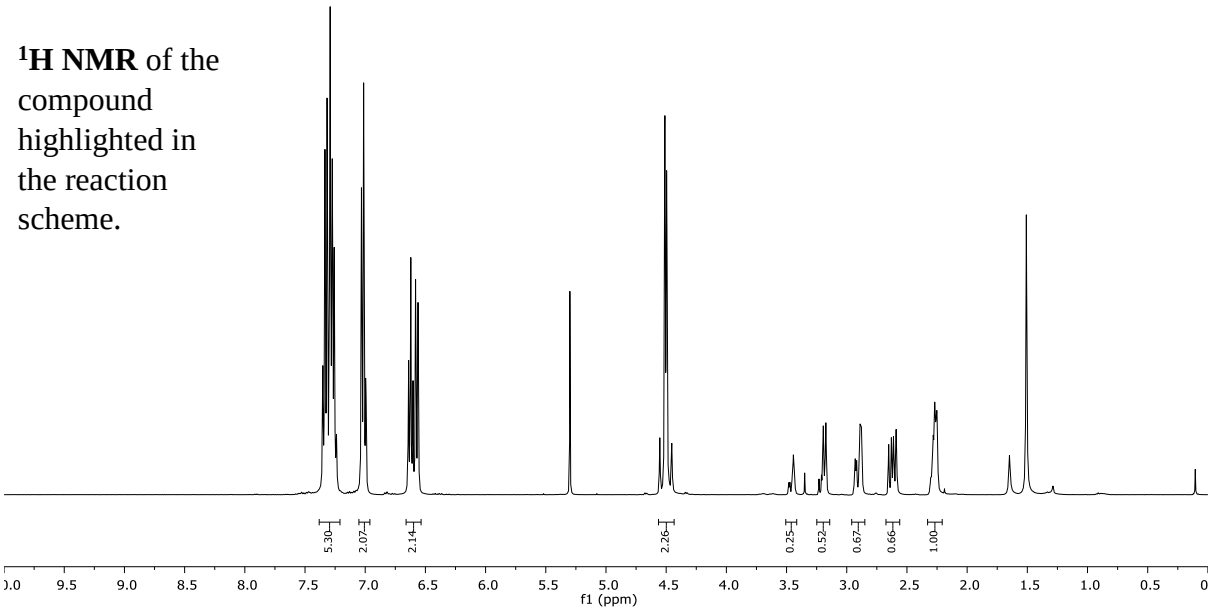

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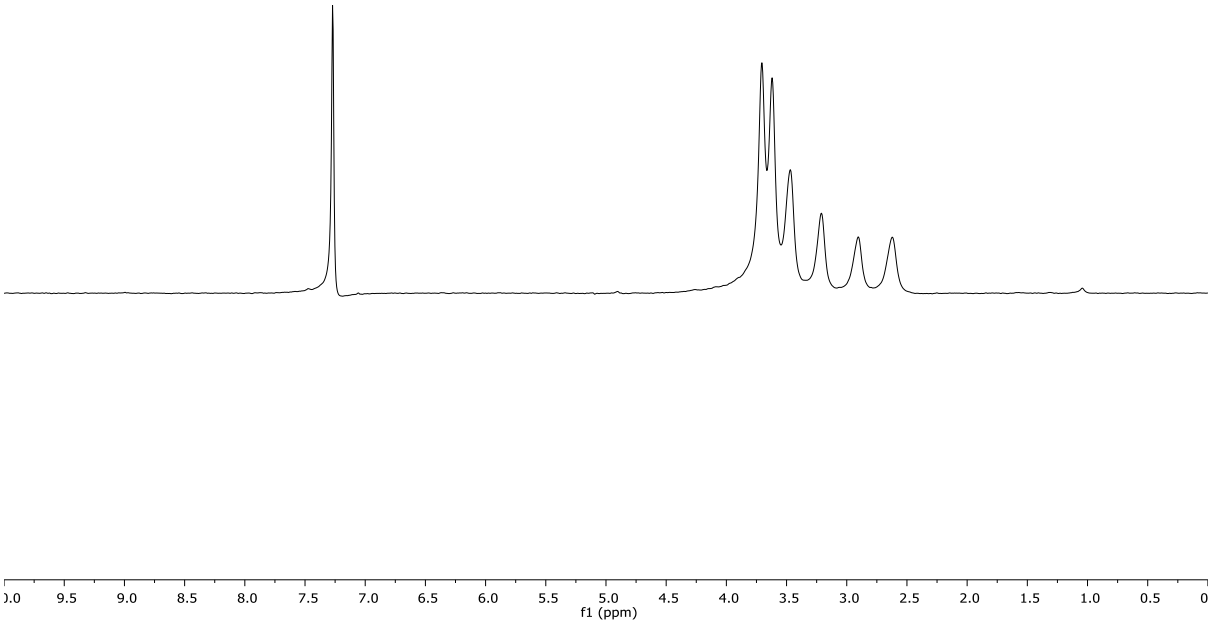

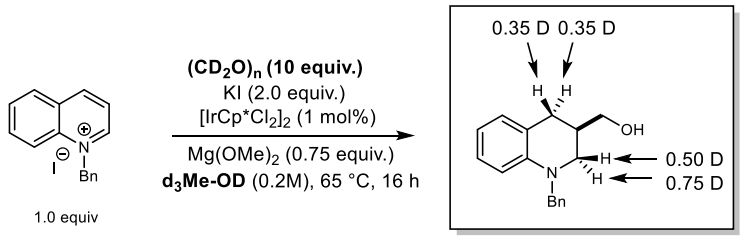

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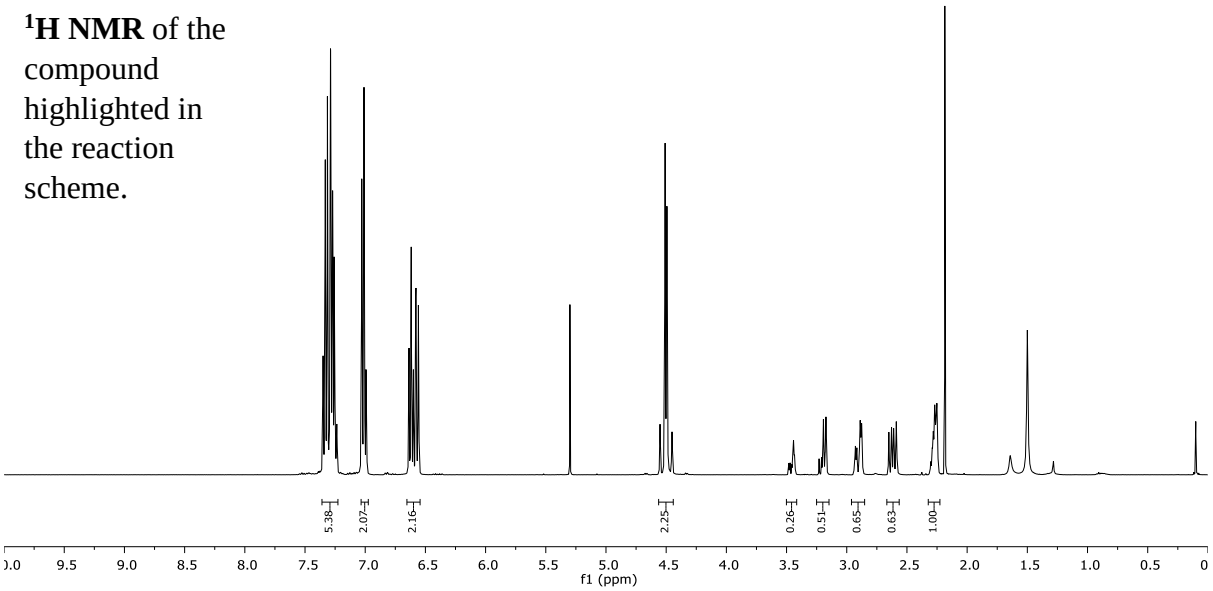

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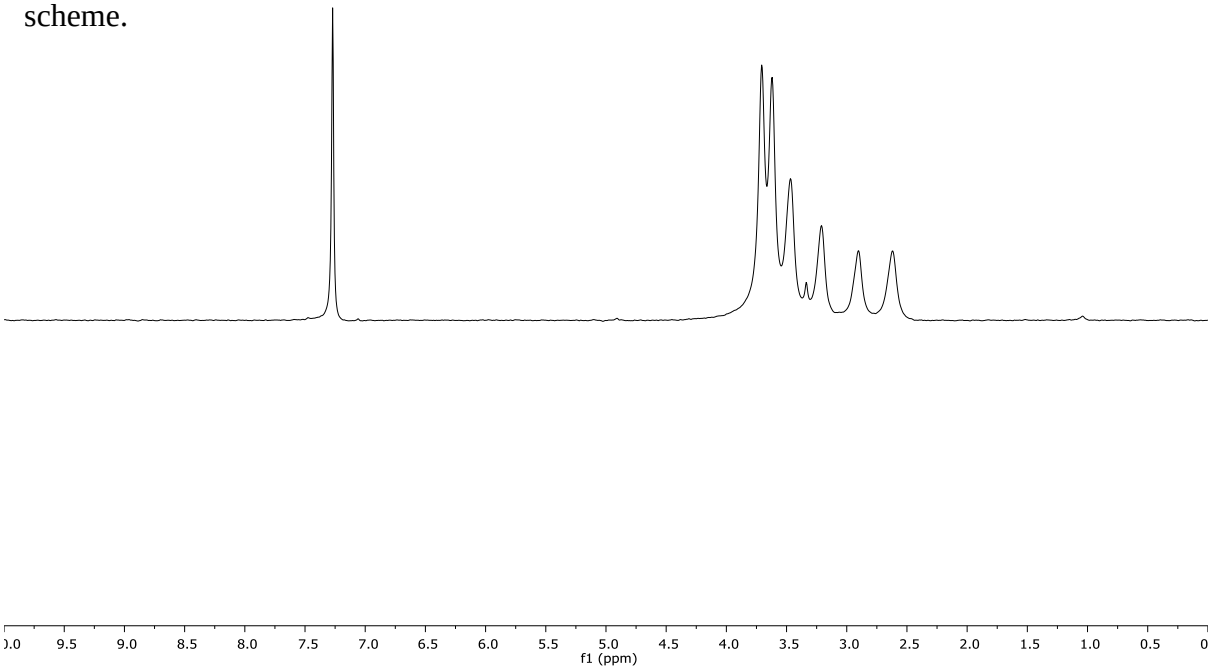

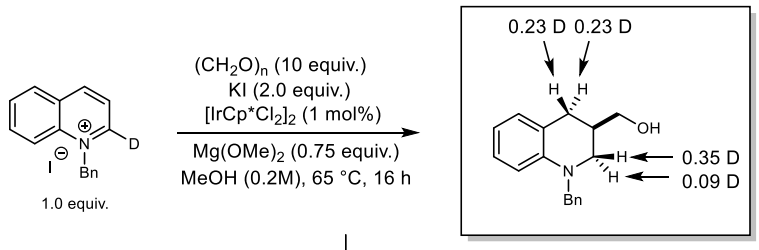

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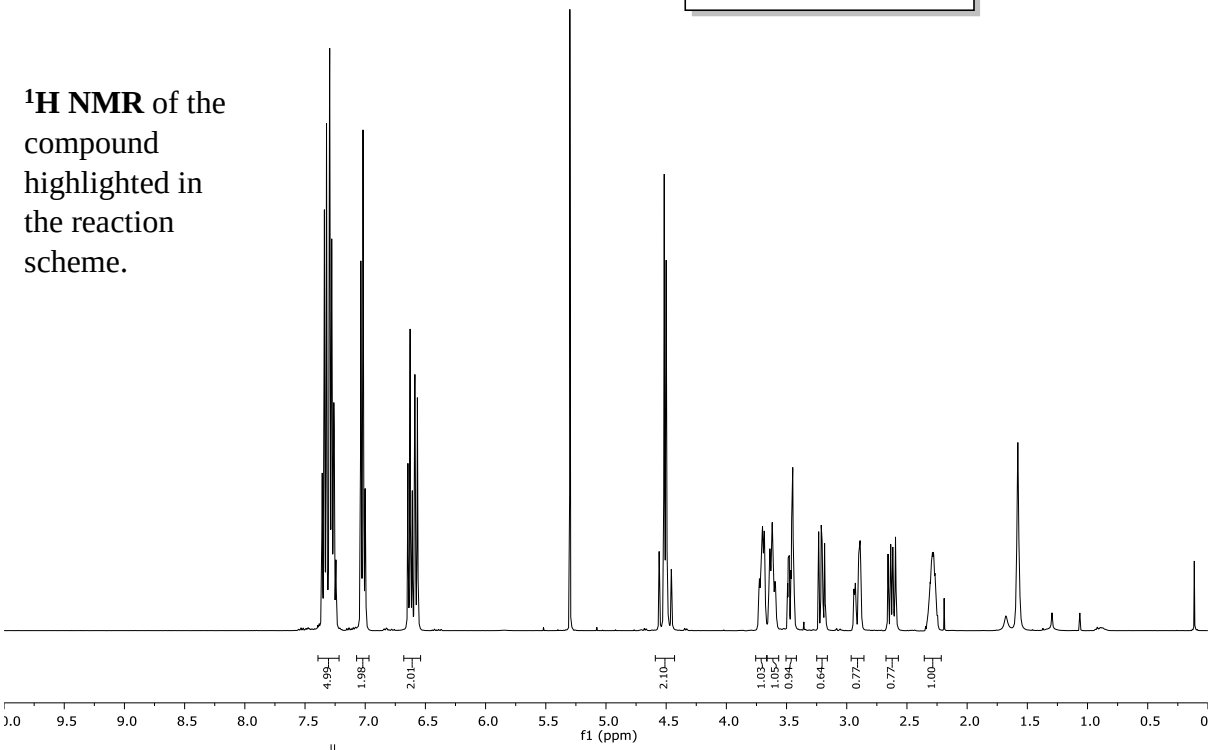

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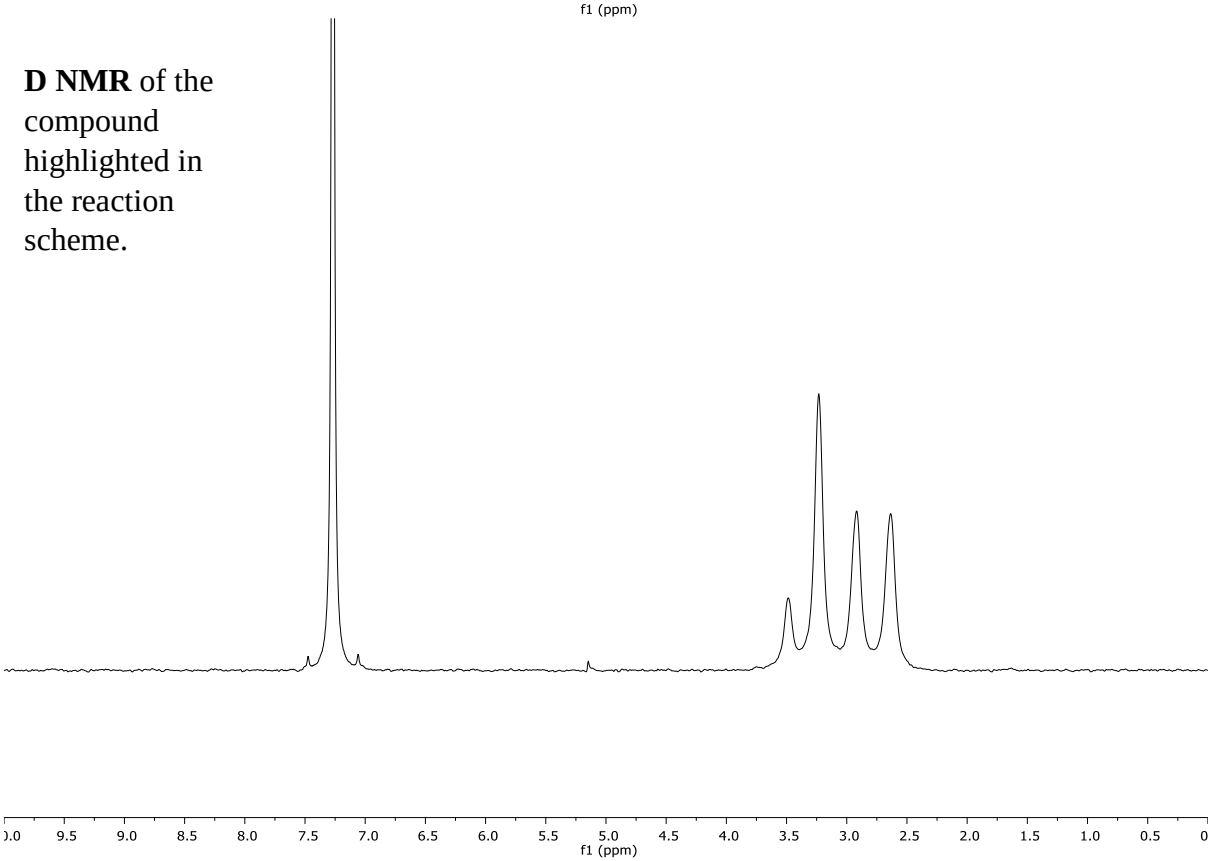

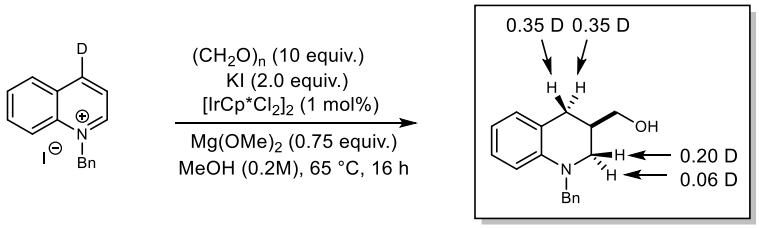

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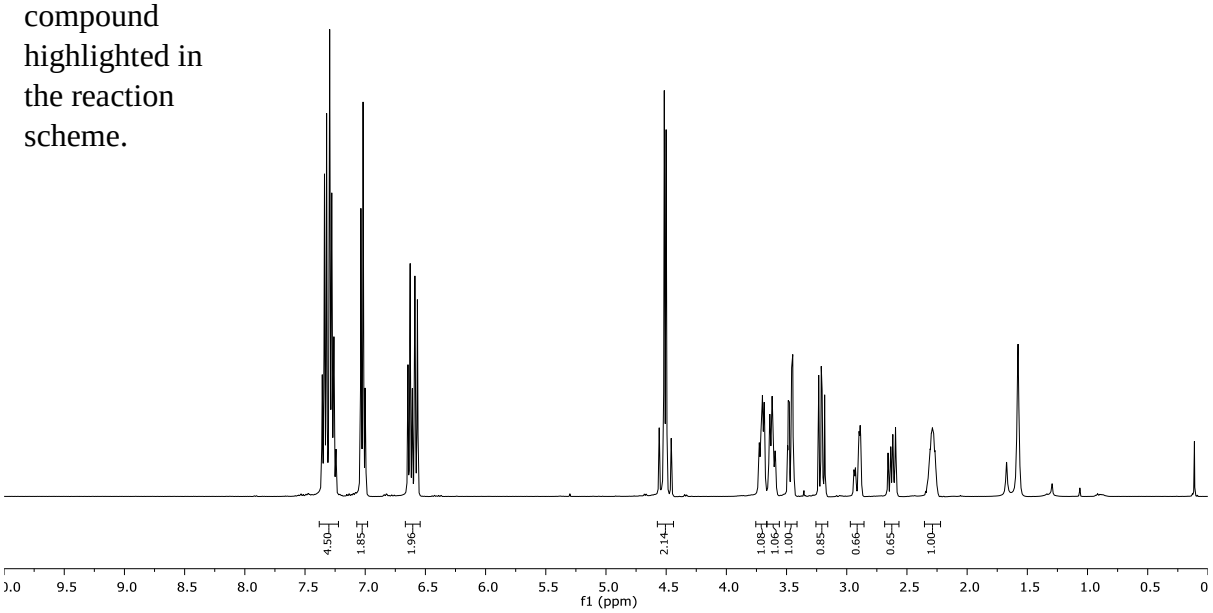

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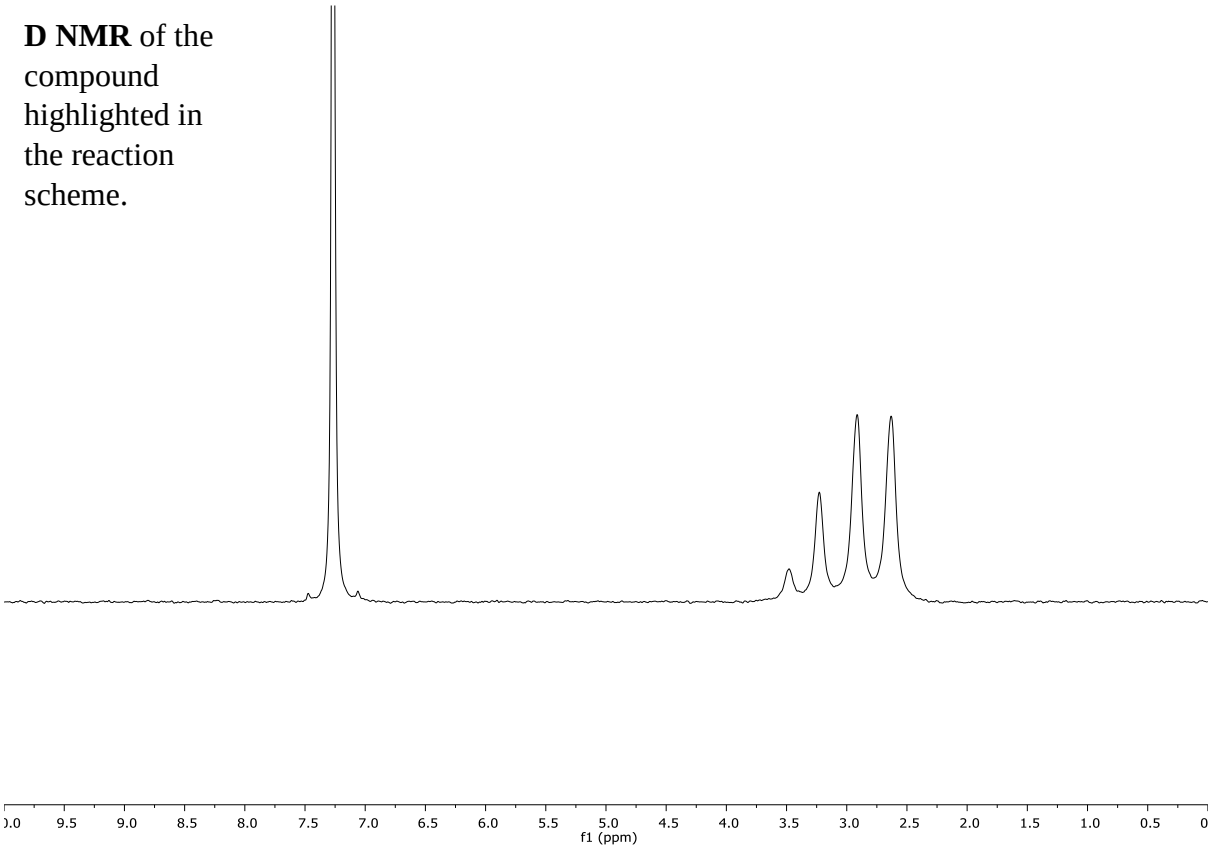

