Dearomative Reductive Functionalisation

Reactions of Azaarenes

A thesis submitted in partial fulfilment of the requirement

for the degree of Doctor of Philosophy (DPhil)

Bruno Marinič

University of Oxford

St John's College

Hillary Term 2023

"I won't pretend to understand the movement of the wind or the waves in the ocean,

or how like the hours, I change softly, slowly, plainly, blindly."

"In zemlja na katero si stopil, ti je vzela del potovanja."

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Declaration

The work described in this thesis was carried out at the University of Oxford, in the Chemistry Research Laboratory, from February 2019 until April 2023, under the supervision of Professor Timothy J. Donohoe. All the work is my own, except where help is acknowledged from a specific person, or a reference is given to a published source or thesis. This work has not been submitted previously for any other degree at this or any other university.

Bruno Marinič

April 2023

Abstract

Chapter 1: Introduction

The introduction gives an overview of the different strategies for the reduction of azaarenes, with a particular focus on transfer hydrogenation approaches for the synthesis of aliphatic *N*-heterocycles. The second half of the introduction presents a brief overview of relevant dearomative reductive functionalisation reactions of azaarenes published in recent years.

Chapter 2: Single-point activation strategy for the reductive hydroxymethylation of pyridines

In this chapter a single-point activation strategy of pyridines is described that allows for the use of a more electronically diverse range of substrates to undergo the dearomative reductive hydroxymethylation reaction. Additionally, a total synthesis of (±)-paroxetine is described, the target was prepared from a key dearomatized intermediate in 3 synthetic steps.

Chapter 3: Expending the scope of electrophiles in the dearomative reductive functionalisation reactions of quinolines

In this chapter the dearomative reductive functionalisation of quinolinium salts to their tetrahydroquinoline analogues is described. Two sets of new reaction conditions are developed with formic acid acting as the terminal reductant under transition-metal-free conditions or rhodium catalysis with very low catalyst loadings. The scope of electrophiles was expanded from just formaldehyde to a wide range of electrophiles, including enones, imides, unsaturated esters and sulfones.

Chapter 4: Expending the scope of electrophiles in the dearomative reductive functionalisation reactions of isoquinolines

In this chapter the dearomative reductive functionalisation of isoquinolinium salts to their tetrahydroisoquinoline counterparts is described. Analogously to the quinoline system, formic acid was used as the source of hydride and the reaction was possible under transition-metal-free conditions or rhodium catalysis with very low catalyst loadings. The scope of electrophiles that were intercepted by the enamine species generated *in situ* was further expanded to include enones, imides, unsaturated esters and sulfones, β-nitrostyrenes and aldehydes.

Chapter 5: Dearomative annulation reactions of isoquinolines

In this chapter various dearomative annulation reactions of activated isoquinolines are presented. The reactivity of *in situ* generated intermediates is exploited further to assemble complex tricyclic frameworks in a single step with excellent diastereoselectivities. The formal [3+3] annulation with methyl vinyl ketone is explored in greater detail including model studies towards the synthesis of the natural products in the crinane-alkaloid family.

Chapter 6: Experimental

This Chapter contains the experimental procedures and spectroscopic data for all the compounds described in this thesis.

Chapter 7: References

The references cited in the thesis can be found in this chapter.

Acknowledgements

First and foremost, I want to express my gratitude to Prof. Tim Donohoe for providing me with the opportunity to work on this DPhil project which has given me a great purpose for the past four years. Thank you for your support and guidance throughout my DPhil journey and most of all for believing in this project and reminding me to maintain a positive outlook despite my pessimistic predisposition. I also extend my thanks to AstraZeneca for funding my DPhil and providing me with a great industrial supervisor in Dr Mark Dow. My time in Oxford would not have been the same without Prof. Angela Russell. You have provided me with invaluable opportunities, from my first research placement to giving me the opportunity to teach organic chemistry to generations of undergraduates at St John's College. I would not be the chemist I am today without your guidance and for that I will always be grateful. Finally, to the person who made this Oxford experience possible in the first place: my high school chemistry professor Zdenka Keuc. You saw the path before I could even imagine it and you worked tirelessly so that I was able to walk it and make my dream come true. I owe you my eternal gratitude.

I have spent over 1500 days as a member of the TJD group and over the years many others have come and gone. However, no matter the group size or composition you all have made coming to work a pleasure on the good days and manageable on the bad ones. I want to especially thank the postdocs who have worked with me on the dearomatisation projects for all the knowledge they have, each in their own way, bestowed upon me. Hamish, for teaching me much of what I know today and for the endlessly entertaining conversations, I hope they will continue for a long time. Marvin, for giving me my best research project and showing me how to work in a focused and goal-oriented manner under the most suboptimal conditions. Nik, for helping me wrap everything up and for the much-needed political radicalisation and reminder of the true dividing lines in our society. Aaron, for being committed to the out-of-lab socialising cause and providing excellent film/TV recommendations throughout. Thank you to Elisa, Jane and Clément, the students I have supervised over the years, for reminding me that sometimes teaching is the best learning experience, I hope you know that I tried my best. From the first retrosynthesis challenge to kayaking on the Pacific Ocean,

I could not have asked for a better partner than Dani. I am beyond grateful for all our conversations that always leave me feeling more secure about the uncertain future. I cannot imagine my time in F8 without Lydia, who has perhaps single-handedly done more to make it a joy coming into work than anyone else. Thank you for all the crucial everyday things I will miss greatly, like our red-carpet fashion police moments and mandatory new album release listening parties in the lab. Elliot provided me with much-needed grounding conversations about chemistry and beyond, as well as many peaceful walks around university parks, for which I am immensely thankful. Tim Jenkins was a wonderful fume hood neighbor and a consistent provider of fun facts (1339 to be exact), I hope I was able to give some knowledge in return. Andrew provided me with much needed financial advice and took on the torch of this research project, while never missing out on a pint when given the opportunity. I should also not forget the longstanding members of F7, thank you to Ciaran for his insights on lefty politics; Dana for the most randomly entertaining conversations; Hannah for all the gambling advice; and Jess for sharing my love of wine. Special thanks to the invaluable support staff at the CRL in the NMR, crystallography, and workshops teams without who much of the lab work would not have been possible.

Although the lab has been at the centre of my DPhil, I would not have made it through this journey without all the Kendrew lunches and college bar trips with my St John's family. Thank you to Adam, for showing me what strength and perseverance look like in the toughest of times, and for keeping up with and encouraging my Drag Race obsession. I want to thank Gemma for sharing my love for sad-girl music, always being down for some drunken shenanigans, and soldiering through every possible bug infestation Oxford threw at us. I am also grateful to Pol, who has been a friend since day one of this DPhil and for weathering the ups and down of chemistry and college life by my side. I want to thank Eddie and Nadia for his friendship and guidance as I transitioned from undergraduate to DPhil student and now as I take my next steps in life. Thank you for all the drinks and conversations, from Star Wars to politics, but most of all for keeping me principled in my actions and thoughts. I owe a great debt of gratitude to Alen, who not only proofread this entire thesis but also engaged in many stimulating chemistry conversations with me over the years. Ana Š. deserves a special thank you for providing me with an abundance of vegan baked goods, Slovenian wine, and

fun tarok evenings. I want to thank Ana Vilhelmina for always reminding me of what is at stake and for sharing my own aspirations for greatness, you have helped me hone my view of the world. Mihail has spoiled us with delicious culinary treats and fuelled my love for Scottish folk songs, for which I am immensely thankful. I am also thankful to Martin, for all the party nights and his fine appreciation of Slovenian memes. I want to extend my gratitude to Jane and Joe, who have been a source of inspiration and made me feel welcome in the unfamiliar SCR world, to many more Italian biscuits.

A special place in my heart is for the friendships that have transcended distance. Thank you to Jasmina and Petra for staying part of my Oxford family even after you left, becoming an adult in your company has been one of my greatest pleasures. I also want to thank Maša for always making room for me in her life and filling my time back home with joy and Balkan music deep cuts. I am grateful to Lara for 13 years of friendship that doesn't seem to have an expiry date in sight. Thank you for all the heartfelt conversations and being a constant presence that has kept me grounded throughout the years.

To my parents, I owe an immeasurable debt of gratitude for their unconditional love and endless support. Words cannot express how thankful I am for all you have given me, I hope you know that without you I would not be where I am today. I also want to thank my brother Gašpar for keeping me thoroughly entertained with the best stories of the shenanigans you and your friends get up to. It has been a great privilege seeing you come into your own and prospering in the craft that you love so much; you make me a proud brother.

Finally, to Indi, who has marked the past four years of my life more than this thesis ever could. I am thankful for your love in all its forms, and for making me believe in a future that is as bright as hope. I cannot wait to see what lies beyond.

"You believe, I believe too,

That you are the river of light

Who I love, that I cling to

In the belly of the empty night."

Abbreviations and Acronyms

Ac	acetyl
acac	acetylacetone
ACE–Cl	1-chloroethyl chloroformate
Am	amyl
Amphos	di-*tert*-butyl(4-dimethylaminophenyl)phosphine
Ar	aryl
aq.	aqueous
ATH	asymmetric transfer hydrogenation
B	base
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bz	benzoyl
CBz	carboxybenzyl
$[CD_2O]_n$	deuterated paraformaldehyde
$[CH_2O]_n$	paraformaldehyde
cod	1,5-cyclooctadiene
conc.	concentrated
COSY	COrrelation SpectroscopY
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
δ	NMR chemical shift
dba	dibenzylideneacetone
DCE	1,2-dichlororthane
DCM	dichloromethane, methylene chloride
DIAD	diidopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO-d_6	deuterated dimethylsulfoxide

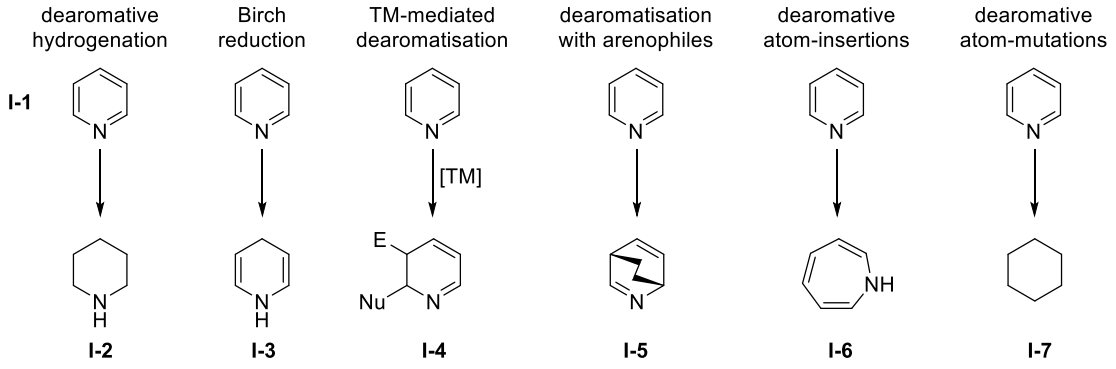
dr	diastereomeric ratio
E	electrophile
EDG	electron donating group
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
equiv.	equivalent(s)
er	enantiomeric ratio
ESI	electrospray ionisation
et al.	(Latin: and others)
EWG	electron withdrawing group
FA	formic acid
FCC	flash column chromatography
[H]	hydride
Het	heteroarom
HFIP	hexafluoroisopropanol
HMBC	Heteronuclear Multiple Bond Correlation spectroscopy
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coherence spectroscopy
i	iso
IR	infrared spectroscopy
L/L_n	ligand
L*	chiral ligand
LA	lewis acid
LDA	lithium diisopropylamide
M	molarity, mol dm^{-3}
[M]	metal
m.p.	melting point
Me	methyl
mol%	mole per cent
MVK	methyl vinyl ketone

n	normal, unbranched alkyl chain
NIS	*N*-iodosuccinimide
NMR	Nuclear Magnetic Resonance spectroscopy
nOe	nuclear Overhauser effect
NOESY	Nuclear Overhauser Effect SpectroscopY
Nu	nucleophile
[Ox]	oxidation
PG	protecting group
Ph	phenyl
Ph*	pentamethylphenyl
Ph*VK	pentamethylphenyl vinyl ketone
PMP	4-methoxyphenyl
ppm	parts per million
PVK	phenyl vinyl ketone
py	pyridine
quant.	quantitative
R	generic substituent
r.t.	room temperature
sat.	saturated
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	tertiary alkyl group, tert-alkyl
TBAF	tetra-n-butylammonium fluoride
Tc	thiophene-2-carboxylate
TFA	trifluoroaceticacid
TH	transfer hydrogenation
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TLC	thin-layer chromatography
TM	transition metal
TMS	trimethylsilyl
Ts	toluenesulfonyl

UV	ultraviolet
νmax	infrared absorption maximum
wt% or w/w%	weight for weight percentage
X	generic halide
Xs	excess

Chapter 1: Introduction

The synthetic chemistry of *N*-containing heterocycles has been extensively investigated for decades. Over the years, the main driving force for organic chemists to find new ways of making and derivatising *N*-heteroarenes with underexplored and complex substitution patterns was their widespread use in medicinal chemistry programmes and pharmaceutical products.[1–5] While considerable progress has been made in the realm of *de novo* synthesis of heterocyclic aromatic systems from simple commercial building blocks, methods for synthesizing their dearomatized (i.e. saturated) counterparts still presents a significant yet exciting synthetic challenge.[6–10] In recent years, the pharmaceutical industry has been shifting their focus towards more complex three-dimensional molecular scaffolds; thus the need for new more general methods to routinely access dearomatized aliphatic heterocycles is gaining prominence as we are attempting to leave "flatland".[11,12] Different reduction strategies have been developed as the main approach to access aliphatic heterocycles from their aromatic counterparts (Scheme 1.1).[13] The abundance and commercial availability of functionally diverse azaarenes makes them excellent precursors for accessing complex three-dimensional scaffolds.[14]

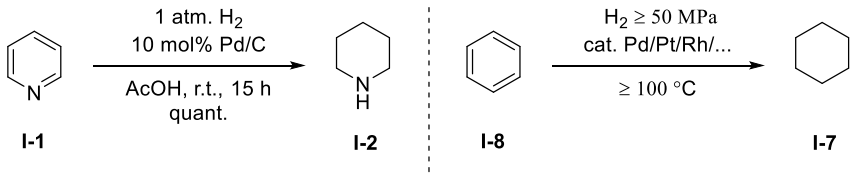


Scheme 1.1: Different strategies for pyridine dearoamtisation

1.1 Hydrogenation of azaarenes

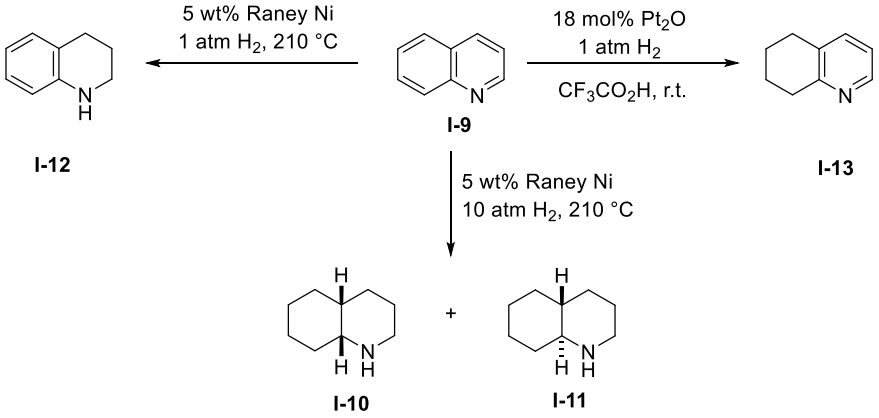
The reduction of pyridine proceeds quantitatively and with relative ease using palladium on carbon as a heterogenous catalyst in acetic acid at room temperature (Scheme 1.2).[15] These conditions are

much milder in comparison to the hydrogenation of benzene, which usually requires high pressures and/or temperatures.[16]



Scheme 1.2: Hydrogenation of pyridine compared to benzene

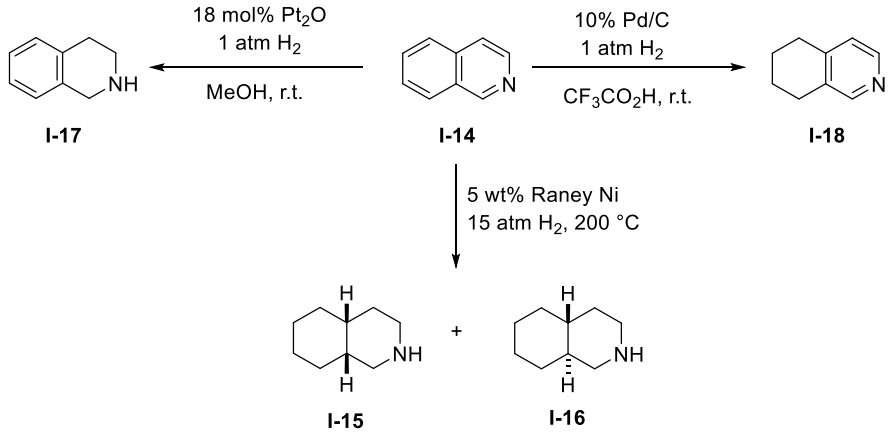
Complete reduction of quinoline, on the other hand, requires much harsher conditions; hydrogenation with Raney nickel proceeded only under elevated temperature and pressure to give a mixture of *cis* **I-10** and *trans* **I-11** decahydroquinolines (the authors do not state the ratio of the isomers).[17] Selective reduction of this heterocyclic ring system can be achieved under analogous conditions using only atmospheric pressures of hydrogen. Finally, selective reduction of the carbocyclic ring proceeded under atmospheric pressures of hydrogen in trifluoroacetic acid using Adams' catalyst (Scheme 1.3).[18]



Scheme 1.3:Partial and complete hydrogenation of quinolines

Analogously to the quinoline example, the nickel-catalysed complete hydrogenation of isoquinoline also necessitates high pressures and temperatures (Scheme 1.4) and delivers corresponding decahydroisoquinolines as a mixture of the *cis* **I-15** and *trans* **I-16** isomers.[19] In this case, selectivity for the reduction of the heterocyclic ring to give the tetrahydroisoquioline (THIQ) can be achieved under atmospheric pressure of hydrogen at room temperature when Adams' catalyst is used.[20] Similarly, the selective carbocyclic reduction also proceeds at ambient temperature under atmospheric

hydrogen pressure with palladium on carbon used as a heterogenous catalyst in trifluoroacetic acid as the solvent.[21]



Scheme 1.4: Partial and complete hydrogenation of isoquinolines

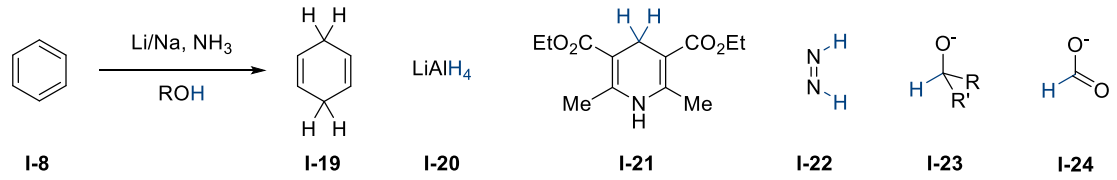
While many hydrogenation procedures that are tolerant of a wide range of functional groups have been successfully developed[22–27], the need to use highly reactive hydrogen gas as the main reagent remains a major drawback of these methodologies.

1.2 Transfer hydrogenation of azaarenes

The formal addition of hydrogen to a molecule from a source other than elemental hydrogen is a process known as transfer hydrogenation (TH). As discussed above, classical hydrogenation reactions require the use of heterogenous catalysts and specialised equipment capable of maintaining high pressures. Furthermore, the use of hydrogen gas represents a significant safety risk, especially on large scales; hence the used of TH can offer some advantages.

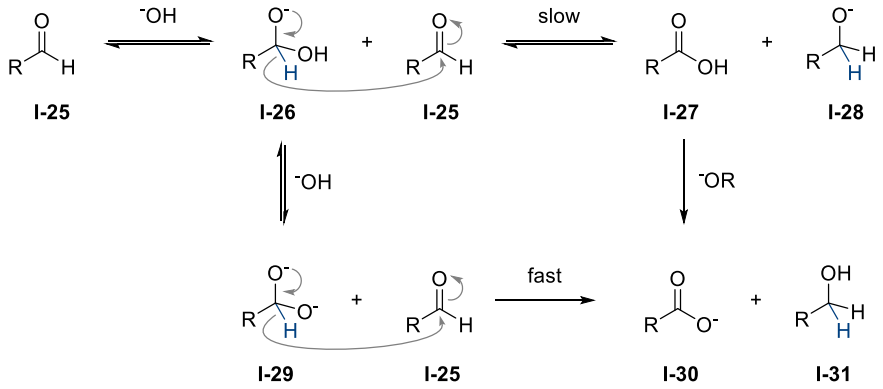
Hydrogen can be transferred from one molecule to another in a variety of ways (Scheme 1.5), the most common being the protonation/deprotonation in tandem with an addition of electrons to yield a net reductive process (e.g.: Birch reduction).[28] Traditional hydride donors (e.g. $NaBH_4$, $LiAlH_4$, etc) perhaps represent the most common way in which hydrogen is transferred from one molecule to another in the form of a hydride addition followed by protonation during the workup. Metal hydrides are not the only potential source of hydrides; 1,4-dihydropyridines (e.g.; Hantzsch ester **I-21**) can donate a hydride to a suitable acceptor in a process driven by re-aromatisation to the corresponding pyridine.[29] Finally, hydrogen can also be transferred via a homolytic pathway; diazines

can transfer hydrogen to alkynes and alkenes in a concerted way, with the formation of N_2 being the main driving force behind these reactions.[30]



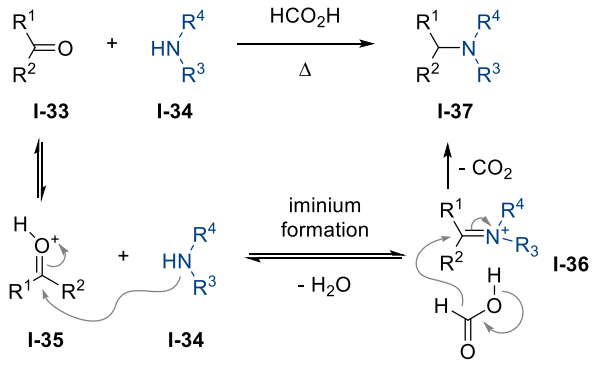
Scheme 1.5: Different transfer hydrogenation reagents

Hydride transfers have been observed for aldehydes since the 19th century. For example, in the Cannizzaro reaction, non-enolizable aldehydes can undergo an intermolecular disproportionation to form the corresponding carboxylic acid **I-27** and alcohol **I-31** (Scheme 1.6).[31] The Canizzaro reaction is significantly accelerated at higher concentrations of a strong base (e.g.: KOH); this is due to the di-anionic intermediate **I-29**, formed under highly basic conditions, being an excellent hydride donor.[32]



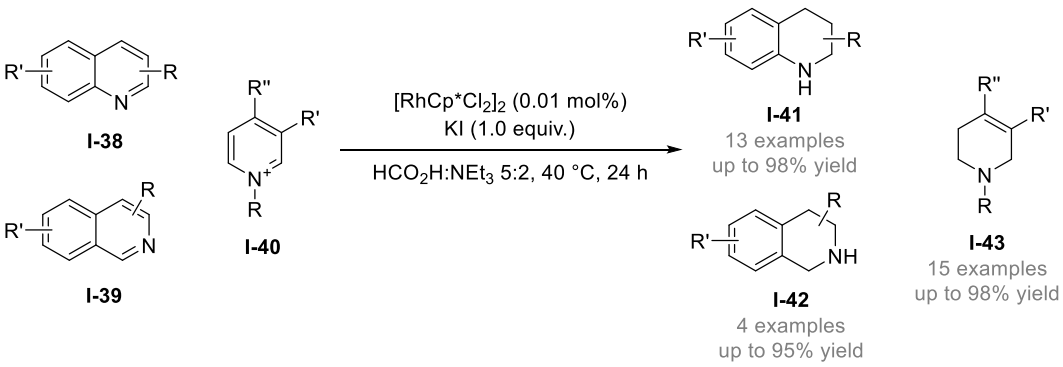
Scheme 1.6: Mechanism of the Canizzaro reaction

Similarly, the use of formic acid (or ammonium formate) as a transfer hydrogenation reagent dates back to the late 1800s. For example, the Leuckart-Wallach reaction is a reductive amination reaction of a ketone and an amine in the presence of an excess formic acid, which under elevated temperatures serves as the terminal reductant.[33–35] When formaldehyde is used instead of a ketone to methylate the amine, this process is known as the Eschweiler–Clarke reductive amination (Scheme 1.7).[36]



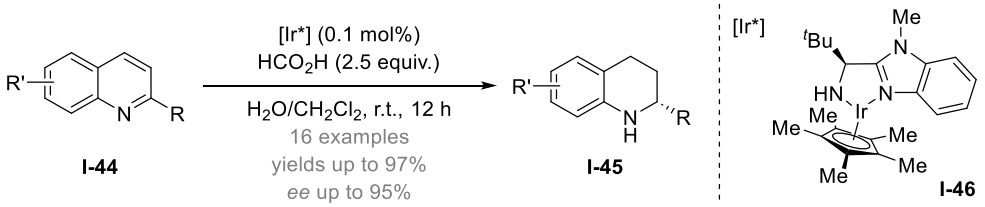
Scheme 1.7: Mechanism of the Leuckart-Wallach reaction

Similar to classic hydrogenation, transition metals have found a central role in catalysing transfer hydrogenation reactions. Their ability to adopt variable oxidation states combined with the possibility of tuning stereoelectronic properties with the use of different ligands makes transition metals ideal catalysts for a plethora of reactions.[37,38] Methodologies utilising transition metal catalysis offer a range of advantages from milder reaction conditions, to enabling enantioselective transformations when chiral catalysts are employed.[39] Transition metals are able to facilitate the addition of reagents to the substrate in cases where direct addition (i.e. metal-free) is energetically unfavourable. Complete and partial reductions can be achieved when the nucleophile in question is a hydride; there is a considerable amount of literature precedent for the transition metal catalysed transfer hydrogenation utilising milder and greener reaction conditions for the reduction of azaarenes.[40–43] The group of Xiao and co-workers in particular has reported substantially on developing greener transfer hydrogenation methods employing the use of formic acid or formate as the source of hydride (Scheme 1.8).[43]



Scheme 1.8: Transfer hydrogenation work by Xiao and co-workers.

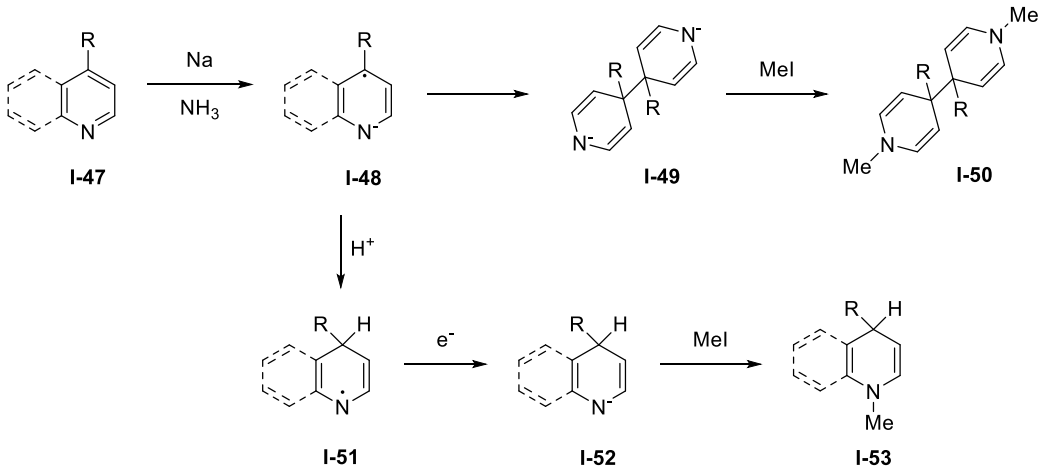
Finally, enantioselective reductions can also be performed using chiral transition metal complexes as the catalysts in TH reactions.[44–50] The Sun group developed such example of an asymmetric transfer hydrogenation (ATH) that uses a biphasic system and a water-soluble iridium catalyst to efficiently reduce a wide range of 2-substituted quinolines in excellent yields and *ee* (Scheme 1.9).[51]



Scheme 1.9: Example of an asymmetric transfer hydrogenation of quinolines

1.2.1 Birch reductions of azaarenes

The Birch reaction is another well-established method for the reduction of arenes using solvated electrons produced when alkali metals are dissolved in liquid ammonia, which are then transferred to the (hetero)aryl ring.[28] Depending on the substituents present on the aromatic ring (electron donating/withdrawing) and nature of the reaction medium (protic/aprotic), different reaction pathways lead to distinct reduced products. Upon addition of an electron to pyridine, the radical anion **I-48** is formed first; then, in the absence of protons, the dimeric dianion **I-49** formed can be quenched with methyl iodide to give **I-50** (Scheme 1.10).

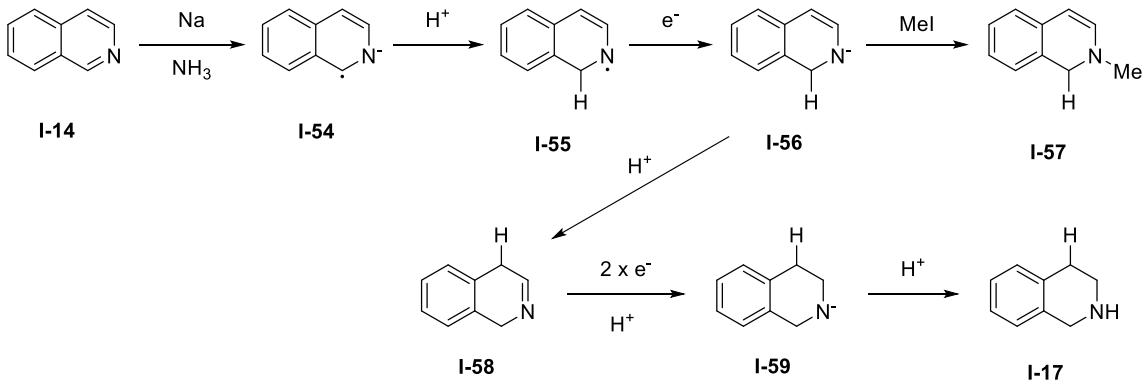


Scheme 1.10: Birch reduction of pyridine and quinoline

When the reaction is carried out in protic medium (e.g.: ethanol), the intermediate **I-49** gets protonated to give the radical **I-51**. A final reduction then furnishes anion **I-52** which can be

quenched with methyl iodide to give the 1,4-dihydropyridine **I-53**.[52] Note that the reduction of quinoline under Birch conditions proceeds in a similar manner to give the corresponding 1,4-dihydroquinoline.[53]

The reactivity of isoquinoline also follows a similar reactivity pattern; when only one equivalent of a proton source is present, anion **I-56** is formed. This intermediate can then be intercepted by methyl iodide to give the 1,2-dihydroisoquinoline **I-57**. In the presence of excess protons, THIQ **I-17** is formed (Scheme 1.11).[54]

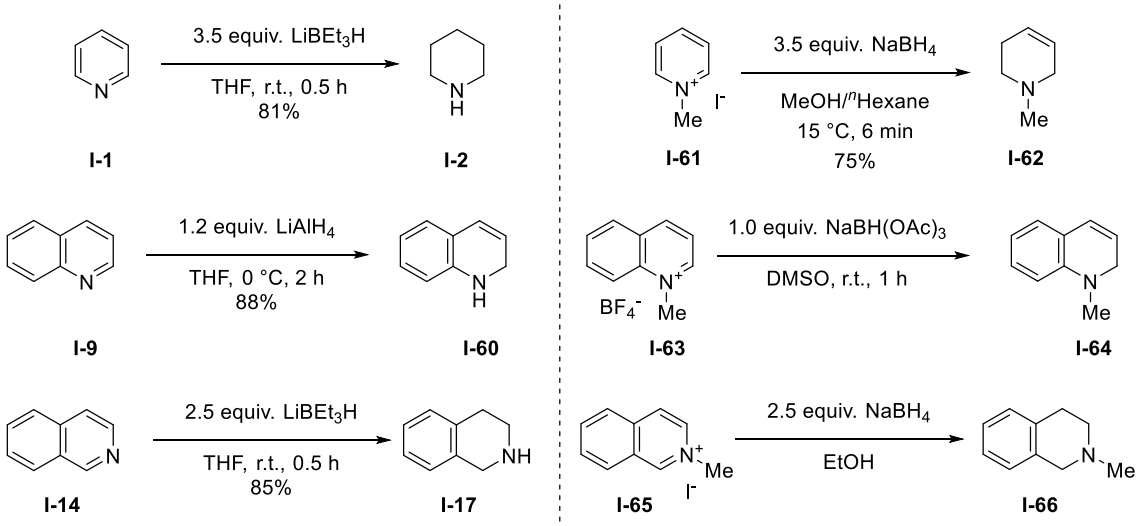


Scheme 1.11: Birch reduction of isoquinoline

1.2.2 Hydride reductions of azaarenes

A good alternative to using hydrogen gas is methodology utilising nucleophilic hydride donors in tandem with the intrinsic electrophilic nature of azaarenes in order to obtain the (partially) saturated *N*-heterocycles. Using e.g. lithium triethylborohydride (Super-Hydride), piperidine can be obtained in 81% yield directly from pyridine (Scheme 1.12).[55] Weaker reducing reagents either do not react with pyridine ($NaBH_4$) or lead to mixtures of partially reduced products ($LiAlH_4$) which are often hard to separate by flash chromatography.[56] Similar to pyridine, the complete reduction of isoquinoline to the corresponding THIQ also requires the use of a Super-Hydride. Quinoline on the other hand will give 1,2-dihydroquinoline upon reaction with lithium aluminium hydride in excellent 88% yield.[57] To enable the use of milder reducing conditions and reagents, various strategies for the activation of azaarenes have been developed; protonation of the nitrogen,[58] Lewis acid coordination,[59] or covalent nitrogen quaternisation[60] are the most common methods used. In contrast to pyridine, *N*-methylpyridinium iodide **I-61** reacts with sodium borohydride to produce the

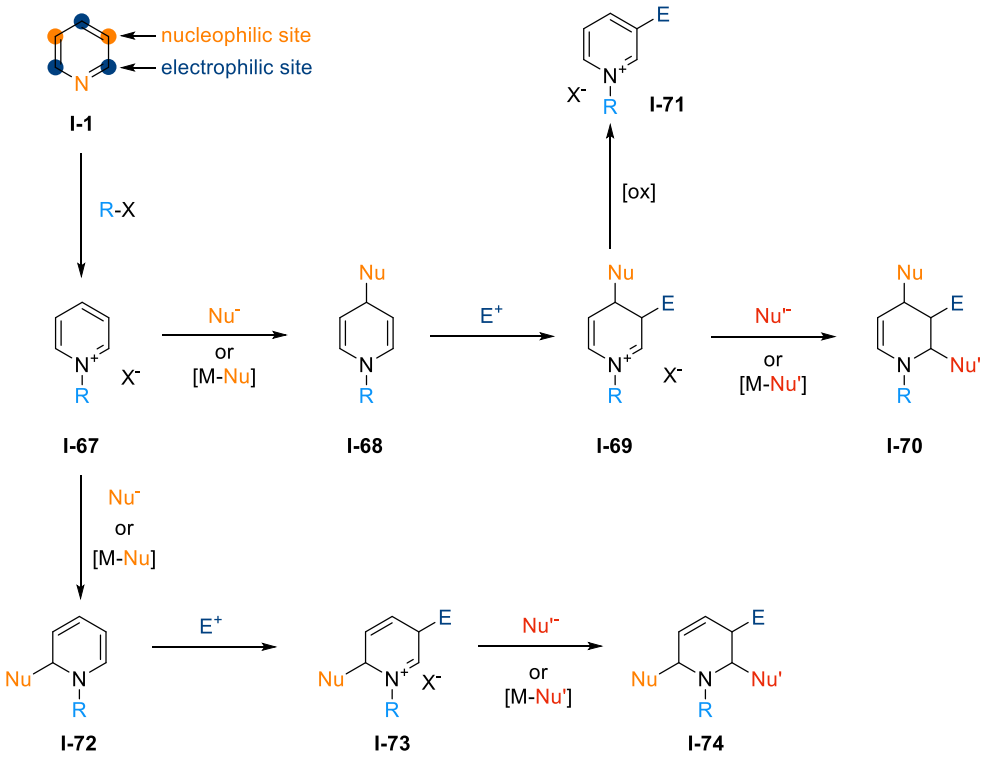
tetrahydropyridine **I-62** in good yield (75%).[61] *N*-Methyl quinolinium tetrafluoroborate **I-63** could be successfully reduced with sodium triacetoxyborohydride[62] and *N*-methyl isoquinolinium iodide **I-65** was readily reduced in the presence of sodium borohydride.[63]



Scheme 1.12: Comparing the reactivity of azaarenes and azaarenium salts

1.3 Reductive functionalisation reactions of azaarenes

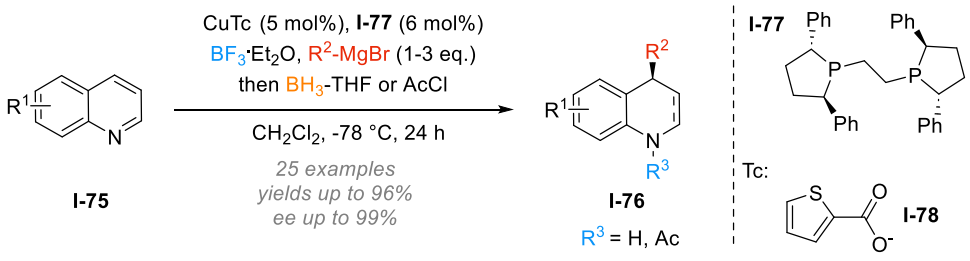
The synthetic utility of a dearomatisation reaction can be enhanced by incorporating a tandem C–C bond formation to furnish dearomatized and fully functionalised aliphatic *N*-heterocycles.[13,64–69] Common and established methods often rely on the arene acting as a nucleophile to initiate dearomatisation, however, in the case of 6-membered azaarenes (pyridine, quinoline, isoquinoline etc.) the reverse scenario, where the arene acts as the electrophile or a radical acceptor, is more appealing. The fundamental concept of this type of reactivity harnesses the intrinsic reactivity of the reactive intermediates revealed following the initial dearomatisation reaction, which then engage in intra- or inter-molecular C–C bond formation (Scheme 1.13). Subsequently, secondary intermediates can then either (i) undergo rearomatisation, or (ii) engage in further C–H or C–C bond formation reactions. The initial dearomatisation can be initiated by a myriad of different species under both metal-catalysed and metal free reaction conditions. The benefit of developing a more general dearomative functionalisation methodology lies in the desire to accomplish a rapid build-up of molecular complexity through cascade processes of readily available molecular scaffolds with potentially high regio- and stereoselectivity.



Scheme 1.13: General scheme of dearomative functionalisation reactions

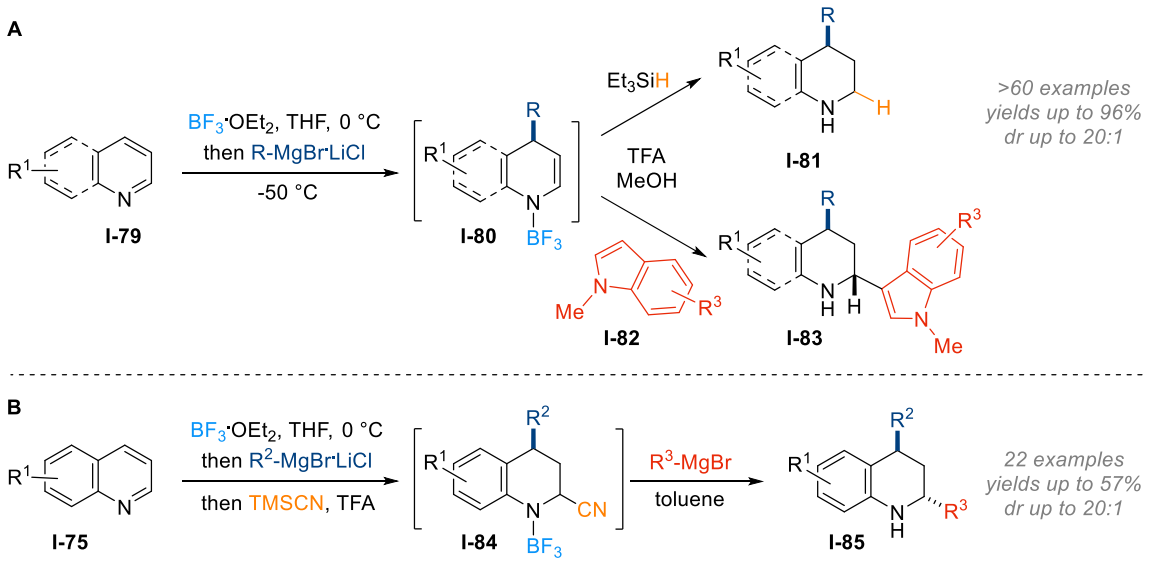
1.3.1 Metal-catalysed reactions

The reductive functionalisation of quinolines has been primarily focused on the introduction of carbon-based nucleophiles onto the arene, as demonstrated by Harutyunyan and co-workers in 2020 (Scheme 1.14).[70] Their work enabled an enantioselective addition-reduction sequence at C4 of quinolines **I-75** through Lewis acid activation of the substrate, using a copper-catalyst in combination with a chiral ligand **I-77** and borane-THF as a reductant. As an alternative to full reduction, the nitrogen could be trapped by reaction with acetyl chloride, resulting in the respective 1,4-dihydroquinoline analogues **I-76**.



Scheme 1.14: Enantioselective reductive C4 functionalisation of non-activated quinolines by Lewis acidic activation and copper catalysis (Harutyanyan, 2020).

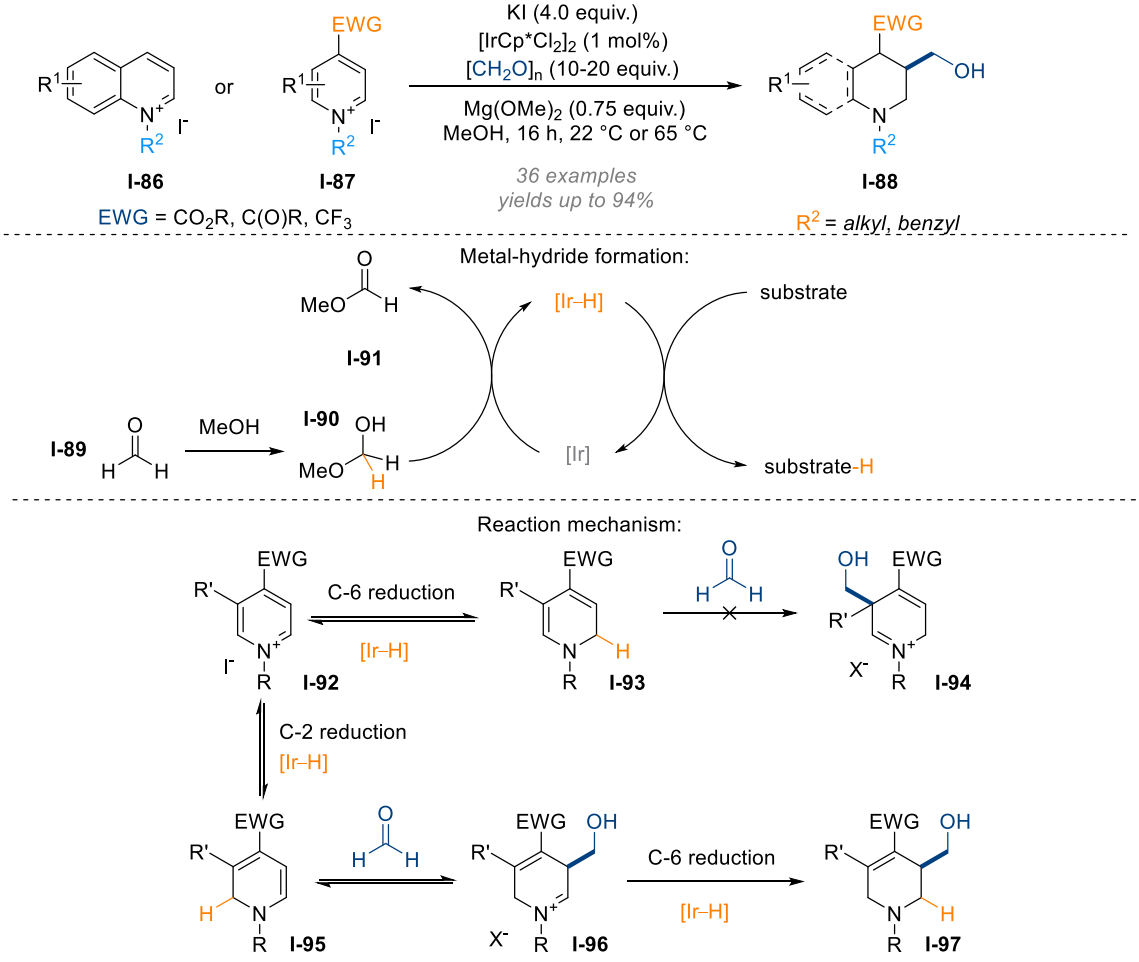
Wang and co-workers applied the principles of nucleophilic dearomatisation to demonstrate C2 and C4 dearomative functionalisation of pyridines and quinolines (Scheme 1.14A).[71,72] The reaction proceeds through the attack of an organometallic reagent under concomitant Lewis acid activation, forming intermediate **I-80** after C4 attack of the nucleophile. Elaboration of intermediate **I-80** can be achieved either by (i) reduction with a hydride source as before, or (ii) by addition of a second nucleophile such as indole to obtain difunctionalised products **I-83** in good yields. However, other arene nucleophiles did not participate in the trapping of the transient iminium species. To allow for a more general dearomative 2,4-functionalisation of quinolines, Wang and co-workers made a crucial modification in the procedure by using TMSCN as a transient nucleophile, which gave rise to a C2 cyano species **I-84** that was not isolated but rather reacted with a Grignard reagent in a subsequent operation *in situ* (Scheme 1.15B).[73] This modification enabled the introduction of a broad scope of residues at C2 (see **I-85**) in moderate yields and with excellent diastereoselectivity.



Scheme 1.15: A: C2 and C4 functionalisation of quinolines and pyridines by Lewis acid activation and reaction with carbon nucleophiles (Wang, 2019 and 2020); B: Modular C2 and C4 functionalisation of quinolines by transient addition of cyanide (Wang, 2022) .

Metal hydrides (which are themselves generated by transfer hydrogenation rather than with molecular hydrogen) are common initiators in the dearomatisation of activated azaarenes. In our group, we have previously developed a reductive hydroxymethylation reaction of activated pyridines and quinolines (Scheme 1.16).[74] The Ir(III) catalyst oxidises the hemiacetal **I-90**, formed upon addition of a methoxide onto formaldehyde, to methyl formate **I-91**, thus generating the active iridium hydride species. The dearomatisation then proceeds *via* hydride addition on C2 (pyridine) or C4 (quinoline)

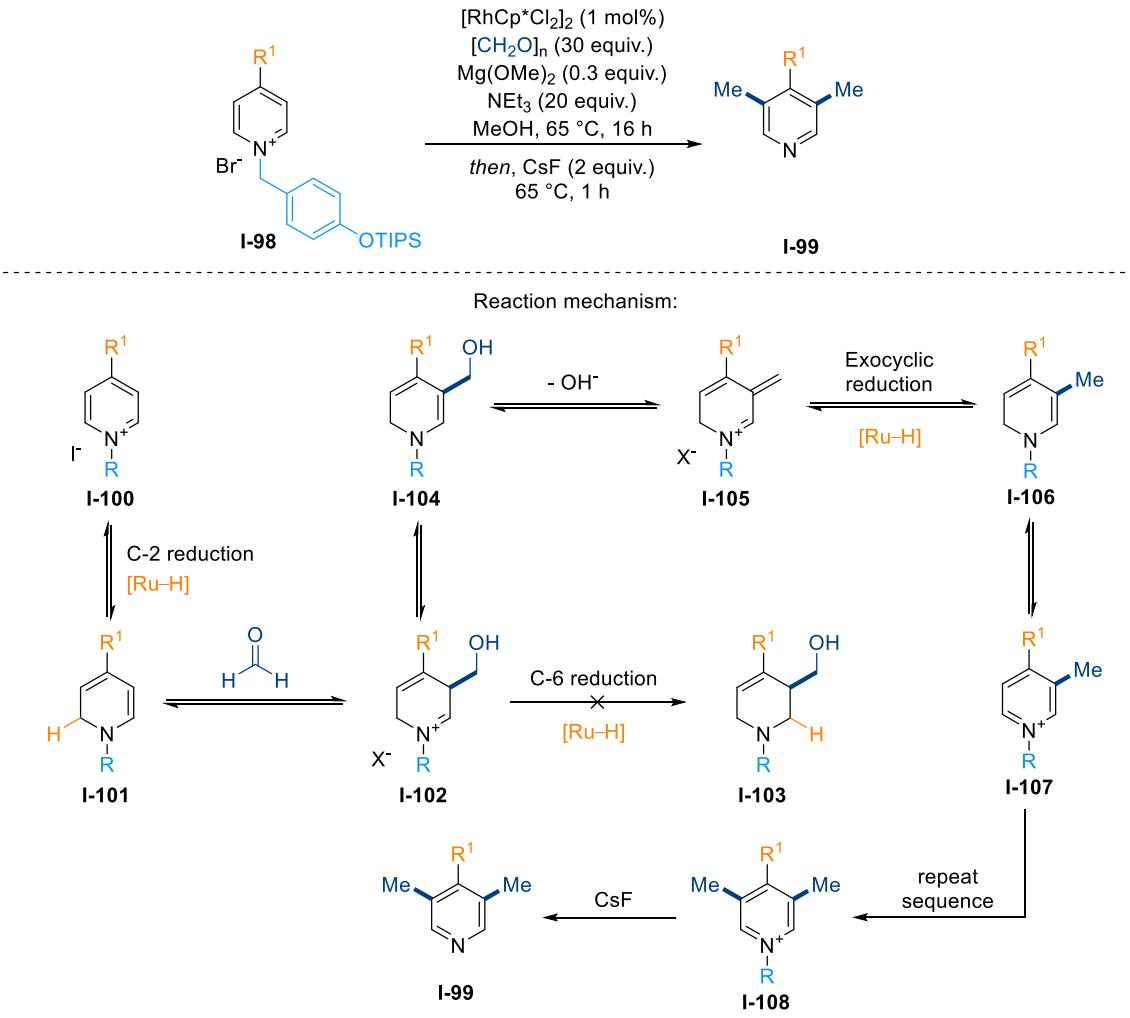
to reveal the reactive enamine **I-95**, that goes on to trap a molecule of formaldehyde. The iminium **I-96** generated in this process then undergoes a final reduction by the metal hydride to furnish the final tetrahydro-pyridine and -quinoline products **I-97**. While the quinolinium salts used in this methodology did not require additional activation, the presence of an electron withdrawing group at the C4-position was key to achieve good reactivity, at least with the pyridine series.



Scheme 1.16: Dearomative reductive hydroxymethylation of quinolinium and pyridinium salts (Donohoe, 2019)

Following this initial work, our group further developed a formal C–H activation process that proceeds *via* an initial dearomatisation coupled with C–C bond formation but then finishes with a rearomative process to regenerate the azaarene (Scheme 1.17).[75] This C3/C5 bismethylation has identical initial steps as the hydroxymethylation discussed above, however, the less basic and thus less reductive reaction conditions allow for the formation of new intermediates. The enamine **I-104**, formed after the trapping of formaldehyde and a tautomerisation, is able to eliminate a molecule of water and form an extended iminium species **I-105**. This intermediate is initially reduced by the

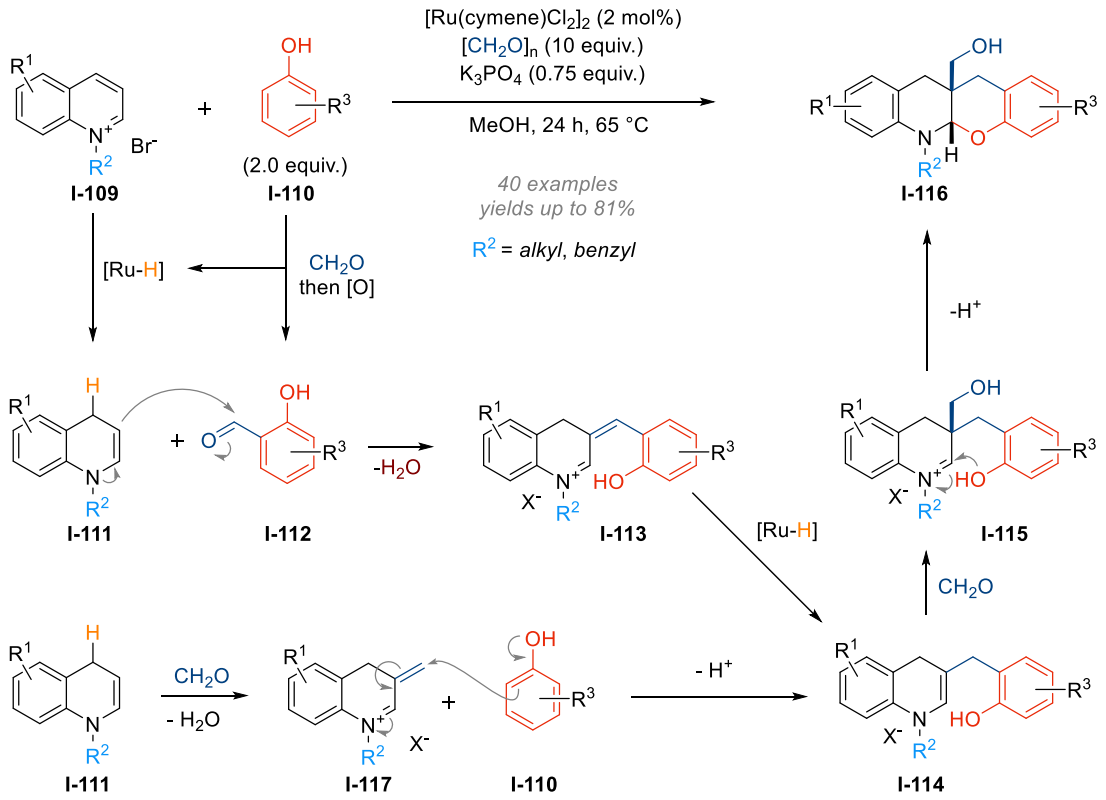
rhodium hydride, and then re-oxidised by the rhodium catalyst to regenerate the now methylated pyridinium salt **I-108**. The reaction sequence then repeats at C5 and the activating group cleaved in a CsF workup to give the bismethylated pyridines **I-99**.



Scheme 1.17: C3 methylation of pyridines through transient dearomatisation of activated pyridines (Donohoe, 2020)

Zhang and co-workers made significant contributions in the area of dearomative reductive functionalisation at the same time as the work discussed in the following chapters of this thesis. Their work focuses on developing cascades by functionalising reactive iminium species formed *in situ* through intramolecular trapping reactions; similar to our work discussed above, formaldehyde is used as both an electrophile and a source of hydride. Their protocol for the incorporation of substituted phenols onto quinolines was published in 2021 (Scheme 1.18).[76] First, the phenol partner **I-110** traps formaldehyde, and a sequential oxidation then gives the aryl aldehyde **I-112**. The reactive enamine

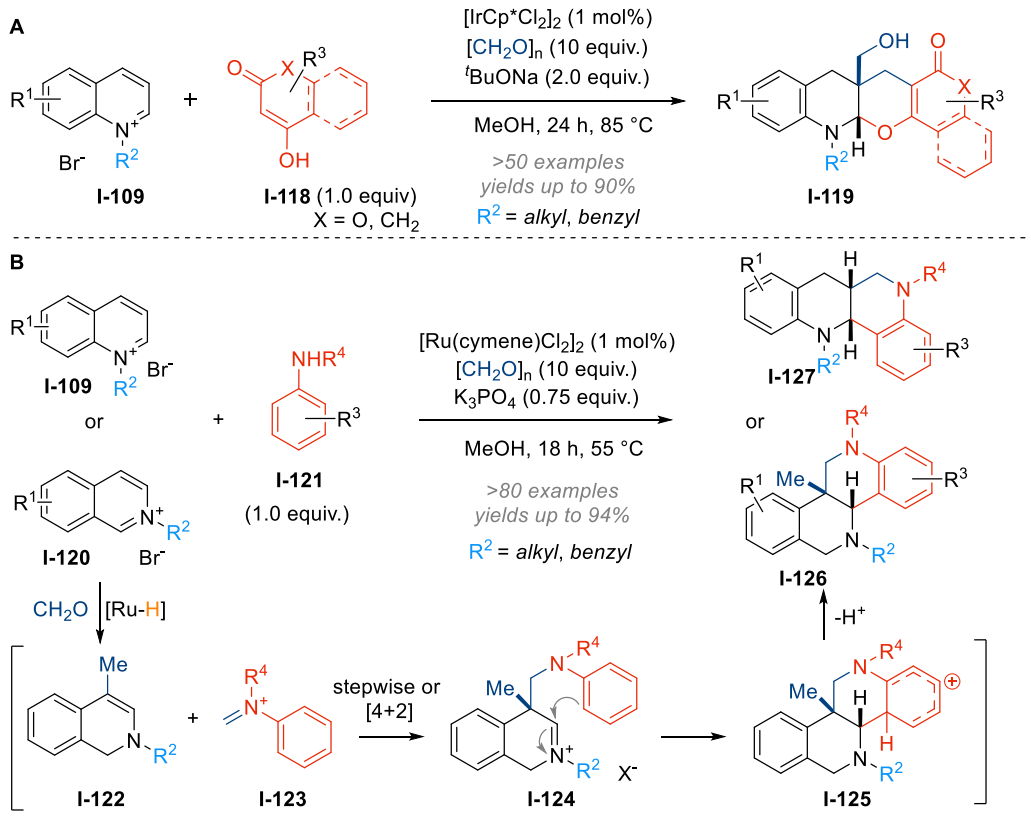
I-111, formed following dearomatisation of the quinolinum salt **I-109**, next intercepts **I-112** and after a E1cB type elimination of water forms an extended α,β-unsaturated iminium **I-113**, which is then reduced to form the 2nd reactive enamine species **I-114**. Trapping of another equivalent of formaldehyde gives the iminium **I-115** which is then intramolecularly intercepted by the proton to deliver the corresponding cis-annulated products **I-116**. Note, that an alternative reaction mechanism is also possible by allowing the initial enamine to attack formaldehyde and thereafter form an extended iminium **I-117**, which can in turn be attacked by the phenol in a Friedel-Crafts-type reaction.



Scheme 1.18: Catalytic reductive tandem functionalisation of quinolinium salts with phenols and formaldehyde (Zhang, 2021).

Zhang's research in the field of annulation reactions led to the expansion of the scope of reaction partners to include cyclic 1,3-dicarbonyls and various aromatic derivatives, resulting in the formation of complex pentacyclic products **I-119** in a single step (Scheme 1.19A).[77] The mechanism of this three-component annulation reaction involves the formation of a good conjugate acceptor by reacting **I-118** with formaldehyde, followed by initial dearomatisation of the quinoline and attack by an enamine via conjugate addition. Subsequent alkylation with formaldehyde yields **I-119**. In a related reaction, Zhang developed a Mannich/Friedel-Crafts cascade annulation of activated quinolines and

isoquinolines to produce complex azaarene products **I-126** and **I-127**.[78] The reaction mechanism involves the attack of an initial enamine species onto formaldehyde, followed by the loss of water and a conjugate reduction by a hydride equivalent to give methylated species **I-122**. The Schiff base **I-123** can then react either stepwise through enamine alkylation of the iminium or in a [4+2] cycloaddition to give intermediates **I-124** or **I-125**, respectively. The former can react to give **I-125** via a Friedel-Crafts type mechanism, while the latter directly collapses to give the product **I-126** through rearomatisation. This high-yielding protocol is broadly applicable to a wide range of substituted (iso)quinolines and anilines.

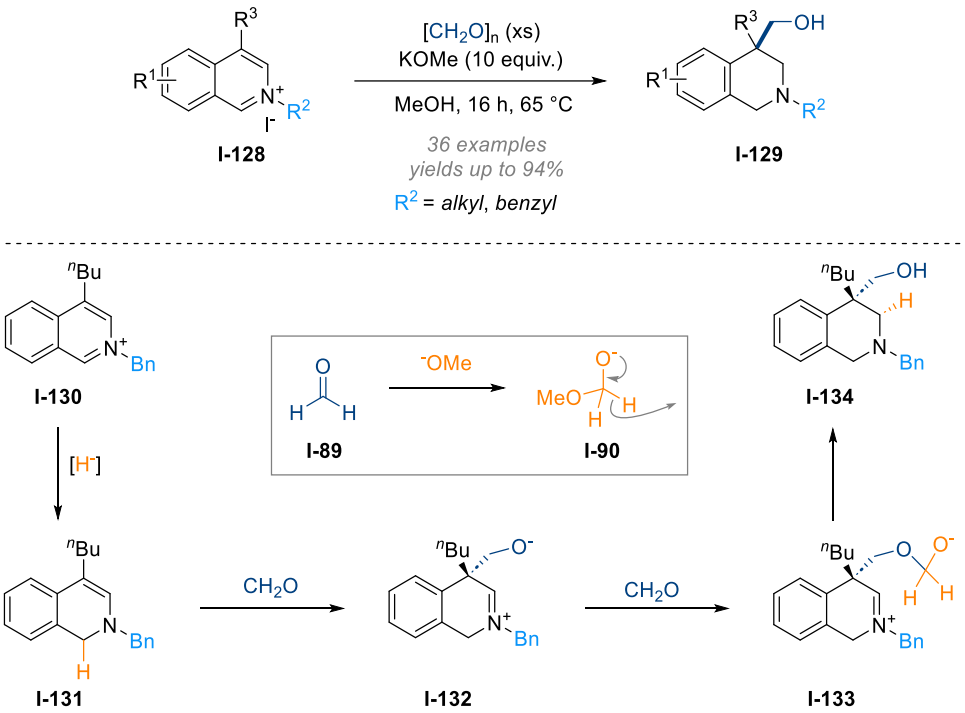


Scheme 1.19: A: Catalytic annulation of isoquinolines with 1,3-dicarbonyl compounds and formaldehyde (Zhang, 2021); B: Mannich-type annulations of activated quinolines and isoquinolines to form polycyclic azaarenes (Zhang, 2022).

1.3.2 Metal-free reactions

Recently, several reports have explored metal-free dearomative functionalisation as an alternative to methods involving transition metal catalysts. In 2019, our group published a new approach to C4 hydroxymethylation of activated isoquinolines, utilizing paraformaldehyde as both an electrophile and reducing agent (Scheme 1.20).[79] The reaction proceeds through a Cannizarro-type mechanism under strongly basic conditions, with a hydride being transferred from formaldehyde to attack the

arene. The final iminium **I-133** species is then reduced via a second hydride transfer from formaldehyde, the relative stereochemistry of hydride addition was proven using D-labelling experiments. Notably, C4 unsubstituted substrates undergo two sequential alkylation reactions, resulting in methyl/hydroxymethyl substitution at that position (R^3 = Me in Scheme 1.20).

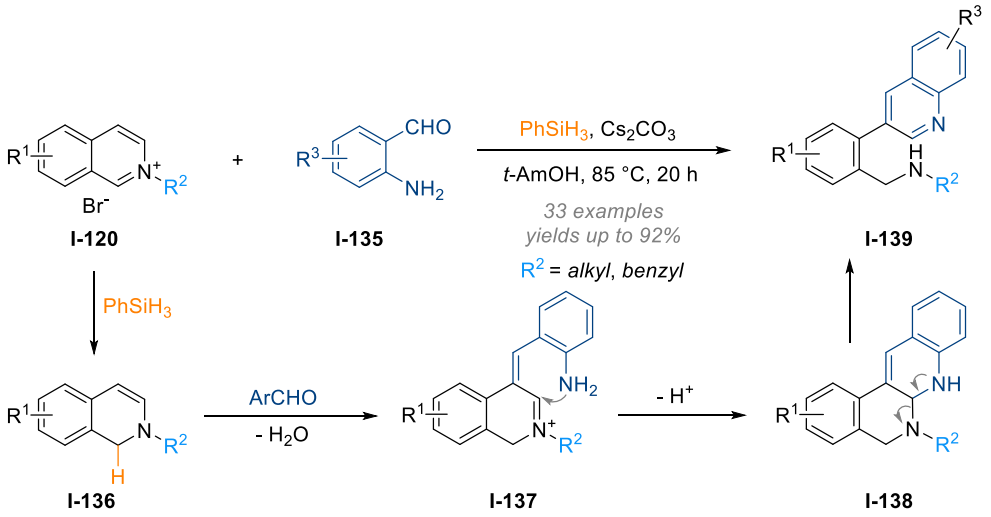


Scheme 1.20: Metal-free C4 hydroxymethylation of isoquinolinium salts with paraformaldehyde (Donohoe, 2019).

Both our and the Zhang group have subsequently gone on to develop metal-free reaction protocols enabling the reductive dearomative functionalisation of (iso)quinolines by employing non-electrophilic reducing agents. Pleasingly, this methodological shift has enabled the incorporation of a wider range of electrophiles by the reactive enamine intermediates. Our group's work in this area will be discussed later in this thesis (See Chapters 3, 4 and 5).

Zhang's group has reported a metal-free approach for the synthesis of 3-substituted quinolines via reductive deconstruction of activated isoquinolines **I-120** utilizing phenylsilane as the reductant under basic conditions (Scheme 1.21).[80] Mechanistically, the reaction proceeds through an initial hydride attack at C1 of the isoquinolinium to give enamine **I-136**, followed by aldol-type condensation onto the aromatic aldehyde **I-135** with concurrent loss of water. The resulting unsaturated iminium **I-137** is then intercepted by the *ortho*-aniline to form the aminal **I-138**, which readily collapses to rearomatize

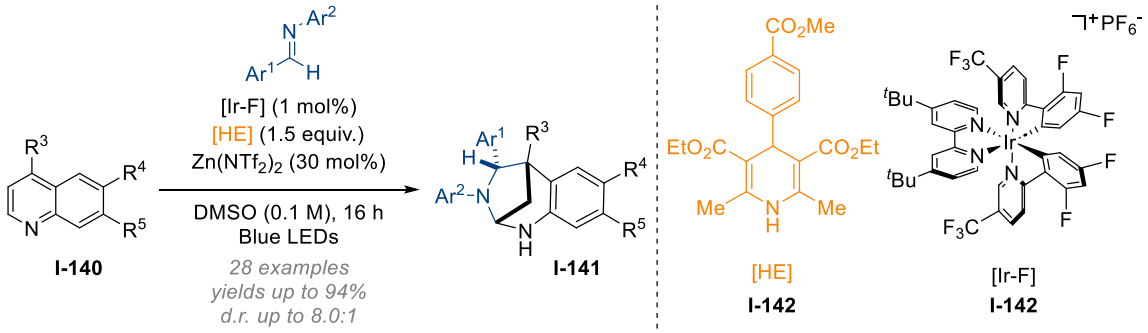
the newly formed quinoline core and form **I-139**. The protocol exhibited a broad functional group tolerance for all three residues, resulting in generally good isolation yields of rearranged quinolines.



Scheme 1.21: Metal-free deconstruction of isoquinolinium salts for the synthesis of C3 arylquinolines (Zhang, 2022).

1.3.3 Photoredox initiated dearomative reductive functionalisation

In recent years, the use of photoredox catalysis for accomplishing dearomative functionalisation via (formal) cycloaddition transformations, has attracted significant attention in the field. The unique reactivity patterns of the high-energy intermediates generated via visible-light-induced excitation have opened new opportunities for the rapid construction of molecular complexity and topology, which are otherwise not easily achieved by known ground-state transformations. The Dixon group has contributed to this area of research by developing an interrupted dearomative Minisci reaction of quinolines with imines (Scheme 1.22).[81] This transformation involves the photocatalytic construction of bridged 1,3-diazepanes via radical addition to the C4-position of the 4-substituted quinoline substrates **I-140**. Subsequently, Hantzsch ester **I-142** promoted reduction gives dihydropyridine intermediates which undergo a two-electron ring closure to form the bridged diazepane core **I-141**. Good efficiency in the construction of sterically congested quaternary centres was observed in this transformation, alongside a generally wide scope of *N*-arylimine and quinoline derivatives.



Scheme 1.22: Dearomative photoredox catalysed intermolecular cycloaddition of quinolines. (Dixon, 2020).

1.4 General research aims

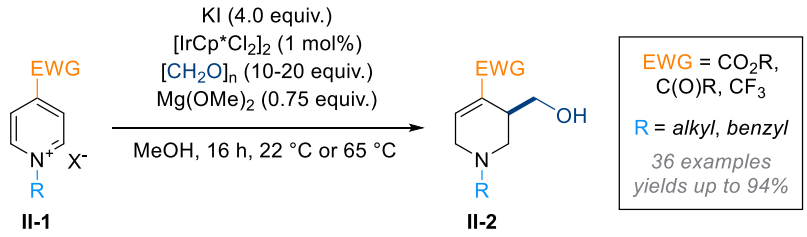
Although significant progress has been made in the field of dearomative functionalisation reactions of azaarenes, it is clear that there are still significant challenges in the way of developing such processes. These limitations primarily stem from the requirement for pre-activating substrates and the constraints imposed by reaction conditions and functional group compatibility. Consequently, these limit the chemical space that can be explored using dearomative functionalization, restricting both the starting materials that can be used and the range of functionalities that can be incorporated into the dearomatized products.

The aim of the research described in this thesis was to develop new more general approaches for the dearomative reductive functionalisation of a range of 6-membered azaarenes. The initial focus of our work was on the development of a single point activation strategy, inspired by previous work conducted in our group, to enable the use of a broader range of electronically diverse pyridines in the reductive hydroxymethylation. Building upon these foundations, our subsequent efforts aimed to expand the scope of electrophiles that could be incorporated into the dearomatized *N*-heterocycles. This broader scope would establish a more general methodology for the reductive functionalization of pyridines, quinolines, and isoquinolines.

Chapter 2: Single-point activation strategy for the reductive hydroxymethylation of pyridines

2.1 Introduction

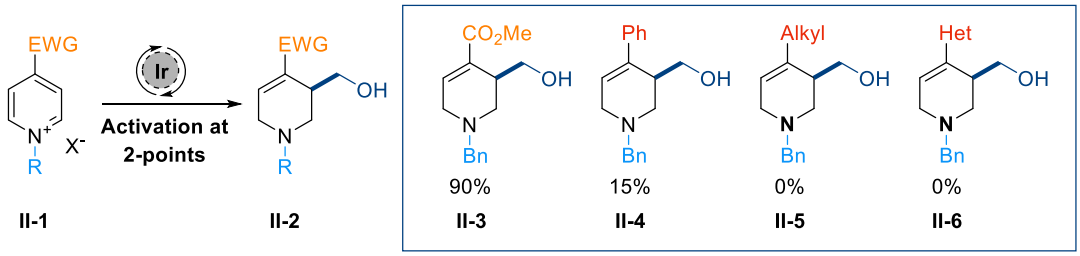
The Donohoe group previously developed an iridium-catalysed interrupted transfer hydrogenation reaction that leads to the reductive hydroxymethylation of pyridines.[74,82] In addition to the formation of two new C–H bonds, a new C–C bond is concurrently formed in a single synthetic step under these reaction conditions (Scheme 2.1).



Scheme 2.1: Iridium-catalysed reductive hydroxymethylation of pyridines (Donohoe 2019)

The successful activation of pyridine substrates can be achieved through (i) the quaternisation of the nitrogen atom, and (ii) the presence of an electron-withdrawing group (EWG) at the 4-position of the pyridine to form a highly electron deficient pyridinium salt, and is crucial to facilitate the initial dearomatisation reaction. The 4-substituent also plays a role in the prevention of (i) initial reduction occurring at C4 and (ii) over reduction *in situ*, resulting exclusively in the desired initiation at the C2-position. Whilst the early work pioneered the 3-hydroxymethylation of pyridines, the presence of an EWG on the *C*4-position presented a substantial limitation to the scope of pyridines that could be hydroxymethylated. While ketones, esters and trifluoromethyl groups are generally well tolerated, less electron-withdrawing functionalities either completely shut down the reaction or gave the corresponding tetrahydropyridines in low yields (Scheme 2.2). The 4-phenyl substituted pyridine substrate, for example, gave low yields of **II-4** under both iridium (15%) and ruthenium (27%) catalysed conditions. Furthermore, alkyl and heteroatom substituted pyridines were completely inert

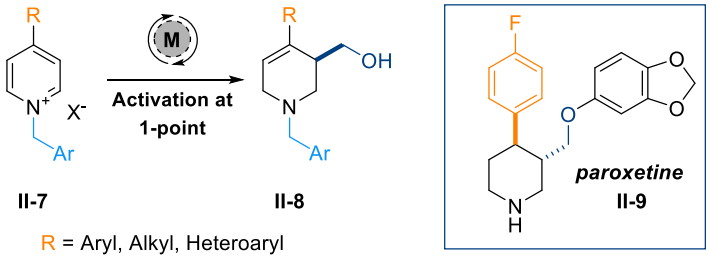
with respect to the reaction conditions. Alkyl substituents were particularly challenging, since the deprotonation of acidic protons led to undesired side-reactions.



Scheme 2.2: Effect of the C4-substituent on the yield of the reductive hydroxymethilation of activated pyridines

2.2 Project aim

In order to address this limitation, we aimed to develop a single point activation strategy that would enable the use of a more electronically diverse set of pyridines, such as, e.g. 4-phenyl pyridine. 4-Aryl substituents were of particular interest as this structural motif is frequently found in small-molecules with therapeutic applications, such as e.g. the antidepressant drug paroxetine (Scheme 2.3).



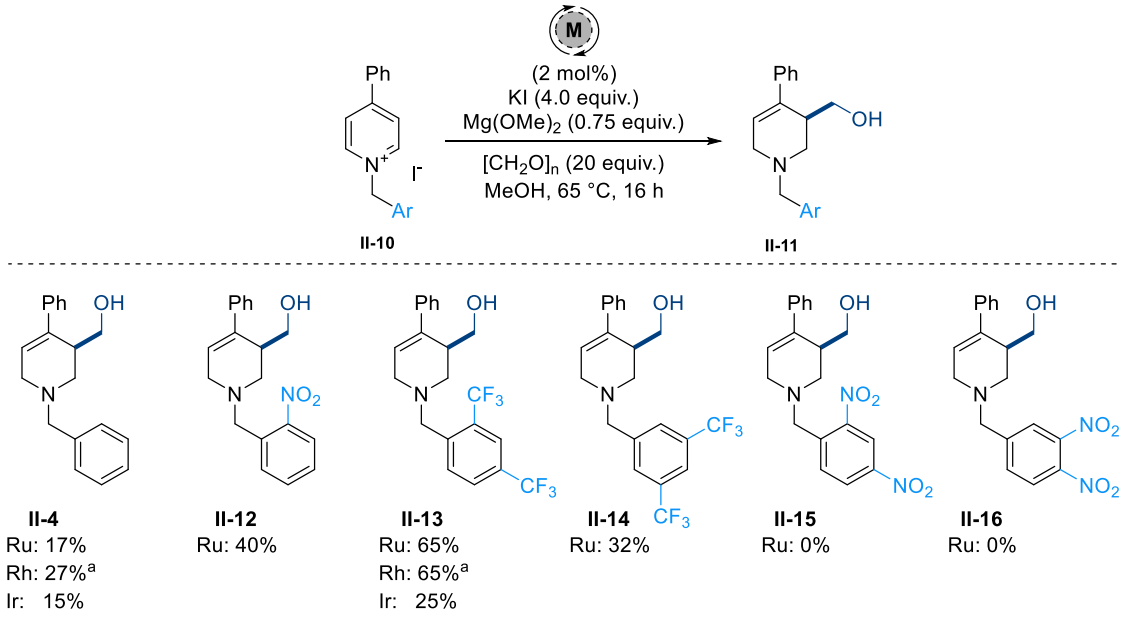
Scheme 2.3: Single point activation of pyridines

2.3 Reaction development

2.3.1 Screening of the activating groups

In order to allow for the use of more electron-rich pyridines in the envisaged hydroxymethylation reaction, we postulated that single point activation of pyridines could be enabled by shifting all of the electron-withdrawing properties solely onto the nature of *N*-activating group.[60] Furthermore, the early analyses of crude reaction mixtures suggested that the troublesome step was the initial dearomative addition of a metal hydride to the C2-position of the starting pyridine. Therefore, we elected to use metals with stronger reductive profiles, such as rhodium and ruthenium, hoping that these would help facilitate the initial *C*2 reduction.[83] In the initial experiments,

N-benzyl-4-phenylpyridinium iodide **II-10** was used as a test substrate (Scheme 2.4). The pyridinium iodide **II-10** was prepared in a single step by reacting the parent 4-phenylpyridine with benzyl iodide following a standard procedure (Chapter 6). The desired products could be easily identified by the disappearance of the high δ aromatic pyridinium peaks in the ^{1}H NMR and the presence of the new exocyclic -CH_2OH peaks between 3.6 and 3.8 ppm. Pleasingly, under both rhodium (27%) and ruthenium (17%) catalysis, the isolated chemical yields of **II-4** were higher compared to that of iridium-catalysed process (15%). To further increase the electron deficiency of the pyridine system, whilst maintaining quaternisation as the single mode of activation, we prepared analogous substrates bearing electron-deficient benzyl groups and subjected them to the outlined metal-catalysed conditions.



Ru = $[Ru(p\text{-cymene})Cl_2]_2$, Ir = $[IrCp^*Cl_2]_2$, Rh = $[RhCp^*Cl_2]_2$, [a]In absence of KI

Scheme 2.4: Screening of different activating groups

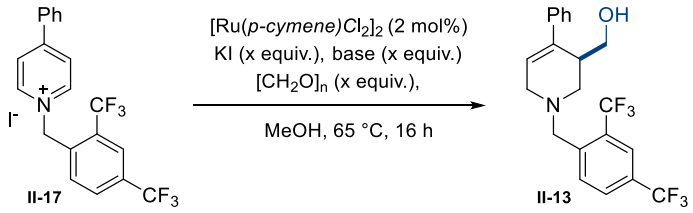
Using $[Ru(p\text{-cymene})Cl_2]_2$ as the pre-catalyst, the 2-nitrobenzyl substrate gave the desired product **II-12** in an improved yield (40%). Both, the 2,4-bistrifluoromethyl and the 3,5-bistrifluoromethyl substrate also furnished the desired products **II-13** and **II-14** in higher yields of 65% and 32%, respectively. Encouraged by the positive correlation between the electron withdrawing ability of the *N*-activating group and the reaction yield, we prepared pyridinium salts activated using benzyl groups bearing two nitro groups each. Unfortunately, these salts proved to be unstable both on standing in

air and under the reaction conditions. When these were subjected to our reaction conditions, no desired products were observed, and the major product of the reaction was the parent pyridine. The 2,4-bistrifluoromethlybenzyl activating group was thus selected as the substitutent with the most optimal balance between reactivity and stability. As expected, $[IrCp^*Cl_2]_2$ was found to generate a far less proficient catalytic species, delivering **II-13** in only 25% yield. Finally, as $[RhCp^*Cl_2]_2$ was also found to deliver **II-13** in a good yield (65%), we opted to continue working with the ruthenium catalyst as it was substantially less expensive compared to the iridium-based reagent.

2.3.2 Reaction optimisation

Substrate **II-17** was taken as a model substrate and subjected to further optimisation and screening (Table 1). We initiated the optimisation by looking at the role of KI, since the importance of iodide ions in similar processes is well demonstrated in the literature.[84,85] Relative to our initial reaction conditions utilising 4 equivalents of KI, decreasing its loading to 2 equivalents (60%, entry 2) and the absence of any KI (40%, entry 3), both lead to a reduced yield of **II-13**. Additionally, using the $[Ru(p\text{-cymene})I_2]_2$ pre-catalyst in the absence of KI did not significantly increase the yield (42%, entry 4), suggesting that simply replacing the counterion is not sufficient to improve the yields, and that the saturation of the active catalyst with iodide counter ions is likely most important factor. Interestingly, increasing the loading of KI to 6 equivalents (entry 5) also lead to a decrease in yield to 50%, most likely due to the increased heterogeneity of the reaction mixture. Finally, using the bromide salt of **II-17** as the substrate, instead of the iodide salt, also led to a slight decrease in yield (61%, entry 6). Using potassium methoxide as the base resulted in a significant drop in yield of **II-13** to 24% (entry 7). Magnesium methoxide loading proved to be crucial with one equivalent increasing the yield to 70% (entries 8-10). A similar trend was observed with paraformaldehyde loading as well, with 30 equivalents increasing the NMR yield of **II-13** to 72% and the isolated yield to 69% (entries 11 and 12, respectively). The addition of an excess of formaldehyde was necessary in order to ensure compete conversion of the enamine formed *in situ*.

Table 2.1: Optimisation of Reaction Conditions



Entry	KI equiv.	$[CH_2O]_n$ equiv.	Base	Base equiv.	Yield of **II-13** (%)[a]
1	4	20	$Mg(OMe)_2$	0.75	65
2	2	20	$Mg(OMe)_2$	0.75	60
3	0	20	$Mg(OMe)_2$	0.75	40
4[b]	0	20	$Mg(OMe)_2$	0.75	42
5	6	20	$Mg(OMe)_2$	0.75	50
6[c]	4	20	$Mg(OMe)_2$	0.75	61
7	4	20	KOMe	1.5	24
8	4	20	$Mg(OMe)_2$	0.5	64
9	4	20	$Mg(OMe)_2$	1.0	70
10	4	20	$Mg(OMe)_2$	2.0	70
11	4	10	$Mg(OMe)_2$	1.0	65
12	**4**	**30**	**$Mg(OMe)_2$**	**1.0**	**72 (69)[d]**

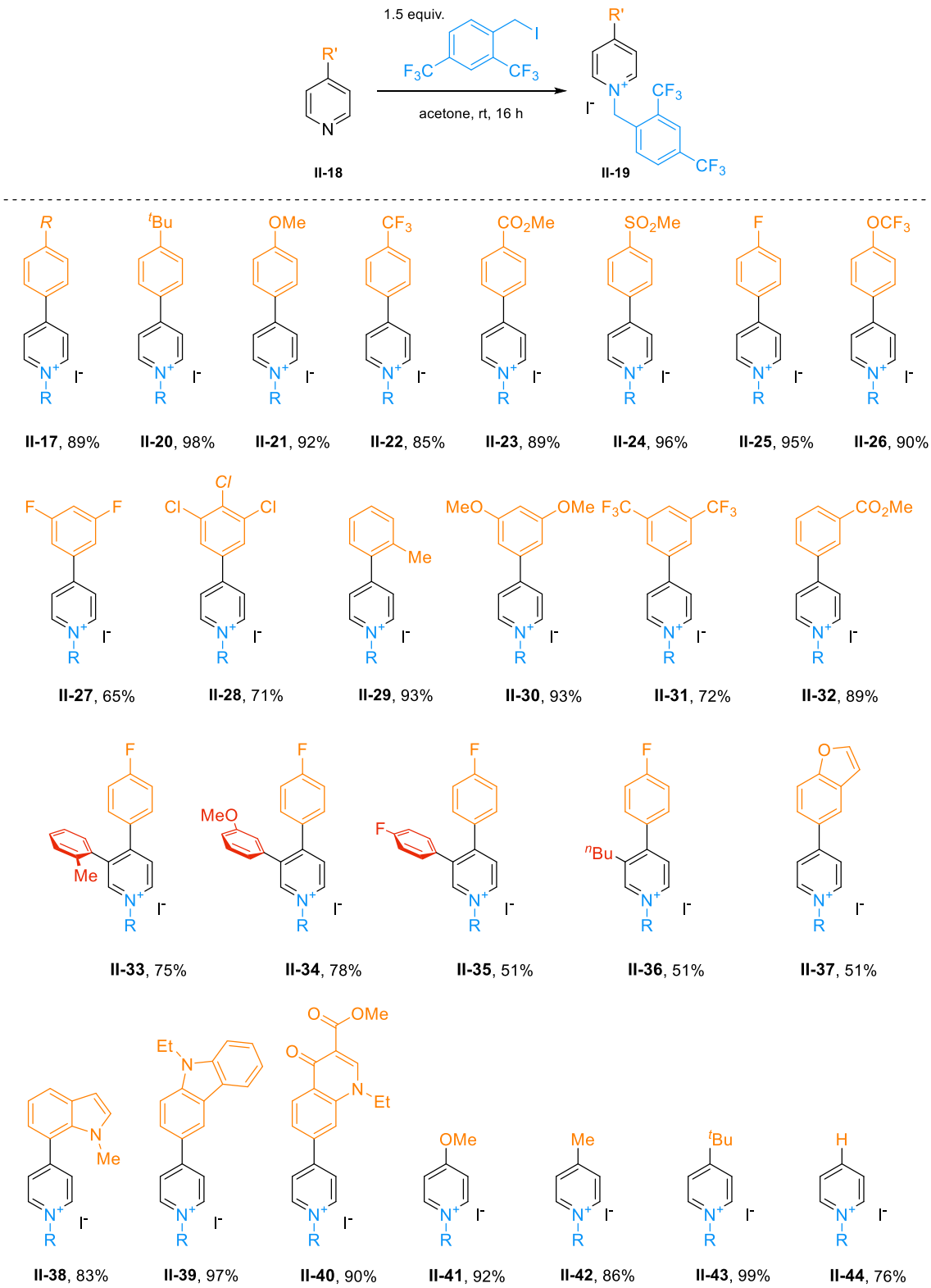
[a]^{1}H NMR yield using trimethoxybenzene as an internal standard, [b]$[Ru(p\text{-cymene})I_2]_2$ as catalyst, [c]Using the bromide salt of **II-17**, [d]isolated yield

2.4 Scope of the reaction

2.4.1 Preparation of the requisite starting materials

With the optimal *N*-activating group and reaction conditions in hand, a range of 4-aryl substituted pyridinium salts **II-19** were next prepared in one step from 2,4-bistrifluoromethylbenzyl iodide and the corresponding pyridine **II-18** (Scheme 2.5). Overall, most of the salts were prepared in excellent

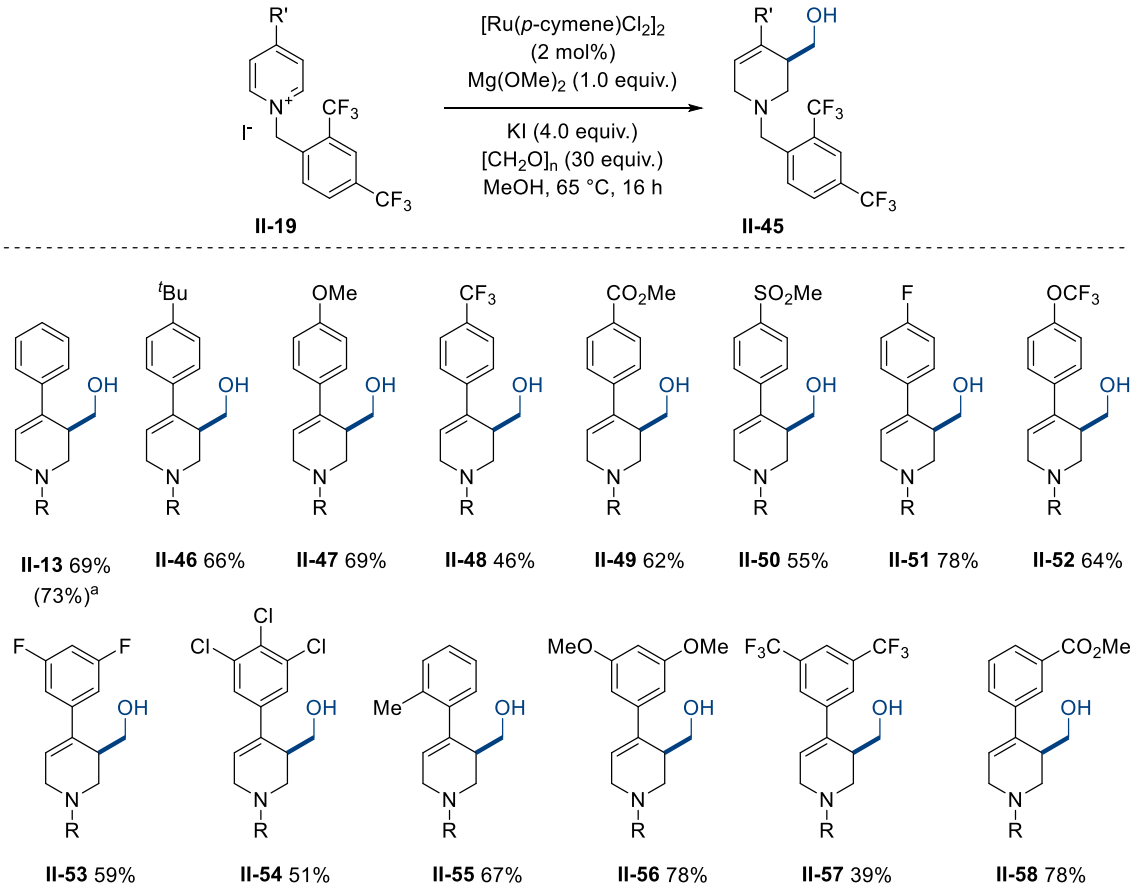
yields (>80%); the few lower yields could usually be attributed to either the reaction being performed on a smaller scale (**II-35** to **II-37**) or incomplete conversion overnight.



Scheme 2.5: Starting material synthesis

2.4.2 4-Aryl substituted pyridinium salts

We started off by exploring the scope of 4-aryl pyridinium salts (Scheme 2.6). The model 4-phenylpyridinium substrate **II-17** gave the product **II-13** in 69% yield. Pleasingly, scaling this reaction to 3 mmol led to the formation of **II-13** in an increased yield of 73%. We found that electron donating groups were also well tolerated under the explored conditions; *tert*-butyl (**II-46**, 66%), methoxy (**II-47**, 69%) and methyl (**II-55**, 67%). Similarly, mildly electron withdrawing groups such as e.g. fluoro (**II-51**, 78%), methyl ester (**II-49**, 62% and **II-58**, 78%), and trifluoromethoxy (**II-52**, 64%), all gave the products in similar yields. On the C4 aromatic group, substitution was tolerated at the *ortho*, *meta*, and *para* positions, as well as 3,5-disubstitution (**II-53**, 59%, **II-56**, 78% and **II-57**, 39%) and 3,4,5-trisubstitution (**II-54**, 51%). Significant drops in yield were only observed with substrates bearing strongly electron withdrawing groups such as e.g. trifluoromethyl (**II-48**, 46%), and substrates bearing multiple EWG's (**II-54** and **II-57**).



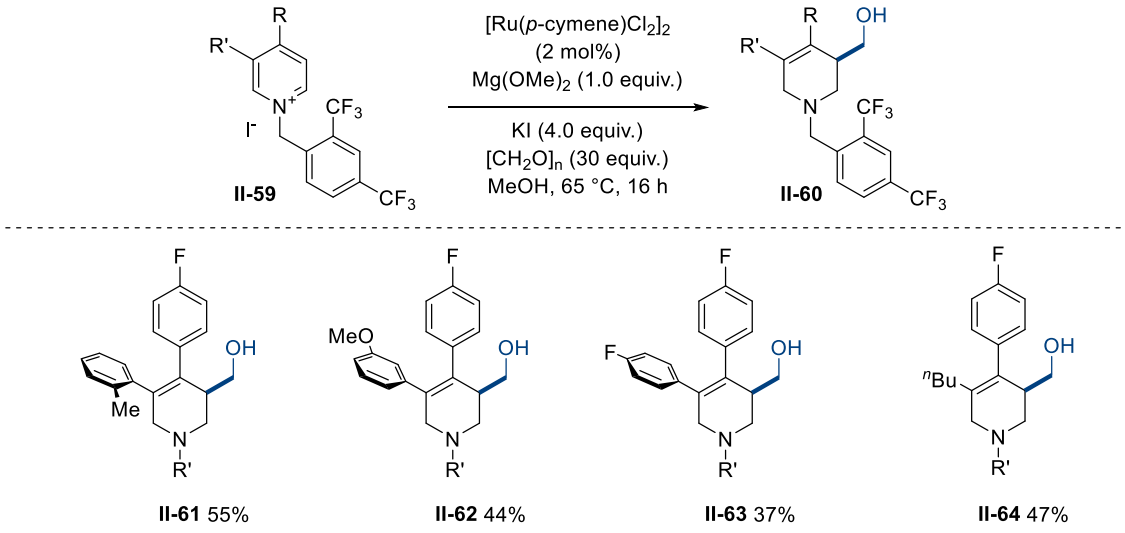
[a]reaction done on 3 mmol scale

Scheme 2.6: 4-Aryl substituted pyridine scope

Of note, substrate **II-51** bearing a 4-fluorophenyl group, a structural motif present in paroxetine, gave the desired product in 78% yield, and was subsequently used as a key intermediate in the total synthesis of (±)-paroxetine **II-9**, *vide infra*.

