TRANSITION METAL CATALYZED REACTIONS AND FUNCTIONALIZED GROUP TRANSFORMATIONS



A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy (DPhil)

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Abstract

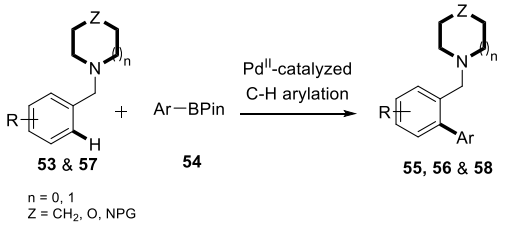
Transition Metal Catalyzed Reactions and Functionalized Group Transformations

Peng Wen Tan Jesus's College DPhil Trinity term 2017

The overall objective of this thesis is to develop contemporary transition-metal-catalyzed strategies and applications to access various biologically and chemically relevant compounds in a direct and elegant fashion.

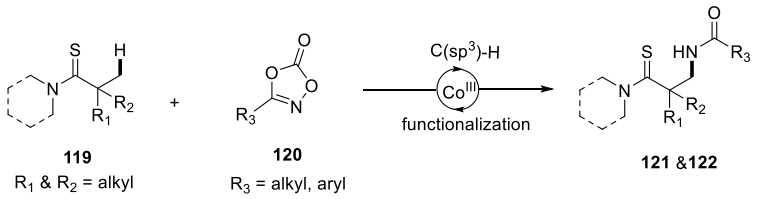
Chapter 1 introduces the recent development and advances in 2 distinctive fields of contemporary transition metal catalysis; transition metal catalyzed C-H functionalization and chemoselective reduction of carboxamides.

Chapter 2 details the state-of-the-art Pd^{II}-catalyzed C(sp^2)-H functionalization cross-coupling reactions. Subsequently, the development of our work on Pd^{II}- catalyzed *ortho*-arylation of benzylic heterocycles (**53** & **57**) with arylboronic acid pinacol esters **54** (Ar-BPin) *via* directed C-H bond activation, is described. This methodology is efficient and applicable to a wide range of functionalized Ar-BPin and benzylic heterocycles, allowing the direct synthesis of important biaryl motifs in modest to good yield.

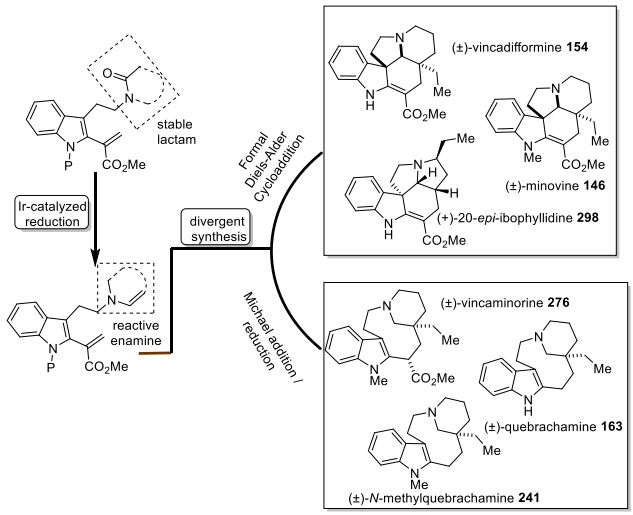


In Chapter 3, recent developments in the field of Co^{III}-catalyzed C-H functionalization is reviewed. Our work on a mild, oxidant-free and selective Cp*Co^{III}-catalyzed amidation of thioamides **119** with robust amidating agents dioxazolones **120** *via* C(sp^3)-H bond activation to generate the

desired amidated products (**121** & **122**) is also disclosed. The method is efficient and allows for the C-H amidation of a wide range of functionalized thioamides with aryl-, heteroaryl- and alkyl-substituted dioxazolones under the Cp*Co^{III} catalytic conditions.



Chapter 4 discusses the recent development in the total synthesis of *Aspidosperma* alkaloids. Our approach for the divergent total syntheses of (±)-vincaminorine **276**, (±)-*N*-methylquebrachamine **241**, (±)-quebrachamine **163**, (±)-minovine **146** and (±)-vincadifformine **154**, each in less than 10 linear steps starting from a single δ-lactam building block is also described. Key to our route design is the late-stage generation of reactive enamine functionality from stable indole-linked δ-lactams *via* a highly chemoselective iridium(I)-catalyzed reduction. The efficiently formed enamine (secodine) intermediates subsequently undergo either a formal *Diels-Alder* cycloaddition or a competitive Michael addition/reduction to access *Aspidosperma*-type alkaloids in excellent diastereoselectivities. An asymmetric variant of this synthetic strategy for the synthesis of (+)-20-*epi*-ibophyllidine **298** is also described.