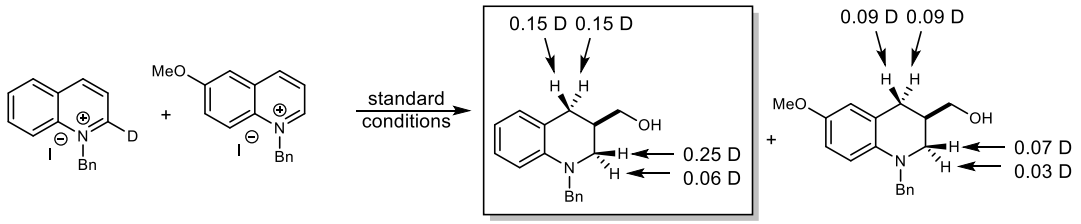

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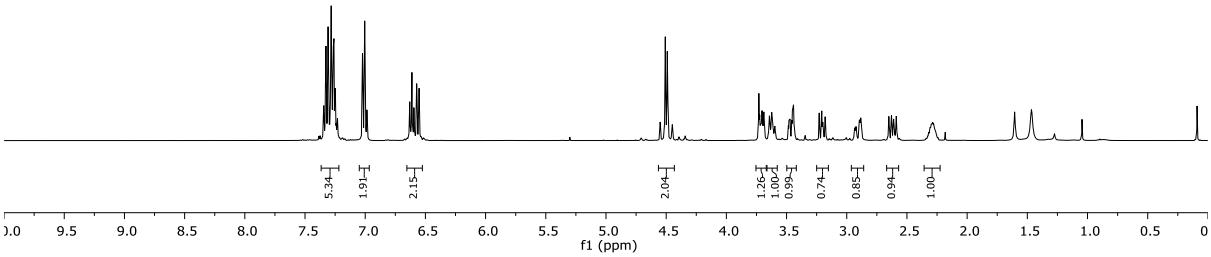

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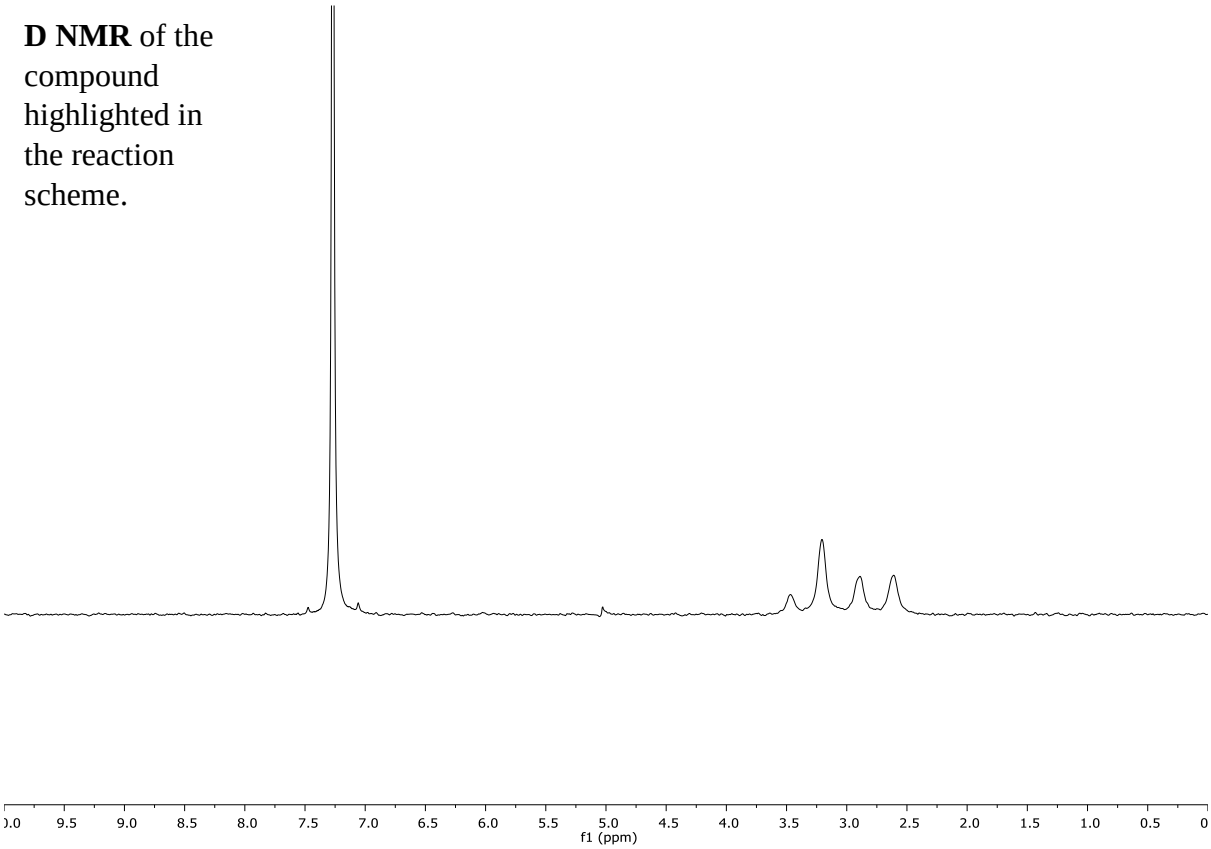

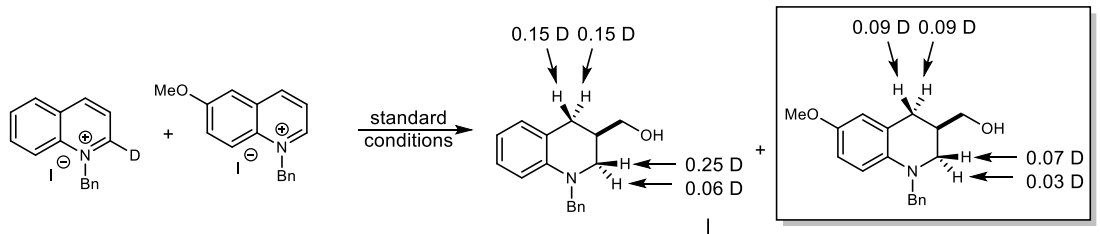

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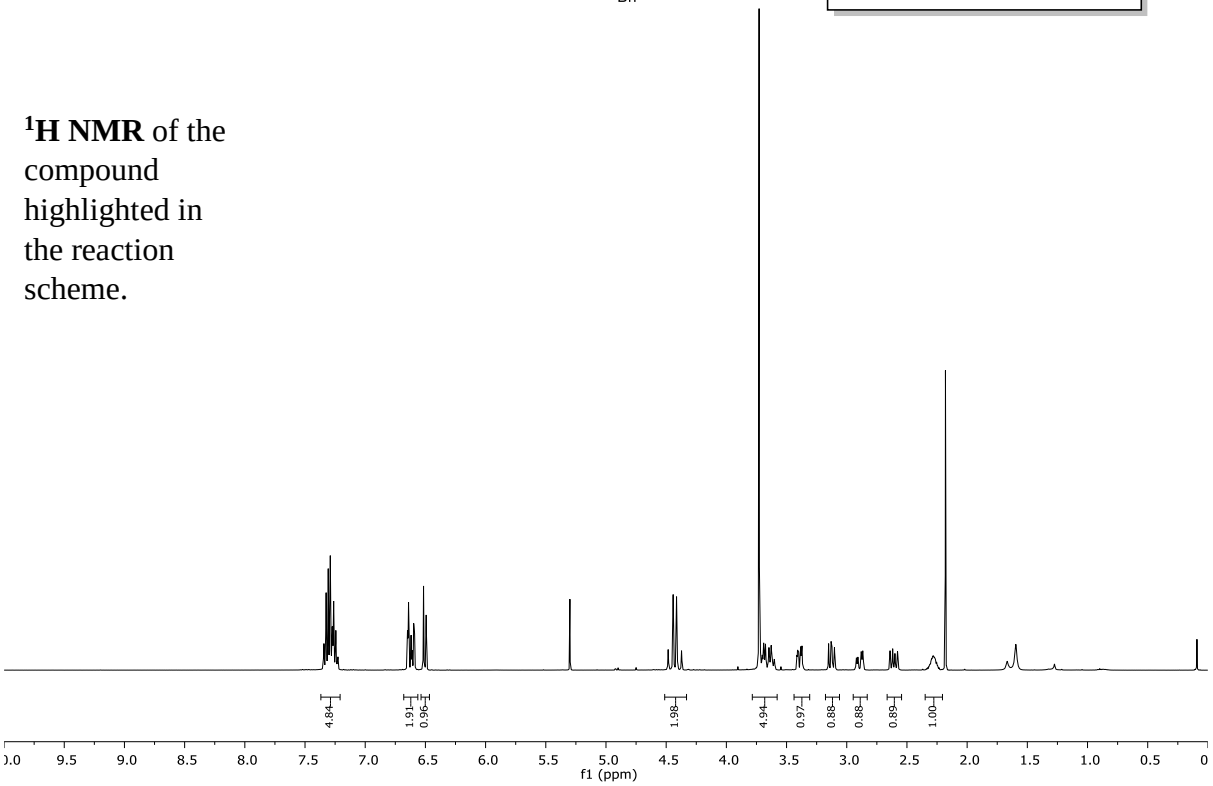

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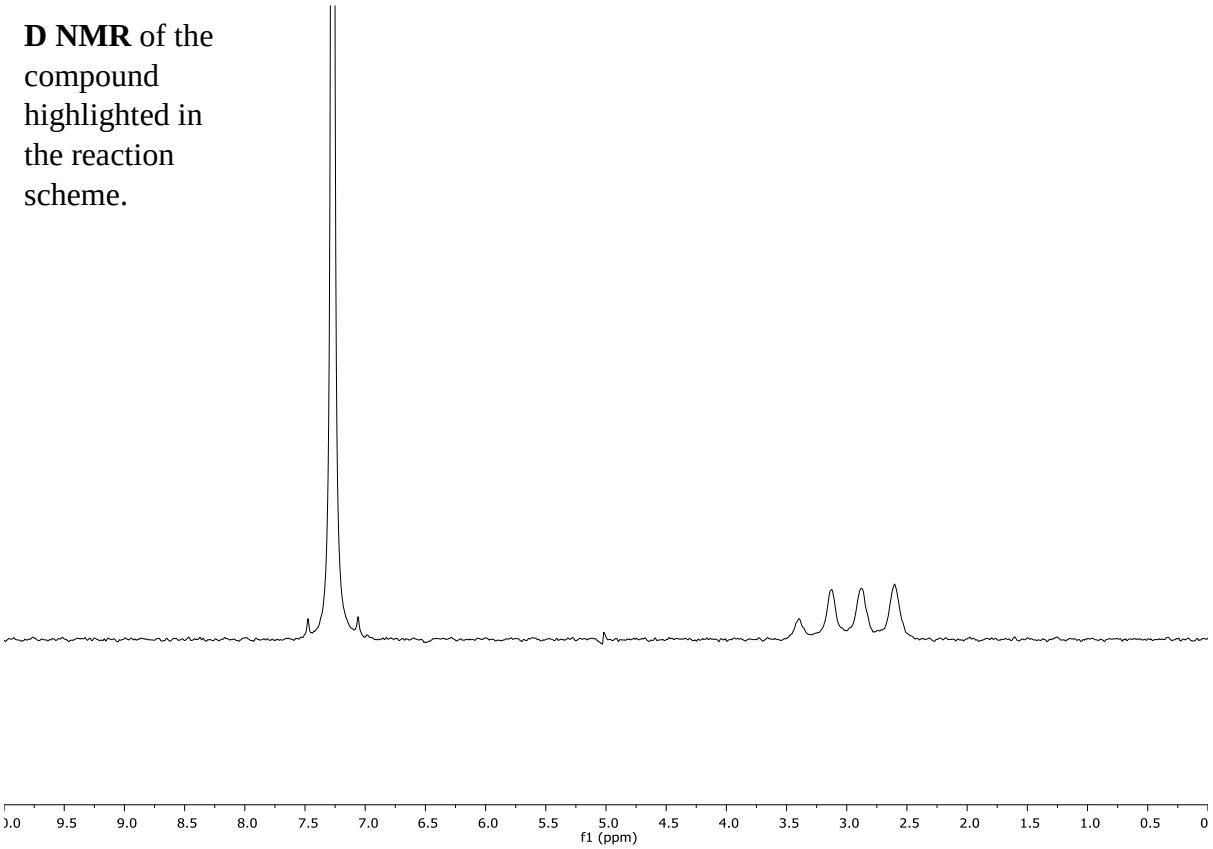

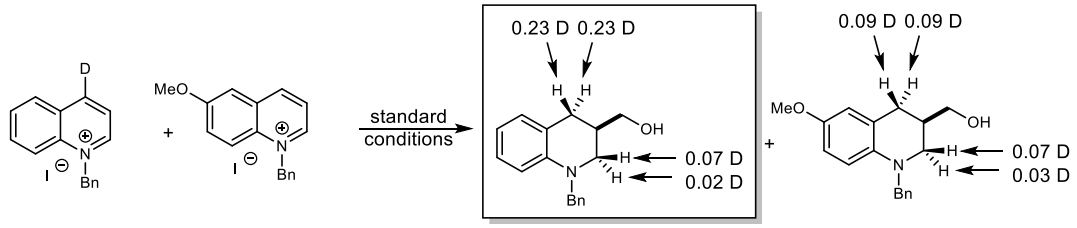

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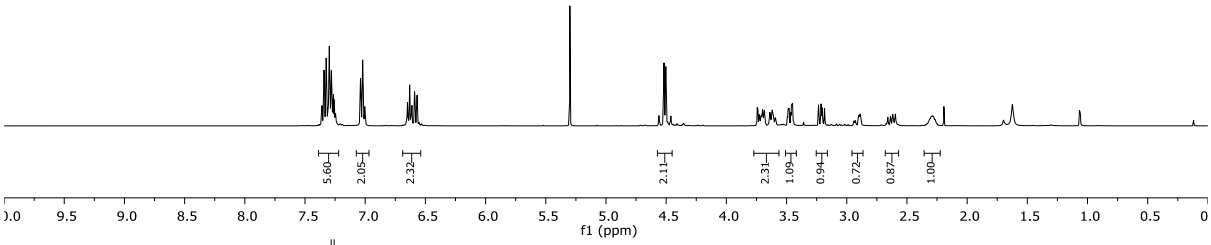

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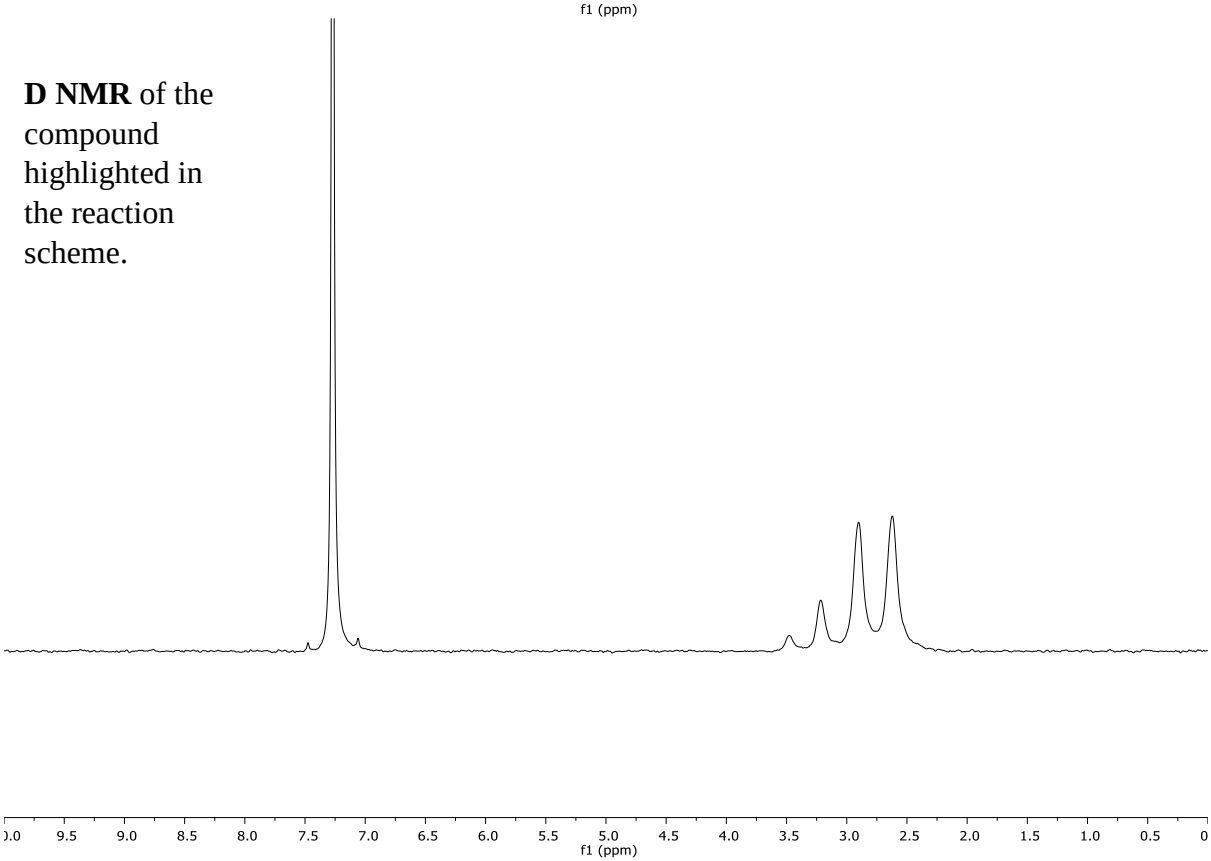

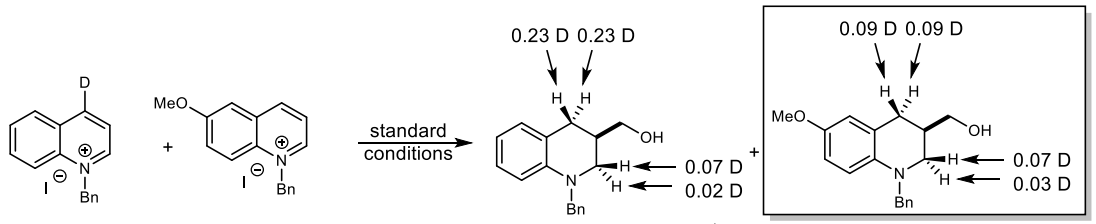

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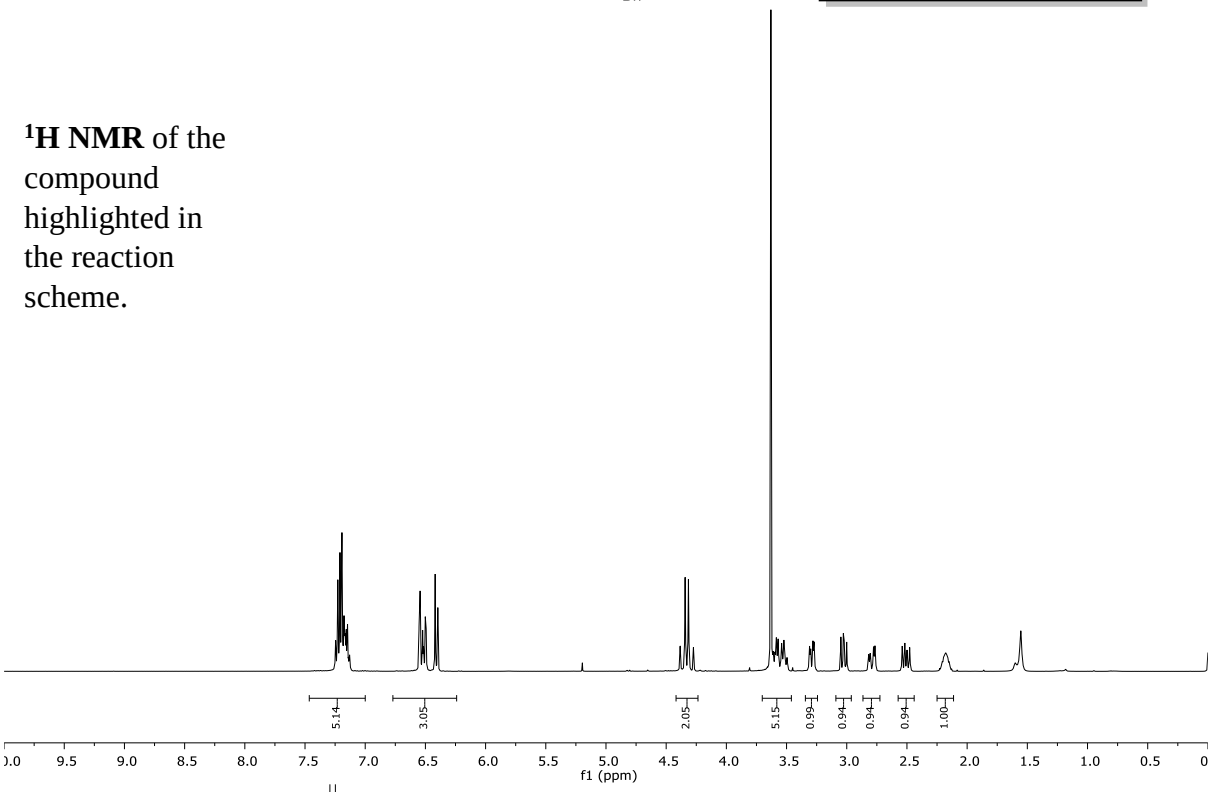