2.4.3 3,4-Disubstituted pyridinium salts

Additionally, we have successfully determined that the substitution at the 3-position of the pyridine is also tolerated, however, the hydroxymethylated products were obtained in lower yet still synthetically useful yields (Scheme 2.7). In this position aromatic groups bearing *ortho* (**II-61**, 55%), *meta* (**II-62**, 44%), and *para* (**II-63**, 37%) substitution along with a *n*-butyl group (**II-64**, 47%) all appeared to be viable substrates.

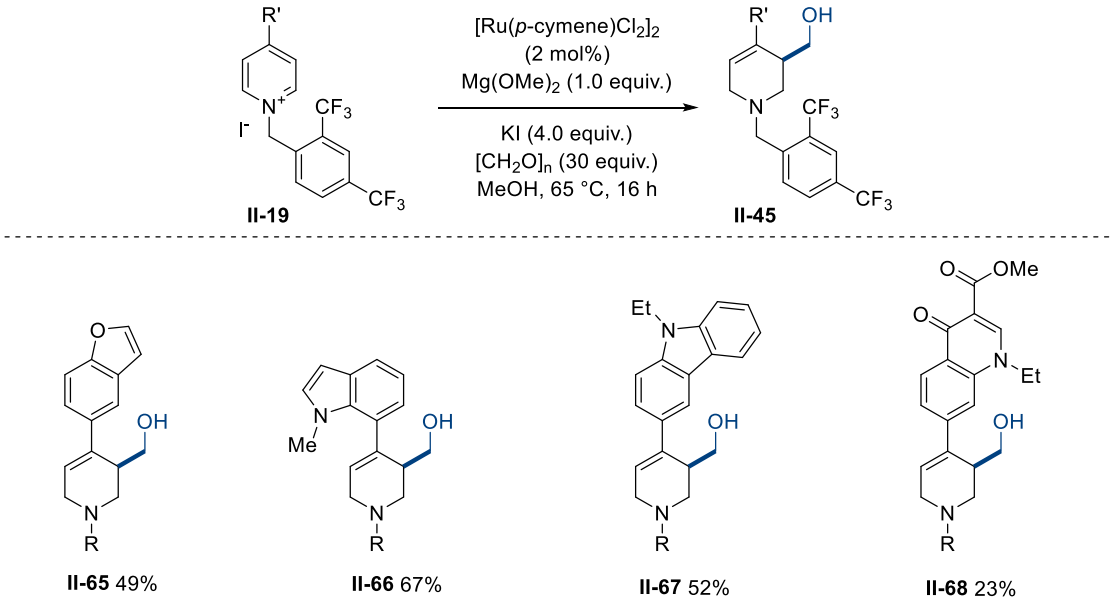


Scheme 2.7: 3,4-Disubstituted pyridine scope

2.4.4 4-Heteroaryl substituted pyridinium salts

The single point activation strategy was then extended further to enable the use of 4-heteroaryl substituted pyridines. These electron rich substrates are completely inactive when using the standard *N*-benzyl activating strategies, which shows the importance of the electron withdrawing nature of *N*-2,4-bistrifluoromethylbenzyl derivative described herein (Scheme 2.8). Pyridinium salts bearing benzofuran (**II-37**), indole (**II-38**), and carbazole (**II-39**) at the C4-position, all reacted successfully to give the corresponding hydroxymethylated products **II-65** (49%), **II-66** (67%), and **II-67** (52%) in good yields. Importantly, these results highlight the ability of this methodology to selectively activate and functionalise pyridines in the presence of other heterocycles. Finally, the

N-2,4-bistrifluoromethylbenzyl salt of Rosoxacin ethyl ester **II-40**, a commercially available quinoline antibiotic, was subjected to the reaction conditions. The desired product **II-68** was isolated in an 23% yield, thus demonstrating that late-stage functionalisation of pharmaceutically highly significant molecules can be achieved using this methodology.

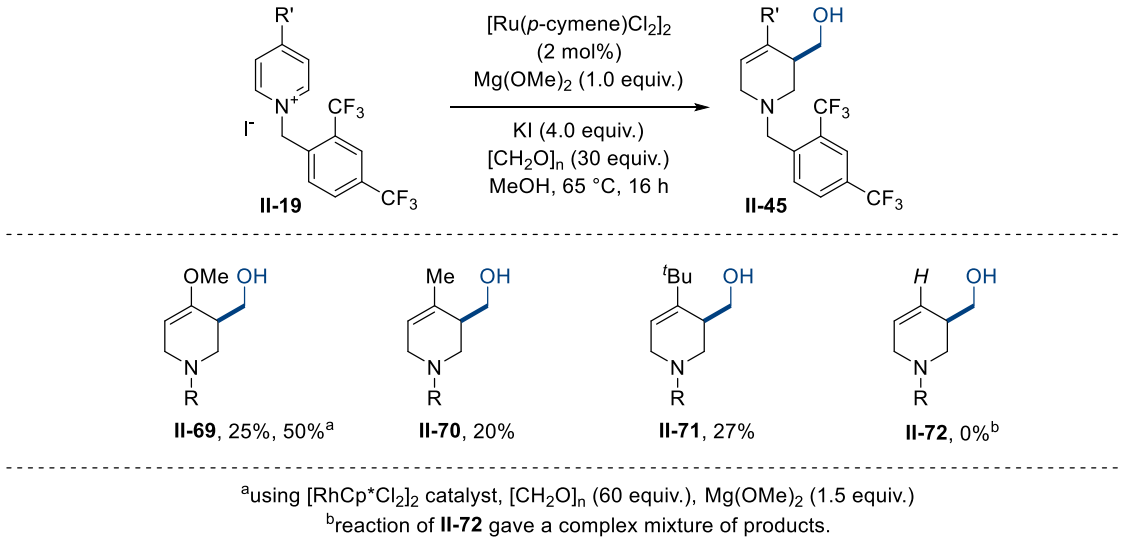


Scheme 2.8: Scope of 4-heteroaryl substituted pyridines

2.4.5 4-Alkyl and 4-alkoxy substituted pyridinium salts

To our delight, the highly electron-rich 4-methoxypyridine was successfully activated using our methodology to give enol ether **II-69** in a 25% yield (Scheme 2.9). A short re-optimisation of conditions was required in this case; by switching to the $[RhCp^*Cl_2]_2$ pre-catalyst and simply increasing both the paraformaldehyde loading and base equivalents, the yield of the desired product **II-69** could be increased to 50%. While the corresponding 4-alkyl substituted products **II-70** and **II-71**, bearing a methyl and *tert*-butyl group respectively, were also formed under these conditions, the isolated yields were only 20% and 27%, respectively. The combined effects of the acidity of the 4-methyl protons and the strongly basic reaction conditions resulted in the formation of unwanted by-products, ultimately lowering the yield of the desired product. We have also postulated that the substantial steric bulk of the *tert*-butyl group interfering with the enamine trapping the desired electrophile, could account for the observed decrease in the reaction yield. However, despite these lower yields, we were able, for the very first time, to demonstrate a proof of concept that simple C4

alkyl-substituted pyridines can now be utilised using this methodology, something that was previously synthetically unviable. Unfortunately, a substrate lacking a 4-substituent (**II-44**) did not undergo the hydroxymethylation reaction successfully and gave complex mixtures of products, indicating that a C4 substituent is still necessary for the desired reactivity.

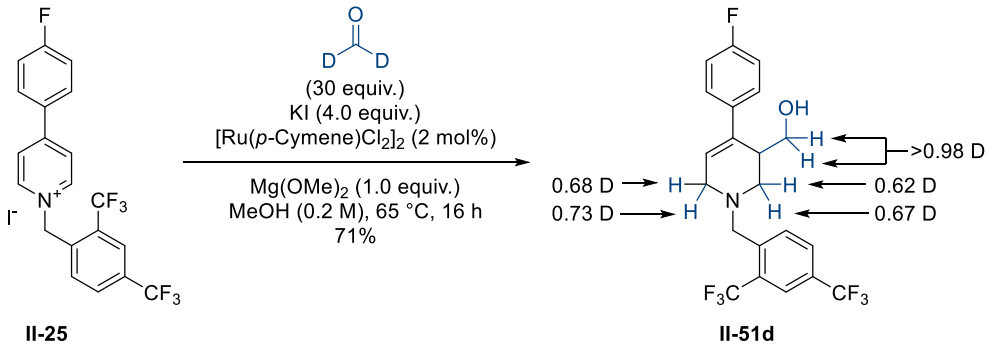


Scheme 2.9: Scope of 4-methoxy and 4-alkyl substrates

2.5 Mechanistic studies

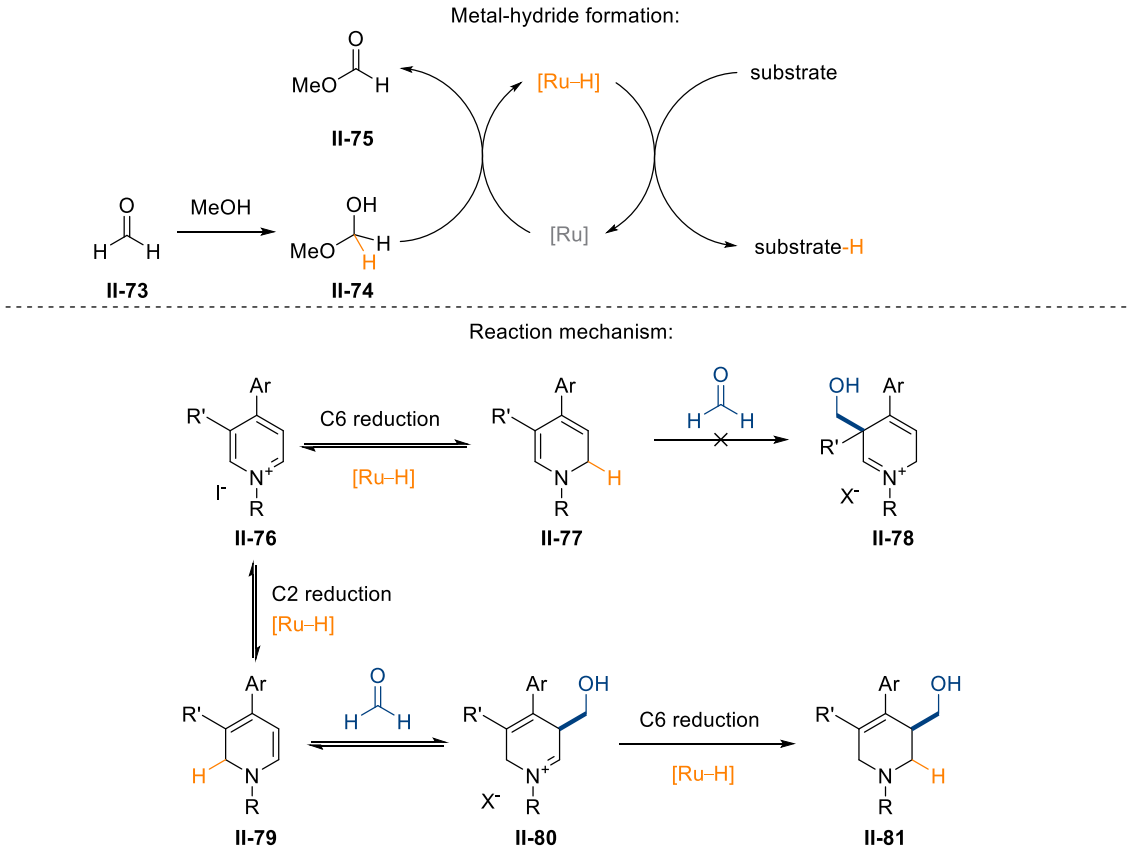
2.5.1 Deuterium labelling

In order to probe the mechanism of the reaction we have subjected **II-25** to the reaction using deuterated paraformaldehyde $[CD_2O]_n$ (Scheme 10). The resulting deuterated product **II-51d** was analysed using ^1H NMR to determine the levels of D incorporation as well as ^2H NMR. Of note, the D incorporation at the C2 and C6 positions was greater than 1 D (1.41 D and 1.29 D respectively), indicating a reversible initial reduction. The complete D incorporation at the exocyclic hydroxymethyl position indicated that no substantial oxidation of the solvent methanol is occurring under these reaction conditions. Furthermore, the observed deuterium incorporation was completely consistent with previous observations made in our group.[74] The high levels of D-incorporation at C2, C6 and the complete incorporation in the exocyclic hydroxymethyl group of the paroxetine core provided a convenient method to access deuterated paroxetine, if so desired.



Scheme 2.10: Deuterium labelling experiment to prepare the core of paroxetine

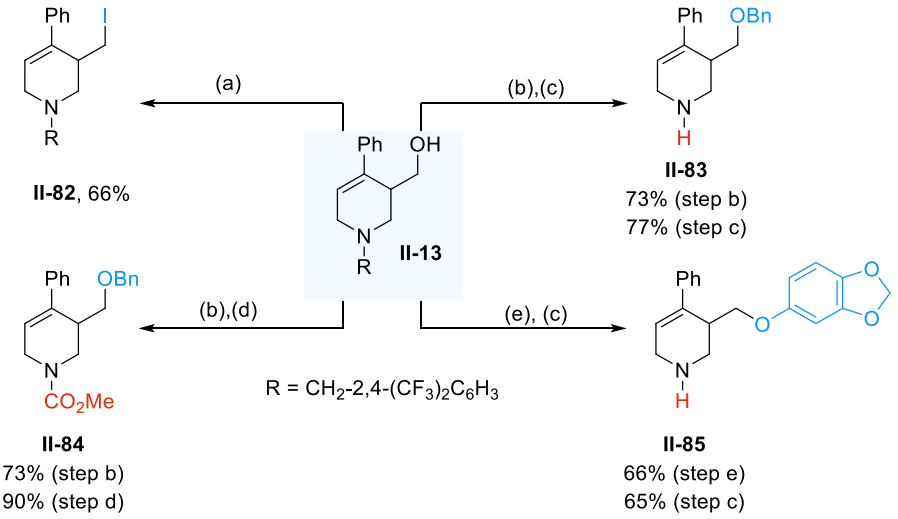
The reaction is thought to proceed *via* the same pathway previously reported in our group, with formaldehyde serving as both the electrophile and source of hydride (Scheme 11).[74] Oxidation of the hemiacetal **II-74** (formed when a molecule of methanol attacks formaldehyde) to methyl formate, furnishes the ruthenium hydride. Reduction can then occur on either C6-or C2-position, with the former forming the inactive enamine **II-77** which can be re-oxidised back to the starting material. Reduction at C2 forms the reactive enamine **II-79** that then goes on to trap formaldehyde to give iminium ion **II-80**. Another reduction at C6 then generates the final product **II-81**.



Scheme 2.11: Proposed reaction mechanism of the reductive hydroxymethylation

2.6 Derivatisation of products

A variety of synthetic transformations were explored to highlight the chemical versatility of the products prepared (Scheme 2.12). Using **II-13** as the model substrate, the hydroxymethyl group could be transformed to the alkyl iodide **II-82** via an Appel reaction in 66% yield. Importantly, removal of the electron-deficient *N*-benzyl group was achieved using sequential: (i) benzyl protection of the free –OH group followed by (ii) treatment with 1-chloroethyl chloroformate (ACE–Cl) and the cleavage of the resulting intermediate with methanol. This protocol afforded the free amine **II-83** in 56% yield over two steps. Using methyl chloroformate in place of the ACE–Cl resulted in a protecting group switch, giving the corresponding carbamate **II-84** in 66% yield over two steps. Alternatively, using a Mitsunobu reaction to install an aryl group, followed by cleavage of the activating group (as described above) could also deliver the corresponding free amine **II-85** in 43% yield over two steps. The successfully implemented synthetic manipulations highlight the potential of this methodology for the further functionalisation of our intermediated into a wide array of products, which can then be converted into highly useful small molecules, such as e.g. (±)-paroxetine.



(a) PPh_3 (2.2 equiv.), I_2 (2.2 equiv.), imidazole (2.5 equiv.) CH_2Cl_2, 0 °C to r.t, 2 h; (b) NaH (10 equiv.), 15-crown-5 (2.0 equiv.), BnBr (10 equiv.), 0 °C to r.t., 2 h; (c) 1-chloroethyl chloroformate (8.0 equiv.), DCE, 120 °C, 16 h then MeOH, 65 °C, 4 h. (d) methyl chloroformate (8.0 equiv.), DCE, 120 °C, 16 h; (e) PPh_3 (1.2 equiv.), sesamol (2.0 equiv.), DIAD (1.2 equiv.), THF, 0→50 °C, 2 h.

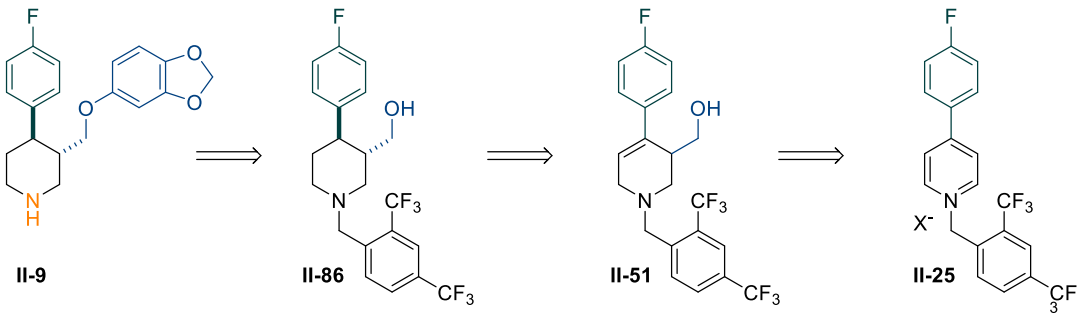
Scheme 2.12: Derivatisations of the model substrate ***II-13***

2.7 Total synthesis of (±)-paroxetine

In order to demonstrate the synthetic utility of the developed methodology, we opted to prepare (±)-paroxetine, a selective serotonin reuptake inhibitor used as a pharmaceutical drug to treat a variety of medical conditions (e.g.: Major Depressive Disorder and Anxiety disorders).[86]

2.7.1 Retrosynthetic analysis

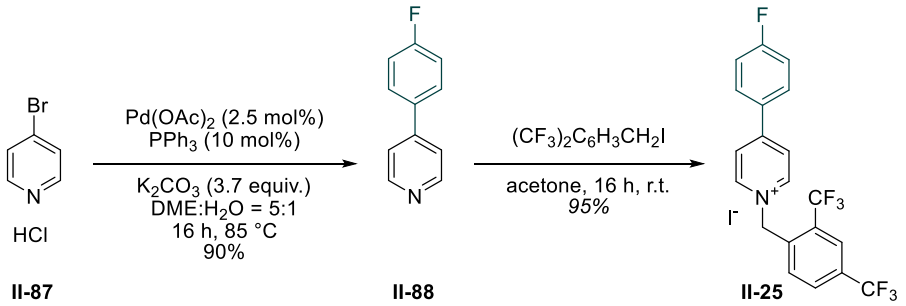
Starting from the paroxetine skeleton, the retrosynthetic analysis begins with a simple deprotection and Mitsunobu sequence. We envisioned setting the requisite relative stereochemistry via a hydroxyl group directed hydrogenation reaction. Finally, the key dearomative hydroxymethylation takes us back to the pyridinium salt **II-25**, which can be prepared in one simple step from the parent pyridine using the established methodology (Scheme 2.13).



Scheme 2.13: Retrosynthetic analysis of paroxetine

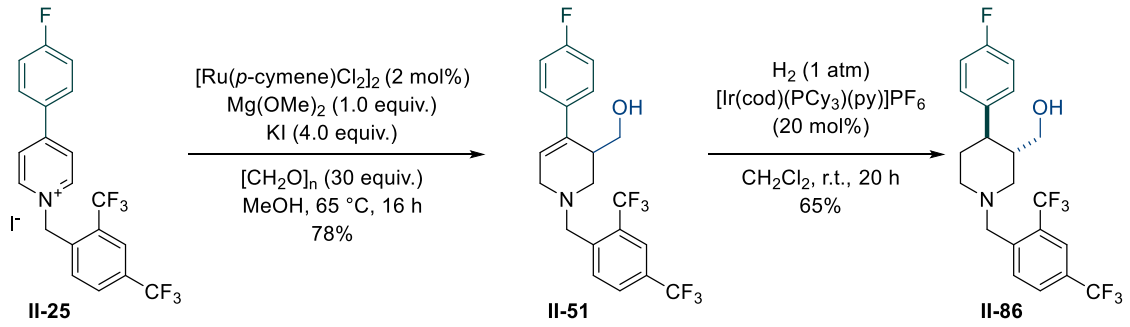
2.7.2 Forward synthesis of (±)-paroxetine

Starting from commercially available 4-bromopyridine hydrochloride, a Suzuki coupling reaction gave the 4-aryl pyridine **II-88** in an excellent yield (90%). Similarly, the subsequent nitrogen quarterisation using the 2,4-bistrifluoromethylbenzyl iodide also proceeded in excellent yield (95%) (Scheme 2.14).



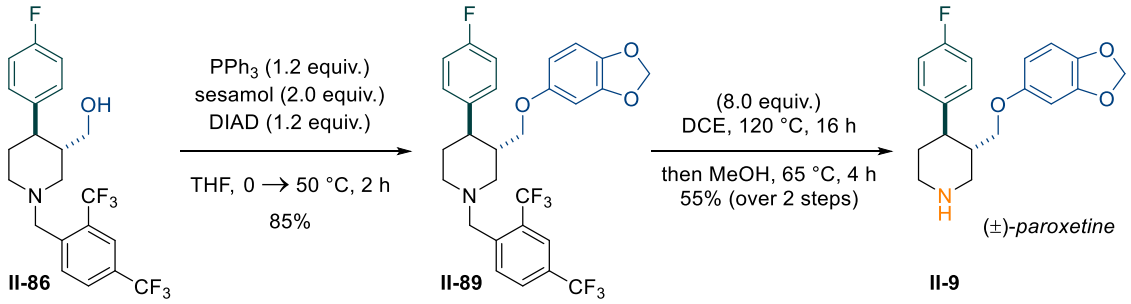
*Scheme 2.14: Preparation of the parent pyridinium salt **II-25***

Following the preparation of the parent pyridinium salt **II-25**, the key dearomative hydroxymethylation gave the desired tetrahydro piperidine **II-51** in 78% yield (Scheme 2.15). Paroxitane could then be prepared from key intermediate **II-51** in three simple synthetic steps. First, using Crabtree's catalyst, a substrate-controlled hydrogenation gave piperidine **II-86**, 3:1 d.r. in crude, after purification the trans-isomer was isolated in 65% yield. The relative stereochemistry was determined using a NOESY experiment where a correlation could be seen between the exocyclic CH_2 and the adjacent benzylic CH (for detailed NOESY analysis see Chapter 6: Experimental details).



Scheme 2.15: Key dearomative hydroxymethylation and stereoselective hydrogenation

Following a Mitsunobu reaction (84%) to give **II-89**, the synthesis was completed by cleavage of the activating group using 1-chloroethyl chloroformate in methanol to give (±)-paroxetine **II-9** in 55% yield (Scheme 2.16). The spectroscopic data matched the report from Carreira *et al* (for detailed comparison see Chapter 6).[87]



Scheme 2.16: Final functional group interconversions

To summarise, we have successfully prepared (±)-paroxetine in only 6 steps and an overall yield of 20%, starting from 4-bromopyridine hydrochloride.

2.8 Conclusion

In conclusion, we have developed a new catalytic system and using a new 2,4-bistrifluoromethylbenzyl-based activating group shifted the boundaries of the dearomative hydroxymethylation reaction. We successfully expanded the substrate scope far beyond what was possible when this project was initiated. Ranging from 4-arylpyridines to the electron-rich 4-methoxypyridine, the dearomative hydroxymethylation proceeded in good yields for the vast majority of substrates. Finally, we have demonstrated the broad synthetic utility of our methodology with a synthesis of (±)-paroxetine, and are confident that this strategy could be used to prepare a wide array of other pharmaceutically relevant small-molecules.

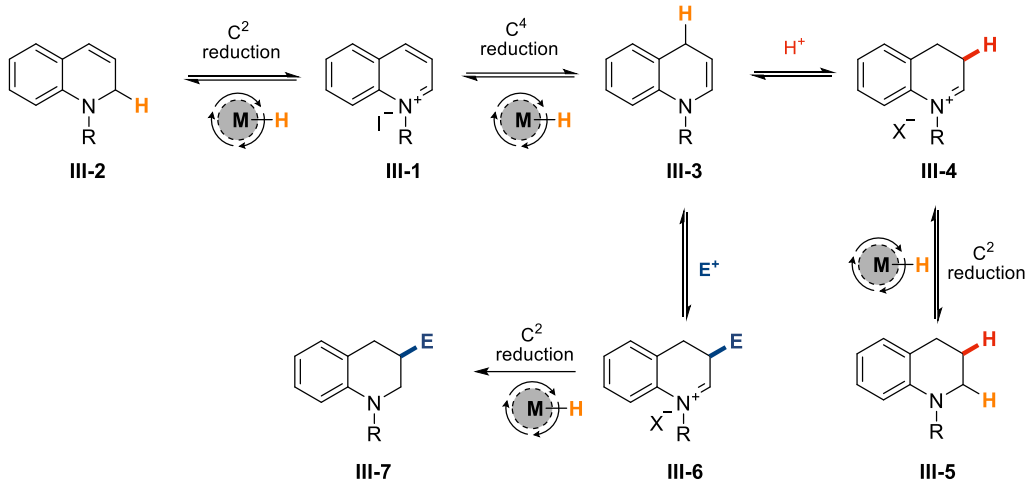
Chapter 3: Expanding the scope of electrophiles in the reductive functionalisation reactions of quinolines

3.1 Introduction

In the Donohoe group, we have recently developed a reductive hydroxymethylation reaction of activated pyridinium and quinolinium salts under iridium catalysis by harnessing formaldehyde as both an electrophile and the terminal reductant.[74] Mechanistically, such reactions proceed *via* an iridium-hydride reduction of the arene to form an enamine intermediate, which then goes on to trap a molecule of formaldehyde. Reduction of the resultant iminium ion by another iridium-hydride species then furnishes the desired dearomatised and hydroxymethylated product. The iridium hydride species is generated by an iridium-catalysed oxidation of the hemi-acetal formed *in situ* through the addition of methanol to a molecule of formaldehyde, thus forming methyl formate species. Formaldehyde as such, has an essential and dual role in this reaction, as it acts as both the electrophile and the source of hydride. However, due to the high electrophilicity and sheer excess of formaldehyde (20-30 equiv.) used in the reaction, no other electrophiles could be employed in this reaction, all our attempts at introducing other electrophiles were unsuccessful with only hydroxymethylated products observed in the reaction mixtures. This presented a significant limitation in the chemical space available to us. Furthermore, substrates bearing groups with acidic protons, especially e.g.: C2-alkyl substituted quinolines and C1-/C3-alkyl substituted isoquinolines, were incompatible with the strongly basic conditions required in this methodology.[79]

3.2 Project aims

In order to expand the scope of chemical space accessible by the dearomative reductive functionalisation reactions of *N*-heterocycles, it has always been our goal to be able to trap a wider range of electrophiles with our *in situ* formed enamine species (Scheme 3.1).



Scheme 3.1: Reaction blueprint for the reductive dearomative functionalisation of quinolines

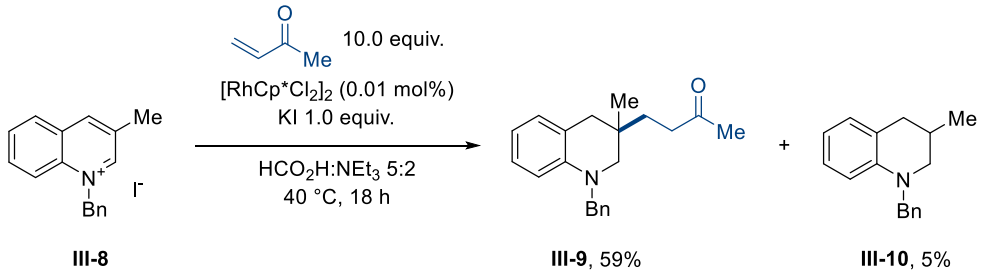
It was clear from the beginning of our studies that in order to expand the scope of the electrophiles, we would have to shift away from formaldehyde and find an alternative source of hydride in the reaction system. There are two major challenges associated with this modification of the reaction conditions. Firstly, the hydridic species formed *in situ* must be a good enough reductant to dearomatize the activated arene, but not too reactive in order the prevent the unwanted reduction of the added electrophile. Secondly, in order to prevent the trapping by the enamine formed *in situ*, the source of the hydridic species must itself not be too electrophilic. Shifting away from basic to acidic reaction conditions, we proposed using formic acid as the hydride source/terminal reductant instead of the originally used paraformaldehyde. Finally, the acidity of the formic acid must be attenuated to limit the competing direct protonation pathway of the enamine intermediate, which would lead to complete reduction thereby preventing the trapping of the desired electrophiles.[88–91]

3.3 Reaction development

3.3.1 Initial hit

To begin with, our primary goal was to develop acidic conditions for the dearomatisation of quinolines and identify a new electrophile that would be compatible with the employed/envisaged conditions. We commenced our screening studies with the C3-methyl-substituted quinolinium salt **III-8** in combination with the commercially available methyl vinyl ketone (MVK). A C3-substituted quinolinium salt was initially chosen for trial reactions, to prevent the incorporation of multiple

electrophile equivalents, as was previously observed in the methylation-hydroxymethilation sequence of C4-unsubstituted isoquinolinium salts.[79] Inspired by the work by Xiao and co-workers in the field of transfer hydrogenation,[92,93] we subjected the quinolinium salt **III-8** and 10 equivalents of MVK to a 5:2 mixture of formic acid and triethylamine in the presence of 0.01 mol% $[RhCp^*Cl_2]_2$ and potassium iodide at 40 °C. Pleasingly, these conditions furnished the desired product **III-9** in 59% yield, with the reduced tetrahydroisoquinoline **III-10** side-product being concurrently isolated in low yield (5%) (Scheme 3.2).



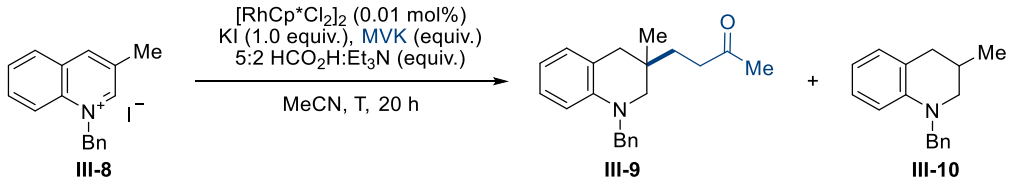
Scheme 3.2: Initial reaction hit

The formation of the undesired product **III-10** is a result of the competing reaction pathway, in which the reactive enamine species undergoes protonation followed by *in situ* reduction. Importantly, note that in the absence of the *N*-activating benzyl group, no desired reactivity was observed and only the fully unreacted starting materials were recovered.

3.3.2 Reaction optimisation

Since our initial reaction hit used a large excess of the electrophile (and has utilised the formic acid triethylamine mixture as a solvent), we set about optimising the reaction conditions with the goal to (i) lower the loadings of reagents required, and (ii) increase the yield of the desired product **III-9** (Table 3.1).

Table 3.1: Optimisation of the reaction conditions: [a] ^{1}H-NMR yield using trimethoxybenzene as internal standard at 0.125 mmol scale, [b] neat, [c] no metal catalyst, [d] no KI, [e] Isolated yield after column chromatography.



entry	MVK (equiv.)	FA:NEt_3 (equiv.)	*c* [M]	T [°C]	Yield [%] **III-9/III-10**[a]
1[b]	10	100	0.12	40	59/5
2	10	10	0.12	40	41/12
3[c]	10	10	0.12	40	15/<5
4	10	10	0.12	60	68/9
5	10	10	0.12	75	80/20
6	2	10	0.12	75	28/50
7	2	10	1.25	75	50/30
8[d]	2	4	1.25	80	62/35
9[c, d]	2	4	1.25	80	74/22
10[c,d]	**5**	**4**	**1.25**	**80**	**86 (78)[e]/<5**
11[c,d]	0	4	1.25	80	0/77[e]

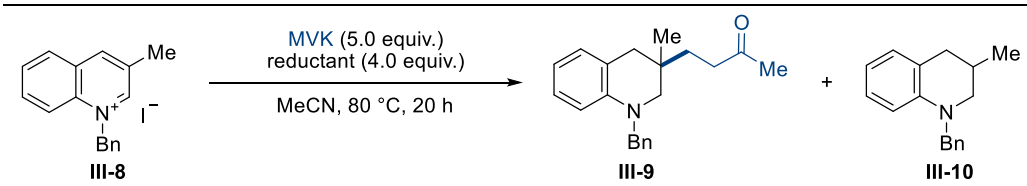
Firstly, we wanted to introduce a co-solvent into the system, in order to ensure a more homogeneous reaction mixture. We have therefore elected to screen a large number of common organic solvents (for details see Chapter 6: Experimental details). Acetonitrile (0.125 M) turned out to be the most suitable choice, as it gave the desired product **III-9** in 41% yield, while using only 10 equivalents of the reductant mixture (*entry 2*). A significant drop in reactivity was observed in the absence of a rhodium catalyst, however a 15% yield of the desired product was still observed, indicating some level of a metal-free background reaction (*entry 3*). Increasing the reaction temperature resulted in

substantial improvement of yield (80% **III-9** at 75 °C; see *entry 4* and *entry 5*). After a successful decrease in the reductant equivalents compared to the initial conditions, we next turned our attention to the electrophile loading. Unfortunately, decreasing the MVK equivalents to 2.0 led to a dramatic drop in yield (28%), with concurrent significant increase in the formation of the undesired reduced product **III-10** (50%, *entry 6*). We then increased the concentration of the reaction by an order of magnitude, in an attempt to favour the more desired pathway while keeping the electrophile loading low. Pleasingly, under the stated conditions the product **III-9** was formed in an improved yield of 50% (*entry 7*). We opted to decrease the required reductant equivalents further, hoping to increase the relative concentration of the electrophile with respect to the amount of protons in the system. To this end, (i) using 4.0 equivalents of the formic acid-triethylamine mixture, (ii) removing KI to ensure greater homogeneity of the reaction mixture, and (iii) a further increase in temperature to 80 °C, led to our first result that was better than the initial reaction hit giving **III-9** in 62% yield (*entry 8*). Surprisingly, and in stark contrast to entry 3, the reaction without any rhodium catalyst at 80 °C, substantially increased the yield of the desired product to 74% (*entry 9*). To establish whether this transformation could indeed proceed in a metal-free fashion, we carried out a series of control experiments with new glassware and new stirrer bars.[94] Additionally, the corresponding quinolinium starting material **III-8** was treated with a metal scavenging resin (Biotage Si-TMT) in an attempt to remove traces of any inherently present metal impurities that could have been introduced during the starting material synthesis. Furthermore, we used new or freshly distilled reagents (for details see Chapter 6: Experimental details). All control experiments furnished the desired product in comparable or higher yield than the analogous rhodium catalysed reactions, strongly indicating the presence of a highly productive transition metal-free background reaction. Finally, an increase in the MVK loading to 5.0 equivalents, gave **III-9** in 86% NMR yield, which dropped slightly to 78% after flash column chromatography (FCC), thus giving us our optimised reaction conditions (*entry 10*). With the understanding of the value of a mild protocol for reduction of the quinoline core, we next performed a reaction whilst omitting MVK, to provide **III-10** in very good yield (77%, *entry 11*).

While we were satisfied with our reaction system after the optimisation, we opted to explore alternative hydride sources in our reductive functionalisation reaction (Table 3.2), in the interest of

completion. Interestingly, the desired reactivity was only observed when using the formic acid triethylamine mixture. Trials utilising pure formic acid, sodium formate and ammonium formate did not deliver the desired reactivity.

Table 3.2: Screening of hydride sources



entry	Reductant	"H-" equiv.	Yield **III-9**	Yield **III-10**
1	HCO_2H:NEt_3 5:2	4	86%	<5%
2	HCO_2H	4	0%	0%
3	HCO_2H:NEt_3 1:1	4	86%	<5%
4	HCO_2H:NEt_3 2:5	4	67%	24%
5	$NaHCO_2$	4	0%	0%
6	NH_4HCO_2	4	0%	0%

The molar ratio of formic acid to triethylamine was key for successful reactivity, as no reaction occurred in the absence of triethylamine. However, a decrease in reactivity was observed when the triethylamine was used in large excess. This observation is in agreement with the preceding literature reports that directly correlate the pH of the reductant mixture to the reactivity of the reaction system.[95]

3.4 Mechanistic studies

3.4.1 Exploring the influence of the metal catalyst

The transition metal-free reactivity we have observed in the control experiments during our optimisation efforts are supported by literature precedent, which is utilised formic acid to reduce imines at high temperatures.[96–98] The Wallach reaction is perhaps the most prominent example of

such approach, where carbonyls (aldehydes and ketones) are converted to amines in a reductive amination reaction, using formic acids as a reductant at elevated temperatures.[34,35] Similarly, in the Leuckart reaction, aldehydes or ketones are converted to primary amines using ammonium salts of formic acid or formamide.[33,99]

Comparing *entry 8* to *entry* 9 the combined yields of the functionalised and simply reduced product are comparable at 97% and 96%, respectively, however more of the desired product was formed in the absence of the rhodium catalyst. This suggested that the metal catalyst likely accelerates the rate of the undesired reaction pathway. In order to explore the differences between these two sets of conditions further, we decided to kinetically profile the reaction of quinolinium **III-8**. We wanted to compare the rate of production of both, the desired and undesired products, under both rhodium-catalysed and transition metal free reaction conditions (Figure 3.1). As the bulk reaction was difficult to study, we opted to make a stock reaction mixture and set up multiple smaller scale (0.063 mmol) reactions at the same time that were then each quenched at the appropriate elapsed reaction time. Crude mixtures obtained this way were analysed by quantitative ^{1}H-NMR spectroscopy using trimethoxybenzene (3.1 mg per $CDCl_3$ aliquot) as an internal standard. Methoxy peaks of TMB (6.09 ppm) and methyl peaks of the product **III-9** (s, 0.97 ppm) and reduced side-product **III-10** (d, 1.05 ppm) were chosen as diagnostic signals for quantification.

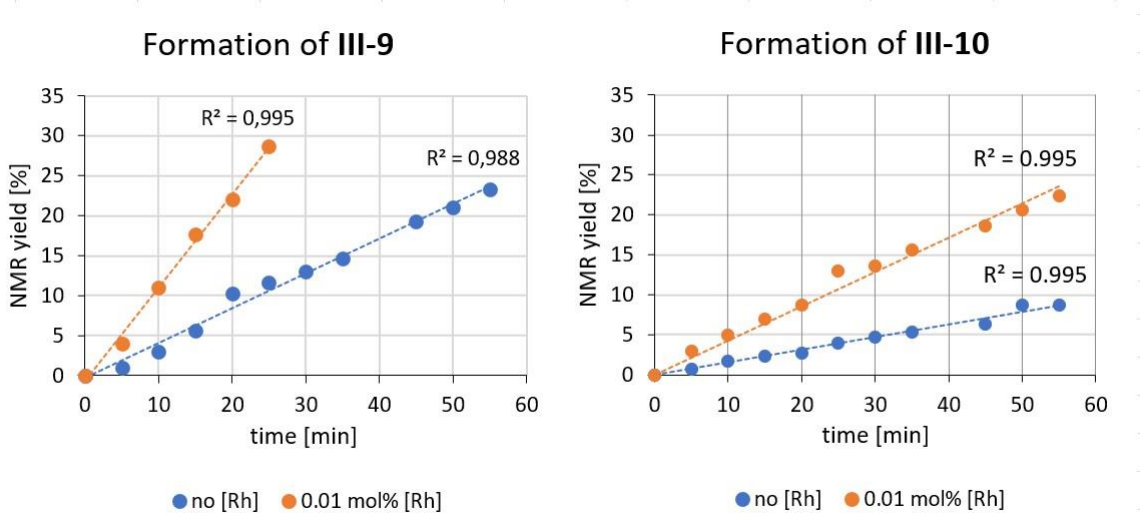


Figure 3.1: Initial rate of reaction for the formation of III-9 and III-10 in the reductive dearomatisation of III-8

Remarkably, with even a low catalyst loading of 0.01 mol% $[RhCp^*Cl_2]_2$, significant increase in the initial reaction rate was observed. While after just 25 minutes the NMR yield of the functionalised

product was at almost 30% under rhodium-catalysis, the analogous reaction under metal free conditions indicated barely over 10% of **III-9** was formed. Interestingly, the initial rate of formation of both the functionalised product **III-9** and the reduced side-product **III-10** was approximately 2.5 times faster in the presence of rhodium catalyst, compared to the metal-free conditions.

We then proceeded by monitoring the reaction for an additional 2 hours, at which point both reactions started to level-off (Figure 3.2). The rhodium catalysed reaction had reached completion (i.e.: SM was completely consumed), while the metal-free reaction reached only about 65% overall conversion. Furthermore, the data suggested that under rhodium catalysed conditions the amount of the side-product **III-10** formed in the first 3 hours of the reaction was approximately 1.8 times higher, compared to that formed under the metal-free conditions.

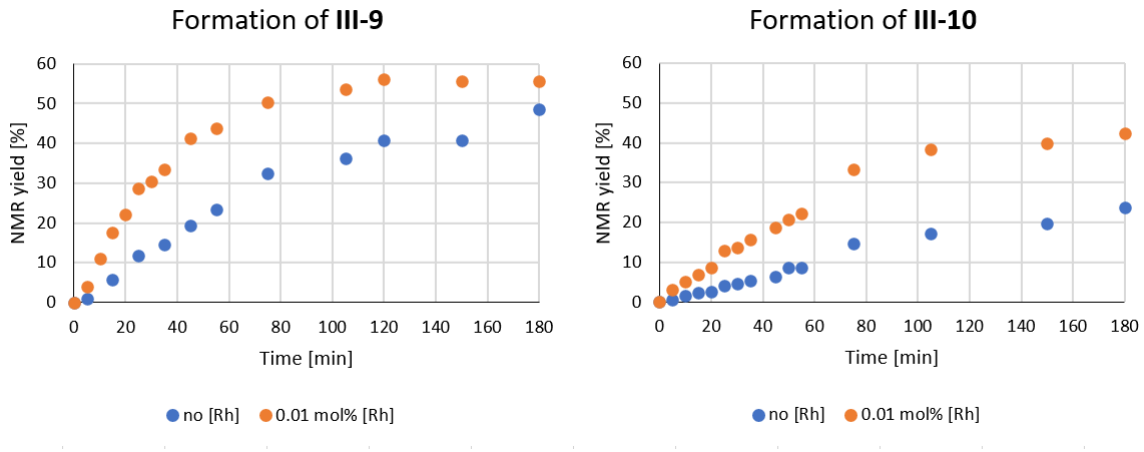


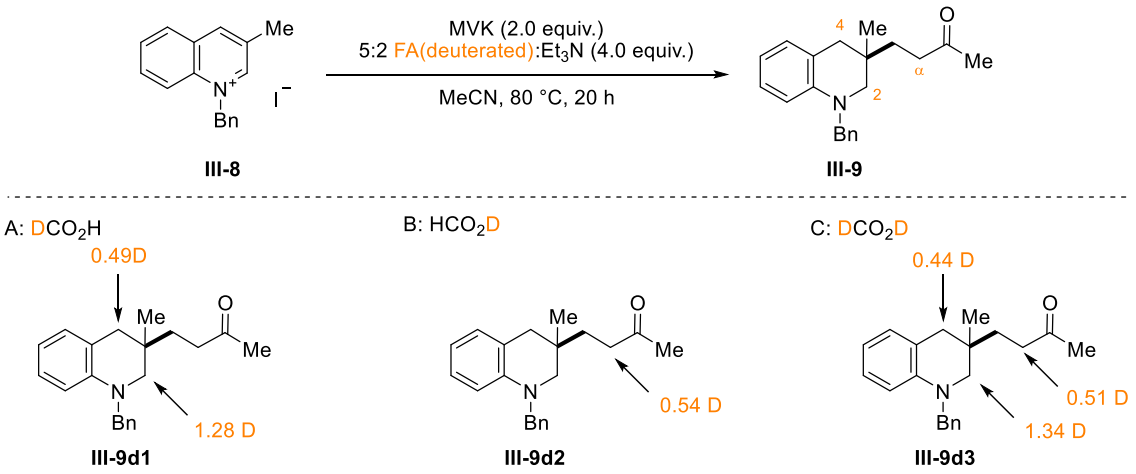
Figure 3.2: Rate of formation of III-9 and III-10 in the reductive dearomatisation of III-8 over 3 hours

Overall, the data indicate that two different hydridic species are present under the two sets of reaction conditions. Under rhodium catalysis, a metal hydride [Cp^*L_nRh-H] is the most likely reductive species, whereas under the metal-free conditions, the formate ion itself is postulated to act as a reductant. The rhodium hydride is likely to be the stronger reducing agent than the formate ion, resulting in an increased rate of all the reduction steps in the reaction mechanism, *vide infra*.

3.4.2 Deuterium labelling experiments

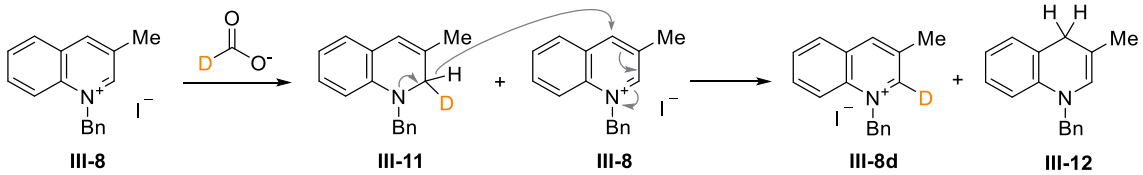
To shed more light on the general mechanism of the dearomatisation, nucleophilic attack and the subsequent reduction, a series of deuterium labelling experiments were undertaken on the quinoline substrate **III-8**. At first, **III-8** was subjected to the optimised metal-free reaction conditions

(Table 3.1, entry 10) with MVK as the electrophile and three appropriately deuterium-labelled reagents (Scheme 3.3).



Scheme 3.3: Results of the deuterium labeling experiments with quinolinium salts

Firstly, the use of formic-d_1 acid (DCO_2H) resulted in the formation of **III-9d1** with deuterium incorporation observed at C2 and C4 positions (Scheme 3.3A). Interestingly, the incorporation at the C2 position was greater than 1 D deuterium and at the C4-position it was less than 0.5 D. This suggested that initial reduction at the C2-position is very likely a reversible chemical process and since the hydride cannot be returned to the CO_2 or formate, it is most likely intercepted by either the starting quinolinium salt **III-8** or the final iminium intermediate **III-14**. Furthermore, the lower incorporation of deuterium in the C4-position suggested that intermediate **III-11d** can itself act as a hydride donor to another equivalent of **III-8**, as the rate of hydride migration should be substantially higher than the rate of deuterium migration (Scheme 3.4).



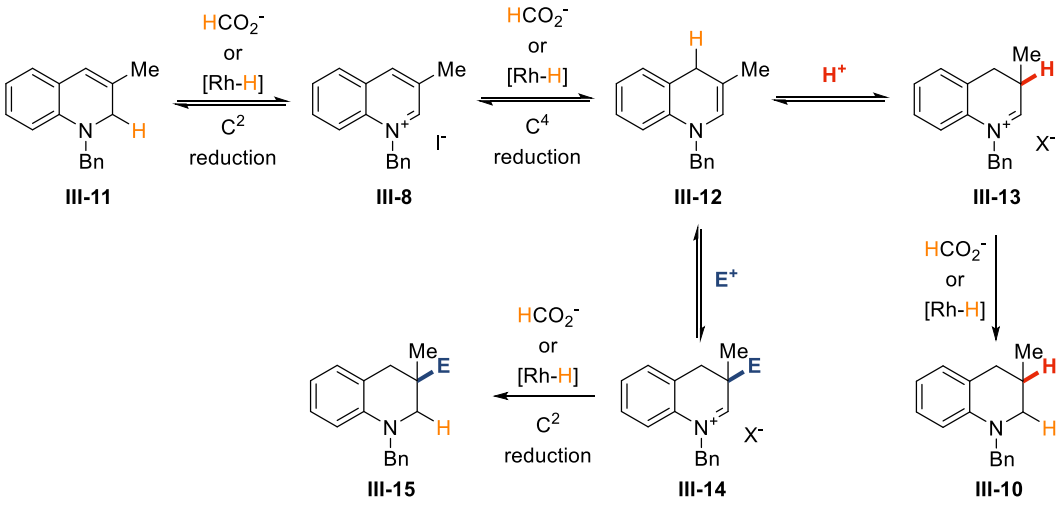
Scheme 3.4: C2-initiation mechanism

It was not possible to determine whether there was any diastereoselectivity in the deuterium incorporation into either the C2 or the C4-positions, as the ^1H NMR signals of the axial and equatorial protons in each peak were not finely resolved. Secondly, an experiment with formic acid-d1 (HCO_2D) led to the formation of **III-9d2** with no deuterium incorporated into either the C2- or C4-position

(Scheme 3.3B). However, deuterium incorporation was observed at the acidic α-carbonyl position (0.54 D); we hypothesized that the incorporation of deuterium at this position results from deuterium trapping of the enol intermediate after the initial 1,4-addition to the electrophile. Finally, using the doubly deuterated formic acid-d2 (DCO_2D) in the analogous experiments led to a cumulative effect of the conditions discussed above (Scheme 3.3C, **III-9d3**).

3.4.3 The proposed reaction mechanism

With the data obtained from the kinetic and deuterium labelling experiments, we felt confident to apply these learnings to propose a mechanism for the dearomative reductive functionalisation of quinoline salts (Scheme 3.5).



Scheme 3.5: Proposed reaction mechanism for the dearimative reductive functionalisation of quinolinium salts

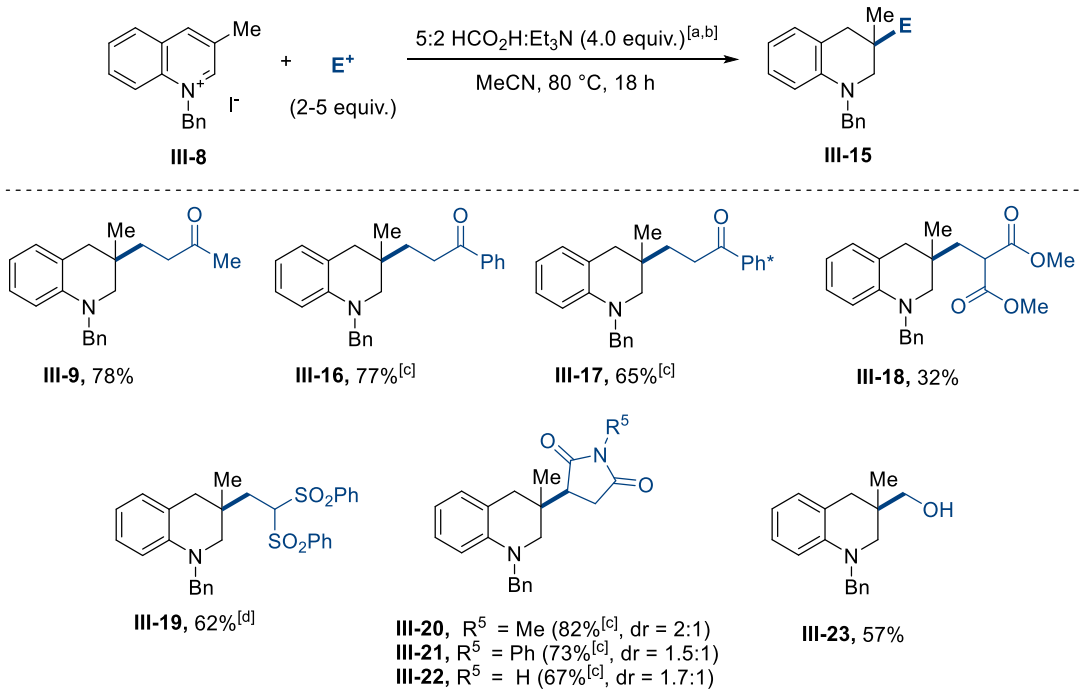
Initially, in the productive pathway, the hydride adds to the C4-position of **III-8**. The resulting enamine **III-12** subsequently traps an electrophile, thus generating iminium species **III-14**. In the final reduction step, hydride is then added to this iminium to form the functionalised product **III-15**. Alternatively, the enamine **III-12** can proceed to trap a proton and generate iminium **III-13**, the reduction of which results in the formation of undesired unfunctionalised tetrahydro quinoline **III-10**. Since a more effective rhodium hydride reducing agent is likely responsible for a faster reduction of the starting arene to form enamine **III-12**, the latter therefore likely also induces a faster formation of the desired product **III-15** via intermediate **III-14**. However, if the enamine intermediate **III-12** is in rapid equilibrium with iminium **III-13**, then this would also be reduced more

rapidly in the presence of a metal catalyst, thus skewing the aforementioned equilibrium towards **III-10**. Ultimately this would result in the increased formation of the undesired side-product, as observed experimentally.

3.5 Scope of reaction

3.5.1 Scope of electrophiles

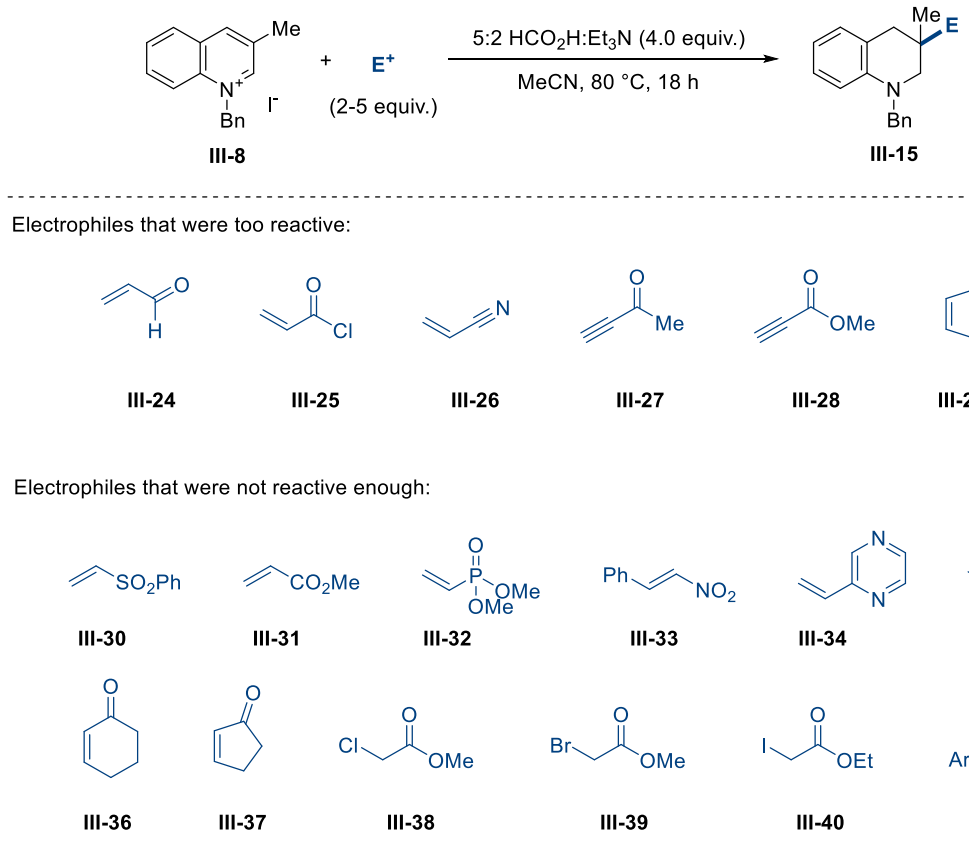
With the optimised conditions in hand (see Table 3.1, entry 8 (with 0.01 mol% $[RhCp^*Cl_2]_2$); and entry 10 for metal-free conditions), we set out to explore the scope of electrophiles and substrates that could be employed in this reductive functionalisation reaction of quinolinium salts. To this end, the substrate **III-8** from the optimisation experiments was reacted with various available electrophiles (Scheme 3.6). A range of α,β-unsaturated ketones including methyl-, phenyl- and pentamethylphenyl (Ph*)[100] vinyl ketone gave the desired products **III-9** (78%), **III-16** (77%) and **III-17** (65%) in good yields. Disappointingly, methyl acrylate was apparently not electrophilic enough to be trapped by the enamine intermediate, however, the more reactive 2-methylenemalonate gave the desired product **III-18** in 32% yield. Similarly, an α,β-unsaturated disulfone could be successfully incorporated in 62% yield to give the functionalised product **III-19** (note that the reaction conditions had to be slightly adjusted in this case, by using double the amount of reductant required as some of it was sequestered by the disulfone electrophile itself). The reaction also successfully proceeded with a diverse set of maleimides to give the corresponding tetrahydroquinolines **III-20**, **III-21** and **III-22** in good yields. The observed diastereoselectivities were rather disappointing, however not too surprising given the lack of inherent bias present in the substrates themselves. Finally, formaldehyde could be also trapped under the discussed conditions to give the hydroxymethylated product **III-23** in 57% yield.



Scheme 3.6: Scope of electrophiles in the reductive functionalisation of quinolines.

[a] Reaction conditions: quinolinium salt **1** (1.0 equiv.), electrophile (5.0 equiv.), 5:2 HCO_2H:Et_3N (4.0 equiv.), MeCN (1.25 M), 80 °C, 18 h. [b] Yields refer to isolated material after column chromatography. [c] Reaction conducted with 2.0 equiv. of an electrophile. [d] Reaction conducted with 4.0 equiv. of an electrophile and 8.0 equiv. of 5:2 HCO_2H:Et_3N. The relative stereochemistry of **III-20** to **III-22** is unassigned.

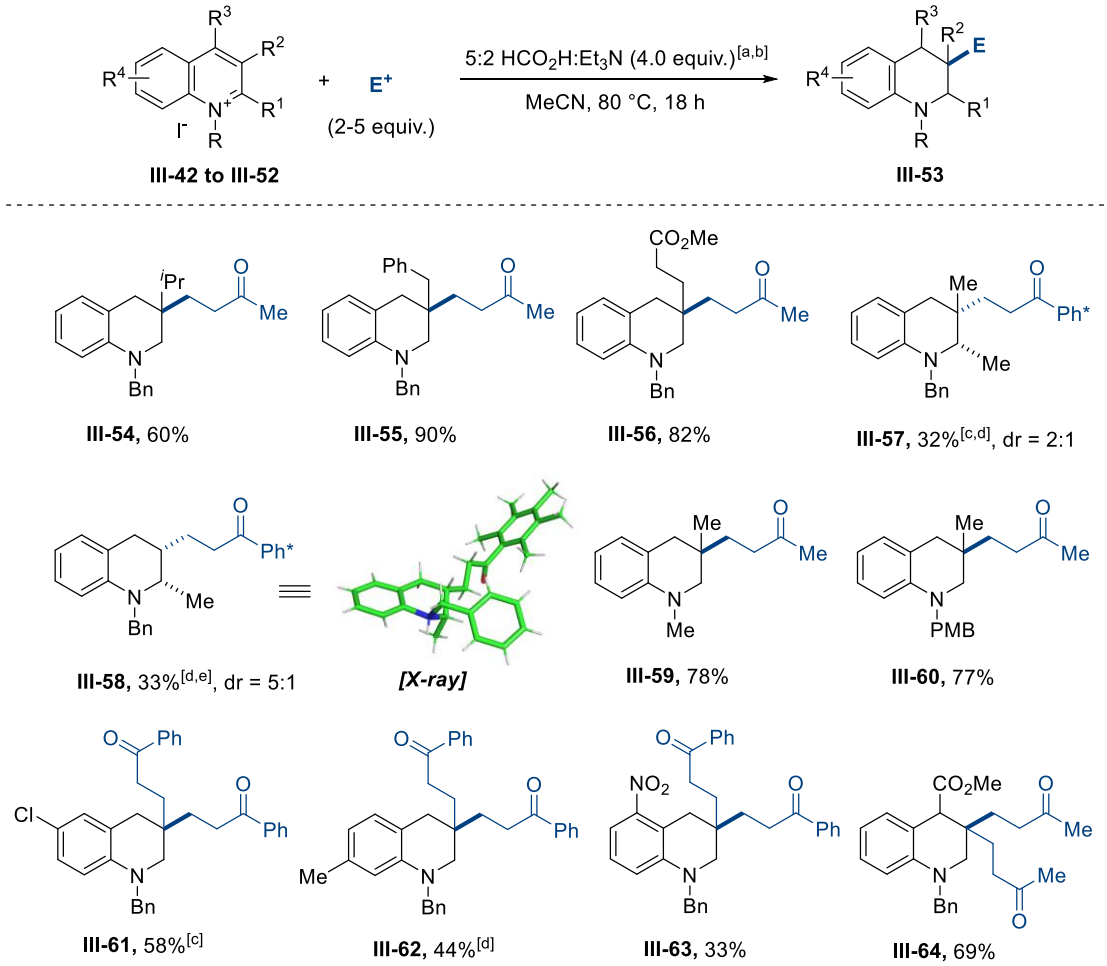
Additionally, a wide range of electrophiles were not suitable for use under our reaction conditions (Scheme 3.7). Some electrophiles were too reactive (e.g.: **III-24** to **III-29**), and resulted in either complete decomposition of the starting materials, or sequestered the hydride so that only unreacted starting material could be observed in the crude reaction mixtures. On the other hand, some electrophiles were not reactive enough due to electronic (e.g.: **III-31** and **III-38**) or steric factors (e.g.: **III-33** and **III-36**), in these instances the undesired reduced product **III-10** was the main compound isolated from the crude reaction mixtures. This clearly illustrates the necessity for a fine balance of factors that needs to be taken into account during substrate selection process.



Scheme 3.7: List of unsuccessful electrophiles

3.5.2 Scope of quinolinium salts

We next moved on to explore the scope of the quinolinium salts that could successfully undergo the dearomative reductive functionalisation (Scheme 3.8). While we primarily focused our efforts on the optimised transition metal-free conditions, certain more challenging cases (such as e.g.: highly substituted or electron rich arene systems) necessitated the use of an additional 0.01 mol% of the rhodium-catalyst to sufficiently increase the yield of the reaction. We started-off by examining the effects of the variation of substituents at the C3-position of the quinoline system on the reaction yield. Using MVK as the electrophile, the previously unreactive and bulky isopropyl quinolinium substrate now gave the desired product **III-54** in 60% yield. Both benzyl (**III-55**, 90%) and propanoate groups (**III-56**, 82%) were also well tolerated and gave the desired products in excellent yields.



Scheme 3.8: Scope of quinolinium salts

[a] Reaction conditions: quinolinium salt **1** (1.0 equiv.), electrophile (5.0 equiv.), 5:2 HCO_2H:Et_3N (4.0 equiv.), MeCN (1.25 M), 80 °C, 18 h. [b] Yields refer to isolated material after column chromatography. [c] Reaction conducted with 2.0 equiv. of an electrophile. [d] Reaction conducted in the presence of 0.01 mol% $[RhCp^*Cl_2]_2$ at 80 °C. [e] Reaction conducted with 1.5 equiv. of electrophile. The deposition number for the XRD of **III-58**·HCl is CCDC 2115931

Substitution at C2-and C4-positions of the quinoline core were also tolerated. Substitution at the C2 -osition led to a substantial drop in yield (around 30%), as was observed with products **III-57** and **III-58**. On the other hand, substitution on the C4 quinoline position gave the desired product **III-64** in good yield. These results seem to imply that substitution likely does not deter the initial dearomative reduction at C4-position, but might be well interfering with the final iminium reduction at C2-position. Note that in the case of **III-58,** a crystal structure of the **III-58·HCl** salt was obtained to confirm the relative stereochemical assignment; for **III-57** the assignment was then made by analogy. The lower yields of **III-58** (which lacks a C3-substituent on the starting quinoline) were

presumably caused by a competing reaction pathway of simple reduction and double substitution at C3 by another equivalent of electrophile.

Pleasingly, changing the activating group on the nitrogen to a PMB or a simple methyl group gave virtually identical results to the previously used benzyl activated quinoliniums furnishing **III-59** and **III-60** in 78% and 77% yield, respectively. As previously mentioned, a lack of a C3 substituent could lead to *'undesired'* double substitution, we decided to harness this reactivity, as demonstrated with the successful formation of **III-61** to **III-64** from quinolines lacking the C3 substituent. Furthermore, substitution on the carbocyclic portion of the quinolinium was not detrimental to the reactivity of the system (as expected), and the double substituted products were isolated in yields ranging from 33% to 58%.

3.6 Conclusion

In conclusion, the scope of electrophiles for the reductive functionalisation of quinolinium salts has been greatly expanded. This was achieved by switching from magnesium methoxide and paraformaldehyde in methanol, to mild acidic conditions, using the formic acid-triethylamine 5:2 complex as the terminal reductant. A wide range of Michael-acceptors (e.g.: ketones, imides, sulfones, malonates etc.) were well tolerated and gave the corresponding C3-functionalised tetrahydroquinolines in good yields, in most cases without the involvement of a transition metal catalyst. Moreover, a variety of substituents and substitution patterns on the parent quinolinium substrate were tolerated, leading to the successful stereoselective synthesis of highly complex ring structures.

Chapter 4: Expanding the scope of electrophiles in the reductive functionalisation reactions of isoquinolines

The work presented in this chapter was completed jointly with the invaluable synthetic efforts from Yonglin Lai, Andrew Tinkler, Dr Marvin Kischkewitz and Dr Nicolas Kratena. Their individual contributions are fully acknowledged where appropriate.

4.1 Introduction

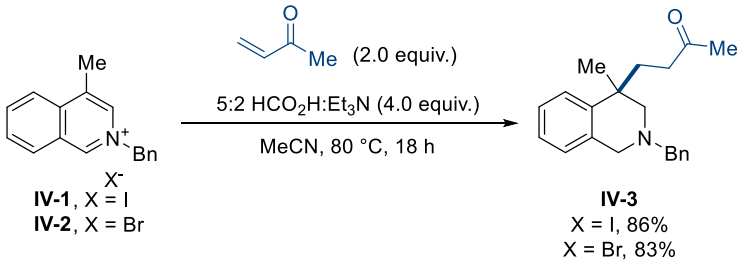
Following on from the set of promising results obtained on the quinoline systems using the new acid mediated conditions (see Chapter 3) in combination with our previous work on pyridines and isoquinolines (see Chapter 1), we were confident that we could expand this methodology to other 6-membered *N*-heterocycles.

4.2 Reaction development

4.2.1 Expanding the existing methodology to isoquinolines

With an optimised general method for the synthesis of functionalised tetrahydroquinolines in hand, we next turned our attention to achieving the dearomative functionalisation of pyridinium salts. Unfortunately, this proved to be substantially more challenging than initially anticipated. Complex mixtures containing inseparable products were obtained consistently (as judged by TLC, LC-MS and NMR analyses), containing compounds that were both aromatic and dearomatized, and had incorporated varying equivalents of the electrophile. We have postulated that one of the main problems associated with the reactivity of pyridinium salts that necessitated our attention lied in striking the right balance of reactivity between dearomatisation of the pyridinium salt and reduction of the electrophile. We have therefore shifted our focus on the dearomative functionalisation of isoquinolines, another important class of *N*-heterocycles.

Pleasingly, Dr Marvin Kischkewitz found that the dearomative reductive functionalisation reaction of quinolines could be extended to isoquinolines without the need for significant re-optimisation. The reaction of the C4-methyl substituted isoquinolinium iodide **IV-1** in combination with 2.0 equivalents of MVK (in the absence of a metal catalyst) proceed smoothly and with even greater efficiency that in the quinoline systems so that the desired functionalised tetrahydroisoquinoline **IV-3** was isolated in 86% yield (Scheme 4.1). A comparable result was achieved for the corresponding bromide salt **IV-2**.



Scheme 4.1: Initial reaction hit for the dearomative reductive functionalisation of isoquinolinium salts

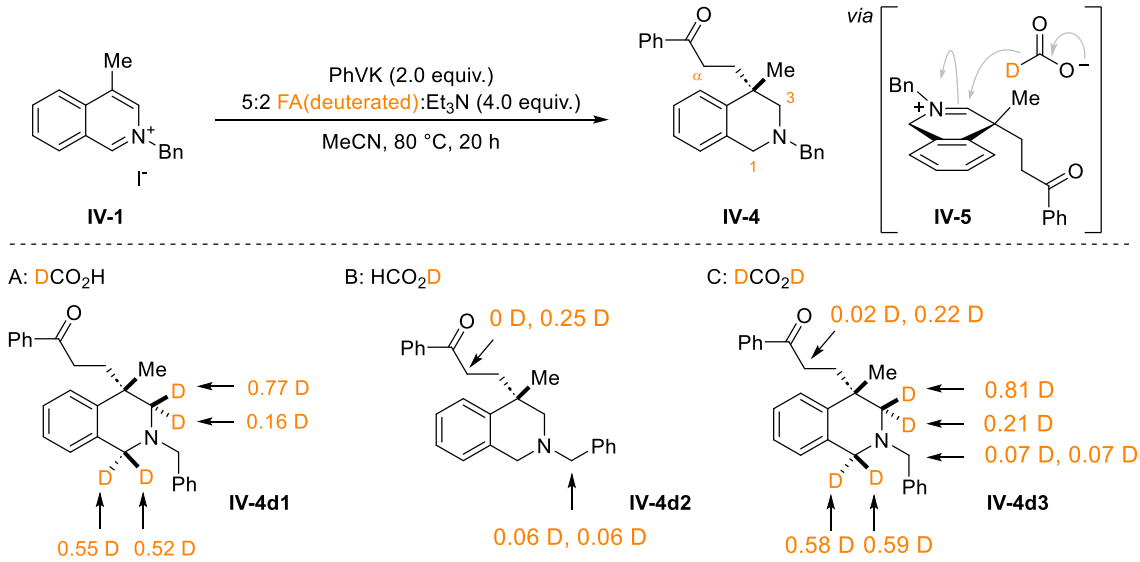
4.3 Mechanistic studies

4.3.1 Deuterium labelling

As we have previously done for the quinoline system, we wanted to shed light on the general mechanism of the dearomatisation, enamine trapping and iminium reduction for the isoquinoline pharmacophore and therefore performed a number of deuterium labelling experiments. The isoquinoline substrate **IV-1** was subjected to the optimised reaction conditions (Scheme 4.1) using phenyl vinyl ketone as the electrophile and three appropriately decorated deuterated reagents (Scheme 4.2).

Firstly, the use of formic-d_1 acid (DCO_2H) resulted in formation of **IV-4d1** with a single atom of deuterium incorporated at the C1- and C3-positions, respectively (Scheme 4.2A). As expected, there was no apparent selectivity in the deuterium addition to the C1-position (0.55 D vs 0.52 D), due to the fact, that the hydride addition occurs from both faces of isoqinolinium with equal probability. Interestingly, deuterium incorporation at the C3-position showed a significant facial selectivity of 4:1 (0.77 D vs 0.16 D). Finally, NOESY analysis of parent tetrahydroisoquinoline **IV-4** conclusively

confirmed that the majority of the deuterium incorporation (0.77 D) had occurred *syn* to the methyl substituent; the second hydride delivery preferentially proceeded to the less hindered face of the iminium.



Scheme 4.2: Results of the deuterium labelling experiments with isoquinolinium salts

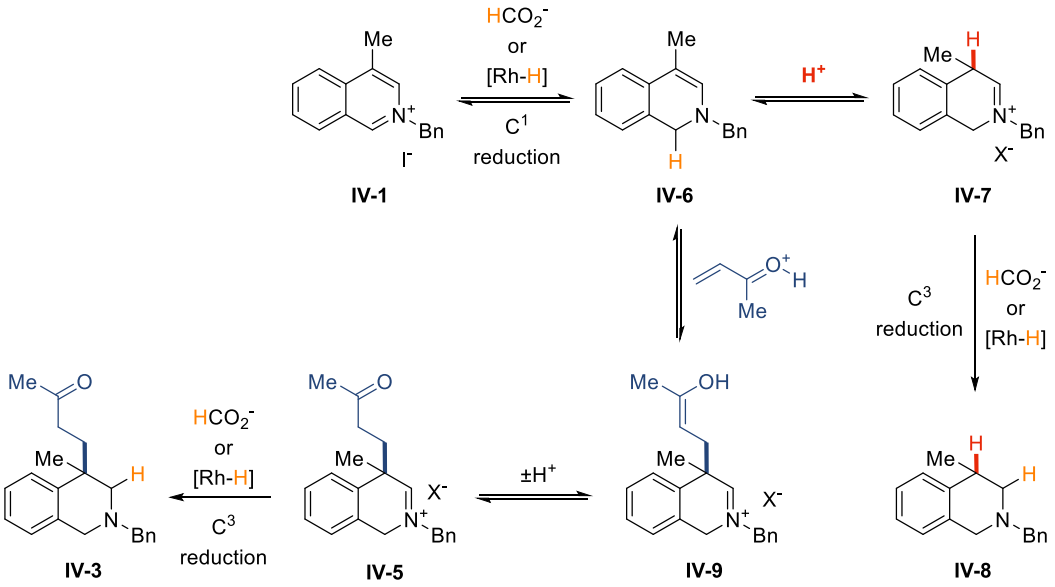
Secondly, an experiment with formic acid-d_1 (HCO_2D) led to the formation of **IV-4d2** with no deuterium being incorporated at either the C1 or C3-positions (Scheme 4.2B). Instead, deuterium incorporation was observed on the acidic *N*-benzyl group (0.12 D; the deuterium exchange there likely occurs before the initial dearomatisation of the isoquinolinium), and at the CH_2 group alpha to the ketone (0.25 D). We assumed that the incorporation of deuterium at the α-carbonyl position was a result of deuterium trapping of the enol intermediate after the initial 1,4-addition, but were perplexed by the low D incorporation. However, quenching the reaction with D_2O (promoting an exchange process during the work-up) resulted in a significantly higher incorporation of deutirium at the α-carbonyl position (0.49 D) consistent with the observations previously made in the quinoline system (see Chapter 3).

Thirdly, using formic acid-d_2 (DCO_2D) led to a cumulative effect of the variations discussed above (Scheme 4.2C) to give the deuterated product **IV-4d3**. Finally, to explore whether the use of a metal catalyst could further affect the mechanism of the reductive functionalisation reaction, two additional experiments were performed in the presence of Rh catalyst ($[RhCp^*Cl_2]_2$) under the same reaction

conditions. Using either formic-d_1 acid and formic acid-d_1 as reductant ultimately resulted in the same levels of deuterium incorporations observed.

4.3.2 Proposed reaction mechanism

Using the data from the deuterium labelling experiments we felt confident in proposing a mechanism for the dearomative reductive functionalisation of isoquinolinium salts (Scheme 4.3).



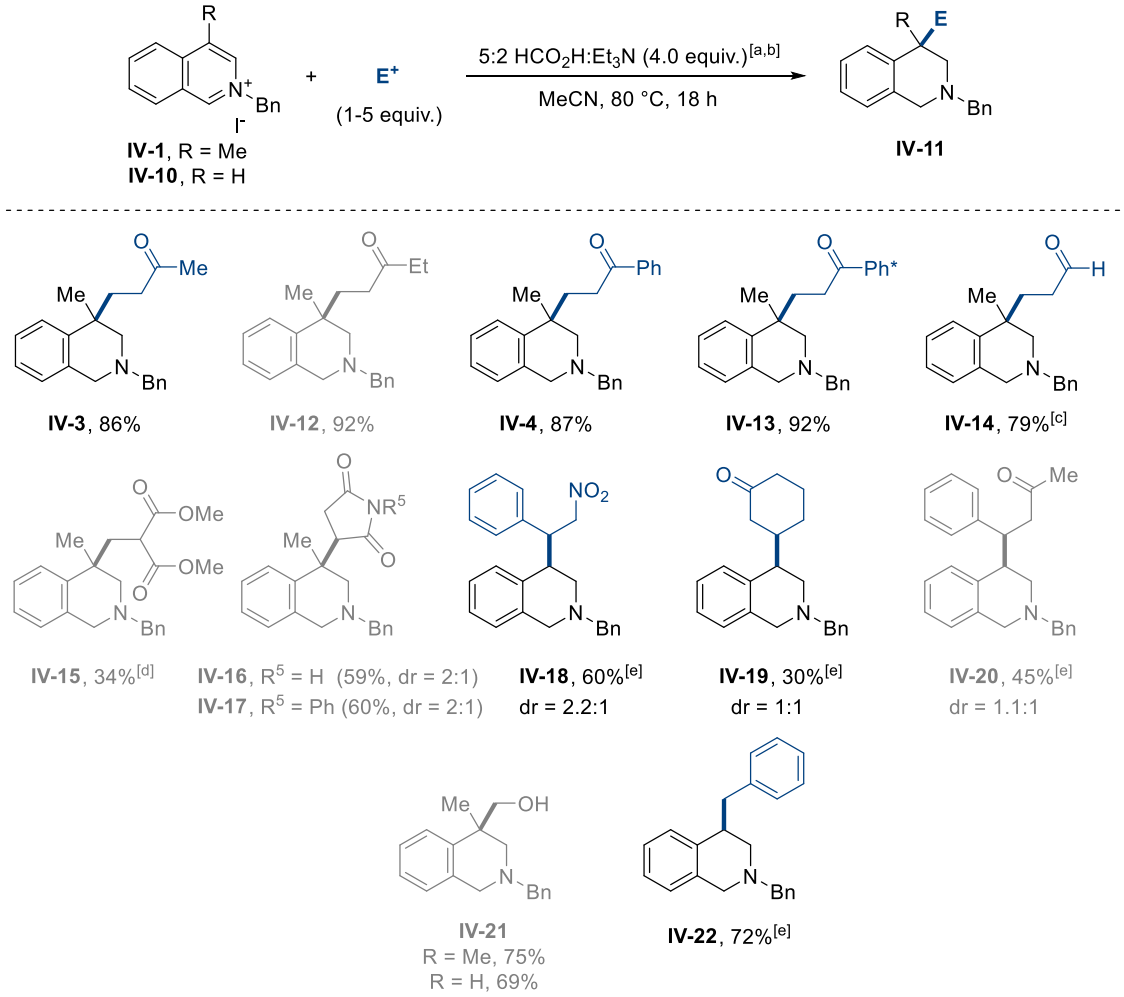
Scheme 4.3: Proposed reaction mechanism for the dearimative reductive functionalisation of isoquinolinium salts

Following on from the reaction mechanism proposed for the quinoline salts (Chapter 3), a similar mechanism most likely applies for reduction of isoquinolinium; this can take place in the presence or absence of a metal catalyst. Initially, the dearomatisation proceeds with the addition of a hydride to the C1-position of **IV-1**. The resulting enamine **IV-6** then undergoes a 1,4-addition to an enone (MVK for example), generating the iminium **IV-9**. Finally, a keto-enol tautomerisation gives **IV-5** that is then reduced *via* a hydride addition reaction to form the product **IV-3**. Given the similarity between the proposed mechanisms for the quinoline and isoquinoline systems, we propose that the enamine **IV-6** is in a rapid equilibrium with the iminium species **IV-7** (formed after the enamine traps a proton). Note that in some cases we did observe small amounts of products derived from the reduction of **IV-8**, however in comparison to the ones in quinoline system, these were negligible.

4.4 Scope of reaction

4.4.1 Scope of electrophiles

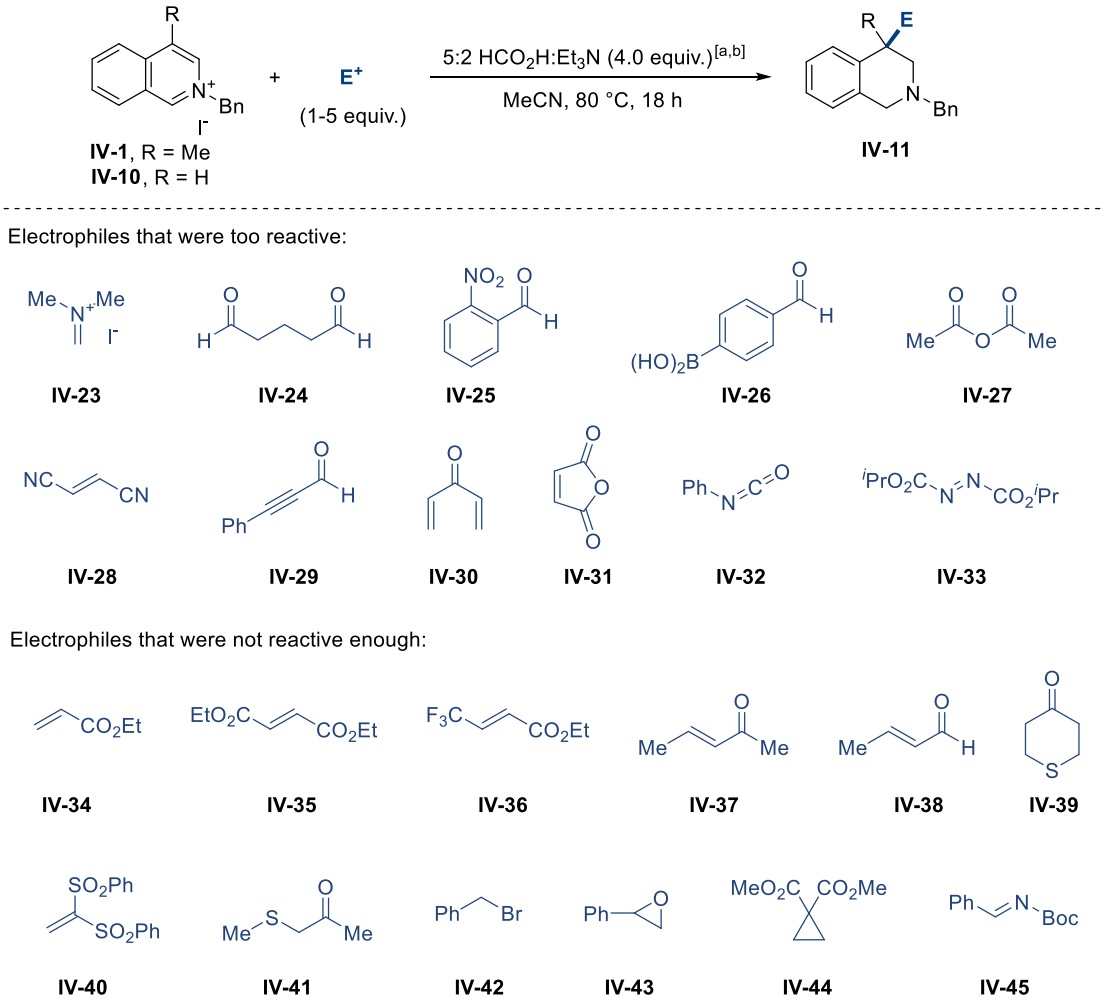
Using the same isoquinolinium iodide **IV-1**, we wanted to explore the scope of electrophiles that could be introduced into the reductive functionalisation reaction (Scheme 4.4). Starting with a range of enones, we were pleased to see that ethyl vinyl ketone (**IV-12**, 92%), phenyl vinyl ketone (**IV-4**, 87%), and Ph* vinyl ketone (**IV-13**, 87%) all gave the desired products in excellent yields.



Scheme 4.4: Scope of electrophiles in the dearomative functionalisation of isoquinolinium salts

[a] Reaction conditions: isoquinolinium salt **IV-1** or **IV-10** (1.0 equiv.), electrophile (2.0 equiv.), 5:2 HCO_2H:Et_3N (4.0 equiv.), MeCN (1.25 m), 80 °C, 18 h. [b] Yields refer to isolated material after FCC. [c] Reaction conducted in the presence of 0.01 mol% $[RhCp^*Cl_2]_2$ at 50 °C. [d] Reaction conducted in the presence of 0.01 mol% $[RhCp^*Cl_2]_2$ at 75 °C. [e] Reaction conducted with 1.0 equiv. of electrophile Note in case of **IV-22** E^+= benzaldehyde. The relative stereochemistry of **IV-16, IV-17, IV-18** and **IV-20** is unassigned. Compounds highlighted in grey were prepared by Y.L., and. M.K.

Note that we were also able to introduce an unprotected aldehyde when acrolein was used in the reaction to give **IV-14** in 79% yield, using this method. In this case, a low 0.01 mol% loading of the $[RhCp^*Cl_2]_2$ was used so that the reaction could be performed at 50 °C, bellow the boiling point of acrolein, thus highlighting the advantage of using the milder and alternative metal-catalysed protocol. Analogous to the quinoline system, methyl acrylate was not electrophilic enough to be successfully trapped in the reaction and only the simply reduced product **IV-8** was observed by NMR analysis. On the other hand, the more electrophilic 2-methylenemalonate delivered the desired product **IV-15**, albeit in a lower yield of 34%. Moreover, the reaction proceeded efficiently with different maleimides, affording the functionalised products **IV-16** and **IV-17** in 59% and 60% yield, respectively. Like in the quinoline examples the diastereoselectivity of the maleimide trapping was rather poor, giving the two products in a 2:1 ratio. Using the C4 unsubstituted isoquinolinium salt **IV-10**, we tested sterically encumbered electrophiles which were not suitable partners for C4-substituted substrates. Pleasingly, we found that both β-nitrostyrene, cyclohexanone, and benzyldeneacetone underwent the desired transformation to give the desired products **IV-18** (60%%), **IV-19** (30%), and **IV-20** (45%) respectively, thus further expanding the scope of electrophiles. The β-substituted 1,4-acceptors were completely unreactive with the quinoline substrates and with the C4-substituted isoquinolines. Additionally, a wide range of electrophiles were not suitable for use under our reaction conditions (Scheme 4.5). Some were either too reactive (**IV-23** to **IV-33**), or not reactive enough due to electronic (e.g.: **IV-34**) or steric factors (e.g.: **IV-37**), clearly illustrating the fine balance that needs to be struck in substrate selection.

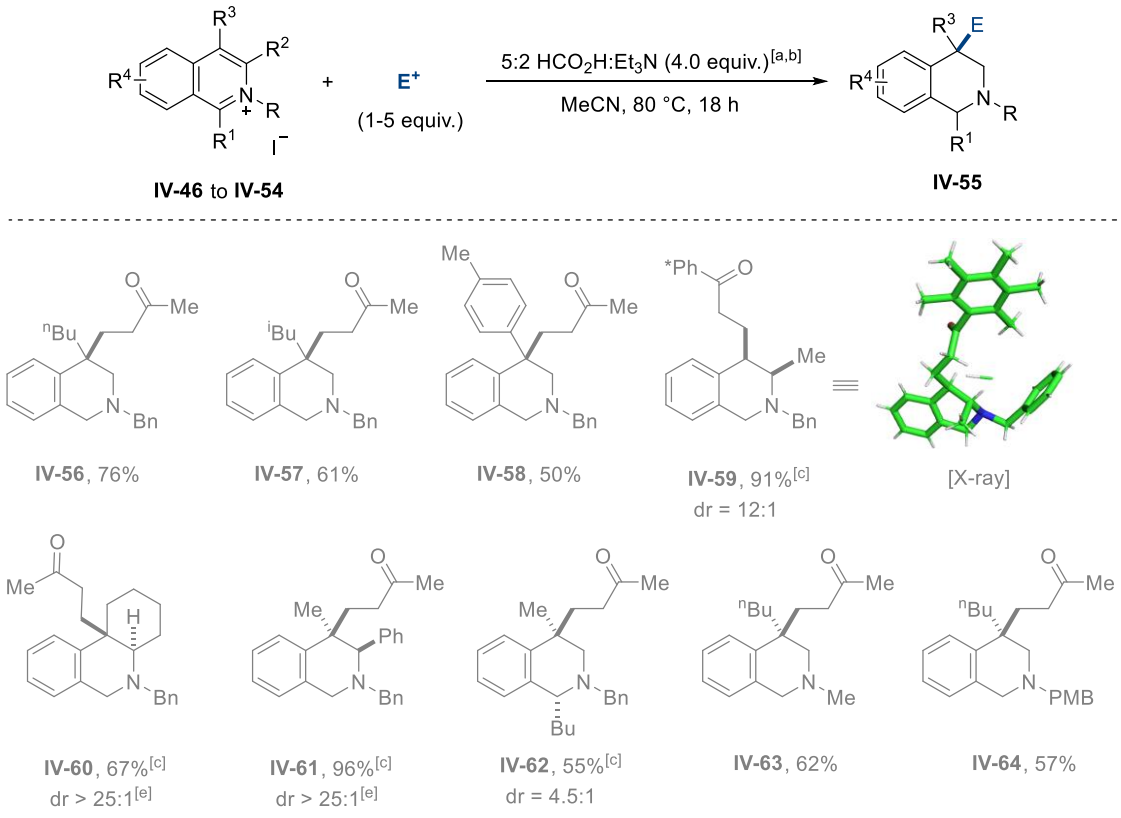


Scheme 4.5: Electrophiles that were not compatible with our reaction conditions

4.4.2 Scope of quinolinium salts

Using MVK as the electrophile, we next investigated the effect of different substituents on the C4-position of the isoquinoline (Scheme 4.6). We found that butyl (**IV-56**, 76%) and the more sterically encumbered isobutyl (**IV-57**, 61%) and aryl (**IV-58**, 50%) substituents were all well tolerated in the reaction and showed a reverse correlation between yield and the steric bulk of the C4-substituent. Both the C4-isobutyl and *p*-tolyl substituted substrates were not very reactive in the previous basic hydroxymethylation reaction conditions[79] yet here they gave the desired functionalised THIQ products in reasonable yields.[79] Encouraged by these results we decided to examine a series of more challenging C1-and C3-substituted arenes. Starting with a reaction of a C3-methyl substituted isoquinoline with Ph* vinyl ketone to give the functionalised product **IV-59** in excellent 91% yield (d.r. ≥ 25:1). Moreover, two 3,4-disubstituted substrates were successfully utilised

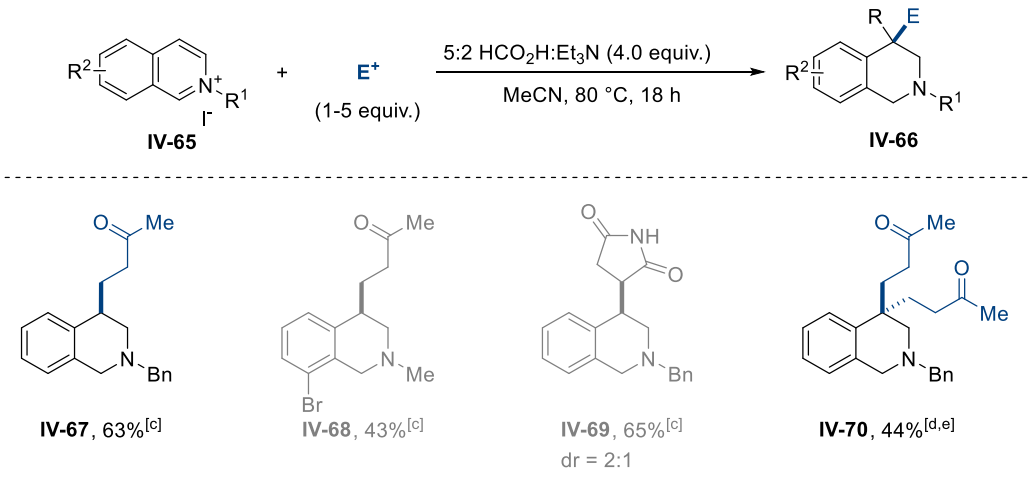
in the reaction, furnishing products **IV-60** and **IV-61** in good 67% and excellent 96% yield respectively, both as single diastereoisomers. Pleasingly, a C1-and C4-disubstituted isoquinoline substrate underwent the reaction to give the desired THIQ **IV-62** in 55% yield (with significant diastereoselectivity of 4.5:1). Furthermore, the presence of Rh-catalyst turned out to be crucial to observe the desired reactivity in these poly-substituted substrates; as only traces of the desired products were observed without the catalyst at 80 °C. In analogy to the quinolinium substrates, the activating group on the nitrogen atom was not limited to a benzyl, as both methyl and para-methoxybenzyl also gave the desired products **IV-63** and **IV-64** in good, but surprisingly lower yields compared to the benzyl activated isoquinolinium **IV-46**.



Scheme 4.6: Scope of isoquinolinium salts

[a] Reaction conditions: isoquinolinium salts **IV-46** to **IV-54** (1.0 equiv.), electrophile (2.0 equiv.), 5:2 HCO_2H:Et_3N (4.0 equiv.), MeCN (1.25 m), 80 °C, 18 h. [b] Yields refer to isolated material after column chromatography. [c] Reaction conducted in the presence of 0.01 mol% $[RhCp^*Cl_2]_2$ at 75 °C. For compound with d.r. >25:1 only one diastereomer was detectable in the crude ^{1}H-NMR spectrum. The relative stereochemistry of compounds **IV-60** and **IV-61** was assigned by NOESY experiments; The deposition number for the XRD of **IV-59** is CCDC 2115932. The compound highlighted in grey were prepared by Y.L., M.K, and N.K.