Declarations and copyright

I declare that thesis has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree at this or any other university or institute of learning. Any work done in collaboration with a research colleague has been fully acknowledged and referenced within the text. All compounds in the experimental chapter 5 were synthesised and characterised by myself unless otherwise stated.

I was admitted as a probationary research student in October 2013 and as a candidate for the degree of Doctor of Philosophy in October 2014; the higher study for which this is a record was carried out in the University of Oxford and Institute of Chemical & Engineering Sciences (ICES), Singapore between 2013 and 2017.

Peng Wen Tan

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Last but not the least, I will like to thank my family members for their unwavering support over the years.

Abbreviations

°C	Degrees Celsius
Å	Ångström
Ac	Acetyl
Ad	Adamantyl
Aq	Aqueous
App	Apparent
Ar	Aryl
atm	atmosphere
BINAP	2,2'-Bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1´-binaphtalene-2,2´-diol
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
Bp	Boiling point
bpy	2,2'-Bipyridine
BQ	1,4-Benzoquinone
Bzq	Benzo[*h*]quinolone
br	Broad
n-Bu	*n*-Butyl
CDI	1,1'-Carbonyldiimidazole
COE	Cyclooctene
Conc	Concentration
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
Cy	Cyclohexyl
d	Doublet
DA	Diels–Alder
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMA	Dimethylacetamide
DCE	1,2-dichloroethane
DCM	Dichloromethane
dd	Doublet of doublets
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarisation transfer
DG	Directing group
DIAD	Di*iso*propyl azodicarboxylate
DIBAL	Di*iso*butylaluminium hydride
DIPEA	*N*,*N*-di*iso*propylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
dq	Doublet of quartets

dr	Diastereoisomeric ratio
dt	Doublet of triplets
ee	Enantiomeric excess
EI	Electron impact
ent	Enantiomer
equiv	Equivalents
ES	ElectroSpray Ionisation
Et	Ethyl
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	Electron donating group
EWG	Electron withdrawing group
FCC	Flash column chromatography
g	Gram
h	Hour(s)
HMBC	Heteronuclear multiple-bond correlation experiment
HPLC	High performance liquid chromatography
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear single-quantum coherence experiment
Hz	Hertz
IBX	2-iodoxybenzoic acid
IMDA	Intramolecular Diels-Alder
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
IPA	*Iso*propylalcohol
J	Coupling constant
LDA	Lithium di*iso*propylamide
[M]	Metal complex
M	Molar concentration
m	Multiplet
MBS	*p*-methoxybenzenesulfonyl
Me	Methyl
mg	Milligram
MHz	Mega hertz
min	Minute(s)
mL	Millilitre
μL	Microlitre
mmol	Millimole
mM	Millimolar
mol	Mole
MOM	Methoxymethyl
mp	Melting point
MS	Molecular sieves
MS	Low resolution mass spectrometry
Ms	Methanesulfonyl
m/z	Mass to charge ratio
NBS	*N*-Bromosuccinimide

NCTS	*N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide
NIS	*N*-Iodosuccinimide
NMR	Nuclear Magnetic Resonance
NMO	4-Methylmorpholine *N*-oxide
Ns	*Para*-nitrobenzenesulfonyl
Nu	Nucleophile
o	Ortho
OH	Hydroxy
OTf	Trifluoromethanesulfonate
p	Para
PE	Petroleum ether bp 30-40 °C
PG	Protecting group
Ph	Phenyl
Piv	Pivaloyl
Pin	Pinacol
PMB	*Para*-methoxybenzyl
PMDS	Polydimethylsiloxane
ppm	Parts per million
Pr	Propyl
pym	Pyrimidyl
pyr	Pyridine
q	Quartet
R	Generic substituent
RE	Reductive elimination
rac	Racemic
R_f	Retardation factor
quint	Quintet
RCM	Ring-closing metathesis
rt	Room temperature
s	Singlet
SE_{Ar}	Electrophilic aromatic substitution
sxt	Sextet
t	Triplet
TBA	Tetra-*n*-butylammonium
TBAF	Tetrabutylammonium fluoride
t-Bu	*tert*-butyl
TES	Triethylsilane
Temp	Temperature
t/*tert*	Tertiary
Tf	Triflate
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Tri*iso*propylsilane
TLC	Thin layer chromatography
TMDS	1,1,3,3-Tetramethyldisiloxane