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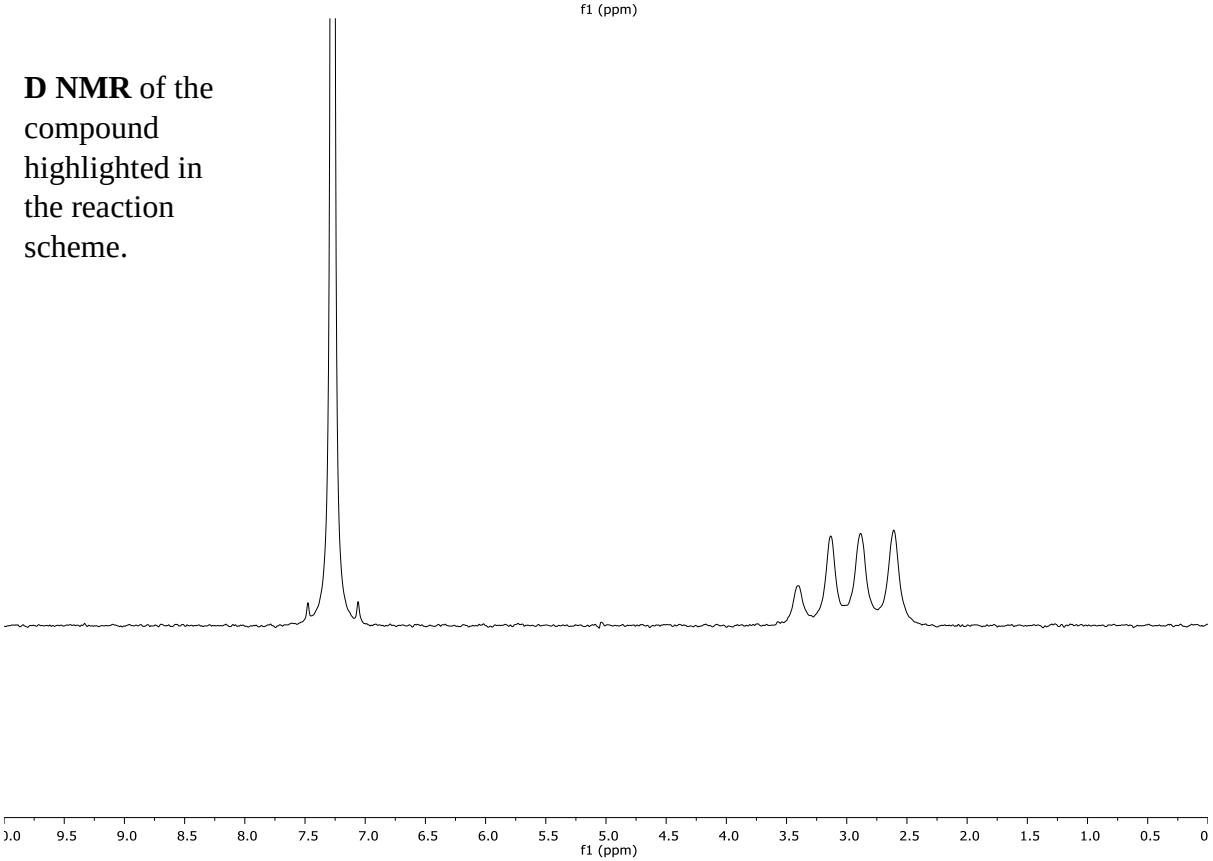

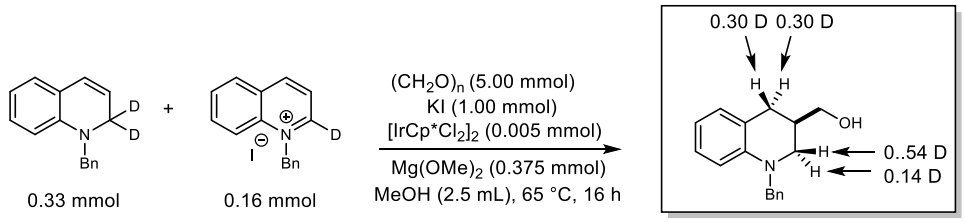

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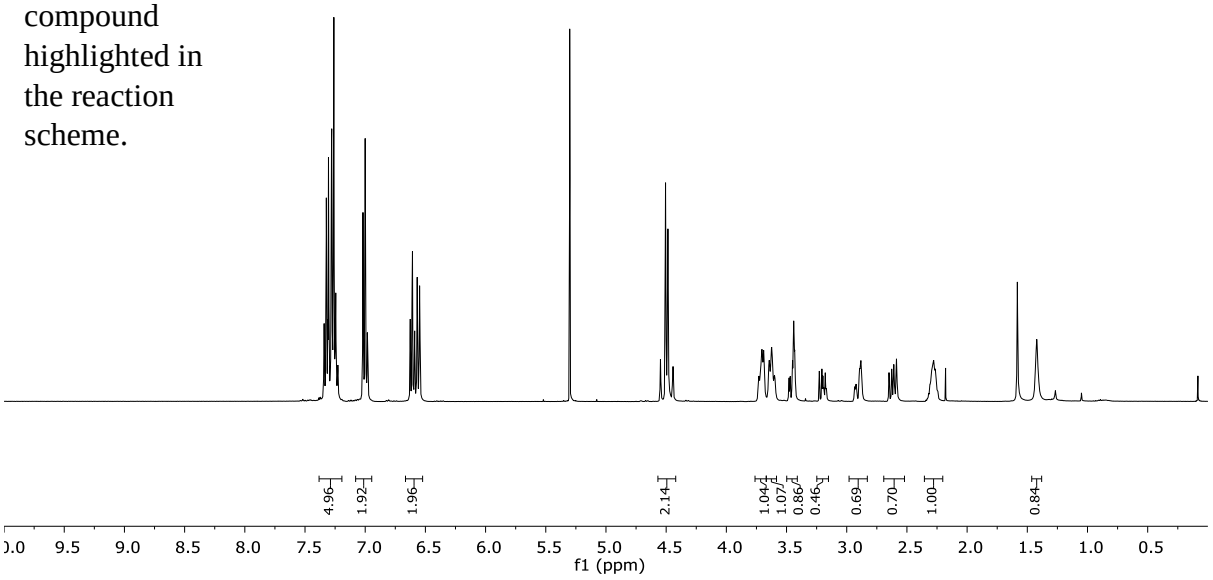

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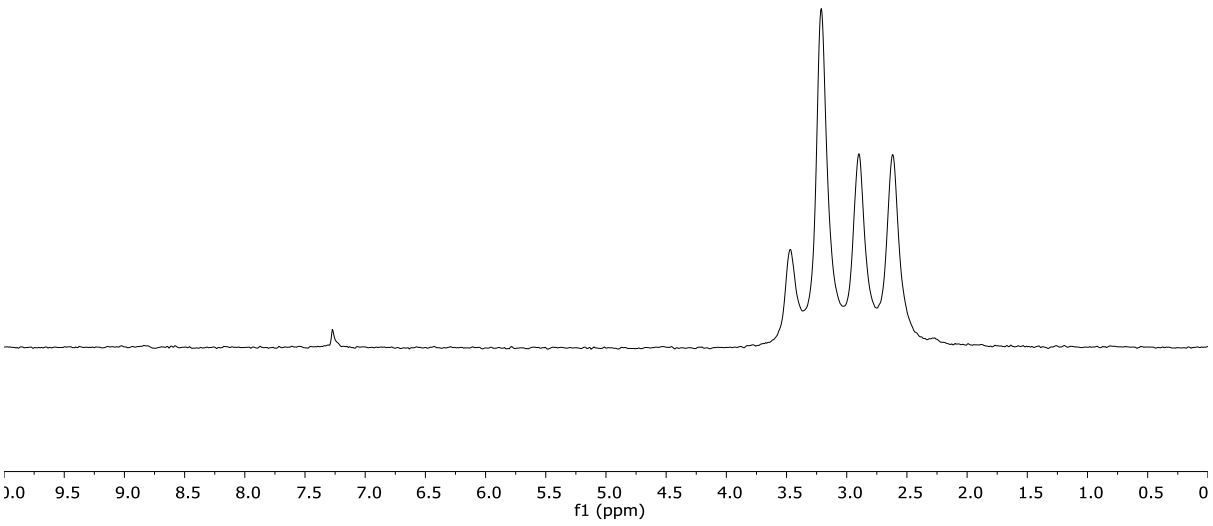
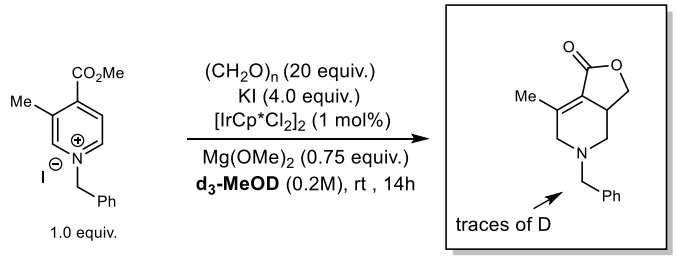


Appendix 3: Mechanistic NMR spectra for Chapter 3



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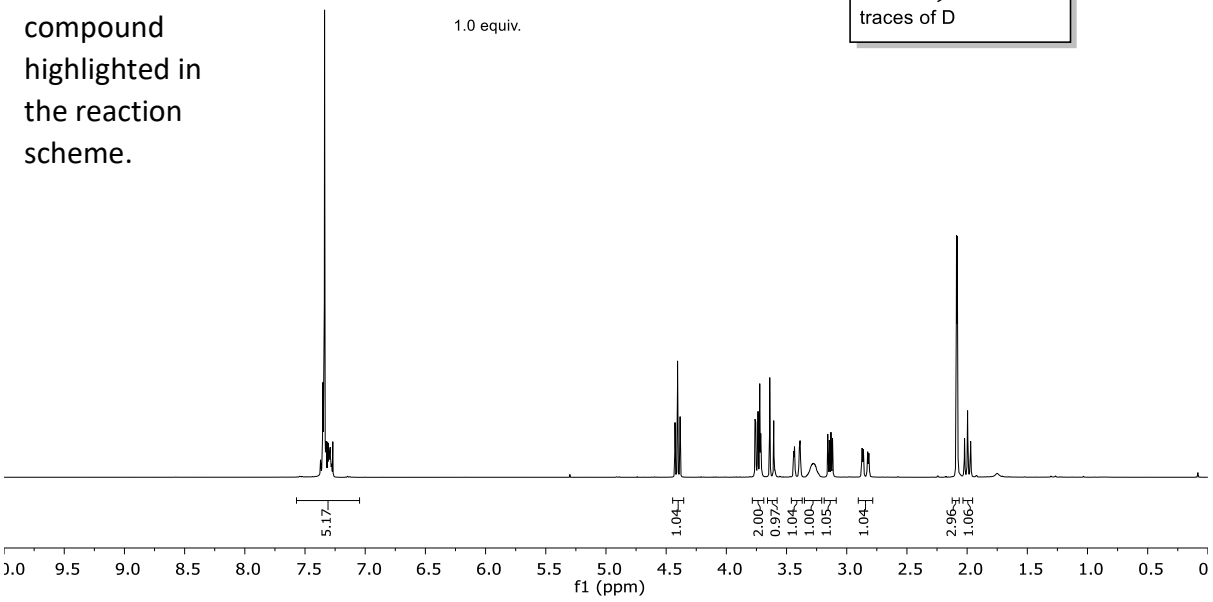

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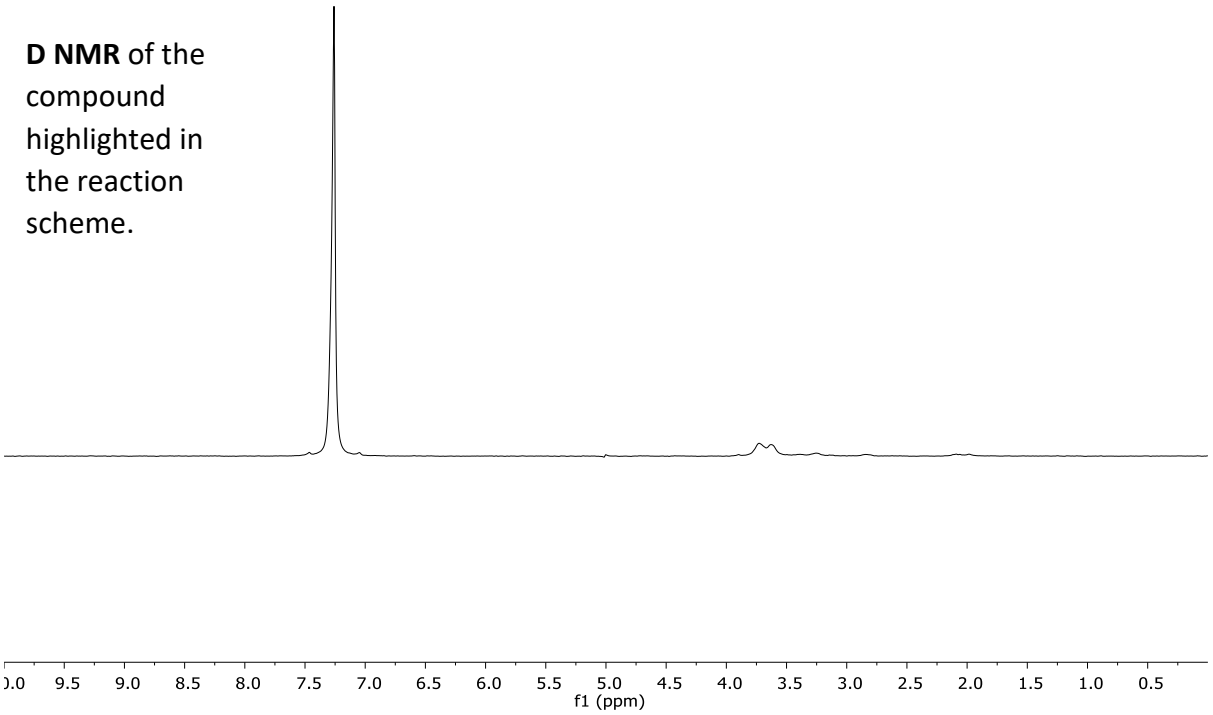

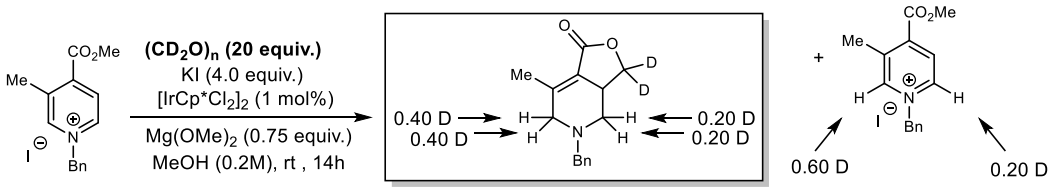

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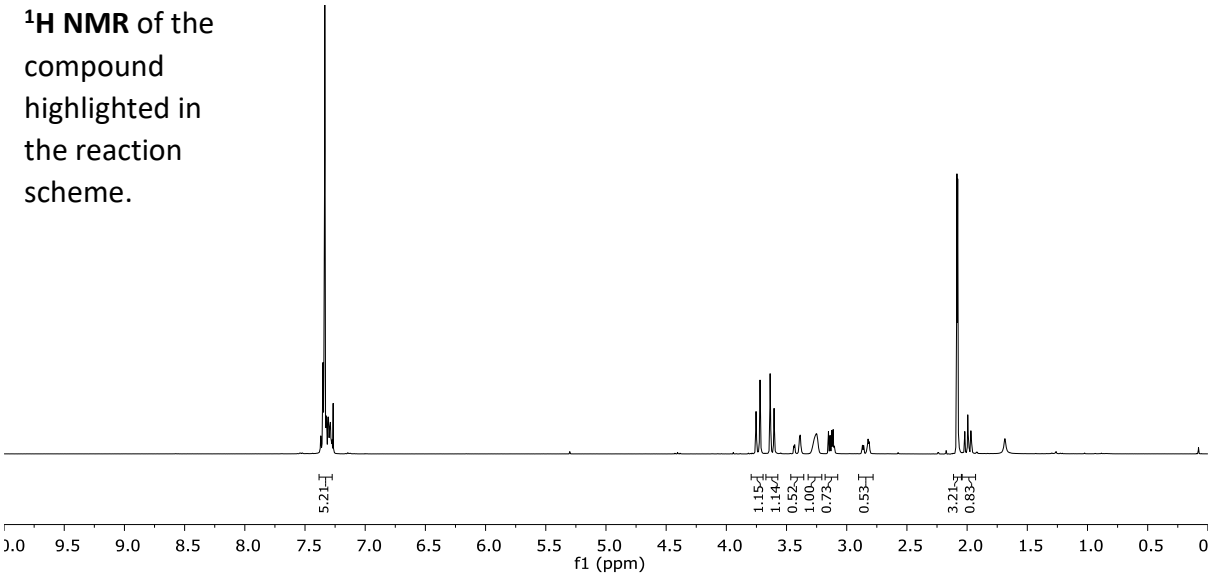

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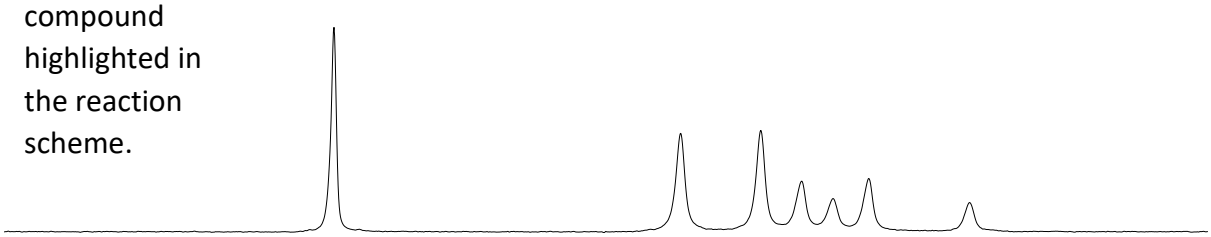

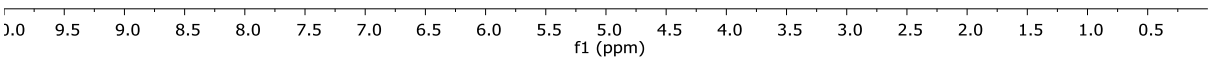

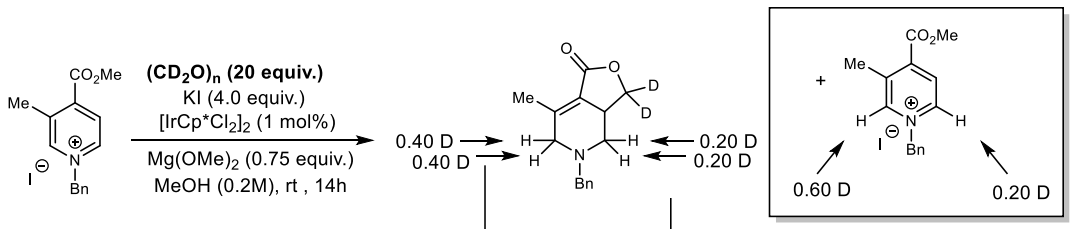

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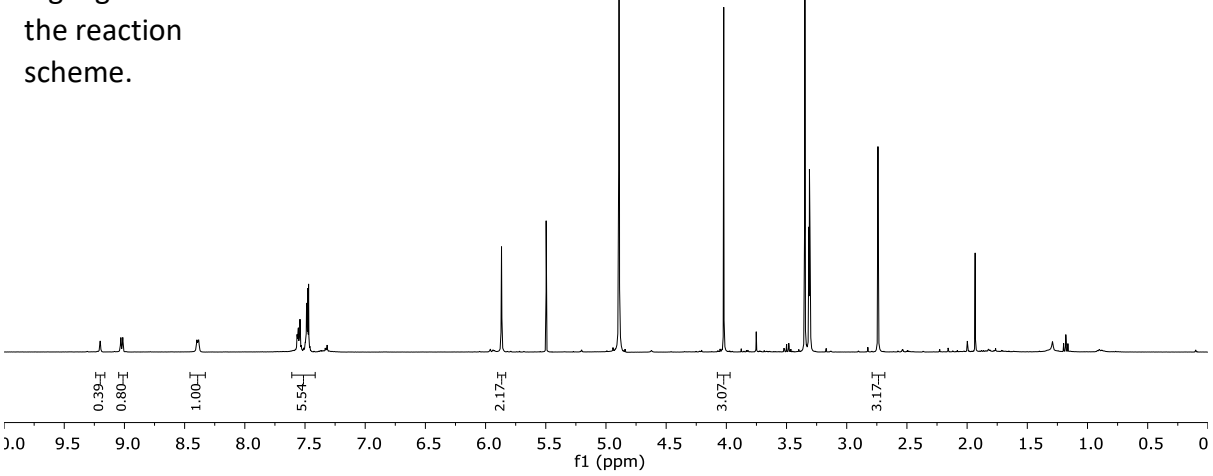

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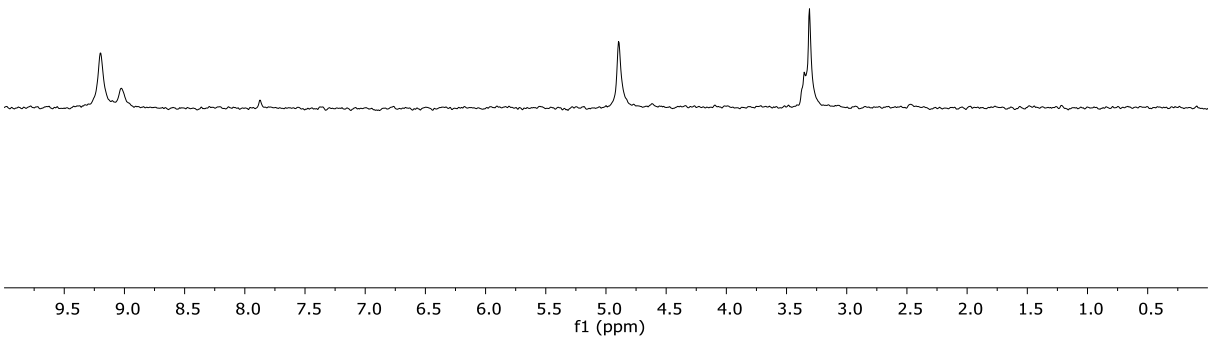