We next turned our attention to the C4-unsubstituted isoquinolinium substrates. Pleasingly, the undesired double addition of MVK to **IV-10** could almost completely be circumvented by simply reducing the amount of electrophile used in the reaction to 1.0 equivalent. MVK and maleimide delivered the mono-functionalised products **IV-67** (63%) and **IV-69** (65%) in good yields. Interestingly, the same 2:1 diastereoselectivity was observed with maleimide for both C4-substituted and C4-unsubstituted isoquinolines. A observed with the reactivity displayed in the quinoline series, we could access the bis-functionalised product **IV-70** in 44%, by increasing the electrophile equivalents.



Scheme 4.7: Scope of C4-unsubstituted isoquinolines

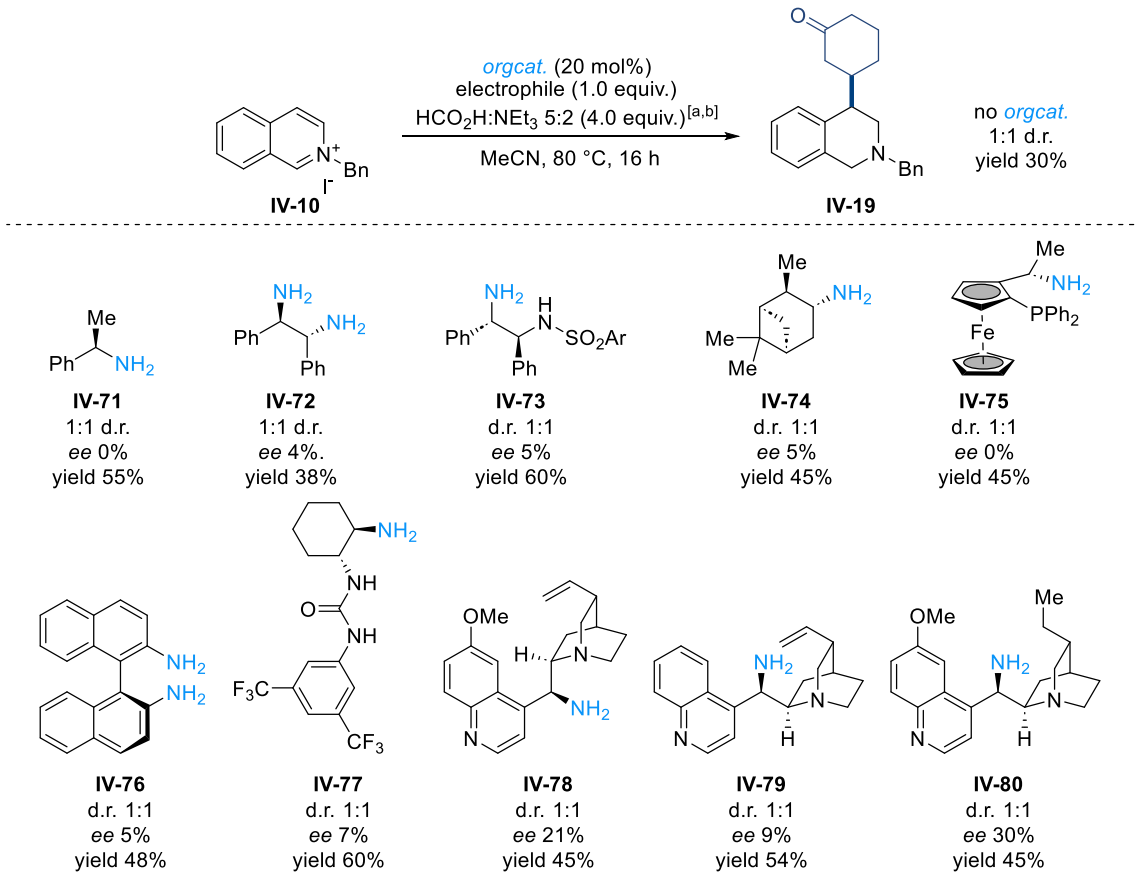
[a] Reaction conditions: isoquinolinium salt **IV-65** (1.0 equiv.), electrophile (2.0 equiv.), 5:2 HCO_2H:Et_3N (4.0 equiv.), MeCN (1.25 m), 80 °C, 18 h. [b] Yields refer to isolated material after column chromatography. [c] Reaction conducted with 1.0 equiv. of electrophile [d] Reaction conducted in the presence of 0.01 mol% $[RhCp^*Cl_2]_2$ at 75 °C. [e] Reaction conducted with 5.0 equiv. of electrophile; The relative stereochemistry of **IV-67** is unassigned. The compound highlighted in grey were prepared by Y.L. and M.K.

4.5 Developing an enantioselective version of the reaction

Having prepared a large number of highly functionalised and pharmaceutically interesting THIQ's, we next turned our attention to develop an enantioselective version of our reaction.

4.5.1 Using organocatalysis for enantioselectivity

Our initial idea was to employ a simple chiral primary amine organocatalyst to achieve the desired enantioselective variation of our reaction. When primary amines are used to control the enantioselectivity of the conjugate addition to enones, cyclohexenone is often used as the model electrophile.[101–103] We have therefore decided to use it as an electrophile in our reaction to form **IV-19** and have screened a diverse range of chiral primary amines (Scheme 4.8). Interestingly all of the tested primary amine organocatalysts resulted in an increase in the reaction yield from the 30% yield obtained in the absence of an amine additive. On the other hand, the enantiomeric excess of the products, as determined by chiral HPLC separation, was below 10% *ee* for most of the amine additives. The only promising results were obtained using the cinchona derived primary amines[104] where the *ee* could be increased to up to 30% using **IV-80**, however the d.r. remained unchanged at 1:1 in all cases, leaving us with little to work with in this case.

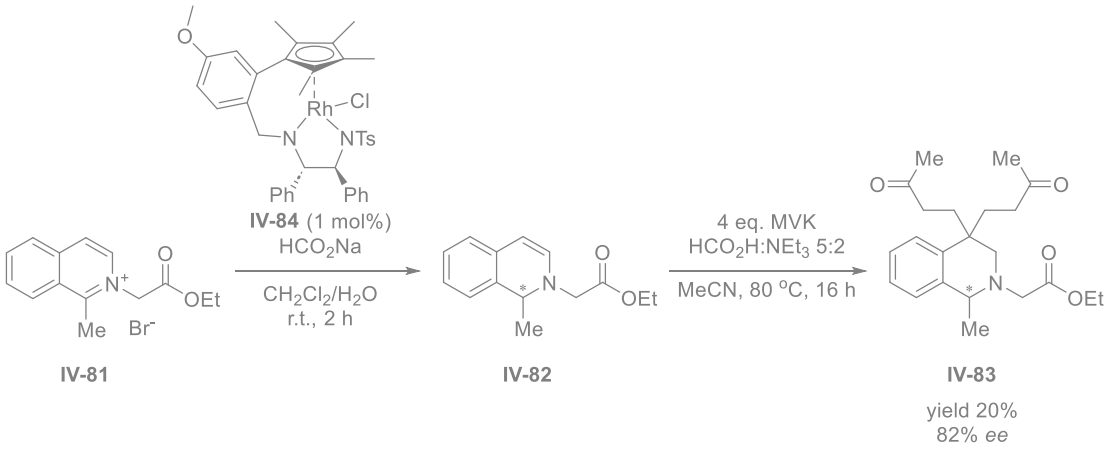


Scheme 4.8: Screening of chiral primary amines

[a] Reaction conditions: isoquinolinium salt **IV-10** (1.0 equiv.), electrophile (1.0 equiv.), 5:2 HCO_2H:Et_3N (4.0 equiv.), MeCN (1.25 M), 80 °C, 16 h. [b] Yields refer to isolated material after FCC, *ee*'s are determined using chiral HPLC.

4.5.2 Using a chiral metal catalyst for enantioselectivity

At the same time, Dr Nicolas Kratena explored an alternative approach using a chiral metal catalyst to achieve enantioselectivity. This yielded a significantly more promising result, when Andrew Tinkler was able to obtain the bis-functionalised product **IV-83** in 20% yield and 82% *ee* (Scheme 4.9). The metal-catalysed approach seemed to be significantly more promising, delivering products in consistently higher *ee*'s without much optimisation. Based on these observations, we decided that the aforementioned strategy should take precedence over the initially anticipated organocatalytic approach, and has formed the basis of Andrew Tinkler's DPhil project.



Scheme 4.9: Enantioselective reaction using a chiral metal catalyst

4.6 Conclusion

In conclusion the scope of electrophiles for the reductive functionalisation of isoquinolinium salts has been greatly expanded. This was achieved by switching from basic conditions using paraformaldehyde to milder acidic conditions using the formic acid-triethylamine 5:2 complex as the terminal reductant. A wide range of Michael-acceptors (ketones, imides, sulfones, malonates) as well as various aldehydes were well tolerated and gave the C4 functionalised tetrahydroisoquinolines in good yields, in most cases without the involvement of a transition metal catalyst. Moreover, a variety of substituents and substitution patterns on the parent isoquinolinium substrate were tolerated leading to the stereoselective synthesis of complex ring structures, including pharmaceutically relevant structures. While we have been unable to develop an enantioselective reaction as of yet, the initial results are promising.

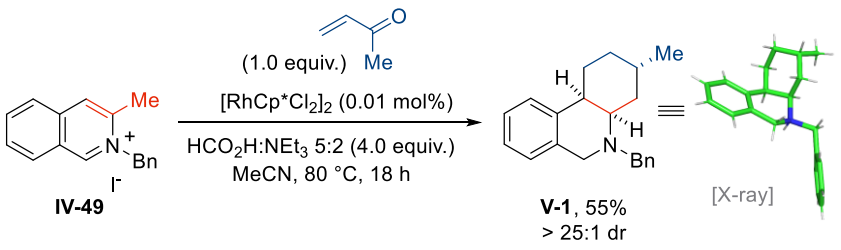
Chapter 5: Annulation reaction of isoquinolines and their application in total synthesis

5.1 Project aims

The rapid assembly of complex polycyclic systems present in various natural products and pharmaceutically-relevant compounds was at the core of our pursuit to develop new dearomatisation strategies. The main approach we have taken so far utilised activated azaarenium salts, with the reaction proceeding by *in situ* unveiling of the nucleophilic enamine moiety and the subsequent trapping of 1,4-acceptor-type electrophiles (for details see Chapter 4). After the trapping we postulated that both the iminium formed, as well as the remaining carbonyl group of the electrophile, could undergo further reactions to form more complex annulated scaffolds. We have therefore set out to develop a range of annulation strategies with considerable potential to expand on the utility of our reductive functionalisation methodology.

5.2 Formal [3+3] annulation reactions

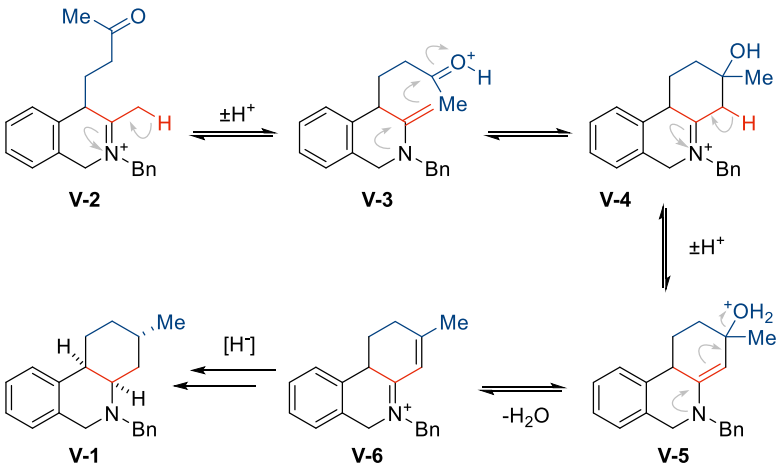
Pleasingly, the reaction of 3-methylisoquinolinium iodide **IV-49** with MVK yielded the desired annulated product under the previously developed metal catalysed conditions (see Chapter 4) in 55% yield as a single diastereoisomer (Scheme 5.1). The relative stereochemistry of the product was unambiguously determined using single-crystal X-ray crystallography.



Scheme 5.1: Formal [3+3] annulation reaction with 3-methylisoquinolinium iodide

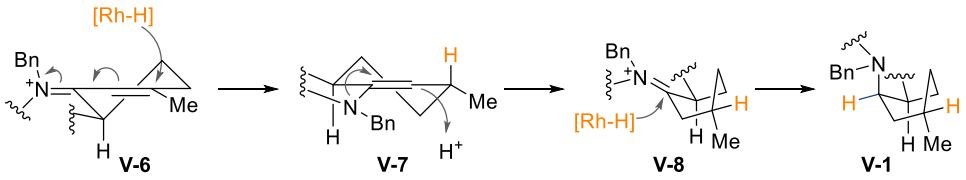
We believe this formal [3+3] annulation reaction proceeds via a similar mechanism to the standard isoquinolinium dearomatisation (See Chapter 4), with the acidic 3-methyl group likely playing a pivotal role in the mechanism. After trapping of the MVK, the iminium **V-2** can be deprotonated to

form the reactive enamine **V-3**, which can then react with the remaining carbonyl group in an 6-*enolendo-exo*-trig cyclisation (Scheme 5.2). The resulting iminium **V-4** can then undergo a second deprotonation forming the enamine **V-5**, from which a molecule of water can be eliminated in a E1cB fashion. Finally, the resultant α,β-unsaturated iminium **V-6** then undergoes two consecutive hydride additions to give the target annulated product **V-1**.



Scheme 5.2: Proposed mechanism of the formal [3+3] annulation reaction

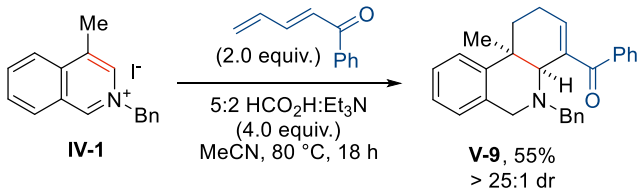
In order to explain the relative stereochemistry, we must look at the final hydride additions in more detail (Scheme 5.3). The aromatic ring acts as a conformational lock in this case, thus redrawing the α,β-unsaturated iminium **V-6** as a half-chair suggests that the first hydride is added from the top face in accordance with the Fürst-Plattner rule. The resulting enamine **V-7** can then trap a proton to give the final iminium **V-8**; finally, the rhodium-hydride is delivered equatorially, on the convex side of the molecule. It is interesting to note that the boat like confirmation and axial position of the methyl group are observed in the product crystal structure, we have assumed that the molecule adopts a similar reactive conformation during the final hydride addition.



Scheme 5.3: Stereochemical outcome of the final hydride additions

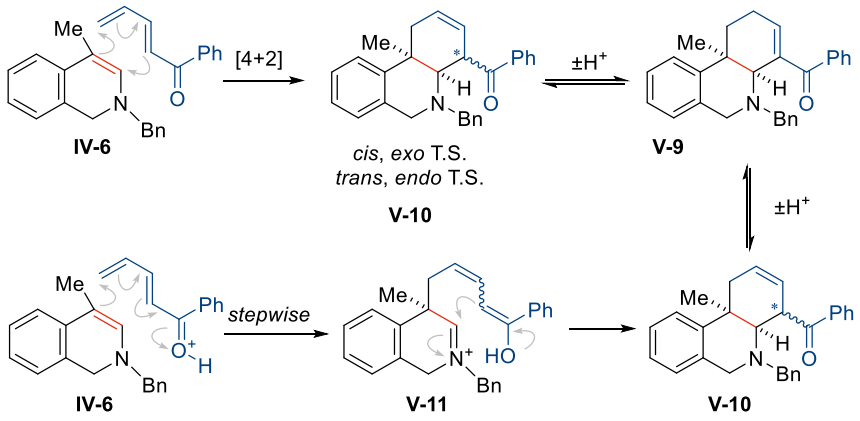
5.3 Formal [4+2] annulation reactions

In parallel to the work discussed above, Dr. Marvin Kischkewitz explored the feasibility of a formal [4+2] annulation reaction. Using a dienone electrophile, in conjunction with 4-methylisoquinolinium iodide **IV-1**, the desired annulated product **V-9** was also obtained in 55% yield as a single diastereoisomer (Scheme 5.4). The relative stereochemistry of the product was determined using nOe NMR experiments, where a clear interaction between the methyl group and the hydrogen on the ring junction could be observed.



Scheme 5.4: A formal [4+2] annulation reaction

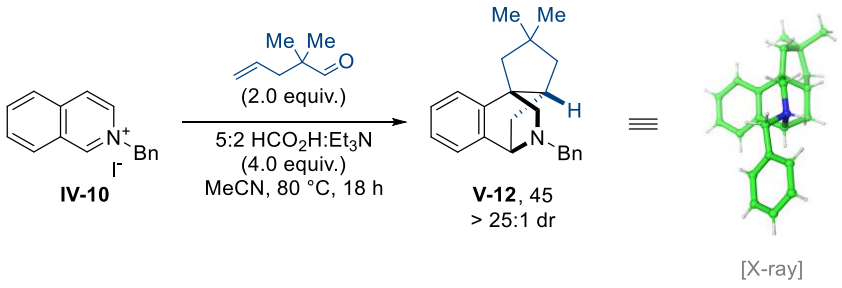
We considered two possible mechanisms, that could be used to explain the progress of this reaction: (i) an inverse electron demand Diels-Alder reaction or, (ii) a stepwise annulation mechanism (Scheme 5.5). In the former the enamine **IV-6** generated after the initial dearomatisation undergoes a concerted [4+2] cycloaddition reaction to give **V-10**. Note that the relative stereochemistry of the α-carbonyl centre depends on whether the reaction proceeds through an *exo* or *endo* transition state, however this stereochemical information is lost upon isomerisation of the double bond into conjugation with the carbonyl group to give the final product **V-9**. Alternatively, the enamine **IV-6** can undergo 1,6-attack on the dienone giving the iminium **V-11**. A 6-*enolexo*-*exo*-trig cyclisation followed by a double bond isomerisation yields the annulated product **V-9**.



Scheme 5.5: Proposed reaction mechanism of the formal [4+2] annulation reaction

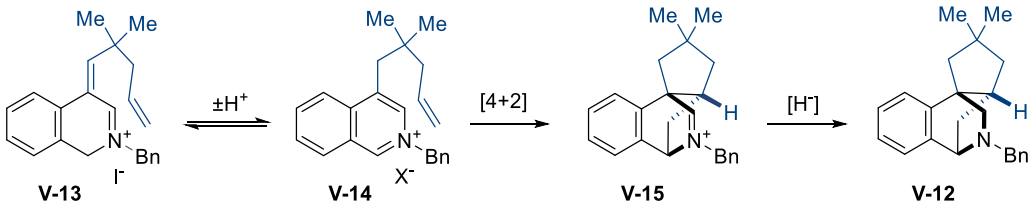
5.4 Intramolecular Diels-Alder reaction

Meanwhile, Dr Nicolas Kratena explored the aldehyde alkylation strategy that we previously developed (Chapter 4) to force an intramolecular Diels-Alder (IMDA) reaction. Using an aldehyde bearing an α-*gem*-dimethyl group and a γ-alkene in combination with the unsubstituted isoquinolinium **IV-10**, the corresponding annulation product **V-12** containing a 6-6-fused ring system could be obtained in 45% yield as a single diasteroisomer (Scheme 5.6); its relative stereochemistry of the product was determined using single-crystal-X-ray crystallography.



Scheme 5.6: An intramolecular Diels-Alder reaction

From a mechanistic standpoint, we proposed that following the trapping of the aldehyde and elimination of water, the resulting α,β-unsaturated iminium **V-13** could undergo a rearomative tautomerisation to give the isoquinolinium **V-14**. The *gem*-dimethyl group would then help bring the terminal alkene into close proximity (promoting the forward rection), thereby enabling an inverse electron demand IMDA reaction to proceed via an *endo* transition state and give the iminium **V-15**. A final reduction completes the reaction to give the observed product **V-12** (Scheme 5.7).



Scheme 5.7: Proposed key steps of the IMDA reaction

5.5 Natural product target selection

Having successfully developed three distinct classes of dearomative annulation reaction, we next looked to the literature to find precedent and guidance with respect to target selection. A search revealed the amaryllidaceae alkaloid family, which contains seven distinct structural types, three of which, lycorine, crinine and narciclasine, mapped well on the structures formed in our formal [3+3] annulation reactions (Figure 5.1).[105]

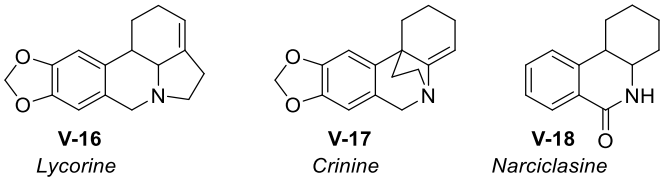


Figure 5.1:Selected amaryllidaceae alkaloid skeletal types

We were particularly drawn to the Crinine scaffold due to the presence of a quaternary carbon located β-to the nitrogen atom (i.e.: a common structural motif present in our dearomatized tetrahydroisoquinoline products). Furthermore, we were encouraged by the wide range of natural products that could be accessed by varying the oxidation patterns on the D-ring of the structures, which we planned to install in the annulation reactions (Figure 5.2).

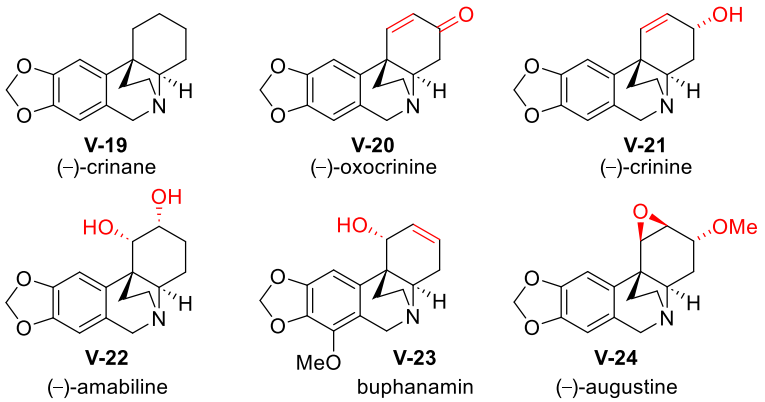
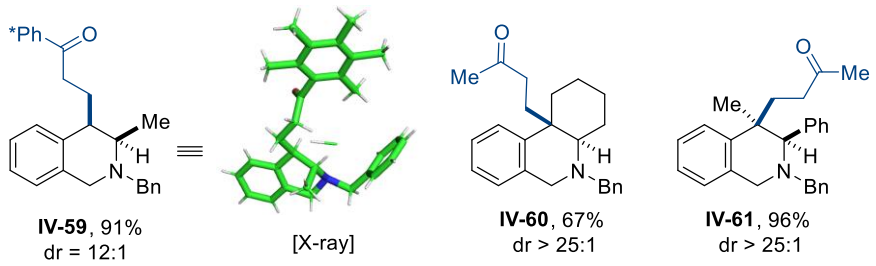


Figure 5.2: Selected natural products in the crinine family

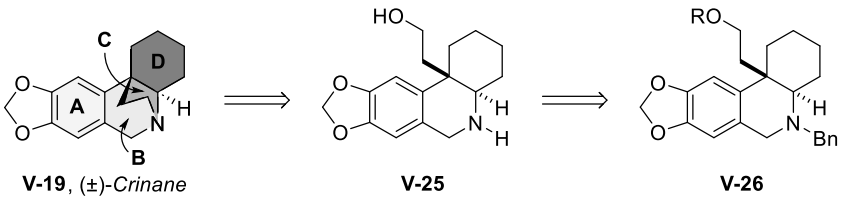
The relative stereochemistry at the ring junction of these natural products is *trans*, this is in contrast to the *cis* ring junctions we have observed in our annulation reactions (see Scheme 5.1). Nonetheless, we were hopeful that we could obtain the desired stereochemistry because we had previously observed that in 3,4-disubstituted isoquinolinium dearomatisations the final hydride delivery happens *trans* to the larger C4-substituent. (Scheme 5.8).



Scheme 5.8: Selected examples of 3,4-disubstituted THIQ products

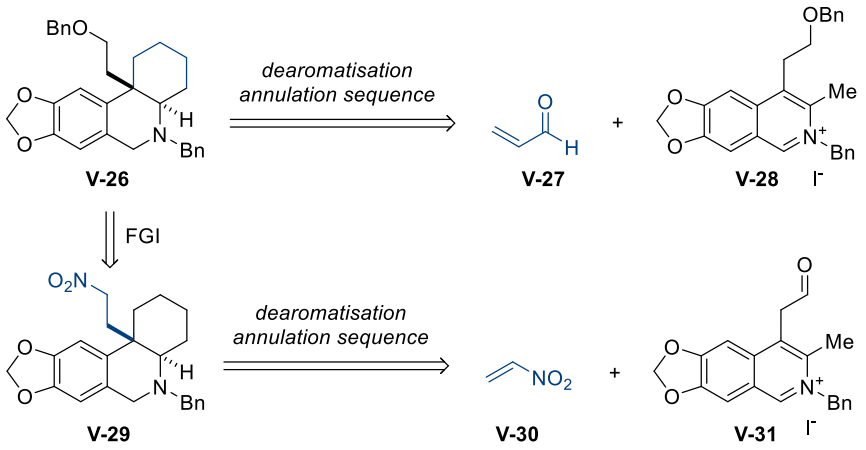
5.6 Retrosynthetic analysis of (±)-Crinane

We decided to close the C-ring of the skeleton last, *via* a cyclisation, as was previously described on related substrates.[106] That would take us back to the amino alcohol **V-25** that could be obtained by a global deprotection of the THIQ **V-26** (Scheme 5.9).



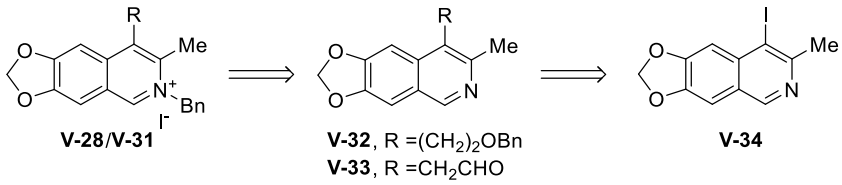
Scheme 5.9: Retrosynthetic analysis of the C-ring

When it came to closing the D-ring, we wanted to explore two alternative strategies. The first approach would use acrolein or an equivalent three-carbon electrophile in a dearomatisation annulation sequence, analogous to the formal [3+3] annulation *vide supra* with the corresponding isoquinolinium salt **V-28** (Scheme 5.10). Alternatively, a functional group interconversion to the nitro group,[107] followed by an intramolecular annulation and reductive functionalisation using nitroethylene or an equivalent two-carbon electrophile would take us back to the isoquinolinium salt **V-31**.



Scheme 5.10: Retrosynthetic analysis for closing the D-ring

Both isoquinoline **V-32** and **V-33** could arguably be prepared from the corresponding halogenated parent isoquinoline **V-34** by either a Suzuki or Heck cross coupling reaction (Scheme 5.11).[108,109] Finally, we envisioned that **V-34** could be synthesised in a *de novo* fashion as its bromo-analogue (missing the 3-methyl group) is reported in the literature.[110]



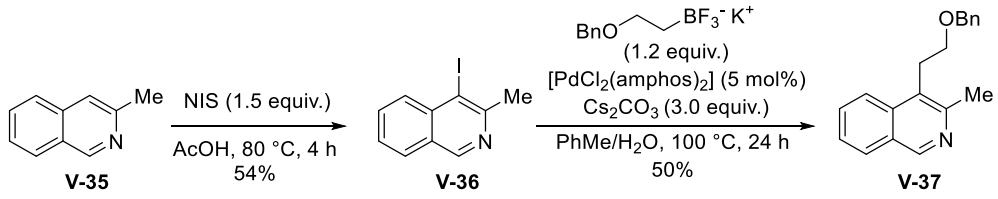
Scheme 5.11: Isoquinolinium retrosynthetic analysis

5.7 Model studies for the closure of the C-ring

Having developed an annulation that maps well onto the D-ring, we wanted to see if the reaction is tolerant with respect to the C4-substitution, seeing as the real system would require the reaction of a 3,4-disubstituted isoquinolinium.

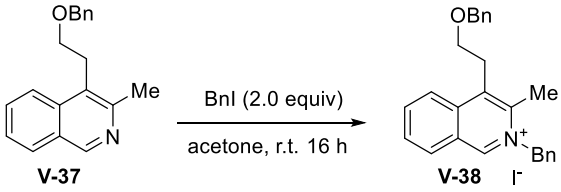
5.7.1 Starting material synthesis

Starting with commercially available 3-methylisoquinoline **V-35**, an iodination at the C4-position using *N*-iodosuccinimide (NIS) proceeded in 54% yield to give **V-36**. The desired C4-substituent could then be relatively easily installed using a Suzuki cross-coupling conditions in moderate yield (**V-37** 50%) (Scheme 5.12).



Scheme 5.12: Synthesis of the parent isoquinolines

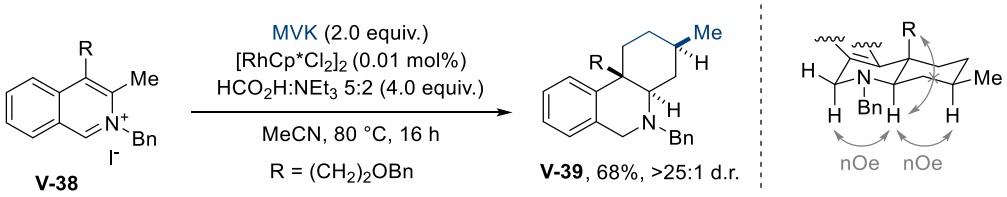
Pleasingly, the *N*-quaternisation with benzyl iodide proceeded without great difficulty, yielding the isoquinolinium iodide **V-38** in 75% yield. (Scheme 5.13)



Scheme 5.13: N-quaternisation reactions

5.7.2 Annulation reactions of 3,4-disubstituted isoquinoliniums

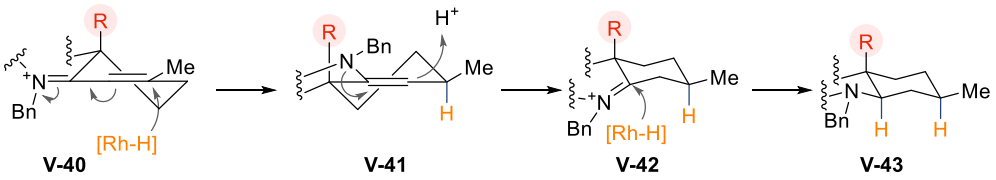
With the desired 3,4-disubstituted isoquinolinium in hand, we proceeded to test the dearomative annulation reaction with MVK as the electrophile. The C4-substituted substrate performed better than the C4-unsubstituted analogues, giving the annulated product **V-39** in 68% yield, as a single diastereomer (Scheme 5.14). Note that in these cases the relative stereochemistry at the ring junction was trans (as predicted; compare to **V-1**). The relative stereochemistry of the products was determined using NOESY experiments; correlations between the two hydrogens highlighted below were unambiguous, a cross-peak between the Me and R groups could also be observed (see Chapter 6).



Scheme 5.14: Dearomative annulation reactions of 3,4-disubstituted isoquinolinium salts

We believe this stereochemical outcome is consistent with our mechanism outlined above (Scheme 5.3). To avoid the unfavourable 1,3-diaxial interactions between the methyl and the large R group we presumed a chair conformation of the ring will be favoured in this instance. This now

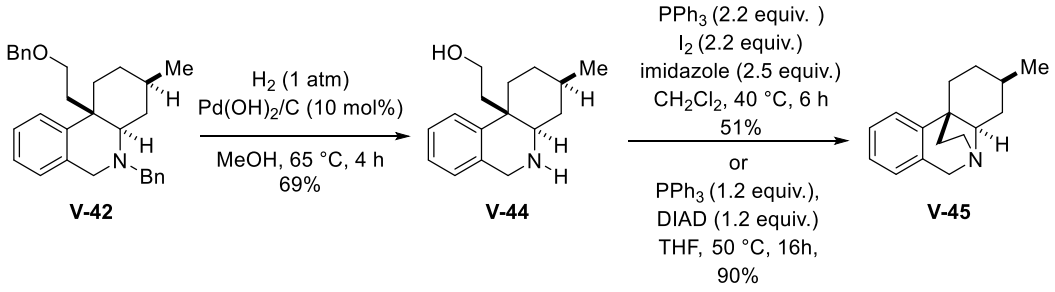
forces the final hydride reduction to occur axially from the site opposite of the large R group (Scheme 5.15).



Scheme 5.15: Stereochemical outcome of the final hydride additions

5.7.3 Closing the C-ring

Following the successful annulation reactions, we turned our attention to a development of one-pot debenzylation of both the amine and the hydroxyl group. Hydrogenation with palladium hydroxide on carbon yielded the desired aminoalcohol **V-44** in 69% yield (Scheme 5.16). Initially, we attempted to close the C-ring using Appel reaction type conditions and were pleased with the 51% isolated yield, compared to the 15% previously reported on similar substrates in the literature.[106] Wanting to see if we could improve the yield further, a visiting student Clément Tanguy, under my supervision, attempted to use Mitsunobu conditions; we were elated when the desired product **V-45** was obtained in an excellent yield of 90%.



Scheme 5.16: Closing the C-ring

We knew that we had obtained the cyclised product when we observed the absence of the OH and NH groups in the ^{1}H NMR, as well as an overall loss of water in the HRMS peak. Furthermore, the relative stereochemical assignment of the final product was proven using nOe NMR experiments that matched our proposed structure (Figure 5.3). We could clearly see an nOe interaction between H_a and H_b, and H_b and H_c but no interaction between H_a and H_c. Additionally, H_f only interacted with H_e and not with H_d.

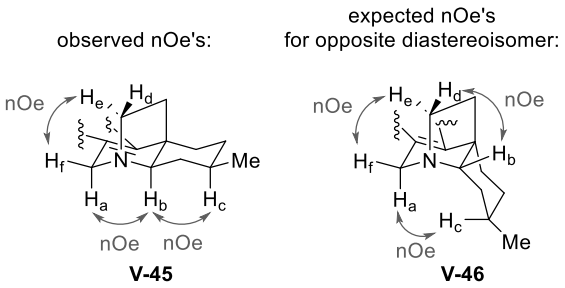
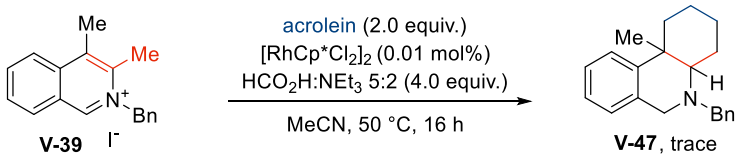


Figure 5.3: Summary of nOe evidence

5.8 Model studies for the closure of the D-ring

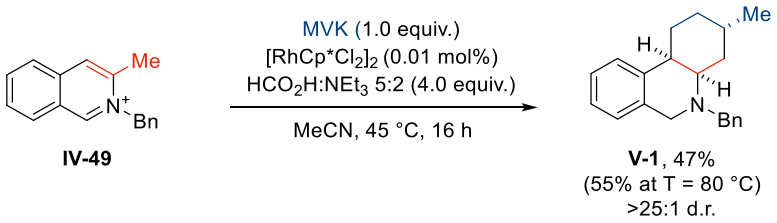
5.8.1 Attempts at intermolecular annulation reactions

Having successfully closed the C-ring on a representative model system, we shifted our attention to the construction of the requisite D-ring. Using our formal [3+3] annulation conditions with MVK, we had formed a D-ring analogue bearing an additional methyl group. We proposed that using acrolein as the electrophile instead of MVK would likely solve this problem. Unfortunately, the reaction of isoquinolinium **V-39** with acrolein at 50 °C (employed because of the lower boiling point of acrolein), only gave trace product and the relative stereochemistry could not be determined at this stage (Scheme 5.17).



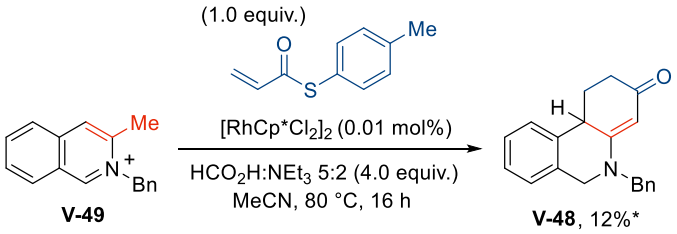
Scheme 5.17: First attempt at an acrolein annulation

This failure was surprising, as the analogous reaction between 4-methylisoquinoline **IV-1** and acrolein proceeded in excellent 79% yield (Chapter 4). To confirm that the aldol steps of the annulation were not the troublesome part of this transformation, we wanted to test a MVK annulation at a lower temperature. The latter proceeded without major issues to give the product **V-1** as a single diastereoisomer, albeit in a slightly reduced yield of 47% (Scheme 5.18).



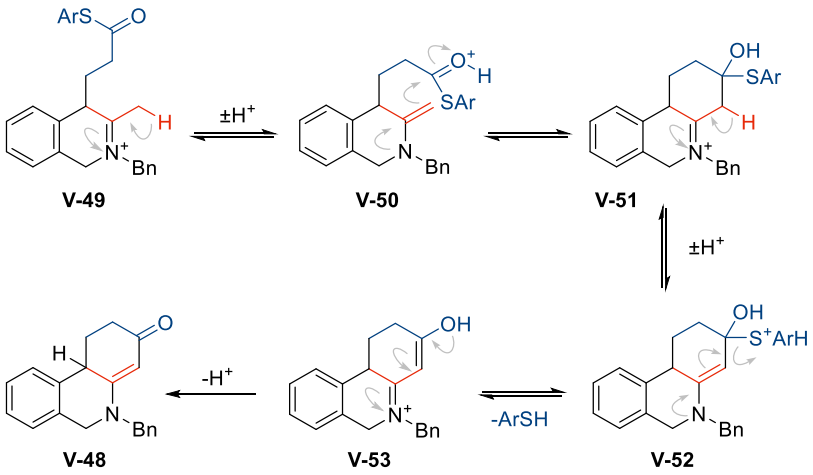
Scheme 5.18: low temperature MVK annulation reaction

This result clearly indicated, that for some reason, the initial trapping of the acrolein must be the key issue in our desired transformation. To address this, we aimed to shift our focus from acrolein to other structurally equivalent three-carbon electrophiles. Methylacrylate was previously unreactive under our reaction conditions and acryloyl chloride was too reactive to give the desired reactivity (Chapter 4). We therefore opted to explore the reactivity of structurally analogous thioesters, as their reactivity should fall somewhere between that of the esters and acid chlorides, and should, in theory, behave similarly to MVK. To this end, using a thioacrylic acid *p*-tolyl ester as the electrophile we were able to observe the formation of the vinylogous amide **V-48** in 12% NMR yield (Scheme 5.19). Unfortunately, **V-48** could not be separated from a complex mixture of unknown impurities and all attempts at optimisation of this transformation resulted in the same NMR yield. Further work will be needed to access the full potential of this promising results for the construction of the D-ring. The vinylogous amide functional group would be a well-suited starting point to access the various oxidation patterns present in the D-ring of the crinine family natural products. Due to time constrains towards the end of my DPhil, this subproject could not be explored beyond the described attempts.



Scheme 5.19: Dearomative annulation reaction using a thioester

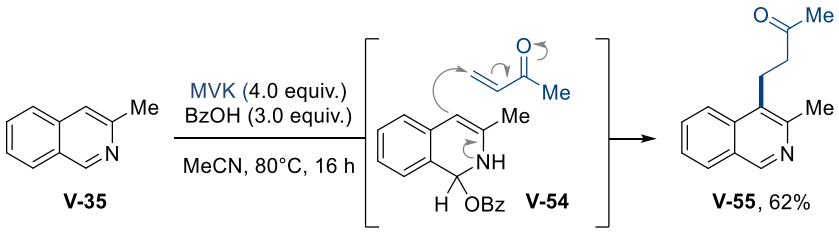
The mechanism of this transformation most likely proceeds through a similar sequence as with enone electrophiles. However, the thiophenol is a good leaving group and can thus be eliminated to give the vinylogous amide, that is not reduced any further by the rhodium catalyst (Scheme 5.20).



Scheme 5.20: Mechanism of the annulation with a thioester electrophile

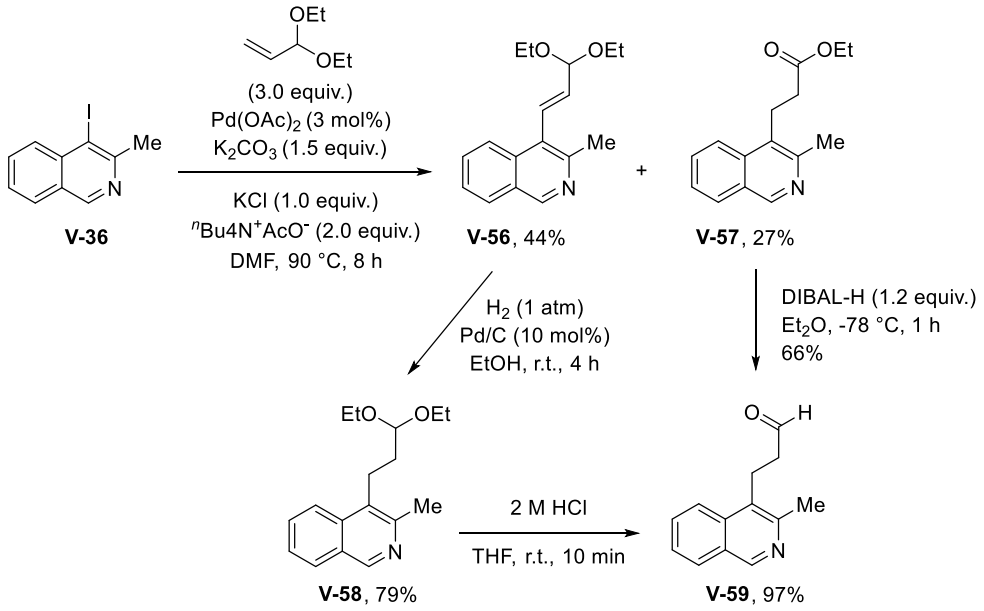
5.8.2 Testing the intramolecular annulation reactions

Having encountered significant challenges in the intermolecular annulation reactions, we thought it might be beneficial to explore an alternative *intramolecular* annulation approach, as outlined in the retrosynthetic analysis above (Scheme 5.11). Seeing as, unlike with MVK, we have had little success with annulations using acrolein or equivalent electrophiles, we opted to prepare quinolines that had incorporated either an MVK or an acrolein equivalent. This would allow us to obtain some insight into the intermolecular annulation reactions we had studied before and potentially troubleshoot some of the issues we have been experiencing. We started by preparing the requisite quinoline with the pre-installed electrophile using a method developed in our group (Scheme 5.21).[111] The reaction gave the desired isoquinoline **V-55** in good yield (62%). Mechanistically, we believe that the benzoic acids initially activates the isoquinoline by protonating it, therefore enabling the resultant benzoate anion to initiate the dearomatisation to reveal the reactive enamine **V-54**. Trapping of the MVK and rearomatisation complete the synthetic transformation.



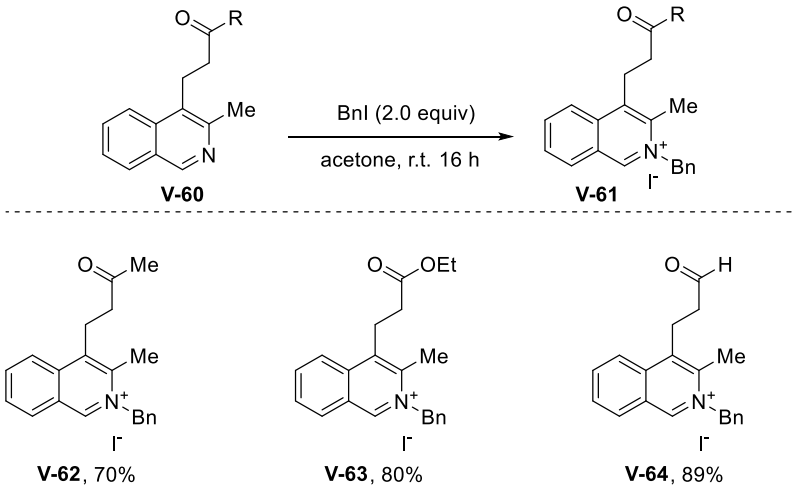
Scheme 5.21: Incorporation of MVK into the parent isoquinoline

A Heck coupling of the 3-methyl-4-iodoisoquinoline **V-36** with acrolein diethyl acetal gave a mixture of the direct coupling product **V-56** in 30% and the rearranged ester **V-57** in 46% (Scheme 5.22). Catalytic hydrogenation of **V-56** with palladium on carbon, followed by an acid-mediated acetal deprotection, gave the desired aldehyde **V-69** (77% over 2 steps). The synthetic route starting from the ester **V-57** was even more direct; a simple DIBAL-H reduction gave the desired aldehyde **V-59** in 66% yield.



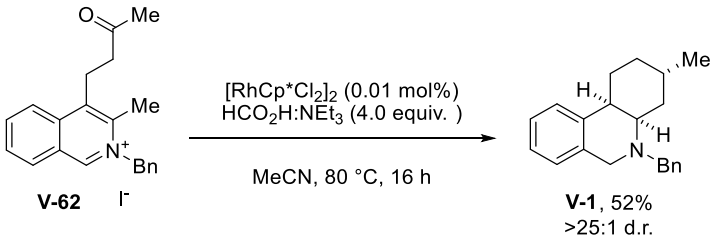
Scheme 5.22: Synthesis of the acrolein incorporated isoquinoline

Finally, the *N*-quaternisation of the key isoquinolines proceeded in good to excellent yields (70-89%) and provided us with substrates to study the dearomative intramolecular annulation reactions (Scheme 5.23).



Scheme 5.23: N-quaternisation reaction of isoquinolines with incorporated electrophiles

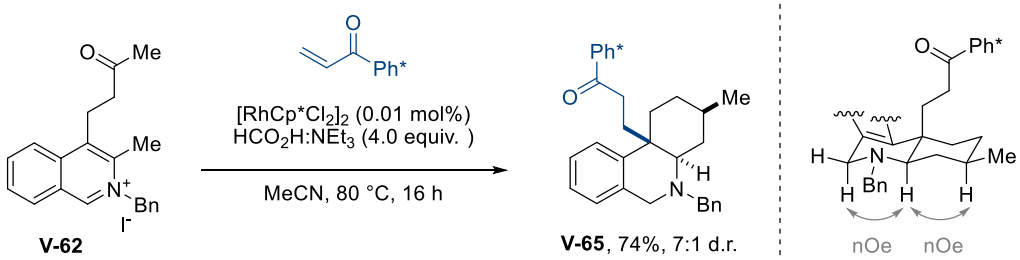
With the relevant starting materials in hand, we next proceeded to test the dearomative intramolecular cyclisation reaction on isoquninolinium **V-62** as this result could be directly compared to the previously performed intermolecular reaction (Scheme 5.1). Pleasingly, we were able to obtain the same annulated product **V-1** as a single diastereoisomer in comparable yield of 52% (Scheme 5.24), using this new approach to closing the D-ring. Since the NMR spectrum of the product **V-1** obtained in the intramolecular annulation reaction exactly matched the product of the intermolecular annulation discussed earlier, we could assign the relative stereochemistry by analogy.



Scheme 5.24: Dearomative intramolecular cyclisation with pre installed MVK

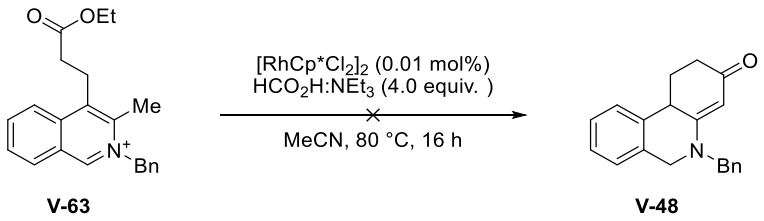
Having confirmed that the intramolecular cyclisation is not only feasible, but also proceeds with equal efficiency and stereoselectivity as the intermolecular reaction, we wanted to explore the possibility of trapping electrophiles in tandem with the annulation process. Ph* vinyl ketone was selected as the electrophile in test reactions, as cyclisation onto its carbonyl would not be possible, thus preventing potential undesired mixtures of annulated products. In test reactions, the desired annulated and functionalised product **V-65** were successfully obtained in 74% yield in a 7:1 diastereomeric ratio

(Scheme 5.26). The relative stereochemistry of the major diastereoisomer was consistent with the mechanism discussed above (Scheme 5.16) and was determined using NOESY NMR experiments.



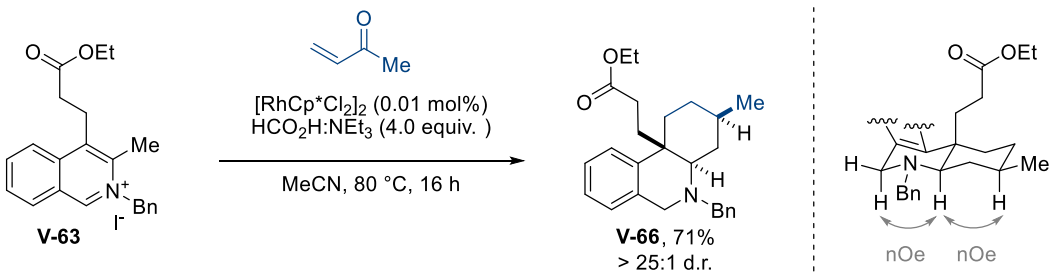
Scheme 5.25: Dearomative intramolecular annulation with electrophile trapping

We were hopeful that the isoquinolinium salt **V-63** with the tethered ester group would allow us to access the vinylogous amide **V-48** in an improved yield. Unfortunately, no desired annulation took place on this substrate, as only reduction of the starting isoquinolinium took place (Scheme 5.26). This observation indicated that the enamine intermediate (which is key to the annulation process) is likely not nucleophilic enough to enable attack on the ester group.



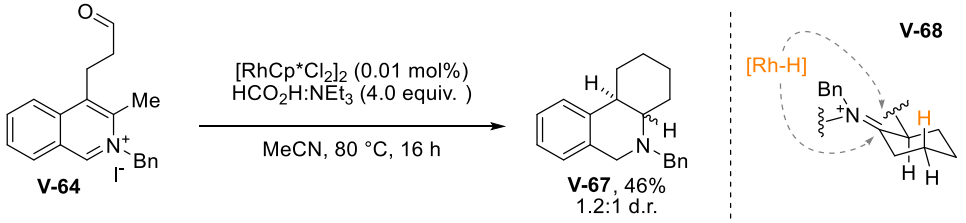
Scheme 5.26: Attempting an intramolecular annulation on an ethyl ester

In order to rule out any other effect of the ester group on the reactivity of the isoquinoline system, we have subjected **V-63** to the standard reductive functionalisation conditions using MVK as the electrophile (Scheme 5.27); the MVK was successfully trapped, and the annulation proceeded in excellent yield (71%) to give **V-66**, as previously described the ester group remained intact. The annulation product was obtained as a single diastereoisomer and the relative stereochemistry was asigned using NOESY NMR experiments.



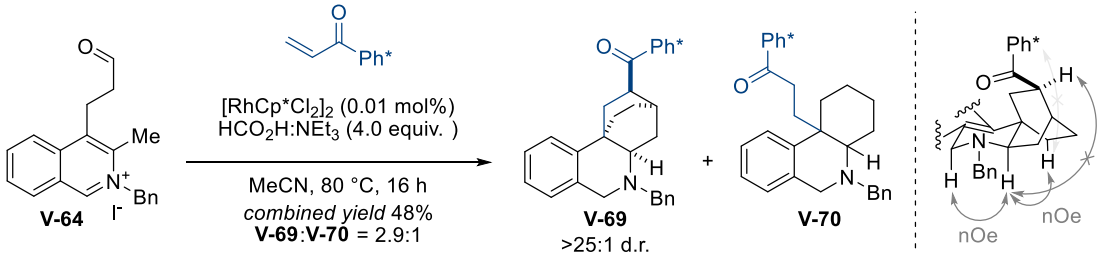
Scheme 5.27: Dearomatisation annulation sequence in the presence of an ester group

Finally, we moved onto the isoquinoline system with a tethered aldehyde. While the dearomative intramolecular annulation proceeded in moderate yield (46%), the product **V-67** was obtained as a 1.2:1 ratio of diastereoisomers (Scheme 5.28). This was not too surprising as both sides of the final iminium ion **V-68** are almost equivalent in the absence of any additional substituents on the D-ring. This suggested that the D-ring methyl group present in the annulations discussed above, likely has a key role in the stereochemical outcome of the final hydride addition, seeing as whenever it was present, all products were obtained with high or complete diastereoselectivity.



Scheme 5.28: Intramolecular annulations with the preinstalled acrolein moiety

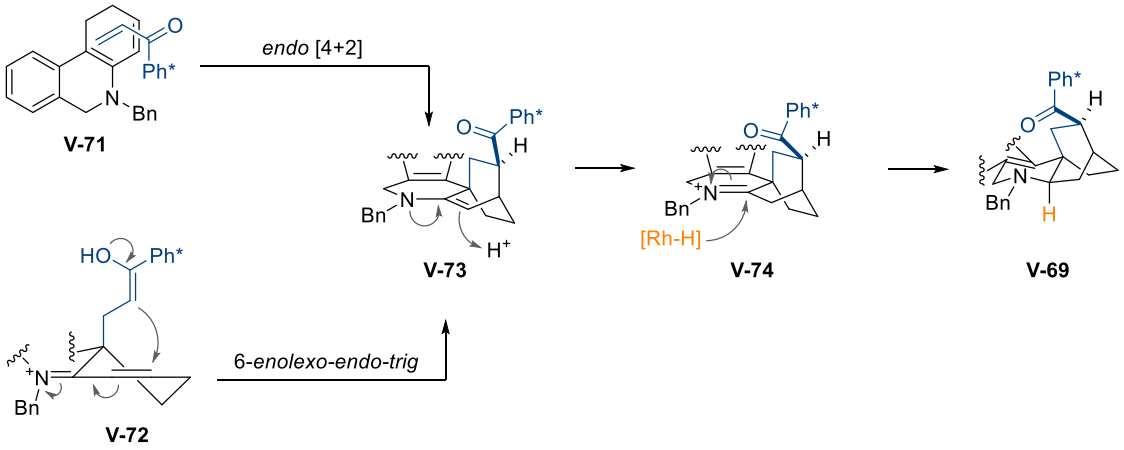
Having seen previously that isoquinolines bearing a large substituent in the C4-position gave the dearomatized and annulated products in high diastereoselectivity, we wanted to see if introducing an external electrophile that would be incorporated at the C4-position would have the same effect. To our surprise a doubly annulated 6-6 ring fused product **V-69** was obtained in this transformation (Scheme 5.29). The desired product **V-70** was also present albeit as a minor component of an inseparable mixture.



Scheme 5.29: Intramolecular annulations and functionalisation with the preinstalled acrolein moiety

There are two possible reaction pathways that could be operating here; in both the intramolecular condensation happens first to form the diene **V-71**, then a stepwise formal [4+2] annulation or a concerted Diels-Alder reaction takes place (Scheme 5.30). From our deuterium labelling studies on the isoquinoline system (Chepter 4) we know that the enol formed after trapping of the enone electrophiles is relatively long lived, as such an intramolecular 6-*enolexo-endo-trig* cyclisation between

the enol and the α,β-unsaturated iminium in **V-72**, to give the enamine **V-73** could be envisioned. However, the high level of diastereoselectivity observed in this transformation suggest that a Diels-Alder reaction between the *in situ* formed diene **V-71** and Ph* vinyl ketone as the dienophile is also possible. Both pathways would result the same enamine **V-73**, that can then get protonated to give iminium **V-74**, the final hydride is then delivered from the less hindered face to give the final product **V-75**.



Scheme 5.30: Proposed mechanism for the formation of the bis annulated product ***V-69***

5.9 Conclusion

Overall, significant progress has been made with respect to the exploration of dearomative annulation reactions for the purpose of total synthesis of therapeutically relevant natural products. We have managed to develop a robust route to close the C-ring, and have made important proof of principle advances on the construction of the D-ring of crinine family natural products. Time constrains towards the end of this DPhil have meant that I was unable to bring the work in this chapter to a full close, however a visiting student Clément Tanguy has recently joined the project and will continue this work.

Chapter 6: Conclusion and future work

In this thesis we have described the evolution of the dearomative reductive functionalisation of pyridines, quinolines and isoquinolines to access highly desirable and complex structures. This work has contributed to the expanding field of dearomatisation chemistry and has made significant steps towards developing general methods for the dearomative functionalisation of azaarenes as well as demonstrating their synthetic utility.

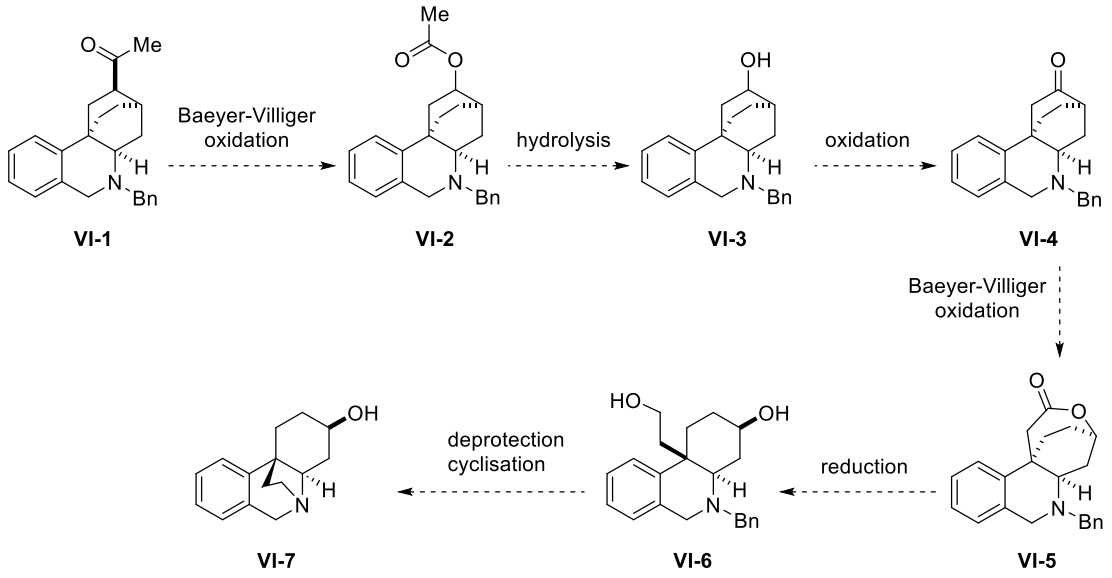
To that effect, a new catalytic system utilizing a novel 2,4-bistrifluoromethylbenzyl-based activating group has been developed and the boundaries of the dearomative hydroxymethylation reaction of pyridinium salts have been expanded. The substrate scope has been greatly broadened, ranging from 4-arylpyridines to electron-rich 4-methoxypyridine, with the reaction proceeding in good yields for the majority of substrates. Additionally, the synthetic utility of this methodology has been demonstrated through the successful synthesis of (±)-paroxetine, indicating its potential for the preparation of various pharmaceutically relevant small molecules.

Moreover, the scope of electrophiles for the reductive functionalization of (iso)quinolinium salts has also been significantly expanded. By transitioning from basic conditions using paraformaldehyde to milder acidic conditions, employing formic acid-triethylamine 5:2 complex as the terminal reductant, a wide range of 1,4-acceptors were well tolerated, leading to the synthesis of C4 functionalized tetrahydroisoquinolines in good yields. Furthermore, the method accommodated diverse substituents and substitution patterns on the parent (iso)quinolinium substrate, enabling the stereoselective synthesis of complex ring structures, including those of pharmaceutical importance.

Overall, this research has made significant progress in exploring dearomative annulation reactions for the total synthesis of therapeutically relevant natural products, such as the crinine alkaloid family. A robust route has been established for closing the C-ring, and important proof-of-principle advancements have been made in constructing the D-ring.

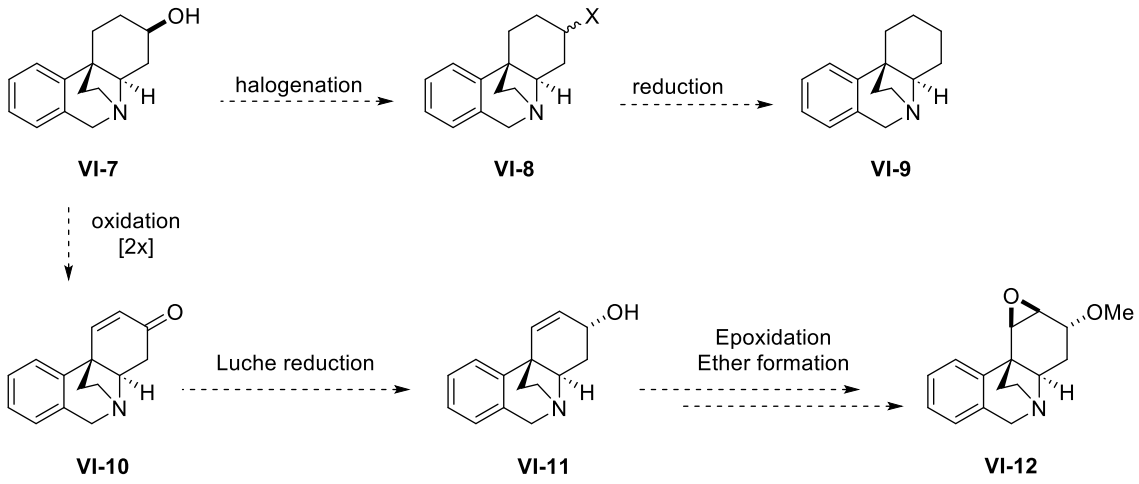
While the work in this thesis has been focused on expanding upon previous group work and developing new methodologies for the dearomative functionalisation of azaarenes, we have been unable to develop a method that would allow for the transformation to occur enantioselectively. However, the initial results are promising for future development, and we are confident that phase transfer conditions combined with the right catalyst will enable us good reactivity and enantioselectivity.

Finally, while time constraints prevented the completion of the work towards the synthesis of the crinine family alkaloid natural products, we could envision a clear synthetic path that arises from our most promising results (Scheme 6.1). The polycyclic compound **VI-1** prepared in Chapter 5 could undergo a double Baeyer-Villiger oxidation sequence that would yield the lactone **VI-5**. Reduction of this species would result in opening of the ring to give the diol **VI-6**, which could close the C-ring using the chemistry discussed in Chapter 5, thus yielding a promising intermediate **VI-7** for further functionalisation.



*Scheme 6.1: Proposed future work on the synthesis of **VI-7***

Taking **VI-7** and subjecting it to a variety of redox transformations we could envision the preparation of **VI-9**, an analogue of (±)-crinine, **VI-10** an analogue of (±)-oxocrinine, and **VI-12** an analogue of (±)-augustine (Scheme 6.2).



*Scheme 6.2: Proposed functionalisation of **VI-7** to crinine derivatives*

Chapter 7: Experimental

7.1 Experimental techniques

7.1.1 Chemicals and solvents

Unless stated otherwise, all chemicals were purchased from commercial suppliers (Sigma-Aldrich, Fluorochem, Alfa Aesar, TCI) and used without further purification. Formic acid/triethylamine 5:2 complex was purchased from Sigma-Aldrich and used without further purification. Rh-catalyst stock solutions were prepared in a 25 mL volumetric flask by dissolving 2 mg $[RhCp^*Cl_2]_2$ in acetonitrile. All solvents used were HPLC grade or p.a. unless stated otherwise. Pentamethylphenyl vinyl ketone was prepared according to a published procedure.[112]

7.1.2 Glassware and reaction conditions

Reactions were carried out in flasks, oven-dried microwave vials, or fresh GC vials under an atmosphere of air unless otherwise stated.

7.1.3 Analytical techniques

^1H, and ^{13}C NMR spectra were recorded on a Bruker AVIII400 Spectrometer (^1H: 400 MHz and ^{13}C: 101 MHz), Bruker AVII500 (^1H: 500 MHz and ^{13}C: 126 MHz) or a Bruker AvanceIV600 (^1H: 600 MHz and ^{13}C: 151 MHz) in $CDCl_3$, DMSO-d_6 or C_6D_6 and referenced to residual solvent peaks. Chemical shifts δ are quoted in parts per million (ppm) to the nearest 0.01 for ^1H 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), pentet (p), hexet (h), heptet (hept), and multiplet (m). Assignments were based upon COSY, HSQC and HMBC experiments. Where unambiguous assignments could not be made the candidate positions are indicated by solidus "/". Low temperature[113] single crystal X-ray diffraction data were collected using a (Rigaku) Oxford Diffraction SuperNova diffractometer for **III-58·HCl**, **V-1·HCl** and **V-12** and data were collected for **IV-59·HCl** at , Beamlime I19-1, Diamond Light Source.[114] Raw frame data were reduced using CrysAlisPro and the structures were solved using 'Superflip'[115] before refinement with CRYSTALS.[116] The structures were then

modified, improved and optimised by full-matrix least squares on F^2 as per the SI (CIF). 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). Melting points (m.p.) were obtained using a Lecia VMGT heated-stage microscope and are uncorrected.

7.1.4 Chromatography

Analytical thin layer chromatography was performed on pre-coated silica gel aluminium sheets from Merck (TLC Silica Gel 60 F_{254}). Spots were visualized either by the quenching of UV fluorescence or by staining with phosphomolybdic acid/cerium sulfate, potassium permanganate or vanillin solutions. Preparative flash column chromatography was carried out using Geduran Silica Gel 60 (40 μm – 63 μm) from Merck.

7.2 General procedures

7.2.1 General procedure A: Preparation of benzyl iodides

To a solution of the corresponding benzyl chloride or bromide (1.00 equiv.) in acetone (0.5 M) at 0 °C was added NaI (2.00 equiv.) and the reaction mixture was stirred in the dark at room temperature for 16 hours. Reaction was quenched with brine (20 mL) and the aqueous layer extracted with Et_2O (2 x 40 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. FCC (0-2% Et_2O in Pentane) afforded the benzyl iodides.

7.2.2 General procedure B: Preparation of 4-*aryl* pyridines

4-Bromopyridine hydrochloride (1.00 equiv.), triphenylphosphine (20 mol%), boronic acid (1.20 equiv.), and potassium carbonate (3.70 equiv.) were added to a 3-necked flask fitted with a reflux condenser. The vessel was evacuated and backfilled with argon three times then dimethoxyethane and water (5:1 0.1 M) were added and solution purged with argon for 10 minutes. Palladium(II) acetate (2.5 mol%) was added and the solution heated at 85 °C for 16 hours. The solution was cooled, diluted with 50 mL of water, and extracted with EtOAc (50 mL) three times. The organic layers were

combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to give the product.

7.2.3 General procedure C: Preparation of bisarylpyridines

3-Bromo-4-(4-fluorophenyl)pyridine **S5** (1.5 mmol, 1.00 equiv.), triphenylphosphine (10 mol%), potassium carbonate (2.70 equiv.), and arylboronic acid (1.10 equiv.) were dissolved in a 5:1 mixture of DME:H_2O (0.1 M) which was then purged with Ar for 10 minutes. $Pd(OAc)_2$ was added and the solution heated for 16 hours at 85 °C. The solution was cooled, diluted with EtOAC and extracted three times with EtOAC. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography to give the product.

7.2.4 General procedure D: Preparation of benzyl pyridinium iodide salts.

A mixture of the corresponding pyridine (1.00 equiv.) and benzyl iodide (1.50/2.00 equiv.) in acetone (0.5 M) was stirred in the dark at room temperature for 16 hours. Diethyl ether (10 mL) was added and the resulting suspension was sonicated (15 min) and then filtered. The resultant solid was washed with diethyl ether and dried under vacuum to give the benzyl pyridinium iodide salts as crystalline solids.

7.2.5 General procedure E: Hydroxymethylation of pyridinium iodides

Substrate (1.00 equiv.), KI (4.00 equiv.), paraformaldehyde (30.0 equiv.), and $[Ru(p\text{-cymene})Cl_2]_2$ (2 mol%) was added to a microwave vial. MeOH (0.2 M) and $Mg(OMe)_2$ (1.00 equiv, 0.89M in MeOH) was added and the solution heated at 65 °C for 16 hours. The solution concentrated under reduce pressure and re-dissolved in CH_2Cl_2 (30 mL), brine (50 mL) and water (50 mL). The solution was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography (FCC) to furnish amines.

Reaction to form **2k/XX** was also performed in an rbf with a reflux condenser attached and gave exactly the same yield on 0.50 mmol scale.

7.2.6 General procedure F: Preparation of quinolinium salts

A mixture of the corresponding quinoline (1.0 equiv.) and benzyl iodide (2.0 equiv.) in acetone (0.5 M) was stirred in the dark at room temperature for 20 – 48 hours. Addition of diethyl ether (10 mL) resulted in precipitation and the resulting suspension was sonicated (15 min). The solids were collected by filtration, washed with diethyl ether and dried under vacuum to give the benzyl quinolinium iodide salts as crystalline solids.

7.2.7 General procedure G: Preparation of tetrahydroquinolines

Quinolinium salt (0.125 mmol, 1.00 equiv.) and electrophile (1.00 to 5.00 equiv.) were dissolved in MeCN (0.10 mL, 1.25 M). Upon addition of HCO_2H:NEt_3 5:2 complex (42 μL, 4.00 equiv.) the reaction mixture was heated to 80 °C for 16 hours. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched with an aqueous solution of K_2CO_3 (10 mL, 0.1 M). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to furnish the corresponding amines.

7.2.8 General procedure H: Metal-catalysed preparation of tetrahydroquinolines

Quinolinium salt (1.00 equiv.), and $[RhCp^*Cl_2]_2$ (0.01 mol%) were added to a microwave vial. MeCN (1.25 M), electrophile (1.0 – 5.0 equiv.) and HCO_2H:NEt_3 (5:2, 4.0 equiv.) were added and the solution heated at 80 °C for 20 hours. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched with an aqueous solution of K_2CO_3 (10 mL, 0.1 M). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to furnish the corresponding amines.

7.2.9 General procedure I: Preparation of isoquinolinium salts

A mixture of the corresponding isoquinoline (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. Addition of diethyl ether (10 mL) resulted in precipitation and the resulting suspension was sonicated (15 min). The solids were collected by filtration, washed with diethyl ether, and dried under vacuum to give the benzyl quinolinium iodide salts as crystalline solids. Where necessary additional purification by column chromatography was performed.

7.2.10 General procedure J: Synthesis of tetrahydroisoquinolines

Isoquinolinium salt (0.125 mmol, 1.00 equiv.) and electrophile (1.00 to 5.00 equiv.) were dissolved in MeCN (0.10 mL, 1.25 M). Upon addition of HCO_2H:NEt_3 5:2 complex (42 μL, 4.00 equiv.) the reaction mixture was heated to 80 °C for 18 hours. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched with an aqueous solution of K_2CO_3 (10 mL, 0.1 M). The solution was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to furnish the respective amines

7.2.11 General procedure K: Rhodium catalysed synthesis of tetrehydroisoquinolines

Isoquinolinium salt (1.00 equiv.), and $[RhCp^*Cl_2]_2$ (0.01 mol%) was added to a microwave vial. MeCN (1.25 M), electrophile (1.0-2.0 equiv.) and HCO_2H:NEt_3 (5:2, 4.0 equiv.) were added and the solution heated at 80 °C for 18 hours. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched with an aqueous solution of K_2CO_3 (10 mL, 0.1 M). The solution was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to furnish the respective amines.

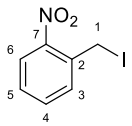
7.2.12 General procedure L: Alkylation of isoquinolinium salts with aldehydes

Isoquinolinium salt (0.125 mmol, 1.0 equiv.) and aldehyde (1.0 to 4.0 equiv.) are dissolved in MeCN (0.10 mL ≙ 1.25 M). Upon addition of HCO_2H:NEt_3 5:2 complex (42 µL, 4.0 equiv.) the reaction mixture is heated to 80 °C for 18 hours. The reaction was diluted with CH_2Cl_2 (10 mL) and quenched with an aqueous solution of K_2CO_3 (10 mL, 0.1 M). The solution was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash column chromatography to furnish the respective amines.

7.3 Experimental details

7.3.1 The synthesis of benzyl iodides

2-Nitrobenzyl iodide (S1)

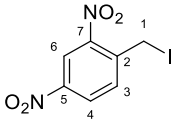


The title compound was prepared by General Procedure A using 2-nitrobenzyl bromide (6.48 g, 30.0 mmol) to give the *iodide* **S1** (7.10 g, 90%) as an orange solid. Spectroscopic data was consistent with that reported in the literature.[117]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.2, 1.4 Hz, 1H, C^{6}**H**), 7.60 – 7.40 (m, 3H, 3 x Ar**CH**), 4.79 (s, 2H, C^{1}**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5 (C^{7}), 135.1 (C^{2}), 134.0 (ArCH), 132.4 (ArCH), 129.2 (ArCH), 125.9 (ArCH), 0.0 ($C^{1}H_2$).

2,4-*Din*itrobenzyl iodide (S2)



Title compound was prepared by General Procedure A using 2,4-dinitrobenzyl bromide (217 mg, 1.00 mmol) to give the *iodide* **S2** (273 mg 89%) as a yellow solid.

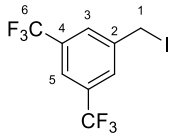
m.p. not obtained due to the rapid decomposition of the material.

HRMS (ESI): Exact mass calculated for $C_7H_4O_4N_2{}^{127}I$ $[M]^-$: 306.92212, found: 306.92142**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 2.4 Hz, 1H, C^{6}**H**), 8.40 (dd, *J* = 8.5, 2.4 Hz, 1H, C^{4}**H**), 7.73 (d, *J* = 8.5 Hz, 1H, C^{3}**H**), 4.84 (s, 2H, 2 x C^{1}**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.93 (C^{2}), 133.67(C^{6}H), 128.01 (C^{4}H), 121.52 (C^{3}H), –2.78 ($C^{1}H_2$), signal for C^{5} and C^{7} not observed.

IR (neat) (cm^{-1}): 3124, 2924, 1704, 1603, 1536, 1346, 1198, 1085, 892, 506.

3,5-Bis(trifluoromethyl)benzenyl iodide (S3)

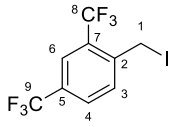


Title compound was prepared using General Procedure A using 3,5-bis(trifluoromethyl)benzyl bromide (0.37 mL, 2.00 mmol) to yield the *iodide* **S3** (700 mg, 99%) as a yellow solid. Spectroscopic data was consistent with that reported in the literature.[118]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 2H, 2 x C^3**H**), 7.76 (s, 1H, C^5**H**), 4.49 (s, 2H, C^1**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, (C^2), 132.4 (q, *J* = 33.6 Hz, 2 x C^4), 128.9 (q, *J* = 3.1 Hz, 2 x C^3H), 123.1 (q, *J* = 273 Hz, 2 x C^6F_3), 122.0 – 121.8 (m, C^5H), 1.3 (C^1H_2).

2,4-Bis(trifluoromethyl)benzenyl iodide (S4)



Title compound was prepared using General Procedure A using 2,4-bis(trifluoromethyl)benzyl bromide (0.38 mL, 2.00 mmol) to yield the *iodide* **S4** (700 mg, 99%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_9H_5F_6^{127}$ $[M-I]^+$: 227.0290, found: 227.0293.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H, C^6**H**), 7.76 (d, *J* = 8.3 Hz, 1H, C^4**H**), 7.70 (d, *J* = 8.3 Hz, 1H, C^3**H**), 4.61 (s, 2H, C^1**H$_2$**).

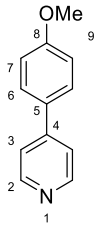
^{13}C NMR (126 MHz, $CDCl_3$) δ 142.3 (C^2), 133.6 (C^3H), 130.4 (q, *J* = 33.7 Hz, C^5/ C^7), 129.4 (q, *J* = 3.7 Hz, C^4H), 128.4 (q, *J* = 31.6 Hz, C^5/C^7), 124.05 – 123.52 (m, C^6H), 123.5 (q, *J* = 274.5 Hz, C^8F_3/ C^9F_3), 123.30 (q, *J* = 272.3 Hz, C^8F_3/ C^9F_3), –2.53 (q, *J* = 2.5 Hz, C^1H_2).

^{19}F NMR (377 MHz, $CDCl_3$) δ –60.7, –63.0.

IR (neat) (cm^{-1}): 1628, 1345, 1273, 1175, 1119, 1082, 1053, 913, 844, 671

7.3.2 The synthesis of pyridine precursors

4-(4-Methoxyphenyl)pyridine (S5)

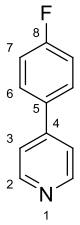


The title compound was prepared according to General Procedure B using 4-methoxyphenylboronic acid (547 mg, 3.60 mmol) and was purified by FCC (10% - 20% EtOAc in pentane) to give *pyridine* **S5** (1.60 g, 76%) as a white solid. The spectroscopic data was consistent with previous reports.[119]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 – 8.57 (m, 2H, 2 x C^{2}**H**), 7.65 – 7.56 (m, 2H, 2 x C^{6}**H**), 7.50 – 7.43 (m, 2H, 2 x C^{3}**H**), 7.05 – 6.98 (m, 2H, 2 x C^{7}**H**), 3.87 (s, 3H, C^{9}**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7 (C^{8}), 150.4 (2 x C^{2}H), 148.0 (C^{4}), 130.5 (C^{5}), 128.3 (2 x C^{6}H), 121.2 (2 x C^{3}H), 114.7 (2 x C^{7}H), 55.6 ($C^{9}H_3$).

4-(4-Fluorophenyl)pyridine (II-88)

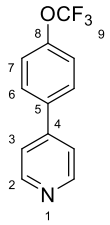


The title compound was prepared according to General Procedure B using 4-fluorobenzene boronic acid (1.68 g, 12.0 mmol) and was purified by FCC (10% - 20% EtOAc in pentane) to give *pyridine* **II-88** (1.56 g, 90% yield) as a colourless glass. The spectroscopic data was consistent with previous literature reports.[120]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 – 8.67 (m, 2H, 2 x C^{2}**H**), 7.67 – 7.57 (m, 2H, 2 x C^{6}**H**), 7.53 – 7.47 (m, 2H, 2 x C^{3}**H**), 7.24 – 7.13 (m, 2H, 2 x C^{7}**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6 (d, J = 249.3 Hz, C^{8}), 150.3 (2 x C^{2}H), 147.6 (C^{4}), 134.3 (C^{5}), 128.9 (d, J = 8.3 Hz, 2 x C^{6}H), 121.6 (2 x C^{3}H), 116.3 (d, J = 21.6 Hz, 2 x C^{7}H).

4-(4-(Trifluoromethoxy)phenyl)pyridine (S6)



The title compound was prepared according to General Procedure B using 4-trifluoromethoxyphenylboronic acid (2.47 g, 12.0 mmol) and was purified by FCC (10% - 20% EtOAc in pentane) to give *pyridine* **S6** (2.19 g, 92%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{13}H_8F_3NO$ $[M+H]^+$:240.0631, found: 240.0632.

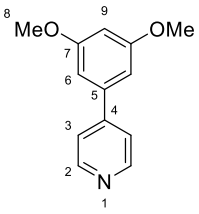
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 – 8.65 (m, 2H, 2 x C^2**H**), 7.70 – 7.62 (m, 2H, 2 x C^6**H**), 7.51 – 7.45 (m, 2H, 2 x C^3**H**), 7.38 – 7.30 (m, 2H, 2 x C^7**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5 (2 x C^2H), 150.1 (C^8), 147.2 (C^4), 136.9 (C^5), 128.7 (2 x C^6H), 121.7 (2 x C^3H), 121.6 (2 x C^7H), 120.6 (q, J = 257.7 Hz, C^9F_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ –57.8.

IR (neat) (cm^{-1}): 2982, 1596, 1516, 1488, 1252, 1207, 1154, 1110, 805, 674.

4-(3,5-Dimethoxyphenyl)pyridine (S7)



The title compound was prepared according to General Procedure B using 4-trifluoromethoxyphenylboronic acid (2.19 g, 12.0 mmol) and was purified by FCC (20% - 50% EtOAc in pentane) to give *pyridine* **S7** (1.74 g, 81%) as a white solid.

m.p. (EtOAc): 56 – 58 °C

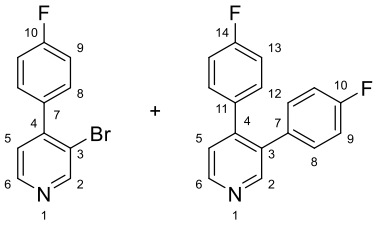
HRMS (ESI): Exact mass calculated for $C_{13}H_{14}NO_2$ $[M+H]^+$: 216.1019, found: 216.1020.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.62 (m, 2H, 2 x C^2**H**), 7.50 – 7.44 (m, 2H, 2 x C^3**H**), 6.75 (d, *J* = 2.3 Hz, 2H, 2 x C^6**H**), 6.53 (t, *J* = 2.3 Hz, 1H, C^9**H**), 3.85 (s, 6H, 3 x C^8**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (2 x C^7), 150.4 (2 x C^2H), 148.5 (C^4), 140.5 (C^5), 121.9 (2 x C^3H), 105.4 (2 x C^6H), 100.9 (C^9H), 55.6 (2 x C^8H_3).

IR (neat) (cm^{-1}): 2979, 2845, 1586, 1336, 1226, 1198, 1165, 1029, 852, 818.

3-Bromo-4-(4-fluorophenyl)pyridine (S8) and 3,4-bis(4-fluorophenyl)pyridine (S9)



The title compound were prepared according to General Procedure B using 3,4-dibromopyridine (2.37 g, 10.0 mmol) and 4-fluorophenylboronic acid (1.52 g, 10.9 mmol) and was purified by FCC (2% EtOAc in pentane) to give *arylpyridine* **S8** (1.27 g, 51%) as a white solid followed by *bisarylpyridine* **S9** (182 mg, 7% yield) as a white solid.

Data for **S8**:

m.p. (EtOAc): 66 - 68 °C

HRMS (ESI): Exact mass calculated for $C_{11}H_8BrFN$ $[M+H]^+$: 251.9819, found: 251.9821

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 0.6 Hz, 1H, C^2**H**), 8.55 (d, *J* = 4.9 Hz, 1H, C^5**H**), 7.49 – 7.37 (m, 2H, 2 x C^8**H**), 7.25 (dd, *J* = 4.9, 0.6 Hz, 1H, C^6**H**), 7.22 – 7.11 (m, 2H, 2 x C^9**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1 (d, *J* = 249.0 Hz, C^{10}), 152.8, (C^2H), 148.9 (C^4), 148.5 (C^5H), 134.3 (d, *J* = 3.5 Hz, C^7), 130.9 (d, *J* = 8.4 Hz, 2 x C^8H), 125.7 (C^6H), 121.0 (C^3), 115.7 (d, *J* = 21.7 Hz, 2 x C^9H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –112.3 (tt, *J* = 8.6, 5.4 Hz).

IR (neat) (cm^{-1}): 3048, 3011, 2161, 1970, 1605, 1583, 1510, 1470, 1228, 831.

Data for **S9**:

m.p. (EtOAc): 108 - 110 °C

HRMS (ESI): Exact mass calculated for $C_{17}H_{12}F_2N$ $[M+H]^+$: 268.0932, found: 268.0932.

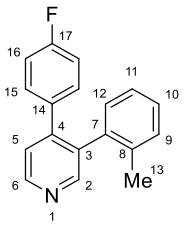
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.1 Hz, 1H, C^{5}**H**), 8.61 (d, *J* = 0.7 Hz, 1H, C^{2}**H**), 7.31 (dd, *J* = 5.1, 0.7 Hz, 1H, C^{6}**H**), 7.16 – 7.05 (m, 4H, 2 x C^{9}**H** + 2 x C^{13}**H**), 7.04 – 6.92 (m, 4H, 2 x C^{8}**H** + 2 x C^{12}**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5 (d, *J* = 248.5 Hz, C^{10}/C^{14}), 162.3 (d, *J* = 247.6 Hz, C^{10}/C^{14}), 151.0 (C^{2}H), 149.0 (C^{5}H), 146.7 (C^{4}), 134.8 (C^{3}), 134.4 (d, *J* = 3.3 Hz, C^{7}/C^{11}), 133.5 (d, *J* = 3.3 Hz, C^{7}/C^{11}), 131.4 (d, *J* = 8.0 Hz, C^{8}H/C^{12}H), 131.0 (d, *J* = 8.3 Hz, C^{8}H/C^{12}H), 124.5 (C^{6}H), 115.5 (d, *J* = 22.0 Hz, C^{9}H + C^{13}H).

^{19}F NMR (377 MHz, $CDCl_3$) δ -113.4 – -113.6 (m), -114.4 – -114.6 (m).

IR (neat) (cm^{-1}): 3050, 3011, 2161, 2034, 1978, 1510, 1228, 1215, 828, 814.

4-(4-Fluorophenyl)-3-(o-tolyl)pyridine (S10)



The title compound was prepared according to General Procedure C using 2-methylphenylboronic acid (150 mg, 1.10 mmol) and purified by FCC (10%-20% EtOAc in pentane) to give *pyridine* **S10** (370 mg, 94% yield) as a white solid.

m.p. (EtOAc) 110 - 112 °C

HRMS (ESI): Exact mass calculated for $C_{18}H_{15}FN$ $[M+H]^+$: 268.1183, found: 268.1182.

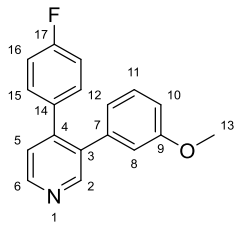
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 5.1 Hz, 1H, C^{5}**H**), 8.54 (d, *J* = 0.7 Hz, 1H, C^{2}**H**), 7.36 (dd, *J* = 5.1, 0.7 Hz, 1H, C^{6}**H**), 7.23 (dd, *J* = 7.4, 1.7 Hz, 1H, C^{12}**H**), 7.19 (td, *J* = 7.4, 1.7 Hz, 1H, C^{11}**H**), 7.15 – 7.07 (m, 4H, C^{9}**H** + C^{10}**H** + 2 x C^{15}**H**), 6.96 – 6.86 (m, 2H, 2 x C^{16}**H**), 1.87 (s, 3H, C^{13}**H**$_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (d, *J* = 248.4 Hz, C^{17}), 151.3 (C^{2}H), 148.9 (C^{5}H), 147.4 (C^{4}), 137.2 (C), 136.2 (C), 135.7 (C), 134.7 (d, *J* = 3.3 Hz, C^{14}), 130.8 (d, *J* = 8.7 Hz, ArCH + 2 x C^{15}H), 130.4 (ArCH), 128.2 (C^{12}H), 126.0 (C^{11}H), 124.0 (C^{6}H), 115.4 (d, *J* = 21.7 Hz, 2 x C^{16}H), 20.1 ($C^{13}H_3$).

^{19}F NMR (377 MHz, $CDCl_3$) δ -113.5 (tt, *J* = 8.8, 5.3 Hz).

IR (neat) (cm^{-1}): 2994, 1602, 1512, 1477, 1218, 831, 779, 756, 746, 729.

4-(4-Fluorophenyl)-3-(3-methoxyphenyl)pyridine (S11)



The title compound was prepared according to General Procedure C using 2-methylphenylboronic acid (167 mg, 1.10 mmol) and purified by FCC (10%-30% EtOAc in pentane) to give *pyridine* **S11** (402 mg, 96% yield) as a pale yellow oil.

HRMS (ESI): Exact mass calculated for $C_{18}H_{15}FNO$ $[M+H]^+$: 280.1132, found: 280.1130.

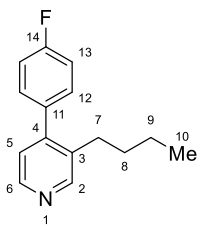
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 0.7 Hz, 1H, C^2**H**), 8.62 (d, *J* = 5.1 Hz, 1H, C^5**H**), 7.31 (dd, *J* = 5.1, 0.7 Hz, 1H, C^6**H**), 7.20 (dd, *J* = 8.4, 7.6 Hz, 1H, C^{11}**H**), 7.17 – 7.11 (m, 2H, 2 x C^{15}**H**), 7.02 – 6.92 (m, 2H, 2 x C^{16}**H**), 6.83 (ddd, *J* = 8.4, 2.6, 1.0 Hz, 1H, C^{12}**H**), 6.72 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H, C^{10}**H**), 6.67 (dd, *J* = 2.6, 1.6 Hz, 1H, C^8**H**), 3.68 (s, 3H, C^{13}**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (d, *J* = 248.2 Hz, C^{17}), 159.6 (C^9), 151.1 (C^2H), 148.9 (C^5H), 146.8 (C^4), 139.0 (C), 135.8 (C), 134.7 (d, *J* = 3.5 Hz, C^{14}), 131.1 (d, *J* = 8.3 Hz, 2 x C^{15}H), 129.6 (C^{11}H), 124.6 (C^6H), 122.4 (C^{10}H), 115.5 (d, *J* = 21.5 Hz, 2 x C^{16}H), 115.5 (C^8H), 113.4 (C^{12}H), 55.3 ($C^{13}H_3$).

^{19}F NMR (377 MHz, $CDCl_3$) δ -113.8 (tt, *J* = 8.5, 5.2 Hz).

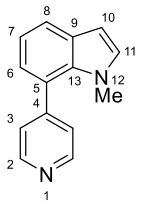
IR (neat) (cm^{-1}): 3039, 2938, 1605, 1512, 1472, 1221, 1160, 1046, 1016, 828.

3-Butyl-4-(4-fluorophenyl)pyridine (S12)



3-Bromo-4-(4-fluorophenyl)pyridine **S8** (1.00 equiv.), S-PHOS (4 mol%), potassium phosphate (4.00 equiv.), and alkylboronic acid (2.00 equiv.) were dissolved in PhMe (8 mL per mmol of aryl bromide) which was then purged with Ar for 10 minutes. $Pd_2(dba)_3$ (2 mol%) was added and the solution heated for 16 hours at 100 °C. The solution was cooled, diluted with EtOAC and extracted three times with EtOAC. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was carried through without further purification.

1-Methyl-7-(pyridin-4-yl)-1H-indole (S13)



4-Pyridylboronic acid (830 mg, 6.75 mmol), 7-bromo-1-methyl-1H-indole (945 mg, 4.50 mmol), potassium carbonate (1.55 g, 11.25 mmol), and triphenylphosphine (118 mg, 10 mol%) were dissolved in dioxane:water (40 mL:10 mL). The solution was purged with argon for 10 minutes, then palladium acetate (25 mg, 2.5 mol%) was added. The reaction was heated at 80 °C under argon for 14 hours, then cooled, and diluted with EtOAc (50 mL) and water (50 mL). The solution was separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL, the organic layers were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by FCC (20%-50% EtOAc in Pentane) to yield *heterocycle* **S13** (500 mg, 53% yield) as a white solid.

m.p. (EtOAc) 130 - 132 °C;

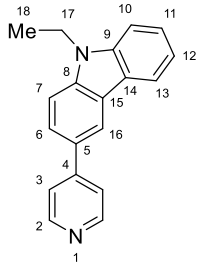
HRMS (ESI): Exact mass calculated for $C_{14}H_{13}N_2$ $[M+H]^+$: 209.1073, found: 209.1074.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 – 8.64 (m, 2H, 2 x C^2**H**), 7.68 (dd, *J* = 7.9, 1.2 Hz, 1H, C^6**H**), 7.43 – 7.36 (m, 2H, 2 x C^3**H**), 7.15 (dd, *J* = 7.9, 7.2 Hz, 1H, C^7**H**), 7.05 – 6.98 (m, 2H, C^8**H** + C^{11}**H**), 6.58 (d, *J* = 3.1 Hz, 1H, C^{10}**H**), 3.36 (s, 3H, C^{12}**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3 (2 x $C^{2}H$), 148.9 (C), 133.4 (C), 131.4 ($C^{11}H$), 130.2 (C), 125.3 (2 x $C^{3}H$), 124.1 ($C^{8}H$), 123.9 (C), 121.5 ($C^{6}H$), 119.3 ($C^{7}H$), 101.7 ($C^{10}H$), 37.2 ($C^{12}H_3$).

IR (neat) (cm^{-1}): 3012, 2160, 2031, 1978, 1511, 1470, 1229, 831, 822, 792.

9-Ethyl-3-(pyridin-4-yl)-9H-carbazole (S14)



4-Pyridylboronic acid (1.23 g, 10.0 mmol), 3-bromo-9-ethyl-9H-carbazole (3.28 g, 12.0 mmol), potassium carbonate (3.70 g, 27.0 mmol), and triphenylphosphine (262 mg, 10 mol%) were dissolved in dioxane:water (80 mL:20 mL). The solution was purged with argon for 10 minutes, then palladium acetate (56 mg, 2.5 mol%) was added. The reaction was heated at 80 °C under argon for 14 hours, then cooled, and diluted with EtOAc (100 mL) and water (100 mL). The solution was separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL, the organic layers were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by FCC (10%-40% EtOAc in Pentane) to yield *heterocycle* **S14** (1.00 g, 30% yield) as a white solid.

m.p. (EtOAc) 161 - 163 °C

HRMS (ESI): Exact mass calculated for $C_{19}H_{17}N_2$ $[M+H]^+$: 273.1386, found: 273.1386.