TMS	Trimethylsilyl
TMSI	Trimethylsilyl iodide
t_R	Retention time (HPLC)
Ts	*Para*-toluenesulfonyl
TS	Transition state
UV	Ultraviolet
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-tri*iso*propylbiphenyl

Chapter 1: General Introduction

1.1 Contemporary transition metal catalysis in organic synthesis

The use of transition metal catalysis in complex organic syntheses has been well-established over the last century. Not only do the transition metal catalysts lower the activation energy profile of the reaction, but also coordination of the transition metal center to functional groups can dramatically alter its reactivity pattern.[1–5] This has thus enabled the synthetic community to stabilize highly reactive intermediates poised for new transformations. Additionally, transition metal catalyzed reactions often exhibit good control of chemoselectivity, thus reducing the production of unwanted by-products to facilitate the forging of new chemical bonds in an efficient and straightforward fashion.[2–4]

In the last decade, transition metal catalysis has continued to evolve remarkably with the aid of state-of-the-art technologies, e.g. high throughput screenings, advanced spectroscopic techniques and computational studies in theoretical calculations, to play a significant role in the discovery of modern-day synthetic methodology. The phenomenal potential in this field to uncover new modes of chemical activation pathways has created a platform to access a wide range of important and novel catalytic transformations that are often unprecedented within the arena of organic chemistry (Figure 1).

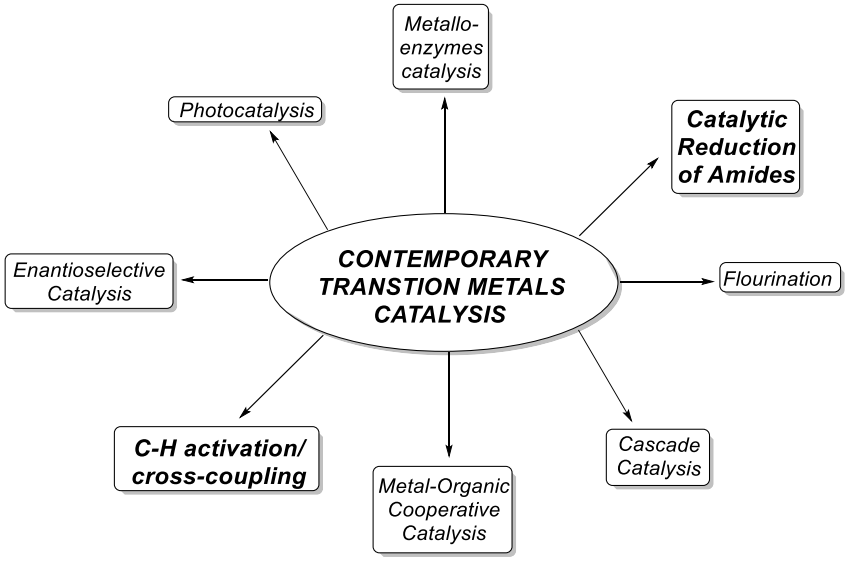


Figure 1: Selected contemporary transition metal catalyzed reactions.

1.2 Thesis objectives

The overall objective of this thesis is to develop contemporary transition-metal-catalyzed strategies and applications to access various biologically and chemically relevant compounds in a direct and elegant fashion. Over the last decade, the synthetic community has witnessed the remarkable advances in two distinctive fields: C-H functionationalization and chemoselective reduction of carboxamides. As we recognized their continuing growth potential in the discovery of novel transformations, the aim of this thesis is directed towards the improvement and further development on the existing work reported in these fields. Synthetic efforts in achieving our goal are detailed in the following chapters.

Chapter 2 includes the current advances in Pd^{II}-catalyzed $C(sp^2)$-H functionalization cross-coupling reactions, followed by our work on the development of a Pd^{II}-catalyzed *ortho*-arylation of a range of benzylic heterocycles with arylboronic acid pinacol esters to afford biaryl products in a single step.