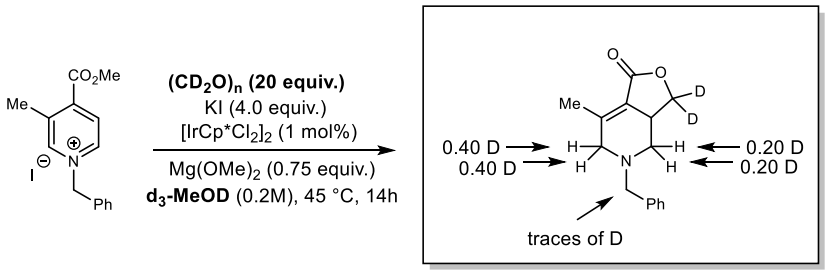

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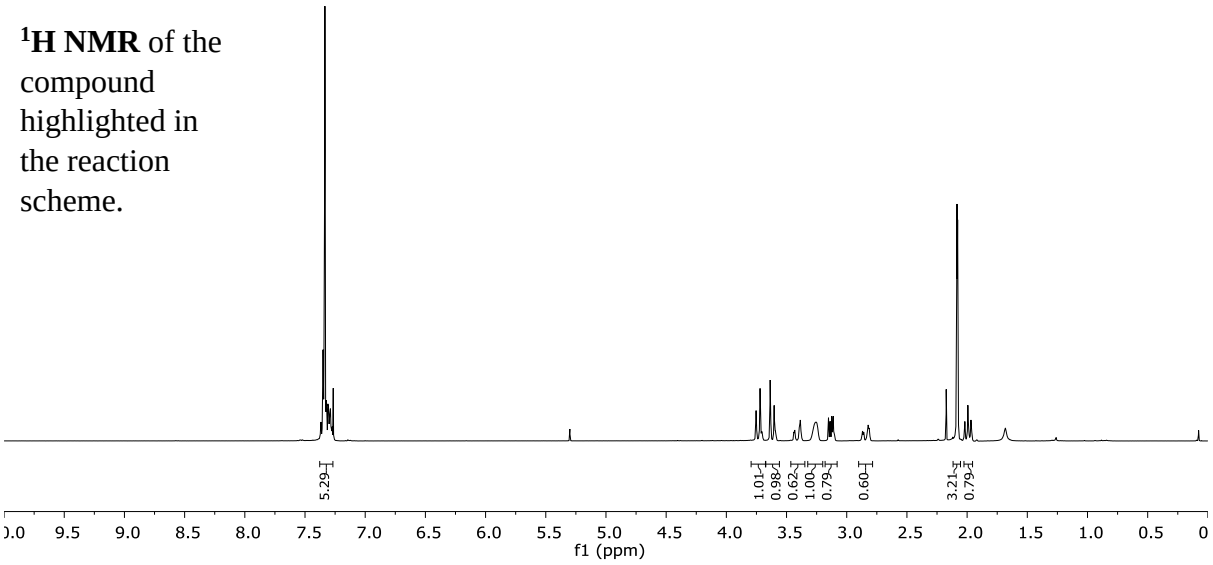
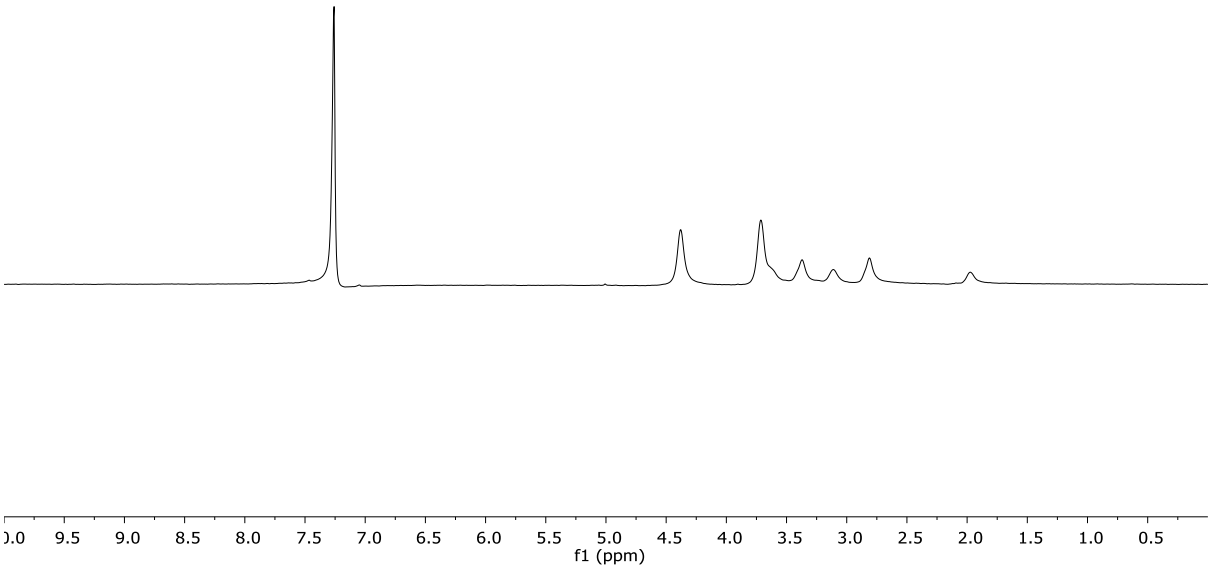


D NMR of the compound highlighted in the reaction scheme.

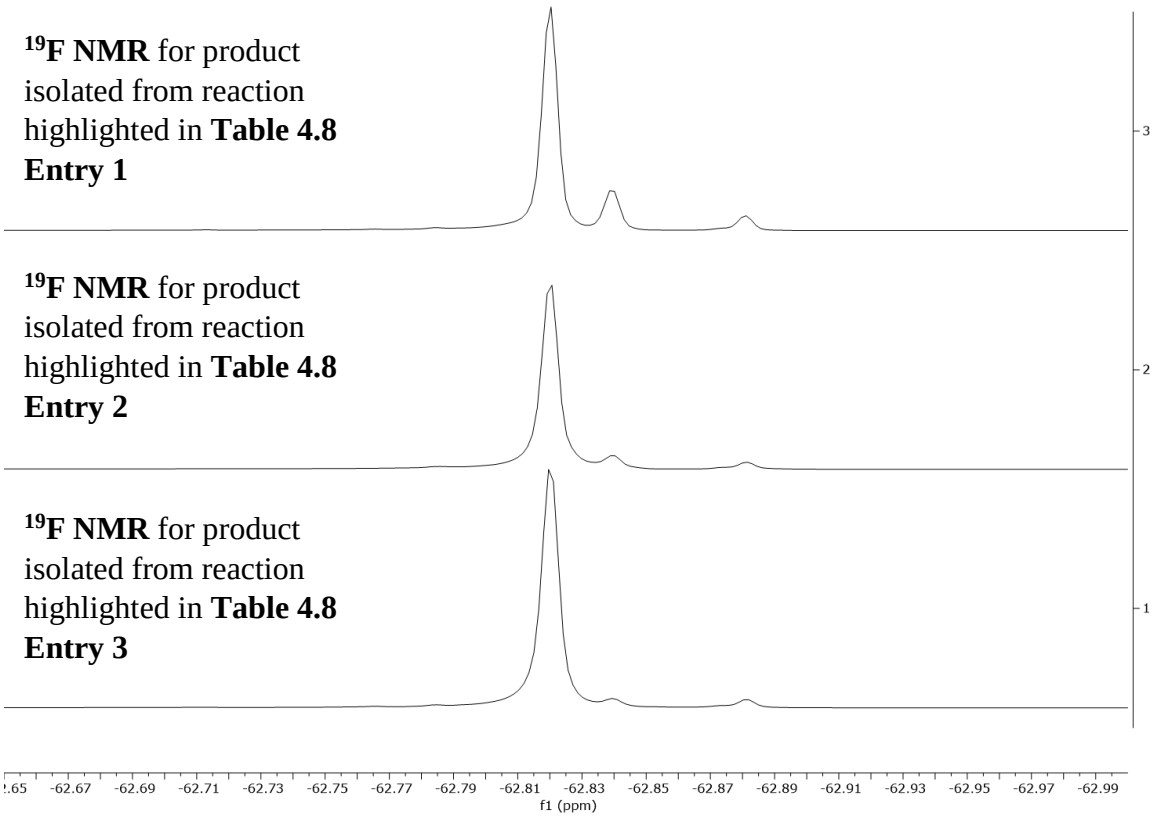


Appendix 4: Mechanistic NMR spectra for Chapter 4

^{19}F NMR for product isolated from reaction highlighted in **Table 4.8** **Entry 1**

^{19}F NMR for product isolated from reaction highlighted in **Table 4.8** **Entry 2**

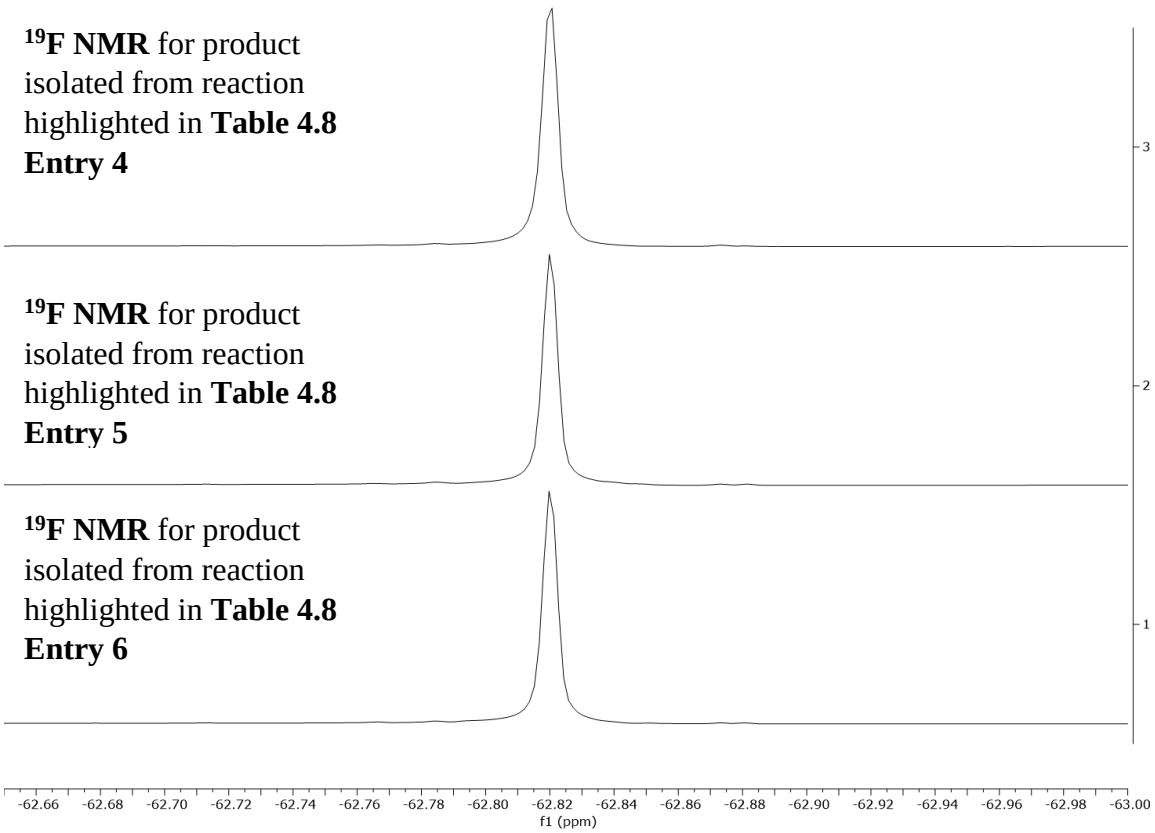
^{19}F NMR for product isolated from reaction highlighted in **Table 4.8** **Entry 3**



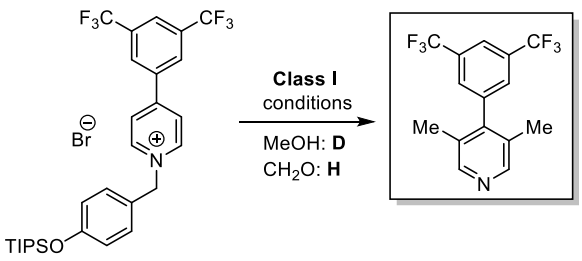
^{19}F NMR for product isolated from reaction highlighted in **Table 4.8** **Entry 4**

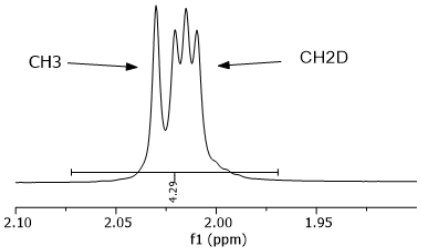
^{19}F NMR for product isolated from reaction highlighted in **Table 4.8** **Entry 5**

^{19}F NMR for product isolated from reaction highlighted in **Table 4.8** **Entry 6**

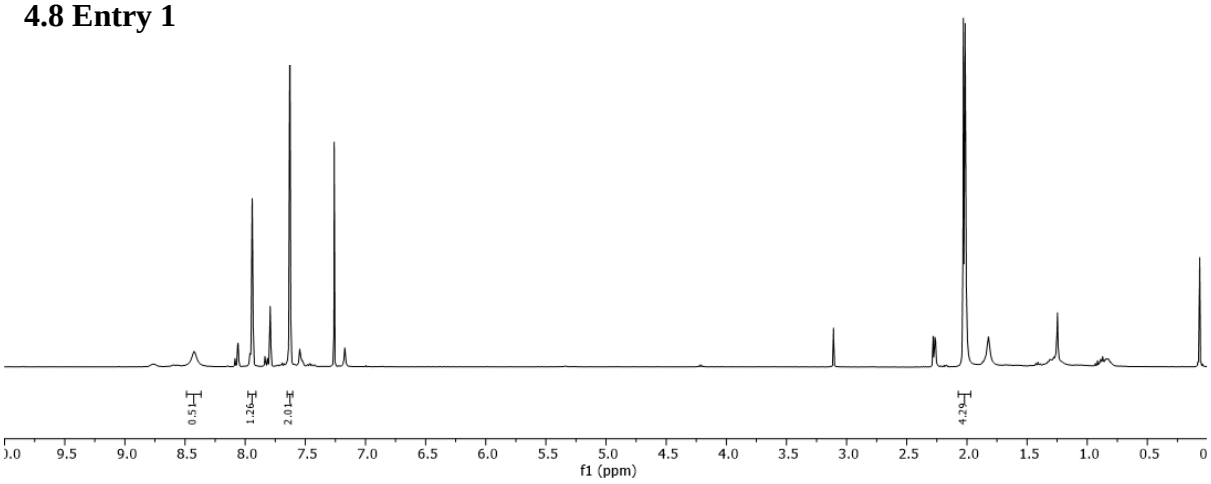


Mechanistic Reaction: **Table 4.8 Entry 1**

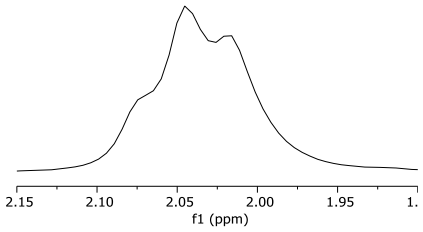


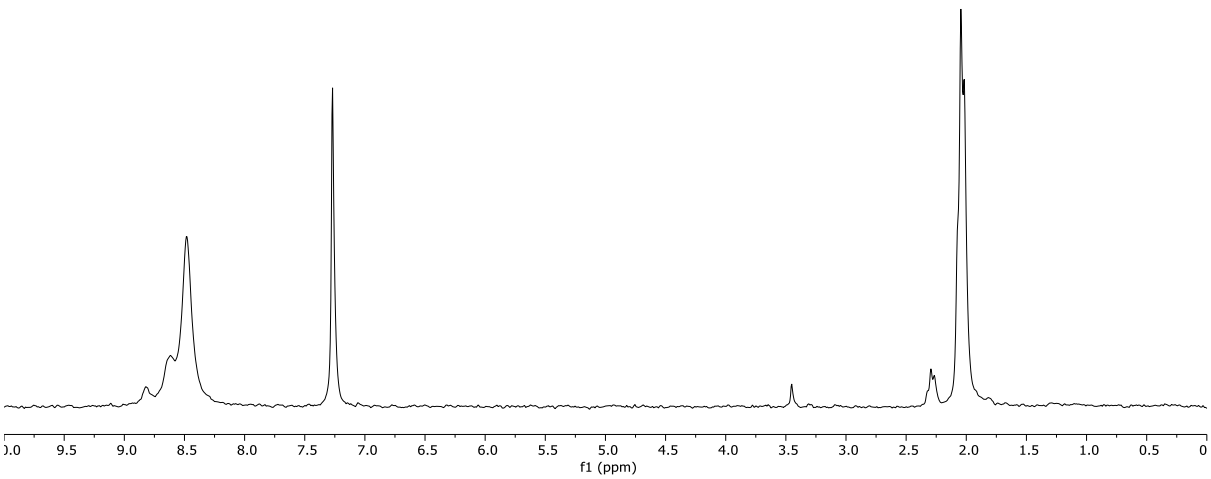


^{1}H NMR for product isolated from reaction highlighted in **Table 4.8 Entry 1**

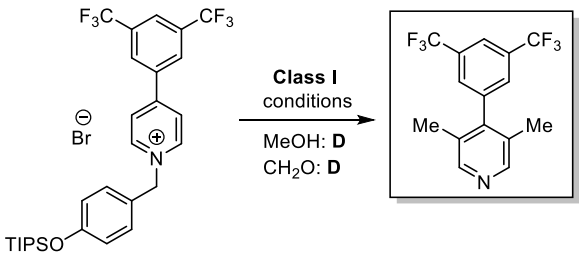


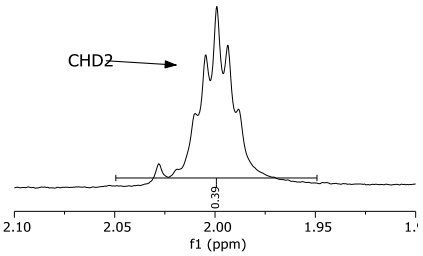
D NMR for product isolated from reaction highlighted in **Table 4.8 Entry 1**



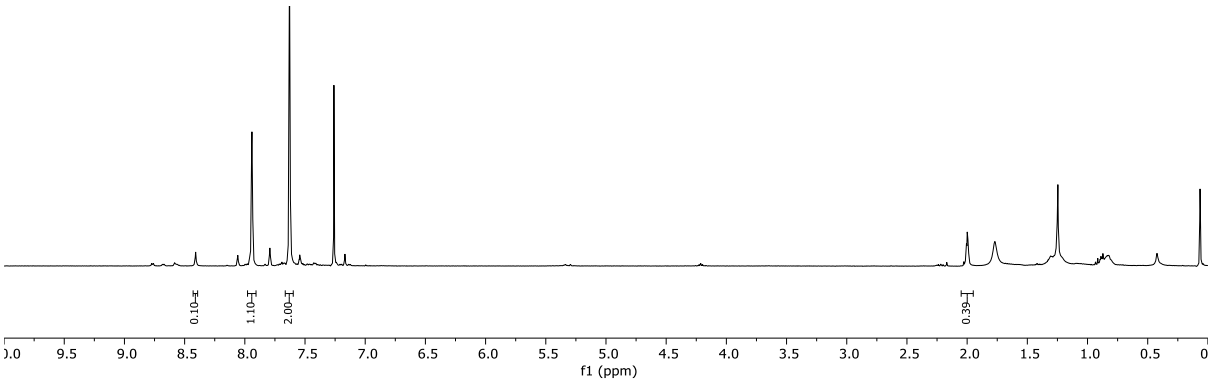


Mechanistic Reaction: **Table 4.8 Entry 2**

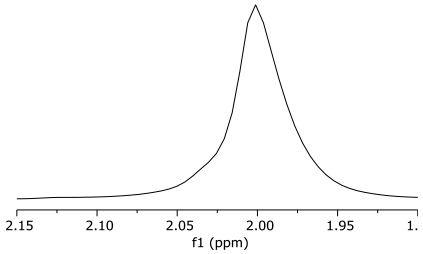


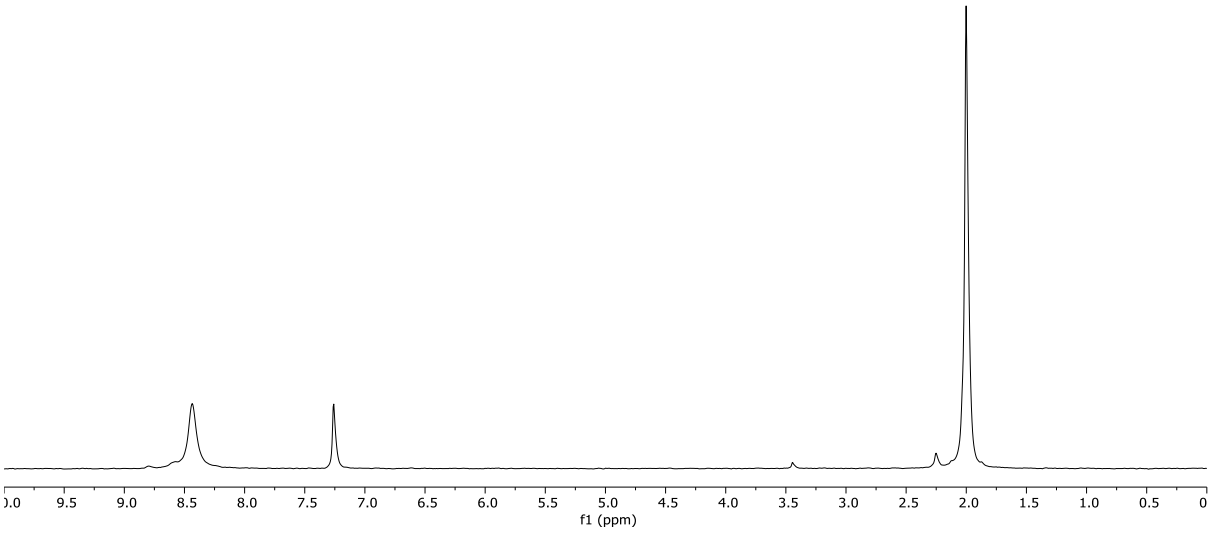


^{1}H NMR for product isolated from reaction highlighted in **Table 4.8 Entry 2**