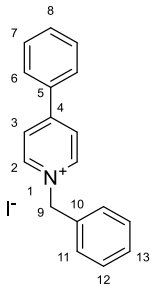
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 – 8.64 (m, 2H, 2 x C^{2}**H**), 8.40 (d, *J* = 1.8 Hz, 1H, C^{16}**H**), 8.17 (dt, *J* = 7.8, 1.0 Hz, 1H, C^{13}**H**), 7.77 (dd, *J* = 8.5, 1.8 Hz, 1H, C^{6}**H**), 7.67 – 7.59 (m, 2H, 2 x C^{3}**H**), 7.55 – 7.41 (m, 3H, C^{7}**H** + C^{10}**H** + C^{11}**H**), 7.29 (ddd, *J* = 7.8, 7.0, 1.1 Hz, 1H, C^{12}**H**), 4.41 (q, *J* = 7.2 Hz, 2H, C^{17}**H$_2$**), 1.47 (t, *J* = 7.2 Hz, 3H, C^{18}**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3 ($C^{2}H$), 149.3 (C^{4}), 140.6 (C), 140.5 (C), 128.9 (C), 126.4 ($C^{11}H$), 124.8 ($C^{6}H$), 123.8 (C), 123.0 (C), 121.7 (2 x $C^{3}H$), 120.7 ($C^{13}H$), 119.5 ($C^{12}H$), 119.2 ($C^{16}H$), 109.1 ($C^{7}H$/$C^{10}H$), 108.9 ($C^{7}H$/$C^{10}H$), 37.9 ($C^{17}H_2$), 14.0 ($C^{18}H_3$).

IR (neat) (cm^{-1}): 2983, 2161, 1594, 1472, 1459, 1232, 1217, 804, 757, 735.

7.3.3 The synthesis of pyridinium salts

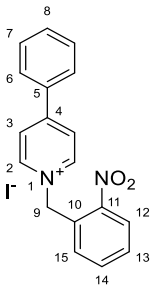
_N_-Benzyl-4-phenylpyridinium iodide (S15)



The title compound was prepared by General Procedure D using 4-phenyl pyridine (1.41 g, 9.10 mmol) and benzyl iodide (4.78 g 18.2 mmol) to give salt **S15** (3.46 g, 91%) as a yellow solid. Spectroscopic data was consistent with that reported in the literature.[74]

^{1}H NMR (400 MHz, DMSO) δ 9.26 (d, *J* = 7.1 Hz, 2H, 2 x C^{2}**H**), 8.55 (d, *J* = 7.1 Hz, 2H, 2 x C^{3}**H**), 8.12 – 8.01 (m, 2H, 2 x C^{7}**H**), 7.69 – 7.61 (m, 3H, 2 x C^{6}**H** + C^{8}**H**), 7.61 – 7.56 (m, 2H, 2 x C^{12}**H**), 7.51 – 7.39 (m, 3H, 2 x C^{11}**H** + C^{13}**H**), 5.87 (s, 2H, C^{9}**H$_2$**).
^{13}C NMR (101 MHz, DMSO) δ 155.1 (C^{4}), 144.8 (2 x C^{2}H), 134.5 (C), 133.5 (C), 132.2 (C^{8}H), 129.7 (2 x C^{6}H), 129.3 (C^{13}H), 129.2 (2 x C^{11}H), 128.7 (2 x C^{12}H), 128.2 (2 x C^{7}H), 125.0 (2 x C^{3}H), 62.4 (C^{9}H$_2$).

_N_-(2-Nitrobenzyl)-4-phenylpyridinium iodide (S16)



The title compound was prepared by General Procedure D using 4-phenyl pyridine (1.41 g, 9.1 mmol) and 2-nitrobenzyl iodide **S1** (4.78 g 18.2 mmol) to give salt **S16** (3.46 g, 91%) as a yellow solid.

m.p. (acetone) 196-198 °C

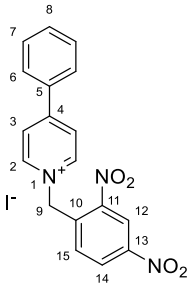
HRMS (ESI): Exact mass calculated for $C_{18}H_{15}O_2N_2$ $[M]^+$: 291.11280, found: 291.11275;

^{1}H NMR (400 MHz, DMSO) δ 9.18 – 9.08 (d, *J*=7.1 Hz, 2H, 2 x C^{2}**H**), 8.68 – 8.57 (d, *J*=7.1 Hz, 2H, 2 x C^{3}**H**), 8.28 (dd, *J* = 8.1, 1.4 Hz, 1H, C^{12}**H**), 8.18 – 8.08 (m, 2H, 2 x ArC**H**), 7.86 – 7.62 (m, 5H, 5 x ArC**H**), 7.19 (dd, *J* = 7.7, 1.4 Hz, 1H, C^{15}**H**), 6.24 (s, 2H, C^{9}**H$_2$**).

^{13}C NMR (101 MHz, DMSO) δ 155.5 (ArC), 147.5 (ArC), 145.6 (2 x C^{2}H), 135.0 (ArCH), 133.5 (ArC), 132.4 (ArCH), 130.4 (ArCH), 130.0 (C^{15}H), 129.8 (2 x ArCH), 129.6 (ArC), 128.3 (2 x ArCH), 125.6 (C^{12}H), 124.9 (2 x C^{3}H), 59.9 (C^{9}H$_2$).

IR (neat) (cm^{-1}): 1637, 1514, 1440, 1347, 1335, 1200, 861, 790, 772, 747.

***N*-(2,4-Dinitrobenzyl)-4-phenylpyridinium iodide (S17)**

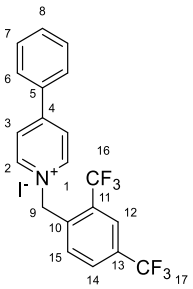


Title compound was prepared by General Procedure D using 4-phenyl pyridine (65.7 mg, 0.42 mmol) and 2,4-bisnitrobenzyl iodide **S2** (261 mg, 0.85 mmol) to give salt **S17** (185 mg, 95%) as a red-brown solid. This compound was found to be highly hydroscopic and water in the atmosphere readily cleaved the bond between N^1 and C^9. Due to this instability full characterisation data was not obtained.

HRMS (ESI): Exact mass calculated for $C_{18}H_{14}O_2N_3[M]^+$ m/z: 336.09788, found 336.09787.

^{1}H NMR (400 MHz, DMSO) δ 9.13 (d, *J* = 7.0 Hz, 2H, 2 x C^2**H**), 8.91 (d, *J* = 2.4 Hz, 1H, C^{12}**H**), 8.68 (d, *J* = 7.0 Hz, 2H, 2 x C^3**H**), 8.51 (dd, *J* = 8.6, 2.4 Hz, 1H, C^{14}**H**), 8.18 – 8.10 (m, 2H, 2 x C^7**H**), 7.76 – 7.62 (m, 3H, 2 x C^6**H** + C^8**H**), 7.37 (d, *J* = 8.6 Hz, 1H, C^{15}**H**), 6.34 (s, 2H, C^9**H$_2$**).

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-phenylpyridinium iodide (II-17)**



The title compound was prepared by General Procedure D using 4-phenyl pyridine (517 mg, 3.33 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (2.37 g, 6.66 mmol) to give the pyridinium **II-17** (1.51 g, 89%) as a yellow solid.

m.p. (acetone): 221-223 °C

HRMS (ESI): Exact mass calculated for $C_{20}H_{14}F_6N$ $[M]^+$ m/z: 382.10250, found: 382.10225

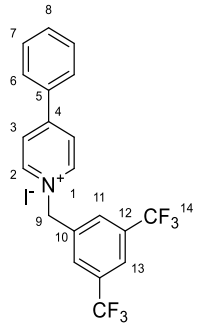
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (d, J = 7.0 Hz, 2H, 2 x C^2**H**), 8.63 (d, J = 7.0 Hz, 2H, 2 x C^3**H**), 8.22 (s, 1H, C^{12}**H**), 8.13 (m, 3H, 2 x C^7**H** + C^{14}**H**), 7.72 – 7.64 (m, 3H, 2 x C^6**H** + C^8**H**), 7.43 (d, J = 8.2 Hz, 1H, C^{15}**H**), 6.21 (s, 2H, 2 x C^9**H**$_2$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 155.9 (C), 145.8 (2 x C^{2}H), 136.8 (C), 133.3 (C), 132.6 (C^{8}H), 131.0 (C^{15}H), 130.5 (q, J = 3.9 Hz, C^{14}H), 129.9 (q, J = 33.5 Hz, C^{11}/C^{13}), 129.8 (2 x C^{6}H), 128.4 (2 x C^{7}H), 127.8 (q, J = 31.7 Hz, C^{11}/C^{13}), 124.9 (2 x C^{3}H), 124.0 – 123.5 (m, C^{12}H), 123.22 (q, J = 274.6 Hz, C^{16}F$_3$/C^{17}F$_3$), 123.18 (q, J = 272.6 Hz, C^{16}F$_3$/C^{17}F$_3$), 58.9 (q, J = 3.1 Hz, C^{9}H$_2$).

^{19}F NMR (377 MHz, DMSO-d_6) δ –59.0, –61.5.

IR (neat) (cm^{-1}):2984, 2161, 1978, 1639, 1343, 1284, 1270, 1181, 1168, 1137.

***N*-(3,5-bis(Trifluoromethyl)benzyl)-4-phenylpyridinium iodide (S18)**



Title compound was prepared by General Procedure D using 4-phenyl pyridine (155 mg, 1.00 mmol) and 3,5-bis(trifluoromethy)benzyl iodide **S3** (708.1 mg, 2.00 mmol) to give the pyridinium **S18** (435 mg, 88%) as a yellow solid.

m.p. (acetone): >350 °C

HRMS (ESI): Exact mass calculated for $C_{20}H_{14}F_6N$ $[M]^+$: 382.1025, found 382.1031.

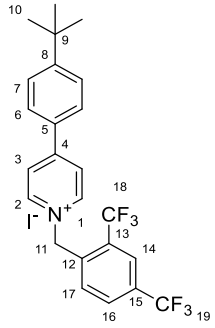
^{1}H NMR (400 MHz, DMSO) δ 9.30 (d, J = 7.1 Hz, 2H, 2 x C^2**H**), 8.57 (d, J = 7.1 Hz, 2H, 2 x C^3**H**), 8.4 (d, J = 1.7 Hz, 2H, 2 x C^{11}**H**), 8.23 (s, 1H, C^{13}**H**), 8.12 – 8.06(m, 2H, 2 x ArC**H**), 7.74 – 7.49 (m, 3H, 3 x ArC**H**), 5.99 (s, 2H, C^9**H**$_2$).

^{13}C NMR (126 MHz, DMSO) δ 155.3 (C^4), 145.0 (2 x C^{2}H), 137.0 (C), 133.5 (C), 132.3 (ArCH), 130.9 (q, J = 33.0 Hz, 2 x C^{12}), 130.6 (q, J = 3.8 Hz, 2 x C^{11}H), 129.7 (2 x ArCH), 128.3 (2 x ArCH), 125.0 (2 x C^{3}H), 123.7 – 123.2 (m, C^{13}H), 123.1 (q, J = 273.1 Hz, 2 x C^{14}F$_3$), 61.0 (C^{9}H$_2$).

^{19}F NMR (377 MHz, DMSO) δ –61.2.

IR (neat) (cm^{-1}): 3021, 2960, 1635, 1280, 1167, 1113, 910, 771, 744, 683.

N-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-(*tert*-butyl)phenyl)pyridinium iodide (II-20)



The title compound was prepared by General Procedure D using 4-(4-(*tert*-butyl)phenyl)pyridine (423 mg, 2.0 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.06 g, 3.00 mmol) to give the pyridinium **II-20** (1.11 g, 98%) as a yellow solid.

m.p. (acetone): 255-257 °C

HRMS (ESI): Exact mass calculated for $C_{24}H_{22}NF_6$ $[M]^+$: 438.16510, found 438.16490.

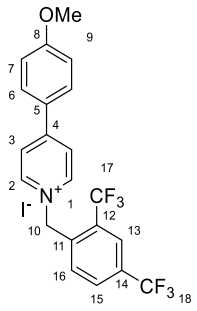
^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.10 (d, *J* = 7.0 Hz, 2H, 2 x C^2**H**), 8.61 (d, *J* = 7.0 Hz, 2H, 2 x C^3**H**), 8.23 (s, 1H, C^{14}**H**), 8.15 (d, *J* = 8.3 Hz, 1H, C^{16}**H**), 8.09 (d, *J* = 8.6 Hz, 2H, 2 x C^6**H**), 7.69 (d, *J* = 8.6 Hz, 2H, 2 x C^7**H**), 7.44 (d, *J* = 8.3 Hz, 1H, C^{17}**H**), 6.20 (s, 2H, 2 x C^{11}**H**), 1.36 (s, 9H, 3 x C^{10}**H**$_3$).

^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 155.9 (C), 155.7 (C), 145.7 (2 x C^{3}H), 136.8 (C^{12}), 131.1 (C^{17}H), 130.6 – 130.4 (m, C^{16}H+C), 129.95 (q, *J* = 33.4 Hz, C^{13}/C^{15}), 128.3 (2 x C^{6}H), 127.8 (q, *J* = 31.7 Hz, C^{13}/C^{15}), 126.7 (2 x C^{7}H), 124.5 (2 x C^{2}H), 124.0 – 123.7 (m, C^{14}H), 123.18 (q, *J* = 274.7 Hz, C^{18}F$_3$/C^{19}F$_3$), 123.15 (q, *J* = 272.7 Hz, C^{18}F$_3$/C^{19}F$_3$), 58.8 (q, *J* = 3.4 Hz, C^{11}H$_2$), 34.9 (C^9), 30.8 (3 x C^{10}H$_3$).

^{19}F NMR (377 MHz, DMSO-*d*$_6$) δ –59.0, –61.5.

IR (neat) (cm^{-1}): 3659, 2981, 1341, 1270, 1182, 1166, 1131, 1084, 1052, 826.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-methoxyphenyl)pyridinium iodide (II-21)**



The title compound was prepared by General Procedure D using 4-(4-methoxyphenyl)pyridine (460 mg, 2.50 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.46 g, 4.20 mmol) to give the pyridinium **II-21** (1.23 g, 92%) as a yellow solid.

m.p. (acetone): 215-217 °C

HRMS (ESI): Exact mass calculated for $C_{21}H_{16}ONF_6$ $[M]^+$: 412.1130, found: 412.1131.

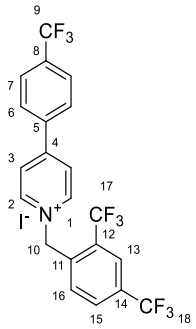
^{1}H NMR (400 MHz, DMSO) δ 9.02 (d, *J* = 7.2 Hz, 2H, 2 x C^2**H**), 8.57 (d, *J* = 7.2 Hz, 2H, 2 x C^3**H**), 8.22 (s, 1H, C^{13}**H**), 8.18 (d, *J* = 9.0 Hz, 2H, 2 x C^6**H**), 8.12 (dd, *J* = 8.2, 2.2 Hz, 1H, C^{15}**H**), 7.38 (d, *J* = 8.2 Hz, 1H, C^{16}**H**), 7.22 (d, *J* = 9.0 Hz, 2H, 2 x C^7**H**), 6.15 (s, 2H, C^{10}**H$_2$**), 3.90 (s, 3H, C^9**H$_3$**).

^{13}C NMR (126 MHz, DMSO) δ 163.1 (C^8), 155.1 (C^4), 145.4 (2 x C^2H), 137.1 (C^{11}), 130.7 (C^{16}H), 130.5 (q, *J* = 3.9 Hz, C^{15}H), 130.4 (2 x C^6H), 129.8 (q, *J* = 33.3 Hz, C^{12}/C^{14}), 127.7 (q, *J* = 31.7 Hz, C^{12}/C^{14}), 125.1 (C^5), 124.0 – 123.6 (m, C^{13}H), 123.5 (2 x C^3H), 123.2 (q, *J* = 274.6 Hz, $C^{17}F_3$/$C^{18}F_3$), 123.1 (q, *J* = 272.4 Hz, $C^{17}F_3$/$C^{18}F_3$), 115.3 (2 x C^7H), 58.6 (q, *J* = 3.3 Hz, $C^{10}H_2$), 55.8 (C^9H_3).

^{19}F NMR (377 MHz, DMSO) δ –59.1, –61.4.

IR (neat) (cm^{-1}): 2981, 1640, 1599, 1344, 1271, 1166, 1122, 1084, 1053, 833.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-(trifluoromethyl) phenyl)pyridinium iodide (II-22)**



The title compound was prepared by General Procedure D using 4-(4-(trifluoromethyl) phenyl)pyridine (446 mg, 2.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.06 g, 3.00 mmol) to give the pyridinium **II-22** (987 mg, 85%) as a yellow solid.

m.p. (acetone): 226-228 °C

HRMS (ESI): Exact mass calculated for $C_{21}H_{13}NF_9$ $[M]^+$: 450.08900, found 450.08860.

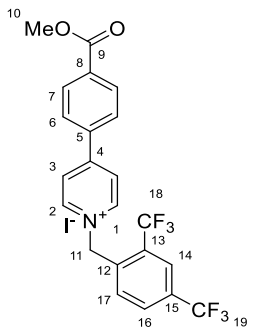
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (d, J = 7.1 Hz, 2H, 2 x C^2**H**), 8.69 (d, J = 7.1 Hz, 2H, 2 x C^3**H**), 8.32 (d, J = 8.3 Hz, 2H, 2 x C^6**H**), 8.23 (s, 1H, C^{13}**H**), 8.14 (d, J = 8.4 Hz, 1H, C^{15}**H**), 8.05 (d, J = 8.3 Hz, 2H, 2 x C^7**H**), 7.45 (d, J = 8.4 Hz, 1H, C^{16}**H**), 6.25 (s, 2H, 2 x C^{10}**H$_2$**).

^{13}C NMR (126 MHz, DMSO-d_6) δ 154.5 (C), 146.2 (2 x C^{3}H), 137.5 (C), 136.7 (C), 131.8 (q, J = 32.4 Hz, C^8/C^{12}/C^{14}), 131.1 (C^{16}H), 130.5 (d, J = 3.8 Hz, C^{15}H), 130.0 (q, J = 33.3 Hz, C^8/C^{12}/C^{14}), 129.4 (2 x C^{6}H), 127.9 (q, J = 31.7 Hz, 2 x C^{7}H), 126.5 (q, J = 3.8 Hz, C^8/C^{12}/C^{14}), 125.9 (2 x C^{2}H), 124.0 – 123.7 (m, C^{13}H), 123.17 (q, J = 274.6 Hz, C^{9}F$_3$), 123.15 (q, J = 272.4 Hz, 2 x C^{17}F$_3$/C^{18}F$_3$), 59.2 (q, J = 3.4 Hz, C^{10}H$_2$).

^{19}F NMR (376 MHz, DMSO-d_6) δ –59.0, –61.5.

IR (neat) (cm^{-1}): 3660, 2981, 1325, 1276, 1167, 1127, 1109, 1084, 1072, 1057.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-(methoxycarbonyl) phenyl)pyridinium iodide (II-23)**



The title compound was prepared by General Procedure D using 4-(4-(methoxycarbonyl) phenyl)pyridine (426 mg, 2.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.06 g, 3.00 mmol) to give the pyridinium **II-23** (1.01 g, 89%) as a yellow solid.

m.p. (acetone): 236-238 °C

HRMS (ESI): Exact mass calculated for $C_{22}H_{16}O_2NF_6$ $[M]^+$: 440.10797, found 440.10834

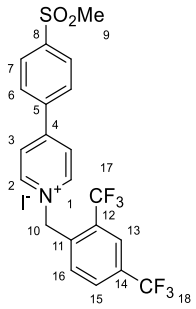
^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.19 (d, *J* = 7.0 Hz, 2H, 2 x C^2**H**), 8.68 (d, *J* = 7.0 Hz, 2H, 2 x C^3**H**), 8.26 (d, *J* = 8.8 Hz, 2H, 2 x C^6**H**), 8.22 (s, 1H, C^{14}**H**), 8.20 (d, *J* = 8.8 Hz, 2H, 2 x C^7**H**), 8.13 (d, *J* = 8.3 Hz, 1H, C^{16}**H**), 7.44 (d, *J* = 8.3 Hz, 1H, C^{17}**H**), 6.24 (s, 2H, 2 x C^{11}**H$_2$**), 3.92 (s, 3H, 3 x C^{10}**H$_3$**).

^{13}C NMR (126 MHz, DMSO) δ 165.6 (C^{9}O), 154.7(C), 146.2 (2 x C^{2}H), 137.7 (C), 136.7 (C), 132.6 (C), 131.0 (C^{17}H), 130.5 (d, *J* = 3.8 Hz, C^{16}H), 130.3 (2 x C^{6}H), 130.0 (q, *J* = 33.3 Hz, C^{13}/C^{15}), 128.9 (2 x C^{7}H), 127.9 (q, *J* = 31.7 Hz, C^{13}/C^{15}), 125.7 (2 x C^{3}H), 124.1 – 123.6 (m, C^{14}H), 123.21 (q, *J* = 274.6 Hz, C^{18}F$_3$/C^{19}F$_3$), 123.17 (q, *J* = 272.7 Hz, C^{18}F$_3$/C^{19}F$_3$), 59.2 (q, *J* = 3.3 Hz, C^{11}H$_2$), 52.7 (C^{10}H$_3$).

^{19}F NMR (377 MHz, DMSO) δ –59.00, –61.46.

IR (neat) (cm^{-1}): 3660, 2981, 1719, 1348, 1277, 1179, 1137, 1118, 1084, 1055.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-(methylsulfonyl) phenyl)pyridinium iodide (II-24)**



The title compound was prepared by General Procedure D using 4-(4-(methylsulfonyl) phenyl)pyridine (466 mg, 2.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.06 g, 3.00 mmol) to give the pyridinium **II-24** (1.13 g, 96%) as a yellow solid.

m.p. (acetone): 247-249 °C

HRMS (ESI): Exact mass calculated for $C_{21}H_{16}O_2NF_6{}^{32}S$ $[M]^+$: 460.08005, found 460.08010.

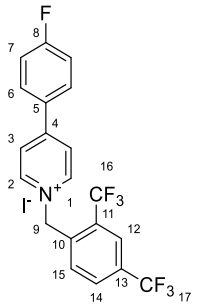
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (d, J = 6.7 Hz, 2H, 2 x C^2**H**), 8.70 (d, J = 7.1 Hz, 2H, 2 x C^3**H**), 8.36 (d, J = 8.6 Hz, 2H, 2 x C^6**H**), 8.23 (s, 1H, C^{13}**H**), 8.20 (d, J = 8.6 Hz, 2H, 2 x C^7**H**), 8.14 (d, J = 7.5 Hz, 1H, C^{15}**H**), 7.47 (d, J = 8.2 Hz, 1H, C^{16}**H**), 6.26 (s, 2H, 2 x C^{10}**H$_2$**), 3.35 (s, 3H, C^9**H$_3$)**.

^{13}C NMR (126 MHz, DMSO-d_6) δ 154.3 (C), 146.2 (2 x C^{2}H), 143.6 (C), 138.2 (C), 136.6 (C), 131.1 (C^{16}H), 130.5 (d, J = 3.7 Hz, C^{15}H), 130.0 (q, J = 33.3 Hz, C^{12}/C^{14}), 129.5 (2 x C^{6}H), 128.1 (2 x C^{7}H), 127.9 (q, J = 31.7 Hz, C^{12}/C^{14}), 126.0 (2 x C^{3}H), 124.1 – 123.6 (m, C^{13}H), 123.18 (q, J = 274.5 Hz, 2 x C^{17}F$_3$/C^{18}F$_3$), 123.15 (q, J = 272.7 Hz, 2 x C^{17}F$_3$/C^{18}F$_3$), 59.2 (d, J = 3.3 Hz, C^{10}H$_2$), 43.2 (C^{9}H$_3$).

^{19}F NMR (376 MHz, DMSO-d_6) δ–59.0, –61.5.

IR (neat) (cm^{-1}): 2981, 1703, 1639, 1345, 1274, 1172, 1123, 1085, 1054, 961.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-fluorophenyl)pyridinium iodide (II-25)**



The title compound was prepared by General Procedure D using 4-(4-fluorophenyl)pyridine (345 mg, 2.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.06 g, 3.00 mmol) to give the pyridinium **II-25** (1.00 g, 95%) as a yellow solid.

m.p. (acetone): 225-227 °C

HRMS (ESI): Exact mass calculated for $C_{20}H_{13}NF_7$ $[M]^+$: 400.09307, found 400.09342.

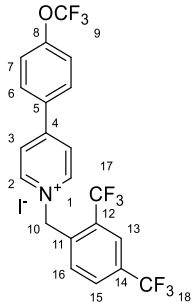
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (d, J = 7.1 Hz, 2H, 2 x C^2**H**), 8.61 (d, J = 7.1 Hz, 2H, 2 x C^3**H**), 8.28 – 8.19 (m, 3H, 2 x C^6**H** and C^{12}**H**), 8.12 (dd, J = 8.3, 2.2 Hz, 1H, C^{15}**H**), 7.53 (t, J = 8.8 Hz, 2H, 2 x C^7**H**), 7.41 (d, J = 8.3 Hz, 1H, C^{14}**H**), 6.20 (s, 2H, 2 x C^9**H**$_2$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 164.8 (d, J = 251.9 Hz, C^8), 154.8 (C^4), 145.9 (2 x C^{2}H), 136.8 (C^5), 131.2 (d, J = 9.3 Hz, 2 x C^{6}H), 131.0 (C^{15}H), 130.5 (q, J = 4.0 Hz, C^{14}H), 130.0 (q, J = 33.2 Hz, C^{11}/C^{13}), 129.9 (q, J = 2.9 Hz, C^{10}), 127.9 (q, J = 31.8 Hz, C^{11}/C^{13}), 124.9 (2 x C^{3}H), 123.9-123.8 (m, C^{12}H), 123.21 (q, J = 274.6 Hz, C^{16}F$_3$/C^{17}F$_3$), 123.17 (q, J = 272.7 Hz, C^{16}F$_3$/C^{17}F$_3$), 117.0 (d, J = 22.0 Hz, 2 x C^{7}H), 58.9 (q, J = 2.8 Hz, C^{9}H$_2$).

^{19}F NMR (377 MHz, DMSO-d_6) δ –59.0, –61.5, –107.2 (tt, J = 8.9, 5.2 Hz).

IR (neat) (cm^{-1}): 3009, 2939, 1636, 1497, 1343, 1284, 1265, 1225, 1168, 1136.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-(trifluoromethoxy) phenyl)pyridinium iodide (II-26)**



The title compound was prepared by General Procedure D using 4-(4-(trifluoromethoxy) phenyl)pyridine (482 mg, 2.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.06 g, 3.00 mmol) to give the pyridinium **II-26** (1.07 g, 90%) as a yellow solid.

m.p. (acetone): 210-212 °C

HRMS (ESI): Exact mass calculated for $C_{21}H_{13}ONF_9$ $[M]^+$: 466.08479, found 466.08372

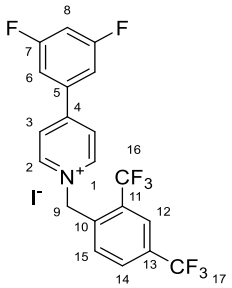
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (d, J = 6.7 Hz, 2H, 2 x C^2**H**), 8.64 (d, J = 6.7 Hz, 2H, 2 x C^3**H**), 8.27 (d, J = 8.6 Hz, 2H, 2 x C^6**H**), 8.22 (s, 1H, C^{13}**H**), 8.13 (d, J = 8.2 Hz, 1H, C^{15}**H**), 7.67 (d, J = 8.6 Hz, 2H, 2 x C^7**H**), 7.45 (d, J = 8.2 Hz, 1H, C^{16}**H**), 6.22 (s, 2H, 2 x C^{10}**H$_2$**).

^{13}C NMR (126 MHz, DMSO-d_6) δ 154.5 (C), 151.1 (C), 146.0 (2 x C^{2}H), 136.7 (C), 132.6 (C), 131.1 (C^{16}H), 130.9 (2 x C^{6}H), 130.5 (d, J = 3.8 Hz, C^{15}H), 130.0 (q, J = 33.3 Hz, C^{12}/C^{14}), 127.9 (q, J = 31.6 Hz, C^{12}/C^{14}), 125.3 (2 x C^{3}H), 124.0 – 123.7 (m, C^{13}H), 123.18 (q, J = 274.5 Hz, C^{17}F$_3$/C^{18}F$_3$), 123.15 (q, J = 272.7 Hz, C^{17}F$_3$/C^{18}F$_3$), 121.9 (2 x C^{7}H), 120.0 (q, J = 257.7 Hz, C^{9}F$_3$), 59.1 (q, J = 3.3 Hz, C^{10}H$_2$).

^{19}F NMR (376 MHz, DMSO-d_6) δ –56.6, –59.0, –61.5.

IR (neat) (cm^{-1}): 2981, 1638, 1342, 1269, 1212, 1166, 1123, 1084, 1052, 829.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(3,5-difluorophenyl)pyridinium iodide (II-27)**



The title compound was prepared by General Procedure D using 4-(3,5-difluorophenyl)pyridine (382 mg, 2.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.06 g, 3.00 mmol) to give the pyridinium **II-27** (714 mg, 65%) as a yellow solid.

m.p. (acetone): 233-235 °C

HRMS (ESI): Exact mass calculated for $C_{20}H_{12}NF_8$ $[M]^+$: 418.08365, found 418.08416.

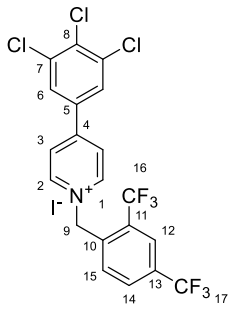
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (d, J = 7.0 Hz, 2H, 2 x C^2**H**), 8.69 (d, J = 7.0 Hz, 2H, 2 x C^3**H**), 8.23 (s, 1H, C^{12}**H**), 8.12 (d, J = 7.6 Hz, 1H, C^{14}**H**), 8.04 – 7.91 (m, 2H, 2 x C^6**H**), 7.64 (tt, J = 9.2, 2.3 Hz, 1H, C^8**H**), 7.40 (d, J = 8.2 Hz, 1H, C^{15}**H**), 6.22 (s, 2H, 2 x C^9**H**$_2$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 163.1 (dd, J = 247.5, 12.4, Hz, 2 x C^7), 153.3 (C^4), 146.2 (2 x C^{2}H), 137.2 – 136.0 (m, C^5+ C^{10}), 130.9, (C^{15}H), 130.5 (C^{14}H), 130.0 (q, J = 33.2 Hz, C^{11}/C^{13}), 127.9 (q, J = 31.8 Hz, C^{11}/C^{13}), 125.6 (2 x C^{3}H), 123.9 (C^{12}H), 123.17 (q, J = 275.0 Hz, C^{16}F$_3$/C^{17}F$_3$), 123.14 (q, J = 272.4 Hz, C^{16}F$_3$/C^{17}F$_3$), 112.3 – 111.8 (m, 2 x C^{6}H), 107.7 (t, J = 26.0 Hz, C^{8}H), 59.2 (q, J = 2.5 Hz, C^{9}H$_2$).

^{19}F NMR (377 MHz, DMSO-d_6) δ –59.0, –61.4, –107.7 (t, J = 8.5 Hz).

IR (neat) (cm^{-1}): 2981, 1339, 1275, 1177, 1117, 1084, 1054, 991, 839.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(3,4,5-trichlorophenyl)pyridinium iodide (II-28)**



The title compound was prepared by General Procedure D using 4-(3,4,5-trichlorophenyl)pyridine (186 mg, 0.72 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (530 mg 1.50 mmol) to give the pyridinium **II-28** (314 mg, 71%) as a yellow solid.

m.p. (acetone): 277-279 °C

HRMS (ESI): Exact mass calculated for $C_{20}H_{11}N^{35}Cl_3F_6$ $[M]^+$: 483.98558, found 483.98567.

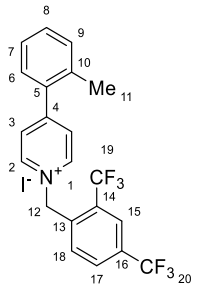
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (d, J = 7.1 Hz, 2H, 2 x C^2**H**), 8.74 (d, J = 7.1 Hz, 2H, 2 x C^3**H**), 8.47 (s, 2H, 2 x C^6**H**), 8.24 (s, 1H, C^{12}**H**), 8.12 (d, J = 8.2 Hz, 1H, C^{14}**H**), 7.36 (d, J = 8.2 Hz, 1H, C^{15}**H**), 6.22 (s, 2H, 2 x C^9**H**$_2$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 152.4 (C^4), 146.2 (2 x C^{2}H), 136.7 (C), 134.4 (C), 134.2 (C), 133.8 (C), 130.8 (C^{15}H), 130.7 – 130.3 (m, C^{14}H), 130.0 (q, J = 33.2 Hz, C^{11}/C^{13}), 128.9 (2 x C^{6}H), 127.8 (q, J = 31.7 Hz, C^{11}/C^{13}), 125.7 (2 x C^{3}H), 124.01 – 123.63 (m, C^{12}H), 123.15 (q, J = 270.0 Hz, C^{16}F$_3$ + C^{17}F$_3$), 59.25 (s, C^{9}H$_2$).

^{19}F NMR (377 MHz, DMSO-d_6) δ –59.1, –61.4.

IR (neat) (cm^{-1}): 3659, 2981, 1639, 1381, 1347, 1288, 1274, 1186, 1136, 1117.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(o-tolyl)pyridinium iodide (II-29)**



The title compound was prepared by General Procedure D using 4-(o-tolyl)pyridine (285 mg, 2.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.06 g, 3.00 mmol) to give the pyridinium **II-29** (815 mg, 93%) as a yellow solid.

m.p. (acetone): 225-257 °C

HRMS (ESI): Exact mass calculated for $C_{21}H_{16}NF_6$ $[M]^+$: 396.11815, found 396.11719.

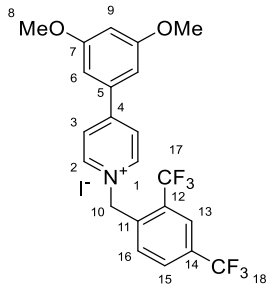
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (d, J = 7.0 Hz, 2H, 2 x C^2**H**), 8.31 (d, J = 7.0 Hz, 2H, 2 x C^3**H**), 8.24 (s, 1H, C^{15}**H**), 8.17 (d, J = 8.2 Hz, 1H, C^{17}**H**), 7.55 – 7.40 (m, 5H, C^6**H**, C^7**H**, C^8**H**, C^9**H** and C^{18}**H**), 6.23 (s, 2H, 2 x C^{12}**H$_2$**), 2.39 (s, 3H, 3 x C^{11}**H$_3$**).

^{13}C NMR (126 MHz, DMSO-d_6) δ 158.5 (C^4), 145.3 (2 x C^{2}H), 136.5 (C), 135.6 (C), 135.4 (C), 131.5 (ArCH), 131.4 (ArCH), 130.7 (ArCH), 130.6 (C^{17}H), 130.1 (q, J = 33.2 Hz, C^{19}/C^{20}), 129.8 (ArCH), 128.5 (2 x C^{3}H), 128.0 (q, J = 31.7 Hz, C^{19}/C^{20}), 126.8 (ArCH), 123.9 (C^{15}H), 123.2 (q, J = 271.4 Hz, C^{19}F$_3$ + C^{20}F$_3$), 59.2 (s, C^{12}H$_2$), 19.9 (C^{11}H$_3$).

^{19}F NMR (376 MHz, DMSO-d_6) δ –58.9, –61.5.

IR (neat) (cm^{-1}): 2981, 1640, 1345, 1269, 1169, 1119, 1084, 1054, 762.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(3,5-dimethoxyphenyl) pyridinium iodide (II-30)**



The title compound was prepared by General Procedure D using 4-(3,5-dimethoxyphenyl)pyridine (430 mg, 2.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.06 g, 3.00 mmol) to give the pyridinium **II-30** (1.06 g, 93%) as a yellow solid.

m.p. (acetone): 235-237 °C

HRMS (ESI): Exact mass calculated for $C_{22}H_{18}O_2NF_6$ $[M]^+$: 442.12362, found 442.12302.

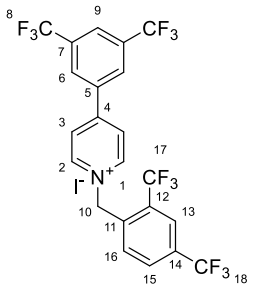
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (d, J = 7.1 Hz, 2H, 2 x C^2**H**), 8.65 (d, J = 7.1 Hz, 2H, 2 x C^3**H**), 8.22 (s, 1H, C^{13}**H**), 8.12 (d, J = 7.6 Hz, 1H, C^{15}**H**), 7.39 (d, J = 8.2 Hz, 1H, C^{16}**H**), 7.25 (d, J = 2.2 Hz, 2H, 2 x C^6**H**), 6.82 (t, J = 2.2 Hz, 1H, C^9**H**), 6.21 (s, 2H, 2 x C^{10}**H**$_2$), 3.88 (s, 6H, 6 x C^8**H**$_3$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 161.4 (2 x C^{7}H), 155.8 (C^4), 145.8 (2 x C^{2}H), 136.9 (C^{11}), 135.3 (C^5), 130.8, (C^{16}H), 130.5 (d, J = 3.8 Hz, C^{15}H), 129.9 (q, J = 33.3 Hz, C^{12}/C^{14}), 127.8 (q, J = 31.8 Hz, C^{12}/C^{14}), 125.3 (2 x C^{3}H), 124.1 – 123.7 (m, C^{13}H), 123.22 (q, J = 274.4, Hz, C^{17}F$_3$/C^{18}F$_3$), 123.18 (q, J = 272.1, Hz, C^{17}F$_3$/C^{18}F$_3$), 106.4 (2 x C^{6}H), 104.2 (C^{9}H), 59.0 (q, J = 3.3 Hz, C^{10}H$_2$), 55.8 (2 x C^{8}H$_3$).

^{19}F NMR (377 MHz, DMSO-d_6) δ –59.0, –61.4.

IR (neat) (cm^{-1}): 2981, 2889, 1341, 1275, 1182, 1156, 1135, 1115, 1083, 1064.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(3,5-bis(trifluoromethyl) phenyl) pyridinium iodide (II-31)**



The title compound was prepared by General Procedure D using 4-(3,5-bis(trifluoromethyl) phenyl)pyridine (285 mg, 1.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (530 mg, 1.50 mmol) to give the pyridinium **II-31** (454 mg, 72%) as a yellow solid.

m.p. (acetone): 259-261 °C

HRMS (ESI): Exact mass calculated for $C_{22}H_{12}NF_{12}$ $[M]^+$: 518.07726, found 518.07581.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (d, J = 7.1 Hz, 2H, 2 x C^2**H**), 8.87 (d, J = 7.1 Hz, 2H, 2 x C^3**H**), 8.78 (s, 2H, 2 x C^6**H**), 8.45 (s, 1H, C^9**H**), 8.24 (s, 1H, C^{13}**H**), 8.12 (d, J = 8.2 Hz, 1H, C^{15}**H**), 7.35 (d, J = 8.2 Hz, 1H, C^{16}**H**), 6.28 (s, 2H, 2 x C^{10}**H**).

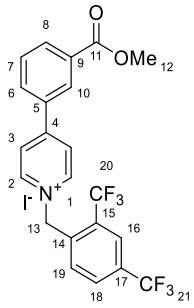
^{13}C NMR (126 MHz, DMSO-d_6) δ 153.1 (C^4), 146.2 (2 x C^{2}H), 136.9 (C), 136.3 (C), 131.5 (q, J = 33.5 Hz, 2 x C^7), 130.6 (C^{16}H), 130.5 (q, J = 3.9 Hz, C^{15}H), 130.0 (q, J = 33.3 Hz, C^{12}/C^{14}), 129.5 (q, J = 4.0 Hz, 2 x C^{6}H), 127.8 (q, J = 31.8 Hz, C^{12}/C^{14}), 126.5 (2 x C^{3}H), 125.6 – 125.3 (m, C^{9}H), 123.9 (C^{13}H), 123.19 (q, J = 274.6 Hz, C^{17}F$_3$/C^{18}F$_3$), 123.15 (q, J = 272.7 Hz, C^{17}F$_3$/C^{18}F$_3$), 123.1 (q, J = 273.2 Hz, 2 x C^{8}F$_3$), 59.4 (q, J = 3.5 Hz, C^{10}H$_2$).

^{19}F NMR (377 MHz, DMSO-d_6) δ –59.1, –61.1, –61.5.

IR (neat) (cm^{-1}): 2981, 1639, 1345, 1272, 1176, 1122, 1084, 1053, 671.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(3-(methoxycarbonyl) phenyl)pyridinium iodide**

(II-32)



The title compound was prepared by General Procedure D using 4-(3-(methoxycarbonyl) phenyl)pyridine (427 mg, 2.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.06 g, 3.00 mmol) to give the pyridinium **II-32** (1.01 g, 89%) as a yellow solid.

m.p. (acetone): 206-208 °C

HRMS (ESI): Exact mass calculated for $C_{22}H_{16}O_2NF_6$ $[M]^+$: 440.10797, found 440.10828.

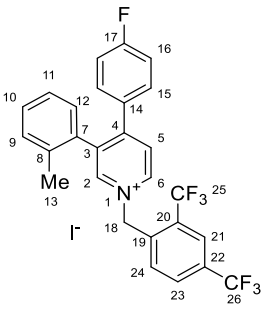
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (d, J = 7.0 Hz, 2H, 2 x C^2**H**), 8.69 (d, J = 7.0 Hz, 2H, 2 x C^3**H**), 8.57 (t, J = 1.7 Hz, 1H, C^{10}**H**), 8.37 (ddd, J = 7.8, 2.1, 1.1 Hz, 1H, C^8**H**), 8.27 – 8.21 (m, 2H, C^6**H** and C^{16}**H**), 8.12 (d, J = 8.2 Hz, 1H, C^{18}**H**), 7.84 (t, J = 7.8 Hz, 1H, C^7**H**), 7.40 (d, J = 8.2 Hz, 1H, C^{19}**H**), 6.23 (s, 2H, 2 x C^{13}**H$_2$**), 3.93 (s, 3H, 3 x C^{12}**H$_3$**).

^{13}C NMR (126 MHz, DMSO-d_6) δ 165.6 (C^{11}), 155.1 (C^4), 146.1 (2 x C^{2}H), 136.9 (C), 134.3 (C), 133.0 (C^{8}H), 132.6 (C^{6}H), 131.2 (C), 130.9 (C^{19}H), 130.5 (d, J = 4.7 Hz, C^{18}H), 130.5 (C^{7}H), 130.0 (q, J = 33.3 Hz, C^{15}/C^{17}), 128.9 (C^{10}H), 127.9 (q, J = 31.7 Hz, C^{15}/C^{17}), 125.7 (2 x C^{3}H), 124.0 – 123.8 (m, C^{16}H), 123.23 (q, J = 274.5 Hz, C^{20}F$_3$/C^{21}F$_3$) 123.2 (q, J = 272.7 Hz, C^{20}F$_3$/C^{21}F$_3$), 59.1 (q, J = 3.6 Hz, C^{13}H$_2$), 52.7 (C^{12}H$_3$).

^{19}F NMR (376 MHz, DMSO-d_6) δ –59.0, –61.5.

IR (neat) (cm^{-1}): 2981, 1707, 1639, 1345, 1273, 1258, 1181, 1119, 1085, 1054.

_N_-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-fluorophenyl)-3-(o-tolyl)pyridinium iodide (II-33)



The title compound was prepared by General Procedure D using 4-(4-fluorophenyl)-3-(*o*-tolyl)pyridine (263 mg, 1.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (530 mg, 1.50 mmol) to give the pyridinium **II-33** (461 mg, 75%) as a yellow solid.

m.p. (acetone): 252-254 °C

HRMS (ESI): Exact mass calculated for $C_{27}H_{19}NF_7^+$ $[M]^+$: 490.100, found 490.1398.

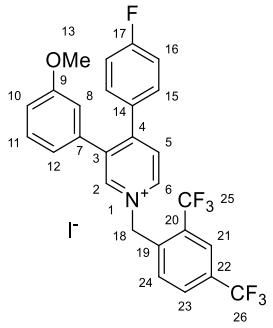
^{1}H NMR (400 MHz, DMSO) δ 9.26 (d, *J* = 1.6 Hz, 1H, C^2**H**), 9.15 (dd, *J* = 6.5, 1.6 Hz, 1H, C^6**H**), 8.40 (d, *J* = 6.5 Hz, 1H, C^5**H**), 8.23 (s, 1H, C^{21}**H**), 8.15 (d, *J* = 8.4 Hz, 1H, C^{23}**H**), 7.52 (d, *J* = 8.4 Hz, 1H, C^{24}**H**), 7.44 – 7.21 (m, 8H, C^9**H**, C^{10}**H**, C^{11}**H**, C^{12}**H**, 2 x C^{15}**H** + 2 x C^{16}**H**), 6.25 (s, 2H, C^2**H$_2$**), 1.89 (s, 3H, C^2**H$_3$**).

^{13}C NMR (126 MHz, DMSO) δ 163.20 (d, *J* = 250.0 Hz, C^{17}), 155.6 (C^4), 146.8 (C^2), 144.3 (C^6), 138.9 (C), 136.9 (C^{19}), 135.7 (C), 133.3 (C), 131.8 (d, *J* = 8.8 Hz 2 x C^{15}H), 131.4 (d, *J* = 3.0 Hz, C^{14}), 130.8 (C^{24}H), 2 x 130.6 (2 x ArCH), 130.5 (q, *J* = 3.6 Hz, C^{23}H), 129.9 (q, *J* = 33.3 Hz, C^{20}/C^{22}), 129.6 (ArCH), 128.7 (C^5), 127.8 (q, *J* = 31.7 Hz, C^{20}/C^{22}), 126.4 (ArCH), 123.9 – 123.6 (m, C^{21}H), 123.2 (q, *J* = 274.4 Hz, C^{25}F$_3$/C^{26}F$_3$), 123.1 (q, *J* = 272.5 Hz, C^{25}F$_3$/C^{26}F$_3$), 116.0 (d, *J* = 22.0 Hz, 2 x C^{16}H), 59.2 (q, *J* = 3.4 Hz, C^{18}H$_2$), 19.3 (C^{13}H$_3$).

^{19}F NMR (377 MHz, DMSO) δ –59.1, –61.4, –109.7 (tt, *J* = 8.7, 5.2 Hz).

IR (neat) (cm^{-1}): 2979, 2932, 1633, 1600, 1483, 1470, 1340, 1281, 1269, 1163.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-fluorophenyl)-3-(3-methoxyphenyl)pyridinium iodide (II-34)**



The title compound was prepared by General Procedure D using 4-(4-fluorophenyl)-3-(3-methoxyphenyl)pyridine (279 mg, 1.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (530 mg, 1.50 mmol) to give the pyridinium **II-34** (495 mg, 78%) as a yellow solid.

m.p. (acetone): 188-190 °C

HRMS (ESI): Exact mass calculated for $C_{27}H_{19}ONF_7^+$ $[M]^+$: 506.1349, found: 506.1347.

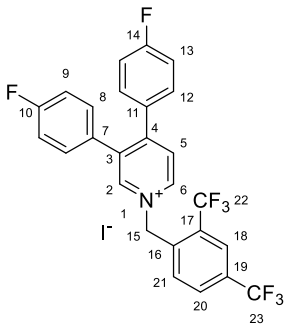
^{1}H NMR (400 MHz, DMSO) δ 9.34 (d, *J* = 1.6 Hz, 1H, C^2**H**), 9.10 (dd, *J* = 6.5, 1.6 Hz, 1H, C^6**H**), 8.33 (d, *J* = 6.5 Hz, 1H, C^5**H**), 8.24 (s, 1H, C^{21}**H**), 8.13 (d, *J* = 8.2 Hz, 1H, C^{23}**H**), 7.49 (d, *J* = 8.2 Hz, 1H, C^{24}**H**), 7.43 (ddt, *J* = 8.3, 5.2, 2.6 Hz, 2H, 2 x C^{15}**H**), 7.37 – 7.28 (m, 3H, C^{11}**H** + 2 x C^{16}**H**), 7.02 (ddd, *J* = 8.4, 2.6, 0.9 Hz, 1H, C^{12}**H**), 6.91 (dd, *J* = 2.6, 1.7 Hz, 1H, C^8**H**), 6.81 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H, C^{10}**H**), 6.26 (s, 2H, C^{18}**H$_2$**), 3.69 (s, 3H, C^{13}**H$_3$**).

^{13}C NMR (126 MHz, DMSO) δ 163.1 (d, *J* = 249.2 Hz, C^{17}), 159.4 (C^9), 155.3 (C^4), 146.5 (C^{2}H), 143.9 (C^{6}H), 139.1 (C), 137.0 (C^{19}), 134.9 (C), 132.0 (d, *J* = 8.9 Hz, 2 x C^{15}H), 131.5 (d, *J* = 3.1 Hz, C^{14}), 130.5 (C^{24}H), 130.4 (C^{23}H), 130.1 (C^{8}H), 129.8 (q, *J* = 33.3 Hz, C^{20}/C^{22}), 129.1 (C^{5}H), 127.7 (q, *J* = 31.9 Hz, C^{20}/C^{22}), 123.9 – 123.5 (m, C^{21}H), 123.21 (q, *J* = 274.5 Hz, C^{25}F$_3$/C^{26}F$_3$), 123.17 (q, *J* = 272.7 Hz, C^{25}F$_3$/C^{26}F$_3$), 121.9 (C^{12}H), 116.0 (d, *J* = 22.1 Hz, 2 x C^{16}H), 115.6 (C^{11}H), 114.6 (C^{10}H), 59.2 (d, *J* = 3.5 Hz, C^{18}H$_2$), 55.3 9 C^{13}H$_3$).

^{19}F NMR (377 MHz, DMSO) δ –59.0, –61.4, –110.1 (tt, *J* = 8.9, 5.4 Hz).

IR (neat) (cm^{-1}): 2922, 1632, 1603, 1341, 1274, 1237, 1180, 1163, 1129, 1086.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-3,4-bis(4-fluorophenyl)pyridinium iodide (II-35)**



The title compound was prepared by General Procedure D using 3,4-bis(4-fluorophenyl)pyridine (158 mg, 0.60 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (350 mg, 1.00 mmol) to give the pyridinium **II-35** (187 mg, 51%) as a yellow solid.

m.p. (acetone): 205-207°C

HRMS (ESI): Exact mass calculated for $C_{26}H_{16}NF_8^+$ $[M]^+$: 494.1150, found 494.1140.

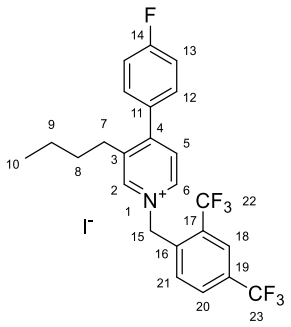
^{1}H NMR (400 MHz, DMSO) δ 9.34 (d, *J* = 1.6 Hz, 1H, C^2**H**), 9.11 (dd, *J* = 6.5, 1.6 Hz, 1H, C^6**H**), 8.34 (d, *J* = 6.5 Hz, 1H, C^5**H**), 8.24 (s, 1H, C^{18}**H**), 8.13 (d, *J* = 8.2 Hz, 1H, C^{20}**H**), 7.49 (d, *J* = 8.2 Hz, 1H, C^{21}**H**), 7.44 – 7.38 (m, 2H, 2 x C^{12}**H**), 7.38 – 7.25 (m, 6H, 2 x C^8**H** + 2 x C^9**H** + 2 x C^{13}**H**), 6.26 (s, 2H, C^2**H$_2$**).

^{13}C NMR (126 MHz, DMSO) δ 163.1 (d, *J* = 249.3 Hz, C^{14}), 162.5 (d, *J* = 247.3 Hz, C^{10}), 155.4 (C^4), 146.5 (C^{2}H), 144.0 (C^{6}H), 138.4 (C^3), 137.0 (C^{16}), 132.2 (2 x C^{8}H/C^{12}H), 132.1 (2 x C^{8}H/C^{12}H), 131.3 (d, *J* = 3.3 Hz, C^7/C^{11}), 130.5 (C), 130.4 (q, *J* = 3.8 Hz, C^{20}H), 130.1 (d, *J* = 3.2 Hz, C^7/C^{11}), 129.8 (q, *J* = 33.3 Hz, C^{17}/C^{19}), 129.1 (C^{5}H), 127.7 (q, *J* = 31.9 Hz, C^{17}/C^{19}), 124.0 – 123.6 (m, C^{18}H), 123.21 (q, *J* = 274.7 Hz, C^{22}F$_3$/C^{23}F$_3$), 123.17 (q, *J* = 272.7 Hz, C^{22}F$_3$/C^{23}F$_3$), 116.1 (d, *J* = 22.1 Hz, 2 x C^{13}H), 116.0 (d, *J* = 21.9 Hz, 2 x C^{9}H), 59.2 (q, *J* = 3.4 Hz, C^{15}H$_2$).

^{19}F NMR (377 MHz, DMSO) δ –59.0, –61.4, –110.1 (td, *J* = 9.0, 4.4 Hz), –111.9 (tt, *J* = 9.0, 5.8 Hz).

IR (neat) (cm^{-1}): 2980, 1633, 1603, 1493, 1463, 1342, 1270, 1168, 1138, 1122.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-3-butyl-4-(4-fluorophenyl)pyridinium iodide (II-36)**



The title compound was prepared by General Procedure D using 3,4-bis(4-fluorophenyl)pyridine (158 mg, 0.60 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (350 mg, 1.00 mmol) to give the pyridinium **II-36** (187 mg, 51%) as a white wax.

HRMS (ESI): Exact mass calculated for $C_{24}H_{21}NF_8^+$ $[M]^+$:456.1557, found 456.1552.

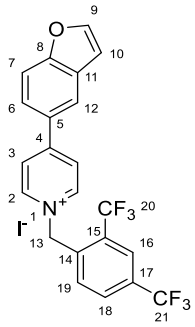
^{1}H NMR (500 MHz, DMSO) δ 9.16 (d, *J* = 1.6 Hz, 1H, C^2**H**), 8.98 (dd, *J* = 6.4, 1.6 Hz, 1H, C^6**H**), 8.24 (s, 1H, C^{18}**H**), 8.15 (dd, *J* = 8.2, 1.9 Hz, 1H, C^{20}**H**), 8.12 (d, *J* = 6.4 Hz, 1H, C^5**H**), 7.70 – 7.59 (m, 2H, 2 x C^{12}**H**), 7.51 – 7.43 (m, 2H, 2 x C^{13}**H**), 7.39 (d, *J* = 8.2 Hz, 1H, C^{21}**H**), 6.22 (s, 2H, C^2**H$_2$**), 2.84 – 2.76 (m, 2H, C^7**H$_2$**), 1.51 – 1.39 (m, 2H, C^8**H$_2$**), 1.19 (q, *J* = 7.4 Hz, 2H, C^9**H$_2$**), 0.76 (t, *J* = 7.3 Hz, 3H, C^{10}**H$_3$**).

^{13}C NMR (126 MHz, DMSO) δ 163.1 (d, *J* = 248.4 Hz, C^{14}), 157.0 (C^4), 145.9 (C^{2}H), 142.8 (C^{6}H), 140.9 (C^3), 136.8 (C^{16}), 131.8 (d, *J* = 3.3 Hz, C^{11}), 131.1 (d, *J* = 8.9 Hz, 2 x C^{12}H), 130.8 (C^{21}H), 130.4 (q, *J* = 20.7 Hz, C^{20}H), 129.9 (q, *J* = 33.2 Hz, C^{17}/C^{19}), 128.9 (C^{5}H), 127.8 (q, *J* = 31.8 Hz, C^{17}/C^{19}), 124.0 – 123.6 (m, C^{18}H), 123.2 (q, *J* = 274.5 Hz, C^{22}F$_3$/C^{23}F$_3$), 123.1 (q, *J* = 272.7 Hz, C^{22}F$_3$/C^{23}F$_3$), 116.2 (d, *J* = 21.9 Hz, 2 x C^{13}H), 59.3(q, *J* = 3.4 Hz, C^{15}H$_2$), 31.2 (C^{8}H$_2$), 29.5 (C^{7}H$_2$), 21.6 (C^{9}H$_2$), 13.4 (C^{10}H$_3$).

^{19}F NMR (377 MHz, DMSO) δ –59.1, –61.4, –110.8 (tt, *J* = 8.9, 5.3 Hz).

IR (neat) (cm^{-1}): 2981, 1638, 1605, 1500, 1464, 1342, 1276, 1183, 1137, 1123.

4-(Benzofuran-5-yl)-*N*-(2,4-bis(trifluoromethyl)benzyl)pyridinium iodide (II-37)



The title compound was prepared by General Procedure D using 4-(benzofuran-5-yl)pyridine (195 mg, 1.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (530 mg, 1.50 mmol) to give the pyridinium **II-37** (278 mg, 51%) as a pale yellow solid.

m.p. (acetone): 247-249 °C

HRMS (ESI): Exact mass calculated for $C_{22}H_{14}ONF_3^+$ $[M]^+$:422.0974, found 422.0981.

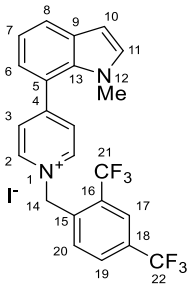
^{1}H NMR (500 MHz, DMSO) δ 9.12 (d, *J* = 7.0 Hz, 2H, 2 x C^2**H**), 8.67 (d, *J* = 7.0 Hz, 2H, 2 x C^3**H**), 8.52 (d, *J* = 2.0 Hz, 1H, C^{12}**H**), 8.23 (s, 1H, C^{16}**H**), 8.20 (d, *J* = 2.3 Hz, 1H, C^9**H**), 8.14 (dd, *J* = 8.2, 2.1 Hz, 1H, C^{18}**H**), 8.10 (dd, *J* = 8.7, 2.1 Hz, 1H, C^6**H**), 7.91 (d, *J* = 8.7 Hz, 1H, C^7**H**), 7.43 (d, *J* = 8.2 Hz, 1H, C^{19}**H**), 7.16 (dd, *J* = 2.3, 1.0 Hz, 1H, C^{10}**H**), 6.20 (s, 2H, C^{13}**H$_2$**).

^{13}C NMR (126 MHz, DMSO) δ 156.5 (C), 156.3 (C), 148.2 (C^{9}H), 145.6 (2 x C^{2}H), 136.9 (C), 131.0 (C^{19}H), 130.5 (q, *J* = 3.8 Hz, C^{18}H), 129.9 (q, *J* = 33.2 Hz, C^{15}/C^{17}), 128.6 (C), 128.4 (C), 127.8 (q, *J* = 31.6 Hz, C^{15}/C^{17}), 124.9 (C^{6}H), 124.8 (2 x C^{3}H), 123.9 – 123.6 (m, C^{16}H), 123.19 (q, *J* = 274.6 Hz, C^{20}F$_3$/C^{21}F$_3$), 123.15 (q, *J* = 272.7 Hz, C^{20}F$_3$/C^{21}F$_3$), 122.4 (C^{12}H), 112.8 (C^{7}H), 107.3 (C^{10}H), 58.8 (q, *J* = 3.4 Hz, C^{13}H$_2$).

^{19}F NMR (377 MHz, DMSO) δ –59.0, –61.4.

IR (neat) (cm^{-1}): 3023, 1638, 1343, 1309, 1270, 1193, 1177, 1150, 1134, 1125.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(1-methyl-1H-indol-7-yl)pyridinium iodide (II-38)**



The title compound was prepared by General Procedure D using 4-(1-methyl-1H-indol-7-yl)pyridine (208 mg, 1.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (530 mg, 1.50 mmol) to give the pyridinium **II-38** (465 mg, 83%) as a pale yellow solid.

m.p. (acetone): 246-248 °C

HRMS (ESI): Exact mass calculated for $C_{23}H_{17}N_2F_6^+$ $[M]^+$: 435.1290, found 432.1288.

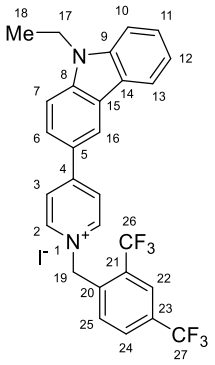
^{1}H NMR (500 MHz, DMSO) δ 9.12 (d, *J* = 6.8 Hz, 2H, 2 x C^2**H**), 8.35 (d, *J* = 6.8 Hz, 2H, 2 x C^3**H**), 8.25 (s, 1H, C^{17}**H**), 8.20 (dd, *J* = 8.3, 2.1 Hz, 1H, C^{19}**H**), 7.83 (dd, *J* = 6.8, 2.1 Hz, 1H, C^6**H**), 7.58 (d, *J* = 8.3 Hz, 1H, C^{20}**H**), 7.47 (d, *J* = 3.2 Hz, 1H, C^{11}**H**), 7.28 – 7.20 (m, 2H, C^7**H** + C^8**H**), 6.67 (d, *J* = 3.2 Hz, 1H, C^{10}**H**), 6.25 (s, 2H, C^{14}**H$_2$**), 3.48 (s, 3H, C^{12}**H$_2$**).

^{13}C NMR (126 MHz, DMSO) δ 157.1 (C^4), 144.6 (2 x C^{2}H), 136.5 (C), 133.0 (C^{11}H), 132.6 (C), 131.7 (C^{20}H), 130.6 (q, *J* = 3.8 Hz, C^{19}H), 130.4 (ArC), 130.1 (q, *J* = 33.2 Hz, C^{16}/C^{18}), 128.7 (2 x C^{3}H), 128.1 (q, *J* = 31.6 Hz, C^{16}/C^{18}), 125.0 (C^{7}H/C^{8}H), 124.1 – 123.8 (m, C^{17}H), 123.7 (C^{6}H), 123.2 (q, *J* = 274.6 Hz, C^{21}F$_3$/C^{22}F$_3$), 123.1 (q, *J* = 272.6 Hz, C^{21}F$_3$/C^{22}F$_3$), 120.4 (ArC), 119.3(C^{7}H/C^{8}H), 101.7 (C^{10}H), 59.1 (q, *J* = 3.1 Hz, C^{14}H$_2$), 37.5 (C^{12}H$_3$).

^{19}F NMR (377 MHz, DMSO) δ –58.93, –61.46.

IR (neat) (cm^{-1}): 1632, 1341, 1308, 1275, 1172, 1129, 1083, 1052, 796, 723.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(9-ethyl-9H-carbazol-3-yl)pyridinium iodide (II-39)**



The title compound was prepared by General Procedure D using 4-(9-ethyl-9H-carbazol-3-yl)pyridine (272 mg, 1.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (530 mg, 1.50 mmol) to give the pyridinium **II-39** (606 mg, 97%) as a yellow solid.

m.p. (acetone): 219-221 °C

HRMS (ESI): Exact mass calculated for $C_{28}H_{21}N_2F_6^+$ $[M]^+$: 499.1603, found 499.1601.

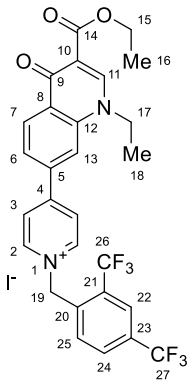
^{1}H NMR (400 MHz, DMSO) δ 9.17 (d, *J* = 2.0 Hz, 1H, C^{16}**H**), 9.05 (d, *J* = 7.2 Hz, 2H, 2 x C^{2}**H**), 8.74 (d, *J* = 7.2 Hz, 2H, 2 x C^{3}**H**), 8.34 (dt, *J* = 7.8, 1.0 Hz, 1H, C^{13}**H**), 8.31 (dd, *J* = 8.8, 2.0 Hz, 1H, C^{6}**H**), 8.24 (s, 1H, C^{22}**H**), 8.14 (dd, *J* = 8.3, 2.0 Hz, 1H, C^{24}**H**), 7.89 (d, *J* = 8.8 Hz, 1H, C^{7}**H**), 7.73 (d, *J* = 8.3, 0.9 Hz, 1H, C^{10}**H**), 7.57 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H, C^{11}**H**), 7.40 (d, *J* = 8.3 Hz, 1H, C^{25}**H**), 7.34 (ddd, *J* = 7.9, 7.2, 0.9 Hz, 1H, C^{12}**H**), 6.17 (s, 2H, C^{19}**H$_2$**), 4.55 (q, *J* = 7.1 Hz, 2H, C^{17}**H$_2$**), 1.37 (t, *J* = 7.1 Hz, 3H, C^{18}**H$_3$**).

^{13}C NMR (126 MHz, DMSO) δ 156.5 (C^{4}), 145.2 (2 x C^{2}H), 142.2 (2 x C), 140.4 (2 x C), 137.4 (C^{20}), 130.5 (C^{24}H + C^{25}H), 129.8 (q, *J* = 33.3 Hz, C^{21}/C^{23}), 127.7 (q, *J* = 31.8 Hz, C^{21}/C^{23}), 127.0 (C^{11}H), 126.0 (C^{6}H), 123.9 – 123.7 (m, C^{22}H), 123.4 (2 x C^{3}H), 123.22 (q, *J* = 274.9 Hz, C^{26}F$_3$/C^{27}F$_3$), 123.22 (C), 123.17 (q, *J* = 272.7 Hz, C^{26}F$_3$/C^{27}F$_3$), 122.4 (C), 121.8 (C^{16}H), 121.0 (C^{13}H), 120.2 (C^{12}H), 110.5 (C^{7}H), 110.1 (C^{10}H), 58.4 (q, *J* = 3.7 Hz, C^{19}H$_2$), 37.4 (C^{17}H$_2$), 13.8 (C^{18}H$_3$).

^{19}F NMR (377 MHz, DMSO) δ –59.1, –61.4.

IR (neat) (cm^{-1}): 3658, 2980, 2973, 1622, 1590, 1494, 1480, 1343, 1273, 1162.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(3-(ethoxycarbonyl)-1-ethyl-4-oxo-1,4-dihydroquinolin-7-yl)pyridinium iodide (II-40)**



The title compound was prepared by General Procedure D using 4-(3-(ethoxycarbonyl)-1-ethyl-4-oxo-1,4-dihydroquinolin-7-yl)pyridine (600 mg, 1.90 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.32 g, 3.70 mmol) to give the pyridinium **II-40** (1.13 g, 90%) as an orange solid.

m.p. (acetone): 209-211 °C

HRMS (ESI): Exact mass calculated for $C_{28}H_{23}O_3N_2F_6^+$ $[M]^+$: 549.1607, found 549.1604.

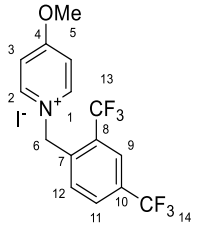
^{1}H NMR (400 MHz, DMSO) δ 9.25 (d, *J* = 6.4 Hz, 2H, 2 x C^2**H**), 8.82 (d, *J* = 7.8 Hz, 3H, 2 x C^3**H** + C^{11}**H**), 8.46 (d, *J* = 8.3 Hz, 1H, C^7**H**), 8.39 (s, 1H, C^{13}**H**), 8.25 (s, 1H, C^{22}**H**), 8.18 – 8.10 (m, 2H, C^6**H** + C^{24}**H**), 7.42 (d, *J* = 8.3 Hz, 1H, C^{25}**H**), 6.27 (s, 2H, C^{19}**H$_2$**), 4.61 (q, *J* = 7.1 Hz, 2H, C^{17}**H$_2$**), 4.25 (q, *J* = 7.1 Hz, 2H, C^{15}**H$_2$**), 1.43 (t, *J* = 7.1 Hz, 3H, C^{18}**H$_3$**), 1.30 (t, *J* = 7.1 Hz, 3H, C^{16}**H$_3$**).

^{13}C NMR (126 MHz, DMSO) δ 172.2 (C^9), 164.4 (C^{14}), 154.8 (C^4), 150.0 (C^{11}H), 146.0 (2 x C^{2}H), 139.2 (C), 137.4 (C), 136.8 (C^{20}), 130.8 (C^{25}H), 130.5 (q, *J* = 4.0 Hz, C^{24}H), 130.0 (C^8), 129.9 (q, *J* = 33.4 Hz, C^{21}/C^{23}), 128.0 (C^{7}H), 127.8 (q, *J* = 31.7 Hz, C^{21}/C^{23}), 126.3 (2 x C^{3}H), 124.1 (C^{6}H), 124.0 – 123.7 (m, C^{22}H), 123.2 (q, *J* = 274.6 Hz, C^{26}F$_3$/C^{27}F$_3$), 123.1 (q, *J* = 272.5 Hz, C^{26}F$_3$/C^{27}F$_3$), 117.6 (C^{13}H), 111.0 (C^{10}), 59.9 (C^{15}H$_2$), 59.2 (q, *J* = 3.3 Hz, C^{19}H$_2$), 48.1 (C^{17}H$_2$), 14.6 (C^{18}H$_3$), 14.3 (C^{16}H$_3$).

^{19}F NMR (377 MHz, DMSO) δ –59.0, –61.4.

IR (neat) (cm^{-1}): 3433, 1720, 1611, 1472, 1348, 1306, 1275, 1219, 1188, 1171.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-methoxypyridinium iodide (II-41)**



The title compound was prepared by General Procedure D using 4-methoxypyridine (0.2 mL, 2.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.06 g, 3.00 mmol) to give the pyridinium **II-41** (853 mg, 92%) as a white solid.

m.p. (acetone): 185-187 °C

HRMS (ESI): Exact mass calculated for $C_{15}H_{12}ONF_6$ $[M]^+$: 336.08176, found 336.08113.

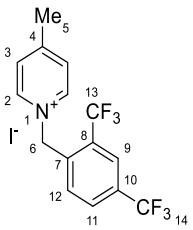
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (d, J = 7.5 Hz, 2H, 2 x C^2**H**), 8.20 (s, 1H, C^9**H**), 8.11 (d, J = 8.2 Hz, 1H, C^{12}**H**), 7.73 (d, J = 7.7 Hz, 1H, C^{11}**H**), 7.30 (d, J = 8.2 Hz, 2H, 2 x C^3**H**), 6.04 (s, 2H, 2 x C^6**H**), 4.15 (s, 3H, 3 x C^5**H**).

^{13}C NMR (126 MHz, DMSO-d_6) δ 171.4 (C^4), 147.1 (2 x C^{2}H), 137.4 (C^7), 130.6 (C^{12}H), 130.5 (d, J = 3.8 Hz, C^{11}H), 129.8 (q, J = 33.3 Hz, C^8/C^{10}), 127.7 (q, J = 31.8 Hz, C^8/C^{10}), 124.1 – 123.6 (m, C^{9}H), 123.2 (q, J = 275.3 Hz, C$^{13}F_3$ + C$^{14}F_3$), 114.0 (2 x C^{3}H), 58.4 (C$^5H_3$), 57.9 (q, J = 3.5 Hz, C$^6H_2$).

^{19}F NMR (377 MHz, DMSO-d_6) δ –59.1, –61.5.

IR (neat) (cm^{-1}): 2981, 1643, 1345, 1269, 1177, 1138, 1085, 1053, 843, 671.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-methylpyridinium iodide (II-42)**



The title compound was prepared by General procedure D using 4-methylpyridine (0.2 mL, 2.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.06 g, 3.00 mmol) to give the pyridinium **II-42** (766 mg, 86%) as a pale brown solid.

m.p. (acetone): 192-194 ºC

HRMS (ESI): Exact mass calculated for $C_{15}H_{12}NF_6^+$ $[M]^+$: 320.0870, found 320.0868.

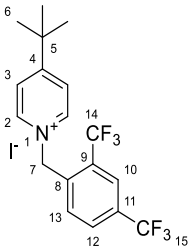
^{1}H NMR (400 MHz, DMSO) δ 8.93 (d, *J* = 6.5 Hz, 2H, 2 x C^2**H**), 8.20 (s, 1H, C^9**H**), 8.13 (dd, *J* = 8.2, 2.0 Hz, 1H, C^{11}**H**), 8.08 (d, *J* = 6.5 Hz, 2H, 2 x C^3**H**), 7.38 (d, *J* = 8.2 Hz, 1H, C^{12}**H**), 6.14 (s, 2H, C^6**H$_2$**), 2.67 (s, 3H, C^5**H$_3$**).

^{13}C NMR (126 MHz, DMSO) δ 160.6 (C^4), 144.7 (2 x C^{2}H), 136.6 (C^7), 131.4 (C^{12}H), 130.5 (q, *J* = 3.9 Hz, C^{11}H$_3$), 130.1 (q, *J* = 33.2 Hz, C^8/C^{10}), 128.9 (2 x C^{3}H), 128.0 (q, *J* = 31.8 Hz, C^8/C^{10}), 124.0 – 123.7 (m, C^{9}H), 123.1 (q, *J* = 273.2 Hz, C^{13}F$_3$/C^{14}F$_3$), 58.9 (q, *J* = 3.1 Hz, C^{6}H$_2$), 21.7 (C^{5}H$_3$).

^{19}F NMR (377 MHz, DMSO) δ –59.0, –61.5.

IR (neat) (cm^{-1}): 2981, 1642, 1346, 1282, 1268, 1178, 1139, 1116, 1085, 1053, 670.

***N*-(2,4-bis(Trifluoromethyl)benzyl)-4-*tert*-buthoxypyridinium iodide (II-43)**



The title compound was prepared by General Procedure D using 4-methylpyridine (0.44 mL, 3.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (1.59 g, 4.50 mmol) to give the pyridinium **II-43** (1.56 g, 99%) as a white solid.

m.p. (acetone): 251-253 °C

HRMS (ESI): Exact mass calculated for $C_{18}H_{18}NF_6^+$ $[M]^+$: 362.1329, found: 362.1338.

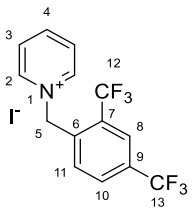
^{1}H NMR (400 MHz, DMSO) δ 8.99 (d, *J* = 7.0 Hz, 2H, 2 x C^2**H**), 8.26 (d, *J* = 7.0 Hz, 2H, 2 x C^3**H**), 8.22 (s, 1H, C^{10}**H**), 8.15 (d, *J* = 8.2 Hz, 1H, C^{12}**H**), 7.36 (d, *J* = 8.2 Hz, 1H, C^{13}**H**), 6.16 (s, 2H, C^7**H$_2$**), 1.40 (s, 9H, 3 x C^2**H$_3$**).

^{13}C NMR (126 MHz, DMSO) δ 171.4 (C^4), 145.1 (2 x C^{2}H), 136.6 (C^8), 131.3 (C^{13}H), 130.6 (q, *J* = 3.7 Hz, C^{12}H), 130.0 (q, *J* = 33.2 Hz, C^9/C^{11}), 127.98 (q, *J* = 31.8 Hz, C^9/C^{11}), 125.6 (2 x C^{2}H), 124.0 – 123.63 (m, C^{10}H), 123.2 (d, *J* = 274.9 Hz, C^{14}F$_3$ + C^{15}F$_3$), 58.8 (q, *J* = 3.3 Hz, C^{7}H$_2$), 36.6 (C^5), 29.54 (3 x C^{6}H$_3$).

^{19}F NMR (377 MHz, DMSO) δ –59.0, –61.5.

IR (neat) (cm^{-1}): 2972, 1642, 1340, 1271, 1177, 1164, 1129, 1084, 1051, 847.

N-(2,4-bis(trifluoromethyl)benzyl)pyridinium (II-44)



The title compound was prepared by General Procedure D using pyridine (81 µL, 1.00 mmol) and 2,4-bis(trifluoromethyl)benzyl iodide **S4** (365 mg, 1.20 mmol) to give the pyridinium **II-44** (311 mg, 76%) as a pale yellow solid.

m.p. (acetone): 199-201 °C

HRMS (ESI): Exact mass calculated for $C_{14}H_{10}NF_6^+$ $[M]^+$: 306.0712, found: 306.0710.

^{1}H NMR (400 MHz, DMSO) δ 9.09 (dd, *J* = 6.7, 1.4 Hz, 2H, 2 x C^{2}**H**), 8.73 (tt, *J* = 7.8, 1.4 Hz, 1H, C^{4}**H**), 8.28 – 8.22 (m, 2H, 2 x C^{3}**H**), 8.20 (d, *J* = 2.0 Hz, 1H, C^{8}**H**), 8.14 (dd, *J* = 8.2, 2.0 Hz, 1H, C^{10}**H**), 7.44 (d, *J* = 8.2 Hz, 1H, C^{11}**H**), 6.22 (s, 2H, C^{5}**H$_2$**).

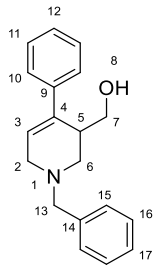
^{13}C NMR (101 MHz, DMSO) δ 147.1 (C^{4}H), 145.8 (C^{2}H), 136.2 (C^{6}), 131.9 (C^{11}H), 130.7 (C^{10}H), 130.3 (q, *J* = 33.3 Hz, C^{7}/C^{9}), 128.8, 128.2 (q, *J* = 31.7 Hz, C^{7}/C^{9}), 124.3 – 123.6 (m, C^{8}H), 123.2 (q, *J* = 273.7 Hz, C^{12}F$_3$ + C^{13}F$_3$), 59.9 (q, *J* = 3.2 Hz, C^{5}H$_2$).

^{19}F NMR (377 MHz, DMSO) δ –59.0, –61.6.

IR (neat) (cm^{-1}): 3076, 2160, 2033, 1482, 1348, 1274, 1177, 1142, 1122, 1055.

7.3.4 The synthesis of tetrahydropyridines

(*N*-Benzyl-4-phenyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-11)



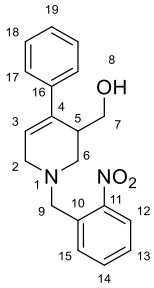
Salt **S15** (187 mg, 0.50 mmol), KI (332 mg, 2.00 mmol), paraformaldehyde (300 mg, 10.0 mmol), and [Ru(*p*-cymene)Cl$_2$]$_2$ (6.1 mg, 2 mol%) was added to a microwave vial. MeOH (2.08 mL, 0.2 M) and Mg(OMe)$_2$ (0.42mL, 0.89M in MeOH) was added and the solution heated at 65 °C for 16 hours. The solution concentrated under reduce pressure and re-dissolved in CH_2Cl_2 (30 m L), brine (50 mL) and water (50 mL). The solution was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The product was purified by FCC (10%-20% EtOAc in pentane) to give *amine* **II-11** (23 mg, 17%) as an yellow oil. Spectroscopic data was consistent with that reported in the literature.[16]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 10H, 10 x C^{Ar}**H**), 6.09 (dd, *J* = 4.7, 1.9 Hz, 1H, C^{3}**H**), 3.80 (dd, *J* = 10.2, 2.5 Hz, 1H, C^{7}**H$_2$**), 3.74 – 3.58 (m, 3H, C^{6}**H$_2$** + C^{13}**H$_2$**), 3.48 – 3.36 (m,

1H, $C^{2}\mathbf{H_2}$), 3.21 (dt, *J* = 11.0, 1.3 Hz, 1H, $C^{6}\mathbf{H_2}$), 2.90 – 2.78 (m, 2H, $C^{2}\mathbf{H_2}$ + $C^{5}\mathbf{H}$), 2.70 (ddd, *J* = 11.1, 3.6, 2.1 Hz, 1H, $C^{13}\mathbf{H_2}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8 (C^{9}), 137.3 (C^{14}), 136.4 (C^{4}), 129.3 (2 x C^{Ar}H), 128.7 (2 x C^{Ar}H), 128.6 (2 x C^{Ar}H), 127.7 (C^{Ar}H), 127.5 (C^{Ar}H), 126.2 (2 x C^{Ar}H), 124.5 (C^{3}H), 65.9 ($C^{7}H_2$), 62.9 ($C^{13}H_2$), 56.2 ($C^{6}H_2$), 53.5 ($C^{2}H_2$), 38.5 (C^{5}H).

(*N*-(2-Nitrobenzyl)-4-phenyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-12)



Salt **S16** (209 mg, 0.50 mmol), KI (332 mg, 2.00 mmol), paraformaldehyde (300 mg, 10.0 mmol), and [Ru(*p*-cymene)Cl_2]$_2$ (6.1 mg, 2 mol%) was added to a microwave vial. MeOH (2.08 mL, 0.2 M) and $Mg(OMe)_2$ (0.42mL, 0.89M in MeOH) was added and the solution heated at 65 °C for 16 hours. The solution concentrated under reduce pressure and re-dissolved in CH_2Cl_2 (30 m L), brine (50 mL) and water (50 mL). The solution was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The product was purified by FCC (20%-50% EtOAc in pentane) to give *amine* **II-12** (65 mg, 40%) as an orange solid.

m.p.(EtOAc) 124-126 °C;

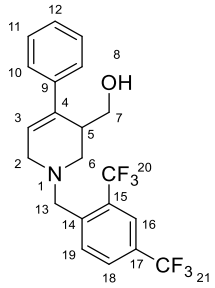
HRMS (ESI): Exact mass calculated for $C_{19}H_{21}O_3N_2$ $[M+H]^+$: 325.15467, found: 325.15454.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.6 Hz, 1H, $C^{12}\mathbf{H}$), 7.64 – 7.54 (m, 2H, 2 x Ar$C\mathbf{H}$), 7.45 (ddd, *J* = 8.6, 6.0, 2.9 Hz, 1H, Ar$C\mathbf{H}$), 7.41 – 7.19 (m, 5H, 5 x Ar$C\mathbf{H}$), 6.02 (dd, *J* = 4.7, 2.2 Hz, 1H, $C^{3}\mathbf{H}$), 4.00 (d, *J* = 14.1 Hz, 1H, $C^{9}\mathbf{H_2}$), 3.88 (d, *J* = 14.1 Hz, 1H, $C^{9}\mathbf{H_2}$), 3.67 (dd, *J* = 10.6, 3.1 Hz, 1H, $C^{7}\mathbf{H_2}$), 3.60 (ddd, *J* = 10.6, 5.2, 1.3 Hz, 1H, $C^{7}\mathbf{H_2}$), 3.38 (dd, *J* = 16.9, 4.7 Hz, 1H, $C^{2}\mathbf{H_2}$), 3.17 (dt, *J* = 11.4, 1.6 Hz, 1H, $C^{6}\mathbf{H_2}$), 2.92 (dt, *J* = 16.9, 2.4 Hz, 1H, $C^{2}\mathbf{H_2}$), 2.87 (br s, 1H, $C^{5}\mathbf{H}$), 2.69 (dd, *J* = 11.4, 3.3 Hz, 1H, $C^{6}\mathbf{H_2}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9 (ArC), 139.7 (ArC), 136.3 (ArC), 133.0 (ArC), 133.0 (ArCH), 131.4 (ArCH), 128.6 (2 x ArCH), 128.6 (ArCH), 127.5 (ArCH), 126.1 (2 x ArCH), 124.9 (ArCH), 124.1 (C^3H), 64.9 (C^7H), 59.1 (C^9H), 54.9 (C^6H), 53.8 (C^2H), 39.2 (C^5H).

IR (neat) (cm^{-1}): 3311, 2928, 2852, 2811, 1726, 1523, 1350, 1127, 1071, 991.

(N-(2,4-bis(Trifluoromethyl)benzyl)-4-phenyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-13)



The title compound was prepared by general procedure E using salt **II-17** (255 mg, 3.00 mmol). Purification by FCC (10%-30% EtOAc in pentane) gave *amine* **II-13** (916 mg, 73%) as an orange oil.

HRMS (ESI): Exact mass calculated for $C_{21}H_{20}F_6NO$ $[M+H]^+$: 416.14436, found: 416.14505.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 1.8 Hz, 1H, C^{16}**H**), 7.91 (d, *J* = 8.3 Hz, 1H, C^{18}**H**), 7.83 (d, *J* = 8.3, 1.9 Hz, 1H, C^{19}**H**), 7.41 – 7.23 (m, 5H, 5 x Ar**H**), 6.08 (dd, *J* = 4.7, 2.2 Hz, 1H, C^3**H**), 4.02 (s, 1H, O^8**H**), 3.87 (s, 2H, C^{13}**H$_2$**), 3.75 (dd, *J* = 10.3, 2.7 Hz, 1H, C^7**H$_2$**), 3.67 (ddd, *J* = 10.3, 4.1, 1.6 Hz, 1H, C^7**H$_2$**), 3.43 (dd, *J* = 16.9, 4.8 Hz, 1H, C^2**H$_2$**), 3.16 (dt, *J* = 11.2, 1.6 Hz, 1H, C^6**H$_2$**), 2.98 (dt, *J* = 16.9, 2.5 Hz, 1H, C^2**H$_2$**), 2.89 (brs, 1H, C^5**H**), 2.78 (ddd, *J* = 11.1, 3.9, 1.5 Hz, 1H, C^6**H$_2$**).

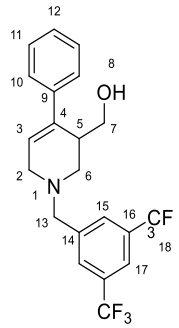
^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2 (C^{14}), 139.7 (C), 136.4 (C), 131.5 (C^{19}H), 129.8 (q, *J* = 31.7 Hz, C^{15}+C^{17}), 129.0 (C^{18}H), 128.7 (2 x ArCH), 127.7 (ArCH), 126.2 (2 x ArCH), 124.1 (C^3H), 123.7 (q, *J* = 274.0 Hz, $C^{20}F_3$/$C^{21}F_3$), 123.5 (q, *J* = 272.4 Hz, $C^{20}F_3$/$C^{21}F_3$), 123.5 – 123.2 (m, C^{16}H), 65.4 (C^7H_2), 58.0 (q, *J* = 2.2 Hz, $C^{13}H_2$), 55.7 (C^6H_2), 53.8 (C^2H_2), 39.1 (C^5H).

^{19}F NMR (376 MHz, $CDCl_3$) δ –59.20, –62.86.

IR (neat) (cm^{-1}): 3376, 2996, 1346, 1283, 1276, 1171, 1126, 1085, 1037, 918.

(N-(3,5-bis(Trifluoromethyl)benzyl)-4-phenyl-1,2,3,6-tetrahydropyridin-3-yl)methanol

(II-14)



The title compound was prepared by general procedure E using salt **S18** (255 mg, 0.50 mmol). Purification by FCC (20% EtOAc in pentane) gave *amine* **II-14** (66 mg, 32%) as an orange oil.

HRMS (ESI): Exact mass calculated for $C_{21}H_{20}F_6NO$ $[M+H]^+$: 416.14436, found: 416.14499.

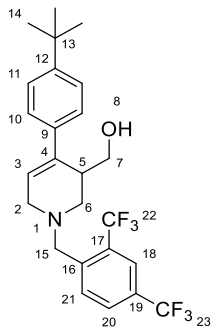
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 3H), 7.40 – 7.23 (m, 5H), 6.06 (dd, *J* = 4.7, 2.2 Hz, 1H), 3.84 (s, 1H), 3.81 (d, *J* = 13.5 Hz, 1H), 3.75 (dd, *J* = 10.2, 2.8 Hz, 1H), 3.73 (d, *J* = 13.5 Hz, 1H), 3.67 (ddd, *J* = 10.3, 4.3, 1.5 Hz, 1H), 3.42 – 3.32 (m, 1H), 3.17 (dt, *J* = 11.1, 1.6 Hz, 1H), 2.94 (dt, *J* = 16.6, 2.4 Hz, 1H), 2.93 – 2.86 (m, 1H), 2.72 (ddd, *J* = 11.1, 3.8, 1.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4 (C^{14}), 139.7 (C), 136.6 (C), 132.0 (q, *J* = 33.3 Hz, 2 x C^{16}), 129.1 (2 x $C^{15}H$), 128.7 (2 x ArCH), 127.7 (ArCH), 126.2 (2 x ArCH), 124.0 (C^3H), 123.5 (q, *J* = 277.6 Hz, 2 x $C^{18}F_3$), 121.9 – 121.5 (m, $C^{17}H$), 65.3 (C^7H_2), 62.0 ($C^{13}H_2$), 55.4 (C^6H_2), 53.5 (C^2H_2), 39.0 (C^5H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –62.79 (d, *J* = 2.6 Hz).

IR (neat) (cm^{-1}): 3376, 2921, 1352, 1276, 1168, 1124, 846, 756, 699, 682.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-(tert-butyl)phenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-46)



The title compound was prepared by General procedure E using salt **II-20** (283 mg, 0.50 mmol). Purification by FCC (10%-30% EtOAc in pentane) gave *amine* **II-46** (157 mg, 66%) as an white solid.

m.p. (acetone): 66-68°C

HRMS (ESI): Exact mass calculated for $C_{25}H_{28}F_6NO$ $[M+H]^+$: 472.20696, found: 472.20642.

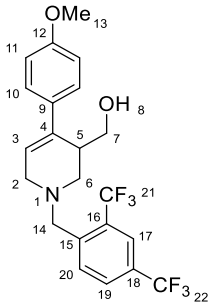
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 2H, C^{18}**H** + C^{21}**H**), 7.83 (dd, *J* = 8.3, 2.4 Hz, 1H, C^{20}**H**), 7.36 (d, *J* = 8.7 Hz, 2H, 2 x C^{10}**H**), 7.30 (d, *J* = 8.7 Hz, 2H, 2 x C^{11}**H**), 6.06 (dd, *J* = 4.8, 2.2 Hz, 1H, C^3**H**), 4.02 (s, 1H, O**H**), 3.86 (s, 2H, C^{15}**H$_2$**), 3.75 (dd, *J* = 10.3, 2.7 Hz, 1H, C^7**H$_2$**), 3.69 (ddd, *J* = 10.3, 4.1, 1.5 Hz, 1H, C^7**H$_2$**), 3.42 (dd, *J* = 16.9, 4.7 Hz, 1H, C^2**H$_2$**), 3.15 (dt, *J* = 11.1, 1.6 Hz, 1H, C^6**H$_2$**), 2.97 (dt, *J* = 16.9, 2.5 Hz, 1H, C^2**H$_2$**), 2.89 (s, 1H, C^5**H**), 2.76 (ddd, *J* = 11.1, 3.9, 1.4 Hz, 1H, C^6**H$_2$**), 1.32 (s, 9H, 3 x C^{14}**H$_3$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7 (C^{12}), 141.2 (C), 136.5 (C), 136.0 (C), 131.5 (C^{21}H), 130.0 (q, *J* = 33.4 Hz, C^{17}/C^{19}), 129.7 (q, *J* = 31.2 Hz, C^{17}/C^{19}), 129.1 (q, *J* = 3.8 Hz, C^{20}H), 125.8 (2 x C^{11}H), 125.6 (2 x C^{10}H), 123.7 (q, *J* = 274.2 Hz, $C^{22}F_3$/$C^{23}F_3$), 123.5 (q, *J* = 272.3 Hz, $C^{22}F_3$/$C^{23}F_3$), 123.4 (C^3H), 123.4 – 123.2 (m, C^{18}H), 65.5 (C^7H_2), 58.0 (q, *J* = 2.2 Hz, C^{15}H), 55.8 (C^6H_2), 53.8 (C^2H_2), 38.8 (C^5H), 34.6 (C^{13}), 31.5 (3 x $C^{14}H_3$).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.9.

IR (neat) (cm^{-1}):3036, 2830, 1344, 1273, 1171, 1121, 1083, 1055, 827, 673.

(N-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-47)



The title compound was prepared by General procedure E using salt **II-21** (270 mg, 0.50 mmol). Purification by FCC (5%-30% EtOAc in pentane) gave *amine* **II-47** (154 mg, 69%) as an orange oil.

HRMS (ESI): Exact mass calculated for $C_{22}H_{22}F_6NO_2$ $[M+H]^+$446.1549:, found: 446.1549.