Similarly, in Chapter 3, recent developments in the field of Co^{III}-catalyzed C-H functionalization is reviewed and Cp*Co^{III}-catalyzed amidation of thioamides *via* C(sp^3)-H bond activation is further disclosed.

In Chapter 4, recent development in the total synthesis of *Aspidosperma* alkaloids is discussed. A new strategy that features a key late-stage generation of reactive enamine functionality from pendant lactams *via* a highly chemoselective iridium(I) catalyzed reduction to access several *Aspidosperma* alkaloids divergently is reported.

1.3 Transition-metal-catalyzed C-H activation/cross-coupling reactions

Transition-metal-catalyzed carbon-carbon and carbon-heteroatom bond-forming cross-coupling reactions represent the integral core of synthetic organic chemistry for the construction of complex, biologically active compounds in pharmaceuticals and agrochemicals.[6] Over the past 50 years, extensive research in this field to develop novel catalysts and ligands, as well as efforts to elucidate the reaction mechanisms has aided in the discovery of new reactivity for a plethora of transformations with good control of selectivity. To date, this approach of transition metal catalyzed cross-coupling of organohalides or pseudohalides with stoichiometric amounts of organotin (Stille), organoboron (Suzuki-Miyaura), organozinc (Negishi), organosilicon (Hiyama-Denmark), organomagnesium (Kumada) reagents, alkenes (Heck) and amines (Buchwald-Hartwig) is still considered as the preferred synthetic tool in both academic and industrial settings due to its high robustness and efficiency (Figure 2).[7–14] Its importance in the field of synthetic chemistry was recognized with the 2010 Nobel Prize in Chemistry, awarded to Suzuki, Negishi and Heck, for "*palladium-catalyzed cross-couplings in organic synthesis*". Nevertheless, prefunctionalization of readily available feedstock to form specific organohalides and

organometallic reagents for cross-coupling can be difficult and additionally the removal of these functionalities after the cross-coupling is intrinsically wasteful. This effect is even more pronounced on an industrial level where the production of fine and pharmaceutical chemicals and intermediates generates enormous amounts of by-products and thus alternative approaches to utilize these natural resources in an atom-economical manner is highly sought after. This has accordingly led many research groups to develop more direct routes for bond formation from unactivated C-H bonds *via* C-H activation/functionalization.[15–23] Moreover, systematic C-H activation/functionalization of complex motifs facilitates structural diversification towards a series of structural analogues for synthetic chemistry and applications.