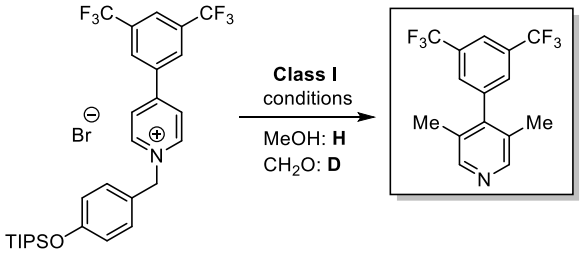


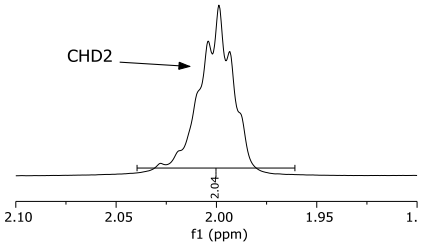
D NMR for product isolated from reaction highlighted in **Table 4.8 Entry 2**



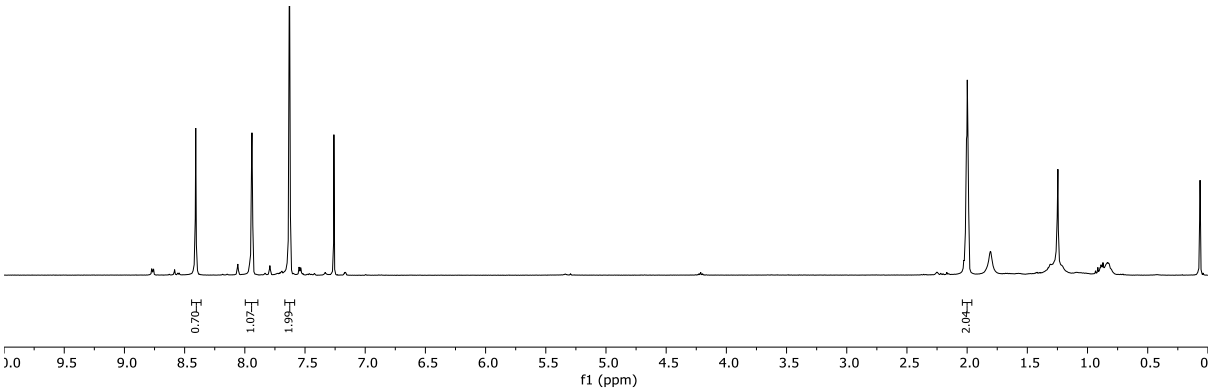


Mechanistic Reaction: **Table 4.8 Entry 3**

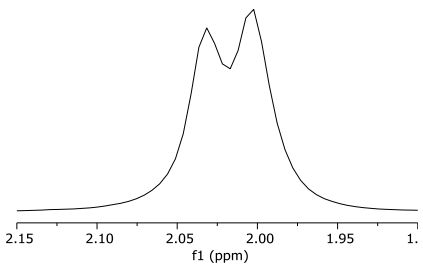


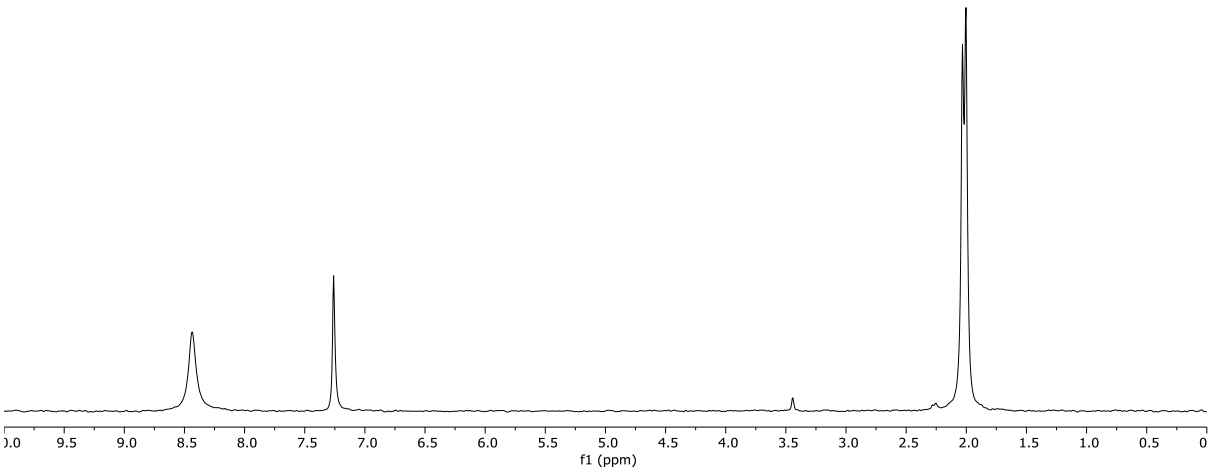


^{1}H NMR for product isolated from reaction highlighted in **Table 4.8 Entry 3**

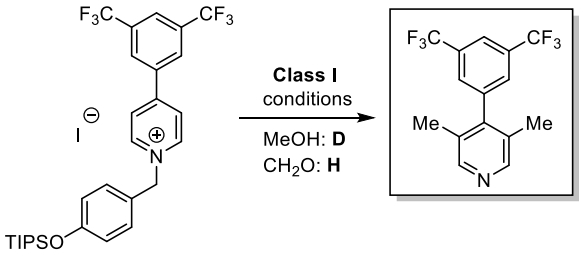


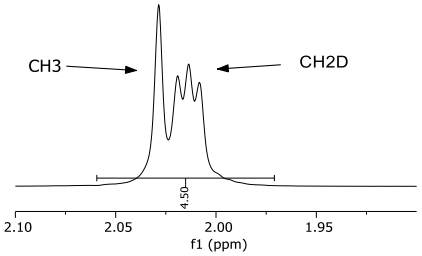
D NMR for product isolated from reaction highlighted in **Table 4.8: Entry 3**



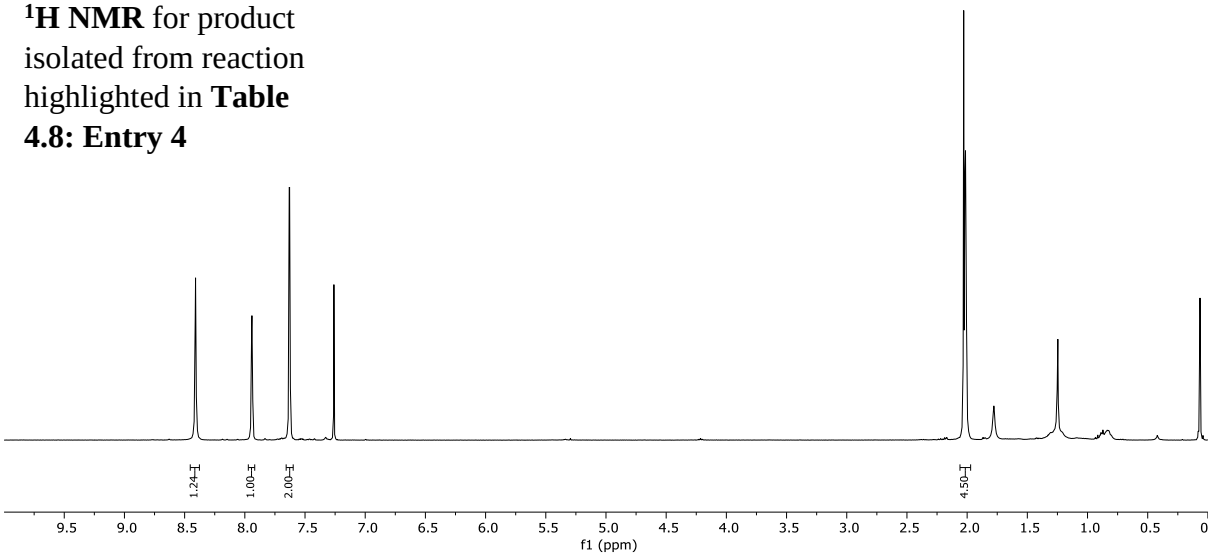


Mechanistic Reaction: **Table 4.8 Entry 4**

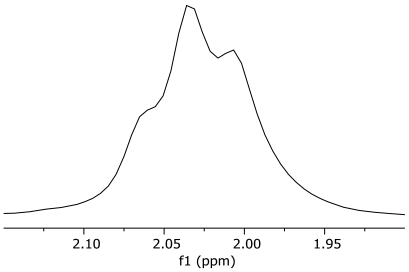




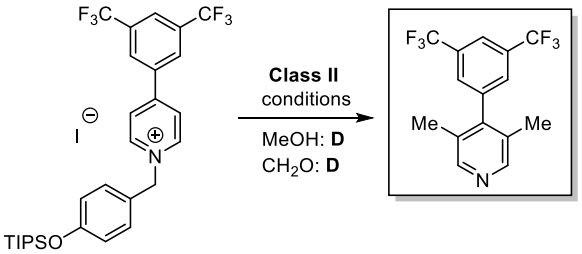
^{1}H NMR for product isolated from reaction highlighted in **Table 4.8: Entry 4**

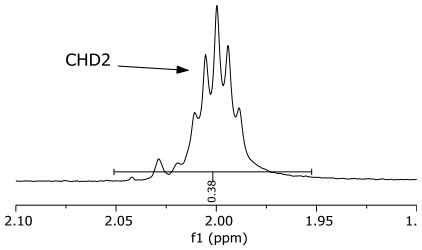


D NMR for product isolated from reaction highlighted in **Table 4.8: Entry 4**

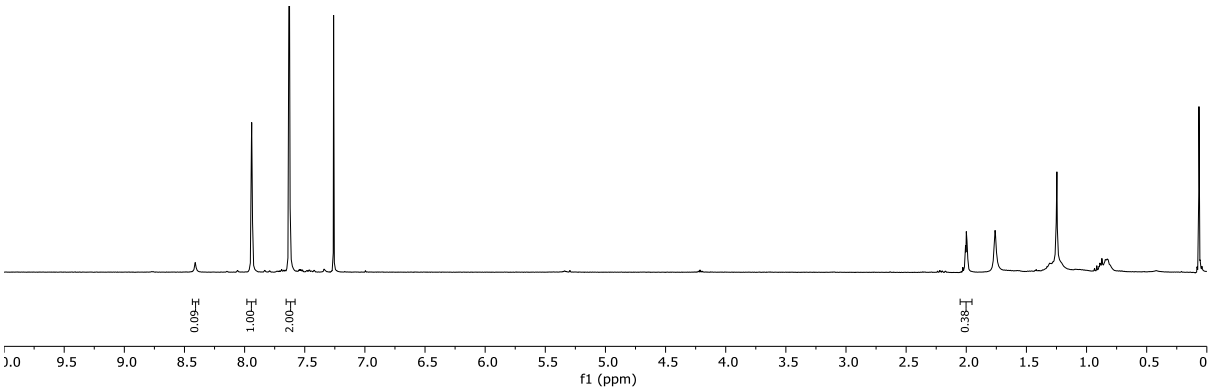


Mechanistic Reaction: **Table 4.8 Entry 5**

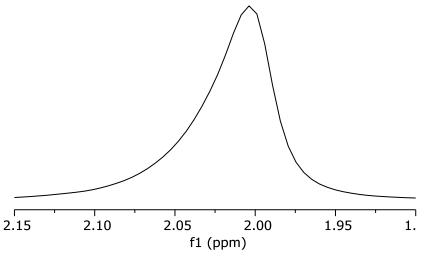


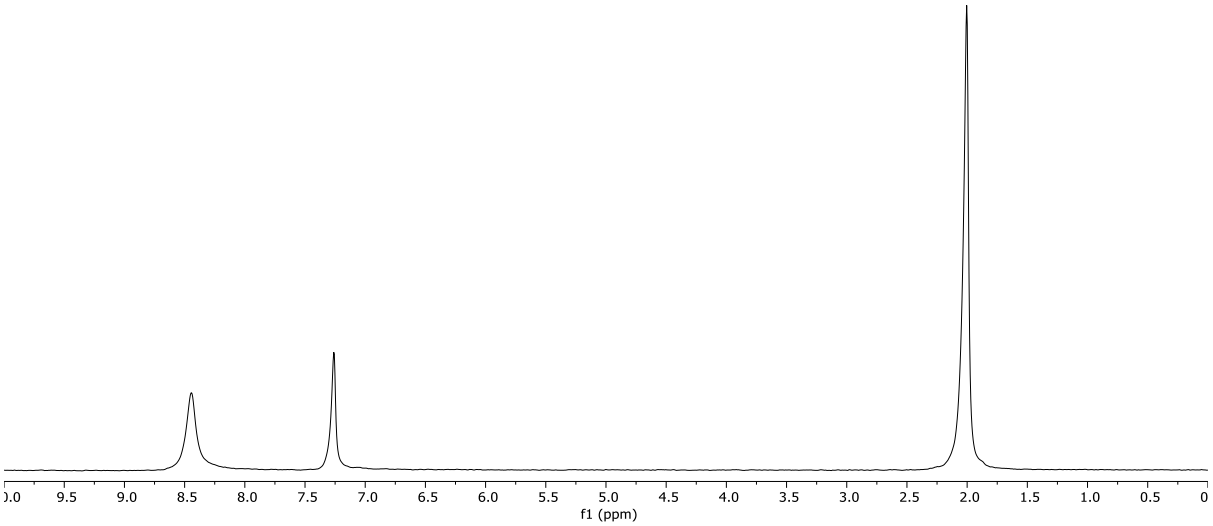


^{1}H NMR for product isolated from reaction highlighted in **Table 4.8 Entry 5**

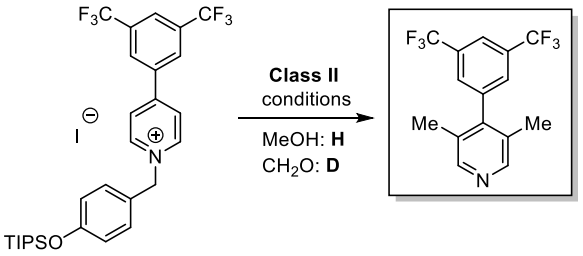


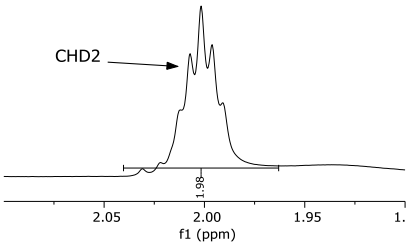
D NMR for product isolated from reaction highlighted in **Table 4.8: Entry 5**



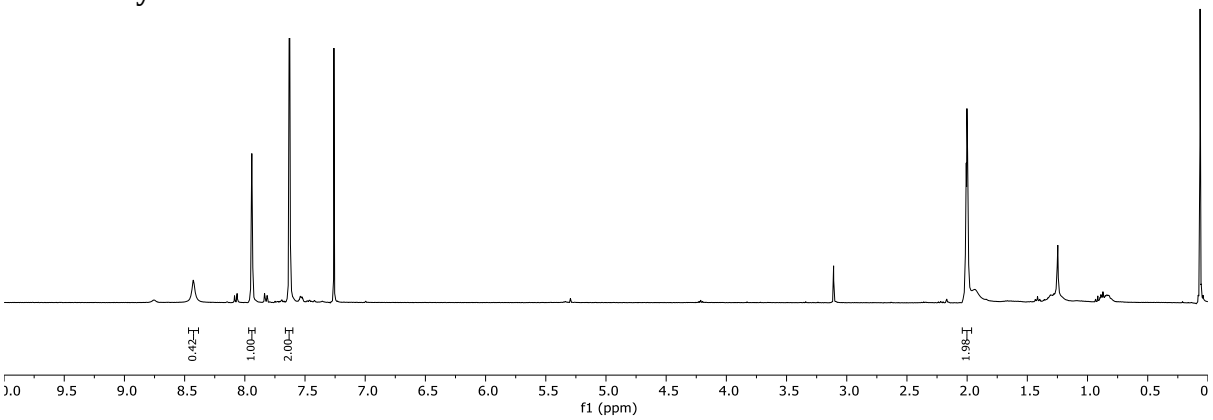


Mechanistic Reaction: **Table 4.8 Entry 6**

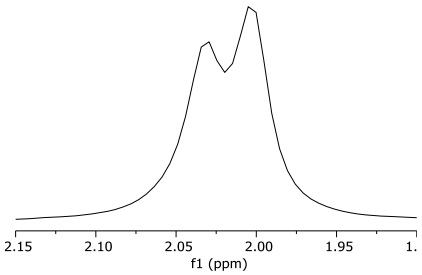


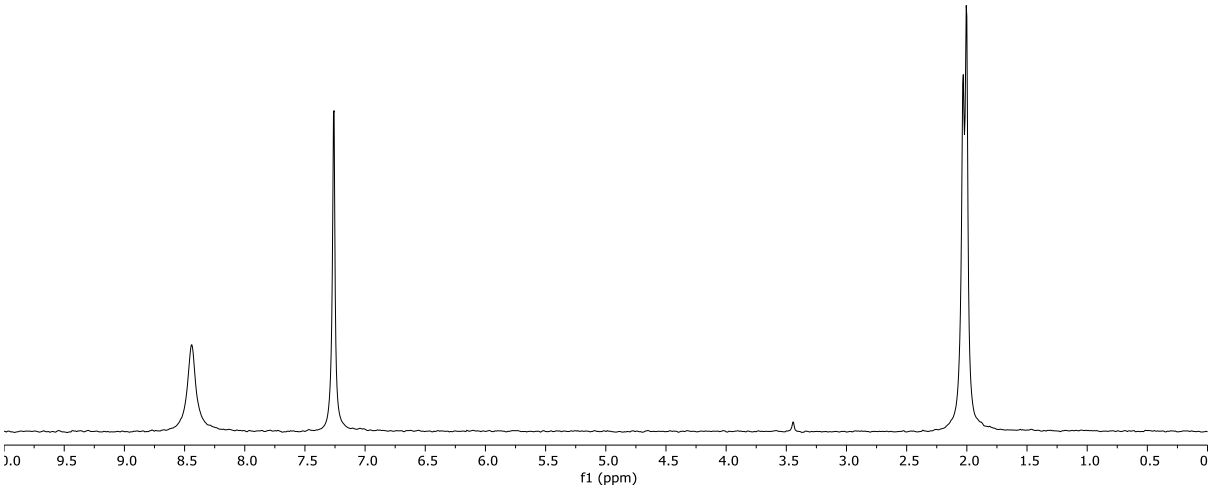


^{1}H NMR for product isolated from reaction highlighted in **Table 4.8 Entry 6**

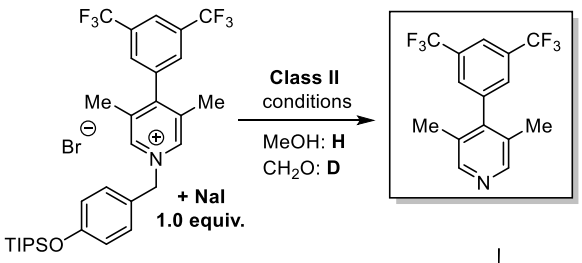


D NMR for product isolated from reaction highlighted in **Table 4.8: Entry 6**

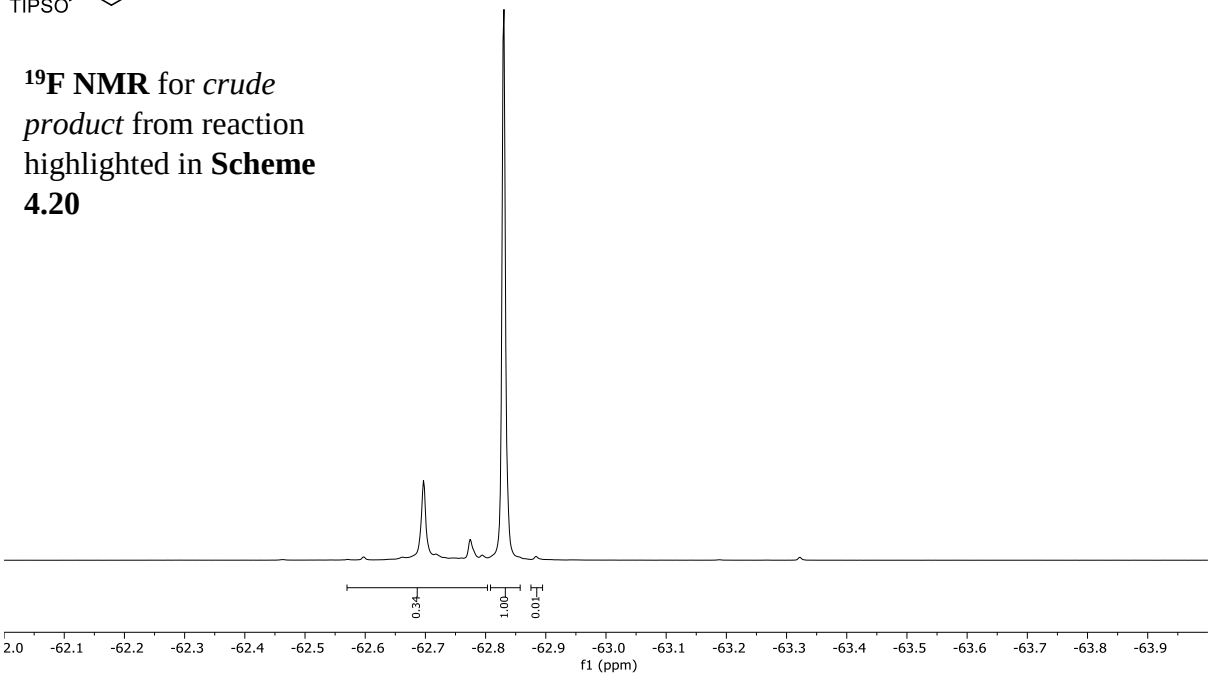




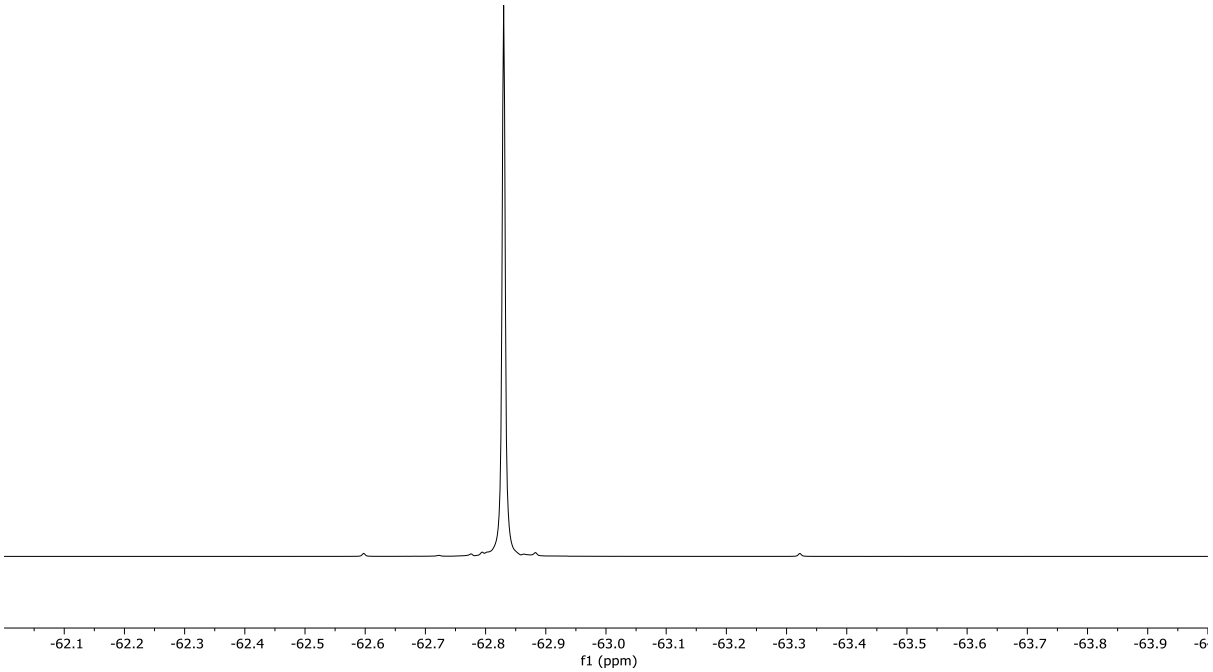
Mechanistic Reaction highlighted in **Scheme 4.20**