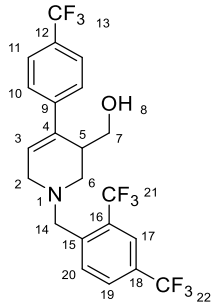
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H, C^{17}**H**), 7.90 (d, *J* = 8.2 Hz, 1H, C^{20}**H**), 7.83 (dd, *J* = 8.3, 1.9 Hz, 1H, C^{19}**H**), 7.30 (d, *J* = 8.9 Hz, 2H, 2 x C^{10}**H**), 6.87 (d, *J* = 8.8 Hz, 2H, 2 x C^{11}**H**), 6.00 (dd, *J* = 4.6, 2.2 Hz, 1H, C^{3}**H**), 4.06 (s, 1H, O**H**), 3.86 (s, 2H, C^{14}**H$_2$**), 3.81 (s, 3H, C^{13}**H$_3$**), 3.75 (dd, *J* = 10.2, 2.7 Hz, 1H, C^{7}**H$_2$**), 3.67 (ddd, *J* = 10.2, 4.0, 1.6 Hz, 1H, C^{7}**H$_2$**), 3.41 (dd, *J* = 16.8, 4.7 Hz, 1H, C^{2}**H$_2$**), 3.14 (dt, *J* = 11.1, 1.6 Hz, 1H, C^{6}**H$_2$**), 2.96 (dt, *J* = 16.8, 2.5 Hz, 1H, C^{2}**H$_2$**), 2.85 (s, 1H, C^{5}**H**), 2.76 (ddd, *J* = 11.1, 3.8, 1.5 Hz, 1H, C^{6}**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3 (C^{12}), 141.2 (C^{15}), 135.7 (C), 132.1 (C), 131.5 (C^{20}H), 130.1 (q, *J* = 33.5 Hz, C^{16}/C^{18}), 129.7 (q, *J* = 31.2 Hz, C^{16}/C^{18}), 129.0 (q, *J* = 4.1 Hz, C^{19}H), 127.2 (2 x C^{10}H), 123.7 (q, *J* = 273.2 Hz, C^{21}F$_3$/C^{22}F$_3$), 123.5 (q, *J* = 272.3 Hz, C^{21}F$_3$/C^{22}F$_3$), 123.3 (m, C^{17}H), 122.6 (C^{3}H), 114.0 (2 x C^{11}H), 65.5 (C^{7}H$_2$), 58.0 (C^{14}H$_2$), 55.8 (C^{6}H$_2$), 55.4 (C^{13}H$_3$), 53.8 (C^{2}H$_2$), 38.9 (C^{5}H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.8.

IR (neat) (cm^{-1}): 2981, 1640, 1599, 1344, 1271, 1166, 1122, 1084, 1053, 833, 671.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-(trifluoromethyl)phenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-48)



The title compound was prepared by General procedure E using salt **II-22** (289 mg, 0.50 mmol). Purification by FCC (10%-20% EtOAc in pentane) gave *amine* **II-48** (112 mg, 46%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{22}H_{19}F_9NO$ $[M+H]^+$: 484.1317, found: 484.1321.

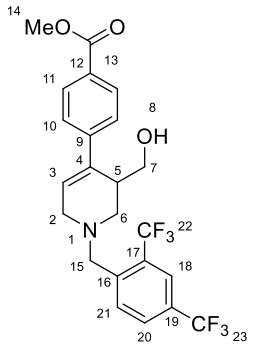
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H, C^{17}**H**), 7.88 (d, *J* = 8.2 Hz, 1H, C^{20}**H**), 7.84 (dd, *J* = 8.4, 1.9 Hz, 1H, C^{19}**H**), 7.59 (d, *J* = 8.2 Hz, 2H, 2 x C^{11}**H**), 7.47 (d, *J* = 8.1 Hz, 2H, 2 x C^{10}**H**), 6.15 (dd, *J* = 4.7, 2.2 Hz, 1H, C^{3}**H**), 3.96 (s, 1H, O**H**), 3.87 (s, 2H, C^{14}**H$_2$**), 3.74 (dd, *J* = 10.4, 2.6 Hz, 1H, C^{7}**H$_2$**), 3.63 (ddd, *J* = 10.4, 4.1, 1.6 Hz, 1H, C^{7}**H$_2$**), 3.45 (dd, *J* = 17.3, 4.8 Hz, 1H, C^{2}**H$_2$**), 3.17 (dt, *J* = 11.2, 1.5 Hz, 1H, C^{6}**H$_2$**), 3.00 (dt, *J* = 17.2, 2.5 Hz, 1H, C^{2}**H$_2$**), 2.89 (brs, 1H, C^{5}**H**), 2.78 (ddd, *J* = 11.1, 3.8, 1.6 Hz, 1H, C^{6}**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.2 (C), 140.9 (C), 135.5 (C), 131.5 (C^{20}H), 130.2 (q, *J* = 33.2 Hz, C^{12}/C^{16}/C^{18}), 129.8 (q, *J* = 31.3 Hz, C^{12}/C^{16}/C^{18}), 129.7 (q, *J* = 32.4 Hz, C^{12}/C^{16}/C^{18}), 129.1 (q, *J* = 3.9 Hz, C^{19}H), 126.5 (2 x C^{10}H), 126.2 (C^{3}H), 125.7 (q, *J* = 3.8 Hz, 2 x C^{11}H), 124.3 (q, *J* = 272.0 Hz, $C^{13}F_3$/$C^{21}F_3$/$C^{22}F_3$), 123.7 (q, *J* = 274.3 Hz, $C^{13}F_3$/$C^{21}F_3$/$C^{22}F_3$), 123.5 (q, *J* = 272.3 Hz, $C^{13}F_3$/$C^{21}F_3$/$C^{22}F_3$), 123.5 – 123.4 (m, C^{17}H), 65.2 ($C^{7}H_2$), 57.9 ($C^{14}H_2$), 55.6 ($C^{6}H_2$), 53.7 ($C^{2}H_2$), 38.9 (C^{5}H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.5, –62.9.

IR (neat) (cm^{-1}): 3320, 1346, 1325, 1275, 1166, 1116, 1083, 1069, 1055, 672.

Methyl-4-(1-(2,4-bis(trifluoromethyl)benzyl)-3-(hydroxymethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoate (II-49)



The title compound was prepared by General procedure E using salt **II-23** (284 mg, 0.50 mmol). Purification by FCC (10-30% EtOAc in pentane) gave *amine* **II-49** (148 mg, 62%) as an off-white solid.

m.p. (acetone): 145-147 °C

HRMS (ESI): Exact mass calculated for $C_{23}H_{22}F_6NO$ $[M+H]^+$: 474.1498, found:474.1501.

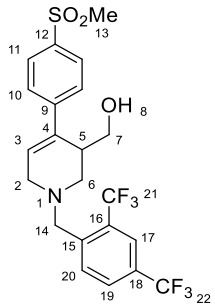
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.5 Hz, 2H, 2 x C^{11}**H**), 7.94 (d, *J* = 1.9 Hz, 1H, C^{18}**H**), 7.89 (d, *J* = 8.2 Hz, 1H, C^{21}**H**), 7.83 (dd, *J* = 8.3, 1.8 Hz, 1H, C^{20}**H**), 7.44 (d, *J* = 8.5 Hz, 2H, 2 x C^{10}**H**), 6.19 (dd, *J* = 4.7, 2.3 Hz, 1H, C^{3}**H**), 3.96 (s, 1H, O**H**), 3.91 (s, 3H, C^{14}**H$_3$**), 3.87 (s, 2H, C^{15}**H$_2$**), 3.75 (dd, *J* = 10.4, 2.6 Hz, 1H, C^{7}**H$_2$**), 3.64 (ddd, *J* = 10.4, 4.2, 1.6 Hz, 1H, C^{7}**H$_2$**), 3.45 (dd, *J* = 17.3, 4.7 Hz, 1H, C^{2}**H$_2$**), 3.17 (dt, *J* = 11.2, 1.5 Hz, 1H, C^{6}**H$_2$**), 2.99 (dt, *J* = 17.3, 2.5 Hz, 1H, C^{2}**H$_2$**), 2.92 (s, 1H, C^{5}**H**), 2.78 (ddd, *J* = 11.3, 3.9, 1.5 Hz, 1H, C^{6}**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.0 (C^{13}O), 144.1 (C), 141.0 (C), 135.7 (C), 131.5 (C^{21}H), 130.2 (q, *J* = 33.5 Hz, C^{17}/C^{19}), 130.0 (2 x C^{11}H), 129.8 (q, *J* = 31.0 Hz, C^{17}/C^{19}), 129.3 (C), 129.1 (q, *J* = 3.8 Hz, C^{20}H), 126.1 (2 x C^{10}H + C^{3}H), 123.7 (q, *J* = 274.3 Hz, $C^{22}F_3$/$C^{23}F_3$), 123.5 (q, *J* = 272.3 Hz, $C^{22}F_3$/$C^{23}F_3$), 123.5 – 123.2 (m, C^{18}H), 65.3 ($C^{7}H_2$), 57.9 (q, *J* = 2.0 Hz, $C^{15}H_2$), 55.6 ($C^{6}H_2$), 53.8 ($C^{2}H_2$), 52.3 ($C^{14}H_3$), 38.8 (C^{5}H).

^{19}F NMR (376 MHz, $CDCl_3$) δ –59.2, –62.8.

IR (neat) (cm^{-1}): 3522,1709, 1630, 1607, 1344, 1283, 1266, 1176, 1170, 1127.

(N-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-(methylsulfonyl)phenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-50)



The title compound was prepared by General procedure E using salt **II-34** (294 mg, 0.50 mmol). Purification my FCC (10%-50% EtOAc in pentane) gave *amine* **II-50** (136 mg, 55%) as a yellow solid.

m.p. (EtOAc): 95-97 °C

HRMS (ESI): Exact mass calculated for $C_{22}H_{22}F_6NOS$ $[M+H]^+$: 494.1195, found: 494.1208.

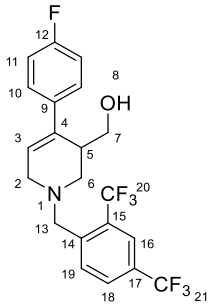
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.8 Hz, 1H, C^{17}**H**), 7.91 (d, *J* = 8.4 Hz, 2H, 2 x C^{11}**H**), 7.87 (d, *J* = 8.2 Hz, 1H, C^{20}**H**), 7.84 (dd, *J* = 8.2, 1.8 Hz, 1H, C^{19}**H**), 7.55 (d, *J* = 8.5 Hz, 2H, 2 x C^{10}**H**), 6.21 (dd, *J* = 4.8, 2.2 Hz, 1H, C^{3}**H**), 3.92 (s, 1H, O**H**), 3.88 (s, 2H, C^{14}**H$_2$**), 3.74 (dd, *J* = 10.4, 2.6 Hz, 1H, C^{7}**H$_2$**), 3.62 (ddd, *J* = 10.5, 4.3, 1.6 Hz, 1H, C^{7}**H$_2$**), 3.47 (dd, *J* = 17.4, 4.8 Hz, 1H, C^{2}**H$_2$**), 3.18 (dt, *J* = 11.2, 1.5 Hz, 1H, C^{6}**H$_2$**), 3.06 (s, 3H, C^{13}**H$_3$**), 3.01 (dt, *J* = 17.5, 2.5 Hz, 1H, C^{2}**H$_2$**), 2.90 (s, 1H, C^{5}**H**), 2.78 (ddd, *J* = 11.2, 3.9, 1.5 Hz, 1H, C^{6}**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2 (C), 140.8 (C), 139.4 (C), 135.2 (C), 131.5 (C^{20}H), 130.3 (q, *J* = 33.6 Hz, C^{16}/C^{18}), 129.8 (q, *J* = 31.1 Hz, C^{16}/C^{18}), 129.1 (q, *J* = 3.8 Hz, C^{19}H), 127.9 (2 x C^{11}H), 127.4 (C^{3}H), 127.1 (2 x C^{10}H), 123.7 (q, *J* = 274.2 Hz, C^{21}F$_3$/C^{22}F$_3$), 123.6 – 123.2 (m, C^{17}H), 123.5 (q, *J* = 272.3 Hz, C^{21}F$_3$/C^{22}F$_3$), 65.2 (C^{7}H$_2$), 57.9 (q, *J* = 2.0 Hz, C^{14}H$_2$), 55.5 (C^{6}H$_2$), 53.7 (C^{2}H$_2$), 44.7 (C^{13}H$_3$), 38.9 (C^{5}H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.1, –62.9.

IR (neat) (cm^{-1}): 3326, 2927, 1620, 1346, 1301, 1275, 1171, 1124, 1084, 1055.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-51)



The title compound was prepared by General procedure E using salt **II-25** (264 mg, 0.50 mmol). Purification by FCC (5%-20% EtOAc in pentane) gave *amine* **II-51** (169 mg, 78%) as a yellow oil.

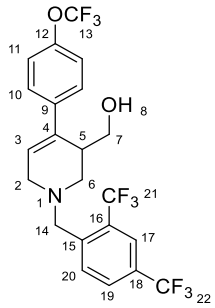
HRMS (ESI): Exact mass calculated for $C_{21}H_{19}F_7NO$ $[M+H]^+$: 434.1349, found: 434.1349

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 1.9 Hz, 1H, C^{16}**H**), 7.88 (d, *J* = 8.2 Hz, 1H, C^{19}**H**), 7.83 (d, *J* = 8.2 Hz, 1H, C^{18}**H**), 7.37 – 7.28 (m, 2H, 2 x C^{10}**H**), 7.07 – 6.98 (m, 2H, 2 x C^{11}**H**), 6.02 (dd, *J* = 4.8, 2.2 Hz, 1H, C^3**H**), 4.08 (s, 1H, O**H**), 3.86 (s, 2H, C^{13}**H$_2$**), 3.74 (dd, *J* = 10.4, 2.6 Hz, 1H, C^7**H$_2$**), 3.63 (ddd, *J* = 10.4, 4.0, 1.7 Hz, 1H, C^7**H$_2$**), 3.41 (dd, *J* = 17.0, 4.8 Hz, 1H, C^2**H**), 3.15 (dt, *J* = 11.2, 1.5 Hz, 1H, C^6**H**), 2.96 (dt, *J* = 17.0, 2.5 Hz, 1H, C^2**H**), 2.83 (s, 1H, C^5**H**), 2.77 (ddd, *J* = 11.1, 3.8, 1.6 Hz, 1H, C^6**H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5 (d, *J* = 246.5 Hz, C^{12}F), 141.0 (C), 135.7 (d, *J* = 3.3 Hz, C^9), 135.5 (C), 131.5 (C^{19}H) 130.1 (q, *J* = 33.6 Hz, C^{15}/C^{17}), 129.8 (q, *J* = 31.0 Hz, C^{15}/C^{17}), 129.1 (q, *J* = 3.7 Hz, C^{18}H), 127.8 (d, *J* = 8.0 Hz, 2 x C^{10}H), 124.1 (C^{3}H), 123.7 (q, *J* = 274.2 Hz, C^{20}F$_3$/C^{21}F$_3$), 123.5 (q, *J* = 272.3 Hz, C^{20}F$_3$/C^{21}F$_3$), 123.4 (dd, *J* = 6.2, 3.8 Hz, C^{16}H), 115.5 (d, *J* = 21.3 Hz, 2 x C^{11}H), 65.3 (C^{7}H$_2$), 58.0 (q, *J* = 2.0 Hz, C^{13}H$_2$), 55.7 (C^{6}H$_2$), 53.7 (C^{2}H$_2$), 39.1 (C^{5}H).

IR (neat) (cm^{-1}): 3279, 2922, 1509, 1345, 1275, 1165, 1122, 1083, 1055, 841.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-(trifluoromethoxy)phenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-52)



The title compound was prepared by General procedure E using salt **II-26** (297 mg, 0.50 mmo). Purification by FCC (5%-20% EtOAc in pentane) gave *amine* **II-52** (162 mg, 64%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{22}H_{19}F_9NO_2$ $[M+H]^+$: 500.1267, found: 500.1259.

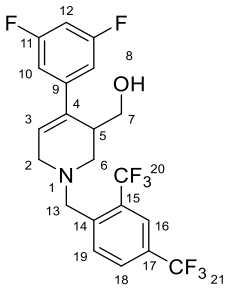
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H, C^{17}**H**), 7.89 (d, *J* = 8.2 Hz, 1H, C^{20}**H**), 7.83 (dd, *J* = 8.2, 1.8 Hz, 1H, C^{19}**H**), 7.38 (d, *J* = 8.8 Hz, 2H, 2 x C^{10}**H**), 7.18 (dd, *J* = 8.9, 1.0 Hz, 2H, C^{11}**H**), 6.10 – 6.04 (m, 1H, C^{3}**H**), 4.00 (s, 1H, O**H**), 3.86 (s, 2H, C^{14}**H$_2$**), 3.74 (dd, *J* = 10.4, 2.6 Hz, 1H, C^{7}**H$_2$**), 3.64 (ddd, *J* = 10.4, 4.1, 1.7 Hz, 1H, C^{7}**H$_2$**), 3.43 (dd, *J* = 17.1, 4.7 Hz, 1H, C^{2}**H$_2$**), 3.16 (dt, *J* = 11.1, 1.5 Hz, 1H, C^{6}**H$_2$**), 2.97 (dt, *J* = 17.1, 2.4 Hz, 1H, C^{2}**H$_2$**), 2.84 (s, 1H, C^{5}**H**), 2.77 (ddd, *J* = 11.1, 3.9, 1.5 Hz, 1H, C^{6}**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7 (q, *J* = 2.0 Hz, C^{12}), 141.0 (C), 138.4 (C), 135.3 (C), 131.5 (C^{20}H), 130.2 (q, *J* = 33.6 Hz, C^{16}/C^{18}), 129.8 (q, *J* = 31.1 Hz, C^{16}/C^{18}), 129.1 (q, *J* = 3.5 Hz, C^{19}H), 127.6 (2 x C^{10}H), 125.0 (C^{3}H), 123.7 (q, *J* = 274.2 Hz, $C^{21}F_3$/$C^{22}F_3$), 123.5 (q, *J* = 272.3 Hz, $C^{21}F_3$/$C^{22}F_3$), 123.5 – 123.3 (m, C^{17}H), 121.1 (2 x C^{11}H), 120.6 (q, *J* = 257.1 Hz, $C^{13}F_3$), 65.3 ($C^{7}H_2$), 57.9 (q, *J* = 2.3 Hz, $C^{14}H_2$), 55.7, ($C^{6}H_2$), 53.7 ($C^{2}H_2$), 39.0 (C^{5}H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –57.9, –59.2, –62.7.

IR (neat) (cm^{-1}): 3245, 2922, 1345, 1275, 1170, 1123, 1083, 1055, 804, 673.

(N-(2,4-bis(Trifluoromethyl)benzyl)-4-(3,5-difluorophenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-53)



The title compound was prepared by General procedure E using salt **II-27** (273 mg, 0.50 mmol). Purification by FCC (5%-15% EtOAc in pentane) gave *amine* **II-53** (132 mg, 59%) as a pale orange oil.

HRMS (ESI): Exact mass calculated for $C_{21}H_{18}F_8NO$ $[M+H]^+$: 452.1255, found: 452.1247.

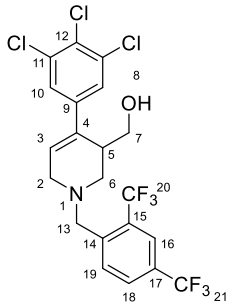
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H, $C^{16}H$), 7.91 – 7.79 (m, 2H, $C^{18}H$ + $C^{19}H$), 6.93 – 6.84 (m, 2H, 2 x $C^{10}H$), 6.72 (tt, *J* = 8.8, 2.3 Hz, 1H, $C^{12}H$), 6.13 (dd, *J* = 4.8, 2.3 Hz, 1H, $C^{3}H$), 3.86 (s, 2H, $C^{13}H_2$), 3.75 (dd, *J* = 10.4, 2.6 Hz, 1H, $C^{7}H_2$), 3.65 (ddd, *J* = 10.4, 4.1, 1.7 Hz, 1H, $C^{7}H_2$), 3.43 (dd, *J* = 17.3, 4.7 Hz, 1H, $C^{2}H_2$), 3.16 (dt, *J* = 10.9, 1.4 Hz, 1H, $C^{6}H_2$), 2.98 (dt, *J* = 17.4, 2.4 Hz, 1H, $C^{2}H_2$), 2.83 – 2.70 (m, 2H, $C^{6}H_2$ + $C^{5}H$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.32 (dd, *J* = 247.9, 13.3 Hz, 2 x $C^{11}F$), 143.1 (t, *J* = 9.2 Hz, C^{9}), 140.8 (C^{14}), 134.7 (t, *J* = 2.5 Hz, C^{4}), 131.5 ($C^{19}H$), 130.2 (q, *J* = 33.5 Hz, C^{15}/C^{17}), 129.8 (q, *J* = 31.2 Hz, C^{15}/C^{17}), 129.1 (q, *J* = 3.8 Hz, $C^{18}H$), 126.2 ($C^{3}H$), 123.7 (q, *J* = 274.2 Hz, $C^{20}F_3$/$C^{21}F_3$), 123.5 (q, *J* = 272.4 Hz, $C^{20}F_3$/$C^{21}F_3$), 123.7 – 123.2 (m, $C^{16}H$), 109.5 – 108.5 (m, 2 x $C^{10}H$), 102.9 (t, *J* = 25.4 Hz, $C^{12}H$), 65.2 ($C^{7}H_2$), 57.9 (q, *J* = 2.0 Hz, $C^{13}H_2$), 55.4 ($C^{6}H_2$), 53.6 ($C^{2}H_2$), 38.8 ($C^{5}H$).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.9, –109.9 (t, *J* = 8.7 Hz).

IR (neat) (cm^{-1}): 3264, 2972, 2848, 1345, 1275, 1171, 1118, 1083, 1055, 988.

(N-(2,4-bis(Trifluoromethyl)benzyl)-4-(3,4,5-trichlorophenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-54)



The title compound was prepared by General procedure E using salt **II-28** (287 mg, 0.47 mmol). Purification my FCC (5%-20% EtOAc in pentane) gave the *amine* **II-54** (124 mg, 51%) as an orange solid.

m.p. (EtOAc): 66-68 °C

HRMS (ESI): Exact mass calculated for $C_{21}H_{17}Cl_3F_6NO$ $[M+H]^+$: 518.0274, found: 518.0274.

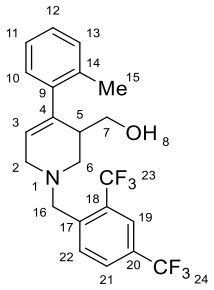
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H, $C^{16}H$), 7.89 – 7.79 (m, 2H, $C^{18}H$ + $C^{19}H$), 7.37 (s, 2H, 2 x $C^{10}H$), 6.11 (dd, *J* = 4.7, 2.3 Hz, 1H, C^3H), 3.86 (s, 2H, $C^{16}H_2$), 3.74 (dd, *J* = 10.4, 2.4 Hz, 1H, C^7H_2), 3.62 (ddd, *J* = 10.5, 4.0, 1.8 Hz, 1H, C^7H_2), 3.43 (dd, *J* = 17.3, 4.7 Hz, 1H, C^2H_2), 3.20 – 3.10 (m, 1H, C^6H_2), 2.97 (dt, *J* = 17.4, 2.4 Hz, 1H, C^2H_2), 2.80 – 2.68 (m, 2H, C^6H_2 + C^5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7 (C^{14}), 139.8 (C), 134.5 (2 x C^{11}), 133.9 (C), 131.5 ($C^{19}H$), 130.3 (C), 130.3 (q, *J* = 33.6 Hz, C^{15}/ C^{17}), 129.8 (q, *J* = 31.2 Hz, C^{15}/ C^{17}), 129.1 (q, *J* = 3.8 Hz, $C^{18}H$), 126.8 (C^3H), 126.5 (2 x $C^{10}H$), 123.7 (d, *J* = 274.3 Hz, $C^{20}F_3$/ $C^{21}F_3$), 123.7 – 123.2 (m, $C^{16}H$), 123.4 (d, *J* = 272.3 Hz, $C^{20}F_3$/ $C^{21}F_3$), 65.1 (C^7H_2), 57.9 (q, *J* = 2.4 Hz, $C^{13}H_2$), 55.4 (C^6H_2), 53.6 (C^2H_2), 38.8 (C^5H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.9.

IR (neat) (cm^{-1}): 3260, 2981, 1640, 1345, 1269, 1169, 1119, 1084, 1054, 762.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(o-tolyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-55)



The title compound was prepared by General procedure E using salt **II-29** (262 mg, 0.50 mmol). Purification by FCC (5%-20% EtOAc in pentane) gave amine **II-55** (144 mg, 67%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{22}H_{22}F_6NO$ $[M+H]^+$: 430.1600, found: 430.1605.

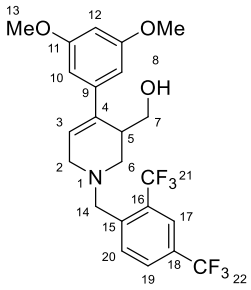
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 2H, C^{19}**H** + C^{22}**H**), 7.77 (dd, *J* = 8.2, 1.9 Hz, 1H, C^{21}**H**), 7.14 – 7.02 (m, 4H, 4 x Ar**H**), 5.63 – 5.57 (m, 1H, C^3**H**), 3.80 (s, 2H, C^{16}**H$_2$**), 3.61 (dd, *J* = 10.4, 2.7 Hz, 1H, C^7**H$_2$**), 3.52 (ddd, *J* = 10.4, 3.6, 1.8 Hz, 1H, C^7**H$_2$**), 3.32 (dd, *J* = 16.4, 4.5 Hz, 1H, C^2**H$_2$**), 3.03 (dt, *J* = 11.1, 1.6 Hz, 1H, C^6**H$_2$**), 2.87 (dt, *J* = 16.4, 2.4 Hz, 1H, C^2**H$_2$**), 2.77 (ddd, *J* = 11.2, 4.0, 1.6 Hz, 1H, C^6**H$_2$**), 2.41 (s, 1H, C^5**H**), 2.23 (s, 3H, C^{15}**H$_3$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1 (C), 141.0 (C), 137.4 (C), 135.8 (C), 131.6 (C^{22}H), 130.3 (ArCH), 130.1 (q, *J* = 33.5 Hz, C^{18}/C^{20}), 129.8 (q, *J* = 31.1 Hz, C^{18}/C^{20}), 129.1 (C^{21}H), 129.1 (ArCH), 127.3 (ArCH), 125.7 (ArCH), 125.3 (C^3H), 123.7 (q, *J* = 274.2 Hz, $C^{23}F_3$/ $C^{24}F_3$), 123.5 (q, *J* = 272.3 Hz, $C^{23}F_3$/ $C^{24}F_3$), 123.4 – 123.2 (m, C^{19}H), 65.0 (C^7H_2), 58.1 (q, *J* = 2.4 Hz, $C^{16}H_2$), 55.9 (C^6H_2), 53.3 (C^2H_2), 41.4 (C^5H), 19.8 ($C^{15}H_3$).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.1, –62.9.

IR (neat) (cm^{-1}): 3658, 2980, 2973, 1345, 1274, 1169, 1123, 1083, 1055, 760.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(3,5-dimethoxyphenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-56)



The title compound was prepared by General procedure E using salt **II-30** (285 mg, 0.50 mmol). Purification by FCC (10%-30% EtOAc in pentane) gave the *amine* **II-56** (186 mg, 78%) as a viscous red oil.

HRMS (ESI): Exact mass calculated for $C_{23}H_{24}F_6NO_3$ $[M+H]^+$: 476.1655, found: 476.1653.

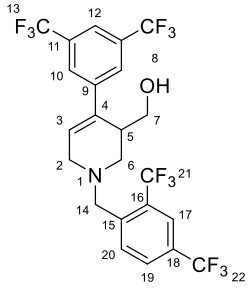
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H, C^{17}**H**), 7.89 (d, *J* = 8.2 Hz, 1H, C^{19}**H**), 7.83 (dd, *J* = 8.2, 1.9 Hz, 1H, C^{20}**H**), 6.50 (d, *J* = 2.2 Hz, 2H, 2 x C^{10}**H**), 6.40 (t, *J* = 2.2 Hz, 1H, C^{12}**H**), 6.07 (dd, *J* = 4.8, 2.2 Hz, 1H, C^{3}**H**), 4.07 (s, 1H, O**H**), 3.85 (s, 2H, C^{14}**H**), 3.79 (s, 6H, 2 x C^{13}**H$_3$**), 3.74 (dd, *J* = 10.3, 2.7 Hz, 1H, C^{7}**H$_2$**), 3.67 (ddd, *J* = 10.3, 4.0, 1.5 Hz, 1H, C^{7}**H$_2$**), 3.41 (dd, *J* = 17.1, 4.6 Hz, 1H, C^{2}**H$_2$**), 3.14 (dt, *J* = 11.1, 1.5 Hz, 1H, C^{6}**H$_2$**), 2.96 (dt, *J* = 17.0, 2.5 Hz, 1H, C^{2}**H$_2$**), 2.82 (brs, 1H, C^{5}**H**), 2.76 (ddd, *J* = 11.1, 3.9, 1.5 Hz, 1H, C^{6}**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0 (2 x C^{11}), 142.0 (C), 141.1 (C), 136.5 (C), 131.5 (C^{19}H), 130.1 (q, *J* = 33.4 Hz, C^{16}/C^{18}), 129.7 (q, *J* = 31.2 Hz, C^{16}/C^{18}), 129.1 (q, *J* = 3.9 Hz, C^{20}H), 124.4 (C^{3}H), 123.7 (q, *J* = 274.1 Hz, $C^{21}F_3$/$C^{22}F_3$), 123.5 (q, *J* = 272.4 Hz, $C^{21}F_3$/$C^{22}F_3$), 123.5 – 123.2 (m, C^{17}H), 104.7 (2 x C^{10}H), 99.5 (C^{12}H), 65.5 ($C^{7}H_2$), 58.0 ($C^{14}H_2$), 55.7 ($C^{6}H_2$), 55.5 (2 x $C^{13}H_3$), 53.7 ($C^{2}H_2$), 39.1 (C^{5}H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.9.

IR (neat) (cm^{-1}): 3298, 2937, 1592, 1345, 1275, 1155, 1121, 1083, 1055, 842.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(3,5-bis(trifluoromethyl)phenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-57)



The title compound was prepared by General procedure E using salt **II-31** (323 mg, 0.50 mmol). Purification by FCC (0%-20% EtOAc in pentane) gave *amine* **II-57** (107 mg, 39%) as an orange oil.

HRMS (ESI): Exact mass calculated for $C_{23}H_{18}F_{12}NO$ $[M+H]^+$: 552.1191, found 552.1186.

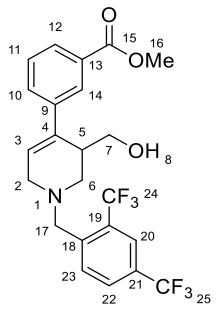
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H, C^{17}**H**), 7.89 – 7.83 (m, 2H, C^{19}**H** + C^{20}**H**), 7.79 (s, 3H, 2 x C^{10}**H** + C^{12}**H**), 6.21 (dd, *J* = 4.8, 2.2 Hz, 1H, C^{3}**H**), 3.89 (s, 2H, C^{14}**H$_2$**), 3.76 (dd, *J* = 10.6, 2. Hz, 1H, C^{7}**H$_2$**), 3.61 (ddd, *J* = 10.6, 4.3, 1.7 Hz, 1H, C^{7}**H$_2$**), 3.47 (dd, *J* = 17.4, 4.7 Hz, 1H, C^{2}**H$_2$**), 3.20 (dt, *J* = 11.2, 1.5 Hz, 1H, C^{6}**H$_2$**), 3.01 (dt, *J* = 17.4, 2.5 Hz, 1H, C^{2}**H$_2$**), 2.90 (s, 1H, C^{5}**H**), 2.80 (ddd, *J* = 11.3, 3.8, 1.6 Hz, 1H, C^{6}**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.9 (C^{9}), 140.7 (C^{15}), 134.5 (C^{4}), 132.1 (q, *J* = 33.1 Hz, 2 x C^{11}), 131.5 (C^{20}H), 130.3 (q, *J* = 33.5 Hz, C^{16}/C^{18}), 129.9 (q, *J* = 31.3 Hz, C^{16}/C^{18}), 129.1 (q, *J* = 3.7 Hz, C^{19}H), 127.8 (C^{3}H), 126.4 (2 x C^{10}H), 123.7 (q, *J* = 274.1 Hz, C^{21}F$_3$/C^{22}F$_3$), 123.7 – 123.2 (m, C^{17}H), 123.4 (q, *J* = 272.8 Hz, 2 x C^{13}F$_3$ + C^{21}F$_3$/C^{22}F$_3$), 121.6 – 121.2 (m, C^{12}H), 65.0 (C^{7}H$_2$), 57.9 (d, *J* = 2.0 Hz, C^{14}H$_2$), 55.5 (C^{6}H$_2$), 53.6 (C^{2}H$_2$), 38.9 (C^{5}H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.85, –62.87.

IR (neat) (cm^{-1}): 3659, 2980, 2972, 2889, 1382, 1275, 1164, 1125, 1083, 965, 954.

Methyl-3-(1-(2,4-bis(Trifluoromethyl)benzyl)-3-(hydroxymethyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoate (II-58)



The title compound was prepared by General procedure E using salt **II-32** (284 mg, 0.50 mmol). Purification by FCC (10-30% EtOAc in pentane) gave *amine* **II-58** (184 mg, 78%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{23}H_{22}F_6NO$ $[M+H]^+$: 474.1498, found:474.1503.

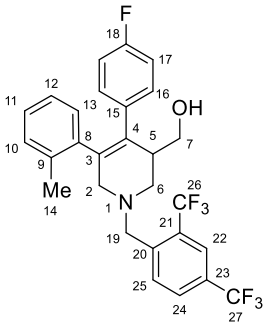
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (t, *J* = 1.8 Hz, 1H, C^{14}**H**), 7.95 (dt, *J* = 9.5, 1.5 Hz, 2H, C^{12}**H** + C^{20}**H**), 7.89 (d, *J* = 8.2 Hz, 1H, C^{23}**H**), 7.83 (dd, *J* = 8.3, 1.9 Hz, 1H, C^{22}**H**), 7.56 (ddd, *J* = 7.8, 1.9, 1.2 Hz, 1H, C^{10}**H**), 7.41 (t, *J* = 7.8 Hz, 1H, C^{11}**H**), 6.14 (dd, *J* = 4.7, 2.2 Hz, 1H, C^{3}**H**), 4.03 (s, 1H, O**H**), 3.92 (s, 3H, C^{16}**H$_3$**), 3.87 (s, 2H, C^{17}**H$_2$**), 3.75 (dd, *J* = 10.4, 2.6 Hz, 1H, C^{7}**H$_2$**), 3.63 (ddd, *J* = 10.4, 4.0, 1.6 Hz, 1H, C^{7}**H$_2$**), 3.44 (dd, *J* = 17.0, 4.7 Hz, 1H, C^{2}**H$_2$**), 3.17 (dt, *J* = 11.2, 1.5 Hz, 1H, C^{6}**H$_2$**), 2.98 (dt, *J* = 16.9, 2.4 Hz, 1H, C^{2}**H$_2$**), 2.93 (s, 1H, C^{5}**H**), 2.79 (ddd, *J* = 11.1, 3.8, 1.5 Hz, 1H, C^{6}**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.2 (C^{15}O), 141.0 (C), 140.0 (C), 135.7 (C), 131.5 (C^{23}H), 130.8 (C^{10}H), 130.6 (C), 130.1 (q, *J* = 33.5 Hz, C^{19}/C^{21}), 129.8 (q, *J* = 31.0 Hz, C^{19}/C^{21}), 129.1 (q, *J* = 3.7 Hz, C^{22}H), 128.82 (C^{11}H/C^{12}H), 128.76 (C^{11}H/C^{12}H), 127.3 (C^{14}H), 125.2 (C^{3}H), 123.7(d, *J* = 274.2 Hz, C^{24}F$_3$/C^{25}F$_3$), 123.5 (d, *J* = 272.3 Hz, C^{24}F$_3$/C^{25}F$_3$), 123.5 – 123.3 (m, C^{20}H), 65.3 (C^{7}H$_2$), 58.0 (d, *J* = 2.3 Hz, C^{17}H$_2$), 55.7 (C^{6}H$_2$), 53.7 (C^{2}H$_2$), 52.3 (C^{16}H$_3$), 38.9 (C^{5}H).

^{19}F NMR (376 MHz, $CDCl_3$) δ –59.2, –62.8.

IR (neat) (cm^{-1}): 3302, 2954, 1722, 1345, 1275, 1170, 1122, 1083, 1054, 757.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-fluorophenyl)-5-(o-tolyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-61)



The title compound was prepared by General procedure E using salt **II-33** (309 mg, 0.50 mmol). Purification by FCC (20% EtOAc in pentane) gave *amine* **II-61** (145 mg, 55%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{28}H_{24}F_7NO$ $[M+H]^+$: 524.1819, found: 524.1818.

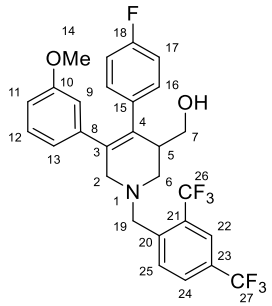
^{1}H NMR (500 MHz, DMSO) δ 8.19 (t, *J* = 8.5 Hz, 1H, C^{25}**H**), 8.11 (dd, *J* = 8.1, 2.2 Hz, 1H, C^{24}**H**), 8.00 (d, *J* = 2.0 Hz, 1H, C^{22}**H**), 7.23 – 6.57 (m, 9H, 9 x ArC**H**), 4.55 – 4.46 (m, 1H, O**H**), 3.04 – 3.80 (m, 2H, C^{19}**H**$_2$), 3.62 – 3.50 (m, 1H, C^7**H**$_2$), 3.38 (d, *J* = 16.8 Hz, 1H, C^2**H**$_2$), 3.29 – 3.08 (m, 2H, C^6**H**$_2$ + C^7**H**$_2$), 2.93 – 2.66 (m, 2H, C^2**H**$_2$ + C^5**H**), 2.62 (td, *J* = 11.2, 3.9 Hz, 1H, C^6**H**$_2$), 2.24 (s, 1H, C^{14}**H**$_3$), 1.89 (s, 2H, C^{14}**H**$_3$).

^{13}C NMR (126 MHz, DMSO) δ 160.6 (d, *J* = 243.3 Hz, C^{18}), 160.5 (d, *J* = 243.0 Hz, C^{18}), 142.9 (C^{20}), 139.5 (C), 139.2 (C), 136.9 (d, *J* = 3.1 Hz, C^{15}), 136.8 (d, *J* = 3.2 Hz, C^{15}), 134.4 (C), 134.0 (C), 133.2 (C), 132.7 (C), 131.8 (q, *J* = 2.8 Hz, C^{25}H), 130.4 (d, *J* = 7.9 Hz, 2 x C^{16}H), 2 x 129.9 (ArCH), 2 x 129.7 (ArCH), 129.6 – 129.3 (m, C^{24}H), 129.2 (C), 128.1 (q, *J* = 32.1 Hz, C^{21}/C^{23}), 128.0 (q, *J* = 33.2 Hz, C^{21}/C^{23}), 2 x 126.9 (ArCH), 125.6 (ArCH), 125.4 (ArCH), 123.6 (q, *J* = 274.3 Hz, C^{26}F$_3$/C^{27}F$_3$), 123.5 (q, *J* = 272.3 Hz, C^{26}F$_3$/C^{27}F$_3$), 122.8 – 122.6 (m, C^{22}H), 114.5 (d, *J* = 21.1 Hz, 2 x C^{17}H), 114.4 (d, *J* = 21.0 Hz, 2 x C^{17}H), 79.2 (C), 61.4 (C^{7}H$_2$), 61.3 (C^{7}H$_2$), 58.3 (C^{2}H$_2$), 57.4 (C^{2}H$_2$), 56.9 (C^{19}H$_2$), 56.8 (C^{19}H$_2$), 51.7 (C^{6}H$_2$), 51.4 (C^{6}H$_2$), 2 x 43.7 (C^{5}H), 19.8 (C^{14}H$_3$), 18.9 (C^{14}H$_3$). Due to presence of rotamers that could not be resolved using VT NMR, doubling of majority of the peaks is observed in the ^{13}C NMR.

^{19}F NMR (377 MHz, DMSO) δ -63.9, -67.6.

IR (neat) (cm^{-1}): 3403, 3063, 2849, 1345, 1275, 1171, 1124, 1054, 835, 757.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-fluorophenyl)-5-(3-methoxyphenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-62)



The title compound was prepared by General procedure E using salt **II-34** (317 mg, 0.50 mmol). Purification by FCC (10-30% EtOAc in pentane) gave *amine* **II-62** (117 mg, 44%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{28}H_{25}F_7NO_2$ $[M+H]^+$: 540.1768, found: 540.1766.

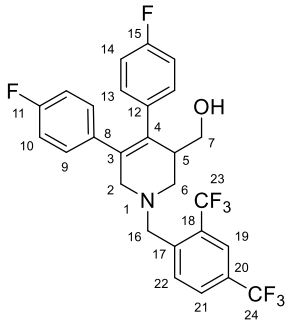
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (m, 2H, C^{22}**H** + C^{24}**H**), 7.87 (d, *J* = 8.6 Hz, 1H, C^{25}**H**), 7.09 – 6.97 (m, 3H, C^{12}**H** + 2 x C^{16}**H**), 6.91 – 6.79 (m, 2H, 2 x C^{17}**H**), 6.65 (ddd, *J* = 8.3, 2.6, 1.0 Hz, 1H, C^{11}**H**), 6.58 (ddd, *J* = 7.6, 1.6, 1.0 Hz, 1H, C^{13}**H**), 6.50 (dd, *J* = 2.6, 1.6 Hz, 1H, C^{9}**H**), 4.16 (s, 1H, O**H**), 3.97 – 3.84 (m, 2H, C^{19}**H$_2$**), 3.72 (d, *J* = 16.6 Hz, 1H, C^{2}**H$_2$**), 3.67 (dd, *J* = 10.4, 2.6 Hz, 1H, C^{7}**H$_2$**), 3.61 (s, 3H, C^{14}**H$_3$**), 3.57 (ddd, *J* = 10.4, 3.9, 1.6 Hz, 1H, C^{7}**H$_2$**), 3.18 (dt, *J* = 11.2, 1.5 Hz, 1H, C^{6}**H$_2$**), 3.00 (dd, *J* = 16.6, 2.4 Hz, 1H, C^{2}**H$_2$**), 2.91 – 2.83 (m, 1H, C^{6}**H$_2$**), 2.74 (brs, 1H, C^{5}**H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7 (d, *J* = 245.7 Hz, C^{18}), 159.3 (C^{10}), 141.0 (C^{8}), 140.9 (C^{20}), 136.3 (d, *J* = 3.3 Hz, C^{15}), 136.0 (C^{4}), 133.1 (C^{3}), 131.4 (C^{14}H), 131.0 (d, *J* = 7.8 Hz, 2 x C^{16}H), 130.2 (q, *J* = 33.5 Hz, C^{21}/C^{23}), 129.8 (q, *J* = 31.0 Hz, C^{21}/C^{23}), 129.1 (C^{11}H + C^{25}H), 123.7 (q, *J* = 274.2 Hz, $C^{26}F_3$/$C^{27}F_3$), 123.7 – 123.3 (m, C^{22}H), 123.5 (q, *J* = 272.3 Hz, $C^{26}F_3$/$C^{27}F_3$), 121.9 (C^{11}H), 115.3 (C^{9}H), 115.1 (d, *J* = 21.4 Hz, 2 x C^{17}H), 112.6 (C^{13}H), 65.2 ($C^{7}H_2$), 58.3 ($C^{2}H_2$), 58.0 (q, *J* = 2.2 Hz, $C^{19}H_2$), 55.7 ($C^{6}H_2$), 55.2 ($C^{14}H_3$), 42.6 (C^{5}H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.8, –114.7 - –116.1 (m).

IR (neat) (cm^{-1}): 3372, 2921, 1601, 1508, 1345, 1275, 1169, 1124, 1083, 1053.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4,5-bis(4-fluorophenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-63)



The title compound was prepared by General procedure E using salt **II-35** (155 mg, 0.25 mmol). Purification by FCC (10-20% EtOAc in pentane) gave *amine* **II-63** (49 mg, 37%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{27}H_{22}F_8NO$ $[M+H]^+$: 528.1568, found: 528.1564.

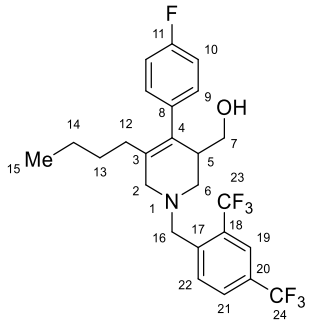
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H, C^{19}**H** + C^{22}**H**), 7.88 (d, *J* = 8.9 Hz, 1H, C^{21}**H**), 7.03 – 6.96 (m, 2H, 2 x C^9**H**/C^{13}**H**), 6.97 – 6.91 (m, 2H, 2 x C^9**H**/C^{13}**H**), 6.88 – 6.83 (m, 2H, 2 x C^{10}**H**/C^{14}**H**), 6.83 – 6.76 (m, 2H, 2 x C^{10}**H**/C^{14}**H**), 4.12 (d, *J* = 5.2 Hz, 1H, O**H**), 3.97 – 3.84 (m, 2H, C^{16}**H$_2$**), 3.69 (d, *J* = 14.5 Hz, 1H, C^2**H$_2$**), 3.67 – 3.63 (m, 1H, C^7**H$_2$**), 3.55 (ddd, *J* = 10.4, 3.9, 1.7 Hz, 1H, C^7**H$_2$**), 3.19 (dt, *J* = 11.2, 1.5 Hz, 1H, C^6**H$_2$**), 2.98 (dd, *J* = 16.6, 2.5 Hz, 1H, C^2**H$_2$**), 2.86 (ddd, *J* = 11.2, 4.0, 1.5 Hz, 1H, C^6**H$_2$**), 2.73 (s, 1H, C^5**H**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7 (d, *J* = 246.6 Hz, C^{11}/C^{15}), 161.7 (d, *J* = 246.1 Hz, C^{11}/C^{15}), 140.8 (C^{17}), 136.0 (d, *J* = 3.4 Hz, C^8/C^{12}), 135.5 (d, *J* = 3.4 Hz, C^8/C^{12}), 135.1 (C^4), 133.6 (C^3), 131.4 (C^{22}H), 131.1 (app, *J* = 7.5 Hz, , 2 x C^{10}H + 2 x C^{14}H), 130.2 (q, *J* = 33.5 Hz, C^{18}/C^{20}), 129.9 (q, *J* = 31.3 Hz, C^{18}/C^{20}), 129.1 (q, *J* = 3.7 Hz, C^{21}H), 123.7 (q, *J* = 274.2 Hz, $C^{23}F_3$/$C^{24}F_3$), 123.5 (m, C^{19}H), 123.5 (q, *J* = 272.3 Hz, $C^{23}F_3$/$C^{24}F_3$), 115.2 (d, *J* = 21.2 Hz, 2 x C^9H/C^{13}H), 115.1 (d, *J* = 21.3 Hz, 2 x C^9H/C^{13}H), 65.1 (C^7H_2), 58.4 (C^2H_2), 58.0 ($C^{16}H_2$), 55.7 (C^6H_2), 42.6 (C^5H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.8, –114.6 - –115.1 (m), –115.1 - –115.6 (m).

IR (neat) (cm^{-1}): 3375, 2923, 1508, 1346, 1275, 1159, 1124, 1054, 833, 674

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-5-butyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-64)



The title compound was prepared by General procedure E using salt **II-36** (58 mg, 0.10 mmol). Purification by FCC (10-20% EtOAc in pentane) gave *amine* **II-64** (23 mg, 47%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{25}H_{27}F_7NO$ $[M+H]^+$: 490.1975, found:490.1972.

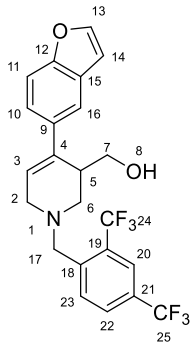
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H, C^{19}**H**), 7.90 (d, *J* = 8.3 Hz, 1H, C^{22}**H**), 7.88 – 7.81 (m, 1H, C^{21}**H**), 7.17 – 7.07 (m, 2H, 2 x C^9**H**), 7.11 – 6.98 (m, 2H, C^{10}**H**), 4.23 (s, 1H, OH), 3.91 – 3.78 (m, 2H, C^{16}**H$_2$**), 3.60 (dd, *J* = 10.3, 2.4 Hz, 1H, C^7**H$_2$**), 3.52 (ddd, *J* = 10.3, 3.6, 1.8 Hz, 1H, C^7**H$_2$**), 3.28 (d, *J* = 15.9 Hz, 1H, C^2**H$_2$**), 3.06 (dt, *J* = 11.0, 1.5 Hz, 1H, C^6**H$_2$**), 2.82 (dd, *J* = 15.8, 2.2 Hz, 1H, C^2**H$_2$**), 2.77 – 2.69 (m, 1H, C^6**H$_2$**), 2.39 (s, 1H, C^5**H**), 1.98 – 1.87 (m, 1H, C^{12}**H$_2$**), 1.82 (m, 1H, C^{12}**H$_2$**), 1.36 – 1.21 (m, 2H, C^{13}**H$_2$**), 1.25 – 1.02 (m, 2H, C^{14}**H$_2$**), 0.75 (t, *J* = 7.2 Hz, 3H, C^{15}**H$_3$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.9 (d, *J* = 245.2 Hz, C^{11}), 141.1 (C^{17}), 136.9 (d, *J* = 3.3 Hz, C^8), 134.7 (C^4), 131.4 (C^{22}H), 130.8 (C^3), 130.6 (d, *J* = 7.7 Hz, 2 x C^9H), 130.1 (q, *J* = 33.6 Hz, C^{18}/C^{20}), 129.7 (q, *J* = 31.1 Hz, C^{18}/C^{20}), 129.1 (q, *J* = 3.7 Hz, C^{21}H), 123.7 (q, *J* = 274.2 Hz, $C^{23}F_3$/$C^{24}F_3$), 123.5 (q, *J* = 272.3 Hz, $C^{23}F_3$/$C^{24}F_3$), 123.6 – 123.1 (m, C^{19}H), 115.3 (d, *J* = 21.2 Hz, 2 x C^{10}H), 65.1 (C^7H_2), 58.1 (q, *J* = 2.0 Hz, $C^{16}H_2$), 56.4 (C^6H_2), 56.3 (C^2H_2), 42.8 (C^5H), 31.9 ($C^{12}H_2$), 30.9 ($C^{13}H_2$), 22.6 ($C^{14}H_2$), 14.0 ($C^{15}H_3$).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.8, –114.9 - –118.9 (m).

IR (neat) (cm^{-1}): 3338, 2970, 1345, 1276, 1161, 1129, 1032, 951, 816, 674.

(4-(Benzofuran-5-yl)-*N*-(2,4-bis(trifluoromethyl)benzyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-65)



The title compound was prepared by General procedure E using salt **II-37** (258 mg, 0.47 mmol). Purification by FCC (20% EtOAc in pentane) gave *amine* **II-65** (49%) as an orange oil.

HRMS (ESI): Exact mass calculated for $C_{23}H_{20}F_6NO_2$ $[M+H]^+$: 456.1393, found: 456.1387.

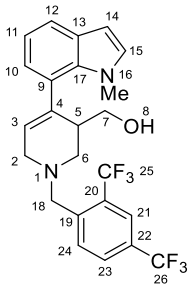
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H, C^{20}**H**), 7.91 (d, *J* = 8.1 Hz, 1H, C^{23}**H**), 7.84 (dd, *J* = 8.2, 1.9 Hz, 1H, C^{22}**H**), 7.62 (d, *J* = 2.2 Hz, 1H, C^{13}**H**), 7.58 (d, *J* = 1.8 Hz, 1H, C^{16}**H**), 7.46 (dt, *J* = 8.6, 0.8 Hz, 1H, C^{11}**H**), 7.31 (dd, *J* = 8.6, 1.9 Hz, 1H, C^{10}**H**), 6.74 (dd, *J* = 2.2, 1.0 Hz, 1H, C^{14}**H**), 6.05 (dd, *J* = 4.7, 2.2 Hz, 1H, C^{3}**H**), 4.14 (s, 1H, O**H**), 3.88 (s, 2H, C^{17}**H$_2$**), 3.75 (dd, *J* = 10.3, 2.7 Hz, 1H, C^{7}**H$_2$**), 3.66 (ddd, *J* = 10.3, 3.9, 1.6 Hz, 1H, C^{7}**H$_2$**), 3.44 (dd, *J* = 16.7, 4.7 Hz, 1H, C^{2}**H$_2$**), 3.18 (dt, *J* = 11.2, 1.6 Hz, 1H, C^{6}**H$_2$**), 2.99 (dt, *J* = 16.8, 2.4 Hz, 1H, C^{2}**H$_2$**), 2.93 (brs, 1H, C^{5}**H**), 2.82 (ddd, *J* = 11.1, 3.9, 1.6 Hz, 1H, C^{6}**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7 (C^{12}), 145.6 (C^{13}H), 141.2 (C^{18}), 136.7 (C), 135.0 (C), 131.5 (C^{23}H), 130.0 (d, *J* = 33.0 Hz, C^{19}/C^{21}), 129.4 (d, *J* = 31.2 Hz, C^{19}/C^{21}), 129.1 – 128.9 (m, C^{22}H), 127.8 (C^{15}), 123.9 (C^{3}H), 123.7 (d, *J* = 274.1 Hz, $C^{24}F_3$/$C^{25}F_3$), 123.5 (q, *J* = 272.4 Hz, $C^{24}F_3$/$C^{25}F_3$), 123.5 – 123.2 (m, C^{20}H), 123.0 (C^{10}H), 118.9 (C^{16}H), 111.4 (C^{11}H), 106.8 (C^{14}H), 65.4 ($C^{7}H_2$), 58.0 (d, *J* = 2.1 Hz, $C^{17}H_2$), 55.8 ($C^{6}H_2$), 53.8, ($C^{2}H_2$), 39.7 (C^{5}H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.8.

IR (neat) (cm^{-1}): 3325, 2923, 1630, 1345, 1274, 1170, 1122, 1083, 1055, 672.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(1-methyl-1H-indol-7-yl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-66)



The title compound was prepared by General procedure E using salt **II-38** (141 mg, 0.25 mmol). Purification by FCC (5%-30% EtOAc in pentane) gave the *amine* **II-66** (78 mg, 67%) as a pale yellow solid.

m.p. (EtOAc): 90-92°C

HRMS (ESI): Exact mass calculated for $C_{24}H_{23}F_6N_2O$ $[M+H]^+$: 469.1709, found: 469.1706.

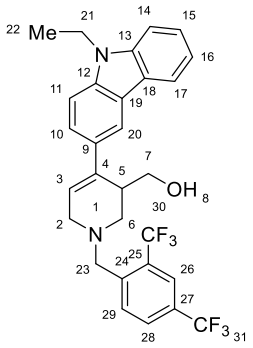
^{1}H NMR (500 MHz, DMSO) δ 8.15 (d, *J* = 8.2 Hz, 1H, C^{24}**H**), 8.06 (d, *J* = 8.3 Hz, 1H, C^{23}**H**), 7.97 (s, 1H, C^{21}**H**), 7.45 (dd, *J* = 7.9, 1.2 Hz, 1H, C^{12}**H**), 7.19 (d, *J* = 3.2 Hz, 1H, C^{15}**H**), 6.97 (t, *J* = 7.5 Hz, 1H, C^{11}**H**), 6.81 (d, *J* = 7.2 Hz, 1H, C^{10}**H**), 6.44 (d, *J* = 3.2 Hz, 1H, C^{14}**H**), 5.70 (t, *J* = 3.4 Hz, 1H, C^{3}**H**), 4.12 (t, *J* = 5.1 Hz, 1H, O**H**), 3.91 (s, 2H, C^{18}**H$_2$**), 3.82 (s, 3H, C^{16}**H$_3$**), 3.54 (td, *J* = 9.6, 5.6 Hz, 1H, C^{7}**H$_2$**), 3.41 – 3.28 (m, 2H, C^{7}**H$_2$** + C^{2}**H$_2$**), 3.08 (m, 1H, C^{2}**H**) 3.03 (dd, *J* = 11.1, 3.7 Hz, 1H, C^{6}**H$_2$**), 2.74 (dd, *J* = 11.2, 4.1 Hz, 1H, C^{6}**H$_2$**), 2.65 (s, 1H, C^{5}**H**). C^{2}**H** at 3.08 hidden underneath the water peak, proven by 2D NMR (COSY)

^{13}C NMR (126 MHz, DMSO) δ 142.5 (C^{19}), 135.2 (C), 133.2 (C), 131.7 (C^{24}H), 130.9 (C^{10}H), 129.4 (C), 128.8 (q, *J* = 4.6 Hz, C^{23}H), 128.0 (q, *J* = 30.7 Hz C^{20} + C^{22}), 126.1 (C^{3}H), 125.6 (C), 123.1 (q, *J* = 272.9 Hz, C^{25}F$_3$/C^{26}F$_3$), 122.2 (m, C^{15}H + C^{21}H), 119.0 (C^{12}H), 118.1 (C^{11}H), 100.4 (C^{14}H), 61.2 (C^{7}H$_2$), 57.0 (C^{18}H$_2$), 52.3 (C^{2}H$_2$), 51.7 (C^{6}H$_2$), 44.1 (C^{5}H), 35.4 (C^{16}H$_3$). 1 of C^{25}F$_3$/C^{26}F$_3$ not observed

^{19}F NMR (471 MHz, DMSO) δ –58.3, –61.4.

IR (neat) (cm^{-1}): 3056, 2882, 1630, 1345, 1301, 1275, 1171, 1122, 1083, 1053, 796.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(9-ethyl-9H-carbazol-3-yl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-67)



The title compound was prepared by General procedure E using salt **II-39** (313 mg, 0.50 mmol). Purification by FCC (10%-50% EtOAc in pentane) gave *amine* **II-67** (147 mg, 52%) as an orange solid

m.p. (EtOAc): 107-109°C

HRMS (ESI): Exact mass calculated for $C_{29}H_{27}F_6N_2O$ $[M+H]^+$: 533.2022, found:533.2015.

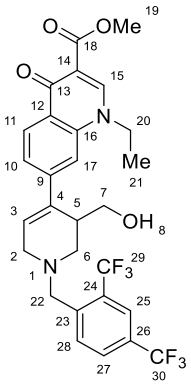
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 – 8.04 (m, 2H, C^{17}**H** + C^{20}**H**), 7.97 – 7.91 (m, 2H, C^{26}**H** + C^{29}**H**), 7.85 (dd, *J* = 8.2, 2.3 Hz, 1H, C^{28}**H**), 7.53 – 7.44 (m, 2H, C^{11}**H** + C^{14}**H**), 7.43 – 7.35 (m, 2H, C^{10}**H** + C^{15}**H**), 7.23 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H, C^{16}**H**), 6.11 (dd, *J* = 4.8, 1.9 Hz, 1H, C^{3}**H**), 4.37 (q, *J* = 7.2 Hz, 2H, C^{21}**H$_2$**), 3.90 (s, 2H, C^{23}**H$_2$**), 3.80 (dd, *J* = 10.3, 2.6 Hz, 1H, C^{7}**H$_2$**), 3.73 (ddd, *J* = 10.3, 3.9, 1.6 Hz, 1H, C^{7}**H$_2$**), 3.52 – 3.44 (m, 1H, C^{2}**H$_2$**), 3.25 – 3.19 (m, 1H, C^{6}**H$_2$**), 3.12 – 2.98 (m, 2H, C^{2}**H$_2$** + C^{5}**H**), 2.87 (ddd, *J* = 11.1, 3.8, 1.5 Hz, 1H, C^{6}**H$_2$**), 1.44 (t, *J* = 7.2 Hz, 3H, C^{22}**H$_3$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3 (C^{24}), 140.5 (C^{12}), 139.7 (C), 137.1 (C), 131.5 (C^{29}H), 130.8 (C), 130.0 (q, *J* = 33.5 Hz, C^{25}/C^{27}), 129.7 (q, *J* = 31.1 Hz, C^{25}/C^{27}), 129.1 (q, *J* = 3.8 Hz, C^{28}H), 125.9 (C^{11}H), 124.3 (C^{14}H), 123.7 (q, *J* = 274.2 Hz, $C^{30}F_3$/$C^{31}F_3$), 123.5 (q, *J* = 272.3 Hz, $C^{30}F_3$/$C^{31}F_3$), 123.5 – 123.2 (m, C^{26}H), 123.2 (C), 123.1 (C), 122.8 (C^{3}H), 120.6 (C^{17}H), 119.0 (C^{16}H), 118.1 (C^{20}H), 108.7 (C^{10}H/C^{15}H), 108.5 (C^{10}H/C^{15}H), 65.7 ($C^{7}H_2$), 58.1 (q, *J* = 2.4 Hz, $C^{23}H_2$), 56.0 ($C^{6}H_2$), 54.0 ($C^{2}H_2$), 39.5 (C^{5}H), 37.8 ($C^{21}H_2$), 14.0 ($C^{22}H_3$).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.8.

IR (neat) (cm^{-1}): 3353, 2971, 2885, 1634, 1379, 1160, 1130, 1108, 951, 817.

Methyl 7-(*N*-(2,4-bis(Trifluoromethyl)benzyl)-3-(hydroxymethyl)-1,2,3,6-tetrahydropyridin-4-yl)-1-ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylate (II-68)



The title compound was prepared by General procedure E using salt **II-40** (169 mg, 0.25 mmol). Purification by FCC (2% MeOH in CH_2Cl_2) gave *amine* **II-68** (33 mg, 23%) as a pale brown solid.

m.p. (CH_2Cl_2**):** 129-131 °C

HRMS (ESI): Exact mass calculated for $C_{28}H_{27}F_6N_2O_4$ $[M+H]^+$: 569.1870, found: 569.1870.

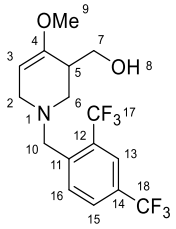
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H, C^{18}**H**), 8.48 (d, *J* = 8.3 Hz, 1H, C^{11}**H**), 7.94 (d, *J* = 1.8 Hz, 1H, C^{25}**H**), 7.90 (d, *J* = 8.5 Hz, 1H, C^{28}**H**), 7.84 (dd, *J* = 8.2, 1.9 Hz, 1H, C^{27}**H**), 7.42 (d, *J* = 9.3 Hz, 2H, C^{10}**H** + C^{17}**H**), 6.18 (dd, *J* = 4.9, 2.2 Hz, 1H, C^{3}**H**), 4.33 – 4.24 (m, 2H, C^{20}**H$_2$**), 3.93 (s, 3H, C^{19}**H$_3$**), 3.90 (s, 2H, 22**H$_2$**), 3.76 (dd, *J* = 10.5, 2.6 Hz, 1H, C^{7}**H$_2$**), 3.63 (ddd, *J* = 10.4, 4.4, 1.4 Hz, 1H, C^{7}**H$_2$**), 3.48 (dd, *J* = 17.4, 4.8 Hz, 1H, C^{2}**H$_2$**), 3.21 (d, *J* = 11.2 Hz, 1H, C^{6}**H$_2$**), 3.03 (d, *J* = 17.3 Hz, 1H, C^{2}**H$_2$**), 2.95 (s, 1H, C^{5}**H**), 2.86 – 2.80 (m, 1H, C^{6}**H$_2$**), 1.55 (t, *J* = 7.2 Hz, 3H, C^{21}**H$_3$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2 (C^{13}), 166.8 (C^{18}), 149.2 (C^{9}H), 144.7 (C^{15}), 140.8 (C^{23}), 139.1 (C^{16}), 136.1 (C^{4}), 131.6 (C^{28}H), 130.2 (q, *J* = 33.6 Hz, C^{24}/C^{26}), 129.8 (q, *J* = 31.1 Hz, C^{24}/C^{26}), 129.1 (q, *J* = 3.7 Hz, C^{27}H), 128.5 (C^{11}H), 127.0 (C^{3}H + C^{12}), 123.7 (q, *J* = 274.2 Hz, $C^{29}F_3$/$C^{30}F_3$), 123.6 – 123.4 (m, C^{25}H), 123.4 (q, *J* = 272.5 Hz, $C^{29}F_3$/$C^{30}F_3$), 123.3 (C^{10}H), 113.4 (C^{17}H), 111.0 (C^{14}), 65.1 ($C^{7}H_2$), 57.9 ($C^{22}H_2$), 55.4 ($C^{6}H_2$), 53.7 ($C^{2}H_2$), 52.3 ($C^{19}H_3$), 49.0 ($C^{20}H_2$), 39.3 (C^{5}H), 14.7 ($C^{21}H_3$).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.9.

IR (neat) (cm^{-1}): 3373, 2360, 1721, 1614, 1468, 1346, 1276, 1165, 1129, 756.

N-(2,4-bis(Trifluoromethyl)benzyl)-4-methoxy-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-69)



N-(2,4-bis(Trifluoromethyl)benzyl)-4-methoxypyridinium iodide **II-41** (116 mg, 0.25 mmol, 1.00 equiv.), paraformaldehyde (450 mg, 60.0 equiv.), and $[RhCp^*Cl_2]_2$ (3.1 mg, 2 mol%) was added to a microwave vial. MeOH (0.83 mL, 0.2 M) and $Mg(OMe)_2$ (0.42 mL, 1.5 equiv, 0.89M in MeOH) was added and the solution heated at 45 °C for 16 hours. The solution concentrated under reduce pressure and re-dissolved in CH_2Cl_2 (30 m L), brine (50 mL) and water (50 mL). The solution was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by FCC (5%-30% EtOAc in Pentane) to furnish the *amine* **II-69** (46 mg, 50%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{16}H_{18}F_6NO_2$ $[M+H]^+$: 370.1236, found: 340.1240.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H, C^{13}**H**), 7.88 (d, *J* = 8.1 Hz, 1H, C^{16}**H**), 7.80 (dd, *J* = 8.2, 2.4 Hz, 1H, C^{15}**H**), 4.72 (dd, *J* = 4.6, 2.4 Hz, 1H, C^3**H**), 3.92 (s, 1H, O**H**), 3.85 (ddd, *J* = 10.2, 3.8, 1.3 Hz, 1H, C^7**H$_2$**), 3.80 (s, 2H, C^{10}**H$_2$**), 3.75 (dd, *J* = 10.2, 3.6 Hz, 1H, C^7**H$_2$**), 3.56 (s, 3H, C^9**H$_3$**), 3.24 (ddt, *J* = 14.5, 4.6, 1.3 Hz, 1H, C^2**H$_2$**), 2.93 – 2.84 (m, 2H, C^2**H$_2$** + C^6**H$_2$**), 2.71 (ddd, *J* = 11.1, 4.4, 1.2 Hz, 1H, C^6**H$_2$**), 2.37 – 2.30 (brs, 1H, C^5**H**).

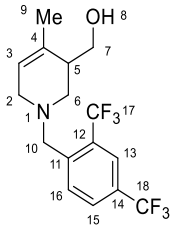
^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6 (C^4), 141.3 (C^{11}), 131.2 (C^{16}H), 129.8 (d, *J* = 33.5 Hz, C^{12}/C^{14}), 129.5 (d, *J* = 30.9 Hz, C^{12}/C^{14}), 128.8 (q, *J* = 4.5 Hz, C^{15}H), 123.6 (q, *J* = 274.2 Hz, $C^{17}F_3$/$C^{18}F_3$),

123.4 (q, J = 272.0 Hz, $C^{17}F_3/C^{18}F_3$), 123.3 – 122.9 (m, $C^{13}H$), 93.0 (C^3H), 65.0 (C^7H_2), 57.5 (d, J = 2.1 Hz, $C^{10}H_2$), 55.2 (C^6H_2), 54.5 (C^9H_3), 51.8 (C^2H_2), 40.1 (C^5H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.3, –62.9.

IR (neat) (cm^{-1}): 3338, 2970, 1379, 13689, 1307, 1160, 1128, 1109, 951, 817.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-methyl-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-70)



The title compound was prepared by General procedure E using salt **II-42** (224 mg, 0.50 mmol). Purification by FCC (10%-20% EtOAc in pentane) gave *amine* **II-70** (35 mg mg, 20%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{16}H_{18}F_6NO$ $[M+H]^+$: 354.1285, found: 354.1287.

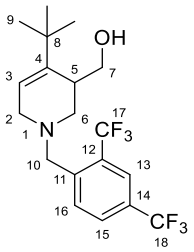
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H, C^{13}**H**), 7.84 (d, J = 8.4 Hz, 1H, C^{16}**H**), 7.80 (dd, J = 8.5, 1.8 Hz, 1H, C^{15}**H**), 5.70 – 5.45 (m, 1H, C^3**H**), 4.36 (s, 1H, O**H**), 3.86 (ddd, J = 10.3, 3.4, 1.8 Hz, 1H, C^7**H$_2$**), 3.80 – 3.74 (m, 3H, C^7**H$_2$** + C^{10}**H$_2$**), 3.26 – 3.12 (m, 1H, C^2**H$_2$**), 2.95 (dt, J = 11.2, 1.6 Hz, 1H, C^6**H$_2$**), 2.74 (dq, J = 15.9, 2.4 Hz, 1H, C^2**H$_2$**), 2.63 (ddd, J = 11.1, 4.0, 1.8 Hz, 1H, C^6**H$_2$**), 2.10 (s, 1H, C^5**H**), 1.78 (q, J = 1.9 Hz, 3H, C^9**H$_3$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1 (C^{11}), 132.3 (C^4), 131.5 ($C^{16}H$), 130.0 (q, J = 33.5 Hz, C^{12}/C^{14}), 129.7 (q, J = 31.0 Hz, C^{12}/C^{14}), 129.0 (q, J = 3.7 Hz, $C^{15}H$), 123.7 (q, J = 274.0 Hz, $C^{17}F_3/C^{18}F_3$), 123.5 (q, J = 272.4 Hz, $C^{17}F_3/C^{18}F_3$), 123.4 – 123.1 (m, $C^{13}H$), 121.7 (C^3H), 65.1 (C^7H_2), 58.1 (d, J = 2.3 Hz, $C^{10}H_2$), 56.1 (C^6H_2), 53.3 (C^2H_2), 41.5 (C^5H), 21.2 (C^9H_3).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.2, –62.9.

IR (neat) (cm^{-1}): 3304, 2920, 2160, 1629, 1345, 1301, 1275, 1167, 1117, 1083.

(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(tert-butyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-71)



The title compound was prepared by General procedure E using salt **II-43** (245 mg, 0.50 mmol). Purification by FCC (10%-20% EtOAc in pentane) gave *amine* **II-71** (53 mg mg, 27%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{19}H_{24}F_6NO$ $[M+H]^+$: 396.1743, found: 396.1757.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (s, 1H, C^{13}**H**), 7.85 (d, *J* = 8.2 Hz, 1H, C^{16}**H**), 7.81 (dd, *J* = 8.2, 1.8 Hz, 1H, C^{15}**H**), 5.66 (dd, *J* = 4.1, 2.4 Hz, 1H, C^{3}**H**), 4.78 (s, 1H, O**H**), 3.92 (ddd, *J* = 10.6, 3.8, 2.2 Hz, 1H, C^{7}**H$_2$**), 3.82 (dd, *J* = 10.6, 2.2 Hz, 1H, C^{7}**H$_2$**), 3.78 (s, 2H, C^{10}**H$_2$**), 3.36 (dd, *J* = 16.4, 4.1 Hz, 1H, C^{2}**H$_2$**), 2.98 (ddd, *J* = 10.8, 2.1, 1.0 Hz, 1H, C^{6}**H$_2$**), 2.78 (dt, *J* = 16.4, 2.2 Hz, 1H, C^{2}**H$_2$**), 2.53 (dt, *J* = 10.7, 2.7 Hz, 1H, C^{6}**H$_2$**), 2.41 (s, 1H, C^{5}**H**), 1.12 (s, 9H, 3 x C^{9}**H$_3$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.4 (C^4), 141.1 (C^{11}), 131.5 (C^{16}H), 130.0 (q, *J* = 32.3 Hz, C^{12}/C^{14}), 129.8 (q, *J* = 32.3 Hz, C^{12}/C^{14}), 129.0 (q, *J* = 3.7 Hz, C^{15}H), 123.7 (q, *J* = 274.2 Hz, $C^{17}F_3$/$C^{18}F_3$), 123.5 (q, *J* = 272.3 Hz, $C^{17}F_3$/$C^{18}F_3$), 123.3 (m, C^{13}H), 119.5 (C^3H), 67.3 (C^7H_2), 58.0 (q, *J* = 2.0 Hz, $C^{10}H_2$), 57.6 (C^6H_2), 53.9(C^2H_2), 37.4 (C^5H), 35.5 (C^8), 30.3 (3 x C^9H_3).

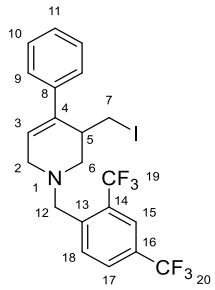
^{19}F NMR (377 MHz, $CDCl_3$) δ –59.1, –62.9.

IR (neat) (cm^{-1}): 3324, 2962, 1345, 1275, 1169, 1122, 1083, 1056, 1029, 672.

7.3.5 Derivatisation of dearomatised products

_N_-(2,4-bis(Trifluoromethyl)benzyl)-3-(iodomethyl)-4-phenyl-1,2,3,6-tetrahydropyridine

(II-82)



Amine **II-13** (83 mg, 0.20 mmol), PPh_3 (115 mg, 0.44 mmol) and imidazole (34 mg, 0.50 mmol) were dissolved in CH_2Cl_2 (4 mL). The solution was cooled to 0 °C, I_2 (112 mg, 0.44 mmol) was added and the reaction was allowed to warm to rt. After 2 h the reaction was quenched with an *aq. sat.* solution of $Na_2S_2O_3$ (5 mL). The solution was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by FCC (0%-2% Et_2O in pentane) to give *iodide* **II-82** (69 mg, 66%) as a yellow oil.

HRMS (ESI): Exact mass calculated for $C_{21}H_{19}F_6NO^{127}I$ [M+H]+: 526.0461, found: 526.0454.

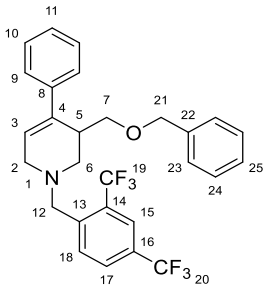
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.2 Hz, 1H, C^{18}**H**), 7.92 (s, 1H, C^{15}**H**), 7.84 (d, *J* = 8.2 Hz, 1H, C^{17}**H**), 7.40 – 7.27 (m, 5H, 5 x ArC**H**), 6.02 (dd, *J* = 4.2, 2.6 Hz, 1H, C^3**H**), 3.94 – 3.81 (m, 2H, C^{12}**H$_2$**), 3.45 (dd, *J* = 11.0, 9.7 Hz, 1H, C^7**H$_2$**), 3.30 (dd, *J* = 17.4, 4.4 Hz, 1H, C^2**H$_2$**), 3.24 – 3.13 (m, 2H, C^6**H$_2$** + C^7**H$_2$**), 3.04 (d, *J* = 11.2 Hz, 1H, C^5**H**), 2.98 (dt, *J* = 17.3, 2.5 Hz, 1H, C^2**H$_2$**), 2.62 (ddd, *J* = 11.5, 3.7, 1.6 Hz, 1H, C^6**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.2 (C^{13}), 139.1 (C), 137.6 (C), 131.6 (C^{18}H), 129.7 (q, *J* = 33.9 Hz, C^{14}/C^{16}), 129.5 (q, *J* = 31.8 Hz, C^{14}/C^{16}), 129.0 (C^{17}H), 128.9 (2 x ArCH), 127.8 (ArCH), 125.8 (2 x ArCH), 124.4 (C^3H), 123.8 (q, *J* = 274.1 Hz, $C^{19}F_3$/$C^{20}F_3$), 123.6 (q, *J* = 272.3 Hz, $C^{19}F_3$/$C^{20}F_3$), 123.2 (C^{15}H), 57.5 ($C^{12}H_2$), 54.5 (C^2H_2), 53.7 (C^6H_2), 41.3 (C^5H), 9.5 (C^7H_2).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.5, –62.8.

IR (neat) (cm^{-1}): 2808, 2161, 1348, 1292, 1279, 1167, 1122, 1084, 1057, 757.

3-((Benzyloxy)methyl)-*N*-(2,4-bis(trifluoromethyl)benzyl)-4-phenyl-1,2,3,6-tetrahydropyridine (S19)



Amine **II-13** (83 mg, 0.20 mmol), 15-crown-5 (80 µL, 0.40 mmol) and benzyl bromide (0.24 mL, 2.00 mmol) were dissolved in THF (1 mL). The solution was cooled to 0 °C and NaH (64 mg, 2.0 mmol) was added portion wise. The reaction mixture was allowed to warm to rt and stir for 2 hours. The reaction was quenched with water (5 mL), the aq layer extracted with CH_2Cl_2 (2 x 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by FCC (0%-4% Et_2O in pentane) to give *amine* **S19** (72 mg, 73%) as a white solid.

m.p. (EtOAc): 78-80 °C

HRMS (ESI): Exact mass calculated for $C_{28}H_{26}F_6NO$ $[M+H]^+$: 506.1911, found: 506.1913.

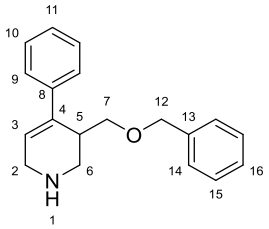
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.2 Hz, 1H, C^{18}**H**), 7.89 (s, 1H, C^{15}**H**), 7.69 (dd, *J* = 7.8, 1.5 Hz, 1H, C^{17}**H**), 7.41 – 7.12 (m, 10H, 10 x ArC**H**), 6.01 (ddd, *J* = 4.5, 2.5, 0.8 Hz, 1H, C^3**H**), 4.45 (d, *J* = 11.8 Hz, 1H, C^{21}**H$_2$**), 4.32 (d, *J* = 11.8 Hz, 1H, C^{21}**H$_2$**), 3.90 – 3.75 (m, 2H, C^{12}**H$_2$**), 3.71 (dd, *J* = 10.0, 9.1 Hz, 1H, C^7**H$_2$**), 3.45 – 3.28 (m, 2H, C^2**H$_2$** + C^7**H$_2$**), 3.18 (ddd, *J* = 11.1, 2.4, 1.2 Hz, 1H, C^6**H$_2$**), 3.09 (dt, *J* = 9.8, 3.1 Hz, 1H, C^5**H**), 3.01 (dt, *J* = 17.1, 2.5 Hz, 1H, C^2**H$_2$**), 2.54 (dd, *J* = 11.2, 3.6 Hz, 1H, C^6**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.7 (C^{13}), 140.0 (C^{22}), 138.4 (C^5), 136.2 (C^4), 131.2 (C^{18}H), 129.5 (q, *J* = 33.3 Hz, C^{14}/C^{16}), 129.3 (q, *J* = 31.3 Hz, C^{14}/C^{16}), 128.7 (C^{17}H+ ArCH), 128.5 (2 x ArCH), 127.7 (4 x ArCH), 127.4 (ArCH), 125.8 (2 x ArCH), 124.6 (C^{3}H), 123.8 (q, *J* = 274.2 Hz, C^{19}F$_3$/C^{20}F$_3$), 123.7 (q, *J* = 272.2 Hz, C^{19}F$_3$/C^{20}F$_3$), 123.1 – 122.9 (m, C^{15}H), 73.1 (C^{21}H$_2$), 70.8 (C^{7}H$_2$), 57.6 (C^{12}H$_2$), 53.8 (C^{2}H$_2$), 52.0 (C^{6}H$_2$), 38.8 (C^{5}H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.8, –62.7.

IR (neat) (cm^{-1}): 2857, 1348, 1280, 1166, 1118, 1085, 1056, 755, 695, 674.

3-((Benzyloxy)methyl)-4-phenyl-1,2,3,6-tetrahydropyridine (II-83)



Amine **S11** (25 mg, 0.05 mmol) added to a microwave vial, dissolved in DCE (0.13 mL), 1-chloroethyl chloroformate (31 µL, 0.40 mmol) was added and the reaction was sealed and heated to 120 °C for 16 h. The reaction was allowed to cool to rt, the solvent was switched to MeOH (1 mL) and heated to reflux for 4 hours. Purification by FCC (0%-10% MeOH in CH_2Cl_2) gave *amine* **II-83** (11 mg, 77%) as a yellow oil

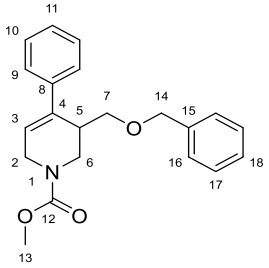
HRMS (ESI): Exact mass calculated for $C_{19}H_{22}NO$ $[M+H]^+$: 280.1696, found: 280.1696.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.16 (m, 10H, 10 x ArC**H**), 5.96 (d, *J* = 3.4 Hz, 1H, C^3**H**), 4.46 (s, 2H, C^{12}**H$_2$**), 3.85 – 3.71 (m, 2H, C^6**H$_2$**), 3.68 (dd, *J* = 12.5, 2.8 Hz, 1H, C^2**H$_2$**), 3.60 (dd, *J* = 9.6, 7.0 Hz, 1H, C^7**H$_2$**), 3.49 (dd, *J* = 9.6, 3.4 Hz, 1H, C^7**H$_2$**), 3.27 (dd, *J* = 12.7, 4.8 Hz, 1H, C^2**H$_2$**), 3.14 (s, 1H, C^5**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0 (C), 137.9 (C), 137.5 (C), 128.8 (2 x ArCH), 128.5 (2 x ArCH), 128.1 (ArCH), 127.9 (ArCH), 127.8 (2 x ArCH), 126.2 (2 x ArCH), 121.1 (C^{3}H), 73.3 (C^{12}H$_2$), 69.9 (C^{7}H$_2$), 44.4 (C^{2}H$_2$), 43.1 (C^{6}H$_2$), 35.2 (C^{5}H).

IR (neat) (cm^{-1}): 3415, 2922, 2853, 1659, 1639, 1593, 1454, 1092, 1073, 1027.

3-((Benzyloxy)methyl)-*N*-(2,4-bis(trifluoromethyl)benzyl)-4-phenyl-1,2,3,6-tetrahydropyridine (II-84)



Amine **S19** (25 mg, 0.05 mmol) added to a microwave vial, dissolved in DCE (0.13 mL), methyl chloroformate (31 µL, 0.40 mmol) was added and the reaction was sealed and heated to 120 °C for 16 h. Afterwards the reaction was allowed to cool to rt, diluted with CH_2Cl_2 (5 mL) and quenched with water (5 mL) The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was purified by FCC (5%-30% EtOAc in pentane) to give *carbamate* **II-84** (16 mg, 90%) as a pale yellow oil.

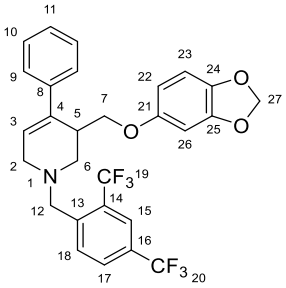
HRMS (ESI): Exact mass calculated for $C_{21}H_{23}NO_3{}^{23}Na$ $[M+Na]^+$: 360.1568, found: 360.1570.

^{1}H NMR (500 MHz, DMSO) δ 7.45 – 7.20 (m, 10H, 10 x ArC**H**), 6.07 (t, *J* = 3.4 Hz, 1H, C^3**H**), 4.44 (d, *J* = 12.2 Hz, 1H, C^{14}**H$_2$**), 4.38 (d, *J* = 12.1 Hz, 1H, C^{14}**H$_2$**), 4.29 – 4.19 (m, 2H, C^2**H$_2$** + C^7**H$_2$**), 3.85 (dt, *J* = 19.1, 2.7 Hz, 1H, C^2**H$_2$**), 3.66 (s, 3H, C^{13}**H$_3$**), 3.31 (ddd, *J* = 9.7, 4.0, 1.0 Hz, 1H, C^6**H$_2$**), 3.27 (t, *J* = 9.2 Hz, 1H, C^6**H$_2$**), 3.20 (ddd, *J* = 13.0, 3.7, 0.9 Hz, 1H, C^7**H$_2$**), 3.10 (brs, 1H, C^5**H**).

^{13}C NMR (126 MHz, DMSO) δ 155.3 (C^{12}), 139.0 (C), 138.1 (C), 135.5 (C), 127.9 (2 x ArCH), 127.6 (2 x ArCH), 126.8 (2 x ArCH), 126.7 (2 x ArCH), 125.0 (2 x ArCH), 122.5 (C^{3}H), 71.8 (C^{14}H$_2$), 69.1 (C^{7}H$_2$), 51.7 (C^{13}H$_3$), 43.2 (C^{2}H$_2$), 41.8 (C^{6}H$_2$), 36.9 (C^{5}H).

IR (neat) (cm^{-1}): 3414, 2920, 2852, 1754, 1696, 1445, 1265, 1209, 1095, 769.

3-((Benzo[d][1,3]dioxol-5-yloxy)methyl)-*N*-(2,4-bis(trifluoromethyl)benzyl)-4-phenyl-1,2,3,6-tetrahydropyridine (S20)



Amine **II-13** (62 mg, 0.15 mmol), PPh_3 (47 mg, 0.18 mmol) and sesamol (41 mg, 0.30 mmol) were dissolved in THF (1.5 mL). The solution was cooled to 0°C and DIAD (35 µL, 0.21 mmol) was added dropwise. The reaction was then heated to 50 °C and stirred for 16 h. The reaction was evaporated, the crude redissolved in CH_2Cl_2 (20 mL), washed with NaOH (2 x 20 mL, 1.0 M) and

dried ($MgSO_4$). The crude material was purified by FCC (0%-5% EtOAc in pentane) to give *amine* **S20** (54 mg, 66%) as a white solid.

m.p. (EtOAc): 110-112 °C

HRMS (ESI): Exact mass calculated for $C_{28}H_{24}F_6NO_3$ $[M+H]^+$: 536.1655, found: 536.1655.

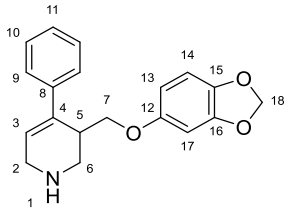
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.82 (m, 2H, C^{15}**H** + C^{18}**H**), 7.44 – 7.39 (m, 2H, C^{11}**H** + C^{17}**H**), 7.38 – 7.32 (m, 2H, 2 x C^9**H**/C^{10}**H**), 7.32 – 7.27 (m, 2H, 2 x C^9**H**/C^{10}**H**), 6.65 (d, *J* = 8.5 Hz, 1H, C^{23}**H**), 6.27 (d, *J* = 2.5 Hz, 1H, C^{26}**H**), 6.14 (dd, *J* = 8.5, 2.5 Hz, 1H, C^{22}**H**), 6.11 (dd, *J* = 4.6, 2.3 Hz, 1H, C^3**H**), 5.90 (dd, *J* = 9.8, 1.4 Hz, 2H, C^{27}**H$_2$**), 4.09 (dd, *J* = 10.3, 8.8 Hz, 1H, C^7**H$_2$**), 3.87 (d, *J* = 14.5 Hz, 1H, C^{12}**H$_2$**), 3.80 (d, *J* = 15.5 Hz, 1H, C^{12}**H$_2$**), 3.77 – 3.73 (m, 1H, C^7**H$_2$**), 3.46 (dd, *J* = 17.2, 4.6 Hz, 1H, C^2**H$_2$**), 3.20 (s, 1H, C^5**H**), 3.16 (dd, *J* = 11.1, 1.4 Hz, 1H, C^6**H$_2$**), 3.12 (dt, *J* = 17.1, 2.4 Hz, 1H, C^2**H$_2$**), 2.53 – 2.40 (m, 1H, C^6**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4 (C^{21}), 148.4 (C^{25}), 142.4 (C^{13}), 141.7 (C^{24}), 139.7 (C^8), 135.7 (C^4), 131.0 (C^{18}H), 129.3 (q, *J* = 33.3 Hz, C^{14}/C^{16}), 129.2 (q, *J* = 31.3 Hz, C^{14}/C^{16}), 128.8 (ArCH), 128.7 – 128.5 (m, C^{17}H), 127.7 (ArCH), 125.7 (ArCH), 125.2 (C^{3}H), 123.8 (q, *J* = 274.1 Hz, C^{19}F$_3$/C^{20}F$_3$), 123.6 (q, *J* = 272.2 Hz, C^{19}F$_3$/C^{20}F$_3$), 123.1 – 122.8 (m, C^{15}H), 107.9 (C^{23}H), 105.3 (C^{22}H), 101.3 (C^{27}H$_2$), 97.9 (C^{26}H), 68.3 (C^{7}H$_2$), 57.1 (q, *J* = 2.1 Hz, C^{12}H$_2$), 54.2 (C^{2}H$_2$), 50.8 (C^{6}H$_2$), 38.3 (C^{5}H).

^{19}F NMR (377 MHz, $CDCl_3$) δ –59.8, –62.8.

IR (neat) (cm^{-1}): 2898, 1629, 1490, 1343, 1271, 1173, 1159, 1119, 1101, 1095.

3-((Benzo[d][1,3]dioxol-5-yloxy)methyl)-4-phenyl-1,2,3,6-tetrahydropyridine (II-85)



Amine **S20** (54 mg, 0.10 mmol) added to a microwave vial, dissolved in DCE (0.25 mL), 1-chloroethyl chloroformate (86 µL, 0.80 mmol) was added and the reaction was sealed and heated to 120 °C for 16 h. The reaction was allowed to cool to rt, the solvent was switched to MeOH (1 mL) and heated

to reflux for 4 hours. Purification by FCC (1%-10% MeOH in CH_2Cl_2) gave *amine* **II-85** (20 mg, 65%) as a yellow oil

HRMS (ESI): Exact mass calculated for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1438, found: 310.1437.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H, 5 x ArC**H**), 6.63 (d, *J* = 8.5 Hz, 1H, C^{14}**H**), 6.42 (d, *J* = 2.4 Hz, 1H, C^{17}**H**), 6.23 (dd, *J* = 8.5, 2.5 Hz, 1H, C^{13}**H**), 6.14 – 6.08 (m, 1H, C^{3}**H**), 5.87 (s, 2H, C^{18}**H$_2$**), 3.94 (t, *J* = 9.1 Hz, 1H, C^{7}**H$_2$**), 3.82 – 3.72 (m, 1H, C^{7}**H$_2$**), 3.63 – 3.49 (m, 2H, C^{2}**H$_2$**), 3.47 – 3.39 (m, 1H, C^{6}**H$_2$**), 3.15 – 3.05 (m, 2H, C^{5}**H** + C^{6}**H$_2$**), 2.92 (s, 1H, N**H**).

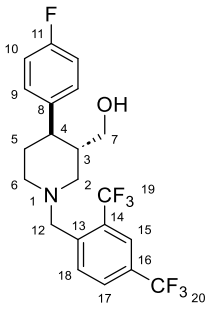
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4 (C^{12}), 148.3 (C^{16}), 141.8 (C^{15}), 140.5 (C^{8}), 136.2 (C^{4}), 128.7 (2 x ArCH), 127.5 (ArCH), 127.0 (C^{3}H), 126.0 (2 x ArCH), 108.0 (C^{14}H), 106.0 (C^{13}H), 101.2 (C^{18}H$_2$), 98.3 (C^{17}H), 69.0 (C^{7}H$_2$), 45.7 (C^{2}H$_2$), 45.2 (C^{6}H$_2$), 36.4 (C^{5}H).

IR (neat) (cm^{-1}): 2919, 2160, 2027, 1977, 1630, 1486, 1179, 1035, 757, 698.

7.3.6 Synthesis of (±)-paroxetine

(*trans*-*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-fluorophenyl)piperidin-3-yl)methanol

(II-86)



A microwave vial was charged with *amine* **II-51** (43 mg, 0.10 mmol) and Crabtree's catalyst (16 mg, 20 mol%) evacuated and back filled with argon. Degassed CH_2Cl_2 (2 mL) were added and the reaction mixture was purged with hydrogen for 5 minutes. The reaction was left to stir for 20 h at room temperature under an atmosphere of hydrogen. The d.r. of the crude was 3:1 *trans*:*cis*, however, purification by FCC (0%-10% EtOAc in pentane) gave a single diastereoisomer of *amine* **II-86** (28 mg, 65%) as a yellow oil

HRMS (ESI): Exact mass calculated for $C_{21}H_{21}F_7NO$ $[M+H]^+$: 436.1506, found: 436.1503.