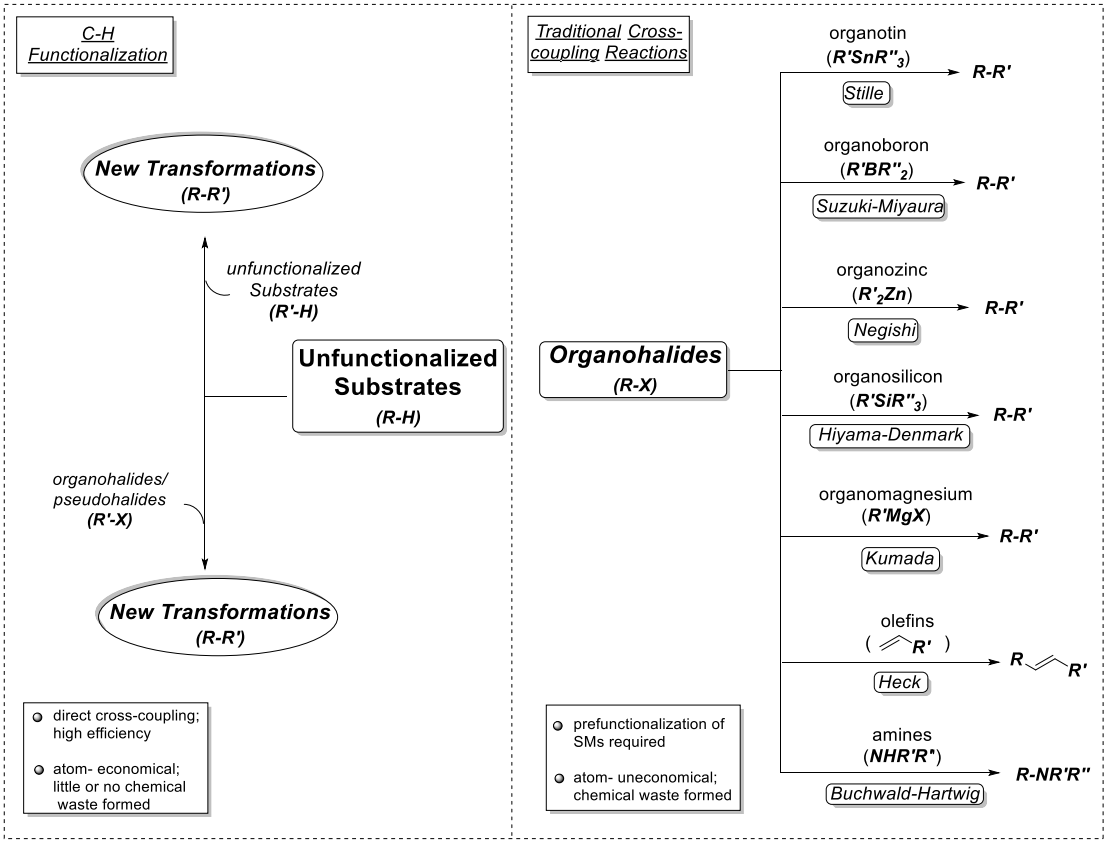


Figure 2: Traditional transition metal catalyzed versus C-H activation cross-coupling reactions

1.4 Transition-metal-catalyzed C-H reduction of carboxamides

Contemporary methodologies for the mild reduction of stable amides that feature an excellent functional group tolerance have attracted the interest of the synthetic community. Over the past decade, transition metal catalyzed reduction of tertiary amides with hydrosilanes has emerged as a key method for amine and enamine synthesis. In 2009, Nagashima *et.al.* successfully reduced carboxamides to amines using 1,1,3,3-tetramethyldisiloxane (TMDS) and chloroplatinic acid hexahydrate ($H_2PtCl_6.6H_2O$)[24] while in 2012, Brookhart *et. al.* successfully reduced secondary amides to amines and imines using a low loading of irdium catalyst, $[Ir(COE)_2Cl]_2$, with diethylsilane as the reductant.[25] Furthermore, Beller *et.al.* and Nagashima *et.al.* established remarkable protocols that utilize non-expensive and environmentally benign base metals (Fe[26,27] and Zn[28,29]) to catalytically reduce secondary and tertiary amides to their corresponding amines efficiently in the presence of readily available hydrosilanes under mild conditions. Our group is particularly interested in Nagashima's pioneering work whereby his group efficiently synthesized enamines from carboxamides using Vaska's complex (*trans*- $(PPh_3)_2(CO)IrCl$) as a catalyst and TMDS under mild conditions (Figure 3).[30–34]

Enamines are an important class of compounds due to their great utility and versatility in organic synthesis[35,36]. Although there are well-known traditional methods to furnish enamines such as the Stork enamine synthesis,[37] the need for additional sequences to access reactive aldehydes and amines is often regarded as inefficient and atom-uneconomical. Considering the widespread use of enamines in organic synthetic community and inspired by Nagashima's work, we envisaged that the rapid access to reactive enamines from stable lactams could allow the synthesis of structurally complex alkaloids with fewer purification steps and greater efficiency.