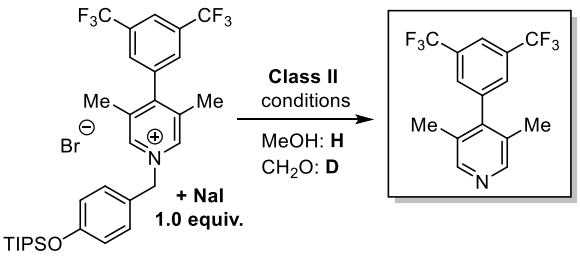
^{19}F NMR for *crude product* from reaction highlighted in **Scheme 4.20**



^{19}F NMR for *isolated product* from reaction highlighted in **Scheme 4.20**

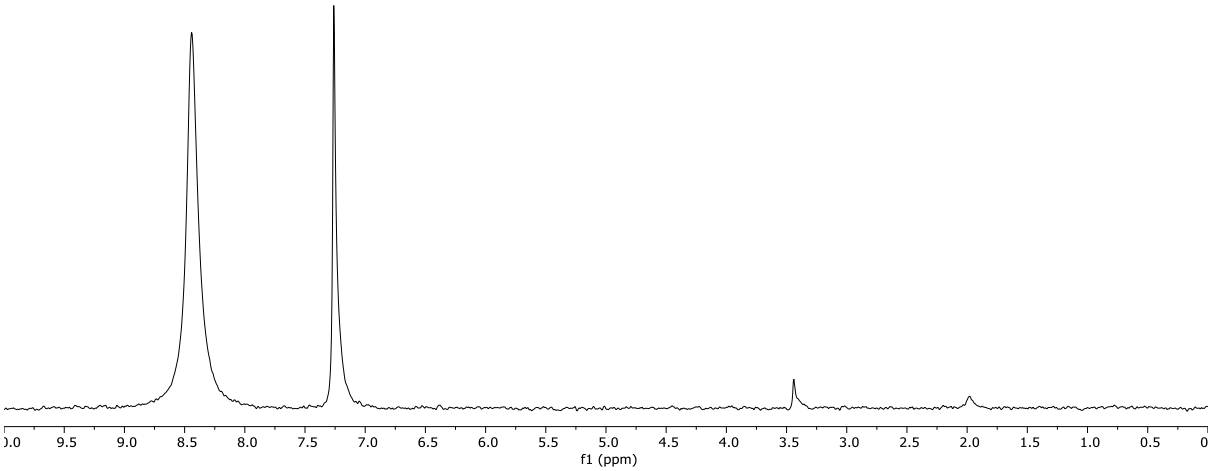


Mechanistic Reaction highlighted in **Scheme 4.20**



^{1}H NMR for product isolated from reaction highlighted in **Scheme 4.20**

D NMR for product isolated from reaction highlighted in **Scheme 4.20**



Appendix 5: X-Ray Crystallographic data for compound 343

Table A.5.1 Crystal data and structure refinement for **343**
Empirical formula: C23 H29 Cl1 Ir1 N1
Formula weight: 547.16
Temperature: 150 K
Wavelength: 1.54184 Å
Crystal system: Orthorhombic
Space group: P 21 21 21
Unit cell dimensions: a = 7.8855(1) Å□ = 90°.
b = 18.5107(3) Å = 90°.
c = 28.7990(4) Å = 90°.
Volume: 4203.68(10) $Å^3$
Z: 8
Density (calculated): 1.729 Mg/m^3
Absorption coefficient: 13.493 mm^{-1}
F(000): 2144
Crystal size: 0.25 x 0.18 x 0.10 mm^3
Theta range for data collection: 3.889 to 76.261°.
Index ranges: -7<=h<=9, -23<=k<=23, -36<=l<=33
Reflections collected: 50302
Independent reflections: 8756 [R(int) = 0.039]
Completeness to theta = 76.261°: 99.8 %
Absorption correction: Semi-empirical from equivalents
Max. and min. transmission: 0.26 and 0.13
Refinement method: Full-matrix least-squares on F^2
Data / restraints / parameters: 8754 / 1300 / 501
Goodness-of-fit on F^2: 0.9754
Final R indices [I>2sigma(I)]: R1 = 0.0264, wR2 = 0.0654
R indices (all data): R1 = 0.0269, wR2 = 0.0658
Absolute structure parameter: -0.015(9)
Largest diff. peak and hole: 1.31 and -0.91 e.$Å^{-3}$

Table A.5.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **343**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Ir(1)	5840(1)	4340(1)	6483(1)	24
Cl(1)	3502(2)	3812(1)	6053(1)	48
C(1)	4738(6)	5320(3)	6336(2)	24
C(2)	3371(6)	5610(3)	6591(2)	29
C(3)	2616(6)	6249(3)	6469(2)	34
C(4)	3194(6)	6630(3)	6074(2)	30
C(5)	2434(8)	7287(3)	5931(2)	40
C(6)	2968(9)	7646(3)	5546(2)	48
C(7)	4325(10)	7377(3)	5283(2)	50
C(8)	5108(8)	6745(3)	5418(2)	39
C(9)	4571(6)	6354(3)	5810(2)	32
C(10)	5327(6)	5693(3)	5954(2)	27
C(11)	6860(7)	5378(3)	5712(2)	35
C(12)	8501(7)	5701(4)	5884(2)	45
N(13)	6751(6)	4576(2)	5803(1)	33
C(14)	8234(9)	4170(4)	5631(2)	52
C(15)	5315(6)	3964(3)	7179(2)	31
C(16)	6195(7)	3372(3)	6946(2)	36
C(17)	7786(7)	3598(3)	6811(2)	32
C(18)	7977(6)	4354(3)	6948(2)	27
C(19)	6469(6)	4559(3)	7193(2)	24
C(20)	3645(7)	3907(4)	7424(2)	47
C(21)	5449(10)	2641(3)	6873(3)	61
C(22)	9166(9)	3158(3)	6587(2)	48
C(23)	9616(6)	4768(3)	6940(2)	39
C(24)	6211(7)	5248(3)	7440(2)	35
Ir(31)	4077(1)	4638(1)	4131(1)	30
Cl(31)	6675(2)	4933(1)	4523(1)	45
C(31)	4493(6)	5539(3)	3728(2)	31
C(32)	5746(7)	5587(3)	3376(2)	34
C(33)	5874(8)	6180(3)	3104(2)	37
C(34)	4746(7)	6770(3)	3161(2)	33
C(35)	4788(8)	7368(3)	2855(2)	42
C(36)	3649(8)	7929(3)	2905(2)	46
C(37)	2468(9)	7917(3)	3263(2)	46
C(38)	2417(8)	7353(3)	3571(2)	41
C(39)	3545(6)	6751(3)	3526(2)	33
C(40)	3499(7)	6132(3)	3816(2)	33
C(41)	2328(7)	6081(3)	4234(2)	37
C(42)	499(7)	5908(4)	4096(3)	57
N(43)	3088(6)	5508(2)	4540(2)	36
C(44)	2097(9)	5355(4)	4957(2)	54
C(45)	4809(5)	3661(4)	3834(3)	39
C(46)	3994(6)	3518(4)	4264(2)	40
C(47)	2269(4)	3728(3)	4221(2)	36
C(48)	2033(5)	4011(3)	3769(2)	37
C(49)	3572(6)	3921(4)	3521(2)	36
C(50)	6594(8)	3472(7)	3704(3)	48
C(51)	4782(9)	3119(7)	4661(3)	54
C(52)	921(7)	3573(5)	4571(2)	47
C(53)	357(8)	4250(6)	3574(2)	52
C(54)	3851(9)	4150(6)	3029(2)	47
C(145)	4821(6)	3513(4)	3964(3)	39
C(146)	3860(7)	3414(4)	4375(3)	40
C(147)	2262(5)	3737(4)	4307(2)	36
C(148)	2164(5)	3969(3)	3836(2)	37
C(149)	3742(7)	3825(4)	3624(2)	36
C(150)	6574(9)	3240(7)	3873(4)	48
C(151)	4540(11)	3110(8)	4820(3)	54
C(152)	878(7)	3734(6)	4648(2)	47
C(153)	544(8)	4216(6)	3595(2)	52
C(154)	4089(10)	3888(7)	3115(3)	47

Table A.5.3 Bond lengths [Å] and angles [°] for **343**.

Ir(1)-Cl(1)	2.4260(13)	C(14)-H(143)	0.956
Ir(1)-C(1)	2.056(5)	C(14)-H(142)	0.949
Ir(1)-N(13)	2.131(4)	C(14)-H(141)	0.958
Ir(1)-C(15)	2.163(5)	C(15)-C(16)	1.461(8)
Ir(1)-C(16)	2.252(5)	C(15)-C(19)	1.429(7)
Ir(1)-C(17)	2.266(5)	C(15)-C(20)	1.498(7)
Ir(1)-C(18)	2.152(5)	C(16)-C(17)	1.379(8)
Ir(1)-C(19)	2.144(4)	C(16)-C(21)	1.490(8)
C(1)-C(2)	1.410(6)	C(17)-C(18)	1.462(7)
C(1)-C(10)	1.380(7)	C(17)-C(22)	1.505(7)
C(2)-C(3)	1.369(7)	C(18)-C(19)	1.435(6)
C(2)-H(21)	0.926	C(18)-C(23)	1.503(7)
C(3)-C(4)	1.414(8)	C(19)-C(24)	1.474(7)
C(3)-H(31)	0.927	C(20)-H(201)	0.969
C(4)-C(5)	1.417(7)	C(20)-H(202)	0.955
C(4)-C(9)	1.420(7)	C(20)-H(203)	0.962
C(5)-C(6)	1.359(9)	C(21)-H(211)	0.958
C(5)-H(51)	0.917	C(21)-H(212)	0.962
C(6)-C(7)	1.403(10)	C(21)-H(213)	0.962
C(6)-H(61)	0.930	C(22)-H(223)	0.963
C(7)-C(8)	1.379(9)	C(22)-H(222)	0.967
C(7)-H(71)	0.921	C(22)-H(221)	0.960
C(8)-C(9)	1.406(7)	C(23)-H(231)	0.960
C(8)-H(81)	0.940	C(23)-H(232)	0.962
C(9)-C(10)	1.423(7)	C(23)-H(233)	0.968
C(10)-C(11)	1.512(7)	C(24)-H(241)	0.961
C(11)-C(12)	1.509(8)	C(24)-H(242)	0.966
C(11)-N(13)	1.511(7)	C(24)-H(243)	0.955
C(11)-H(111)	0.974	Ir(31)-Cl(31)	2.4027(14)
C(12)-H(122)	0.961	Ir(31)-C(31)	2.058(5)
C(12)-H(121)	0.968	Ir(31)-N(43)	2.142(4)
C(12)-H(123)	0.956	Ir(31)-C(45)	2.083(6)
N(13)-C(14)	1.476(7)	Ir(31)-C(46)	2.109(7)
N(13)-H(131)	0.884	Ir(31)-C(47)	2.222(5)
Ir(31)-C(48)	2.243(5)	C(44)-H(442)	0.956
Ir(31)-C(49)	2.238(6)	C(44)-H(441)	0.958
Ir(31)-Cl(31)	2.4027(14)	C(44)-H(443)	0.956
Ir(31)-C(31)	2.058(5)	C(45)-C(46)	1.420(3)
Ir(31)-N(43)	2.142(4)	C(45)-C(49)	1.413(3)
Ir(31)-C(145)	2.216(7)	C(45)-C(50)	1.497(4)
Ir(31)-C(146)	2.377(8)	C(46)-C(47)	1.420(3)
Ir(31)-C(147)	2.255(6)	C(46)-C(51)	1.497(4)
Ir(31)-C(148)	2.128(6)	C(47)-C(48)	1.414(3)
Ir(31)-C(149)	2.114(6)	C(47)-C(52)	1.494(5)
C(31)-C(32)	1.419(7)	C(48)-C(49)	1.419(3)
C(31)-C(40)	1.373(7)	C(48)-C(53)	1.503(5)
C(32)-C(33)	1.352(7)	C(49)-C(54)	1.494(4)
C(32)-H(321)	0.926	C(50)-H(502)	0.964
C(33)-C(34)	1.418(8)	C(50)-H(503)	0.978
C(33)-H(331)	0.926	C(50)-H(501)	0.957
C(34)-C(35)	1.416(8)	C(51)-H(511)	0.966
C(34)-C(39)	1.415(7)	C(51)-H(513)	0.976
C(35)-C(36)	1.382(9)	C(51)-H(512)	0.959
C(35)-H(351)	0.937	C(52)-H(522)	0.967
C(36)-C(37)	1.388(9)	C(52)-H(521)	0.970
C(36)-H(361)	0.927	C(52)-H(523)	0.966
C(37)-C(38)	1.371(9)	C(53)-H(532)	0.970
C(37)-H(371)	0.923	C(53)-H(533)	0.969
C(38)-C(39)	1.432(8)	C(53)-H(531)	0.972
C(38)-H(381)	0.931	C(54)-H(541)	0.963
C(39)-C(40)	1.418(8)	C(54)-H(543)	0.967
C(40)-C(41)	1.520(7)	C(54)-H(542)	0.962
C(41)-C(42)	1.530(8)	C(145)-C(146)	1.416(3)
C(41)-N(43)	1.503(8)	C(145)-C(149)	1.420(3)
C(41)-H(411)	0.979	C(145)-C(150)	1.494(4)
C(42)-H(421)	0.961	C(146)-C(147)	1.408(3)
C(42)-H(422)	0.958	C(146)-C(151)	1.500(4)