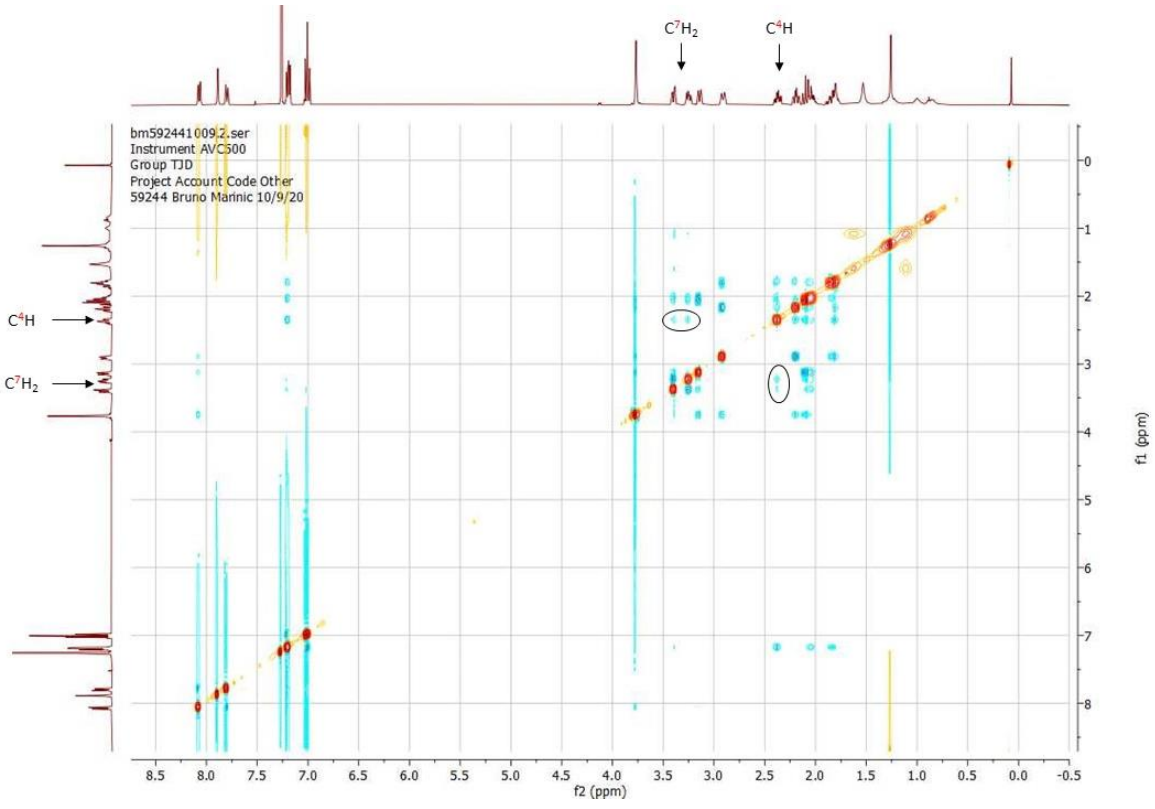
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 1H, C^{18}**H**), 7.89 (s, 1H, C^{15}**H**), 7.80 (d, *J* = 8.2 Hz, 1H, C^{17}**H**), 7.23 – 7.15 (m, 2H, 2 x C^9**H**), 7.06 – 6.95 (m, 2H, 2 x C^{10}**H**), 3.77 (s, 2H, C^{12}**H$_2$**), 3.40 (dd, *J* = 10.8, 3.1 Hz, 1H, C^7**H$_2$**), 3.25 (dd, *J* = 10.8, 6.6 Hz, 1H, C^7**H$_2$**), 3.18 – 3.10 (m, 1H, C^2**H$_2$**), 2.91 (d, *J* = 11.3 Hz, 1H, C^6**H$_2$**), 2.37 (td, *J* = 11.0, 4.9 Hz, 1H, C^4**H**), 2.19 (td, *J* = 11.2, 3.5 Hz, 1H, C^6**H$_2$**), 2.14 – 1.97 (m, 2H, C^2**H$_2$** + C^3**H**), 1.92 – 1.74 (m, 2H, C^5**H$_2$**).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7 (d, *J* = 244.3 Hz, C^{11}), 142.9 (C^{13}), 140.0 (d, *J* = 3.3 Hz, C^8), 130.9 (C^{16}H), 129.4 (q, *J* = 33.2 Hz, C^{14}/C^{16}), 129.3 (q, *J* = 31.3 Hz, C^{14}/C^{16}), 128.9 (d, *J* = 7.7 Hz, 2 x C^9H), 128.7 (q, *J* = 3.8 Hz, C^{17}H), 123.8 (d, *J* = 274.2 Hz, $C^{19}F_3$/$C^{20}F_3$), 123.7 (d, *J* = 272.1 Hz, $C^{19}F_3$/$C^{20}F_3$), 123.3 – 122.9 (m, C^{15}H), 115.6 (d, *J* = 21.2 Hz, 2 x C^{10}H), 64.0 (C^7H_2), 58.4 (q, *J* = 2.5 Hz, $C^{12}H_2$), 57.7 (C^6H_2), 54.4 (C^2H_2), 44.5 (C^3H), 44.3 (C^4H), 34.7 (C^5H).

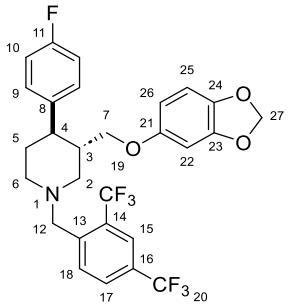
^{19}F NMR (376 MHz, $CDCl_3$) δ –60.0, –62.7, –115.6 to –118.8 (m).

IR (neat) (cm^{-1}): 3257, 2922, 1510, 1345, 1275, 1168, 1122, 1083, 1053, 831.

Relative stereochemistry determined using NOESY experiment:



***trans*-3-((Benzo[d][1,3]dioxol-5-yloxy)methyl)-*N*-(2,4-bis(trifluoromethyl)benzyl)-4-(4-fluorophenyl)piperidine (II-89)**



Amine **II-86** (45 mg, 0.10 mmol), PPh_3 (32 mg, 0.12 mmol) and sesamol (28 mg, 0.20 mmol) were dissolved in THF (1 mL). The solution was cooled to 0°C and DIAD (47 µL, 0.12 mmol) was added dropwise. The reaction was then heated to 50 °C and stirred for 16 h. The reaction was evaporated, the crude redissolved in CH_2Cl_2 (20 mL), washed with NaOH (2 x 20 mL, 1.0 M) and dried ($MgSO_4$). The crude material was purified by FCC (0%-20% Et_2O in pentane) to give *amine* **II-89** (46mg, 84%) as a white solid.

m.p. (EtOAc): 100-102 °C

HRMS (ESI): Exact mass calculated for $C_{28}H_{25}F_7NO_3$ $[M+H]^+$: 556.1717, found: 556.1713.

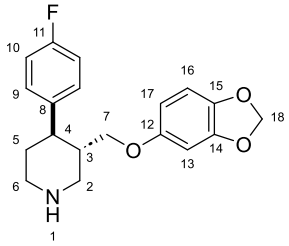
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.2 Hz, 1H, C^{18}**H**), 7.89 (s, 1H, C^{15}**H**), 7.81 (dd, *J* = 8.2, 1.9 Hz, 1H, C^{17}**H**), 7.24 – 7.14 (m, 2H, 2 x C^{9}**H**), 7.04 – 6.94 (m, 2H, 2 x C^{10}**H**), 6.61(d, *J* = 8.4 Hz, 1H, C^{25}**H**), 6.31 (d, *J* = 2.5 Hz, 1H, C^{22}**H**), 6.10 (dd, *J* = 8.5, 2.5 Hz, 1H, C^{26}**H**), 5.87 (s, 2H, C^{27}**H**), 3.85 – 3.72 (m, 2H, C^{12}**H**), 3.57 (dd, *J* = 9.5, 2.4 Hz, 1H, C^{7}**H**$_2$), 3.50 – 3.41 (m, 1H, C^{7}**H**$_2$), 3.26 – 3.15 (m, 1H, C^{2}**H**$_2$), 2.92 (ddt, *J* = 11.3, 4.0, 2.4 Hz, 1H, C^{6}**H**$_2$), 2.51 (td, *J* = 11.1, 4.9 Hz, 1H, C^{4}**H**), 2.32 – 2.16 (m, 3H, C^{2}**H**$_2$ + C^{5}**H** + C^{6}**H**$_2$), 1.95 – 1.76 (m, 2H, C^{5}**H**$_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7 (d, *J* = 244.3 Hz, C^{11}), 154.4 (C^{21}), 148.3 (C^{23}), 142.9 (C^{13}), 141.8 (C^{24}), 139.7 (d, *J* = 3.2 Hz, C^{8}), 130.9 (C^{18}H), 129.4 (q, *J* = 33.3 Hz, C^{14}/C^{16}), 129.3 (q, *J* = 31.3 Hz, C^{14}/C^{16}), 129.0 (d, *J* = 7.7 Hz, 2 x C^{9}H), 128.7 (q, *J* = 3.8 Hz, C^{17}H), 123.8 (q, *J* = 274.2 Hz, $C^{19}F_3$/$C^{20}F_3$), 123.7 (q, *J* = 272.2 Hz, $C^{19}F_3$/$C^{20}F_3$), 123.4 – 123.0 (m, C^{15}H), 115.6 (d, *J* = 21.2 Hz, 2 x C^{10}H), 108.0 (C^{25}H), 105.7 (C^{26}H), 101.2 ($C^{27}H_2$), 98.1 (C^{22}H), 69.7 ($C^{7}H_2$), 58.3 (q, *J* = 2.2 Hz, $C^{12}H_2$), 58.0 ($C^{2}H_2$), 54.3 ($C^{6}H_2$), 44.1 (C^{4}H), 42.4 (C^{3}H), 34.6 ($C^{5}H_2$).

^{19}F NMR (377 MHz, $CDCl_3$) δ –60.0, –62.7, –115.6 to –117.2 (m).

IR (neat) (cm^{-1}): 2918, 2160, 2026, 1503, 1348, 1280, 1198, 1164, 1120, 833.

(±)-*Paroxetine* (II-9)



Amine **II-89** (54 mg, 0.04 mmol) added to a microwave vial, dissolved in DCE (0.13 mL), 1-chloroethyl chloroformate (37 µL, 0.35 mmol) was added and the reaction was sealed and heated to 120 °C for 16 h. The reaction was allowed to cool to rt, the solvent was switched to MeOH (1 mL) and heated to reflux for 4 hours. Purification by FCC (1%-10% 7N NH_3 MeOH in CH_2Cl_2) gave *Paroxetine* **II-9** (8 mg, 55%) as a colourless oil. The spectroscopic data was consistent with previous reports.[121]

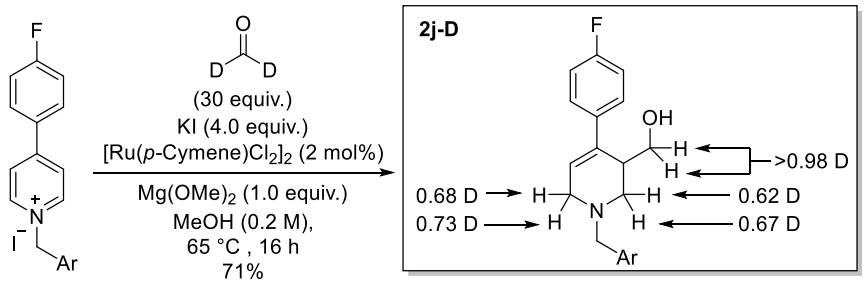
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.12 (m, 2H, 2 x C^{9}**H**), 7.03 – 6.92 (m, 2H, 2 x C^{10}**H**), 6.62 (d, *J* = 8.4 Hz, 1H, C^{16}**H**), 6.33 (d, *J* = 2.5 Hz, 1H, C^{13}**H**), 6.12 (dd, *J* = 8.5, 2.5 Hz, 1H, C^{17}**H**), 5.87 (s, 2H, C^{18}**H$_2$**), 3.57 (dd, *J* = 9.4, 3.0 Hz, 1H, C^{7}**H$_2$**), 3.48 – 3.39 (m, 2H, C^{2}**H$_2$** + C^{7}**H$_2$**), 3.20 (dt, *J* = 11.6, 3.0 Hz, 1H, C^{6}**H$_2$**), 2.80 – 2.73 (m, 1H, C^{6}**H$_2$**), 2.69 (dd, *J* = 12.2, 10.9 Hz, 1H, C^{2}**H$_2$**), 2.59 (td, *J* = 11.7, 4.2 Hz, 1H, C^{4}**H**), 2.08 (tdt, *J* = 10.9, 6.9, 3.4 Hz, 1H C^{3}**H**), 1.87 – 1.77 (m, 1H, C^{5}**H$_2$**), 1.76 – 1.60 (m, 1H, C^{5}**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.67 (d, *J* = 245.0 Hz, C^{11}), 154.6 (C^{12}), 148.3 (C^{14}), 141.7 (C^{15}), 140.1 (d, *J* = 2.9 Hz, C^{8}), 128.9 (d, *J* = 7.7 Hz, 2 x C^{9}H), 115. 6(d, *J* = 21.0 Hz, C^{10}H), 108.0 (C^{16}H), 105.8 (C^{17}H), 101.2 (C^{18}H$_2$), 98.1 (C^{13}H), 69.7 (C^{7}H$_2$), 50.5 (C^{2}H$_2$), 47.2 (C^{6}H$_2$), 44.7 (C^{4}H), 43.1 (C^{3}H), 35.5 (C^{5}H$_2$).

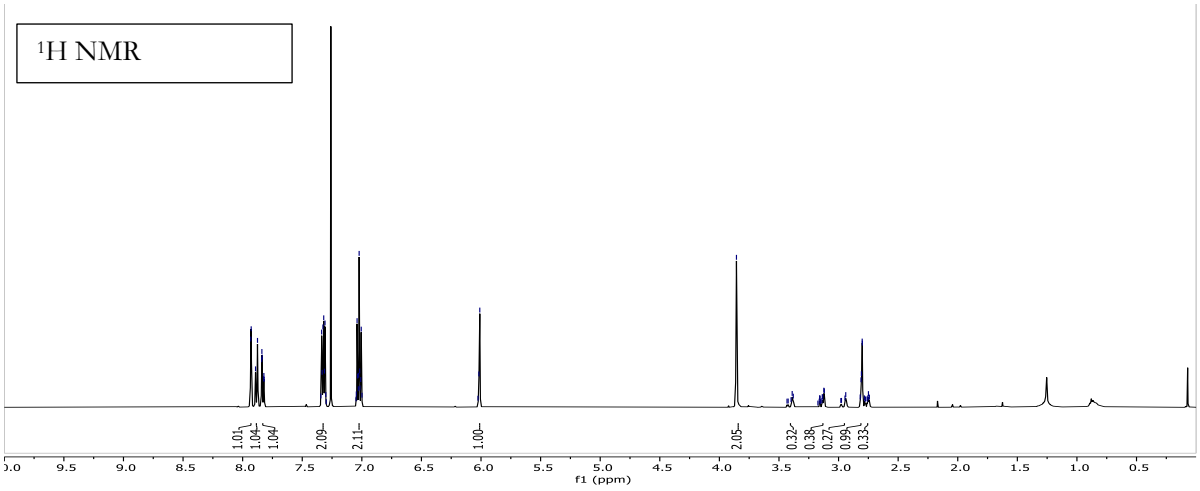
^{19}F NMR (377 MHz, $CDCl_3$) δ –116.6.

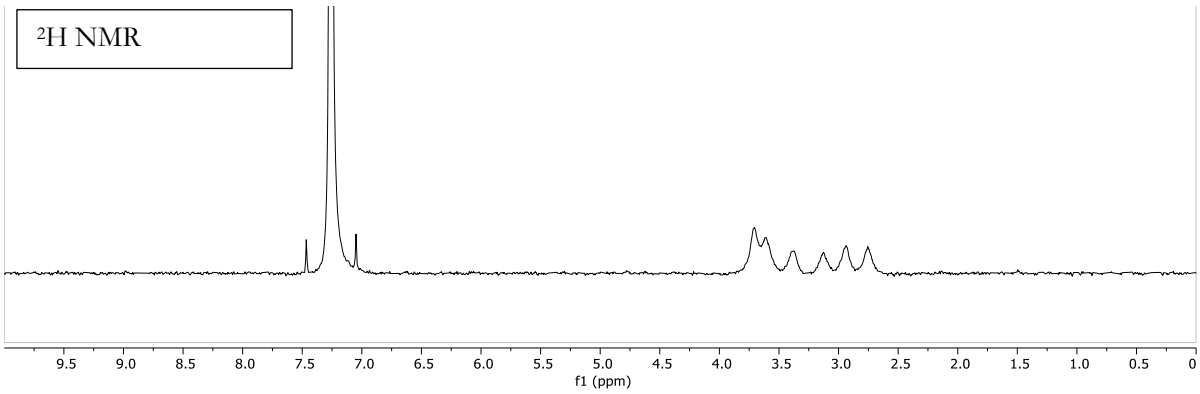
Carbon	13C NMR δ (ppm) Carreira	13C NMR δ (ppm) Donohoe	Δδ (ppm)
C^2H_2	50.3	50.5	0.2
C^3H	43.0	43.1	0.1
C^4H	44.6	44.7	0.1
C^5H_2	35.3	35.5	0.2
C^6H_2	47.1	47.2	0.1
C^7H_2	69.6	69.7	0.1
C^8	140.0	140.1	0.1
C^9H	128.9	128.9	0
$C^{10}H$	115.5	115. 6	0.1
C^{11}	161.6	161.67	0.07
C^{12}	154.5	154.6	0.1
$C^{13}H$	98.1	98.1	0
C^{14}	148.3	148.3	0
C^{15}	141.7	141.7	0
$C^{16}H$	108.0	108.0	0
$C^{17}H$	105.7	105.8	0.1
$C^{18}H_2$	101.2	101.2	0

d-(*N*-(2,4-bis(Trifluoromethyl)benzyl)-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridin-3-yl)methanol (II-51d)

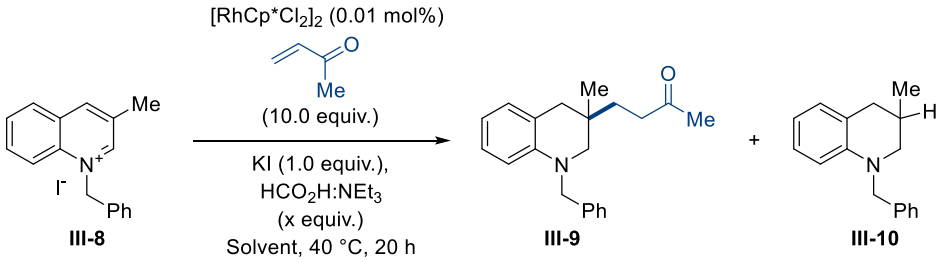


The title compound **2j-D** was prepared by General procedure E using salt **1j** (264 mg, 0.50 mmol) and deuterated paraformaldehyde (480 mg, 15 mmol). Purification by FCC (5%-20% EtOAc in pentane) gave *amine* **2j** (155 mg, 71%) as a yellow oil. Complete deuterium incorporation was observed for the hydroxymethyl group and significant levels of incorporation at the C-2 and C-6 positions. These observations are consistent with the mechanism described above.

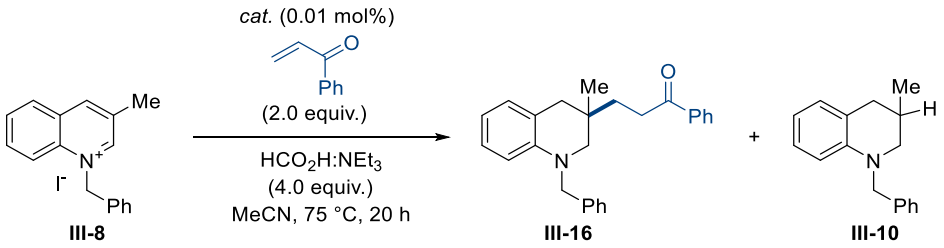




7.3.7 Optimisation of reaction conditions



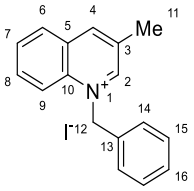
entry	solvent	conc.	equiv. of "H-"	Yield A	Yield B
1	neat	0.13 M	100	59%	5%
2	CH_2Cl_2	0.1 M	10	66% (63%)	/
3	DCE	0.1 M	10	46%	/
4	CCl_3H	0.1 M	10	10%	/
5	THF	0.1 M	10	/	/
6	MeCN	0.1 M	10	41%	12%
7	MeOH	0.1 M	10	Complex mixtures	
8	*i*-PrOH	0.1 M	10	Messy	
9	TFE	0.1 M	10	Sm only	
10	HFIP	0.1 M	10	Sm only	
11	H_2O	0.1 M	10	Complex mixtures	
12	PhMe	0.1 M	10	7%	/



entry	Catalyst	Yield A	Yield B
1	$[RhCp^*Cl_2]_2$	83%	0%
2	$[Ru(p\text{-}cymene)Cl_2]_2$	85%	0%
3	$[IrCp^*Cl_2]_2$	83%	0%

7.3.8 Synthesis of quinolinium salts

N-Benzyl-3-methylquinolinium iodide (III-8)



The title compound was prepared according to General Procedure F using 3-methylquinoline (716 mg, 5.00 mmol) and benzyl iodide (1.25 mL, 10.0 mmol) in acetone (10 mL) to give salt **III-8** as a yellow solid (1.44 g, 80%). Spectroscopic data was consistent with that reported in the literature.[74]

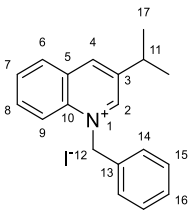
HRMS (ESI): Exact mass calculated for $C_{17}H_{16}N$ $[M+H]^+$: 234.1277, found: 234.1279.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.77 (d, *J* = 1.9 Hz, 1H, C^2**H**), 9.20 (d, *J* = 2.1 Hz, 1H, C^4**H**), 8.43 (dd, *J* = 9.0, 1.0 Hz, 1H, C^9**H**), 8.38 (dd, *J* = 8.2, 1.5 Hz, 1H, C^6**H**), 8.12 (ddd, *J* = 8.8, 7.0, 1.5 Hz, 1H, C^8**H**), 7.97 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H, C^7**H**), 7.45 – 7.30 (m, 5H, 2 x C^{14}**H** + 2 x C^{15}**H** + C^{16}**H**), 6.33 (s, 2H, C^{12}**H**$_2$), 2.71 (s, 3H, C^{11}**H**$_3$).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 151.5 (C^{2}H), 146.8 (C^{4}H), 135.9 (C^{10}), 134.6 (C^{8}H), 133.9 (C^{13}), 132.6 (C^3), 130.0 (C^{6}H), 129.9 (C^{7}H), 129.6 (C^5), 129.0 (2 x C^{14}H/C^{15}H), 128.7 (C^{16}H), 127.2 (2 x C^{14}H/C^{15}H), 119.0 (C^{9}H), 59.9 (C^{12}H$_2$), 18.1 (C^{11}H$_3$).

IR (neat) (cm^{-1}): 2981, 2160, 2034, 2009, 1978, 1523, 1362, 771, 753, 738.

N-Benzyl-3-isopropylquinolinium iodide (III-42)



The title compound was prepared according to General Procedure F using 3-isopropylquinoline (514 mg, 3.00 mmol) and benzyl iodide (0.75 mL, 6.00 mmol) to give salt **III-42** as a yellow solid (746 mg, 65%).

m.p. (acetone): 196 – 198 °C

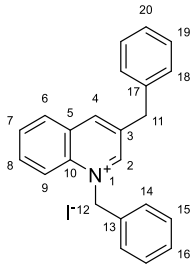
HRMS (ESI): Exact mass calculated for $C_{19}H_{20}N$ $[M+H]^+$: 262.1590, found: 262.1591.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.85 (d, *J* = 2.0 Hz, 1H, C^2**H**), 9.30 (d, *J* = 2.0 Hz, 1H, C^4**H**), 8.43 (dd, *J* = 8.2, 1.6 Hz, 2H, C^{6}H + C^{9}H), 8.13 (ddd, *J* = 8.9, 7.0, 1.5 Hz, 1H, C^{7}H/C^{8}H), 7.98 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H, C^{7}H/C^{8}H), 7.44 – 7.30 (m, 5H, 5 x C^{Ar}**H**), 6.37 (s, 2H, C^{12}**H$_2$**), 3.45 – 3.34 (m, 1H, C^{11}**H**), 1.46 (d, *J* = 6.9 Hz, 6H, 2 x C^{17}**H$_3$**).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 150.3 (C^{2}H), 144.6 (C^{4}H), 142.5 (C^{Ar}), 136.2 (C^{Ar}), 134.8 (C^{8}H), 134.0 (C^{Ar}), 130.3 (C^{6}H), 129.90 (C^{Ar}/C^{7}H), 129.88 (C^{Ar}/C^{7}H), 129.1 (2 x C^{14}H/C^{15}H), 128.7 (C^{16}H), 127.0 (2 x C^{14}H/C^{15}H), 119.0 (C^{9}H), 60.0 (C^{12}H$_2$), 31.3 (C^{11}H), 22.9 (2 x C^{17}H$_3$).

IR (neat) (cm^{-1}): 2981, 2528, 2160, 2031, 1977, 1602, 1509, 770, 751, 733.

N-Benzyl-3-benzylquinolinium iodide (III-43)

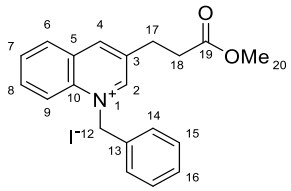


The title compound was prepared according to General Procedure F using 3-benzylquinoline (170 mg, 0.78 mmol) and benzyl iodide (0.19 mL, 1.55 mmol) in acetone (1 mL) to give salt **III-43** as a yellow solid (275 mg, 81%). Spectroscopic data was consistent with that reported in the literature.[2]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H, C^{2}**H**), 9.22 (s, 1H, C^{4}**H**), 8.46 (d, J = 9.0 Hz, 1H, C^{9}**H**), 8.42 (dd, J = 8.3, 1.4 Hz, 1H, C^{6}**H**), 8.14 (ddd, J = 8.8, 7.0, 1.5 Hz, 1H, C^{8}**H**), 7.97 (ddd, J = 8.1, 7.0, 0.9 Hz, 1H, C^{7}**H**), 7.49 – 7.21 (m, 10H, 10 x C^{Ar}**H**), 6.35 (s, 2H, C^{12}**H$_2$**), 4.43 (s, 2H, C^{11}**H$_2$**).

^{13}C NMR (101 MHz, DMSO-d_6) δ 151.1 (C^{2}H), 146.8 (C^{4}H), 138.7 (C^{Ar}), 136.3 (C^{Ar}), 135.9 (C^{Ar}), 135.1 (C^{8}H), 133.9 (C^{Ar}), 130.4 (C^{6}H), 130.0 (C^{Ar}), 129.8 (C^{7}H), 129.03 (2 x C^{Ar}H), 128.99 (2 x C^{Ar}H), 128.9 (2 x C^{Ar}H), 128.7 (C^{16}H/C^{20}H), 127.2 (2 x C^{Ar}H), 126.9 (C^{16}H/C^{20}H), 119.1 (C^{9}H), 60.0 (C^{12}H$_2$), 37.5 (C^{11}H$_2$).

***N*-Benzyl-3-(3-methoxy-3-oxopropyl)quinolinium iodide (III-44)**

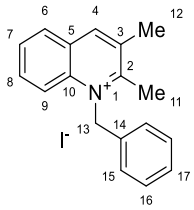


The title compound was prepared according to General Procedure F using 3-methylquinoline (538 mg, 2.50 mmol) and benzyl iodide (0.63 mL, 5.00 mmol) to give salt **III-44** as a yellow solid (983 mg, 91%). Spectroscopic data was consistent with that reported in the literature.[74]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.82 (d, J = 1.9 Hz, 1H, C^{2}**H**), 9.27 (s, 1H, C^{4}**H**), 8.45 (dd, J = 9.0, 1.0 Hz, 1H, C^{9}**H**), 8.39 (dd, J = 8.2, 1.4 Hz, 1H, C^{6}**H**), 8.14 (ddd, J = 8.8, 7.0, 1.5 Hz, 1H, C^{8}**H**), 7.98 (ddd, J = 8.0, 7.0, 0.9 Hz, 1H, C^{7}**H**), 7.48 – 7.23 (m, 5H, 5 x C^{Ar}**H**), 6.34 (s, 2H, C^{12}**H$_2$**), 3.61 (s, 3H, C^{20}**H$_3$**), 3.28 (t, J = 7.3 Hz, 2H, C^{18}**H$_2$**), 2.98 (t, J = 7.3 Hz, 2H, C^{17}**H$_2$**).

^{13}C NMR (101 MHz, DMSO-d_6) δ 172.2 (C^{19}O), 151.3 (C^{2}H), 146.7 (C^{4}H), 136.1 (C^{Ar}), 135.3 (C^{Ar}), 135.0 (C^{8}H), 133.8 (C^{Ar}), 130.3 (C^{6}H), 130.0 (C^{7}H), 129.6 (C^{Ar}), 129.0 (2 x C^{14}H/C^{15}H), 128.8 (C^{16}H), 127.2 (2 x C^{14}H/C^{15}H), 119.0 (C^{9}H), 60.0 (C^{12}H$_2$), 51.6 (C^{20}H$_2$), 33.2 (C^{18}H$_2$), 27.1 (C^{17}H$_2$).

_N_-Benzyl-2,3-dimethylquinolinium iodide (III-45)



The title compound was prepared according to a modified General Procedure F. A solution of 3,4-dimethylquinoline (555 mg, 3.5 mmol) and benzyl iodide (0.88 mL, 7.0 mmol) in 1,4-dioxane (7.0 mL) was heated to 90 °C for 16°h. The reaction mixture was cooled to room temperature, addition of Et_2O (20 mL) resulted in formation of the precipitate which was filtered and washed with Et_2O to give salt **III-45** as a yellow solid (433 mg, 33%).

m.p. (EtOAc): 200 – 202 °C

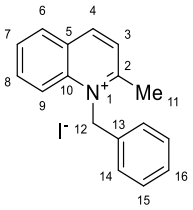
HRMS (ESI): Exact mass calculated for $C_{18}H_{18}N$ $[M+H]^+$:248.1434, found: 248.1436.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H, C^4**H**), 8.33 (dd, J = 8.2, 1.8 Hz, 2H, C^6**H** + C^9**H**), 8.07 (ddd, J = 8.9, 7.0, 1.6 Hz, 1H, C^7**H**/C^8**H**), 7.94 (dd, J = 7.7, 7.7 Hz, 1H, C^7**H**/C^8**H**), 7.43 – 7.29 (m, 3H), 7.15 (dd, J = 7.7, 1.7 Hz, 2H, 2 x C^{15}**H**), 6.37 (s, 2H, C^{13}**H$_2$**), 2.97 (s, 3H, C^{11}**H$_3$**), 2.68 (s, 3H, C^{12}**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3 (C^2), 145.4 (C^4H), 137.8 (C^{Ar}), 134.4 (C^7H/C^8H), 133.7 (C^{Ar}), 133.3 (C^{Ar}), 129.7 (C^7H/C^8H), 129.2 (C^4H), 129.1 (2 x C^{16}H), 128.1 (C^{Ar}/C^{17}H), 127.8 (C^{Ar}/C^{17}H), 125.9 (2 x C^{15}H), 119.2 (C^9H), 55.0 ($C^{13}H_2$), 20.1 ($C^{11}H_3$), 19.7 ($C^{12}H_3$).

IR (neat) (cm^{-1}): 2956, 2529, 2160, 2032, 1977, 1509, 771, 751, 734, 692.

_N_-Benzyl-2-methylquinolinium iodide (III-46)



The title compound was prepared according to a modified General Procedure F. A solution of 3-methylquinoline (0.7 mL, 5.0 mmol) and benzyl iodide (1.25 mL, 10.0 mmol) in 1,4-dioxane (10 mL) was heated to 90 °C for 16°h. The reaction mixture was cooled to room temperature, addition of Et_2O (20 mL) resulted in formation of the precipitate which was filtered and washed with Et_2O to give salt **III-46** as a brown solid (768 mg, 43%).

m.p. (EtOAc): 200 – 204 °C

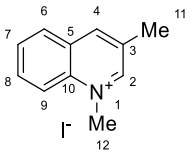
HRMS (ESI): Exact mass calculated for $C_{17}H_{16}N$ $[M+H]^+$: 234.1277, found: 234.1279.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.24 (d, *J* = 8.5 Hz, 1H, C^4**H**), 8.46 (dd, *J* = 8.2, 1.5 Hz, 1H, C^6**H**), 8.39 (d, *J* = 9.0 Hz, 1H, C^9**H**), 8.25 (d, *J* = 8.6 Hz, 1H, C^3**H**), 8.15 (ddd, *J* = 8.9, 7.0, 1.6 Hz, 1H, C^8**H**), 7.98 (dd, *J* = 8.0, 7.0 Hz, 1H, C^7**H**), 7.42 – 7.29 (m, 3H, 3 x C^{Ar}**H**), 7.18 – 7.08 (m, 2H, 2 x C^{Ar}**H**), 6.33 (s, 2H, C^{12}**H$_2$**), 3.08 (s, 3H, C^{11}**H$_3$**).

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 161.7 (C^2), 146.7 (C^{4}H), 138.9 (C^{Ar}), 135.5 (C^{8}H), 133.2 (C^{Ar}), 130.7 (C^{6}H), 129.22 (C^{7}H), 129.20 (2 x C^{15}H), 128.4 (C^{Ar}/C^{16}H), 128.2 (C^{Ar}/C^{16}H), 125.9 (2 x C^{14}H), 125.8 (C^{3}H), 119.2 (C^{9}H), 54.4 (C^{12}H$_2$), 22.8 (C^{11}H$_3$).

IR (neat) (cm^{-1}): 2961, 2530, 2160, 2029, 1977, 1602, 1523, 1350, 827, 771.

1,3-Dimethylquinolinium iodide (III-47)



The title compound was prepared according to a modified General Procedure F. A mixture of 3-methylquinoline (573 mg, 4.00 mmol) and iodomethane (1.24 mL, 20.0 mmol) 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 title compound **III-47** as a yellow solid (1.10 g, 97%).

m.p. (EtOAc): 203 – 205 °C

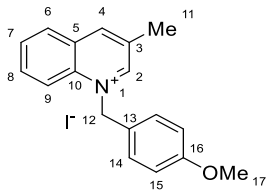
HRMS (ESI): Exact mass calculated for $C_{11}H_{12}N$ $[M+H]^+$: 158.0964, found 158.0965.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, *J* = 1.9 Hz, 1H, C^2**H**), 9.09 (s, 1H, C^4**H**), 8.46 (dd, *J* = 8.9, 1.0 Hz, 1H, C^9**H**), 8.36 (dd, *J* = 8.3, 1.4 Hz, 1H, C^6**H**), 8.21 (ddd, *J* = 8.7, 7.0, 1.1 Hz, 1H, C^8**H**), 8.02 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H, C^7**H**), 4.61 (s, 3H, C^{12}**H$_3$**), 2.64 (s, 3H, C^{11}**H**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3 (C^2H), 145.5 (C^4H), 136.7 (C^{Ar}), 134.3 (C^8H), 132.0 (C^{Ar}), 129.9 (C^7H), 129.5 (C^6H), 128.9 (C), 118.8 (C^9H), 45.2 ($C^{12}H_3$), 17.9 ($C^{11}H_3$).

IR (neat) (cm^{-1}): 2516, 2160, 2029, 1592, 1521, 1230, 868, 773, 748, 608.

***N*-(4-Methoxybenzyl)-3-methylquinolinium iodide (III-48)**



The title compound was prepared according to General Procedure F using 3-methylquinoline (0.27 mL, 2.0 mmol) and 4-methoxybenzyl iodide (975 mg, 3.9 mmol) in acetone (4 mL) to give salt **III-48** as a yellow solid (782 mg, 99%).

m.p. (EtOAc): 190 – 192 °C

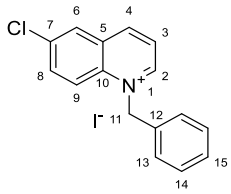
HRMS (ESI): Exact mass calculated for $C_{18}H_{18}NO$ $[M+H]^+$: 264.1383, found: 264.1385.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (d, J = 1.9 Hz, 1H, C^{2}**H**), 9.16 (s, 1H, C^{4}**H**), 8.55 – 8.48 (m, 1H, C^{9}**H**), 8.36 (dd, J = 8.2, 1.5 Hz, 1H, C^{6}**H**), 8.13 (ddd, J = 8.8, 7.0, 1.5 Hz, 1H, C^{8}**H**), 7.97 (ddd, J = 8.0, 7.0, 0.9 Hz, 1H, C^{7}**H**), 7.43 (d, J = 8.8 Hz, 2H, 2 x C^{14}**H**), 6.94 (d, J = 8.8 Hz, 1H, 2 x C^{15}**H**), 6.23 (s, 2H, C^{12}**H$_2$**), 3.72 (s, 3H, C^{17}**H$_3$**), 2.70 (s, 3H, C^{11}**H$_2$**).

^{13}C NMR (101 MHz, DMSO-d_6) δ 159.5 (C^{16}), 151.0 (C^{2}H), 146.6 (C^{4}H), 135.8 (C^{Ar}), 134.5 (C^{8}H), 132.6 (C), 130.0 (C^{6}H), 129.9 (C^{7}H), 129.6 (C^{Ar}), 129.1 (2 x C^{14}H), 125.6 (C^{Ar}), 119.1 (C^{9}H), 114.4 (2 x C^{15}H), 59.6 (C^{17}H$_3$), 55.2 (C^{12}H$_2$), 18.1 (C^{11}H$_3$).

IR (neat) (cm^{-1}): 2956, 2160, 2030, 1977, 1516, 1243, 1180, 1019, 832, 805.

N-Benzyl-6-chloroquinolinium iodide (III-49)

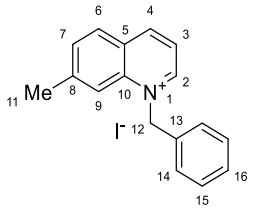


The title compound was prepared according to General Procedure F using 6-chloroquinoline (650 mg, 4.00 mmol) and benzyl iodide (1.00 mL, 8.00 mmol) to give salt **III-49** as an orange solid (1.37 g, 90%). Spectroscopic data was consistent with that reported in the literature. [74]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (dd, J = 5.8, 1.4 Hz, 1H, C^{2}**H**), 9.30 (dt, J = 8.5, 1.1 Hz, 1H, C^{4}**H**), 8.70 (d, J = 2.4 Hz, 1H, C^{6}**H**), 8.54 (d, J = 9.5 Hz, 1H, C^{9}**H**), 8.35 (dd, J = 8.5, 5.8 Hz, 1H, C^{3}**H**), 8.26 (dd, J = 9.4, 2.4 Hz, 1H, C^{8}**H**), 7.46 – 7.32 (m, 5H, 5 x C^{Ar}**H**), 6.39 (s, 2H, C^{11}**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8 (C^{2}H), 147.4 (C^{4}H), 136.3 (C^{Ar}), 135.6 (C^{8}H), 134.5 (C^{Ar}), 133.6 (C^{Ar}), 130.8 (C^{Ar}), 129.3 (C^{6}H), 129.1 (2 x C^{14}H), 128.8 (C^{15}H), 127.3 (2 x C^{13}H), 123.7 (C^{3}H), 121.6 (C^{9}H), 60.2 (C^{11}H$_2$).

***N*-Benzyl-7-methylquinolinium iodide (III-50)**

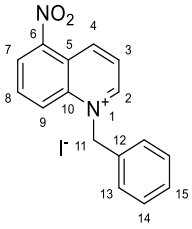


The title compound was prepared according to General Procedure F using 7-methylquinoline (573 mg, 4.00 mmol) and benzyl iodide (1.00 mL, 8.00 mmol) to give salt **III-50** as a yellow solid (1.29 g, 91%). Spectroscopic data was consistent with that reported in the literature. [74]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (dd, *J* = 5.9, 1.5 Hz, 1H, C^{2}**H**), 9.31 (dt, *J* = 8.3, 1.2 Hz, 1H, C^{4}**H**), 8.44 – 8.36 (m, 2H, C^{6}**H** + C^{9}**H**), 8.20 (dd, *J* = 8.3, 5.9 Hz, 1H, C^{3}**H**), 7.88 (dd, *J* = 8.4, 1.4 Hz, 1H, C^{7}**H**), 7.46 – 7.32 (m, 5H, 5 x C^{Ar}**H**), 6.33 (s, 2H, C^{12}**H$_2$**), 2.63 (d, *J* = 0.9 Hz, 3H, C^{11}**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.7 (C^{2}H), 147.6 (C^{4}H), 137.9 (C^{Ar}), 133.8 (C^{Ar}), 132.0 (C^{7}H), 130.4 (C^{6}H), 129.1 (2 x C^{15}H), 128.8 (C^{Ar}/C^{16}H), 128.3 (C^{Ar}/C^{16}H), 127.4 (2 x C^{14}H), 121.4 (C^{3}H), 118.0 (C^{9}H), 59.5 ($C^{12}H_2$), 22.3 ($C^{11}H_3$).

***N*-Benzyl-5-nitroquinolinium iodide (III-51)**



The title compound was prepared according to a modified General Procedure F. 5-Nitroquinoline (522 mg, 3.00 mmol) and benzyl iodide (0.75 mL, 6.00 mmol) in acetone (6.00 mL) were stirred at r.t. in the dark for 2 days to give salt **III-51** as an orange solid (471 mg, 40%).

m.p. (acetone): 189 – 191 °C

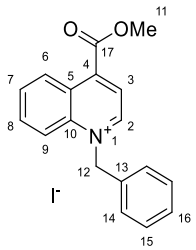
HRMS (ESI): Exact mass calculated for $C_{16}H_{13}N_2O_2$ $[M+H]^+$: 265.0972, found: 265.0973.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (dd, *J* = 5.8, 1.3 Hz, 1H, C^{2}**H**), 9.61 (dt, *J* = 9.0, 1.2 Hz, 1H, C^{4}**H**), 8.90 (dt, *J* = 9.2, 1.0 Hz, 1H, C^{7}**H**), 8.74 (dd, *J* = 7.8, 0.8 Hz, 1H, C^{9}**H**), 8.50 (dd, *J* = 9.0, 5.8 Hz, 1H, C^{3}**H**), 8.37 (dd, *J* = 9.1, 7.8 Hz, 1H, C^{8}**H**), 7.45 – 7.35 (m, 5H, 5 x C^{Ar}**H**), 6.48 (s, 2H, C^{11}**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.0 (C^{2}H), 146.6 (C^{4}H), 137.6 (C^{Ar}), 134.2 (C^{Ar}), 133.4 (C^{8}H), 129.1 (2 x C^{14}H), 128.9 (C^{15}H), 127.4 (2 x C^{13}H), 127.1 (C^{9}H), 125.2 (C^{7}H), 125.0 (C^{3}H), 122.6 (C^{Ar}), 61.1 ($C^{11}H_2$), C^{6} missing.

IR (neat) (cm^{-1}): 2981, 2523, 2160, 2030, 1977, 1525, 1385, 1365, 1244, 746.

N-Benzyl-4-(methoxycarbonyl)quinolinium iodide (III-52)



The title compound was prepared according to a modified General Procedure F. Methyl quinoline-4-carboxylate (710 mg, 3.79 mmol) and benzyl iodide (0.96 mL, 7.60 mmol) in acetone (9 mL) were stirred at rt in the dark for 24 hours to give salt **III-52** as a red solid (650 mg, 42%).

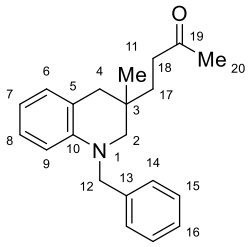
Spectroscopic data was consistent with that reported in the literature.[122]

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (d, *J* = 6.0 Hz, 1H, C^{2}**H**), 8.79 (dd, *J* = 8.6, 1.4 Hz, 1H, C^{6}**H**), 8.63 – 8.56 (m, 2H, C^{3}**H** + C^{9}**H**), 8.27 (ddd, *J* = 8.9, 7.0, 1.5 Hz, 1H, C^{8}**H**), 8.11 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H, C^{7}**H**), 7.45 – 7.33 (m, 5H, 5 C^{Ar}**H**), 6.44 (s, 2H, C^{12}**H$_2$**), 4.11 (s, 3H, C^{11}**H$_3$**).

^{13}C NMR (101 MHz, DMSO-d_6) δ 164.1 (C^{17}O), 151.0 (C^{2}H), 145.0 (C^{Ar}), 138.3 (C^{Ar}), 135.7 (C^{8}H), 133.4 (C^{Ar}), 131.1 (C^{7}H), 129.1 (2 x C^{14}H/C^{15}H), 128.9 (C^{16}H), 127.8 (C^{3}H), 127.5 (2 x C^{14}H/C^{15}H), 126.5 (C^{Ar}), 122.8 (C^{3}H), 119.9 (C^{9}H), 60.7 ($C^{12}H_2$), 54.1 ($C^{11}H_3$).

7.3.9 Synthesis of tetrahydroquinolines

4-(*N*-Benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-3-yl)butan-2-one (III-9)



The title compound was prepared according to General Procedure G using salt **III-8** (45 mg, 0.125 mmol) and methyl vinyl ketone (50 µL, 0.63 mmol) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-9** (30 mg, 78%) as a clear oil.

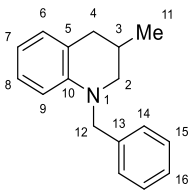
HRMS (ESI): Exact mass calculated for $C_{21}H_{26}NO$ $[M+H]^+$: 308.2009, found: 308.2009.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 5H, 2 x C^{14}**H** + 2 x C^{15}**H** + C^{16}**H**), 7.04 – 6.93 (m, 2H, C^6**H** + C^8**H**), 6.61 (t, *J* = 7.3 Hz, 1H, C^7**H**), 6.56 (d, *J* = 8.2 Hz, 1H, C^9**H**), 4.48 (d, *J* = 3.3 Hz, 2H, C^2**H$_2$**), 3.08 – 2.96 (m, 2H, C^4**H$_2$**), 2.59 (s, 2H, C^{12}**H$_2$**), 2.50 – 2.31 (m, 2H, C^{18}**H$_2$**), 2.11 (s, 3H, C^{20}**H$_3$**), 1.71 – 1.53 (m, 2H, C^{17}**H$_2$**), 0.97 (s, 3H, C^{11}**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9 (C^{19}), 144.7 (C^{10}), 139.2 (C^{13}), 129.9 (C^6H/C^8H), 128.7 (2 x C^{14}H/C^{15}H), 127.3 (C^6H/C^8H), 127.0 (C^{16}H), 126.8 (2 x C^{14}H/C^{15}H), 120.6 (C^5), 116.5 (C^7H), 110.9 (C^9H), 59.8 (C^2H_2), 55.5 ($C^{12}H_2$), 40.7 (C^4H_2), 38.4 ($C^{18}H_2$), 32.5 ($C^{17}H_2$), 30.8 (C^3), 30.1 ($C^{20}H_3$), 23.5 ($C^{11}H_3$).

IR (neat) (cm^{-1}): 2919, 2834, 1714, 1602, 1504, 1497, 1451, 1352, 1282, 1249.

N-Benzyl-3-methyl-1,2,3,4-tetrahydroquinoline (III-10)



The title compound was prepared according to General Procedure G using salt **III-8** (45 mg, 0.125 mmol) in the absence of electrophile. Purification by column chromatography (0%-2% EtOAc in pentane) gave *amine* **III-10** (23 mg, 77%) as a clear oil. Spectroscopic data was consistent with that reported in the literature.[122]

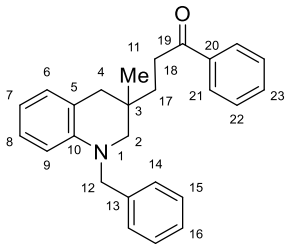
HRMS (ESI): Exact mass calculated for $C_{17}H_{20}N$ $[M+H]^+$: 238.1590, found: 238.1589.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.22 (m, 5H, 2 x C^{14}**H** + 2 x C^{15}**H** + C^{16}**H**), 7.05 – 6.96 (m, 2H, C^6**H** + C^8**H**), 6.61 (td, *J* = 7.3, 1.1 Hz, 1H, C^7**H**), 6.57 – 6.47 (m, 1H, C^9**H**), 4.51 (s, 2H, C^{12}**H$_2$**), 3.31 (ddd, *J* = 11.2, 4.0, 2.2 Hz, 1H, C^2**H$_2$**), 3.06 (dd, *J* = 11.2, 9.6 Hz, 1H, C^2**H$_2$**), 2.85 (ddd, *J* = 15.6, 4.6, 2.2 Hz, 1H, C^4**H$_2$**), 2.53 (dd, *J* = 15.6, 10.5 Hz, 1H, C^4**H$_2$**), 2.28 – 2.13 (m, 1H, C^3**H**), 1.08 (d, *J* = 6.6 Hz, 3H, C^{11}**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3 (C^{10}), 139.2 (C^{13}), 129.3 (C^6H/C^8H), 128.7 (2 x C^{14}H/C^{15}H), 127.3 (C^6H/C^8H), 126.9 (C^{16}H), 126.7 (2 x C^{14}H/C^{15}H), 122.0 (C^5), 116.0 (C^7H), 110.9 (C^9H), 57.0 (C^2H_2), 55.3 ($C^{12}H_2$), 36.6 (C^4H_2), 27.5 (C^3H), 19.2 ($C^{11}H_3$).

IR (neat) (cm^{-1}): 2953, 2922, 1602, 1506, 1494, 1452, 1359, 1349, 1283, 1245.

3-(*N*-Benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-3-yl)-1-phenylpropan-1-one (III-16)



The title compound was prepared according to General Procedure G using salt **III-8** (45 mg, 0.125 mmol) and phenyl vinyl ketone (33 mg, 0.25 mmol) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-16** (37 mg, 77%) as a clear oil.

HRMS (ESI): Exact mass calculated for $C_{26}H_{28}NO$ $[M+H]^+$: 370.2165, found: 360.2168.

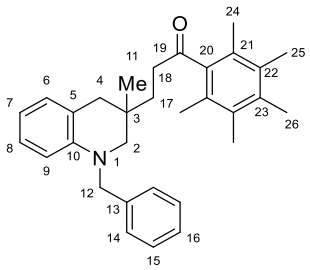
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.82 (m, 2H, 2 x C^{21}**H**), 7.60 – 7.48 (m, 1H, C^{23}**H**), 7.42 (dd, *J* = 8.4, 7.1 Hz, 2H, 2 x C^{22}**H**), 7.32 – 7.16 (m, 5H, 2 x C^{14}**H** + 2 x C^{15}**H** + C^{16}**H**), 7.04 – 6.96 (m,

2H, C^{6}**H** + C^{8}**H**), 6.61 (t, *J* = 1.1 Hz, 1H, C^{7}**H**), 6.56 (d, *J* = 8.1 Hz, 1H, C^{9}**H**), 4.55 – 4.42 (m, 2H, C^{12}**H$_2$**), 3.15 – 3.03 (m, 2H, C^{2}**H$_2$**), 3.03 – 2.82 (m, 2H, C^{18}**H$_2$**), 2.73 – 2.57 (m, 2H, C^{4}**H$_2$**), 1.79 (t, *J* = 8.2 Hz, 2H, C^{17}**H$_2$**), 1.05 (s, 3H, C^{11}**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5 (C^{19}), 144.8 (C^{10}), 139.2 (C^{13}), 137.1 (C^{20}), 133.1 (C^{23}H), 129.9 (C^{6}H/C^{8}H), 128.72 (2 x C^{15}H/C^{22}H), 128.69 (2 x C^{15}H/C^{22}H), 128.2 (2 x C^{21}H), 127.4 (C^{6}H/C^{8}H), 127.0 (C^{16}), 126.9 (2 x C^{14}H), 120.7 (C^{5}), 116.5 (C^{7}H), 111.0 (C^{9}H), 60.0 (C^{2}H$_2$), 55.6 (C^{12}H$_2$), 40.7 (C^{4}H$_2$), 33.33 (C^{17}H$_2$/C^{18}H$_2$), 33.31 (C^{17}H$_2$/C^{18}H$_2$), 31.1 (C^{3}), 23.6 (C^{11}H$_3$).

IR (neat) (cm^{-1}): 2981, 2895, 1683, 1601, 1505, 1450, 1283, 1249, 743, 692.

3-(*N*-Benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one (III-17)



The title compound was prepared according to General Procedure G using salt **III-8** (45 mg, 0.125 mmol) and 2,3,4,5,6-pentamethylphenyl vinyl ketone (51 mg, 0.25 mmol) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-17** (35 mg, 65%) as a white solid.

m.p. (EtOAc): 112 – 114 °C

HRMS (ESI): Exact mass calculated for $C_{31}H_{38}NO$ $[M+H]^+$: 440.2948, found: 440.2942.

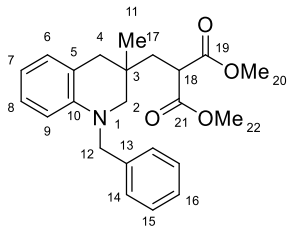
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.21 (m, 5H, 2 x C^{14}**H** + 2 x C^{15}**H** + C^{16}**H**), 7.05 – 6.98 (m, 1H, C^{8}**H**), 6.96 (dd, *J* = 7.4, 1.6 Hz, 1H, C^{6}**H**), 6.61 (td, *J* = 7.3, 1.1 Hz, 1H, C^{7}**H**), 6.55 (dd, *J* = 8.2, 1.1 Hz, 1H, C^{9}**H**), 4.58 – 4.37 (m, 2H, C^{12}**H$_2$**), 3.13 – 2.99 (m, 2H, C^{2}**H$_2$**), 2.76 – 2.55 (m, 4H, C^{4}**H$_2$**

+ C[18]**H$_2$**), 2.24 (s, 3H, C[26]**H$_3$**), 2.19 (s, 6H, 2 x C[24]**H$_3$**/C[25]**H$_3$**), 2.07 (s, 6H, 2 x C[24]**H$_3$**/C[25]**H$_3$**), 1.88 – 1.74 (m, 2H, C[17]**H$_2$**), 1.01 (s, 3H, C[11]**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.1 (C[19]), 144.8 (C[10]), 141.1 (C[Ar]), 139.2 (C[Ar]), 135.6 (C[Ar]), 133.2 (2 x C[Ar]), 129.8 (C[6]H), 128.7 (2 x C[14]H/C[15]H), 127.4 (C[8]H), 127.3 (2 x C[Ar]), 127.0 (C[16]H), 126.7 (2 x C[14]H/C[15]H), 120.6 (C[5]), 116.5 (C[7]H), 111.0 (C[9]H), 60.2 (C[2]H_2), 55.7 (C[12]H_2), 40.6 (C[4]H_2/C[18]H_2), 40.3 (C[4]H_2/C[18]H_2), 32.4 (C[17]H_2), 30.9 (C[3]), 23.3 (C[11]H_3), 17.4 (2 x C[24]H_3/C[25]H_3), 16.8 (C[26]H_3), 16.1 (2 x C[24]H_3/C[25]H_3).

IR (neat) (cm^{-1}): 2922, 1700, 1603, 1506, 1497, 1452, 1357, 1317, 1283, 1249, 745.

Dimethyl 2-((*N*-benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-3-yl)methyl)malonate (III-18)



The title compound was prepared according to a modified General Procedure G using salt **III-8** (45 mg, 0.125 mmol) and dimethyl 2-methylenemalonate (90 mg, 0.625 mmol) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-18** (15 mg, 32%) as a clear oil.

HRMS (ESI): Exact mass calculated for $C_{23}H_{28}NO_4$ $[M+H]^+$: 382.2013, found: 382.2013.

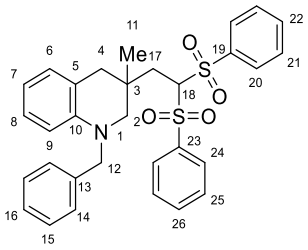
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.09 (m, 5H, 5 x C[Ar]**H**), 6.92 (ddd, *J* = 8.2, 7.3, 1.7 Hz, 1H, C[8]**H**), 6.87 (dd, *J* = 7.4, 1.6 Hz, 1H, C[6]**H**), 6.52 (ddd, *J* = 7.3, 7.3, 1.1 Hz, 1H, C[7]**H**), 6.48 (dd, *J* = 8.2, 1.1 Hz, 1H, C[9]**H**), 4.40 (dd, *J* = 16.9, 16.9 Hz, 2H, C[12]**H$_2$**), 3.63 (s, 6H, C[20]**H$_3$** + C[22]**H$_3$**), 3.40 (t, *J* = 6.5 Hz, 1H, C[18]**H**), 3.08 – 2.82 (m, 2H, C[4]**H$_2$**), 2.66 – 2.39 (m, 2H, C[2]**H$_2$**), 2.07 – 1.93 (m, 2H, C[17]**H$_2$**), 0.89 (s, 3H, C[11]**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.49 (C[19]O/C[21]O), 170.45 (C[19]O/C[21]O), 144.5 (C[Ar]), 139.0 (C[Ar]), 129.9 (C[6]H), 128.7 (2 x C[14]H/C[15]H), 127.4 (C[8]H), 127.0 (C[16]H), 126.8 (2 x C[14]H/C[15]H), 120.2 (C[Ar]),

116.6 ($C^{7}H$), 111.1 ($C^{9}H$), 59.8 ($C^{2}H_2$), 55.6 ($C^{12}H_2$), 52.82 ($C^{20}H_3$/$C^{22}H_3$), 52.81 ($C^{20}H_3$/$C^{22}H_3$), 47.8 ($C^{18}H$), 40.3 ($C^{4}H_2$), 37.8 ($C^{17}H$), 31.3 (C^{3}), 23.1 ($C^{11}H_3$).

IR (neat) (cm^{-1}): 2953, 1753, 1735, 1603, 1576, 1502, 1452, 1436, 1379, 1352.

N-Benzyl-3-(2,2-bis(phenylsulfonyl)ethyl)-3-methyl-1,2,3,4-tetrahydroquinoline (III-19)



The title compound was prepared according to a modified General Procedure G using salt **III-8** (45 mg, 0.125 mmol) and 1,1-bis(phenylsulfonyl)ethylene (154 mg, 0.5 mmol) as electrophile and HCO_2H:NEt_3 5:2 (84 µL, 1.0 mmol) as the terminal reductant. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-19** (42 mg, 62%) as a white solid.

m.p. (EtOAc): 169 – 171 °C

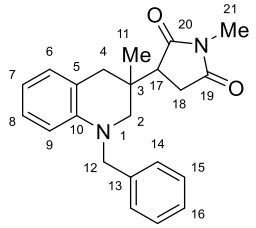
HRMS (ESI): Exact mass calculated for $C_{31}H_{32}NO_4S_2$ $[M+H]^+$: 546.1767, found: 546.1768.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 2H, 2 x C^{Ar}**H**), 7.74 – 7.59 (m, 4H, 4 x C^{Ar}**H**), 7.58 – 7.51 (m, 2H, 2 x C^{Ar}**H**), 7.49 – 7.39 (m, 2H, 2 x C^{Ar}**H**), 7.30 – 7.19 (m, 3H, 3 x C^{Ar}**H**), 7.16 – 6.99 (m, 4H, 2 x C^{Ar}**H** + C^{6}**H** + C^{8}**H**), 6.69 (td, *J* = 7.4, 1.1 Hz, 1H, C^{7}**H**), 6.59 (dd, *J* = 8.3, 1.1 Hz, 1H, C^{9}**H**), 4.59 (t, *J* = 4.0 Hz, 1H, C^{18}**H**), 4.46 (q, *J* = 17.0 Hz, 2H, C^{12}**H$_2$**), 3.14 (dd, *J* = 11.7, 1.2 Hz, 1H, C^{2}**H$_2$**), 3.03 (dd, *J* = 11.6, 2.1 Hz, 1H, C^{2}**H$_2$**), 2.81 (dd, *J* = 16.1, 2.1 Hz, 1H, C^{4}**H$_2$**), 2.57 (d, *J* = 16.1 Hz, 1H, C^{4}**H$_2$**), 2.35 – 2.18 (m, 2H, C^{17}**H$_2$**), 1.12 (s, 3H, C^{11}**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (C^{10}), 138.8 (C^{Ar}), 138.3 (C^{Ar}), 136.7 (C^{Ar}), 134.6 (C^{Ar}H), 134.5 (C^{Ar}H), 130.8 (C^{Ar}H), 130.5 (2 x C^{Ar}H), 129.9 (2 x C^{Ar}H), 129.2 (2 x C^{Ar}H), 129.0 (2 x C^{Ar}H), 128.7 (2 x C^{Ar}H), 127.5 (C^{Ar}H), 127.0 (C^{Ar}H), 126.7 (2 x C^{Ar}H), 119.9 (C^{Ar}), 116.9 (C^{7}H), 111.1 (C^{9}H), 81.1 (C^{18}H), 60.3 ($C^{2}H_2$), 55.3 ($C^{12}H_2$), 39.2 ($C^{4}H_2$), 32.2 (C^{3}), 31.8 ($C^{17}H_2$), 24.2 ($C^{11}H_3$).

IR (neat) (cm^{-1}): 3063, 2924, 1669, 1602, 1500, 1448, 1329, 1287, 1249, 1194.

3-(*N*-Benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-3-yl)-*N*-methylpyrrolidine-2,5-dione (III-20)



The title compound was prepared according to General Procedure G using salt **III-8** (45 mg, 0.125 mmol) and *N*-methylmaleimide (28 mg, 0.25 mmol) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-20** as an inseparable 2:1 diastereomeric mixture (36 mg, 82%) as a clear oil.

HRMS (ESI): Exact mass calculated for $C_{22}H_{25}N_2O_2$ $[M+H]^+$: 349.1911, found: 349.1912.

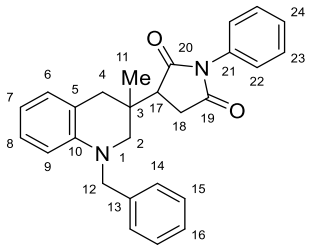
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.15 (m, 10H, 5 x C^{Ar}**H**, *A* + *B*), 7.09 –6.82 (m, 4H, C^8**H**, *A*+*B*, C^8**H**, *A*+*B*), 6.72 – 6.53 (m, 4H, C^9**H**, *A*+*B*, C^7**H**, *A*+*B*), 4.75 – 4.62 (m, 1H, C^{12}**H$_2$**, *B*), 4.57 – 4.47 (m, 2H, C^{12}**H$_2$**, *A*+*B*), 4.39 (d, *J* = 16.6 Hz, 1H, C^{12}**H$_2$**, *A*), 3.86 (dd, *J* = 11.9, 2.2 Hz, 1H, C^2**H$_2$**, *B*), 3.54 – 3.42 (m, 2H, C^4**H$_2$**, *A*, C^2**H$_2$**, *B*), 3.12 – 2.99 (m, 3H, C^{17}**H**, *B*, C^2**H$_2$**, *A*), 3.00 – 2.91 (m, 7H, C^{21}**H$_3$**, *A*+*B*, C^{17}**H**, *A*), 2.84 (d, *J* = 16.1 Hz, 1H, C^4**H$_2$**, *A*), 2.82 – 2.59 (m, 2H, C^4H_2, *B*), 2.58 – 2.48 (m, 2H, C^{18}**H$_2$**, *A*+*B*), 2.45 – 2.30 (m, 2H, C^{18}**H$_2$**, *A*+*B*), 0.95 (s, 3H, C^{11}**H$_3$**, *B*), 0.94 (s, 3H, C^{11}**H$_3$**, *A*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8 ($C^{19}O/C^{20}O$, *B*), 178.6 ($C^{19}O/C^{20}O$, *A*), 176.5 ($C^{19}O/C^{20}O$, *B*), 176.4 ($C^{19}O/C^{20}O$, *A*), 145.7 (C^{10}, *B*), 144.8 (C^{10}, *A*), 139.0 (C^{13}, *B*), 138.7 (C^{13}, *A*), 130.5 (C^8H, *A*), 129.8 (C^8H, *B*), 128.9 (2 x $C^{Ar}H$, *A*/*B*), 128.8 ($C^{Ar}H$, *A*/*B*), 128.7 ($C^{Ar}H$, *A*/*B*), 128.4 ($C^{Ar}H$, *A*/*B*), 127.9 ($C^{Ar}H$, *A*/*B*), 127.6 ($C^{Ar}H$, *A*/*B*), 127.4 ($C^{Ar}H$, *A*/*B*), 127.0 (2 x $C^{Ar}H$, *A*/*B*), 120.5 (C^5, *A*), 120.2 (C^8H, *B*), 118.7 (C^5, *B*), 117.5 (C^7H, *A*), 116.6 (C^7H, *B*), 114.8 (C^8H, *B*), 111.2 (C^9H, *B*), 111.1 (C^9H, *A*), 64.3, 58.7 (C^2H_2, *A*), 58.3 (C^2H_2, *B*), 55.6 ($C^{12}H_2$, *B*), 55.3 ($C^{12}H_2$, *A*), 44.0 ($C^{17}H$, *A*),

43.8 ($C^{17}H$, *B*), 40.3 ($C^{4}H_2$, *B*), 38.8 ($C^{4}H_2$, *A*), 34.3 (C^{3}, *A*), 33.9 (C^{3}, *B*), 30.9 ($C^{18}H_2$, *A*), 30.7 ($C^{18}H_2$, *B*), 24.83 ($C^{21}H_3$, *B*), 24.80 ($C^{21}H_3$, *A*), 19.5 ($C^{11}H_3$, *A*), 19.2 ($C^{11}H_3$, *B*).

IR (neat) (cm^{-1}): 2956, 1771, 1694, 1602, 1498, 1435, 1382, 1355, 1281, 1123.

3-(*N*-Benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-3-yl)-*N*-phenylpyrrolidine-2,5-dione (III-21)



The title compound was prepared according to General Procedure G using salt **III-8** (45 mg, 0.125 mmol) and *N*-phenylmaleimide (43 mg, 0.25 mmol) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-21** as an inseparable 1.5:1 diastereomeric mixture (38 mg, 73%) as a white wax.

HRMS (ESI): Exact mass calculated for $C_{27}H_{27}N_2O_2$ $[M+H]^+$: 411.2067, found: 411.2067.

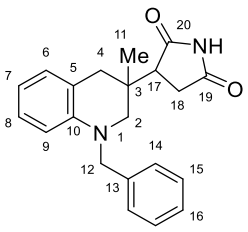
^{1}H NMR (400 MHz, $CDCl_3$, *A* = major diastereomer) δ 7.54 – 7.20 (m, 20H, 20 x C^{Ar}**H**, *A* + *B*), 7.13 – 7.01 (m, 3H, C^{6}**H** + C^{8}**H**, *A*, C^{6}**H**/C^{8}**H**, *B*), 6.98 (dd, *J* = 7.4, 1.6 Hz, 1H, C^{6}**H**/C^{8}**H**, *B*), 6.70 (t, *J* = 7.2 Hz, 2H, C^{7}**H**, *A* + *B*), 6.66 – 6.58 (m, 2H, C^{9}**H**, *A* + *B*), 4.74 (d, *J* = 17.1 Hz, 1H, C^{12}**H$_2$**, *B*), 4.61 – 4.36 (m, 3H, C^{12}**H$_2$**, *A* + *B*), 3.92 (dd, *J* = 12.0, 2.3 Hz, 1H, C^{2}**H$_2$**, *B*), 3.57 (dd, *J* = 16.2, 2.3 Hz, 1H, C^{4}**H$_2$**, *A*), 3.50 (d, *J* = 11.9 Hz, 1H, C^{2}**H$_2$**, *B*), 3.22 (dd, *J* = 8.9, 5.8 Hz, 1H, C^{17}**H**, *B*), 3.18 – 3.06 (m, 3H, C^{2}**H$_2$**, *A*, C^{17}**H**, *A*), 2.94 – 2.63 (m, 6H, C^{4}**H$_2$**, *A* + *B*, $C^{18}H_2$, *A*+*B*), 2.61 – 2.52 (m, 1H, C^{18}**H$_2$**, *A*), 1.09 (s, 3H, C^{11}**H$_3$**, *B*), 1.07 (s, 3H, C^{11}**H$_3$**, *A*).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8 (C^{19}/C^{20}, *B*), 177.5 (C^{19}/C^{20}, *A*), 175.4 (C^{19}/C^{20}, *B*), 175.4 (C^{19}/C^{20}, *A*), 144.9 (C^{10}, *B*), 144.8 (C^{10}, *A*), 139.0 (C^{13}, *B*), 138.7 (C^{13}, *A*), 134.3 (C^{21}, *B*), 132.0 (C^{21}, *A*), 130.6 (C^{6}H/C^{8}H, *A*), 129.8 (C^{6}H/C^{8}H, *B*), 129.31 (C^{Ar}H, *A*/*B*), 129.26 (C^{Ar}H, *A*/*B*), 128.9 (C^{Ar}H, *A*/*B*), 128.8 (C^{Ar}H, *A*/*B*), 128.74 (C^{Ar}H, *A*/*B*), 128.69 (C^{Ar}H, *A*/*B*), 128.0 (C^{Ar}H, *A*/*B*), 127.6

($C^{Ar}H$, *A*/*B*), 127.4 ($C^{Ar}H$, *A*/*B*), 127.0 ($C^{Ar}H$, *A*/*B*), 126.9 ($C^{Ar}H$, *A*/*B*), 126.8 ($C^{Ar}H$, *A*/*B*), 126.6 ($C^{Ar}H$, *A*/*B*), 120.2 (C^{5}, *A*), 118.6 (C^{5}, *B*), 117.53 ($C^{7}H$, *A*), 116.65 ($C^{7}H$, *B*), 111.2 ($C^{9}H$, *A*), 111.1 ($C^{9}H$, *B*), 58.8 ($C^{2}H_2$, *A*), 58.2 ($C^{2}H_2$, *B*), 55.4 ($C^{12}H_2$, *B*), 55.3 ($C^{12}H_2$, *A*), 43.7 ($C^{17}H$, *A*), 43.5 ($C^{17}H$, *B*), 40.4 ($C^{4}H_2$, *B*), 38.8 ($C^{4}H_2$, *A*), 34.7(C^{3}, *A*), 34.2 (C^{3}, *B*), 31.1 ($C^{18}H_2$, *A*), 31.0 ($C^{18}H_2$, *B*), 19.5 ($C^{11}H_3$, *A*), 19.2 ($C^{11}H_3$, *B*).

IR (neat) (cm^{-1}): 2929, 1774, 1707, 1600, 1499. 1453, 1381, 1286, 1180, 1028.

3-(*N*-Benzyl-3-methyl-1,2,3,4-tetrahydroquinolin-3-yl)pyrrolidine-2,5-dione (III-22)



The title compound was prepared according to General Procedure G using salt **III-8** (45 mg, 0.125 mmol) and maleimide (24 mg, 0.25 mmol) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-22** as an inseparable 1.7:1 diastereomeric mixture (28 mg, 67%) as a clear oil.

HRMS (ESI): Exact mass calculated for $C_{21}H_{23}N_2O_2$ $[M+H]^+$: 335.1754, found: 335.1754.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 – 8.14 (m, 2H, NH, *A* + *B*), 7.34 – 7.07 (m, 10H, 10 x C^{Ar}**H**, *A* + *B*), 7.04 – 6.74 (m, 4H, C^{6}**H** + C^{8}**H**, *A* + *B*), 6.63 – 6.45 (m, 4H, C^{7}**H** + C^{9}**H**, *A* + *B*), 4.68 – 4.23 (m, 4H, C^{12}**H$_2$**, *A* + *B*), 3.75 (dd, *J* = 11.9, 2.3 Hz, 1H, C^{4}**H$_2$**, *B*), 3.43 – 3.31 (m, 2H, C^{2}**H$_2$**, *A*, C^{4}**H$_2$**, *B*), 3.04 – 2.98 (m, 1H, C^{17}**H**,*B*), 2.98 – 2.89 (m, 3H, C^{4}**H$_2$** + C^{17}**H**, *A*), 2.75 (d, *J* = 16.2 Hz, 1H, C^{2}**H$_2$**, *A*), 2.70 – 2.41 (m, 4H, C^{2}**H$_2$**, *B*, C^{18}**H$_2$**, *A* + *B*), 2.39 – 2.29 (m, 1H, C^{18}**H$_2$**, *A*), 0.95 (s, 3H, C^{11}**H$_3$**, *B*), 0.93 (s, 3H, C^{11}**H$_3$**, *A*).

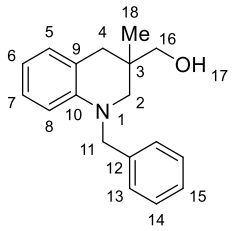
Major diastereoisomer A: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.9 (C^{19}O/ C^{20}O), 176.45 (C^{19}O/ C^{20}O), 144.79 (C^{10}), 138.6 (C^{13}), 130.6 (C^{8}H), 128.9 (2 x C^{14}H/C^{15}H), 127.6 (C^{6}H), 127.4 (C^{16}H), 127.02

(2 x $C^{14}H/C^{15}H$), 120.2 (C^{5}), 117.5 ($C^{7}H$), 111.17 ($C^{9}H$), 58.6 ($C^{2}H_2$), 55.3 ($C^{12}H_2$), 45.2 ($C^{17}H$), 38.7 ($C^{4}H_2$), 34.3 (C^{3}), 32.0 ($C^{18}H_2$), 19.5 ($C^{11}H_3$).

Minor diasteroisomer B: **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.0 ($C^{19}O$/ $C^{20}O$), 176.50 ($C^{19}O$/ $C^{20}O$), 144.83 (C^{10}), 139.0 (C^{13}), 129.8 ($C^{8}H$), 128.7 (2 x $C^{14}H/C^{15}H$), 127.9 ($C^{6}H$), 126.95 ($C^{16}H$), 126.8 (2 x $C^{14}H/C^{15}H$), 118.6 (C^{5}), 116.7 ($C^{7}H$), 111.21 ($C^{9}H$), 58.1 ($C^{2}H_2$), 55.5 ($C^{12}H$), 44.9 ($C^{17}H$), 40.2 ($C^{4}H_2$), 33.9 (C^{3}), 31.9 ($C^{18}H_2$), 19.3 ($C^{11}H_3$).

IR (neat) (cm^{-1}): 3221, 1776, 1701, 1600, 1497, 1453, 1350, 1179, 908, 727.

N-Benzyl-3-(hydroxymethyl)-3'-methyl-1,2,3,4-tetrahydroquinoline (III-23)

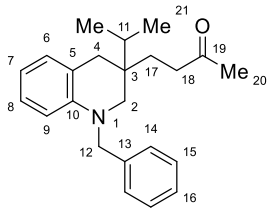


The title compound was prepared according to General Procedure G using salt **III-8** (45 mg, 0.125 mmol) and formaldehyde (19 µL, 0.25 mmol, 37 wt.% in H_2O) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-23** (19 mg, 57%) as a pale-yellow oil. Spectroscopc data was consistent with that reported in the literature.[74]

^{1}H NMR (400 MHz, CDCl3) δ 7.40 – 7.26 (5H, m, $C^{Ar}H$), 7.09 – 7.03 (2H, m, 2H, $C^{5}H$ + $C^{7}H$), 6.69 – 6.62 (2H, m, $C^{6}H$ + $C^{8}H$), 4.59 – 4.47 (2H, m, $C^{9}H2$), 3.55 (1H, d, *J* = 10.8 Hz, $C^{16}H2$), 3.48 (1H, d, *J* = 10.8 Hz, $C^{16}H2$), 3.24 (1H, dd, *J* = 11.5, 1.7 Hz, $C^{2}H2$), 3.10 (1H, d, *J* = 11.5 Hz, $C^{2}H2$), 2.72 (1H, d, *J* = 16.1 Hz, $C^{4}H2$), 2.62 (1H, d, *J* = 16.1 Hz, $C^{4}H2$), 1.74 (1H, bs, OH), 1.09 (3H, s, $C^{18}H3$).

^{13}C NMR (101 MHz, CDCl3) δ 145.1 (C^{10}), 139.5 (C^{9}), 130.2 ($C^{Ar}H$), 129.0 (C^{Ar}), 127.5 ($C^{Ar}H$), 127.3 (2 x $C^{Ar}H$), 127.0 ($C^{Ar}H$), 120.8 (2 x $C^{Ar}H$), 116.0 ($C^{6}H$), 111.3 ($C^{8}H$), 69.2 ($C^{16}H_2$), 57.0 ($C^{2}H_2$), 55.7 ($C^{9}H_2$), 37.4 ($C^{4}H_2$), 34.1 (C^{3}), 22.3 ($C^{18}H_3$).

4-(*N*-Benzyl-3-isopropyl-1,2,3,4-tetrahydroquinolin-3-yl)butan-2-one (III-54)



The title compound was prepared according to General Procedure G using salt **III-42** (45 mg, 0.125 mmol) and methyl vinyl ketone (50 µL, 0.63 mmol) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-54** (25 mg, 60%) as a yellow oil.

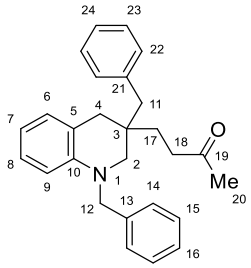
HRMS (ESI): Exact mass calculated for $C_{23}H_{30}NO$ $[M+H]^+$: 336.2322, found: 336.2320.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 5H, 2 x C^{14}**H** + 2 x C^{15}**H** + C^{16}**H**), 7.04 – 6.96 (m, 2H, C^6**H** + C^8**H**), 6.61 (td, *J* = 7.3, 1.1 Hz, 1H, C^7**H**), 6.57 (dd, *J* = 8.7, 1.1 Hz, 1H, C^9**H**), 4.52 (d, *J* = 16.8 Hz, 1H, C^{12}**H$_2$**), 4.42 (d, *J* = 16.8 Hz, 1H, C^{12}**H$_2$**), 3.19 (dd, *J* = 11.6, 1.0 Hz, 1H, C^2**H$_2$**), 2.93 (dd, *J* = 11.6, 2.1 Hz, 1H, C^{11}**H$_2$**), 2.79 (d, *J* = 15.9 Hz, 1H, C^4**H$_2$**), 2.48 (dd, *J* = 16.0, 2.1 Hz, 1H, C^4**H$_2$**), 2.42 – 2.22 (m, 2H, C^{18}**H$_2$**), 2.05 (s, 3H, C^{20}**H$_3$**), 1.80 – 1.53 (m, 3H, C^{11}**H** + C^{17}**H$_2$**), 0.90 (dd, *J* = 6.9, 2.0 Hz, 6H, 2 x C^{21}**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0 (C^{19}), 145.2 (C^{10}), 139.2 (C^{13}), 130.0 (C^6H/C^8H), 128.7 (2 x C^{14}H/C^{15}H), 127.1 (C^6H/C^8H/C^{15}H), 127.01 (C^6H/C^8H/C^{15}H), 126.97 (2 x C^{14}H/C^{15}H), 121.2 (C^5), 116.7 (C^7H), 111.0 (C^9H), 55.7 (C^2H$_2$/C^{12}H$_2$), 55.6 (C^2H$_2$/C^{12}H$_2$), 38.4 (C^4H$_2$), 35.4 (C^3 + C^{18}H$_2$), 35.2 (C^3 + C^{18}H$_2$), 31.4 (C^{11}H), 30.0 (C^{20}H$_3$), 26.2 (C^{17}H$_2$), 17.3 (C^{21}H$_3$), 17.0 (C^{21}H$_3$).

IR (neat) (cm^{-1}): 3027, 2959, 1715, 1602, 1576, 1506, 1452, 1387, 1354, 1280.

4-(*N*-Benzyl-3-benzyl-1,2,3,4-tetrahydroquinolin-3-yl)butan-2-one (III-55)



The title compound was prepared according to General Procedure G using salt **II-43** (45 mg, 0.125 mmol) and methyl vinyl ketone (50 µL, 0.63 mmol) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-55** (43 mg, 90%) as a yellow oil.

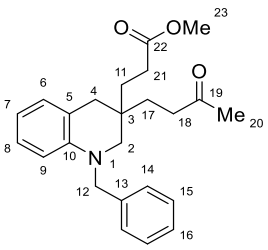
HRMS (ESI): Exact mass calculated for $C_{27}H_{30}NO$ $[M+H]^+$: 384.2322, found: 384.2322.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.18 (m, 8H, 8 x C^{Ar}**H**), 7.12 – 6.96 (m, 4H, 4 x C^{Ar}**H**), 6.68 – 6.59 (m, 2H, C^7**H** + C^9**H**), 4.60 (d, *J* = 16.9 Hz, 1H, C^{12}**H$_2$**), 4.42 (d, *J* = 16.9 Hz, 1H, C^{12}**H$_2$**), 3.07 (brs, *J* = 1.5 Hz, 2H, C^2**H$_2$**), 2.74 – 2.54 (m, 4H, C^4**H$_2$+** C^{11}**H$_2$**), 2.54 – 2.32 (m, 2H, C^{18}**H$_2$**), 2.09 (s, 3H, C^{20}**H$_3$**), 1.73 – 1.48 (m, 2H, C^{17}**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6 (C^{19}), 144.6 (C^{10}), 138.9 (C^{13}), 137.7 (C^{Ar}), 130.6 (2 x C^{Ar}H), 130.1 (C^{Ar}H), 128.7 (2 x C^{Ar}H), 128.2 (2 x C^{Ar}H), 127.4 (C^{Ar}H), 127.04 (C^{Ar}H), 126.99 (2 x C^{Ar}H), 126.5 (C^{Ar}H), 120.3 (C^5), 116.7 (C^7H/C^9H), 111.1 (C^7H/C^9H), 57.8 (C^2H_2), 55.5 ($C^{12}H_2$), 41.7 (C^4H_2/$C^{11}H_2$), 38.3 (C^4H_2/$C^{11}H_2$), 38.1 ($C^{18}H_2$), 34.6 (C^3), 30.1 ($C^{20}H_3$), 29.0 ($C^{17}H_2$).

IR (neat) (cm^{-1}): 3061, 3027, 2920, 1714, 1602, 1576, 1499, 1452, 1354, 1286.

Methyl 3-(*N*-benzyl-3-(3-oxobutyl)-1,2,3,4-tetrahydroquinolin-3-yl)propanoate (III-56)



The title compound was prepared according to General Procedure G using salt **III-44** (45 mg, 0.125 mmol) and methyl vinyl ketone (50 μL, 0.63 mmol) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-56** (39 mg, 82%) as a clear oil.

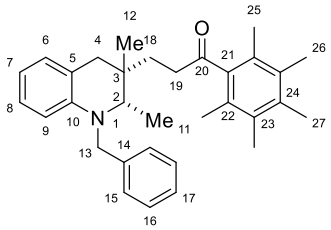
HRMS (ESI): Exact mass calculated for $C_{24}H_{30}NO_3$ $[M+H]^+$: 380.2220, found: 380.2219.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 5H, 2 x C^{14}**H** + 2 x C^{15}**H** + C^{16}**H**), 7.05 – 6.93 (m, 2H, C^6**H** + C^8**H**), 6.66 – 6.56 (m, 2H, C^7**H** + C^9**H**), 4.57 – 4.34 (m, 2H, C^{12}**H$_2$**), 3.65 (s, 3H, C^{23}**H$_3$**), 3.01 (s, 2H, C^4**H$_2$**), 2.62 (s, 2H, C^4**H$_2$**), 2.48 – 2.15 (m, 4H, C^{18}**H$_2$** + C^{21}**H$_2$**), 2.10 (s, 3H, C^{20}**H$_3$**), 1.79 – 1.47 (m, 4H, C^{11}**H$_2$** + C^{17}**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4 (C^{19}O), 174.2 (C^{20}O), 144.8 (C^{10}), 138.9 (C^5), 130.0 (C^{6}H/C^{8}H), 128.7 (2 x C^{14}H/C^{15}H), 127.4 (C^{6}H/C^{8}H), 127.1 (C^{16}H), 126.9 (2 x C^{14}H/C^{15}H), 120.0 (C^{13}), 116.8 (C^{7}H/C^{9}H), 111.1 (C^{7}H/C^{9}H), 57.6 (C^{2}H$_2$), 55.4 (C^{12}H$_2$), 51.8 (C^{23}H$_3$), 39.0 (C^{4}H$_2$), 37.6 (C^{18}H$_2$/C^{21}H$_2$), 32.9 (C^3), 30.1 (C^{20}H$_3$), 29.9 (C^{11}H$_2$/C^{17}H$_2$), 28.4 (C^{18}H$_2$/C^{21}H$_2$), 28.3 (C^{11}H$_2$/C^{17}H$_2$).

IR (neat) (cm^{-1}): 3027, 2925, 1734, 1715, 1602, 1502, 1452, 1436, 1354, 1320.

3-(*N*-Benzyl-2,3-dimethyl-1,2,3,4-tetrahydroquinolin-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one (III-57)



The title compound was prepared according to General Procedure H using salt **III-45** (45 mg, 0.125 mmol) and 2,3,4,5,6-pentamethylphenyl vinyl ketone (51 mg, 0.25 mmol) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-57** (22 mg, 32%) as an inseparable 2:1 diastereomeric mixture as a white wax.

The title compound could not be prepared according to General procedure G and only starting material was recovered from the reaction.

HRMS (ESI): Exact mass calculated for $C_{32}H_4NO$ $[M+H]^+$: 545.3104, found: 545.3102.

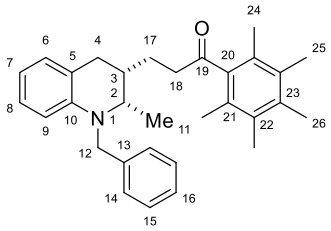
^{1}H NMR (400 MHz, CDCl3) δ 7.35 – 7.17 (m, 10H, 2 x C^{15}**H** + 2 x C^{16}**H** + C^{17}**H**, *A* + *B*), 7.04 – 6.91 (m, 3H, C^6**H** + C^8**H**, *A* + *B*), 6.66 – 6.55 (m, 2H, C^7**H**, *A* + *B*), 6.46 (dd, J = 8.3, 1.1 Hz, 1H, C^9**H**, *A*), 6.40 (d, J = 8.1 Hz, 1H, C^9**H**, *B*), 4.73 (d, J = 16.7 Hz, 1H, C^{13}**H$_2$**, *B*), 4.58 – 4.34 (m, 3H, C^{13}**H$_2$**, *A* + *B*), 3.27 – 3.20 (m, 1H, C^2**H**, *B*), 3.12 – 2.99 (m, 1H, C^2**H$_2$**, *A*), 2.84 (dd, J = 16.4, 3.7 Hz, 2H, C^4**H$_2$**, *A* + *B*), 2.80 – 2.53 (m, 4H, C^{19}**H$_2$**, *A* + *B*), 2.51 – 2.37 (m, 2H, C^4**H$_2$**, *A* + C^{13}**H$_2$**, *B*), 2.29 – 1.94 (m, 30H, 2 x C^{25}**H$_3$** + 2 x C^{26}**H$_3$** + C^{27}**H$_3$**, *A* + *B*), 1.94 – 1.67 (m, 4H, C^{18}**H$_2$**, *A* + *B*), 1.12 – 1.04 (m, 6H, C^{11}**H$_3$**, *A* + *B*), 1.03 (s, 3H, C^{12}**H$_3$**, *A*), 0.99 (s, 3H, C^{12}**H$_3$**, *B*).

Major diastereoisomer *A*: **^{13}C NMR** (151 MHz, CDCl3) δ 212.0 (C^{20}O), 143.5 (C^{10}), 141.0 (C^{21}), 139.8 (C^{14}), 135.6 (C^{Ar}), 133.3 (2 x C^{Ar}), 129.8 (C^6H/C^8H), 128.6 (2 x C^{15}H/C^{16}H), 127.3 (2 x C^{Ar} + C^6H/C^8H), 127.14 (C^{17}H), 126.8 (2 x C^{15}H/C^{16}H), 120.0 (C^5), 116.2 (C^7H), 111.9 (C^9H), 62.0 (C^2H), 54.8 ($C^{12}H_2$), 40.0 ($C^{19}H_2$), 36.74 (C^4H_2), 33.7 (C^3), 33.1 ($C^{18}H_2$), 23.83 ($C^{12}H_3$), 17.4 (2 x $C^{25}H_3$/$C^{26}H_3$), 16.81 ($C^{27}H_3$), 16.09 (2 x $C^{25}H_3$/$C^{26}H_3$), 13.9 ($C^{11}H_3$).

Minor diastereoisomer *B*: **^{13}C NMR** (151 MHz, CDCl3) δ 212.1 (C^{20}O), 143.6 (C^{10}), 141.1 (C^{21}), 139.7 (C^{14}), 135.4 (C^{Ar}), 133.1 (2 x C^{Ar}), 129.5 (C^6H/C^8H), 128.7 (2 x C^{15}H/C^{16}H), 127.4 (2 x C^{Ar} + C^6H/C^8H), 127.11 (C^{17}H), 126.9 (2 x C^{15}H/C^{16}H), 120.2 (C^5), 116.4 (C^7H), 112.2 (C^9H), 61.6 (C^2H), 55.0 ($C^{13}H_2$), 40.3 ($C^{19}H_2$), 36.69 (C^4H_2), 33.8 (C^3), 31.8 ($C^{18}H_2$), 23.77 ($C^{12}H_3$), 17.3 (2 x $C^{25}H_3$/$C^{26}H_3$), 16.78 ($C^{27}H_3$), 16.07 (2 x $C^{25}H_3$/$C^{26}H_3$), 14.3 ($C^{11}H_3$).

IR (neat) (cm^{-1}): 3029, 2923, 1698, 1602, 1497, 1451, 1315, 1116, 1027, 909.

3-(*N*-Benzyl-2-methyl-1,2,3,4-tetrahydroquinolin-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one (III-58)



The title compound was prepared according to General Procedure H using salt **III-46** (45 mg, 0.125 mmol) and 2,3,4,5,6-pentamethylphenyl vinyl ketone (37 mg, 0.19 mmol) as electrophile. Purification by column chromatography (0%-5% EtOAc in pentane) gave *amine* **III-58** (18 mg, 33%) as an inseparable 5:1 diastereomeric ratio as a white wax.

The title compound could not be prepared according to General procedure G and only starting material was recovered from the reaction.

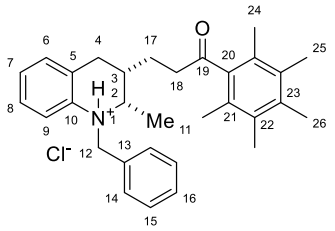
HRMS (ESI): Exact mass calculated for $C_{31}H_{38}NO$ $[M+H]^+$: 440.2948, found: 440.2946.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.18 (m, 10H, 5 x C^{Ar}**H**, *A* + *B*), 7.05 – 6.89 (m, 4H, C^6**H**, *A* + *B*, C^8**H**, *A* + *B*), 6.64 – 6.54 (m, 2H, C^7**H** /C^9**H**, *A* + *B*), 6.45 – 6.37 (m, 2H, C^7**H** /C^9**H**, *A* + *B*), 4.58 – 4.39 (m, 4H, C^{12}**H$_2$**, *A* + *B*), 3.51 – 3.41 (m, 1H, C^2**H**, *A*), 3.39 – 3.29 (q, 1H, C^2**H**, *B*), 2.94 – 2.61 (m, 8H, C^4**H$_2$**, *A* + *B*, C^{18}**H$_2$**, *A* + *B*), 2.28 – 2.00 (m, 32H, C^3**H**, *A* + *B, 2 x* C^{23}**H$_3$**, *A* + *B*, 2 x C^{24}**H$_3$**, *A* + *BI,* C^{26}**H$_3$**, *A* + *B*), 1.87 – 1.73 (m, 4H, C^{17}**H$_2$**, *A* + *B*), 1.19 (d, *J* = 6.5 Hz, 3H, C^{11}**H$_3$**, *B*) 1.07 (d, *J* = 6.5 Hz, 3H, C^{11}**H$_3$**, *A*).

^{13}C NMR (151 MHz, $CDCl_3$, only major diastereomer *A* reported) δ 211.6 (C^{19}O), 144.1 (C^{10}), 140.8 (C^{20}), 139.4 (C^{13}), 135.6 (C^{23}), 133.3 (2 x C^{21}/C^{22}), 129.2 (C^6H/C^8H), 128.7 (2 x C^{14}H/C^{15}H), 127.4 (C^6H/C^8H/2 x C^{Ar}), 127.3 (C^6H/C^8H/2 x C^{Ar}), 126.9 (C^{16}H), 126.5 (2 x C^{14}H/C^{15}H), 120.9 (C^5), 115.8 (C^7H), 111.7 (C^9H), 57.1 (C^2H), 54.0 ($C^{12}H_2$), 43.5 (C^4H_2), 36.0 (C^3H), 29.9 ($C^{18}H_2$), 26.6 ($C^{17}H_2$), 17.4 (2 x $C^{24}H_3$/$C^{25}H_3$), 16.8 ($C^{26}H_3$), 16.1 (2 x $C^{24}H_3$/$C^{25}H_3$), 12.2 ($C^{11}H_3$).

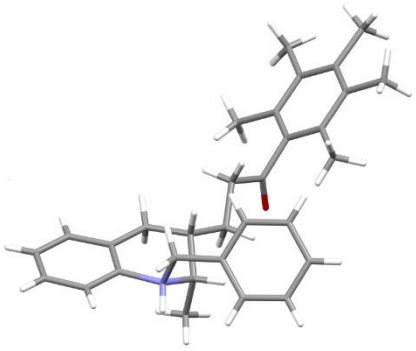
IR (neat) (cm^{-1}): 2924, 1699. 1602, 1499, 1451, 1377, 1353, 1251. 743, 697.

3-(*N*-Benzyl-2-methyl-1,2,3,4-tetrahydroquinolin-3-yl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one (III-58·HCl)



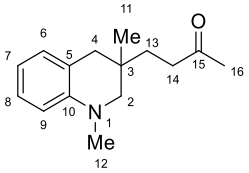
In a 25 mL round bottom flask under argon was charged quinoline product **III-58** (35 mg, 0.08 mmol, 1.0 eq.) in dry diethyl ether (1.5 mL). The solution was chilled to 0 °C and 2M HCl in diethyl ether (0.06 mL, 0.12 mmol, 1.5 eq.) was introduced dropwise. After 15 minutes the solids were collected via filtration to give the title compound **III-58·HCl** (38 mg, 99%) as a white solid. A single crystal for X-ray diffraction was obtained by slow evaporation from the CH_2Cl_2/heptane solvent system.