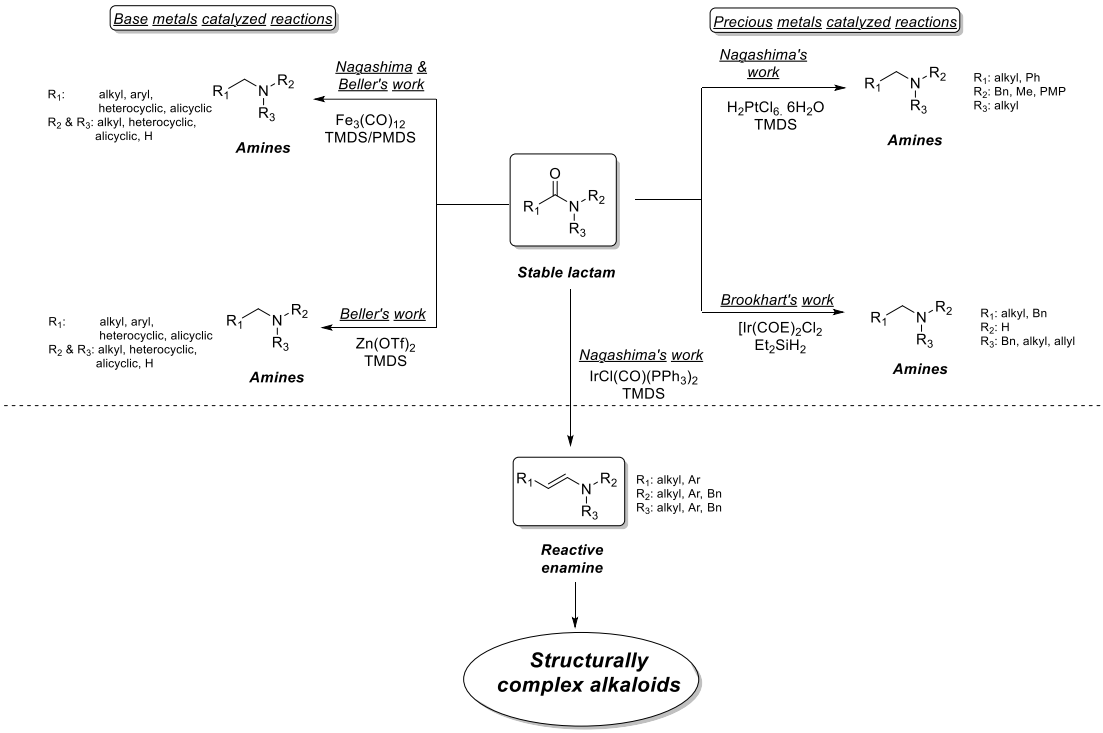


Figure 3: Transition metal catalyzed reduction of amides for amine and enamine synthesis

Chapter 2: Palladium (II)-Catalyzed C(sp^2)-H Arylation Of Benzylamines

2.1 Introduction

The field of C-H activation/functionalization has received immense attention from the organic community over the last decade due to its straight forward and step economical approach to achieve carbon-carbon or carbon-heteroatom bond formations from unactivated C-H precursors. By harnessing the knowledge obtained from the traditional metal-catalyzed cross-coupling reactions of organohalides or pseudohalides with organometallic reagents, researchers have actively disclosed contemporary and novel methodologies that would forge carbon-carbon and carbon-heteroatom bonds from essentially inert and ubiquitous C-H bonds *via* C-H activation.[15–23]

For more than 80 years, the synthesis of biaryl compounds, commonly found in various biologically active natural products such as polyketides, terpenes, lignans and peptides, has been a focus of interest in the synthetic community (Figure 4).[38–43] It was not until in the recent decades that biaryl compounds have received greater recognition due to their success in the field of asymmetric catalysis where they have been widely employed as catalysts (e.g. BINOL) for enantioselective reactions[44] and as a privileged structure in the pharmaceutical industry. Consequently, modern synthetic methods that greatly enhance the effectiveness of existing approaches for the construction of biaryl compounds in a steadfast manner, such as those in the field of C-H activation / functionalization, are highly desirable.

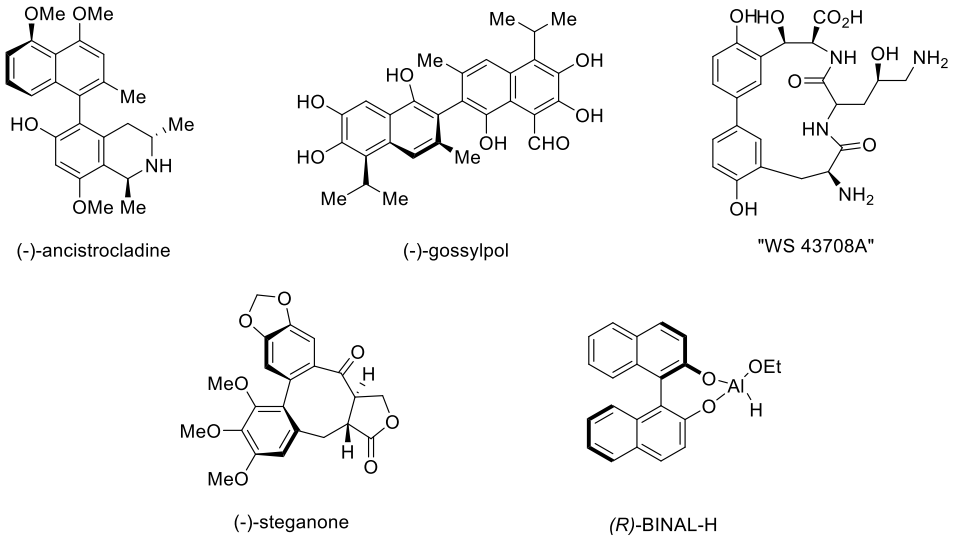
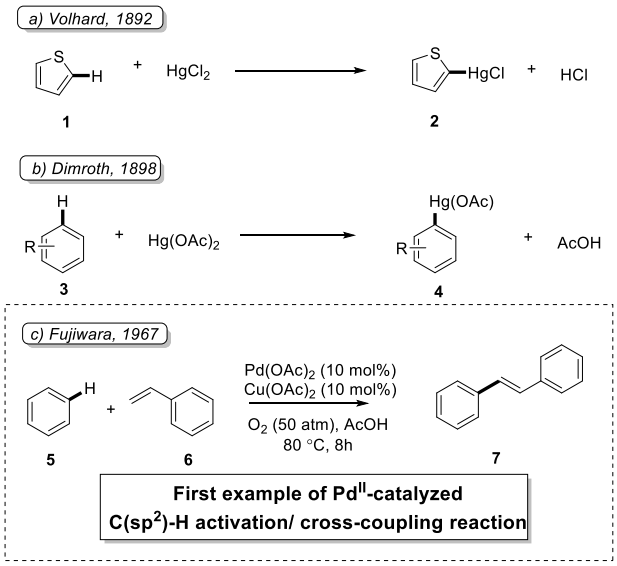