C(42)-H(423)	0.957	C(147)-C(148)	1.424(3)
N(43)-C(44)	1.462(7)	C(147)-C(152)	1.470(4)
N(43)-H(431)	0.880	C(148)-C(149)	1.411(3)
C(148)-C(153)	1.525(4)	C(15)-Ir(1)-C(18)	64.98(18)
C(149)-C(154)	1.497(4)	C(16)-Ir(1)-C(18)	62.9(2)
C(150)-H(1502)	0.963	Cl(1)-Ir(1)-C(19)	137.62(13)
C(150)-H(1501)	0.964	C(1)-Ir(1)-C(19)	97.27(17)
C(150)-H(1503)	0.977	N(13)-Ir(1)-C(19)	139.50(17)
C(151)-H(1512)	0.964	C(15)-Ir(1)-C(19)	38.74(19)
C(151)-H(1513)	0.969	C(16)-Ir(1)-C(19)	63.65(19)
C(151)-H(1511)	0.968	C(17)-Ir(1)-C(18)	38.53(19)
C(152)-H(1521)	0.973	C(17)-Ir(1)-C(19)	63.90(18)
C(152)-H(1523)	0.967	C(18)-Ir(1)-C(19)	39.03(17)
C(152)-H(1522)	0.968	Ir(1)-C(1)-C(2)	123.6(4)
C(153)-H(1532)	0.970	Ir(1)-C(1)-C(10)	117.6(3)
C(153)-H(1531)	0.970	C(2)-C(1)-C(10)	118.7(4)
C(153)-H(1533)	0.970	C(1)-C(2)-C(3)	121.9(5)
C(154)-H(1542)	0.965	C(1)-C(2)-H(21)	119.7
C(154)-H(1543)	0.962	C(3)-C(2)-H(21)	118.4
C(154)-H(1541)	0.965	C(2)-C(3)-C(4)	119.7(5)
		C(2)-C(3)-H(31)	119.9
Cl(1)-Ir(1)-C(1)	85.95(13)	C(4)-C(3)-H(31)	120.3
Cl(1)-Ir(1)-N(13)	82.52(13)	C(3)-C(4)-C(5)	121.6(5)
C(1)-Ir(1)-N(13)	76.87(18)	C(3)-C(4)-C(9)	119.9(5)
Cl(1)-Ir(1)-C(15)	101.43(14)	C(5)-C(4)-C(9)	118.5(5)
C(1)-Ir(1)-C(15)	113.14(19)	C(4)-C(5)-C(6)	121.6(6)
N(13)-Ir(1)-C(15)	169.31(18)	C(4)-C(5)-H(51)	119.3
Cl(1)-Ir(1)-C(16)	94.37(15)	C(6)-C(5)-H(51)	119.1
C(1)-Ir(1)-C(16)	151.2(2)	C(5)-C(6)-C(7)	120.3(6)
N(13)-Ir(1)-C(16)	131.77(19)	C(5)-C(6)-H(61)	120.2
C(15)-Ir(1)-C(16)	38.6(2)	C(7)-C(6)-H(61)	119.5
Cl(1)-Ir(1)-C(17)	118.92(14)	C(6)-C(7)-C(8)	119.3(6)
C(1)-Ir(1)-C(17)	155.08(19)	C(6)-C(7)-H(71)	119.9
N(13)-Ir(1)-C(17)	106.23(18)	C(8)-C(7)-H(71)	120.8
C(15)-Ir(1)-C(17)	63.13(19)	C(7)-C(8)-C(9)	121.9(6)
C(16)-Ir(1)-C(17)	35.6(2)	C(7)-C(8)-H(81)	119.0
Cl(1)-Ir(1)-C(18)	156.54(15)	C(9)-C(8)-H(81)	119.1
C(1)-Ir(1)-C(18)	116.60(19)	C(4)-C(9)-C(8)	118.4(5)
N(13)-Ir(1)-C(18)	107.77(18)	C(4)-C(9)-C(10)	118.3(5)
C(8)-C(9)-C(10)	123.4(5)	C(15)-C(16)-C(17)	109.5(4)
C(9)-C(10)-C(1)	121.5(4)	Ir(1)-C(16)-C(21)	126.1(4)
C(9)-C(10)-C(11)	122.2(4)	C(15)-C(16)-C(21)	124.0(5)
C(1)-C(10)-C(11)	116.3(4)	C(17)-C(16)-C(21)	126.5(6)
C(10)-C(11)-C(12)	112.5(4)	Ir(1)-C(17)-C(16)	71.7(3)
C(10)-C(11)-N(13)	104.7(4)	Ir(1)-C(17)-C(18)	66.5(3)
C(12)-C(11)-N(13)	112.4(5)	C(16)-C(17)-C(18)	108.0(4)
C(10)-C(11)-H(111)	109.4	Ir(1)-C(17)-C(22)	129.7(4)
C(12)-C(11)-H(111)	109.3	C(16)-C(17)-C(22)	127.9(5)
N(13)-C(11)-H(111)	108.3	C(18)-C(17)-C(22)	124.0(5)
C(11)-C(12)-H(122)	110.1	Ir(1)-C(18)-C(17)	74.9(3)
C(11)-C(12)-H(121)	109.1	Ir(1)-C(18)-C(19)	70.2(2)
H(122)-C(12)-H(121)	108.8	C(17)-C(18)-C(19)	107.5(4)
C(11)-C(12)-H(123)	109.1	Ir(1)-C(18)-C(23)	132.1(4)
H(122)-C(12)-H(123)	110.1	C(17)-C(18)-C(23)	124.9(5)
H(121)-C(12)-H(123)	109.6	C(19)-C(18)-C(23)	125.9(5)
C(11)-N(13)-Ir(1)	112.3(3)	Ir(1)-C(19)-C(18)	70.8(3)
C(11)-N(13)-C(14)	113.4(5)	Ir(1)-C(19)-C(15)	71.3(3)
Ir(1)-N(13)-C(14)	118.1(4)	C(18)-C(19)-C(15)	108.1(4)
C(11)-N(13)-H(131)	103.9	Ir(1)-C(19)-C(24)	126.3(3)
Ir(1)-N(13)-H(131)	102.4	C(18)-C(19)-C(24)	125.5(4)
C(14)-N(13)-H(131)	104.6	C(15)-C(19)-C(24)	126.3(5)
N(13)-C(14)-H(143)	110.2	C(15)-C(20)-H(201)	108.8
N(13)-C(14)-H(142)	109.9	C(15)-C(20)-H(202)	109.8
H(143)-C(14)-H(142)	109.3	H(201)-C(20)-H(202)	109.5
N(13)-C(14)-H(141)	108.6	C(15)-C(20)-H(203)	109.1
H(143)-C(14)-H(141)	109.1	H(201)-C(20)-H(203)	109.8
H(142)-C(14)-H(141)	109.7	H(202)-C(20)-H(203)	109.9
Ir(1)-C(15)-C(16)	74.0(3)	C(16)-C(21)-H(211)	109.5
Ir(1)-C(15)-C(19)	69.9(2)	C(16)-C(21)-H(212)	108.5
C(16)-C(15)-C(19)	106.8(4)	H(211)-C(21)-H(212)	109.5
Ir(1)-C(15)-C(20)	128.9(4)	C(16)-C(21)-H(213)	109.6
C(16)-C(15)-C(20)	125.5(5)	H(211)-C(21)-H(213)	110.2
C(19)-C(15)-C(20)	126.9(5)	H(212)-C(21)-H(213)	109.5
Ir(1)-C(16)-C(15)	67.4(3)	C(17)-C(22)-H(223)	108.9
Ir(1)-C(16)-C(17)	72.8(3)	C(17)-C(22)-H(222)	110.1
H(223)-C(22)-H(222)	109.5	Cl(31)-Ir(31)-C(49)	130.97(13)
C(17)-C(22)-H(221)	109.0	C(31)-Ir(31)-C(49)	93.8(2)
H(223)-C(22)-H(221)	110.0	N(43)-Ir(31)-C(49)	144.3(2)
H(222)-C(22)-H(221)	109.3	C(45)-Ir(31)-C(49)	37.95(13)
C(18)-C(23)-H(231)	108.8	C(46)-Ir(31)-C(49)	63.49(17)
C(18)-C(23)-H(232)	108.3	C(47)-Ir(31)-C(48)	36.92(10)
H(231)-C(23)-H(232)	110.4	C(47)-Ir(31)-C(49)	61.80(15)
C(18)-C(23)-H(233)	108.6	C(48)-Ir(31)-C(49)	36.92(12)
H(231)-C(23)-H(233)	109.9	Cl(31)-Ir(31)-C(31)	86.82(14)
H(232)-C(23)-H(233)	110.9	Cl(31)-Ir(31)-N(43)	83.18(14)
C(19)-C(24)-H(241)	110.1	C(31)-Ir(31)-N(43)	76.01(18)
C(19)-C(24)-H(242)	109.0	Cl(31)-Ir(31)-C(145)	95.15(16)
H(241)-C(24)-H(242)	109.0	C(31)-Ir(31)-C(145)	126.6(2)
C(19)-C(24)-H(243)	109.3	N(43)-Ir(31)-C(145)	157.3(2)
H(241)-C(24)-H(243)	109.8	Cl(31)-Ir(31)-C(146)	98.03(15)
H(242)-C(24)-H(243)	109.7	C(31)-Ir(31)-C(146)	161.8(2)
Cl(31)-Ir(31)-C(31)	86.82(14)	N(43)-Ir(31)-C(146)	121.9(2)
Cl(31)-Ir(31)-N(43)	83.18(14)	C(145)-Ir(31)-C(146)	35.69(14)
C(31)-Ir(31)-N(43)	76.01(18)	Cl(31)-Ir(31)-C(147)	127.18(12)
Cl(31)-Ir(31)-C(45)	98.88(15)	C(31)-Ir(31)-C(147)	145.78(17)
C(31)-Ir(31)-C(45)	115.3(2)	N(43)-Ir(31)-C(147)	101.67(18)
N(43)-Ir(31)-C(45)	168.5(2)	C(145)-Ir(31)-C(147)	61.44(17)
Cl(31)-Ir(31)-C(46)	99.50(14)	C(146)-Ir(31)-C(147)	35.28(13)
C(31)-Ir(31)-C(46)	154.6(2)	Cl(31)-Ir(31)-C(148)	157.59(15)
N(43)-Ir(31)-C(46)	129.0(2)	C(31)-Ir(31)-C(148)	111.0(2)
C(45)-Ir(31)-C(46)	39.59(14)	N(43)-Ir(31)-C(148)	113.51(17)
Cl(31)-Ir(31)-C(47)	131.70(11)	C(145)-Ir(31)-C(148)	63.56(18)
C(31)-Ir(31)-C(47)	141.46(17)	C(146)-Ir(31)-C(148)	60.83(17)
N(43)-Ir(31)-C(47)	105.86(17)	Cl(31)-Ir(31)-C(149)	126.39(16)
C(45)-Ir(31)-C(47)	64.36(16)	C(31)-Ir(31)-C(149)	102.0(2)
C(46)-Ir(31)-C(47)	38.17(13)	N(43)-Ir(31)-C(149)	150.4(2)
Cl(31)-Ir(31)-C(48)	161.61(13)	C(145)-Ir(31)-C(149)	38.21(14)
C(31)-Ir(31)-C(48)	105.78(18)	C(146)-Ir(31)-C(149)	61.08(18)
N(43)-Ir(31)-C(48)	112.51(17)	C(147)-Ir(31)-C(148)	37.78(12)
C(45)-Ir(31)-C(48)	63.82(16)	C(147)-Ir(31)-C(149)	63.20(17)
C(46)-Ir(31)-C(48)	63.46(16)	C(148)-Ir(31)-C(149)	38.87(14)
Ir(31)-C(31)-C(32)	124.4(4)	C(41)-C(42)-H(421)	111.0
Ir(31)-C(31)-C(40)	117.0(4)	C(41)-C(42)-H(422)	108.6
C(32)-C(31)-C(40)	118.6(5)	H(421)-C(42)-H(422)	109.5
C(31)-C(32)-C(33)	121.2(5)	C(41)-C(42)-H(423)	109.4
C(31)-C(32)-H(321)	119.7	H(421)-C(42)-H(423)	109.2
C(33)-C(32)-H(321)	119.1	H(422)-C(42)-H(423)	109.1
C(32)-C(33)-C(34)	120.7(5)	C(41)-N(43)-Ir(31)	110.7(3)
C(32)-C(33)-H(331)	119.4	C(41)-N(43)-C(44)	114.0(5)
C(34)-C(33)-H(331)	119.8	Ir(31)-N(43)-C(44)	120.0(4)
C(33)-C(34)-C(35)	121.0(5)	C(41)-N(43)-H(431)	103.7
C(33)-C(34)-C(39)	119.1(5)	Ir(31)-N(43)-H(431)	102.6
C(35)-C(34)-C(39)	119.9(5)	C(44)-N(43)-H(431)	103.4
C(34)-C(35)-C(36)	120.4(6)	N(43)-C(44)-H(442)	109.9
C(34)-C(35)-H(351)	119.9	N(43)-C(44)-H(441)	110.0
C(36)-C(35)-H(351)	119.7	H(442)-C(44)-H(441)	109.9
C(35)-C(36)-C(37)	120.1(6)	N(43)-C(44)-H(443)	108.0
C(35)-C(36)-H(361)	120.1	H(442)-C(44)-H(443)	109.2
C(37)-C(36)-H(361)	119.8	H(441)-C(44)-H(443)	109.8
C(36)-C(37)-C(38)	120.9(6)	Ir(31)-C(45)-C(46)	71.2(3)
C(36)-C(37)-H(371)	119.8	Ir(31)-C(45)-C(49)	77.0(3)
C(38)-C(37)-H(371)	119.3	C(46)-C(45)-C(49)	107.89(4)
C(37)-C(38)-C(39)	121.0(6)	Ir(31)-C(45)-C(50)	124.5(4)
C(37)-C(38)-H(381)	119.4	C(46)-C(45)-C(50)	126.78(4)
C(39)-C(38)-H(381)	119.6	C(49)-C(45)-C(50)	124.76(4)
C(38)-C(39)-C(34)	117.7(5)	Ir(31)-C(46)-C(45)	69.2(3)
C(38)-C(39)-C(40)	124.1(5)	Ir(31)-C(46)-C(47)	75.2(2)
C(34)-C(39)-C(40)	118.3(5)	C(45)-C(46)-C(47)	107.87(4)
C(39)-C(40)-C(31)	121.6(5)	Ir(31)-C(46)-C(51)	127.6(4)
C(39)-C(40)-C(41)	122.1(5)	C(45)-C(46)-C(51)	124.78(4)
C(31)-C(40)-C(41)	116.3(5)	C(47)-C(46)-C(51)	126.80(4)
C(40)-C(41)-C(42)	112.4(5)	Ir(31)-C(47)-C(46)	66.6(2)
C(40)-C(41)-N(43)	105.4(4)	Ir(31)-C(47)-C(48)	72.3(2)
C(42)-C(41)-N(43)	112.3(5)	C(46)-C(47)-C(48)	107.90(4)
C(40)-C(41)-H(411)	108.3	Ir(31)-C(47)-C(52)	132.8(4)
C(42)-C(41)-H(411)	109.2	C(46)-C(47)-C(52)	124.79(5)
N(43)-C(41)-H(411)	109.0	C(48)-C(47)-C(52)	126.78(5)
Ir(31)-C(48)-C(47)	70.7(2)	C(49)-C(54)-H(541)	108.5
Ir(31)-C(48)-C(49)	71.4(2)	C(49)-C(54)-H(543)	108.9
C(47)-C(48)-C(49)	107.92(4)	H(541)-C(54)-H(543)	110.7
Ir(31)-C(48)-C(53)	130.8(4)	C(49)-C(54)-H(542)	108.3
C(47)-C(48)-C(53)	124.71(5)	H(541)-C(54)-H(542)	109.8
C(49)-C(48)-C(53)	126.69(5)	H(543)-C(54)-H(542)	110.6
Ir(31)-C(49)-C(48)	71.7(2)	Ir(31)-C(145)-C(146)	78.4(3)
Ir(31)-C(49)-C(45)	65.1(2)	Ir(31)-C(145)-C(149)	67.0(3)
C(48)-C(49)-C(45)	108.00(4)	C(146)-C(145)-C(149)	107.90(4)

Ir(31)-C(49)-C(54)	123.4(4)	Ir(31)-C(145)-C(150)	126.9(4)
C(48)-C(49)-C(54)	124.80(4)	C(146)-C(145)-C(150)	126.73(4)
C(45)-C(49)-C(54)	126.82(4)	C(149)-C(145)-C(150)	124.76(4)
C(45)-C(50)-H(502)	109.0	C(145)-C(146)-Ir(31)	65.9(3)
C(45)-C(50)-H(503)	109.1	C(145)-C(146)-C(147)	107.97(4)
H(502)-C(50)-H(503)	110.1	Ir(31)-C(146)-C(147)	67.6(3)
C(45)-C(50)-H(501)	109.6	C(145)-C(146)-C(151)	124.78(4)
H(502)-C(50)-H(501)	107.9	Ir(31)-C(146)-C(151)	125.8(4)
H(503)-C(50)-H(501)	111.1	C(147)-C(146)-C(151)	126.75(4)
C(46)-C(51)-H(511)	109.3	Ir(31)-C(147)-C(146)	77.1(3)
C(46)-C(51)-H(513)	109.3	Ir(31)-C(147)-C(148)	66.3(2)
H(511)-C(51)-H(513)	110.0	C(146)-C(147)-C(148)	107.98(4)
C(46)-C(51)-H(512)	108.4	Ir(31)-C(147)-C(152)	128.6(4)
H(511)-C(51)-H(512)	108.4	C(146)-C(147)-C(152)	124.73(4)
H(513)-C(51)-H(512)	111.5	C(148)-C(147)-C(152)	126.77(4)
C(47)-C(52)-H(522)	109.2	Ir(31)-C(148)-C(147)	75.9(3)
C(47)-C(52)-H(521)	108.7	Ir(31)-C(148)-C(149)	70.0(2)
H(522)-C(52)-H(521)	109.7	C(147)-C(148)-C(149)	107.87(4)
C(47)-C(52)-H(523)	108.8	Ir(31)-C(148)-C(153)	127.0(4)
H(522)-C(52)-H(523)	109.4	C(147)-C(148)-C(153)	124.74(4)
H(521)-C(52)-H(523)	111.0	C(149)-C(148)-C(153)	126.75(4)
C(48)-C(53)-H(532)	108.5	Ir(31)-C(149)-C(145)	74.8(3)
C(48)-C(53)-H(533)	109.0	Ir(31)-C(149)-C(148)	71.1(2)
H(532)-C(53)-H(533)	110.1	C(145)-C(149)-C(148)	107.87(4)
C(48)-C(53)-H(531)	107.9	Ir(31)-C(149)-C(154)	126.8(4)
H(532)-C(53)-H(531)	110.1	C(145)-C(149)-C(154)	126.74(4)
H(533)-C(53)-H(531)	111.2	C(148)-C(149)-C(154)	124.76(4)
C(145)-C(150)-H(1502)	108.5	C(147)-C(152)-H(1522)	109.0
C(145)-C(150)-H(1501)	107.9	H(1521)-C(152)-H(1522)	108.9
H(1502)-C(150)-H(1501)	109.2	H(1523)-C(152)-H(1522)	109.9
C(145)-C(150)-H(1503)	109.7	C(148)-C(153)-H(1532)	109.0
H(1502)-C(150)-H(1503)	109.7	C(148)-C(153)-H(1531)	109.0
H(1501)-C(150)-H(1503)	111.8	H(1532)-C(153)-H(1531)	110.1
C(146)-C(151)-H(1512)	108.0	C(148)-C(153)-H(1533)	107.6
C(146)-C(151)-H(1513)	109.4	H(1532)-C(153)-H(1533)	110.0
H(1512)-C(151)-H(1513)	109.9	H(1531)-C(153)-H(1533)	111.1
C(146)-C(151)-H(1511)	110.1	C(149)-C(154)-H(1542)	108.7
H(1512)-C(151)-H(1511)	110.2	C(149)-C(154)-H(1543)	108.6
H(1513)-C(151)-H(1511)	109.1	H(1542)-C(154)-H(1543)	109.8
C(147)-C(152)-H(1521)	109.7	C(149)-C(154)-H(1541)	108.2
C(147)-C(152)-H(1523)	109.7	H(1542)-C(154)-H(1541)	109.6
H(1521)-C(152)-H(1523)	109.6	H(1543)-C(154)-H(1541)	111.7

Table A.5.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **343**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Ir(1)	22(1)	24(1)	26(1)	-4(1)	0(1)	0(1)
Cl(1)	42(1)	47(1)	54(1)	-13(1)	-13(1)	-9(1)
C(1)	23(2)	23(2)	27(2)	0(2)	-5(2)	3(2)
C(2)	22(2)	30(2)	33(2)	1(2)	1(2)	4(2)
C(3)	23(2)	40(3)	38(3)	-4(2)	-1(2)	4(2)
C(4)	27(2)	30(2)	32(2)	-1(2)	-5(2)	4(2)
C(5)	41(3)	33(3)	47(3)	-1(2)	-11(3)	10(2)
C(6)	54(4)	39(3)	51(4)	6(3)	-20(3)	4(3)
C(7)	68(4)	45(3)	35(3)	12(2)	-9(3)	1(3)
C(8)	50(3)	41(3)	24(2)	1(2)	-3(2)	-1(3)
C(9)	37(3)	29(2)	29(2)	-2(2)	-5(2)	0(2)
C(10)	30(2)	29(2)	22(2)	-5(2)	0(2)	0(2)
C(11)	47(3)	35(3)	22(2)	1(2)	8(2)	4(2)
C(12)	35(3)	51(3)	48(3)	5(3)	17(2)	-1(2)
N(13)	42(2)	35(2)	23(2)	-9(2)	3(2)	9(2)
C(14)	57(4)	63(4)	35(3)	-3(3)	19(3)	25(3)
C(15)	28(2)	40(3)	24(2)	10(2)	6(2)	-3(2)
C(16)	43(3)	23(2)	40(3)	10(2)	-4(2)	-1(2)
C(17)	32(3)	26(2)	38(3)	1(2)	-1(2)	9(2)
C(18)	24(2)	30(2)	27(2)	0(2)	-1(2)	0(2)
C(19)	25(2)	28(2)	18(2)	-1(2)	-6(2)	2(2)
C(20)	29(3)	57(4)	53(3)	19(3)	10(2)	-3(2)
C(21)	71(5)	28(3)	84(5)	-5(3)	-4(4)	-12(3)
C(22)	50(3)	43(3)	51(3)	-5(2)	4(3)	22(3)
C(23)	25(2)	51(3)	40(3)	4(2)	0(2)	-9(2)
C(24)	41(3)	37(3)	27(2)	-4(2)	-4(2)	10(2)
Ir(31)	30(1)	29(1)	31(1)	-11(1)	9(1)	-8(1)
Cl(31)	37(1)	60(1)	40(1)	-21(1)	2(1)	-9(1)
C(31)	34(3)	27(2)	31(2)	-11(2)	8(2)	-11(2)
C(32)	37(3)	32(2)	33(2)	-10(2)	13(2)	-11(2)
C(33)	40(3)	36(2)	35(2)	-10(2)	15(2)	-8(3)
C(34)	36(3)	31(2)	33(2)	-7(2)	3(2)	-7(2)
C(35)	54(3)	35(3)	38(3)	-4(2)	5(2)	-12(2)
C(36)	54(4)	41(3)	44(3)	-2(3)	-1(3)	-7(3)
C(37)	48(3)	38(3)	53(3)	-8(3)	3(3)	6(3)
C(38)	45(3)	33(3)	44(3)	-6(2)	9(3)	0(2)
C(39)	33(2)	31(2)	34(2)	-15(2)	5(2)	-9(2)
C(40)	33(2)	31(2)	34(3)	-13(2)	11(2)	-13(2)
C(41)	38(3)	29(2)	44(3)	-10(2)	15(2)	-2(2)
C(42)	33(3)	46(3)	90(5)	-9(4)	19(3)	-5(2)
N(43)	41(2)	28(2)	39(2)	-15(2)	21(2)	-6(2)
C(44)	69(4)	42(3)	51(3)	-18(3)	36(3)	-13(3)
C(45)	43(2)	28(2)	45(2)	-13(2)	3(2)	-4(2)
C(46)	52(2)	30(1)	39(2)	-5(2)	-4(2)	-5(2)
C(47)	45(2)	27(1)	36(2)	-9(1)	3(2)	-13(1)
C(48)	43(2)	29(2)	39(2)	-9(1)	-2(1)	-11(1)
C(49)	48(2)	26(2)	35(2)	-13(1)	2(1)	-11(1)
C(50)	46(2)	36(3)	61(3)	-13(3)	2(3)	-2(3)
C(51)	73(3)	44(2)	45(3)	-2(3)	-13(3)	4(3)
C(52)	61(3)	33(3)	47(3)	-18(3)	13(2)	-18(3)
C(53)	56(3)	42(2)	58(3)	-10(2)	-15(2)	0(2)
C(54)	70(3)	31(3)	40(2)	-5(2)	5(3)	-9(3)
C(145)	43(2)	28(2)	45(2)	-13(2)	3(2)	-4(2)
C(146)	52(2)	30(1)	39(2)	-5(2)	-4(2)	-5(2)
C(147)	45(2)	27(1)	36(2)	-9(1)	3(2)	-13(1)
C(148)	43(2)	29(2)	39(2)	-9(1)	-2(1)	-11(1)
C(149)	48(2)	26(2)	35(2)	-13(1)	2(1)	-11(1)
C(150)	46(2)	36(3)	61(3)	-13(3)	2(3)	-2(3)
C(151)	73(3)	44(2)	45(3)	-2(3)	-13(3)	4(3)
C(152)	61(3)	33(3)	47(3)	-18(3)	13(2)	-18(3)
C(153)	56(3)	42(2)	58(3)	-10(2)	-15(2)	0(2)
C(154)	70(3)	31(3)	40(2)	-5(2)	5(3)	-9(3)

Table A.5.5 Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^3$) for **343**.

	x	y	z	U(eq)
H(21)	2957	5365	6847	34
H(31)	1731	6430	6646	40
H(51)	1553	7474	6101	48
H(61)	2435	8071	5455	58
H(71)	4682	7623	5022	59
H(81)	6030	6572	5243	46
H(111)	6763	5458	5379	42
H(122)	9449	5459	5743	67
H(121)	8569	5642	6217	67
H(123)	8524	6204	5808	67
H(143)	8046	3662	5663	78
H(142)	9216	4303	5801	78
H(141)	8395	4282	5309	78
H(201)	3787	3611	7699	70
H(202)	3266	4377	7513	70
H(203)	2831	3688	7219	70
H(211)	6055	2396	6632	92
H(212)	5547	2372	7158	92
H(213)	4271	2687	6791	92
H(223)	9844	2937	6826	72
H(222)	9876	3464	6397	72
H(221)	8659	2791	6396	72
H(231)	10261	4645	7211	58
H(232)	9355	5276	6938	58
H(233)	10241	4634	6663	58
H(241)	6655	5216	7750	53
H(242)	6803	5627	7276	53
H(243)	5027	5355	7451	53
H(321)	6499	5209	3333	41
H(331)	6710	6199	2879	44
H(351)	5599	7385	2617	51
H(361)	3666	8315	2700	56
H(371)	1707	8292	3295	55
H(381)	1629	7361	3812	49
H(411)	2355	6544	4398	44
H(421)	-206	5852	4366	85
H(422)	73	6295	3909	85
H(423)	477	5470	3919	85
H(442)	1883	5793	5123	81
H(441)	2696	5022	5152	81
H(443)	1041	5148	4862	81
H(502)	6602	3003	3558	72
H(503)	7292	3463	3985	72

H(501)	7017	3816	3485	72
H(511)	4810	2608	4590	80
H(513)	4115	3202	4941	80
H(512)	5927	3285	4697	80
H(522)	433	3104	4509	71
H(521)	1430	3575	4878	71
H(523)	52	3939	4547	71
H(532)	-93	3863	3383	78
H(533)	-412	4352	3828	78
H(531)	554	4677	3385	78
H(541)	3200	3838	2830	71
H(543)	5046	4114	2959	71
H(542)	3465	4640	2996	71
H(1502)	6495	2751	3761	72
H(1501)	7184	3244	4163	72
H(1503)	7123	3544	3640	72
H(1512)	3626	3096	5042	80
H(1513)	5444	3417	4934	80
H(1511)	4982	2629	4768	80
H(1521)	332	3263	4651	71
H(1523)	1327	3839	4954	71
H(1522)	50	4096	4562	71
H(1532)	-70	3795	3484	78
H(1531)	-146	4483	3814	78
H(1533)	871	4518	3334	78
H(1542)	3818	3433	2968	71
H(1543)	5272	3995	3072	71
H(1541)	3373	4264	2990	71
H(431)	4012	5713	4649	54
H(131)	5902	4431	5625	50
H(1531)	-146	4483	3814	78
H(1533)	871	4518	3334	78
H(1542)	3818	3433	2968	71
H(1543)	5272	3995	3072	71
H(1541)	3373	4264	2990	71
H(431)	4012	5713	4649	54
H(131)	5902	4431	5625	50

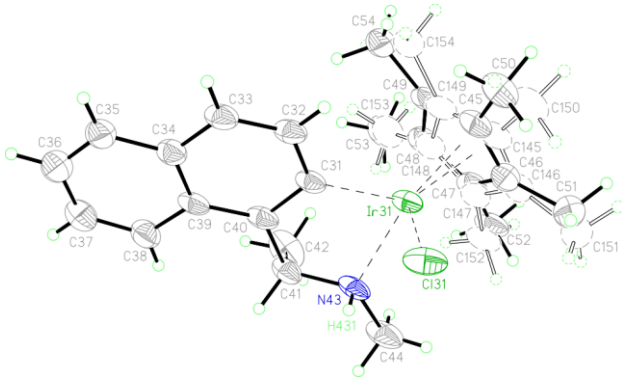
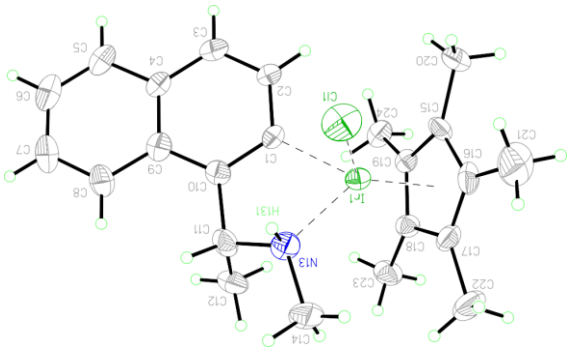


Table A.5.6 Hydrogen bonds for **343** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(42)-H(423)...C(53)	0.96	2.47	3.420(9)	172
C(42)-H(423)...C(153)	0.96	2.50	3.449(9)	170
C(54)-H(1543)...C(50)	1.16	2.31	3.168(9)	128



Appendix 6: X-Ray Crystallographic data for compound 348

Table A.6.1. Crystal data and structure refinement for **348**.