^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 7.92 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.78 – 7.74(m, 2H), 7.42 – 7.38 (m, 2H), 7.34 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.30 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.26 – 7.21 (m, 2H), 4.80 (d, *J* = 13.0 Hz, 1H), 4.35 (d, *J* = 13.1 Hz, 1H), 3.67 (dd, *J* = 6.8, 3.0 Hz, 1H), 3.02 (dd, *J* = 16.6, 4.9 Hz, 1H), 2.94 (t, *J* = 7.5 Hz, 1H), 2.73 – 2.49 (m, 2H), 2.25 (s, 3H), 2.20 (s, 6H), 2.14 (d, J = 7.1 Hz, 1H), 2.07 (s, 6H), 2.00 (s, 1H), 1.85 (d, *J* = 6.6 Hz, 1H), 1.79 – 1.67 (m, 1H), 1.41 (d, *J* = 6.8 Hz, 3H).



Crystal data $C_{31}H_{38}ClNO$ = 476.10, triclinic, a = 9.2443(4), b = 16.6064(5), c = 18.4379(7) Å, β = 97.470(3)°, Z = 4, T = 300 K, space group P-1, 28854 reflections measured, 11191 unique (R_{int} = 0.049), which were used in all calculations.

4-(1,3-Dimethyl-1,2,3,4-tetrahydroquinolin-3-yl)butan-2-one (III-59)



The title compound was prepared according to General Procedure G using quinolinium salt **III-47** (36 mg, 0.125 mmol) and methyl vinyl ketone (50 µL, 0.63 mmol) as electrophile. Purification by column chromatography (0-10% EtOAc in pentane) furnished *amine* **III-59** (23 mg, 78%) as a light-yellow oil.

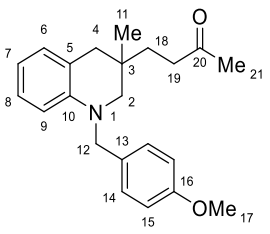
HRMS (ESI): Exact mass calculated for $C_{15}H_{22}NO$ $[M+H]^+$: 232.1696, found: 232.1698.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.04 (m, 1H, C^8**H**), 6.93 (d, *J* = 1.1 Hz, 1H, C^6**H**), 6.66 – 6.56 (m, 2H, C^7**H** + C^9**H**), 2.95 – 2.83 (m, 5H, C^2**H$_2$** + C^{12}**H$_3$**), 2.60 – 2.51 (m, 2H, C^4**H$_2$**), 2.51 – 2.43 (m, 2H, C^{14}**H$_2$**), 2.14 (s, 3H, C^{16}**H$_3$**), 1.69 – 1.52 (m, 2H, C^{13}**H$_2$**), 0.95 (s, 3H, C^{11}**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1 (C^{15}), 145.6 (C^{10}), 129.6 (C^6H), 127.2 (C^8H), 121.1 (C^5), 116.5 (C^7H), 110.8 (C^9H), 61.4 (C^2H_2), 40.3 (C^4H_2), 39.3 ($C^{12}H_3$), 38.6 ($C^{14}H_2$), 32.7 ($C^{13}H_2$), 30.9 (C^3), 30.0 ($C^{16}H_3$), 23.6 ($C^{11}H_3$).

IR (neat) (cm^{-1}): 3657, 2980, 1714, 1603, 1503, 1461, 1375, 1278, 1160, 747.

4-(*N*-(4-Methoxybenzyl)-3-methyl-1,2,3,4-tetrahydroquinolin-3-yl)butan-2-one (III-60)



The title compound was prepared according to General Procedure G using quinolinium salt **III-48** (49 mg, 0.125 mmol) and methyl vinyl ketone (50 µL, 0.63 mmol) as electrophile. Purification by column chromatography (0-10% EtOAc in pentane) furnished *amine* **III-60** (33 mg, 77%) as a pale yellow oil.

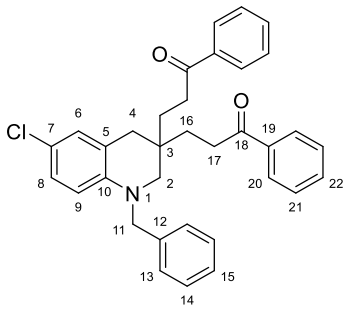
HRMS (ESI): Exact mass calculated for $C_{22}H_{28}NO_2$ $[M+H]^+$: 338.2115, found: 338.2112.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.9 Hz, 2H, 2 x C^{14}**H**), 7.01 (ddd, *J* = 8.2, 7.3, 1.7 Hz, 1H, C^8**H**), 7.00 – 6.92 (m, 1H, C^6**H**), 6.86 (d, *J* = 8.7 Hz, 2H, 2 x C^{15}**H**), 6.64 – 6.55 (m, 2H, C^7**H** + C^9**H**), 4.48 – 4.33 (m, 2H, C^{12}**H$_2$**), 3.79 (s, 3H, C^{17}**H$_3$**), 3.05 – 2.93 (m, 2H, C^4**H$_2$**), 2.58 (s, 2H, C^2**H$_2$**), 2.50 – 2.30 (m, 2H, C^{19}**H$_2$**), 2.11 (s, 3H, C^{21}**H$_3$**), 1.70 – 1.52 (m, 2H, C^{18}**H$_2$**), 0.96 (s, 3H, C^8**H$_3$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0 ($C^{20}O$), 158.7 (C^{16}), 144.8 (C^{10}), 131.1 (C^{Ar}), 129.9 (C^6H), 128.0 (2 x $C^{14}H$), 127.3 (C^8H), 120.6 (C^{Ar}), 116.4 (C^7H/C^9H), 114.1 (2 x $C^{15}H$), 110.9 (C^7H/C^9H), 59.5 (C^4H_2), 55.4 ($C^{17}H_3$), 54.8 ($C^{12}H_2$), 40.7 (C^2H_2), 38.4 ($C^{19}H_2$), 32.5 ($C^{18}H_2$), 30.8 (C^3), 30.0 ($C^{21}H_2$), 23.5 ($C^{11}H_3$).

IR (neat) (cm^{-1}): 2980, 1714, 1603, 1509, 1457, 1352, 1282, 1244, 1170, 1034.

3,3'-(*N*-Benzyl-6-chloro-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(1-phenylpropan-1-one) (III-61)



The title compound was prepared according to General Procedure G using quinolinium salt **III-49** (48 mg, 0.125 mmol) and phenyl vinyl ketone (66 mg, 0.50 mmol) as electrophile. Purification by column chromatography (5-20% EtOAc in pentane) gave *amine* **III-61** (38 mg, 58%) as a pale-yellow solid.

m.p. (EtOAc): 148 – 150 °C.

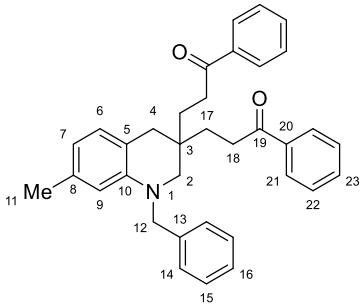
HRMS (ESI): Exact mass calculated for $C_{34}H_{32}NO_2Cl$ $[M+H]^+$: 522.2205, found: 522.2196.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.80 (m, 4H, 4 x C^{20}**H**), 7.60 – 7.51 (m, 2H, 2 x C^{22}**H**), 7.46 – 7.37 (m, 4H, 4 x C^{21}**H**), 7.31 – 7.12 (m, 5H, 5 x C^{Ar}H), 7.02 – 6.90 (m, 2H, C^7**H** + C^8**H**), 6.51 (d, *J* = 8.7 Hz, 1H, C^9**H**), 4.45 (s, 2H, C^{11}**H$_2$**), 3.13 (s, 2H, C^4**H$_2$**), 3.06 – 2.78 (m, 4H, 2 x C^{17}**H$_2$**), 2.71 (s, 2H, C^2**H$_2$**), 1.92 – 1.74 (m, 4H, 2 x C^{16}**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6 (2 x C^{18}O), 151.6 (C^7Cl), 146.0 (C^{Ar}), 137.6 (2 x C^{Ar}), 136.8 (C^{Ar}), 133.3 (2 x C^{22}H), 129.0 (2 x C^{13}H/C^{14}H), 128.8 (4 x C^{21}H), 128.1 (4 x C^{20}H), 127.5 (C^6H + C^8H + C^{15}H), 126.7 (2 x C^{14}H/C^{13}H), 114.8 (C^9H), 113.8 (C^{Ar}), 112.2 (C^6H), 57.5 (C^4H_2), 56.1 ($C^{11}H_2$), 35.3 (C^2H_2), 32.6 (C^3), 32.4 (2 x $C^{17}H_2$), 29.0 (2 x $C^{16}H_2$).

IR (neat) (cm^{-1}): 3059, 2159, 2028, 1686, 1596, 1503, 1447, 1298, 1278, 1222.

3,3'-(*N*-Benzyl-7-methyl-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(1-phenylpropan-1-one) (III-62)



The title compound was prepared according to General Procedure H using quinolinium salt **III-50** (45 mg, 0.125 mmol) and phenyl vinyl ketone (66 mg, 0.50 mmol) as electrophile. Purification by column chromatography (5-20% EtOAc in pentane) gave *amine* **III-62** (27 mg, 44%) as a pale brown solid.

General procedure G afforded the title compound in a significantly reduced yield of 29%.

m.p. (EtOAc): 123 – 125 °C

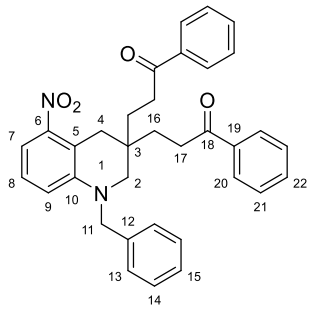
HRMS (ESI): Exact mass calculated for $C_{35}H_{35}NO_2$ $[M+H]^+$: 502.2741, found: 502.2741.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.78 (m, 4H, 4 x C^{21}**H**), 7.55 – 7.45 (m, 2H, 2 x C^{23}**H**), 7.43 – 7.34 (m, 4H, 4 x C^{22}**H**), 7.29 – 7.08 (m, 5H, 5 x C^{Ar}H), 6.88 (d, *J* = 7.8 Hz, 1H, C^6**H**), 6.48 – 6.41 (m, 2H, C^7**H** + C^9**H**), 4.44 (s, 2H, C^{12}**H$_2$**), 3.07 (s, 2H, C^4**H$_2$**), 3.00 – 2.78 (m, 4H, 2 x C^{18}**H$_2$**), 2.69 (s, 2H, C^2**H$_2$**), 2.19 (s, 3H, C^{11}**H$_3$**), 1.90 – 1.71 (m, 4H, 2 x C^{17}**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1 (2 x C^{19}O), 144.9 (C^{10}), 139.1 (C^{13}), 137.1 (C^8), 137.0 (2 x C^{20}), 133.1 (2 x C^{23}H), 129.9 (C^6H), 128.73 (2 x C^{14}H), 128.67 (4 x C^{22}H), 128.2 (4 x C^{21}H), 127.2 (2 x C^{15}H), 127.1 (C^{16}H), 117.8 (C^7H), 117.3 (C^5), 111.7 (C^9H), 57.7 (C^4H_2), 55.3 ($C^{12}H_2$), 39.1 (C^2H_2), 33.3 (C^3), 32.7 (2 x $C^{18}H_2$), 29.2 (2 x $C^{17}H_2$), 21.7 ($C^{11}H_3$).

IR (neat) (cm^{-1}): 3657, 2980, 2921, 1682, 1512, 1449, 1379, 1251, 1158, 741.

3,3'-(*N*-Benzyl-5-nitro-1,2,3,4-tetrahydroquinoline-3,3-diyl)bis(1-phenylpropan-1-one) (III-63)



The title compound was prepared according to General Procedure G using quinolinium salt **III-51** (49 mg, 0.125 mmol) and phenyl vinyl ketone (66 mg, 0.50 mmol) as electrophile. Purification by column chromatography (5-20% EtOAc in pentane) gave *amine* **III-63** (22 mg, 33%) as an orange solid.

m.p. (EtOAc): 168 – 170 °C

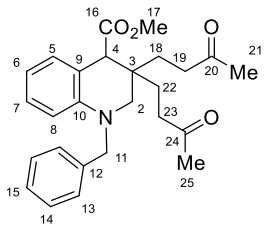
HRMS (ESI): Exact mass calculated for $C_{34}H_{32}N_2O_4$ $[M+H]^+$: 533.446, found: 533.2434.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 4H, 4 x C^{20}**H**), 7.51 – 7.42 (m, 2H, 2 x C^{22}**H**), 7.35 (dd, *J* = 8.4, 7.0 Hz, 4H, 4 x C^{21}**H**), 7.22 – 7.05 (m, 5H, 5 x C^{Ar}H), 7.04 – 6.95 (m, 2H, C^7**H** + C^8**H**), 6.69 (dd, *J* = 6.4, 3.2 Hz, 1H, C^9**H**), 4.47 (s, 2H, C^{11}**H$_2$**), 3.15 (s, 2H, C^4**H$_2$**), 3.01 – 2.88 (m, 2H, 2 x C^{17}**H$_2$**), 2.84 – 2.72 (m, 4H, C^2**H$_2$** + 2 x C^{17}**H$_2$**), 1.86 – 1.65 (m, 4H, 2 x C^{16}**H$_2$**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.6 (2 x C^{18}O), 151.6 (C^6), 146.0 (C^{10}), 137.6 (2 x C^{Ar}), 136.8 (C^{Ar}), 133.3 (2 x C^{22}H), 129.0 (2 x C^{13}H/C^{14}H), 128.8 (4 x C^{20}H/C^{21}H), 128.1 (4 x C^{20}H/C^{21}H), 127.5 (C^8H + C^{15}), 126.7 (2 x C^{13}H/C^{14}H), 114.8 (C^9H), 113.8 (C^{Ar}), 112.2 (C^7H), 57.5 (C^4H_2), 56.1 ($C^{11}H_2$), 35.3 (C^2H_2), 32.6 (C^3), 32.4 (2 x $C^{17}H_2$), 29.0 (2 x $C^{16}H_2$).

IR (neat) (cm^{-1}): 3061, 2922, 1680, 1600, 1521, 1496, 1449, 1350, 1288, 1213.

Methyl 1-benzyl-3,3-bis(3-oxobutyl)-1,2,3,4-tetrahydroquinoline-4-carboxylate (III-64)



The title compound was prepared according to General Procedure G using quinolinium salt **III-52** (50 mg, 0.12 mmol, 1.0 eq.), MVK (33 mg, 0.43 mmol, 3.5 eq.) and 5:2 HCO_2H:Et_3N (41 mL, 0.46 mmol, 4.0 eq.) in MeCN (0.1 mL) and was purified by column chromatography (pentane:EtOAc = 30:1 to 4:1) to furnish diketone **III-64** (36 mg, 69%) as a light-yellow oil.

HRMS (ESI): Exact mass calculated for $C_{26}H_{32}NO_4$ $[M+H]^+$: 422.2326 found: 422.2325.

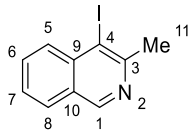
^{1}H NMR (400 MHz, $CDCl_3$) d 7.36 – 7.28 (m, 2H, C^{13}**H**), 7.27 – 7.20 (m, 3H, C^{14}**H** + C^{15}**H**), 7.11 – 6.98 (m, 2H, C^5**H** + C^6**H**), 6.65 (dd, *J* = 8.4, 1.1 Hz, 1H, C^8**H**), 6.60 (td, *J* = 7.3, 1.1 Hz, 1H, C^7**H**), 4.60 (d, J = 16.9 Hz, 1H, C^{11}**H$_a$**), 4.47 (d, *J* = 16.9 Hz, 1H, C^{11}**H$_b$**), 3.66 (s, 3H, C^{17}**H$_3$**), 3.63 – 3.70 (d, *J* = 12.0, 1H, C^2**H$_a$**) 3.50 (d, *J* = 2.1 Hz, 1H, C^4**H**), 2.78 (dd, *J* = 12.0, 2.1 Hz, 1H, C^2**H$_b$**), 2.62 (ddd, *J* = 17.4, 10.9, 5.0 Hz, 1H, C^{19}**H$_a$**), 2.41 (ddd, *J* = 17.1, 10.9, 5.5 Hz, 1H, C^{19}**H$_b$**), 2.27 – 2.10 (m, 5H, C^{23}**H$_2$** + C^{21}**H$_3$**), 2.00 (s, 3H, C^{25}**H$_3$**), 1.69 – 1.37 (m, 4H, C^{18}**H$_2$** + C^{22}**H$_2$**).

^{13}C NMR (151 MHz, $CDCl_3$) d 208.0 ($C^{20}O$), 207.8 ($C^{24}O$), 173.6 (C^{16}), 144.1 (C^{10}), 138.6 (C^{12}), 130.3 ($C^{5}H$), 129.0 ($C^{7}H$), 128.8 (2 x $C^{14}H_2$), 127.1 ($C^{15}H$), 126.9 (2 x $C^{13}H_2$), 116.5 (C^{9}), 116.4 ($C^{6}H$), 111.4 ($C^{8}H$), 54.8 ($C^{11}H_2$), 52.8 ($C^{2}H_2$), 52.3 ($C^{4}H$), 52.1 ($C^{17}H_3$), 37.2 ($C^{19}H_2$), 36.9 ($C^{23}H_2$), 34.6 (C^{3}), 30.22 ($C^{21}H_3$), 30.17 ($C^{25}H_3$), 26.6 ($C^{18}H_2$), 26.4 ($C^{22}H_2$).

IR (neat) (cm^{-1}): 2947, 2925, 1713, 1602, 1507, 1355, 1244, 1159, 746.

7.3.10 Synthesis of isoquinolines

4-Iodo-3-methylisoquinoline (V-36)



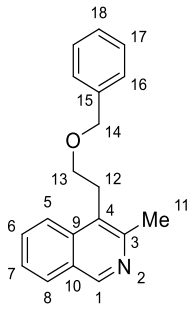
The title compound was prepared following a literature procedure by Miller and co-workers.[123] 3-methylisoquinoline (716 mg, 5.00 mmol, 1.00 equiv.) and *N*-iodosuccinimide (1.35 g, 6.00 mmol, 1.50 equiv.) were dissolved in acetic acid (10.0 mL, 0.5 M). The mixture was allowed to stir at 80 °C for 3 h. The mixture was then diluted in CH_2Cl_2 (10.0 mL), neutralized with aq. K_2CO_3 (10.0 mL, 0.10 M), washed with aq. $Na_2S_2O_3$ (10.0 mL) and brine (10.0 mL). The combined organic layers were dried using $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (5% EtOAc in pentane) gave the desired product **V-36** (734 mg, 2.73 mmol, 55%) as a yellow solid.

Spectroscopic data matched that reported in the literature.[123]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H, C^{1}**H**), 8.09 (dq, J = 8.6, 0.8 Hz, 1H, C^{5}**H**), 7.88 (dt, J = 8.1, 1.0 Hz, 1H, C^{8}**H**), 7.75 (ddd, J = 8.4, 6.9, 1.3 Hz, 1H, C^{6}**H**), 7.59 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H, C^{7}**H**), 3.00 (s, 3H, C^{11}**H$_3$**).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.1 (C^{3}), 151.9 ($C^{1}H$), 138.5 (C^{9}), 132.0 ($C^{6}H$), 131.2 ($C^{5}H$), 128.0 ($C^{8}H$), 127.7 (C^{10}), 127.3 ($C^{7}H$), 99.3 (C^{4}), 30.4 ($C^{11}H_3$).

4-(2-(Benzyloxy)ethyl)-3-methylisoquinoline (V-37)



The title compound was synthesized following a literature procedure by Molander and co-workers.[108]

4-Iodo-3-methylisoquinoline **V-36** (620 mg, 2.30 mmol, 1.00 equiv.), potassium phenoxylethyl trifluoroborate (725 mg, 3.00 mmol, 1.30 equiv.) and Cs_2CO_3 (2.25 g, 6.90 mmol, 3.00 equiv.) were dissolved in a 4:1 toluene:water mixture (9.2 mL, 0.25 M). The flask was topped with an air condenser and the reaction mixture was purged with argon. $PdCl_2(Amphos)_2$ (81.0 mg, 0.115 mmol, 5 mol%) was added, and the reaction was allowed to stir at reflux (110 °C) for 18 h. The reaction was allowed to cool down and was the diluted in CH_2Cl_2 (10.0 mL), washed with brine (10.0 mL), then dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (10% EtOAc in pentane) gave the desired product **V-37** (296 mg, 1.00 mmol, 50%) as a clear oil.

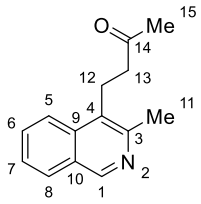
HRMS (ESI): Exact mass calculated for $C_{15}H_{17}NO_2Na$ $[M+Na]^+$: 300.1359, found: 300.1357.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.07 (s, 1H, C^1**H**), 7.99 (dd, *J* = 8.6, 1.1 Hz, 1H, C^5**H**), 7.92 (dt, *J* = 8.2, 1.0 Hz, 1H, C^6**H**), 7.67 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H, C^7**H**), 7.52 (ddd, *J* = 8.0, 6.8, 1.0 Hz, 1H, C^8**H**), 7.37 – 7.24 (m, 5H, 5 x C^{Ar}**H**), 4.54 (s, 2H, C^{14}**H$_2$**), 3.73 (dd, *J* = 8.2, 7.1 Hz, 2H, C^{13}**H$_2$**), 3.41 (t, *J* = 7.7 Hz, 2H, C^{12}**H$_2$**), 2.74 (s, 3H, C^{11}**H$_3$**).

^{13}C NMR (151 MHz, $CDCl_3$) δ 150.6 (C^1H), 150.3 (C^3), 138.4 (C^{15}), 135.7 (C^9), 130.4 (C^6H), 128.5 (C^{17}H), 128.4 (C^8H), 127.8 (C^{18}H), 127.7 (C^{16}H), 127.4 (C^{10}), 125.9 (C^7H), 124.6 (C^4), 122.8 (C^5H), 73.3 ($C^{14}H_2$), 69.4 ($C^{13}H_2$), 29.0 ($C^{12}H_2$), 22.6 ($C^{11}H_3$).

IR (neat) (cm^{-1}): 3399, 3031, 2859, 2360, 2341, 1623, 1577, 1497, 1454, 1362.

4-(3-Methylisoquinolin-4-yl)butan-2-one (V-55)



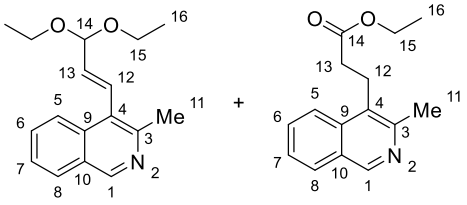
The title compound was prepared following a literature procedure.[111] In a 1.5 mL GC vial equipped with a magnetic stir bar, 3-methylisoquinoline (286 mg, 2.00 mmol, 1.0 equiv.), BzOH (244 mg, 0.75 mmol, 3.0 equiv.), MVK (0.66 mL, 8.00 mmol, 4.0 equiv.), and MeCN (16 mL, 0.125 mmol) were combined. The vial was placed in a pre-heated oil bath and heated at 80 °C for 18 h. The reaction mixture was taken up in CH_2Cl_2 (15 mL) and quenched with 0.1 M K_2CO_3 solution (20 mL). The layers were separated, and the aqueous phase was further extracted with CH_2Cl_2 (15 mL × 2). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (5%-10% Et_2O in acetone) to give the functionalised isoquinoline **V-55** (266 mg, 62%) as a yellow oil.

Spectroscopic data matched that reported in the literature.[111]

^{1}H NMR (600 MHz, CDCl3) δ 9.06 (s, 1H, C^1H), 7.93 (d, J = 8.1 Hz, 1H, C^9H), 7.90 (d, J = 8.6 Hz, 1H, C^6H), 7.70 (t, J = 7.7 Hz, 1H, C^8H), 7.52 (t, J = 7.5 Hz, 1H, C^7H), 3.32 (t, J = 8.0 Hz, 2H, $C^{13}H_2$), 2.74 (t, J = 8.4 Hz, 2H, $C^{12}H_2$), 2.70 (s, 3H, $C^{15}H_3$), 2.19 (s, 3H, $C^{11}H_3$).

^{13}C NMR (150 MHz, CDCl3) δ 207.7 (C^{13}), 150.5 (C^1H), 149.3 (C^3), 135.0 (C^{10}), 130.6 (C^8H), 128.5 (C^9H), 127.4 (C^5), 126.9 (C^4), 126.0 (C^7H), 122.3 (C^6H), 43.3 ($C^{12}H_2$), 30.1 ($C^{15}H_3$), 22.4 ($C^{11}H_3$), 22.0 ($C^{13}H_2$).

(*E*)-4-(3,3-Diethoxyprop-1-en-1-yl)-3-methylisoquinoline (V-56) and Ethyl 3-(3-methyl-isoquinolin-4-yl) propanoate (V-57)



The title compounds were prepared following a literature procedure.[109] 4-Iodo-3-methylisoquinoline**V-36** (750 mg, 2.79 mmol, 1.00 equiv.), tetrabutylammonium hydrogen diacetate (1.68 g, 5.58 mmol, 2.00 equiv.), K_2CO_3 (579 mg, 4.19 mmol, 1.50 equiv.), KCl (208 mg, 2.79 mmol, 1.00 equiv.) and palladium(II) acetate (31.4 mg, 0.14 mmol, 5 mol%) were added in a vial. Under inert atmosphere (Ar), dry DMF (11.2 mL, 0.25 M) and acrolein diethyl acetal (1.28 mL, 8.37 mmol, 3.00 equiv.) were added. The reaction was allowed to stir at 90 °C for 18 h. after which the mixture was diluted with EtOAc (10.0 mL), washed with water (2 x 10.0 mL), with 1% aq. LiCl (2 x 10.0 mL) and brine (10.0 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (10% EtOAc in pentane) gave the desired product **V-56** (333 mg, 1.23 mmol, 44%) as a yellow oil and the side-product **V-57** (183 mg, 0.75 mmol, 27%) as a yellow oil.

Spectroscopic data for **V-56**:

HRMS (ESI+): Exact mass calculated for $C_{17}H_{22}NO_2$ $[M+H]^+$: 272.1645, found: 272.1685.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.09 (s, 1H, C^1**H**), 8.02 (dq, J = 8.5, 0.9 Hz, 1H, C^5**H**), 7.92 (dt, J = 8.1, 1.0 Hz, 1H, C^8**H**), 7.65 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H, C^6**H**), 7.52 (ddd, J = 8.0, 6.8, 1.1 Hz, 1H, C^7**H**), 7.02 (ddt, J = 16.4, 1.5, 0.7 Hz, 1H, C^{12}**H**), 5.97 (dd, J = 16.4, 4.7 Hz, 1H, C^{13}**H**), 5.22 (dd, J = 4.7, 1.3 Hz, 1H, C^{14}**H**), 3.79 (dq, J = 9.5, 7.1 Hz, 2H, 2 x C^{15}**H$_2$**), 3.67 (dq, J = 9.4, 7.0 Hz, 2H, 2 x C^{15}**H$_2$**), 2.71 (s, 3H, C^{11}**H$_3$**), 1.30 (t, J = 7.1 Hz, 6H, 2 x C^{16}**H$_3$**).

^{13}C NMR (151 MHz, $CDCl_3$) δ 151.0 (C^{1}H), 149.0 (C^9), 135.0 (C^{13}H), 134.8 (C^9), 130.5 (C^{7}H), 128.0 (C^{8}H), 127.1 (C^{10}), 126.2 (C^{6}H), 125.8 (C^{4}H), 124.1 (C^{5}H), 101.3 (C^{14}H), 61.4 (2 x C^{15}H$_2$), 23.4 (C^{11}H$_3$), 15.5 (C^{16}H$_3$).

IR (neat) (cm^{-1}): 3403, 3060, 2842, 1718, 1620, 1572, 1497, 1442, 1335, 1178.

Spectroscopic data for **V-57**:

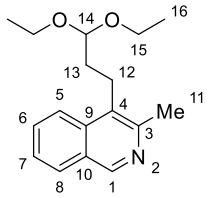
HRMS (ESI+): Exact mass calculated for $C_{15}H_{17}NO_2Na$ $[M+Na]^+$: 266.1152, found: 266.1161.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.07 (s, 1H, C^1**H**), 7.97 (dt, J = 8.5, 0.9 Hz, 1H, C^5**H**), 7.93 (dt, J = 8.2, 1.0 Hz, 1H, C^8**H**), 7.70 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H, C^6**H**), 7.53 (ddd, J = 8.0, 6.8, 1.0 Hz, 1H, C^7**H$_2$**), 4.17 (q, J = 7.2 Hz, 2H, C^{15}**H$_2$**), 3.42 – 3.36 (m, 2H, C^{12}**H$_2$**), 2.74 (s, 3H, C^{11}**H$_3$**), 2.64 – 2.57 (m, 2H, C^{13}**H$_2$**), 1.26 (t, J = 7.2 Hz, 3H, C^{16}**H$_3$**).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.9 (C^{14}), 150.7 (C^{1}H), 149.5 (C^3), 135.1 (C^9), 130.7 (C^{6}H), 128.5 (C^{8}H), 127.5 (C^{10}), 126.5 (C^4), 126.0 (C^{7}H), 122.4 (C^{5}H), 60.8 (C^{15}H$_2$), 34.2 (C^{13}H$_2$), 23.7 (C^{12}H$_2$), 22.3 (C^{11}H$_3$), 14.3 (C^{16}H$_3$).

IR (neat) (cm^{-1}): 3391, 2360, 1732, 1624, 1578, 1501, 1467, 1445, 1424, 1296.

4-(3,3-Diethoxypropyl)-3-methylisoquinoline (V-58)



The title compound was prepared following a literature procedure.[109] (E)-4-(3,3-diethoxyprop-1-en-1-yl)-3-methylisoquinoline **V-56** (192 mg, 0.71 mmol, 1.00 equiv.) was dissolved in dry methanol (2.6 mL, 0.28 M). N_2 was bubbled under vigorous stirring, then palladium on carbon loading 10wt% (192 mg, 10 wt% in Pd) was added, H_2 was bubbled under vigorous stirring. The reaction was allowed to stir at 25 °C (room temperature) for 5 h, after which the reaction was diluted with CH_2Cl_2 (10.0 mL), filtered through celite to give the desired product **V-58** (160 mg, 0.586 mmol, 82%) as a yellow oil. The compound was >95% pure by NMR and was carried over without further purification.

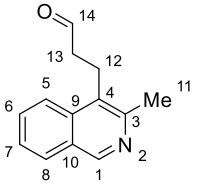
HRMS (ESI+): Exact mass calculated for $C_{17}H_{23}NO_2Na$ $[M+Na]^+$: 296.1621, found: 296.1618.

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.05 (d, J = 0.8 Hz, 1H, C^1**H**), 8.02 (dt, J = 8.5, 0.9 Hz, 1H, C^5**H**), 7.92 (dt, J = 8.1, 1.0 Hz, 1H, C^8**H**), 7.71 – 7.66 (m, 1H, C^6**H**), 7.51 (ddd, J = 8.0, 6.8, 1.0 Hz, 1H, C^7**H**), 4.59 (t, J = 5.4 Hz, 1H, C^{14}**H**), 3.70 (dq, J = 9.3, 7.0 Hz, 2H, 2 x C^{15}**H$_2$**), 3.54 (dq, J = 9.3, 7.0 Hz, 2H, 2 x C^{15}**H$_2$**), 3.15 – 3.09 (m, 2H, C^{12}**H$_2$**), 2.73 (s, 3H, C^{11}**H$_3$**), 1.98 – 1.90 (m, 2H, C^{13}**H$_2$**), 1.24 (dt, J = 12.9, 7.0 Hz, 6H, 2 x C^{16}**H$_3$**).

^{13}C NMR (151 MHz, $CDCl_3$) δ 150.2 (C^{1}H), 149.3 (C^3), 135.3 (C^9), 130.3 (C^{6}H), 128.4 (C^{8}H), 127.9 (C^{10}), 127.5 (C^4), 125.9 (C^{7}H), 122.8 (C^{5}H), 102.8 (C^{14}H), 61.7 (2 x C^{15}H$_2$), 33.8 (C^{13}H$_2$), 23.2 (C^{12}H$_2$), 22.3 (d, J = 5.9 Hz, C^{11}H$_3$), 15.5 (d, J = 3.8 Hz, 2 x C^{16}H$_3$).

IR (neat) (cm^{-1}): 3406, 3058, 2361, 1624, 1578, 1501, 1444, 1372, 1346, 1210.

3-(3-Methylisoquinolin-4-yl)propanal (V-59)



Procedure 1:

The title compound was prepared following a literature procedure.[124] Ethyl 3-(3-methylisoquinolin-4-yl) propanoate **V-57** (370 mg, 1.53 mmol, 1.00 equiv.) was dissolved in CH_2Cl_2 (8.0 mL, 0.2 M) at -78 °C. DIBAL-H in CH_2Cl_2 1.00 M (0.53 mL, 0.53 mmol, 1.50 equiv.) was slowly added to the mixture under inert atmosphere. The reaction was allowed to stir at -78 °C for 2.5 h, then diluted with CH_2Cl_2 (10.0 mL), quenched with sequentially methanol (1.0 mL), water (1.5 mL) and sat. Rochelle's salt (1.5 mL) under stirring for 1 h. After washing with brine (10.0 mL), the reaction was dried with $MgSO_4$ and concentrated *in vacuo* to give the desired product **V-59** (201 mg, 1.0 mmol, 66%) as a clear oil. The compound was >95% pure by NMR and was carried over without further purification.

Procedure 2:

The title compound was prepared following a literature procedure.[109] 4-(3,3-diethoxypropyl)-3-methylisoquinoline**V-58** (271 mg, 0.99 mmol, 1.00 equiv.) was dissolved in THF (6.6 mL, 0.15 M), to which aq. 2 M HCl solution was added dropwise to achieve pH 1. The reaction was allowed to stir at 25 °C (room temperature) for 15 min. Aq. Na_2CO_3 was added dropwise to achieve pH 7, and EtOAc (10.0 mL) was used to extract the product. The reaction was dried with $MgSO_4$ and concentrated *in vacuo* to give the desired product **V-59** (191 mg, 0.96 mmol, 97%) as a clear oil. The compound was >95% pure by NMR and was carried over without further purification.

HRMS (ESI+): Exact mass calculated for $C_{13}H_{14}NO$ $[M+H]^+$: 200.1070, found: 200.1067.

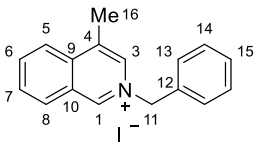
^{1}H NMR (600 MHz, $CDCl_3$) δ 9.92 (d, J = 1.2 Hz, 1H, C^{14}**H**), 9.08 (d, J = 0.8 Hz, 1H, C^1**H**), 7.95 (dt, J = 8.1, 1.0 Hz, 1H, C^5**H**), 7.90 (dq, J = 8.6, 0.9 Hz, 1H, C^8**H**), 7.71 (ddd, J = 8.4, 6.8, 1.3 Hz, 1H, C^7**H**), 7.54 (ddd, J = 8.0, 6.8, 1.0 Hz, 1H, C^6**H**), 3.41 – 3.34 (m, 2H, C^{12}**H$_2$**), 2.83 – 2.77 (m, 2H, C^{13}**H$_2$**), 2.73 (s, 3H, C^{12}**H$_3$**).

^{13}C NMR (151 MHz, $CDCl_3$) δ 201.0 ($C^{14}H$), 150.8 (C^1H), 149.4 (C^3), 134.9 (C^9), 130.8 (C^7H), 128.6 (C^5H), 127.5 (C^{10}), 126.4 (C^4H), 126.1 (C^6H), 122.2 (C^8H), 43.8 ($C^{13}H_2$), 22.4 ($C^{12}H_3$), 20.5 ($C^{12}H_2$).

IR (neat) (cm^{-1}): 3028, 2925, 2730, 2360, 2341, 1723, 1623, 1578, 1500, 1447.

7.3.11 Synthesis of isoquinolinium salts

N-Benzyl-4-methylisoquinolinium iodide (IV-1)



The title compound was prepared according to the General Procedure I using 4-methylisoquinoline (858 mg, 6.00 mmol, 1.0 equiv.) and benzyl iodide (1.13 mL, 9.00 mmol) in acetone (0.5 M). The resultant solid was washed with diethyl ether and dried under vacuum. Further drying under high vacuum at 70 °C for 10 hours gave the salt **IV-1** (2.09 g, 97%) as a yellow solid.

m.p. (acetone): 126 – 128 °C

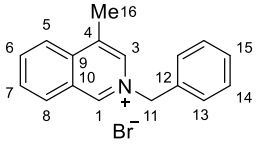
HRMS (ESI): Exact mass calculated for $C_{17}H_{16}N$ $[M]^+$: 234.1277, found 234.1278.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H, C^1**H**), 8.80 (s, 1H, C^3**H**), 8.54 (dd, J = 8.3, 1.1 Hz, 1H, C$^{5/8}$**H**), 8.36 (dd, J = 8.6, 1.1 Hz, 1H, C$^{5/8}$**H**), 8.30 (dd, J = 6.9, 1.4 Hz, 1H, C$^{6/7}$**H**), 8.09 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H, C$^{6/7}$**H**), 7.66 – 7.57 (m, 2H, 2 x C^{14}**H**), 7.50 – 7.37 (m, 3H, 2 x C^{13}**H** + C^{15}**H**), 5.94 (s, 2H, C^{11}**H**$_2$), 2.76 (s, 3H, C^{16}**H**$_3$)

^{13}C NMR (101 MHz, DMSO-d_6) δ 148.3 (C^{1}H), 137.0 (C^{Ar}H), 136.6 (C^Q), 135.2 (C^Q), 134.2 (C^Q), 133.3 (C^{3}H), 131.1 (2 x C^{Ar}H), 129.3 (C^{15}H), 129.2 (2 x C^{13}H), 128.8 (2 x C^{14}H), 126.9 (C^Q), 124.4 (C^{Ar}), 63.2 (C^{11}H$_2$), 15.8 (C^{16}H$_3$)

IR (neat) (cm^{-1}): 3672, 2999, 2886, 1474, 1460, 1380, 1252, 1152, 1072, 954.

N-Benzyl-4-methylisoquinolinium bromide (IV-2)



The title compound was prepared according to a modified General Procedure I. A mixture of 4-methylisoquinoline (500 mg, 3.49 mmol, 1.0 eq.) and benzyl bromide (0.50 mL, 4.19 mmol, 1.2 eq.) in dioxane (10 mL) was stirred at 90 °C for 24 h. The reaction mixture was filtered. The resultant solid was sonicated in Et_2O (10 mL) for 5 min and washed with ether (50 mL) then dried under vacuum to give isoquinolinium bromide **IV-2** (1.01 g, 92%) as an off-white solid.

m.p. (acetone): 197 °C

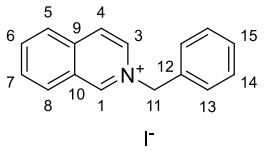
HRMS (ESI): Exact mass calculated for $C_{17}H_{16}N$ $[M]^+$: 234.1277, found: 234.1279.

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.24 (s, 1H, C^1**H**), 8.82 (t, *J* = 1.3 Hz, 1H, C^3**H**), 8.54 (dt, *J* = 8.2, 1.1 Hz, 1H, C$^{5/8}$**H**), 8.37 (dd, *J* = 8.6, 1.1 Hz, 1H, C$^{5/8}$**H**), 8.30 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H, C$^{6/7}$**H**), 8.09 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, C$^{6/7}$**H**), 7.64 – 7.59 (m, 2H, 2 x C^{Ar}**H**), 7.48 – 7.41 (m, 3H, 3 x C^{Ar}**H**), 5.94 (s, 2H, C^{11}**H$_2$**), 2 2.76 (s, 1H, C^{18}**H$_3$**);

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 148.4 (C^{1}H), 137.0 (C$^{5/8}$H), 136.6 (C^{Ar}), 135.2 (C^{Ar}), 134.3 (C^{Ar}), 133.3 (C^{3}H), 131.2 (C^{Ar}H), 131.1 C^{Ar}H), 129.3 (C^{Ar}H), 129.2 (2 x C^{Ar}H), 128.8 (2 x C^{Ar}H), 127.0 (C^{Ar}), 124.4 (C$^{5/8}$H), 63.2 (C^{11}H$_2$), 15.7 (C^{16}H$_3$);

IR (neat) (cm^{-1}): 3418, 3006, 2164, 2032, 1978, 1642, 1399, 1170, 1116, 871,744, 699.

N-Benzylisoquinolinium iodide (IV-10)



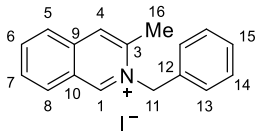
The title compound was prepared according to General Procedure I using isoquinoline (1.00 g, 7.74 mmol) and benzyl iodide (1.9 mL, 15.48 mmol) to give salt **IV-10** (2.6 g, 97%) as a pale-yellow solid. Spectroscopic data was consistent with that reported in the literature.[79]

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.28 (s, 1H, C^1**H**), 8.83 (dd, *J* = 6.8, 1.5 Hz, 1H C^3**H**), 8.61 (d, *J* = 6.8 Hz, 1H, C^4**H**), 8.54 (d, *J* = 8.47 Hz, 1H, C^5**H**), 8.36 (dd, *J* = 8.3, 1.1 Hz, 1H, C^8**H**), 8.28

(ddd, J = 8.3, 7.0, 1.2 Hz, 1H, C^{7}**H**), 8.10 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H, C^{6}**H**), 7.62 – 7.55 (m, 2H, 2 x C^{Ar}**H**), 7.50 – 7.38 (m, 3H, 3 x C^{Ar}**H**), 5.98 (s, 2H, C^{11}**H$_2$**).

^{13}C NMR (101 MHz, DMSO-d_6) δ 150.2 (C^{1}H), 137.2 (C^{7}H), 137.1 (C^{Ar}), 134.8 (C^{3}H), 134.3 (C^{Ar}), 131.4 (C^{6}H), 130.6 (C^{5}H), 129.3 (C^{15}H), 129.2 (2 x C^{Ar}H), 128.8 (2 x C^{Ar}H), 127.4 (C^{8}H), 127.3 (C^{Ar}), 126.3 (C^{4}H), 63.4 (C^{11}H$_2$).

2-Benzyl-3-methylisoquinolin-2-ium iodide (IV-49)



The title compound was prepared according to General Procedure I using 3-methylisoquinoline (430 mg, 3.00 mmol, 1.0 eq.) and benzyl iodide (0.56 mL, 4.5 mmol 1.5 eq.) in acetone (6 mL) to give salt **IV-49** (907 mg, 84%) as a yellow solid.

m.p. (acetone): 201 °C

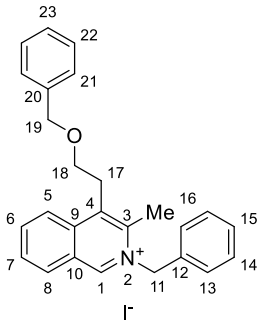
HRMS (ESI): Exact mass calculated for $C_{17}H_{16}N$ $[M]^+$: 234.1277, found: 234.1277.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (s, 1H, C^{1}**H**), 8.54 (s, 1H, C^{4}**H**), 8.50 (d, J = 8.4 Hz, 1H, C$^{5/8}$**H**), 8.28 – 8.22 (m, 2H, C$^{6/7}$**H** + C$^{5/8}$**H**), 8.03 (dt, J = 8.2, 4.0 Hz, 1H, C$^{6/7}$**H**), 7.48 – 7.38 (m, 3H, 3 x C^{Ar}**H**), 7.36 – 7.30 (m, 2H, 2 x C^{Ar}**H**), 6.09 (s, 2H, C^{11}**H$_2$**), 2.76 (s, 3H, C^{16}**H$_3$**);

^{13}C NMR (101 MHz, DMSO-d_6) δ 151.5 (C^{1}H), 144.3 (C^{Ar}), 138.0 (C^{Ar}), 137.2 (C^{8}), 133.3 (C^{Ar}), 130.5 (C$^{6/7}$), 130.2 (C$^{5/8}$H), 129.2 (2 x C^{Ar}H), 128.7 (C^{Ar}H), 127.5 (2 x C^{Ar}H), 126.6 (C^{4}H), 126.3 (C$^{6/7}$H), 126.1 (C^{Ar}), 60.6 (C^{11}H$_2$), 19.2 (C^{18}H$_3$);

IR (neat) (cm^{-1}): 2982, 2162, 1645, 1439, 1400, 1344, 913, 747, 740, 706.

***N*-Benzyl-4-(2-(benzyloxy)ethyl)-3-methylisoquinolinium iodide (V-38)**



The title compound was synthesized following General Procedure I. 4-(2-(Benzyloxy)ethyl)-3-methylisoquinoline **V-37** (261 mg, 1.00 mmol, 1.00 equiv.) and benzyl iodide (0.260 mL, 2.10 mmol, 2.00 equiv.) were dissolved in a acetone (2.10 mL, 0.50 M) and stirred at r.t. overnight. Cold Et_2O (5.0 mL) was added dropwise to allow for the precipitation of the desired product **V-38** (372 mg, 0.715 mmol, 75%) as a yellow solid.

m.p. 195-197 °C

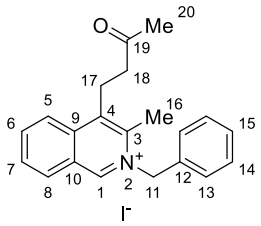
HRMS (ESI+): Exact mass calculated for $C_{26}H_{27}NO$ $[M]^+$: 369.2087, found: 369.2051.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.06 (s, 1H, C^1**H**), 8.76 (d, J = 8.2 Hz, 1H, C^8**H**), 8.16 (d, J = 8.7 Hz, 1H, C^5**H**), 8.12 – 8.05 (m, 1H, C^6**H**), 7.90 (t, J = 7.5 Hz, 1H, C^7**H**), 7.35 (q, J = 2.5 Hz, 3H, 3 x C^{Ar}**H**), 7.26 – 7.18 (m, 5H, 5 x C^{Ar}**H**), 7.12 – 7.06 (m, 2H, 2 x C^{Ar}**H**), 6.33 (s, 2H, C^{11}**H$_2$**), 4.41 (s, 2H, C^{19}**H$_2$**), 3.81 (t, J = 6.4 Hz, 2H, C^{18}**H$_2$**), 3.49 (t, J = 6.4 Hz, 2H, C^{17}**H$_2$**), 2.81 (s, 3H, C^{16}**H$_3$**).

^{13}C NMR (151 MHz, $CDCl_3$) δ 150.7 (C^1H), 142.9 (C^3), 138.1 (C^4), 137.5 (C^{Ar}H), 137.4 (C^6H), 134.7 (C^9), 132.6 (C^{Ar}H), 132.2 (C^8H), 130.4 (C^7H), 129.8 (2 x C^{Ar}H), 129.4 (C^{Ar}H), 128.6 (2 x C^{Ar}H), 128.1 (C^{Ar}H), 127.7 (2 x C^{Ar}H), 127.5 (2 x C^{Ar}H), 126.5 (C^{10}H), 123.7 (C^5H), 73.6 ($C^{19}H_2$), 68.7 ($C^{18}H_2$), 62.7 ($C^{11}H_2$), 29.8 ($C^{17}H_2$), 17.2 ($C^{16}H_3$).

IR (neat) (cm^{-1}): 3414, 3063, 2885, 1724, 1633, 1603, 1496, 1454, 1362, 1269.

***N*-Benzyl-3-methyl-4-(3-oxobutyl)isoquinolinium iodide (V-62)**



The title compound was prepared by General Procedure I using 4-(3-methylisoquinolin-4-yl)butan-2-one **V-55** (213 mg, 1.0 mmol, 1.0 equiv.) and benzyl iodie (0.25 mL, 2.0 mmol, 2.0 equiv.) in acetone (2 mL) to give salt **V-62** (303 mg, 70%) as a yellow solid

m.p. (acetone): 184-186 °C

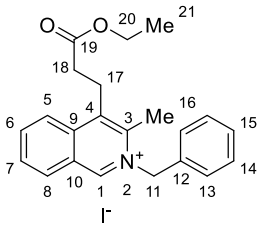
HRMS (ESI): Exact mass calculated for $C_{21}H_{22}NO$ $[M]^+$: 304.1696, found: 204.1705.

^{1}H NMR (400 MHz, CDCl3) δ 10.69 (s, 1H, C^1**H**), 8.64 (dd, J = 8.3, 1.1 Hz, 1H, C^8**H**), 8.19 – 8.08 (m, 2H, C^5**H** + C^6**H**), 7.89 (ddd, J = 8.1, 6.4, 1.5 Hz, 1H, C^7**H**), 7.44 – 7.33 (m, 3H, 3 x C^{Ar}H), 7.33 – 7.21 (m, 2H, 2 x C^{Ar}H), 6.30 (s, 2H, C^{11}**H$_2$**), 3.45 (t, J = 7.0 Hz, 2H, C^{18}**H$_2$**), 2.90 (t, J = 7.1 Hz, 2H, C^{17}**H$_2$**), 2.87 (s, 3H, C^{16}**H$_3$**), 2.21 (s, 3H, C^{20}**H$_3$**).

^{13}C NMR (101 MHz, CDCl3) δ 206.1 (C^{19}O), 150.0 (C^3), 142.3 (C^{1}H), 137.42 (C^{5}H), 137.39 (C^{Ar}), 136.4 (C^{Ar}), 132.2 (C^{Ar}), 132.0 (C^{8}H), 130.3 (C^{7}H), 129.7 (2 x C^{Ar}H), 129.4 (C^{Ar}H), 127.7 (2 x C^{Ar}H), 126.3 (C^{Ar}), 123.3 (C^{6}H), 62.8 (C^{11}H$_2$), 42.4 (C^{17}H), 30.1 (C^{18}H$_2$), 22.5 (C^{20}H$_3$), 17.1 (C^{16}H$_3$).

IR (neat) (cm^{-1}): 2981, 2890, 2362, 1703, 1632, 1387, 1360, 1261, 949, 708.

***N*-Benzyl-4-(3-ethoxy-3-oxopropyl)-3-methylisoquinolinium iodide (V-63)**



The title compound was prepared by General Procedure I using ethyl 3-(3-methylisoquinolin-4-yl) propanoate **V-57** (150 mg, 0.6 mmol, 1.0 equiv.) and benzyl iodie (0.15 mL, 1.2 mmol, 2.0 equiv.) in acetone (1.2 mL) to give salt **V-63** (220 mg, 80%) as a yellow solid.

m.p. (acetone): 214-216 °C

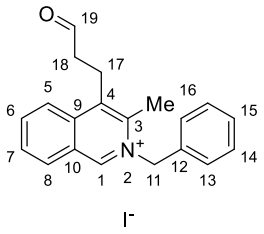
HRMS (ESI): Exact mass calculated for $C_{22}H_{24}NO_2$ $[M]^+$: 334.1802, found:

^{1}H NMR (400 MHz, CDCl3) δ 11.01 (d, *J* = 8.0 Hz, 1H, C^1**H**), 8.75 (d, *J* = 8.3 Hz, 1H, C^8**H**), 8.22 – 8.10 (m, 2H, C^5**H** + C^6**H**), 7.91 (t, *J* = 7.6 Hz, 1H, C^7**H**), 7.40 – 7.33 (m, 3H, 3 x C^{Ar}**H**), 7.25 (bs, 2H, 2 x C^{Ar}**H**), 6.36 (s, 2H, C^{11}**H$_2$**), 4.13 (q, *J* = 7.1 Hz, 2H, C^{20}**H$_2$**), 3.51 (t, *J* = 8.1 Hz, 2H, C^{18}**H$_2$**), 2.87 (s, 3H, C^{16}**H$_2$**), 2.67 (t, *J* = 8.1 Hz, 2H, C^{17}**H$_2$**), 1.23 (t, *J* = 7.1 Hz, 3H, C^{21}**H$_2$**).

^{13}C NMR (101 MHz, CDCl3) δ 171.6 (C^{19}O), 150.9 (C^3), 142.3 (C^1H), 137.7 (C^6H), 137.5 (C^{Ar}), 135.6 (C^{Ar}), 132.5 (C^8H+C^{Ar}), 130.5 (C^7H), 129.8 (2 x C^{Ar}H), 129.5 (C^{Ar}H), 127.6 (2 x C^{Ar}H), 126.5 (C^{Ar}), 123.2 (C^5H), 62.8 ($C^{11}H_2$), 61.4 ($C^{20}H_2$), 33.6 ($C^{17}H_2$), 24.3 ($C^{18}H_2$), 17.0 ($C^{16}H_3$), 14.3 ($C^{21}H_3$).

IR (neat) (cm^{-1}): 2981, 2890, 1698, 1452, 1310, 1206, 1109, 1028, 911, 733.

2-Benzyl-3-methyl-4-(3-oxopropyl) isoquinolin-2-ium iodide (V-64)



The title compound was prepared by General Procedure I using ethyl 3-(3-methylisoquinolin-4-yl) propanoate **V-59** (100 mg, 0.5 mmol, 1.0 equiv.) and benzyl iodie (0.6 mL, 1.0 mmol, 2.0 equiv.) in acetone (1.2 mL) to give salt **V-64** (185 mg, 89%) as a yellow solid.

m.p. (acetone): 168-170 °C

HRMS (ESI+): Exact mass calculated for $C_{20}H_{21}NO$ $[M]^+$: 291.1618, found: 291.1602.

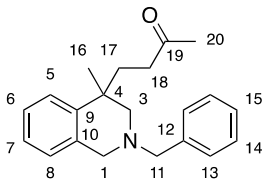
^{1}H NMR (600 MHz, $CDCl_3$) δ 10.55 (s, 1H, C^{19}**H**), 9.87 (s, 1H, C^{1}**H**), 8.62 (dt, J = 8.3, 1.0 Hz, 1H, C^{8}**H**), 8.18 – 8.13 (m, 2H, C^{5}**H** + C^{Ar}**H**), 7.91 (ddd, J = 8.1, 4.8, 3.1 Hz, 1H, C^{7}**H**), 7.42 – 7.40 (m, 2H, C^{6}**H** + C^{Ar}**H**), 7.26 (s, 4H, 4 x C^{Ar}**H**), 6.27 (s, 2H, C^{11}**H_2**), 3.51 (dd, J = 8.4, 7.0 Hz, 2H, C^{17}**H_2**), 3.03 – 2.98 (m, 2H, C^{18}**H_2**), 2.89 (s, 3H, C^{16}**H_3**).

^{13}C NMR (151 MHz, $CDCl_3$) δ 199.3 (C^{19}HO), 150.2 (C^{1}H), 142.4 (C^{3}), 137.7 (C^{Ar}), 137.5 (C^{9}), 136.1 (C^{4}), 132.3 (C^{8}H), 132.1 (C^{10}), 130.6 (C^{7}H), 129.9 (2 x C^{Ar}H), 129.7 (C^{6}H), 127.9 (2 x C^{Ar}H), 126.5 (C^{Ar}H), 123.3 (C^{5}H), 63.1 ($C^{11}H_2$), 42.9 ($C^{18}H_2$), 21.1 ($C^{17}H_2$), 17.2 ($C^{16}H_3$).

IR (neat) (cm^{-1}): 3476, 3063, 2839, 2363, 1720, 1634, 1603, 1497, 1454, 1398.

7.3.12 Synthesis of tetrahydroisoquinolines

***N*-Benzyl-4-(butan-2-one)-4-methyl-1,2,3,4-tetrahydroisoquinoline (IV-3)**



The title compound was prepared by General Procedure J using *N*-benzyl-4-methylisoquinolinium iodide **IV-1** (45 mg, 0.125 mmol) and methyl vinyl ketone (21 μL, 0.250 mmol). Purification by column chromatography (5% EtOAc in pentane) gave amine **IV-3** (33 mg, 86%) as a yellow oil.

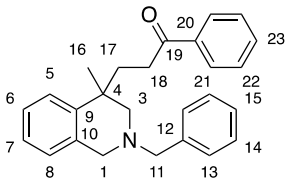
HRMS (ESI): Exact mass calculated for $C_{21}H_{26}ON$ $[M+H]^+$: 308.2009, found 308.2011.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.21 (m, 6H, 6 x C^{Ar}**H**), 7.21 – 7.14 (m, 1H, C^{Ar}**H**), 7.10 (td, *J* = 7.3, 1.5 Hz, 1H, C^{Ar}**H**), 6.99 (ddd, *J* = 7.6, 1.6, 0.7 Hz, 1H, C^{Ar}**H**), 3.74 – 3.49 (m, 2H, $C^{1/11}$**H_2**), 3.61 (q, *J* = 13.0 Hz, 2H, $C^{1/11}$**H_2**), 2.57 (dd, *J* = 11.5, 1.3 Hz, 1H, C^{3}**H_2**), 2.45 (ddd, *J* = 16.1, 11.7, 4.9 Hz, 1H, C^{18}**H_2**), 2.30 (dd, *J* = 11.4, 0.8 Hz, 1H, C^{3}**H_2**), 2.12 – 1.99 (m, 2H, C^{17}**H_2**+ C^{18}**H_2**), 2.02 (s, 3H, C^{20}**H_3**), 1.80 (ddd, *J* = 15.1, 11.8, 4.9 Hz, 1H, C^{17}**H_2**), 1.24 (s, 3H, C^{16}**H_3**)

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.3 ($C^{19}O$), 142.2 (C^{Q}), 138.7 (C^{Q}), 134.9 (C^{Q}), 129.2 (2 x C^{Ar}), 128.4 (2 x C^{Ar}), 127.3 (C^{Ar}), 126.7 (C^{Ar}), 126.5 (C^{Ar}), 126.2 (C^{Ar}), 125.8 (C^{Ar}), 63.0 ($C^{1/11}H_2$), 61.8 ($C^{3}H_2$), 57.6 ($C^{1/11}H_2$), 39.7 ($C^{18}H_2$), 37.8 (C^{4}), 36.1 ($C^{17}H_2$), 30.1 ($C^{20}H_3$), 27.8 ($C^{16}H_3$)

IR (neat) (cm^{-1}): 2927, 2799, 1714, 1493, 1452, 1162, 1096, 914, 760, 700.

***N*-Benzyl-4-methyl-4-(1-phenylpropan-1-one)-1,2,3,4-tetra-hydroisoquinoline (IV-4)**



The title compound was prepared by General Procedure J using *N*-benzyl-4-methylisoquinolinium iodide **IV-1** (45 mg, 0.125 mmol) and phenyl vinyl ketone (33 mg, 0.250 mmol). Purification by flash column chromatography (2.5% EtOAc in pentane) gave amine **IV-4** (40 mg, 87%) as a yellow oil.

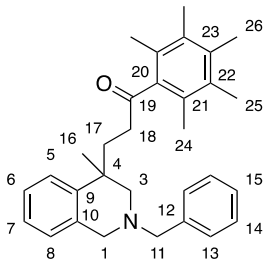
HRMS (ESI): Exact mass calculated for $C_{26}H_{28}ON$ $[M+H]^+$: 370.2165, found 370.2165.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.69 (m, 2H, 2 x C^{Ar}**H**), 7.48 – 7.39 (m, 1H, C^{Ar}**H**), 7.37 – 7.24 (m, 4H, 4 x C^{Ar}**H**), 7.24 – 7.13 (m, 4H, 4 x C^{Ar}**H**), 7.13 – 7.07 (m, 1H, C^{Ar}**H**), 7.03 (td, *J* = 7.4, 1.4 Hz, 1H, C^{Ar}**H**), 6.94 – 6.88 (m, 1H, C^{Ar}**H**), 3.64 (d, *J* = 14.6 Hz, 1H, C^{1}**H**$_2$), 3.53 (s, 2H, C^{11}**H**$_2$), 3.43 (d, *J* = 14.6 Hz, 1H, C^{1}**H**$_2$), 2.98 (ddd, *J* = 16.4, 11.3, 4.9 Hz, 1H, C^{18}**H**$_2$), 2.63 (d, *J* = 11.3, 1H, C^{3}**H**$_2$), 2.52 (ddd, *J* = 16.8, 11.2, 4.8 Hz, 1H, C^{18}**H**$_2$), 2.29 (d, *J* = 11.5 Hz, 1H, C^{3}**H**$_2$), 2.16 (ddd, *J* = 14.1, 11.3, 4.8 Hz, 1H, C^{17}**H**$_2$), 2.01 – 1.85 (m, 1H, C^{17}**H**$_2$), 1.23 (s, 3H, C^{16}**H**$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.8 ($C^{19}O$), 142.2 (C^{Q}), 138.6 (C^{Q}), 137.2 (C^{Q}), 135.0 (C^{Q}), 132.9 (C^{Ar}), 129.2 (2 x C^{Ar}), 128.6 (2 x C^{Ar}), 128.4 (2 x C^{Ar}), 128.1 (2 x C^{Ar}), 127.3 (C^{Ar}), 126.7 (C^{Ar}), 126.6 (C^{Ar}), 126.2 (C^{Ar}), 125.8 (C^{Ar}), 63.1 ($C^{11}H_2$), 62.3 ($C^{3}H_2$), 57.5 ($C^{1}H_2$), 38.0 (C^{4}), 37.0 ($C^{17}H_2$), 34.8 ($C^{18}H_2$), 28.1 ($C^{16}H_3$)

IR (neat) (cm^{-1}): 2925, 2854, 1681, 1597, 1449, 1273, 1240, 1113, 760, 700.

***N*-Benzyl-4-methyl-4-(1-pentamethylphenylpropan-1-one)-1,2,3,4-tetra-hydroisoquinoline (IV-13)**



The title compound was prepared by General Procedure **E** using *N*-benzyl-4-methylisoquinolinium iodide **IV-1** (45 mg, 0.125 mmol) and pentamethylphenyl vinyl ketone (51 mg, 0.250 mmol). Purification by flash column chromatography (CH_2Cl_2) gave amine **IV-13** (51 mg, 92%) as a yellow oil.

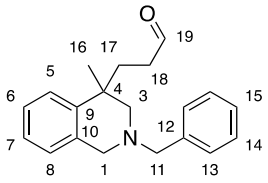
HRMS (ESI): Exact mass calculated for $C_{31}H_{38}ON$ $[M+H]^+$: 440.2948, found 440.2952.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.14 (m, 6H, 6 x C^{Ar}**H**), 7.08 (td, *J* = 7.6, 1.5 Hz, 1H, C^{Ar}**H**), 6.99 (td, *J* = 7.4, 1.3 Hz, 1H, C^{Ar}**H**), 6.86 (dd, *J* = 7.6, 1.4 Hz, 1H, C^{Ar}**H**), 3.58 – 3.39 (m, 4H, C^1**H**$_2$ + C^{11}**H**$_2$), 2.76 – 2.63 (m, 1H, C^{18}**H**$_2$), 2.46 (d, *J* = 11.3 Hz, 1H, C^3**H**$_2$), 2.32 (d, *J* = 11.3 Hz, 1H, C^3**H**$_2$), 2.35 – 2.06 (m, 2H, C^{17}**H**$_2$ + C^{18}**H**$_2$), 2.12 (s, 3H, C^{26}**H**$_3$), 2.06 (s, 6H, 2 x C^{24}**H**$_3$), 1.90 (s, 6H, 2 x C^{25}**H**$_3$), 1.99 – 1.77 (m, 1H, C^{17}**H**$_2$), 1.24 (s, 3H, C^{16}**H**$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.4 (C^{19}), 141.8 (C^Q), 141.2 (C^Q), 138.6 (C^Q), 135.4 (C^Q), 135.0 (C^Q), 133.1 (2 x C^Q), 129.0 (2 x C^{Ar}), 128.4 (2 x C^{Ar}), 127.4 (2 x C^Q), 127.2 (C^{Ar}), 126.7 (C^{Ar}), 126.6 (C^{Ar}), 126.1 (C^{Ar}), 125.8 (C^{Ar}), 63.3 ($C^{11}H_2$), 62.6 (C^3H_2), 57.5 (C^1H_2), 41.9 ($C^{18}H_2$), 37.9 (C^4), 35.5 ($C^{17}H_2$), 28.9 ($C^{16}H_3$), 17.3 (2 x $C^{24/25}H_3$), 16.8 ($C^{26}H_3$), 16.0 (2 x $C^{24/25}H_3$)

IR (neat) (cm^{-1}): 2926, 2800, 1698, 1493, 1452, 1311, 910, 759, 730, 700.

***N*-Benzyl-4-methyl-4-propanal-1,2,3,4-tetra-hydroisoquinoline (IV-14)**



The title compound was prepared by a modified version of General Procedure K using *N*-benzyl-4-methylisoquinolinium iodide **IV-1** (45 mg, 0.125 mmol), acrolein (17 μL, 0.250 mmol), HCO_2H:NEt_3 (5:2) (42 μL, 0.500 mmol), and 0.1 mL of the catalyst stock solution (corresponding to 0.01 mol% of $[RhCp^*Cl_2]_2$) was added to a sealed vial and the solution was heated at 47 °C for 20 hours. The reaction mixture was diluted with dichloromethane (10 mL) and quenched with potassium carbonate (10 mL, 0.1 M). The phases were separated, and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were concentrated *in vacuo*. The crude material was purified by flash column chromatography (15-20% EtOAc in pentane) to give *amine* **IV-14** (29 mg, 79%) as a yellow oil.

The title compound could not be prepared according to General procedure J and only starting material was recovered from the reaction.

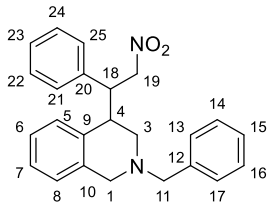
HRMS (ESI): Exact mass calculated for $C_{20}H_{24}ON$ $[M+H]^+$: 294.1852, found 294.1853.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (t, *J* = 1.6 Hz, 1H, C^{19}**H**), 7.33 – 7.13 (m, 6H, 6 x C^{Ar}**H**), 7.10 (dddd, *J* = 8.5, 7.8, 1.5, 0.7 Hz, 1H, C^{Ar}**H**), 7.03 (td, *J* = 7.3, 1.5 Hz, 1H, C^{Ar}**H**), 6.91 (ddt, *J* = 7.5, 1.5, 0.7 Hz, 1H, C^{Ar}**H**), 3.65 (d, *J* = 14.7 Hz, 1H, C^1**H**$_a$), 3.52 (s, 2H, C^{11}**H**$_2$), 3.42 (d, *J* = 14.7 Hz, 1H, C^1**H**$_b$), 2.53 (d, *J* = 11.5, 1H, C^3**H**$_a$), 2.45 – 2.31 (m, 1H, C^{18}**H**$_2$), 2.23 (d, *J* = 11.5 Hz, 1H, C^3**H**$_b$), 2.09 – 1.94 (m, 2H, C^{17}**H**$_a$ + C^{18}**H**$_2$), 1.88 – 1.76 (m, 1H, C^{17}**H**$_b$), 1.17 (s, 3H, C^{16}**H**$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2 (C^{19}O), 141.8 (C^Q), 138.4 (C^Q), 134.9 (C^Q), 129.3 (2 x C^{Ar}), 128.4 (2 x C^{Ar}), 127.3 (C^{Ar}), 126.7 (C^{Ar}), 126.6 (C^{Ar}), 126.1 (C^{Ar}), 126.0 (C^{Ar}), 63.0 ($C^{11}H_2$), 62.0 (C^3H_2), 57.3 (C^1H_2), 40.1 ($C^{18}H_2$), 37.7 (C^4), 34.6 ($C^{17}H_2$), 27.5 ($C^{16}H_3$)

IR (neat) (cm^{-1}): 2926, 1721, 1683, 1493, 1453, 1369, 910, 760, 731, 700.

***N*-Benzyl-4-(2-nitro-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (IV-18)**



The title compound was prepared according to General Procedure J using isoquinolinium salt **IV-10** (43 mg, 0.125 mmol), (*E*)-(2-nitrovinyl)benzene (19 mg, 0.125 mmol), 5:2 HCO_2H:Et_3N (42 µL, 0.50 mmol) in MeCN (0.1 mL) and was purified by column chromatography (4% EtOAc in pentane) to furnish the diastereomeric tetrahydroisoquinolines **IV-18*A*** (19 mg, 41%) and **IV-18*B*** (9 mg, 19%) as colourless oils.

Data for **major diastereomer IV-18*A*:**

HRMS (ESI): Exact mass calculated for $C_{24}H_{25}N_2O_2$ $[M+H]^+$: 373.1911, found: 373.1901.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 5H, 5 x C^{Ar}**H**), 7.21 – 7.04 (m, 7H, 7 x C^{Ar}**H**), 6.98 (dd, *J* = 7.6, 1.5 Hz, 1H, C^{Ar}**H**), 6.90 (dd, *J* = 7.6, 1.5 Hz, 1H, C^{Ar}**H**), 4.64 – 4.59 (m, 2H, C^{19}**H$_2$**), 4.03 (td, *J* = 9.5, 6.8 Hz, 1H, C^{18}**H**), 3.94 (d, *J* = 15.4 Hz, 1H, C^{1}**H$_2$**), 3.47 (s, 2H, C^{11}**H$_2$**), 3.26 (d, *J* = 15.5 Hz, 1H, C^{1}**H$_2$**), 2.93 (dt, *J* = 9.3, 2.5 Hz, 1H, C^{4}**H**), 2.67 (dt, *J* = 11.5, 1.6 Hz, 1H, C^{3}**H$_2$**), 2.32 (dd, *J* = 11.6, 3.2 Hz, 1H, C^{3}**H$_2$**)

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4 (C^{Ar}), 138.1 (C^{Ar}), 135.8 (C^{Ar}), 134.2 (C^{Ar}), 129.7 (C^{Ar}H), 129.3 (2 x C^{Ar}H), 128.8 (2 x C^{Ar}H), 128.5 (2 x C^{Ar}H), 128.1 (2 x C^{Ar}H), 127.4 (C^{Ar}H), 127.3 (C^{Ar}H), 127.3 (C^{Ar}H), 127.1 (C^{Ar}H), 125.7 (C^{Ar}H), 79.9 (C^{19}H), 63.0 ($C^{11}H_2$), 55.9 ($C^{1}H_2$), 53.4 ($C^{3}H_2$), 48.3 (C^{18}H), 43.8 (C^{4}H)

IR (neat) (cm^{-1}): 3029, 2921, 2805, 1551, 1495, 1454, 1378, 1089, 911, 757, 735, 701.

Data for **minor diastereomer IV-18*B*:**

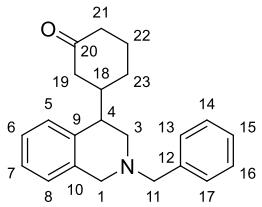
HRMS (ESI): Exact mass calculated for $C_{24}H_{25}N_2O_2$ $[M+H]^+$: 373.1911, found: 373.1904.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.40 (m, 5H, 5 x C^{Ar}**H**), 7.37 – 7.30 (m, 1H, C^{Ar}**H**), 7.26 – 7.06 (m, 6H, 6 x C^{Ar}**H**), 6.81 – 6.74 (m, 2H, 2 x C^{Ar}**H**), 5.19 (dd, *J* = 14.1, 12.2 Hz, 1H, C^{19}**H$_2$**), 4.18 (dd, *J* = 14.1, 3.8 Hz, 1H, C^{19}**H$_2$**), 4.08 – 3.96 (m, 2H, C^{18}**H** + C^{1}**H$_2$**), 3.83 (d, *J* = 12.2 Hz, 1H, C^{11}**H$_2$**), 3.41 (d, *J* = 14.9 Hz, 1H, C^{1}**H$_2$**), 3.31 (d, *J* = 12.3 Hz, 1H, C^{11}**H$_2$**), 3.01 (t, *J* = 4.6 Hz, 1H, C^{4}**H**), 2.91 (d, *J* = 12.3 Hz, 1H, C^{3}**H$_2$**), 2.07 (dd, *J* = 12.4, 4.3 Hz, 1H, C^{3}**H$_2$**)

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9 (C^{Ar}), 138.0 (C^{Ar}), 136.5 (C^{Ar}), 135.1 (C^{Ar}), 130.3 (2 x C^{Ar}H), 128.9 (2 x C^{Ar}H), 128.8 (2 x C^{Ar}H), 128.6 (C^{Ar}H), 127.8 (2 x C^{Ar}H), 127.8 (C^{Ar}H), 127.2 (C^{Ar}H), 127.1 (C^{Ar}H), 127.0 (C^{Ar}H), 126.7 (C^{Ar}H), 75.4 ($C^{19}H_2$), 63.1 ($C^{11}H_2$), 57.4 ($C^{1}H_2$), 50.4 (C^{18}H), 49.2 ($C^{3}H_2$), 43.8 (C^{4}H)

IR (neat) (cm^{-1}): 3029, 2804, 1547,1495, 1453, 1380, 1088, 756, 738, 700.

3-(*N*-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)cyclohexan-1-one (IV-19)



The title compound was prepared according to General Procedure J using isoquinolinium salt **IV-10** (43 mg, 0.125 mmol), cyclohex-2-en-1-one (12 mg, 0.125 mmol), 5:2 HCO_2H:Et_3N (42 μL, 0.50 mmol) in MeCN (0.1 mL) and was purified by flash column chromatography (6-10% EtOAc in pentane) to furnish tetrahydroisoquinoline **IV-19** (12 mg, 30%) as an inseparable 1:1 diastereomeric mixture as a colourless oil.

Data for **both diastereomers A and B** (from the mixture):

HRMS (ESI): Exact mass calculated for $C_{22}H_{26}NO$ $[M+H]^+$: 320.2009, found: 320.2009.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.24 (m, 5H, 5 x C^{Ar}**H$_{A+B}$**), 7.18 – 7.07 (m, 3H, 3 x C^{Ar}**H$_{A+B}$**), 7.04 – 6.96 (m, 1H, C^{Ar}**H$_{A+B}$**), 7.04 – 6.96 (m, 1H, $C^{1}H_{2A+B}$), 3.76 – 3.66 (m, 1H, $C^{11}H_{2A+B}$), 3.59 –

3.51 (m, 1H, $C^{11}\mathbf{H_{2A+B}}$), 3.47 – 3.34 (m, 1H, $C^{1}\mathbf{H_{2A+B}}$), 3.47 – 3.34 (m, 1H, $C^{3}\mathbf{H_{2A+B}}$), 2.79 (q, *J* = 4.2 Hz, 0.5H, $C^{4}\mathbf{H}_{A/B}$), 2.66 (q, *J* = 4.0 Hz, 0.5H, $C^{4}\mathbf{H}_{A/B}$), 2.54 – 2.44 (m, 1H, $C^{3}\mathbf{H_{2A+B}}$), 2.42 – 1.93 (m, 6H, $C^{18}\mathbf{H}_{A+B}$ + $C^{19}\mathbf{H_{2A+B}}$ + $C^{21}\mathbf{H_{2A+B}}$ + $C^{22}\mathbf{H_{2A/B}}$), 1.87 – 1.79 (m, 0.5H, $C^{23}\mathbf{H}_{A/B}$), 1.65 – 1.42 (m, 2H, $C^{23}\mathbf{H_{2A/B}}$ + $C^{22}\mathbf{H_{2A/B}}$), 1.41 – 1.29 (m, 0.5H, $C^{23}\mathbf{H_{2A/B}}$)

^{13}C NMR (151 MHz, $CDCl_3$) δ 212.6 ($C^{20}{}_{A/B}$), 212.3 ($C^{20}{}_{A/B}$), 138.6 ($C^{Ar}{}_{A/B}$), 138.4 ($C^{Ar}{}_{A/B}$), 136.2 ($C^{Ar}{}_{A/B}$), 136.2 ($C^{Ar}{}_{A/B}$), 135.7 ($C^{Ar}{}_{A/B}$), 135.7 ($C^{Ar}{}_{A/B}$), 129.4 (2 x $C^{Ar}H_{A/B}$), 129.3 (2 x $C^{Ar}H_{A/B}$), 128.9 ($C^{Ar}H_{A/B}$), 128.6 ($C^{Ar}H_{A/B}$), 128.5 (2 x $C^{Ar}H_{A/B}$), 128.4 (2 x $C^{Ar}H_{A/B}$), 127.4 ($C^{Ar}H_{A/B}$), 127.4 ($C^{Ar}H_{A/B}$), 126.7 ($C^{Ar}H_{A/B}$), 126.6 ($C^{Ar}H_{A/B}$), 126.2 ($C^{Ar}H_{A/B}$), 126.2 (2 x $C^{Ar}H_{A/B}$), 126.0 ($C^{Ar}H_{A/B}$), 63.2 ($C^{11}H_{2A/B}$), 63.0 ($C^{11}H_{2A/B}$), 56.7 ($C^{1}H_{2A/B}$), 56.6 ($C^{1}H_{2A/B}$), 52.0 ($C^{3}H_{2A/B}$), 51.7 ($C^{3}H_{2A/B}$), 47.2 ($C^{19}H_{2A/B}$), 45.3 ($C^{19}H_{2A/B}$), 44.1 ($C^{4}H_{A/B}$), 44.0 ($C^{4}H_{A/B}$), 43.4 ($C^{18}H_{A/B}$), 42.9 ($C^{18}H_{A/B}$), 41.6 ($C^{21}H_{A/B}$), 41.6 ($C^{21}H_{A/B}$), 30.1 ($C^{23}H_{2A/B}$), 28.7 ($C^{23}H_{2A/B}$), 25.8 ($C^{22}H_{2A/B}$), 25.6 ($C^{22}H_{2A/B}$)

IR (neat) (cm^{-1}): 3027, 2926, 2864, 2799, 2757, 1708, 1494, 1345, 1312, 1093.

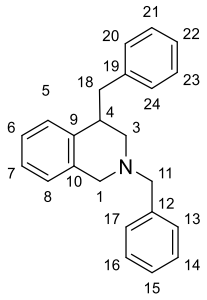
For reaction with an organocatalyst:

The title compound was prepared according to a modified version of General Procedure J using isoquinolinium salt **IV-10** (43 mg, 0.125 mmol), cyclohex-2-en-1-one (12 mg, 0.125 mmol), 5:2 HCO_2H:Et_3N (42 μL, 0.50 mmol) and the chiral primary amine **IV-80** (8 mg, 20 mol%) in MeCN (0.1 mL) and was purified by flash column chromatography (6-10% EtOAc in pentane) to furnish tetrahydroisoquinoline **IV-19** (12 mg, 30%) as an inseparable 1:1 diastereomeric mixture as a colourless oil. Both diastereoisomers were contained the same enantiomeric ratio of 65:35 (i.e.: 30% *ee*). Chiral HPLC: Chiralpak IC with guard, 2 % IPA, 98 % hexane, 1.0 mL/min, 25 °C, λ = 220 nm, 10 μL injection.

Diastereoisomer A: t_R (major) = 14.5 min, t_R (minor) = 17.8 min;

Diastereoisomer B: t_R (major) = 21.4 min, t_R (minor) = 16.1 min.

2,4-Dibenzyl-1,2,3,4-tetrahydroisoquinoline (IV-22)

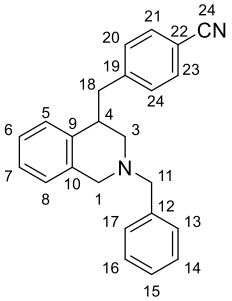


The title compound was prepared according to General Procedure L using isoquinolinium salt **IV-10** (43 mg, 0.125 mmol), benzaldehyde (13 mg, 0.125 mmol), 5:2 HCO_2H:Et_3N (42 μL, 0.5 mmol) in MeCN (0.1 mL) and was purified by column chromatography (2.5% EtOAc in pentane) to furnish tetrahydroisoquinoline **IV-22** (28 mg, 72%) as a colourless oil. Spectroscopic data are in accordance with those described in the literature.[125]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H, 2 x C^{Ar}**H**), 7.42 – 7.31 (m, 3H, 3 x C^{Ar}**H**), 7.25 – 7.12 (m, 6H, 6 x C^{Ar}**H**), 7.07 – 7.00 (m, 3H, 3 x C^{Ar}**H**), 3.90 (d, *J* = 14.8 Hz, 1H, C^1**H$_2$**), 3.74 (d, *J* = 12.9 Hz, 1H, C^{11}**H$_2$**), 3.56 (d, *J* = 12.8 Hz, 1H, C^{11}**H$_2$**), 3.46 (d, *J* = 14.8 Hz, 1H, C^1**H$_2$**), 3.07 – 2.97 (m, 3H, C^{18}**H$_2$** + C^4**H**), 2.79 (d, *J* = 11.5 Hz, 1H, C^3**H$_2$**), 2.39 (d, *J* = 11.6 Hz, 1H, C^3**H$_2$**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9 (C^{Ar}), 138.7 (C^{Ar}), 138.7 (C^{Ar}), 135.2 (C^{Ar}), 129.6 (2 x C^{Ar}H), 129.5 (2 x C^{Ar}H), 128.8 (C^{Ar}H), 128.5 (2 x C^{Ar}H), 128.4 (2 x C^{Ar}H), 127.3 (C^{Ar}H), 126.6 (C^{Ar}H), 126.3 (C^{Ar}H), 126.0 (2 x C^{Ar}H), 63.1 ($C^{11}H_2$), 56.8 (C^1H_2), 53.1 (C^3H_2), 42.9 ($C^{18}H_2$), 41.5 (C^4H).

4-((2-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)methyl)benzonitrile (S21)



The title compound was prepared according to General Procedure L using isoquinolinium salt **IV-10** (40 mg, 0.115 mmol), 4-cyanobenzaldehyde (23 mg, 0.17 mmol) and 5:2 HCO_2H:Et_3N (39 µL, 0.46 mmol) in MeCN (0.1 mL) and was purified by column chromatography (10% EtOAc in pentane) to furnish nitrile **S21** (23 mg, 58%) as a colourless solid.

m.p.: 113 °C ($CHCl_3$)

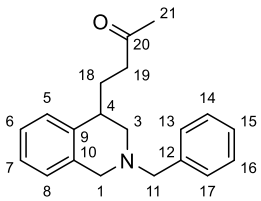
HRMS (ESI): Exact mass calculated for $C_{24}H_{23}N_2$ $[M+H]^+$: 339.1856, found: 339.1855.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.2 Hz, 2H, C^{21}**H** + C^{23}**H**), 7.40 – 7.33 (m, 5H, C^{Bn}**H**), 7.22 – 7.15 (m, 2H, C^6**H** + C^7**H**), 7.13 (dd, *J* = 6.6, 2.6 Hz, 1H, C^5**H**), 7.07 – 7.04 (m, 1H, C^8**H**), 6.98 (d, *J* = 7.8 Hz, 2H, C^{20}**H** + C^{24}**H**), 3.95 (d, *J* = 14.9 Hz, 1H, C^1**H**$_a$), 3.78 (d, *J* = 12.7 Hz, 1H, C^{11}**H**$_a$), 3.49 (d, *J* = 14.8 Hz, 1H, C^1**H**$_b$), 3.44 (d, *J* = 12.7 Hz, 1H, C^{11}**H**$_b$), 3.19 – 3.01 (m, 1H, C^{18}**H**$_a$), 3.00 – 2.90 (m, 2H, C^{18}**H**$_b$ + C^4**H**), 2.68 (d, *J* = 11.6 Hz, 1H, C^3**H**$_a$), 2.42 – 2.26 (m, 1H, C^3**H**$_b$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 146.6 (C^{19}), 138.5 (C^{12}), 137.8 (C^9), 135.1 (C^{10}), 132.0 (C^{20}H + C^{24}H), 130.1 (C^{21}H + C^{23}H), 129.7 (C^{13}H + C^{17}H), 128.7 (C^5H), 128.4 (C^{14}H + C^{16}H), 127.3 (C^{15}H), 126.6 (C^8H), 126.3 (C^7H), 126.2 (C^6H), 119.1 (C^{22}), 109.7 (C^{24}N), 62.8 ($C^{11}H_2$), 57.1 (C^1H_2), 52.1 (C^3H_2), 42.8 ($C^{18}H_2$), 41.2 (C^4H).

IR (neat) (cm^{-1}): 3028, 2922, 2800, 2755, 2226, 1606, 1091, 851, 749, 700.

4-(*N*-Benzyl-1,2,3,4-tetrahydroisoquinolin-4-yl)butan-2-one (IV-67)



The title compound was prepared according to General Procedure J using isoquinolinium salt **IV-10** (43 mg, 0.125 mmol), methyl vinyl ketone (10 µL, 0.125 mmol), 5:2 HCO_2H:Et_3N (42 µL, 0.50 mmol) in MeCN (0.1 mL) and was purified by flash column chromatography (6-10% EtOAc in pentane) to furnish tetrahydroisoquinoline **IV-67** (23 mg, 63%) as a colourless oil.

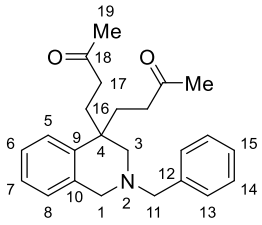
HRMS (ESI): Exact mass calculated for $C_{20}H_{24}NO$ $[M+H]^+$: 294.1852, found: 294.1850.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.16 (m, 5H, 5 x C^{Ar}**H**), 7.13 – 7.01 (m, 3H, 3 x C^{Ar}**H**), 6.92 (d, *J* = 6.7 Hz, 1H, C^{Ar}**H**), 3.73 (d, *J* = 14.8 Hz, 1H, C^{1}**H$_2$**), 3.67 (d, *J* = 13.0 Hz, 1H, C^{11}**H$_2$**), 3.47 (d, *J* = 13.0 Hz, 1H, C^{11}**H$_2$**), 3.40 (d, *J* = 14.8 Hz, 1H, C^{1}**H$_2$**), 2.76 – 2.66 (m, 1H, C^{4}**H**), 2.61 (ddd, *J* = 11.6, 3.6, 1.2 Hz, 1H, C^{3}**H$_2$**), 2.45 (dd, *J* = 11.6, 4.3 Hz, 1H, C^{3}**H$_2$**), 2.31 (ddd, *J* = 16.2, 9.2, 6.6 Hz, 1H, C^{19}**H$_2$**), 2.19 (ddd, *J* = 16.8, 9.4, 5.6 Hz, 1H, C^{19}**H$_2$**), 1.99 (s, 3H, C^{21}**H$_3$**), 1.98 – 1.87 (m, 2H, 2 x C^{18}**H$_2$**)

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1 (C^{20}O), 138.8 (C^{Ar}), 138.4 (C^{Ar}), 135.2 (C^{Ar}), 129.2 (2 x C^{Ar}H), 128.5 (2 x C^{Ar}H), 128.4 (C^{Ar}H), 127.3 (C^{Ar}H), 126.6 (C^{Ar}H), 126.3 (C^{Ar}H), 126.0 (C^{Ar}H), 62.9 ($C^{11}H_2$), 56.9 ($C^{1}H_2$), 53.9 ($C^{3}H_2$), 41.4 ($C^{19}H_2$), 38.0 (C^{4}H), 30.0 ($C^{21}H_3$), 30.0 ($C^{18}H_2$)

IR (neat) (cm^{-1}): 2925, 2797, 1712, 1493, 1452, 1366, 1159, 1095, 740, 700.

4,4'-(2-Benzyl-1,2,3,4-tetrahydroisoquinoline-4,4-diyl)bis(butan-2-one) (IV-70)



The title compound was prepared according to modified General Procedure K using isoquinolinium salt **IV-10** (43 mg, 0.125 mmol), methyl vinyl ketone (50 µL, 0.61 mmol), 5:2 HCO_2H:Et_3N (42 µL, 0.50 mmol) in MeCN (0.1 mL) and was purified by flash column chromatography (2% MeCN in 1:1 pentane:CH_2Cl_2) to furnish tetrahydroisoquinoline **IV-70** (20 mg, 44%) as a colourless oil.

General procedure J gave the title compound in comparable yield of 45%, however this procedure resulted in formation of an impurity that made purification significantly more challenging and a clean sample of 5x could not be obtained without significant losses in yield.

HRMS (ESI): Exact mass calculated for $C_{24}H_{30}NO_2$ $[M+H]^+$: 364.2271, found: 364.2274.

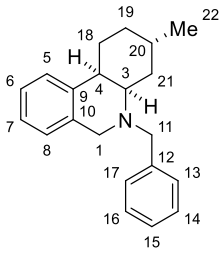
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 5H, 5 x C^{Ar}**H**), 7.24 – 7.08 (m, 3H, 3 x C^{Ar}**H**), 7.00 (dd, J = 7.5, 1.4 Hz, 1H, C^{Ar}**H**), 3.60 – 3.53 (m, 4H, C^{1}**H$_2$** + C^{11}**H$_2$**), 2.51 – 2.37 (m, 4H, C^{3}**H$_2$** + C^{17}**H$_2$**), 2.12 – 1.96 (m, 10H, C^{16}**H$_2$** + C^{17}**H$_2$** + 2 x C^{9}**H$_3$**), 1.84 – 1.74 (m, 2H, C^{16}**H$_2$**)

^{13}C NMR (101 MHz, $CDCl_3$) □□ 208.9 (C^{18}), 139.5 (C^{Ar}), 138.3 (C^{Ar}), 135.9 (C^{Ar}), 129.4 (2 x C^{13}H/C^{14}H), 128.4 (2 x C^{13}H/C^{14}H), 127.4 (C^{Ar}H), 126.9 (C^{Ar}H), 126.7 (C^{Ar}H), 126.3 (C^{Ar}H), 126.0 (C^{Ar}H), 63.1 ($C^{11}H_2$), 59.4 ($C^{1}H_2$), 57.4 ($C^{3}H_2$), 40.2 ($C^{17}H_2$), 39.5 (C^{4}H), 35.0 ($C^{19}H_3$), 30.1 ($C^{16}H_2$)

IR (neat) (cm^{-1}): 2925, 2797, 1712, 1493, 1452, 1366, 1159, 1095, 740, 700.

7.3.13 Annulation reactions

_N_-Benzyl-3-methyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (V-1)



The title compound was prepared according to General Procedure K using isoquinolinium salt **V-49** (45 mg, 0.125 mmol), methyl vinyl ketone (10 µL, 0.125 mmol), 5:2 HCO_2H:Et_3N (42 µL, 0.50 mmol), $[RhCp^*Cl]_2$ (7.7 µg, 0.0125 µmol, 0.01 mol%) in MeCN (0.1 mL) and was purified by flash column chromatography (1-2% EtOAc in pentane) to furnish the annulated tetrahydroisoquinoline **V-1** (20 mg, 55%) as a single diastereomer as a colourless oil.

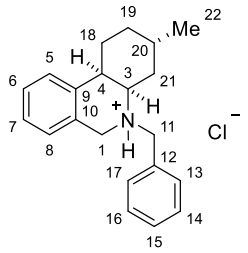
HRMS (ESI): Exact mass calculated for $C_{21}H_{26}N$ $[M+H]^+$: 292.2060, found: 292.2054.

^{1}H NMR (400 MHz, $CDCl_3$) 7.52 – 7.46 (m, 2H, 2 x C^{Ar}**H**), 7.43 – 7.35 (m, 2H, 2 x C^{Ar}**H**), 7.35 – 7.29 (m, 1H, C^{Ar}**H**), 7.21 – 7.07 (m, 3H, 3 x C^{Ar}**H**), 6.92 (d, *J* = 7.5 Hz, 1H, C^{Ar}**H**), 4.39 (d, *J* = 13.0 Hz, 1H, C^{1}**H$_2$**), 3.86 (d, *J* = 15.4 Hz, 1H, C^{11}**H$_2$**), 3.29 (d, *J* = 14.7 Hz, 1H, C^{11}**H$_2$**), 3.12 (d, *J* = 13.0 Hz, 1H, C^{1}**H$_2$**), 2.89 (d, *J* = 3.2 Hz, 1H, C^{3}**H**), 2.73 (dt, *J* = 11.9, 3.5 Hz, 1H, C^{4}**H**), 2.36 – 2.26 (m, 1H, C^{21}**H$_2$**), 2.26 – 2.15 (m, 1H, C^{18}**H$_2$**), 1.98 – 1.85 (m, 2H, C^{19}**H** + C^{20}**H$_2$**), 1.80 (dq, *J* = 13.3, 3.6 Hz, 1H, C^{18}**H$_2$**), 1.35 (ddd, *J* = 14.8, 11.9, 3.1 Hz, 1H, C^{21}**H$_2$**), 1.31 – 1.16 (m, 1H, C^{19}**H$_2$**), 0.97 (d, *J* = 6.5 Hz, 3H, C^{22}**H$_3$**);

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 (C^{Ar}), 140.4 (C^{Ar}), 134.6 (C^{Ar}), 128.7 (2 x C^{Ar}H), 128.4 (2 x C^{Ar}H), 128.1 (C^{Ar}H), 126.9 (C^{Ar}H), 126.1 (C^{Ar}H), 126.0 (C^{Ar}H), 125.6 (C^{Ar}H), 58.3 (C^{3}H), 56.8 ($C^{1}H_2$), 56.0 ($C^{11}H_2$), 42.5 (C^{4}H), 37.5 ($C^{21}H_2$), 35.6 ($C^{19}H_2$), 32.4 ($C^{18}H_2$), 26.0 (C^{20}H), 22.7 (C^{22}H);

IR (neat) (cm^{-1}):2946, 2922, 2786, 1379, 1369, 1155, 1069, 966, 744, 699.