Empirical formula: C31 H37 Cl I N
Formula weight: 586.00
Temperature: 150 K
Wavelength: 1.54184 Å
Crystal system: Orthorhombic
Space group: P 21 21 21
Unit cell dimensions: a = 8.5320(2) Å □= 90°.
b = 11.8356(4) Å □= 90°.
c = 26.5692(7) Å □ = 90°.

Volume: 2682.99(13) $Å^3$
Z: 4

Density (calculated) : 1.451 Mg/m^3

Absorption coefficient: 10.425 mm^{-1}
F(000) : 1200

Crystal size: 0.21 x 0.08 x 0.06 mm^3
Theta range for data collection: 4.089 to 76.403°.
Index ranges: -10<=h<=10, -13<=k<=14, -33<=l<=27
Reflections collected: 32233
Independent reflections: 5587 [R(int) = 0.051]
Completeness to theta = 76.403°: 99.5 %
Absorption correction: Semi-empirical from equivalents
Max. and min. transmission: 0.54 and 0.20

Refinement method: Full-matrix least-squares on F^2
Data / restraints / parameters: 5587 / 0 / 309

Goodness-of-fit on F^2: 1.0278
Final R indices [I>2sigma(I)] R1 = 0.0409, wR2 = 0.1159
R indices (all data) : R1 = 0.0415, wR2 = 0.1166
Absolute structure parameter: 0.187(4)
Extinction coefficient: 28(4)

Largest diff. peak and hole: 1.46 and -0.94 e.$Å^{-3}$

Table A.6.2 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **348**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
I(1)	4835(1)	3454(1)	6111(1)	21
Cl(2)	2495(2)	4526(2)	5942(1)	55
N(3)	4490(9)	4178(6)	6833(2)	53
C(4)	4060(9)	3362(7)	7227(3)	48
C(5)	3064(10)	2482(7)	6964(3)	49
C(6)	3349(9)	2310(6)	6460(3)	47
C(7)	2533(9)	1476(7)	6197(3)	46
C(8)	1401(11)	827(8)	6433(3)	57
C(9)	1048(9)	998(7)	6944(3)	50
C(10)	-155(11)	329(8)	7182(3)	60
C(11)	-499(10)	527(10)	7682(4)	69
C(12)	226(13)	1370(9)	7944(4)	71
C(13)	1399(11)	2024(8)	7725(3)	57
C(14)	1863(9)	1856(6)	7217(3)	49
C(15)	5590(11)	2863(7)	7452(3)	56
C(16)	6571(15)	3786(9)	7729(4)	78
C(17)	5267(14)	1872(9)	7811(4)	81
C(21)	7390(7)	3450(6)	6061(3)	43
C(22)	6781(9)	2371(7)	5910(3)	46
C(23)	5774(10)	2565(7)	5462(3)	48
C(24)	5825(9)	3753(6)	5358(3)	45
C(25)	6808(9)	4314(7)	5707(3)	46
C(26)	8551(9)	3620(8)	6466(3)	55
C(27)	7141(10)	1253(6)	6124(4)	58
C(28)	5027(10)	1696(7)	5130(3)	58
C(29)	4968(12)	4313(7)	4929(3)	55
C(31)	7230(10)	5523(7)	5726(3)	50
C(32)	8760(11)	5900(7)	5698(3)	51
C(33)	9115(11)	7034(8)	5693(4)	59
C(34)	7934(11)	7849(8)	5720(4)	63
C(35)	6357(12)	7490(8)	5731(4)	62
C(36)	6021(11)	6347(7)	5744(3)	58
C(37)	10821(11)	7427(8)	5665(5)	73
C(38)	5029(12)	8358(7)	5741(5)	83

Table A.6.3 Bond lengths [Å] and angles [°] for **348**.

I(1)-Cl(2)	2.4080(19)	C(16)-H(161)	1.049
I(1)-N(3)	2.121(6)	C(16)-H(163)	1.062
I(1)-C(6)	2.074(7)	C(16)-H(162)	1.059
I(1)-C(21)	2.184(6)	C(17)-H(172)	0.970
I(1)-C(22)	2.164(7)	C(17)-H(171)	0.971
I(1)-C(23)	2.172(7)	C(17)-H(173)	0.975
I(1)-C(24)	2.201(7)	C(21)-C(22)	1.436(11)
I(1)-C(25)	2.241(7)	C(21)-C(25)	1.475(10)
N(3)-C(4)	1.471(10)	C(21)-C(26)	1.477(10)
N(3)-H(32)	0.906	C(22)-C(23)	1.485(11)
N(3)-H(31)	0.896	C(22)-C(27)	1.473(11)
C(4)-C(5)	1.515(11)	C(23)-C(24)	1.433(11)
C(4)-C(15)	1.552(11)	C(23)-C(28)	1.498(10)
C(4)-H(41)	0.986	C(24)-C(25)	1.417(11)
C(5)-C(6)	1.375(11)	C(24)-C(29)	1.508(10)
C(5)-C(14)	1.433(11)	C(25)-C(31)	1.477(12)
C(6)-C(7)	1.396(11)	C(26)-H(262)	0.977
C(7)-C(8)	1.385(11)	C(26)-H(263)	0.971
C(7)-H(71)	0.955	C(26)-H(261)	0.970
C(8)-C(9)	1.404(12)	C(27)-H(271)	0.970
C(8)-H(81)	0.944	C(27)-H(273)	0.987
C(9)-C(10)	1.442(11)	C(27)-H(272)	0.968
C(9)-C(14)	1.428(12)	C(28)-H(282)	0.975
C(10)-C(11)	1.382(13)	C(28)-H(281)	0.976
C(10)-H(101)	0.948	C(28)-H(283)	0.974
C(11)-C(12)	1.366(15)	C(29)-H(292)	0.974
C(11)-H(111)	0.933	C(29)-H(293)	0.977
C(12)-C(13)	1.393(13)	C(29)-H(291)	0.963
C(12)-H(121)	0.942	C(31)-C(32)	1.381(12)
C(13)-C(14)	1.421(12)	C(31)-C(36)	1.420(12)
C(13)-H(131)	0.947	C(32)-C(33)	1.377(12)
C(15)-C(16)	1.561(12)	C(32)-H(321)	0.945
C(15)-C(17)	1.537(12)	C(33)-C(34)	1.397(14)
C(15)-H(151)	0.987	C(33)-C(37)	1.529(13)
C(34)-C(35)	1.411(13)	C(22)-I(1)-C(25)	64.8(3)
C(34)-H(341)	0.950	C(23)-I(1)-C(24)	38.2(3)
C(35)-C(36)	1.383(12)	C(23)-I(1)-C(25)	64.1(3)
C(35)-C(38)	1.530(13)	C(24)-I(1)-C(25)	37.2(3)
C(36)-H(361)	0.957	I(1)-N(3)-C(4)	114.4(5)
C(37)-H(372)	0.961	I(1)-N(3)-H(32)	113.0
C(37)-H(371)	0.973	C(4)-N(3)-H(32)	112.1
C(37)-H(373)	0.966	I(1)-N(3)-H(31)	109.1
C(38)-H(382)	0.968	C(4)-N(3)-H(31)	109.5
C(38)-H(383)	0.968	H(32)-N(3)-H(31)	97.3
C(38)-H(381)	0.964	N(3)-C(4)-C(5)	105.2(6)
		N(3)-C(4)-C(15)	108.3(6)
Cl(2)-I(1)-N(3)	80.9(2)	C(5)-C(4)-C(15)	112.9(7)
Cl(2)-I(1)-C(6)	85.5(2)	N(3)-C(4)-H(41)	110.7
N(3)-I(1)-C(6)	77.0(3)	C(5)-C(4)-H(41)	110.2
Cl(2)-I(1)-C(21)	144.8(2)	C(15)-C(4)-H(41)	109.4
N(3)-I(1)-C(21)	101.2(3)	C(4)-C(5)-C(6)	116.9(7)
C(6)-I(1)-C(21)	129.5(3)	C(4)-C(5)-C(14)	122.7(7)
Cl(2)-I(1)-C(22)	154.4(2)	C(6)-C(5)-C(14)	120.4(8)
N(3)-I(1)-C(22)	124.7(3)	C(5)-C(6)-I(1)	116.5(6)
C(6)-I(1)-C(22)	101.1(3)	C(5)-C(6)-C(7)	120.3(7)
C(21)-I(1)-C(22)	38.6(3)	I(1)-C(6)-C(7)	122.8(5)
Cl(2)-I(1)-C(23)	114.3(2)	C(6)-C(7)-C(8)	120.8(7)
N(3)-I(1)-C(23)	164.6(3)	C(6)-C(7)-H(71)	118.9
C(6)-I(1)-C(23)	105.3(3)	C(8)-C(7)-H(71)	120.2
C(21)-I(1)-C(23)	65.3(3)	C(7)-C(8)-C(9)	120.5(8)
C(22)-I(1)-C(23)	40.0(3)	C(7)-C(8)-H(81)	120.5
Cl(2)-I(1)-C(24)	93.6(2)	C(9)-C(8)-H(81)	119.0
N(3)-I(1)-C(24)	144.2(3)	C(8)-C(9)-C(10)	119.8(8)
C(6)-I(1)-C(24)	138.2(3)	C(8)-C(9)-C(14)	119.3(7)
C(21)-I(1)-C(24)	64.0(3)	C(10)-C(9)-C(14)	121.0(8)
C(22)-I(1)-C(24)	64.9(3)	C(9)-C(10)-C(11)	118.7(9)
Cl(2)-I(1)-C(25)	107.1(2)	C(9)-C(10)-H(101)	120.1
N(3)-I(1)-C(25)	110.7(3)	C(11)-C(10)-H(101)	121.3
C(6)-I(1)-C(25)	165.9(3)	C(10)-C(11)-C(12)	121.3(8)
C(21)-I(1)-C(25)	38.9(3)	C(10)-C(11)-H(111)	119.2
C(12)-C(11)-H(111)	119.5	C(21)-C(22)-C(23)	107.2(6)
C(11)-C(12)-C(13)	121.2(9)	I(1)-C(22)-C(27)	126.6(6)
C(11)-C(12)-H(121)	119.2	C(21)-C(22)-C(27)	127.9(7)
C(13)-C(12)-H(121)	119.6	C(23)-C(22)-C(27)	124.8(7)
C(12)-C(13)-C(14)	121.3(9)	C(22)-C(23)-I(1)	69.7(4)
C(12)-C(13)-H(131)	120.3	C(22)-C(23)-C(24)	106.8(7)
C(14)-C(13)-H(131)	118.3	I(1)-C(23)-C(24)	72.0(4)
C(5)-C(14)-C(9)	118.5(8)	C(22)-C(23)-C(28)	127.7(7)
C(5)-C(14)-C(13)	125.0(8)	I(1)-C(23)-C(28)	130.0(6)
C(9)-C(14)-C(13)	116.5(8)	C(24)-C(23)-C(28)	124.9(7)
C(4)-C(15)-C(16)	111.5(8)	I(1)-C(24)-C(23)	69.8(4)
C(4)-C(15)-C(17)	112.2(7)	I(1)-C(24)-C(25)	72.9(4)
C(16)-C(15)-C(17)	109.8(8)	C(23)-C(24)-C(25)	110.5(7)
C(4)-C(15)-H(151)	106.5	I(1)-C(24)-C(29)	124.9(6)
C(16)-C(15)-H(151)	109.2	C(23)-C(24)-C(29)	124.3(7)
C(17)-C(15)-H(151)	107.4	C(25)-C(24)-C(29)	125.2(7)
C(15)-C(16)-H(161)	105.9	I(1)-C(25)-C(21)	68.5(4)
C(15)-C(16)-H(163)	108.3	I(1)-C(25)-C(24)	69.9(4)
H(161)-C(16)-H(163)	110.6	C(21)-C(25)-C(24)	106.9(7)
C(15)-C(16)-H(162)	106.5	I(1)-C(25)-C(31)	127.4(6)
H(161)-C(16)-H(162)	112.3	C(21)-C(25)-C(31)	124.7(7)
H(163)-C(16)-H(162)	112.7	C(24)-C(25)-C(31)	128.4(7)
C(15)-C(17)-H(172)	109.0	C(21)-C(26)-H(262)	107.8
C(15)-C(17)-H(171)	110.6	C(21)-C(26)-H(263)	106.9
H(172)-C(17)-H(171)	109.0	H(262)-C(26)-H(263)	109.8
C(15)-C(17)-H(173)	109.3	C(21)-C(26)-H(261)	110.7
H(172)-C(17)-H(173)	109.8	H(262)-C(26)-H(261)	110.6
H(171)-C(17)-H(173)	109.1	H(263)-C(26)-H(261)	111.0
I(1)-C(21)-C(22)	70.0(4)	C(22)-C(27)-H(271)	111.6
I(1)-C(21)-C(25)	72.6(4)	C(22)-C(27)-H(273)	110.0
C(22)-C(21)-C(25)	108.5(6)	H(271)-C(27)-H(273)	109.7
I(1)-C(21)-C(26)	128.6(5)	C(22)-C(27)-H(272)	109.4
C(22)-C(21)-C(26)	124.6(7)	H(271)-C(27)-H(272)	108.3
C(25)-C(21)-C(26)	126.5(7)	H(273)-C(27)-H(272)	107.8
I(1)-C(22)-C(21)	71.5(4)	C(23)-C(28)-H(282)	109.0
I(1)-C(22)-C(23)	70.3(4)	C(23)-C(28)-H(281)	111.2
H(282)-C(28)-H(281)	109.1	C(33)-C(34)-H(341)	121.1
C(23)-C(28)-H(283)	109.7	C(35)-C(34)-H(341)	120.1
H(282)-C(28)-H(283)	108.7	C(34)-C(35)-C(36)	119.6(9)
H(281)-C(28)-H(283)	109.1	C(34)-C(35)-C(38)	120.2(9)
C(24)-C(29)-H(292)	112.0	C(36)-C(35)-C(38)	120.2(9)
C(24)-C(29)-H(293)	107.5	C(31)-C(36)-C(35)	121.3(9)
H(292)-C(29)-H(293)	107.5	C(31)-C(36)-H(361)	120.1
C(24)-C(29)-H(291)	111.0	C(35)-C(36)-H(361)	118.6
H(292)-C(29)-H(291)	110.5	C(33)-C(37)-H(372)	109.5
H(293)-C(29)-H(291)	108.2	C(33)-C(37)-H(371)	109.0
C(25)-C(31)-C(32)	122.8(8)	H(372)-C(37)-H(371)	109.3
C(25)-C(31)-C(36)	119.3(8)	C(33)-C(37)-H(373)	108.6
C(32)-C(31)-C(36)	117.8(8)	H(372)-C(37)-H(373)	110.0
C(31)-C(32)-C(33)	121.6(9)	H(371)-C(37)-H(373)	110.4
C(31)-C(32)-H(321)	119.4	C(35)-C(38)-H(382)	109.9
C(33)-C(32)-H(321)	119.1	C(35)-C(38)-H(383)	109.9
C(32)-C(33)-C(34)	120.9(9)	H(382)-C(38)-H(383)	109.4
C(32)-C(33)-C(37)	120.4(9)	C(35)-C(38)-H(381)	109.1
C(34)-C(33)-C(37)	118.6(8)	H(382)-C(38)-H(381)	110.0
C(33)-C(34)-C(35)	118.7(9)	H(383)-C(38)-H(381)	108.6

Table A.6.4 Anisotropic displacement parameters ($Å^2$x 10^3) for **348**. The anisotropic displacement factor exponent takes the form: -2□^{2}[h^2 $a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
I(1)	19(1)	18(1)	26(1)	1(1)	-1(1)	-1(1)
Cl(2)	41(1)	57(1)	66(1)	11(1)	0(1)	6(1)
N(3)	59(4)	45(3)	55(3)	-7(3)	0(3)	-2(3)
C(4)	45(4)	48(4)	50(4)	0(3)	1(3)	2(4)
C(5)	49(4)	50(4)	48(4)	8(3)	-5(3)	4(3)
C(6)	43(4)	38(3)	58(4)	6(3)	14(3)	-4(3)
C(7)	49(4)	45(4)	43(3)	6(3)	4(3)	-17(3)
C(8)	56(5)	52(4)	62(5)	-5(4)	-7(4)	-11(4)
C(9)	39(4)	52(4)	57(4)	13(3)	0(3)	-2(3)
C(10)	44(4)	61(4)	74(5)	24(4)	1(4)	-5(4)
C(11)	41(4)	94(7)	72(5)	32(5)	8(4)	-13(5)
C(12)	60(5)	85(6)	69(5)	10(5)	18(5)	2(6)
C(13)	57(5)	56(5)	56(4)	2(4)	2(4)	2(4)
C(14)	43(4)	44(4)	59(4)	8(3)	-1(3)	3(3)

C(15)	51(5)	55(4)	62(4)	2(4)	-10(4)	-9(4)
C(16)	98(9)	62(6)	74(6)	2(5)	-32(6)	-6(5)
C(17)	72(7)	78(6)	94(7)	32(5)	-32(6)	-18(5)
C(21)	32(3)	47(3)	50(3)	4(3)	5(3)	1(3)
C(22)	34(3)	43(4)	62(4)	-5(3)	2(3)	15(3)
C(23)	53(4)	50(4)	41(3)	-12(3)	9(3)	0(3)
C(24)	47(4)	49(4)	39(3)	0(3)	6(3)	3(3)
C(25)	38(4)	55(4)	44(3)	6(3)	8(3)	-10(3)
C(26)	42(4)	64(5)	59(4)	2(4)	-4(3)	-8(4)
C(27)	49(4)	44(4)	81(5)	-1(4)	1(5)	2(3)
C(28)	53(4)	56(4)	66(4)	-13(3)	1(4)	-10(4)
C(29)	58(5)	58(4)	48(3)	7(3)	-2(4)	10(4)
C(31)	43(4)	56(4)	51(4)	1(3)	4(3)	2(3)
C(32)	49(5)	44(4)	60(4)	3(3)	-1(4)	-4(3)
C(33)	49(5)	62(5)	65(5)	13(4)	2(4)	-3(4)
C(34)	56(5)	54(5)	78(6)	14(4)	-2(4)	-11(4)
C(35)	61(5)	49(5)	76(6)	-1(4)	-2(4)	0(4)
C(36)	50(4)	47(4)	76(5)	1(4)	4(4)	-1(4)
C(37)	49(5)	48(5)	123(9)	12(5)	-13(5)	-13(4)
C(38)	63(6)	39(4)	148(10)	-8(5)	0(6)	4(5)

Table A.6.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **348**.

	x	y	z	U(eq)
H(41)	3453	3733	7496	57
H(71)	2765	1360	5849	55
H(81)	843	272	6252	68
H(101)	-684	-240	6996	72
H(111)	-1232	68	7844	83
H(121)	-74	1510	8280	85
H(131)	1915	2589	7915	68
H(151)	6202	2565	7166	68
H(161)	7316	3350	7976	117
H(163)	7233	4236	7456	117
H(162)	5760	4307	7922	117
H(172)	6239	1470	7873	122
H(171)	4513	1353	7664	122
H(173)	4849	2162	8127	122
H(262)	9595	3554	6318	83
H(263)	8397	4382	6593	83
H(261)	8409	3067	6732	83
H(271)	6196	825	6193	87
H(273)	7819	825	5892	87
H(272)	7707	1348	6437	87
H(282)	4180	2050	4940	87
H(281)	5785	1375	4895	87
H(283)	4589	1092	5335	87
H(292)	4995	3857	4623	82
H(293)	3871	4390	5028	82
H(291)	5381	5056	4865	82
H(321)	9583	5368	5682	61
H(341)	8179	8631	5738	75
H(361)	4950	6117	5775	69
H(372)	10865	8166	5516	110
H(371)	11412	6900	5457	110
H(373)	11245	7449	6002	110
H(382)	4075	8008	5862	125
H(383)	4855	8653	5405	125
H(381)	5322	8975	5958	125
H(32)	5290	4633	6929	79
H(31)	3752	4714	6812	79