***N*-Benzyl-3-methyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridin-5-ium chloride (V-1·HCl)**



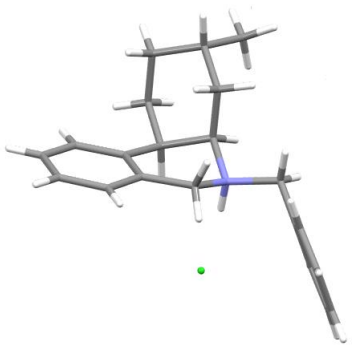
The hydrochloride of **V-1** was formed by dissolving **V-1** (94 mg, 0.32 mmol) in degassed Et_2O (3 mL) and adding 2M HCl in diethyl ether (0.18 mL, 0.35 mmol) dropwise at 0 °C. After stirring at 0° C for 20 min the reaction mixture was filtered to give **V-1·HCl** (100 mg, 85%) as a colourless solid.

m.p. (CH_2Cl_2): 176 °C.

HRMS (ESI): Exact mass calculated for $C_{21}H_{27}N$ $[M]^+$: 292.2060, found: 292.2061.

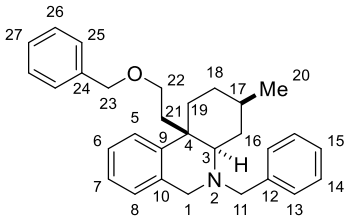
^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers 60:40) δ 12.82 (s, 1H), 12.21 (s, 1H), 7.93 – 7.86 (m, 2H), 7.69 – 7.64 (m, 3H), 7.43 (m, 7H), 7.34 – 7.27 (m, 2H), 7.25 – 7.14 (m, 4H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.99 (dd, *J* = 7.8, 1.3 Hz, 1H), 4.59 (dd, *J* = 16.0, 4.2 Hz, 2H), 4.48 (dd, *J* = 13.6, 3.9 Hz, 2H), 4.46 – 4.38 (m, 2H), 4.30 (dd, *J* = 13.5, 5.7 Hz, 1H), 4.13 (dd, *J* = 12.7, 7.0 Hz, 1H), 3.97 (dd, *J* = 15.8, 5.2 Hz, 4H), 3.07 (dt, *J* = 9.1, 4.5 Hz, 1H), 2.40 (dtd, *J* = 14.2, 9.0, 3.4 Hz, 1H), 2.28 – 2.01 (m, 3H), 1.91 – 1.70 (m, 5H), 1.65 (ddd, *J* = 12.4, 4.8 Hz, 1H), 1.42 (dddd, *J* = 13.8, 4.1 Hz, 1H), 1.24 – 1.11 (m, 3H), 0.94 (d, *J* = 6.8 Hz, 4H), 0.86 (d, *J* = 7.3 Hz, 3H).

Crystal data $C_{21}H_{26}ClN$, M = 327.90, orthorombic, a = 11.29240(10), b = 13.6629(2), c = 23.2273(2) Å, β = 90°, Z = 8, T = 150 K, space group $Pna2_1$, 43420 reflections measured, 6973 unique (R_{int} = 0.027), which were used in all calculations.



***N*-Benzyl-10b-(2-(benzyloxy)ethyl)-3-methyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridine**

(V-39)



The title compound was prepared following General procedure K using *N*-benzyl-4-(2-(benzyloxy)ethyl)-3-methylisoquinolinium iodide **V-40** (124 mg, 0.25 mmol, 1.00 equiv.) and methyl vinyl ketone (42.0 μL, 0.50 mmol, 2.00 equiv.). Flash chromatography (2% EtOAc in pentane) gave the desired product **V-42** (53.2 mg, 0.125 mmol, 50%) as a clear oil.

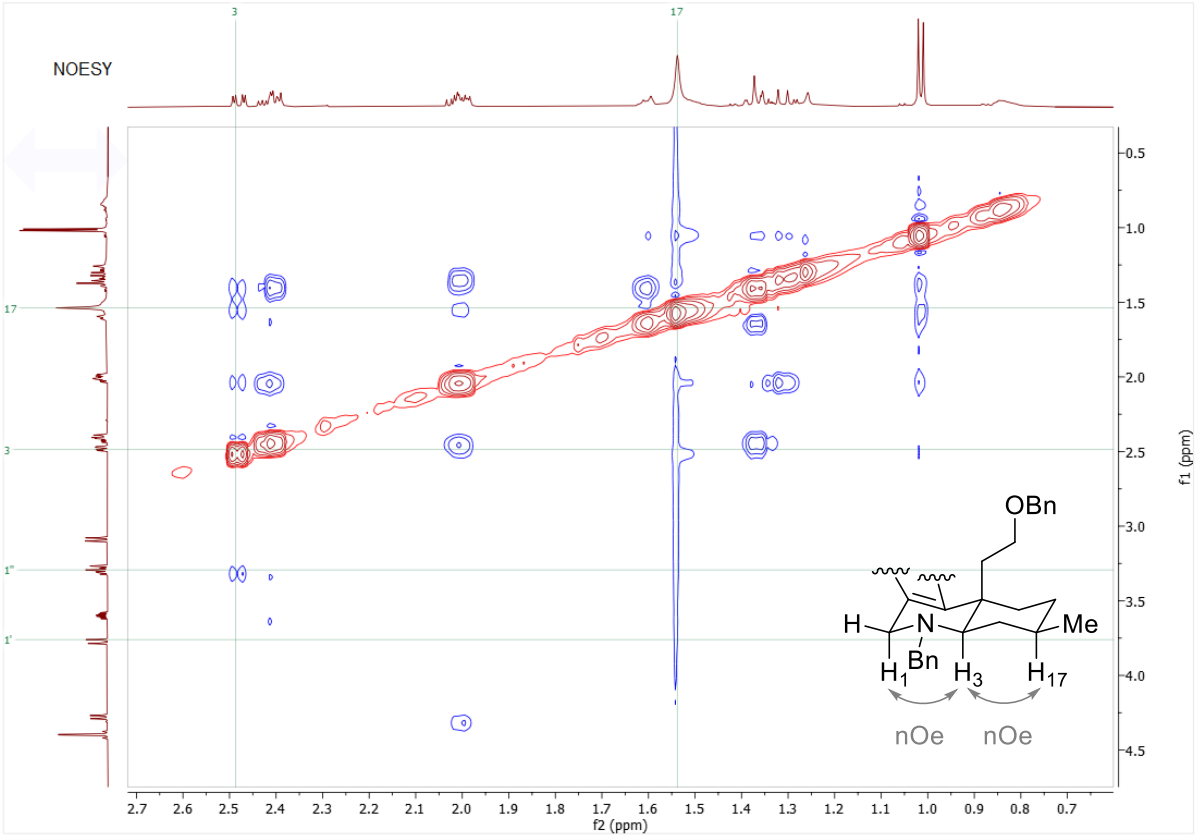
HRMS (ESI): Exact mass calculated for $C_{30}H_{36}NO$ $[M+H]^+$: 426.2791, found: 426.2799.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 8H, C^5**H** + 7 x C^{Ar}**H**), 7.25 – 7.17 (m, 3H, 3 x C^{Ar}**H**), 7.10 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 1H, C^7**H**), 7.06 (td, *J* = 7.4, 1.4 Hz, 1H, C^6**H**), 6.91 – 6.83 (m, 1H, C^8**H**), 4.40 (d, *J* = 2.7 Hz, 2H, C^{23}**H$_2$**), 4.28 (d, *J* = 12.7 Hz, 1H, C^{11}**H$_2$**), 3.77 (d, *J* = 15.6 Hz, 1H, C^1**H$_2$**), 3.60 (ddd, *J* = 9.9, 9.1, 5.2 Hz, 1H, C^{22}**H$_2$**), 3.34 – 3.25 (m, 2H, C^1**H$_2$** + C^{22}**H$_2$**), 3.09 (d, *J* = 12.7 Hz, 1H, C^{11}**H$_2$**), 2.48 (ddd, *J* = 12.3, 3.7, 0.0 Hz, 1H, C^3**H**), 2.41 (td, *J* = 6.3, 2.8 Hz, 1H, C^{21}**H$_2$**), 2.00 (ddd, *J* = 11.5, 5.8, 2.6 Hz, 1H, $C^{18/19}$**H$_2$**), 1.63 – 1.55 (m, 1H, $C^{18/19}$**H$_2$**), 1.51 (d, *J* = 11.7 Hz, 1H, C^{17}**H**), 1.45 – 1.22 (m, 5H, 2x $C^{18/19}$**H$_2$,** C^{16}**H$_2$,** C^{21}**H$_2$**), 1.01 (d, *J* = 6.5 Hz, 3H, C^{20}**H$_3$**).

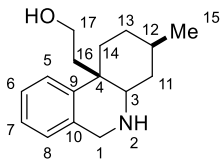
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.0 (C^{Ar}H), 140.5 (C^9), 139.0 (C^{Ar}H), 134.8 (C^{Ar}H), 128.8 (2 x C^{Ar}H), 128.5 (C^4H + C^{Ar}H), 128.4 (2 x C^{Ar}H), 127.8 (2 x C^{Ar}H), 127.5 (C^{Ar}H), 126.9 (C^{Ar}H), 126.5 (C^8H), 125.8 (C^{Ar}H), 125.7 (C^6H), 125.6 (C^7H), 73.2 (C^{23}H), 68.7 (C^{22}H), 67.0 (C^3H), 57.3 (C^{11}H), 57.1 (C^1H), 40.6 (C^4H), 34.4 (C^{21}H), 33.7 ($C^{18/19}$H), 33.3 (C^{11}H), 32.4 (C^{17}H), 29.8 ($C^{18/19}$H), 22.8 (C^{20}H).

IR (neat) (cm^{-1}): 2926, 2868, 1718, 1669, 1602, 1495, 1455, 1365, 1255, 1103.

Relative stereochemistry was determined using nOe interactions:



2-(3-Methyl-2,3,4,4a,5,6-hexahydrophenanthridin-10b(1H)-yl)ethan-1-ol (V-44)



The title compounp was prepared following a literature procedure.[126] *N*-benzyl-10b-(2-(benzyloxy)ethyl)-3-methyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridine **V-39** (50.0 mg, 0.118 mmol, 1.00 equiv.) was dissolved in MeOH (2.50 mL, 0.005 M). Aq. HCl (0.20 mL, 1.00 M) was added dropwise, and N_2 was bubbled under vigorous stirring. Palladium hydroxide on carbon loading 20 wt% (6.0 mg, 20 mol%) was added, and H_2 was bubbled under vigorous stirring. The reaction was allowed to stir at 65 °C (reflux) for 3 h, after which the reaction was diluted with CH_2Cl_2 (10.0 mL), washed with brine (2 x 10.0 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (1% MeOH in DCM) gave the desired product **V-44** (19.9 mg, 0.081 mmol, 69%) as a clear oil.

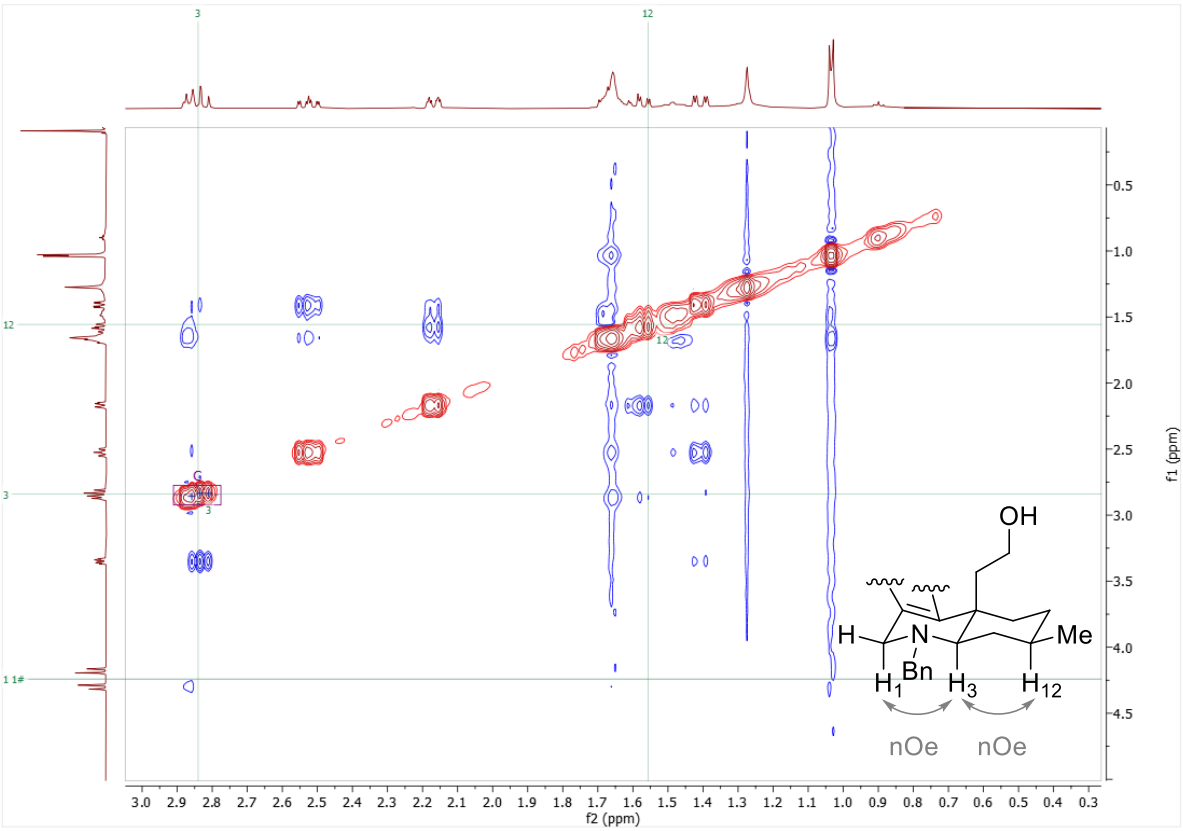
HRMS (ESI): Exact mass calculated for $C_{16}H_{24}NO$ $[M+H]^+$: 246.1852, found: 246.1863.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.13 (m, 3H, C^{5}**H** + C^{6}**H** + C^{7}**H**), 7.04 (d, *J* = 7.5 Hz, 1H, C^{8}**H**), 5.00 (s, 2H, O**H** + N**H**), 4.28 (d, *J* = 15.1 Hz, 1H, C^{1}**H$_2$**), 4.15 (d, *J* = 15.2 Hz, 1H, C^{1}**H$_2$**), 3.33 (ddd, *J* = 11.8, 4.2, 2.9 Hz, 1H, C^{17}**H$_2$**), 2.91 – 2.76 (m, 2H, C^{17}**H$_2$** + C^{3}**H**), 2.50 (ddd, *J* = 14.7, 11.5, 2.9 Hz, 1H, C^{16}**H$_2$**), 2.21 – 2.10 (m, 1H, $C^{13/14}$**H$_2$**), 1.72 – 1.59 (m, 4H, $C^{13/14}$**H$_2$** + C^{12}**H** + C^{11}**H$_2$**), 1.54 (dd, *J* = 12.8, 3.3 Hz, 1H, $C^{13/14}$**H$_2$**), 1.50 – 1.42 (m, 1H, C^{11}**H$_2$**), 1.42 – 1.34 (m, 1H, C^{16}**H$_2$**), 1.01 (d, *J* = 5.0 Hz, 3H, C^{15}**H$_3$**).

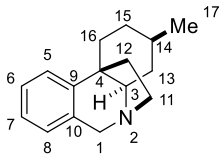
^{13}C NMR (126 MHz, $CDCl_3$) δ 141.6 (C^{9}), 133.5 (C^{10}), 127.0 (C^{7}), 126.7 (C^{8}), 126.3 (C^{6}), 125.4 (C^{5}), 60.0 (C^{3}), 58.1 (C^{17}), 48.6 (C^{1}), 41.8 (C^{4}), 39.2 (C^{16}), 38.2 ($C^{13/14}$), 36.0 ($C^{13/14}$), 32.4 (C^{12}), 30.3 (C^{11}), 22.2 (C^{15}).

IR (neat) (cm^{-1}): 3402, 2925, 2860, 1652, 1494, 1457, 1311, 1192, 1090, 1042.

Relative stereochemistry was determined using nOe interactions:



(5S,10bR)-3-Methyl-2,3,4,4a-tetrahydro-1H,6H-5,10b-ethanophenanthridine (V-45)



Appel conditions:

2-(3-Methyl-2,3,4,4a,5,6-hexahydrophenanthridin-10b(1H)-yl)ethan-1-ol **V-44** (30 mg, 0.12 mmol, 1.00 equiv.), triphenyl phosphine (68 mg, 0.26 mmol, 2.20 equiv.), and imidazole (20 mg, 0.3 mmol, 2.5 equiv.) were dissolved in CH_2Cl_2 (0.25 mL) and cooled down to 0 °C. Iodine () was added slowly and then the reaction mixture was heated to 40 °C for 6 hours. the reaction was diluted with CH_2Cl_2 (5.0 mL), washed with aq. $Na_2S_2O_3$ (5 mL), then washed with aq. NaOH (5 mL, 2.0 M), the organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (1% MeOH in DCM) gave the desired product **V-45** (14 mg, 51%) as an off-white wax.

Mitsunobu conditions (*this protocol was performed by Clément Tanguy*):

2-(3-Methyl-2,3,4,4a,5,6-hexahydrophenanthridin-10b(1H)-yl)ethan-1-ol **V-44** (20 mg, 0.08 mmol, 1.00 equiv.) and triphenyl phosphine (25.5 mg, 0.1 mmol, 1.20 equiv.) were dissolved in THF (0.4 mL, 0.2 M). The solution was cooled to 0 °C and DIAD (20 µL, 0.097 mmol, 1.20 equiv.) was added dropwise. The reaction was allowed to stir at 50 °C for 16 h, after which the reaction was diluted with CH_2Cl_2 (15.0 mL), washed with aq. NaOH (2 x 15 mL, 2.0 M), dried with $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (1% MeOH in DCM) gave the desired product **V-45** (17 mg, 0.073 mmol, 90%) as a red wax.

HRMS (ESI): Exact mass calculated for $C_{16}H_{22}N$ $[M+H]^+$: 228.1747, found: 228.1788.

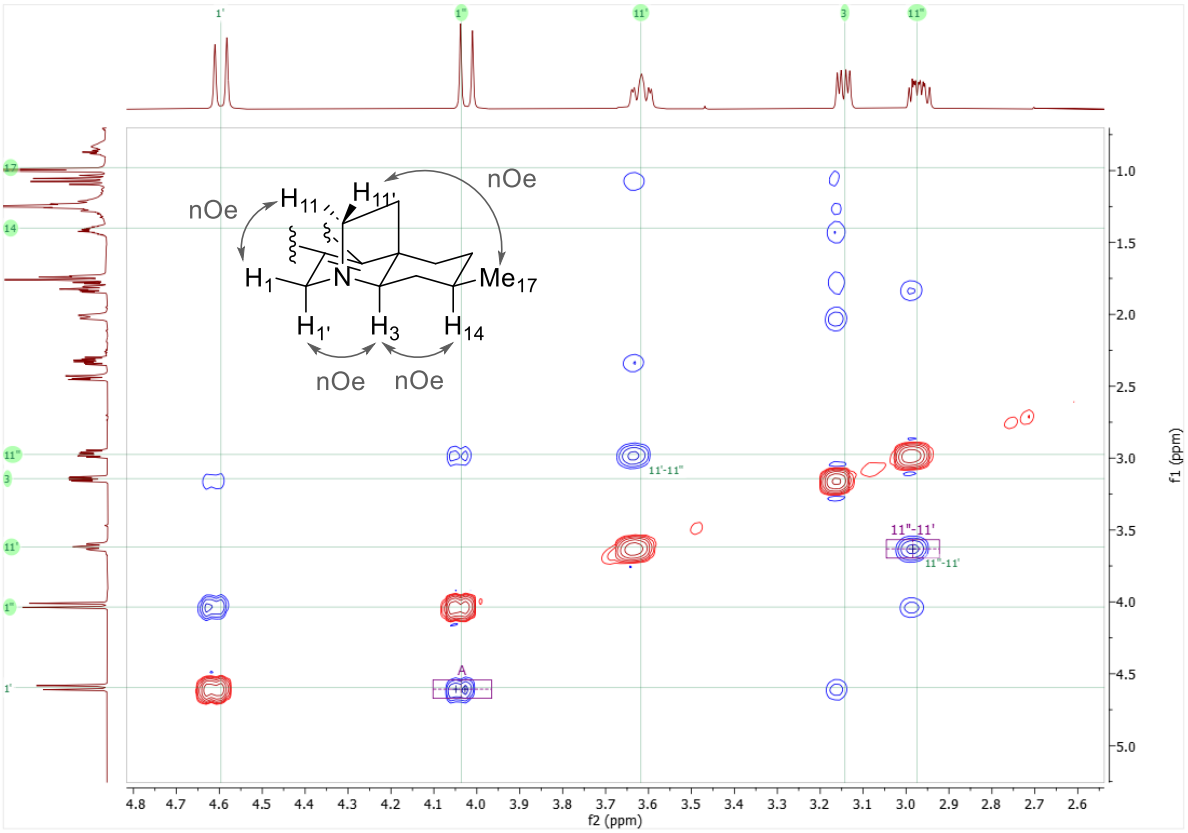
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 – 7.13 (m, 3H, C^5**H** + C^6**H** + C^7**H**), 7.06 – 7.02 (m, 1H, C^8**H**), 4.60 (d, *J* = 16.7 Hz, 1H, C^1**H$_2$**), 4.02 (d, *J* = 16.7 Hz, 1H, C^1**H$_2$**), 3.62 (ddd, *J* = 13.9, 10.7, 3.9 Hz, 1H, C^{11}**H$_2$**), 3.15 (dd, *J* = 12.1, 5.4 Hz, 1H, C^3**H**), 3.01 – 2.93 (m, 1H, C^{11}**H$_2$**), 2.47 – 2.41 (m, 1H, C^{16}**H$_2$**), 2.32 (ddd, *J* = 12.4, 10.8, 6.4 Hz, 1H, C^{12}**H$_2$**), 2.02 (dp, *J* = 12.8, 2.5 Hz, 1H, C^{13}**H$_2$**), 1.82

(ddd, J = 12.7, 9.0, 3.9 Hz, 1H, $C^{12}\mathbf{H_2}$), 1.79 – 1.72 (m, 2H, $C^{15}\mathbf{H_2}$ + $C^{16}\mathbf{H_2}$), 1.47 – 1.36 (m, 1H, $C^{14}\mathbf{H}$), 1.32 – 1.18 (m, 1H, $C^{15}\mathbf{H_2}$), 1.06 (q, J = 12.4 Hz, 1H, $C^{13}\mathbf{H}$), 1.00 (d, J = 6.5 Hz, 3H, $C^{17}\mathbf{H_3}$).

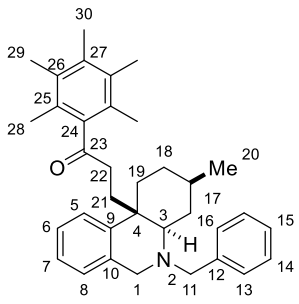
^{13}C NMR (151 MHz, $CDCl_3$) δ 146.9 (C^9), 130.2 (C^{10}), 127.4 (C^7H), 126.7 (C^6H), 126.6 (C^8H), 122.9 (C^5H), 67.8 (C^3H), 61.0 (C^1H_2), 51.8 ($C^{11}H_2$), 43.1 (C^4), 36.8 ($C^{12}H_2$), 34.9 ($C^{13}H_2$), 30.7 (C^{14}H), 30.2 ($C^{15}H_2$), 28.3 ($C^{16}H_2$), 22.3 ($C^{17}H_3$).

IR (neat) (cm^{-1}): 3445, 2952, 2926, 2854, 2360, 2341, 1486, 1459, 1375, 1345.

Relative stereochemistry was determined using nOe interactions:



3-(5-Benzyl-3-methyl-2,3,4,4a,5,6-hexahydrophenanthridin-10b(1H)-yl)-1-(2,3,4,5,6-pentamethylphenyl)propan-1-one (V-65)



The title compound was prepared according to General Procedure K using isoquinolinium salt **V-62** (54 mg, 0.125 mmol), Ph* vinyl ketone (26 mg, 0.125 mmol), 5:2 HCO_2H:Et_3N (42 µL, 0.50 mmol), $[RhCp^*Cl]_2$ (7.7 µg, 0.0125 µmol, 0.01 mol%) in MeCN (0.1 mL) and was purified by flash column chromatography (1-2% EtOAc in pentane) to furnish the annulated tetrahydroisoquinoline **V-65** (32 mg, 74%) as a single diastereomer as a colourless oil.

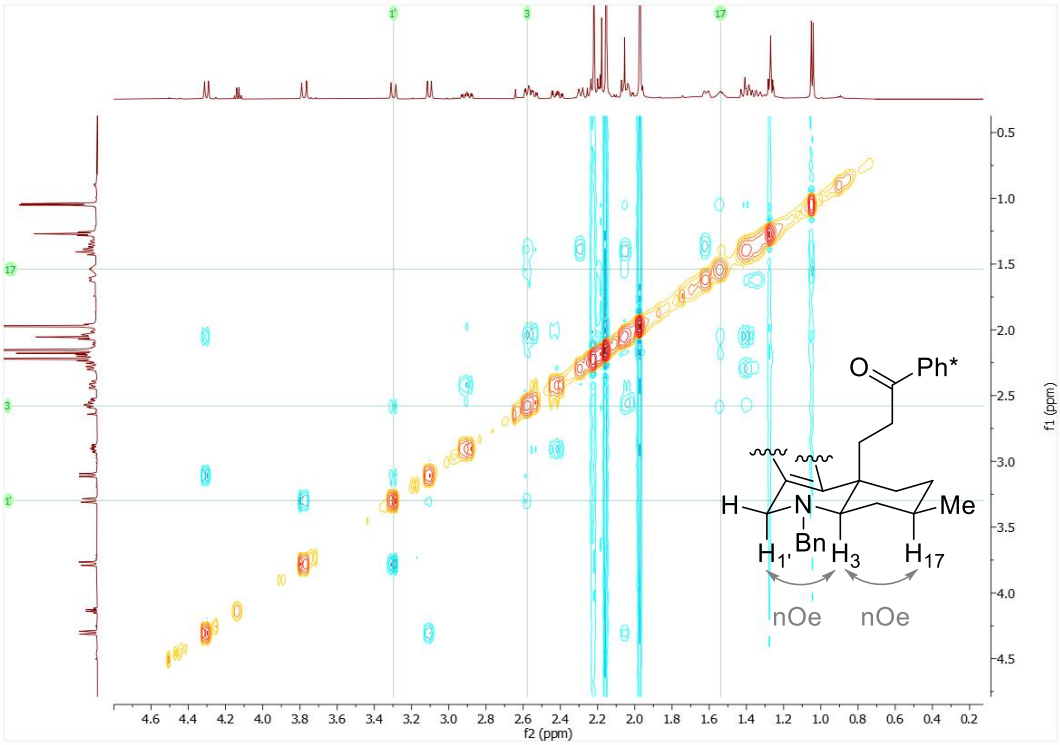
HRMS (ESI): Exact mass calculated for $C_{35}H_{44}NO$ $[M+H]^+$: 494.3417, found: 494.3431.

^{1}H NMR (600 MHz, CDCl3) δ 7.36 – 7.32 (m, 2H, 2 x C^{13}**H**), 7.29 – 7.21 (m, 3H, 2 x C^{14}**H** + C^{15}**H**), 7.19 – 7.16 (m, 1H, C^5**H**), 7.11 – 7.06 (m, 1H, C^6**H**), 7.04 (td, *J* = 7.4, 1.4 Hz, 1H, C^7**H**), 6.85 (dd, *J* = 7.5, 1.5 Hz, 1H, C^8**H**), 4.30 (d, *J* = 12.7 Hz, 1H, C^{11}**H$_2$**), 3.78 (d, *J* = 15.6 Hz, 1H, C^1**H$_2$**), 3.30 (d, *J* = 15.5 Hz, 1H, C^1**H$_2$**), 3.10 (d, *J* = 12.8 Hz, 1H, C^{11}**H$_2$**), 2.90 (ddd, *J* = 18.2, 12.5, 4.3 Hz, 1H, C^{22}**H$_2$**), 2.60 – 2.56 (m, 1H, C^3**H**), 2.56 – 2.51 (m, 1H, C^{21}**H$_2$**), 2.47 – 2.37 (m, 1H, C^{22}**H$_2$**), 2.32 – 2.27 (m, 1H, C^{18}**H$_2$**), 2.22 (s, 3H, C^{30}**H$_3$**), 2.15 (s, 6H, 2 x C^{28}**H$_3$**), 2.08 – 2.05 (m, 1H, C^{16}**H$_2$**), 2.04 – 2.00 (m, 1H, C^{21}**H$_2$**), 1.97 (s, 6H, 2 x C^{29}**H$_3$**), 1.65 – 1.58 (m, 1H, C^{19}**H$_2$**), 1.57 – 1.49 (m, 1H, C^{17}**H**), 1.43 – 1.38 (m, 2H, C^{16}**H$_2$** + C^{18}**H$_2$**), 1.37 – 1.32 (m, 1H, C^{19}**H$_2$**), 1.05 (d, *J* = 6.5 Hz, 3H, C^{20}**H$_3$**).

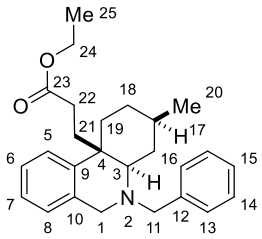
^{13}C NMR (151 MHz, CDCl3) δ 213.3 (C^{23}O), 142.8 (C^9), 141.5 (C^{24}), 140.4 (C^{12}), 135.2 (C^{27}), 134.8 (C^{10}), 133.1 (C^{26}), 128.8 (2 x C^{13}H), 128.4 (2 x C^{14}H), 127.4 (C^{25}, 126.9 (C^{15}H), 126.6 (C^8H), 125.7 (C^7H), 125.6 (C^6H), 125.4 (C^5H), 67.0 (C^3H), 57.5 ($C^{11}H_2$), 57.2 (C^1H_2), 42.0 ($C^{22}H_2$), 40.3 (C^4), 34.5 ($C^{16}H_2$), 33.8 ($C^{18}H_2$), 32.5 (C^{17}H), 29.6 ($C^{19}H_2$), 27.6 ($C^{21}H_2$), 22.7 ($C^{20}H_3$), 17.2 (2 x $C^{29}H_3$), 16.8 ($C^{30}H_3$), 16.0 (2 x $C^{28}H_3$).

IR (neat) (cm^{-1}): 2949, 1697, 1493, 1453, 1381, 1310, 1070, 911, 735, 699.

Relative stereochemistry was determined using nOe interactions:



Ethyl 3-(*N*-benzyl-3-methyl-2,3,4,4a,5,6-hexahydrophenanthridin-10b(1H)-yl)propanoate (V-66)



The title compound was prepared according to General Procedure K using isoquinolinium salt **V-63** (57 mg, 0.125 mmol), methyl vinyl ketone (20 µL, 0.125 mmol), 5:2 HCO_2H:Et_3N (42 µL, 0.50 mmol), $[RhCp^*Cl]_2$ (7.7 µg, 0.0125 µmol, 0.01 mol%) in MeCN (0.1 mL) and was purified by flash column chromatography (1-2% EtOAc in pentane) to furnish the annulated tetrahydroisoquinoline **V-66** (35 mg, 71%) as a single diastereomer as a colourless oil.

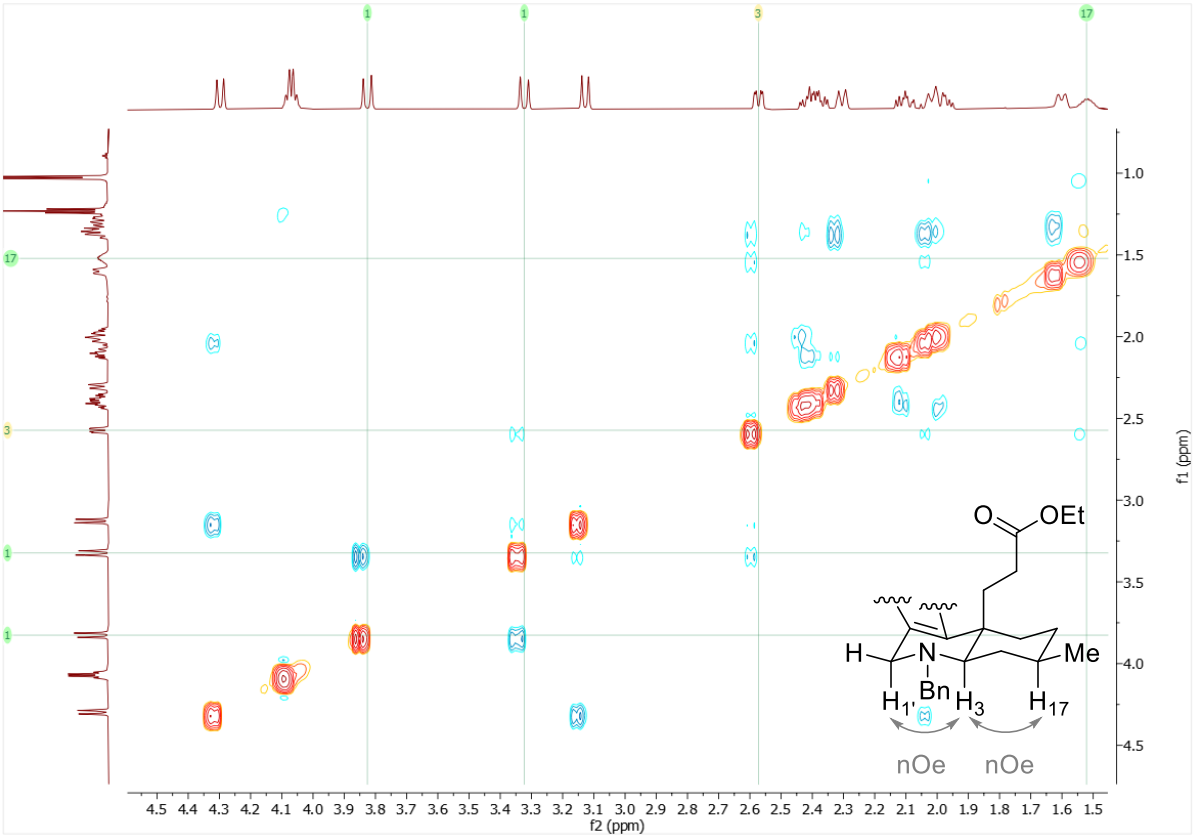
HRMS (ESI): Exact mass calculated for $C_{26}H_{34}NO_2$ $[M+H]^+$: 392.2584, found: 392.2589.

^{1}H NMR (600 MHz, CDCl3) δ 7.38 (d, J = 7.5 Hz, 2H, 2 x C^{13}**H**), 7.32 (t, J = 7.5 Hz, 2H, 2 x C^{14}**H**), 7.28 – 7.22 (m, 1H, C^{15}**H**), 7.19 (d, J = 7.9 Hz, 1H, C^{5}**H**), 7.12 (t, J = 7.5 Hz, 1H, C^{6}**H**), 7.07 (t, J = 7.4 Hz, 1H, C^{7}**H**), 6.88 (d, J = 7.6 Hz, 1H, C^{8}**H**), 4.30 (d, J = 12.8 Hz, 1H, C^{11}**H$_2$**), 4.07 (q, J = 1.0 Hz, 2H, C^{24}**H$_2$**), 3.83 (d, J = 15.6 Hz, 1H, C^{1}**H$_2$**), 3.32 (d, J = 15.6 Hz, 1H, C^{1}**H$_2$**), 3.13 (d, J = 12.8 Hz, 1H, C^{11}**H$_2$**), 2.57 (dd, J = 12.3, 3.7 Hz, 1H, C^{3}**H**), 2.46 – 2.34 (m, 2H, C^{16}**H$_2$** + C^{18}**H$_2$**), 2.30 (dd, J = 13.2, 3.3 Hz, 1H, C^{22}**H$_2$**), 2.16 – 2.06 (m, 1H, C^{16}**H$_2$**), 2.06 – 1.92 (m, 2H, C^{18}**H$_2$** + C^{22}**H$_2$**), 1.60 (d, J = 3.6 Hz, 1H, C^{21}**H$_2$**), 1.52 (tq, J = 10.5, 4.9 Hz, 1H, C^{17}**H**), 1.41 – 1.33 (m, 2H, C^{19}**H$_2$**), 1.30 (td, J = 12.6, 3.3 Hz, 1H, C^{21}**H$_2$**), 1.23 (t, J = 1.0 Hz, 3H, C^{25}**H$_3$**), 1.03 (d, J = 1.1 Hz, 3H, C^{20}**H$_3$**).

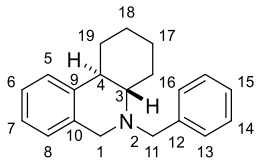
^{13}C NMR (101 MHz, CDCl3) δ 174.8(C^{23}O), 142.6(C^{9}), 140.5(C^{12}), 134.9(C^{10}), 128.8 (2 x C^{14}H), 128.4 (2 x C^{13}H), 126.9(C^{15}H), 126.6(C^{8}H), 125.8(C^{7}H), 125.7(C^{6}H), 125.6(C^{5}H), 66.8(C^{3}H), 60.2($C^{24}H_2$), 57.3 ($C^{11}H_2$), 57.1(C^{1}, 40.5(C^{4}), 33.8 ($C^{19}H_2$), 33.5($C^{22}H_2$), 32.4(C^{17}H), 30.4 ($C^{21}H_2$),29.6 ($C^{16}H_2$), 28.5 ($C^{18}H_2$), 22.7 ($C^{20}H_3$), 14.4 ($C^{25}H_3$).

IR (neat) (cm^{-1}): 3030, 2360, 2341, 1733, 1494, 1453, 1300, 1191, 1115, 1029.

Relative stereochemistry was determined using nOe interactions:



5-Benzyl-1,2,3,4,4a,5,6,10b-octahydrophenanthridine (V-67)



The title compound was prepared according to General Procedure K using isoquinolinium salt **V-64** (52 mg, 0.125 mmol), 5:2 HCO_2H:Et_3N (42 µL, 0.50 mmol), AND $[RhCp^*Cl]_2$ (7.7 µg, 0.0125 µmol, 0.01 mol%) in MeCN (0.1 mL) and was purified by flash column chromatography (1-2% EtOAc in pentane) to furnish the annulated tetrahydroisoquinoline **V-66** (16 mg, 46%) as a 1.2:1 mixture of diastereoisomers. The major diastereoisomer could be partially separated and its spectroscopic data is presented here:

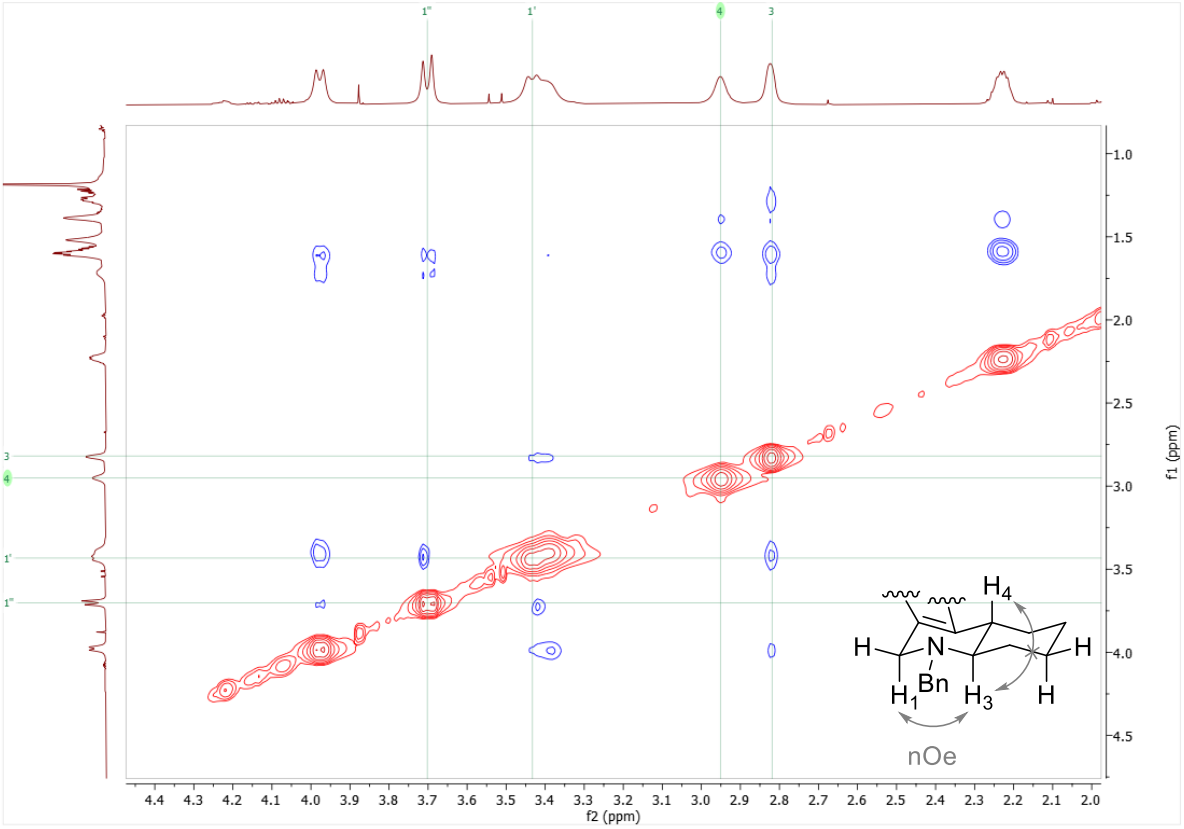
HRMS (ESI): Exact mass calculated for $C_{20}H_{24}N$ $[M+H]^+$: 278.1903, found: 278.1898.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, J = 7.5 Hz, 2H, 2 x C^{14}**H**), 7.33 (t, J = 7.6 Hz, 2H, 2 x C^{13}**H**), 7.26 (s, 1H, C^{15}**H**), 7.22 (d, J = 7.7 Hz, 1H, C^5**H**), 7.15 (t, J = 7.5 Hz, 1H, C^6**H**), 7.08 (t, J = 7.4 Hz, 1H, C^7**H**), 6.93 (d, J = 7.6 Hz, 1H, C^8**H**), 4.05 (d, J = 13.2 Hz, 1H, C^{11}**H$_2$**), 3.80 – 3.75 (m, 1H, C^1**H$_2$**), 3.50 (d, J = 20.3 Hz, 2H, C^1**H$_2$** + C^{11}**H$_2$**), 3.02 (s, 1H, C^4**H**), 2.89 (d, J = 7.3 Hz, 1H, C^3**H**), 2.30 (dd, J = 13.0, 6.5 Hz, 1H, $C^{19/16}$**H$_2$**), 1.70 – 1.61 (m, 2H, 2 x $C^{19/16}$**H$_2$**), 1.58 (s, 2H, 2 x $C^{17/18}$**H$_2$**), 1.40 – 1.28 (m, 1H, $C^{19/16}$**H$_2$**), 1.26 (d, J = 1.9 Hz, 2H, $C^{17/18}$**H$_2$**).

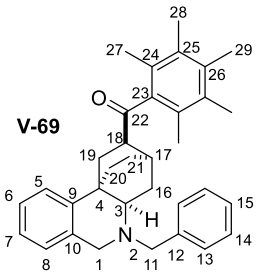
^{13}C NMR (151 MHz, $CDCl_3$) δ 140.0 (C^{12}), 138.8 (C^9), 135.1 (C^{10}), 128.8 (2 x C^{14}H), 128.4 (2 x C^{13}H), 127.1 (C^5H), 127.0 (C^{15}H), 126.4 (C^8H), 126.2 (C^6H), 125.5 (C^7H), 58.2 (C^3H), 57.9 ($C^{11}H_2$), 53.4 (C^1H_2), 40.4 (C^4H), 30.4 ($C^{19/16}H_2$), 29.9 ($C^{17/18}H_2$), 24.1 ($C^{17/18}$H), 22.8 ($C^{16/19}$H).

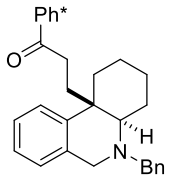
IR (neat) (cm^{-1}): 3026, 2935, 2795, 2360, 2341, 1494, 1451, 1368, 1263, 1099.

Relative stereochemistry was determined using nOe interactions:



3-(5-Benzyl-2,3,4,4a,5,6-hexahydrophenanthridin-10b(1H)-yl)-1-(2,3,4,5,6-pentamethylphenyl) propan-1-one (V-69)





V-70

The title compound was prepared according to General Procedure K using isoquinolinium salt **V-64** (57 mg, 0.125 mmol), Ph* vinyl ketone (26 mg, 0.125 mmol), 5:2 HCO_2H:Et_3N (42 µL, 0.50 mmol), $[RhCp^*Cl]_2$ (7.7 µg, 0.0125 µmol, 0.01 mol%) in MeCN (0.1 mL). Following FCC a inseperable mixture of **V-69** and **V-70** of 4:1 was obtained (combined yield of 48%).

Spectroscopic data for **V-69:**

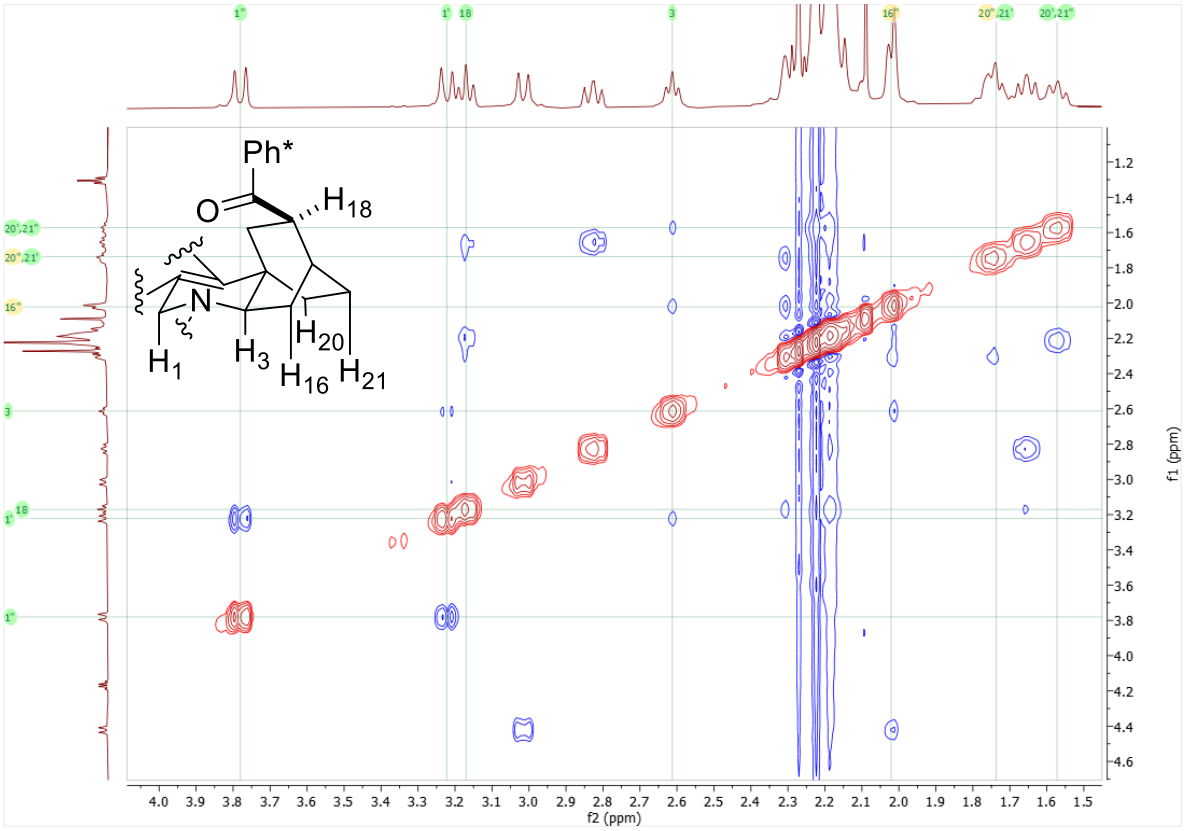
HRMS (ESI): Exact mass calculated for $C_{34}H_{40}NO$ $[M+H]^+$: 478.3104, found: 478.3115.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, J = 7.6 Hz, 2H, 2 x C^{14}**H**), 7.35 (t, J = 7.6 Hz, 2H, 2 x C^{13}**H**), 7.29 – 7.26 (m, 1H, C^{15}**H**), 7.24 (d, J = 7.9 Hz, 1H, C^{5}**H**), 7.13 (t, J = 7.5 Hz, 1H, C^{6}**H**), 7.03 (td, J = 7.5, 1.3 Hz, 1H, C^{7}**H**), 6.84 (d, J = 7.6 Hz, 1H, C^{8}**H**), 4.39 (d, J = 13.3 Hz, 1H, C^{11}**H$_2$**), 3.75 (d, J = 15.1 Hz, 1H, C^{1}**H$_2$**), 3.19 (d, J = 15.1 Hz, 1H, C^{1}**H$_2$**), 3.14 (t, J = 9.9 Hz, 1H, C^{3}**H**), 2.99 (d, J = 13.3 Hz, 1H, C^{11}**H$_2$**), 2.79 (ddd, J = 12.9, 9.9, 2.4 Hz, 1H, C^{16}**H$_2$**), 2.63 – 2.54 (m, 1H, C^{18}**H**), 2.31 – 2.26 (m, 1H, C^{17}**H**), 2.24 (s, 3H, C^{29}**H$_3$**), 2.19 (s, 6H, 2 x $C^{27/28}$**H$_3$**), 2.17 – 2.13 (m, 7H, $C^{20/21}$**H$_2$** + $C^{27/28}$**H$_3$**), 2.01 – 1.95 (m, 2H, C^{16}**H$_2$**), 1.78 – 1.67 (m, 2H, 2 x $C^{20/21}$**H$_2$**), 1.62 (ddd, J = 13.5, 9.7, 1.7 Hz, 1H, C^{19}**H$_2$**), 1.54 (ddd, J = 13.1, 7.7, 2.5 Hz, 1H, $C^{20/21}$**H$_2$**).

^{13}C NMR (151 MHz, $CDCl_3$) δ 212.8 (C^{22}), 142.1 (C^{9}), 140.4 (C^{Ar}), 140.0 (C^{12}), 135.5 (C^{Ar}), 134.3 (C^{10}), 129.0 (2 x C^{14}H), 128.4 (2 x C^{13}H), 126.9 (C^{15}H), 126.4 (C^{6}H), 126.4 (C^{5}H), 126.1 (C^{8}H), 125.6 (C^{7}H), 61.7 (C^{18}H), 57.4 ($C^{11}H_2$), 56.3 ($C^{1}H_2$), 52.1 (C^{3}H), 36.6 (C^{4}), 32.8 ($C^{19}H_2$), 31.0 ($C^{20/21}H_2$), 29.4 ($C^{16}H_2$), 27.1 (C^{17}H), 26.2 ($C^{20/21}H_2$), 21.1 (C^{18}H), 18.1 (d, J = 37.6 Hz, 2 x $C^{Ph*}H_3$), 16.9 (2 x $C^{29}H_3$), 16.2 ($C^{Ph*}H_3$).

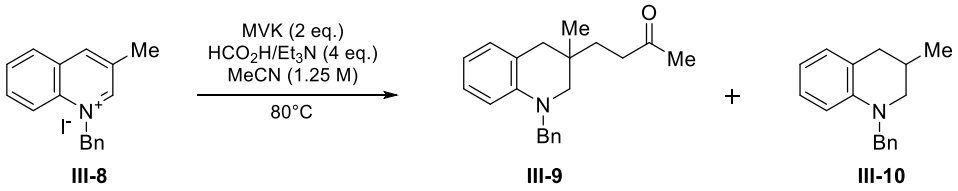
IR (neat) (cm^{-1}): 3027, 2866, 2787, 1690, 1494, 1453, 1383, 1310, 1257, 1109.

Relative stereochemistry was determined using nOe interactions:



7.3.14 Investigation into reaction kinetics

Reactions were carried out in GC vials using 20 mg of *N*-Benzyl-3-methylquinolinium iodide (**1a**), and a "Mastermix", containing aliquots of 8.9 μL methyl vinyl ketone, 18.7 μL 5:2 formic acid-triethylamine complex and $[RhCp^*Cl_2]_2$ in acetonitrile (45 μL). The new vials (without magnetic stirring) were placed in an 80 °C oil bath and heated for the time indicated before quenching by dilution in CH_2Cl_2/0.1 M aqueous K_2CO_3. Crude mixtures obtained this way were analysed by quantitative ^{1}H-NMR using trimethoxybenzene (3.1 mg per $CDCl_3$ aliquot) as an internal standard. Methoxy peaks of TMB (6.09 ppm) and methyl peaks of the product **3a** (0.97 ppm) and reduced side-product **2a** (1.05 ppm) were chosen as diagnostic signals for quantification.

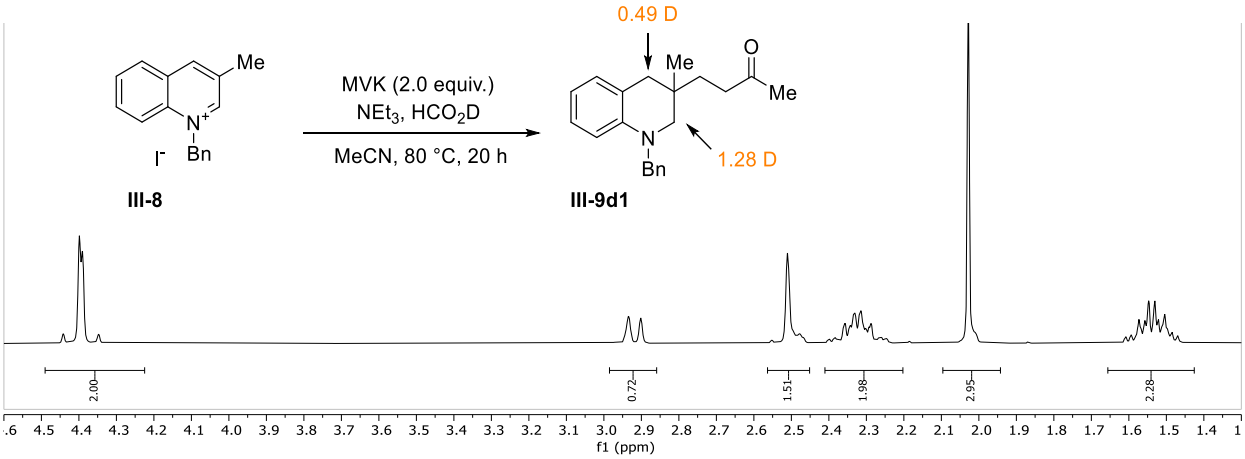


7.3.15 Deuterium labelling experiments

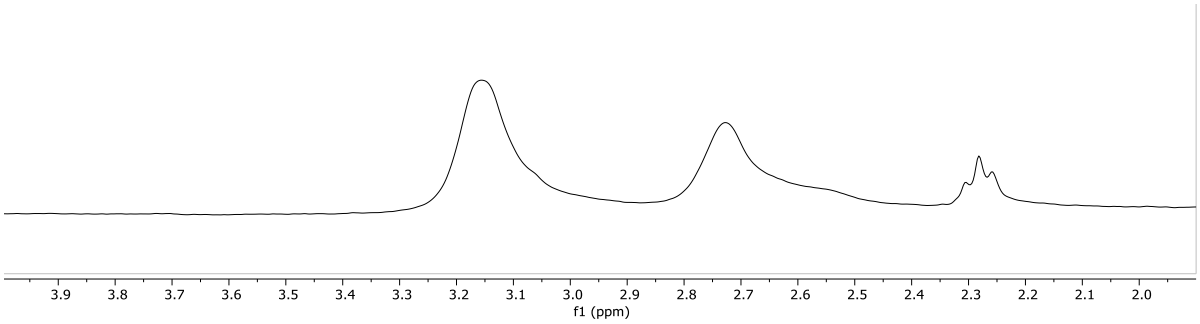
Formic-d acid, formic acid-d and formic acid-d_2 were purchased from Sigma Aldrich and used without further purification. All reactions were performed following General Procedure B or E, using deuterated reagents where specified in the reaction scheme.

Reaction with formic-d acid (DCO_2H):

^{1}H NMR

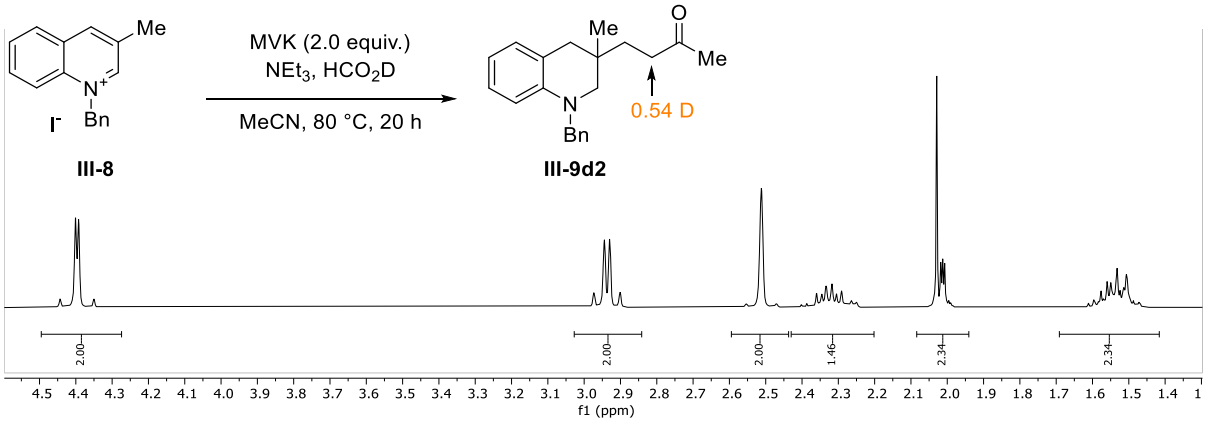


^{2}H NMR

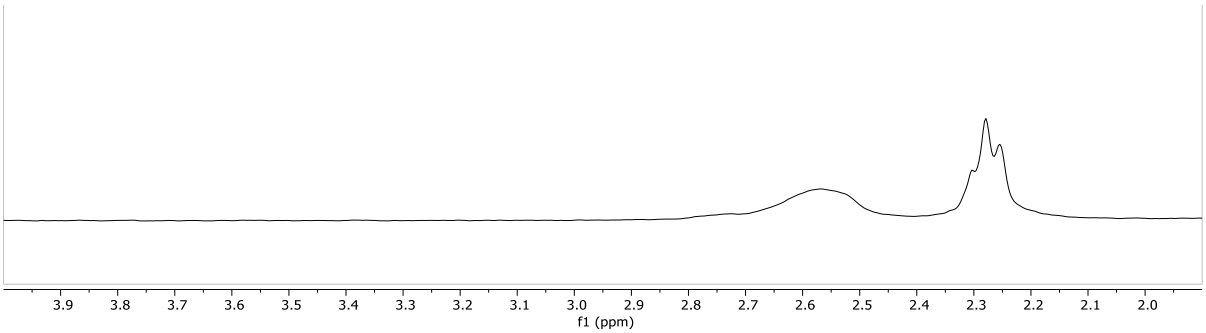


Reaction with formic acid-d (HCO_2D):

^{1}H NMR

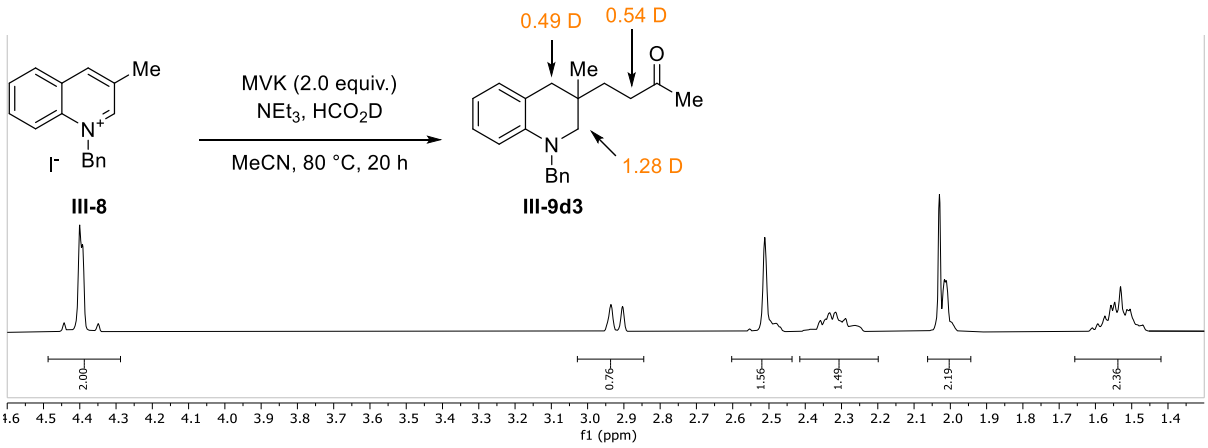


^{2}H NMR



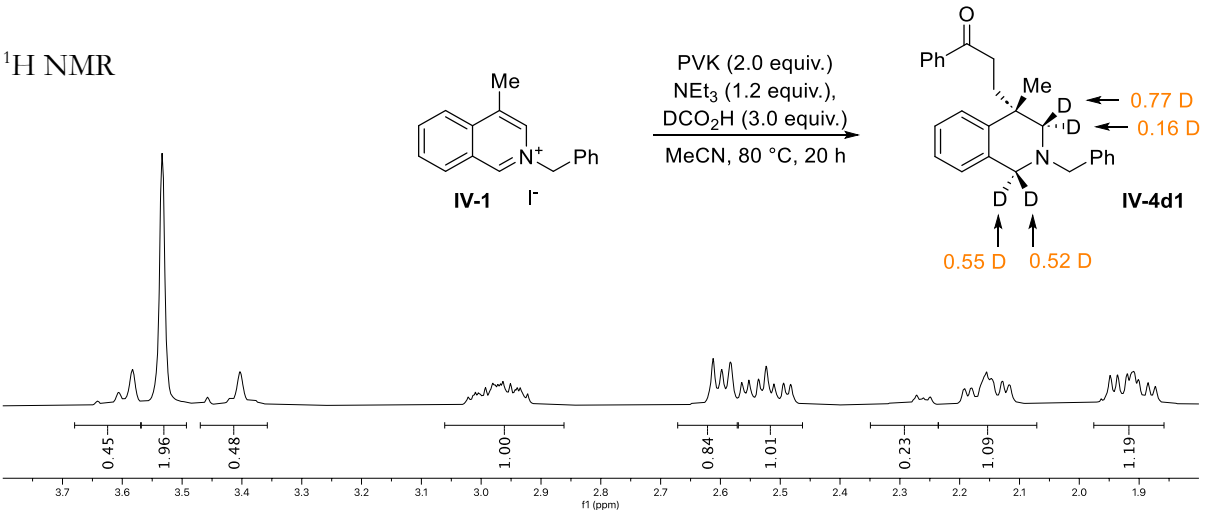
Reaction with formic acid-d_2 (DCO_2D):

^{1}H NMR

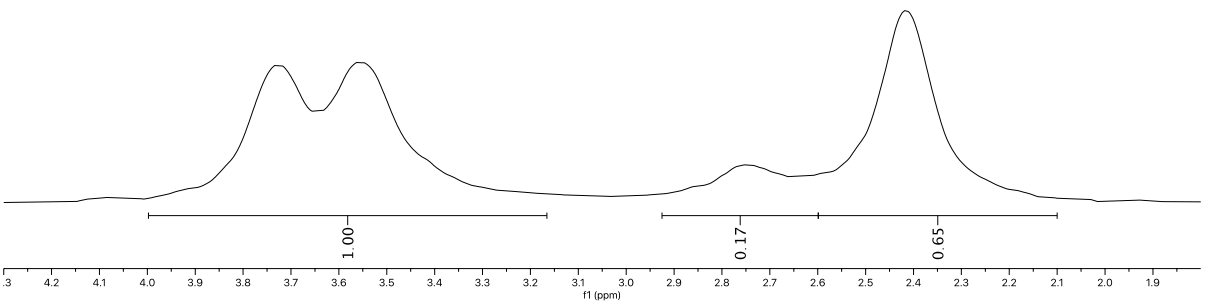


Reaction with formic-d acid (DCO_2H):

^{1}H NMR

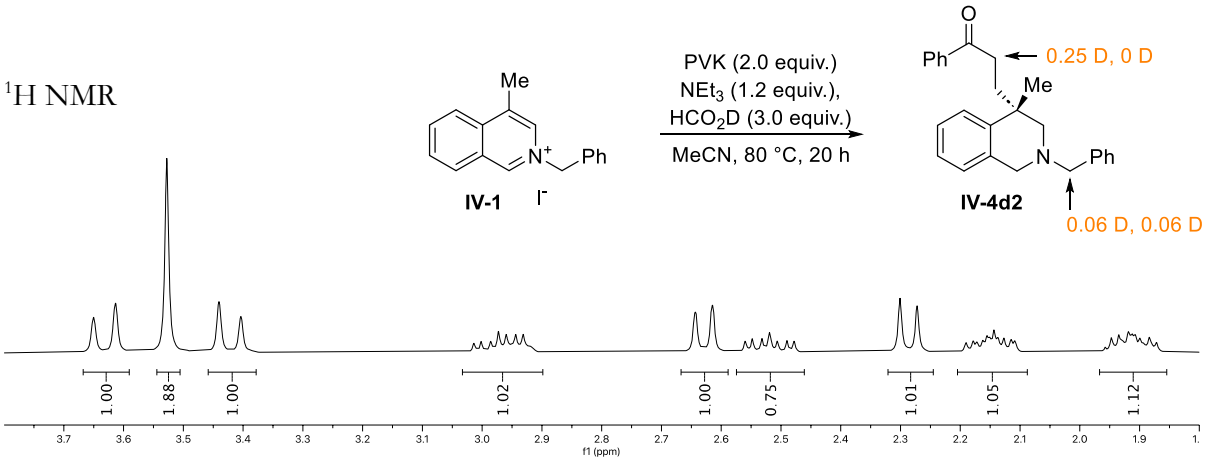


^{2}H NMR

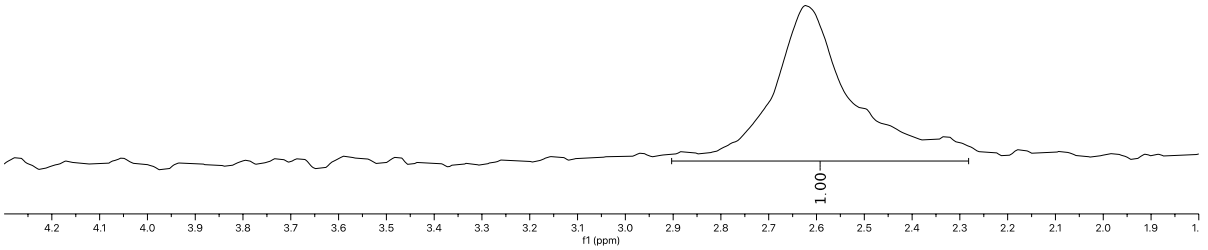


Reaction with formic acid-d (HCO_2D):

^{1}H NMR

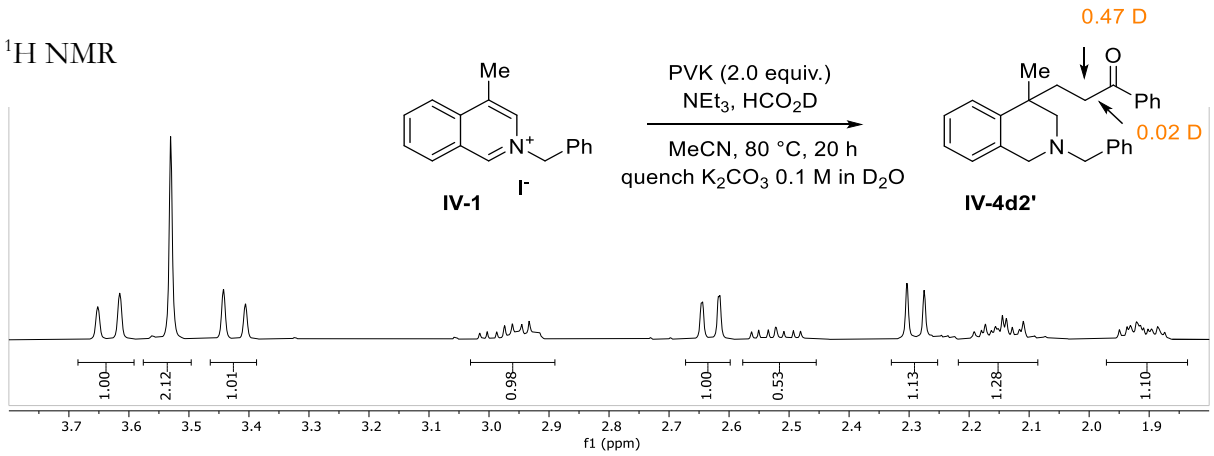


^{2}H NMR

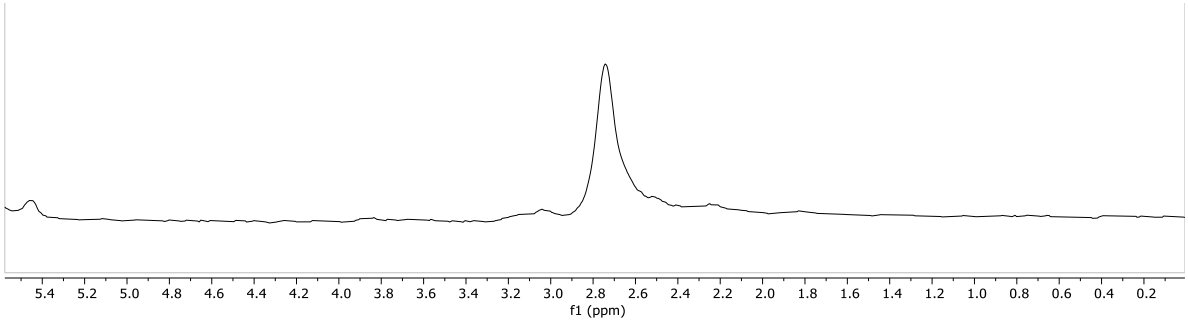


Reaction with formic acid-d (HCO_2D) and quench with 0.1 K_2CO_3 in D_2O:

^{1}H NMR

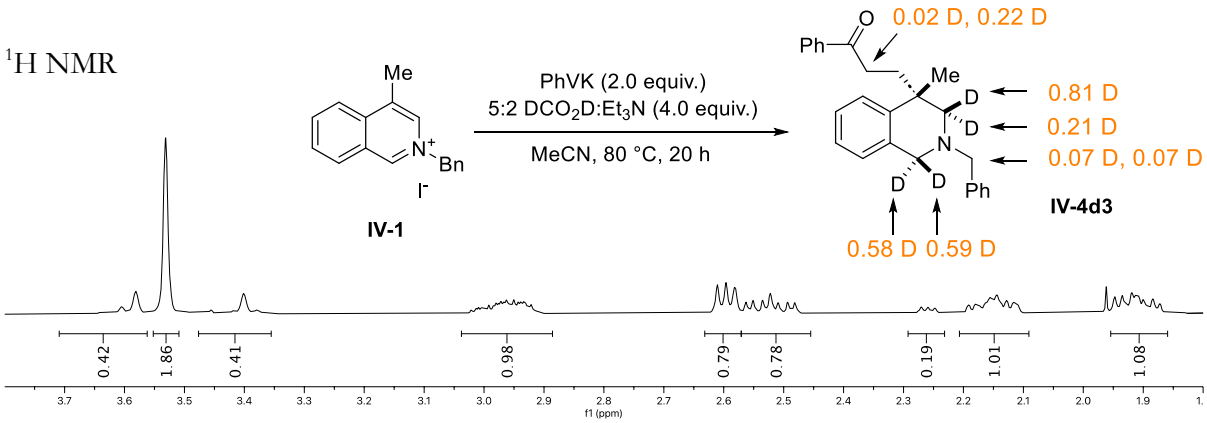


^{2}H NMR

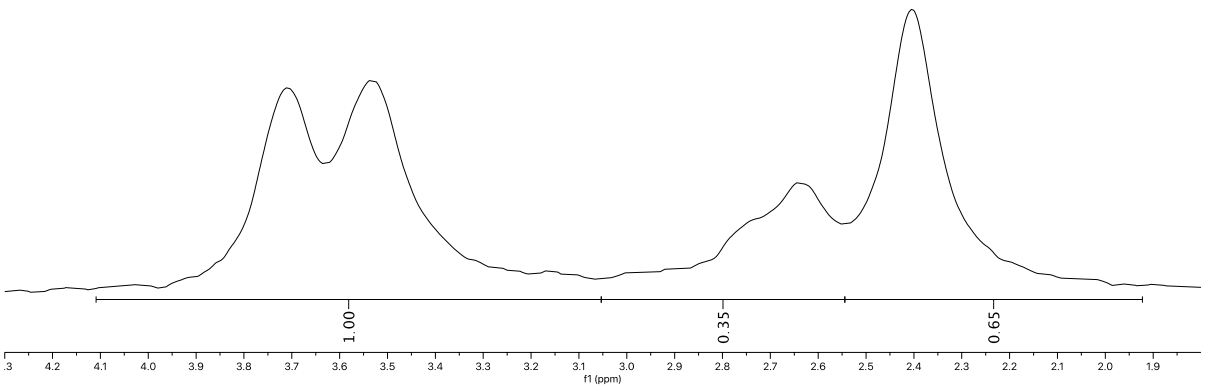


Reaction with formic acid-d_2 (DCO_2D):

^{1}H NMR



^{2}H NMR



Chapter 8: References

[1] Z. Časar, *Synthesis of Heterocycles in Contemporary Medicinal Chemistry*, Springer International Publishing, Basel, CH, **2016**.

[2] M. Baumann, I. R. Baxendale, *Beilstein J. Org. Chem.* **2013**, *9*, 2265–2319.

[3] J. D. Scott, R. M. Williams, *Chem Rev* **2002**, *102*, 1669–1730.

[4] A. F. Pozharskii, A. T. Soldatenkov, A. R. Katritzky, *Heterocycles in Life and Society : An Introduction to Heterocyclic Chemistry, Biochemistry and Applications*, Wiley, **2011**.

[5] M. Rubiralta, A. Diez, E. Giralt, Piperidine. *Structure, preparation, reactivity, and synthetic applications of piperidine and its derivatives*, Elsevier, Amsterdam **1991**.

[6] A. Katrizky, C. Ramsden, J. Joule, V. Zhdankin, Editors, *Handbook of Heterocyclic Chemistry, Third Edition*, Elsevier, **2010**.

[7] U. K. Sharma, E. V. Van der Eycken, *Flow Chemistry for the Synthesis of Heterocycles*, Springer, Basel, **2018**.

[8] Z. Yin, Z. Wang, X. F. Wu, *Chin. J. Org. Chem.* **2019**, *39*, 573–590.

[9] J. Prunet, *Synthesis of Heterocycles by Metathesis Reactions*, Springer, Basel, **2016**.

[10] Y. Landais, *Free-Radical Synthesis and Functionalization of Heterocycles*, Springer, Basel, **2018**.

[11] F. Lovering, J. Bikker, C. Humblet, *J Med Chem* **2009**, *52*, 6752–6756.

[12] F. Lovering, *Med. Chem. Commun.* **2013**, *4*, 515–519.

[13] C. J. Huck, D. Sarlah, *Chem* **2020**, *6*, 1589–1603.

[14] W. C. Wertjes, E. H. Southgate, D. Sarlah, *Chem. Soc. Rev.* **2018**, *47*, 7996–8017.

[15] N. Tanaka, T. Usuki, *Eur. J. Org. Chem.* **2020**, 5514–5522.

[16] H. Bi, X. Tan, R. Dou, Y. Pei, M. Qiao, B. Sun, B. Zong, *Green Chem.* **2016**, *18*, 2216–2221.

[17] H. Okazaki, K. Onishi, M. Soeda, Y. Ikefuji, R. Tamura, I. Mochida, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3167–3174.

[18] M. Hönel, F. W. Vierhapper, *J. Chem. Soc., Perkin Trans. 1* **1980**, 1933–1939.

[19] H. Okazaki, K. Onishi, Y. Ikefuji, R. Tamura, *J. Chem. Soc., Perkin Trans. 2* **1990**, 1321–1327.

[20] G. W. Gribble, T. C. Barden, D. A. Johnson, *Tetrahedron* **1988**, *44*, 3195–3202.

[21] J. Z. Ginos, *J. Org. Chem.* **1975**, *40*, 1191–1195.

[22] Z. Y. Ding, T. Wang, Y. M. He, F. Chen, H. F. Zhou, Q. H. Fan, Q. Guo, A. S. C. Chan, *Adv. Synth. Catal.* **2013**, *355*, 3727–3735.

[23] Y. Kita, K. Yamaji, K. Higashida, K. Sathaiah, A. Iimuro, K. Mashima, *Chem. Eur. J.* **2015**, *21*, 1915–1927.

[24] L. Shi, Z. S. Ye, L. L. Cao, R. N. Guo, Y. Hu, Y. G. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 8286–8289.

[25] M.-W. Chen, Y. Ji, J. Wang, Q.-A. Chen, L. Shi, Y.-G. Zhou, *Org. Lett.* **2017**, *19*, 4988–4991.

[26] R. B. Miller, J. J. Svoboda, *Synth. Commun.* **1994**, *24*, 1187–1193.

[27] J. Wen, R. Tan, S. Liu, Q. Zhao, X. Zhang, *Chem. Sci.* **2016**, *7*, 3047–3051.

[28] A. J. Birch, *Q. Rev. Chem. Soc.* **1950**, *4*, 69–93.

[29] A. Bruckmann, M. A. Pena, C. Bolm, *Synlett* **2008**, 900–902.

[30] L. G. Spears, J. S. Hutchinson, *J. Chem. Phys.* **1988**, *88*, 240–249.

[31] S. Cannizzaro, *Justus Liebigs Ann. Chem.* **1853**, *88*, 129–130.

[32] R. J. L. Martin, *Aust. J. Chem.* **1954**, *7*, 335–347.

[33] R. Leuckart, *Berichte der deutschen chemischen Gesellschaft* **1885**, *18*, 2341–2344.

[34] O. Wallach, *Justus Liebigs Ann Chem* **1893**, *272*, 99–122.

[35] O. Wallach, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 3992–3993.

[36] J. J. Li, *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*, Springer, **2021**.

[37] R. Nie, Y. Tao, Y. Nie, T. Lu, J. Wang, Y. Zhang, X. Lu, C. C. Xu, *ACS Catal.* **2021**, *11*, 1071–1095.
[38] D. Baidilov, D. Hayrapetyan, A. Y. Khalimon, *Tetrahedron* **2021**, *98*, 132435.
[39] A. A. Mishra, B. M. Bhanage, *Chirality* **2021**, *33*, 337–378.
[40] G. E. Dobereiner, A. Nova, N. D. Schley, N. Hazari, S. J. Miller, O. Eisenstein, R. H. Crabtree, *J. Am. Chem. Soc.* **2011**, *133*, 7547–7562.
[41] J. Wu, W. Tang, A. Pettman, J. Xiao, *Adv. Synth. Catal.* **2013**, *355*, 35–40.
[42] J. Wu, C. Wang, W. Tang, A. Pettman, J. Xiao, *Chem. Eur. J.* **2012**, *18*, 9525–9529.
[43] R. Yamaguchi, C. Ikeda, Y. Takahashi, K. I. Fujita, *J. Am. Chem. Soc.* **2009**, *131*, 8410–8412.
[44] T. Wang, L. G. Zhuo, Z. Li, F. Chen, Z. Ding, Y. He, Q. H. Fan, J. Xiang, Z. X. Yu, A. S. C. Chan, *J. Am. Chem. Soc.* **2011**, *133*, 9878–9891.
[45] Z. S. Ye, M. W. Chen, Q. A. Chen, L. Shi, Y. Duan, Y. G. Zhou, *Angew. Chem. Int. Ed.* **2012**, *51*, 10181–10184.
[46] M. Renom-Carrasco, P. Gajewski, L. Pignataro, J. G. de Vries, U. Piarulli, C. Gennari, L. Lefort, *Chem. Eur. J.* **2016**, *22*, 9528–9532.
[47] W. B. Wang, S. M. Lu, P. Y. Yang, X. W. Han, Y. G. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537.
[48] D. W. Wang, X. B. Wang, D. S. Wang, S. M. Lu, Y. G. Zhou, Y. X. Li, *J. Org. Chem.* **2009**, *74*, 2780–2787.
[49] M. W. Chen, Y. Ji, J. Wang, Q. A. Chen, L. Shi, Y. G. Zhou, *Org. Lett.* **2017**, *19*, 4988–4991.
[50] M. Renom-Carrasco, P. Gajewski, L. Pignataro, J. G. de Vries, U. Piarulli, C. Gennari, L. Lefort, *Adv. Synth. Catal.* **2016**, *358*, 2589–2593.
[51] L. Wang, J. Lin, C. Xia, W. Sun, *J. Org. Chem.* **2021**, *86*, 16641–16651.
[52] A. J. Birch, E. A. Karakhanov, *J. Chem. Soc., Chem. Commun.* **1975**, 480-481.
[53] A. J. Birch, P. G. Lehman, *J. Chem. Soc., Perkin Trans. 1,* **1973**, 2754-2759.
[54] W. Hückel, G. Graner, *Chem. Ber.* **1957**, *90*, 2017–2023.
[55] B. E. Blougb, F. I. Carroll, *Tetrahedron Lett.* **1993**, *34*, 7239-7242.
[56] D. D. Tanner, C.-M. Yang, *J. Org. Chem.* **1993**, *58*, 1840–1846.
[57] M. Jiao, J. Gao, X. Fang, *Org. Lett.* **2020**, *22*, 8566–8571.
[58] J. Tauber, D. Imbri, T. Opatz, *Molecules* **2014**, *19*, 16190–16222.
[59] S. Abou-Shehada, M. C. Teasdale, S. D. Bull, C. E. Wade, J. M. J. Williams, *ChemSusChem* **2015**, *8*, 1083–1087.
[60] B. Marinic, H. B. Hepburn, A. Grozavu, M. Dow, T. J. Donohoe, *Chem. Sci.* **2021**, *12*, 742–746.
[61] M. Cardellini I, G. M. Cingolani I, F. Claudi ', U. Gulini, F. Cantalamessa, F. Venturi, *Eur. J. Med. Chem.* **1987**, *22*, 1-4..
[62] K. Iwai, S. Yokoyama, H. Asahara, N. Nishiwaki, *Bull. Chem. Soc. Jpn.* **2020**, *93*, 50–57.
[63] M. Sugiura, T. Sai, N. Takao, H. Fujiwara, *J. Chem. Soc., Perkin Trans. 2*, **1983**, 907-910.
[64] U. K. Sharma, P. Ranjan, E. V. Van Der Eycken, S. L. You, *Chem. Soc. Rev.* **2020**, *49*, 8721–8748.
[65] S. Das, *Org. Biomol. Chem.* **2022**, *20*, 1838–1868.
[66] Z. Zhang, H. Han, L. Wang, Z. Bu, Y. Xie, Q. Wang, *Org. Biomol. Chem.* **2021**, *19*, 3960–3982.
[67] S. Das, S. Das, *SynOpen* **2022**, *6*, 86–109.
[68] S. Ishigaki, Y. Nagashima, D. Yukimori, J. Tanaka, T. Matsumoto, K. Miyamoto, M. Uchiyama, K. Tanaka, *Nat. Commun.* **2023**, *14*, 652.
[69] J. Jia, F. Hu, Y. Xia, *Synthesis* **2022**, *54*, 92–110.
[70] X. Yan, L. Ge, M. Castiñeira Reis, S. R. Harutyunyan, *J. Am. Chem. Soc.* **2020**, *142*, 20247–20256.
[71] D. Wang, Z. Wang, Z. Liu, M. Huang, J. Hu, P. Yu, *Org. Lett.* **2019**, *21*, 4459–4463.

[72] L. Dong, X. Ma, Y. Fan, D. Wang, *Asian J. Org. Chem.* **2020**, *9*, 1571–1575.
[73] S. Zheng, D. Wang, M. Huang, P. Yu, *Chem. Asian J.* **2022**, *17*, e202200077.
[74] A. Grozavu, H. B. Hepburn, P. J. Smith, H. K. Potukuchi, P. J. Lindsay-Scott, T. J. Donohoe, *Nat. Chem.* **2019**, *11*, 242–247.
[75] A. Grozavu, H. B. Hepburn, E. P. Bailey, P. J. Lindsay-Scott, T. J. Donohoe, *Chem. Sci.* **2020**, *11*, 8595–8599.
[76] J. Yang, H. Zhao, Z. Tan, L. Cao, H. Jiang, C. Ci, P. H. Dixneuf, M. Zhang, *ACS. Catal.* **2021**, *11*, 9271–9278.
[77] L. Gong, H. Zhao, J. Yang, H. Jiang, M. Zhang, *Chem. Commun.* **2021**, *57*, 8292–8295.
[78] H. Zhao, Y. Wu, C. Ci, Z. Tan, J. Yang, H. Jiang, P. H. Dixneuf, M. Zhang, *Nat. Commun.* **2022**, *13*, 2393.
[79] B. M. Reeves, H. B. Hepburn, A. Grozavu, P. J. Lindsay-Scott, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2019**, *131*, 15844–15848.
[80] W. Mao, H. Zhao, M. Zhang, *Chem. Commun.* **2022**, *58*, 4380–4383.
[81] J. A. Leitch, T. Rogova, F. Duarte, D. J. Dixon, *Angew. Chem. Int. Ed.* **2020**, *59*, 4121–4130.
[82] H. B. Hepburn, T. J. Donohoe, *Chem. Eur. J.* **2020**, *26*, 1963–1967.
[83] D. Wang, D. Astruc, *Chem. Rev.* **2015**, *115*, 6621–6686.
[84] J. Wu, C. Wang, W. Tang, A. Pettman, J. Xiao, *Chem. Eur. J.* **2012**, *18*, 9525–9529.
[85] J. Wu, W. Tang, A. Pettman, J. Xiao, *Adv. Synth. Catal.* **2013**, *355*, 35–40.
[86] A. J. Wagstaff, S. M. Cheer, A. J. Matheson, D. Ormrod, K. L. Goa, M. Ansseau, S. Kasper, *Drugs* **2002**, *4*, 655-703.
[87] S. Krautwald, M. A. Schafroth, D. Sarlah, E. M. Carreira, *J. Am. Chem. Soc.* **2014**, *136*, 3020–3023.
[88] R. Nie, Y. Tao, Y. Nie, T. Lu, J. Wang, Y. Zhang, X. Lu, C. C. Xu, *ACS Catal.* **2021**, *11*, 1071–1095.
[89] A. E. Cotman, *Chem. Eur. J.* **2021**, *27*, 39–53.
[90] F. Foubelo, M. Yus, *Chem. Rec.* **2015**, *15*, 907–924.
[91] Y. M. He, Q. H. Fan, *ChemCatChem.* **2015**, *7*, 398–400.
[92] J. Wu, C. Wang, W. Tang, A. Pettman, J. Xiao, *Chem. Eur. J.* **2012**, *18*, 9525–9529.
[93] J. Wu, W. Tang, A. Pettman, J. Xiao, *Adv. Synth. Catal.* **2013**, *355*, 35–40.
[94] E. O. Pentsak, D. B. Eremin, E. G. Gordeev, V. P. Ananikov, *ACS Catal.* **2019**, *9*, 3070–3081.
[95] X. Zhou, X. Wu, B. Yang, J. Xiao, *J. Mol. Catal. A: Chem.* **2012**, *357*, 133–140.
[96] A. De, N. C. Ghosal, S. Mahato, S. Santra, G. v. Zyryanov, A. Majee, *ChemistrySelect* **2018**, *3*, 4058–4066.
[97] Y. Wei, C. Wang, X. Jiang, D. Xue, Z. T. Liu, J. Xiao, *Green Chem.* **2014**, *16*, 1093–1096.
[98] S. Bokale-Shivale, M. A. Amin, R. T. Sawant, M. Y. Stevens, L. Turanli, A. Hallberg, S. B. Waghmode, L. R. Odell, *RSC Adv.* **2020**, *11*, 349–353.
[99] J. J. Li, *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications: Fourth Expanded Edition*, Springer, **2009**.
[100] R. J. Armstrong, T. J. Donohoe, *Tetrahedron Lett.* **2021**, *74*, 153151.
[101] P. Melchiorre, *Angew. Chem. Int. Ed.* **2012**, *51*, 9748–9770.
[102] O. Lifchits, M. Mahlau, C. M. Reisinger, A. Lee, C. Farès, I. Polyak, G. Gopakumar, W. Thiel, B. List, *J. Am. Chem. Soc.* **2013**, *135*, 6677–6693.
[103] L. W. Xu, J. Luo, Y. Lu, *Chem. Commun.* **2009**, 1807–1821.
[104] C. Cassani, R. Martín-Rapún, E. Arceo, F. Bravo, P. Melchiorre, *Nat. Protoc.* **2013**, *8*, 325–344.
[105] N. Unver, *Phytochem. Rev.*, **2007**, pp. 125–135.
[106] F. Rousst, J.-C. O. Uirton, A. Tomas, H.-P. Husson, Tetrahedron **1998**, *54*, 10363-10378.
[107] D. J. Hart, S. Patterson, J. P. Unch, *Synlett* **2003**, *9*, 1334-1338.

[108] N. Fleury-Brégeot, M. Presset, F. Beaumard, V. Colombel, D. Oehlrich, F. Rombouts, G. A. Molander, *J. Org. Chem.* **2012**, *77*, 10399–10408.
[109] N. Mahmoodi, R. K. Harijan, V. L. Schramm, *J. Am. Chem. Soc.* **2020**, *142*, 14222–14233.
[110] K. V. Rao, L. S. Kapicak, *J. Heterocycl. Chem.* **1976**, *13*, 1073–1077.
[111] A. J. Day, T. C. Jenkins, M. Kischkewitz, K. E. Christensen, D. L. Poole, T. J. Donohoe, *Org. Lett.* **2023**, *25*, 614-618.
[112] T. Keumi, T. Inagaki, N. Nakayama, M. Taniguchi, T. Morita, H. Kitajima, *J. Org. Chem.* **1989**, *54*, 4034–4038.
[113] J. Cosier, A. M. Glazer, *J. Appl. Crystallogr.* **1986**, *19*, 105–107.
[114] D. R. Allan, H. Nowell, S. A. Barnett, M. R. Warren, A. Wilcox, J. Christensen, L. K. Saunders, A. Peach, M. T. Hooper, L. Zaja, S. Patel, L. Cahill, R. Marshall, S. Trimnell, A. J. Foster, T. Bates, S. Lay, M. A. Williams, P. V. Hathaway, G. Winter, M. Gerstel, R. W. Wooley, *Crystals* **2017**, *7*, 336.
[115] L. Palatinus, G. Chapuis, *J. Appl. Crystallogr.* **2007**, *40*, 786–790.
[116] P. Parois, R. I. Cooper, A. L. Thompson, *Chem. Cent. J.* **2015**, *9*, 30.
[117] M. Alajarín, A. Pastor, R. Á. Orenes, J. W. Steed, R. Arakawa, *Chem. Eur. J.* **2004**, *10*, 1383–1397.
[118] D. F. J. Caputo, C. Arroniz, A. B. Dürr, J. J. Mousseau, A. F. Stepan, S. J. Mansfield, E. A. Anderson, *Chem. Sci.* **2018**, *9*, 5295–5300.
[119] X. Zhang, A. McNally, *Angew. Chem. Int. Ed.* **2017**, *56*, 9833–9836.
[120] S. Panda, A. Coffin, Q. N. Nguyen, D. J. Tantillo, J. M. Ready, *Angew. Chem. Int. Ed.* **2016**, *128*, 2245–2249.
[121] S. Krautwald, M. A. Schafroth, D. Sarlah, E. M. Carreira, *J. Am. Chem. Soc.* **2014**, *136*, 3020–3023.
[122] A. Kaga, H. Hayashi, H. Hakamata, M. Oi, M. Uchiyama, R. Takita, S. Chiba, *Angew. Chem. Int. Ed.* **2017**, *129*, 11969–11973.
[123] J. F. Miller, K. S. Gudmundsson, L. D. A. Richardson, S. Jenkinson, A. Spaltenstein, M. Thomson, P. Wheelan, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3026–3030.
[124] D. S. Zuckerman, K. A. Woerpel, *Tetrahedron* **2019**, *75*, 4118–4129.
[125] B. Sundararaju, M. Achard, G. V. M. Sharma, C. Bruneau, *J. Am. Chem. Soc.* **2011**, *133*, 10340–10343.
[126] M. Kischkewitz, B. Marinic, N. Kratena, Y. Lai, H. B. Hepburn, M. Dow, K. E. Christensen, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2022**, *61*, e202204682.