Figure 4: Various biologically and chemically relevant natural and unnatural biaryls.

2.2 Pioneering work

The earliest work of metal promoted C(sp^2)-H activation was first reported by Volhard in 1892 where his team demonstrated the electrophilic C(sp^2)-H activation of thiophene **1** with mercury(II) chloride to afford chloromercurythiophene **2** (Scheme 1a).[45] Not long after, Dimroth and his co-workers also disclosed similar electrophilic C(sp^2)-H activation of various aromatic compounds **3** with $Hg(OAc)_2$ to prepare a range of arylmecury acetates **4** (Scheme 1b).[46] More interestingly, it was not until in 1967 that Fujiwara and his co-workers first discovered C(sp^2)-H activation cross-coupling of benzene **5** and styrene **6** in the presence of $Pd(OAc)_2$ as a catalyst and oxidant $Cu(OAc)_2$ to form (*E*)-1,2-diphenylethene **7** (Scheme 1c).[47]

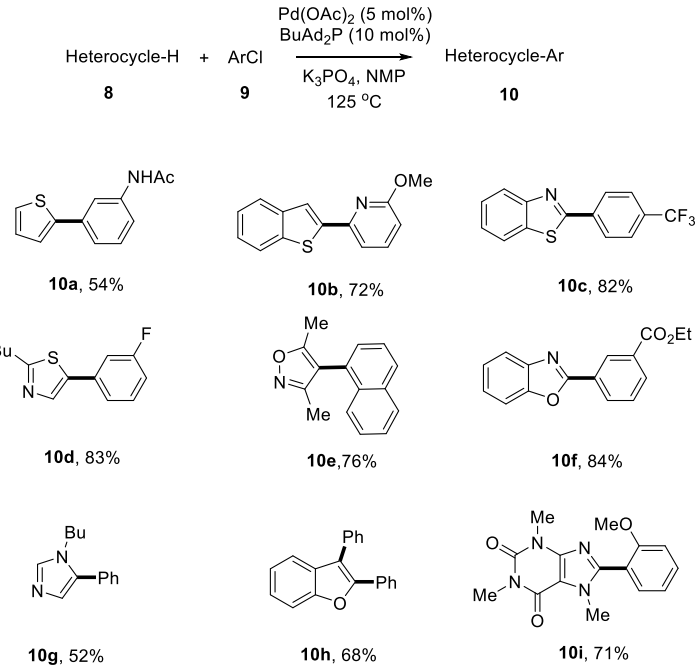


Scheme 1: Pioneering examples of C(sp^2)-H activation

2.3 C-H Functionalization of Electron-Rich Heterocycles

2.3.1 Daugulis's C(sp^2)-H arylation of electron-rich heterocycles

One of the approaches that demonstrated the concept of C-H activation was for electron-rich heterocycle arylation and it was not until 2007 that a general method was first reported (Scheme 2). In the presence of $Pd(OAc)_2$ and an electron-rich phosphine ligand (butyl-di-1-adamantylphosphine), Daugulis and co-workers performed arylation with aryl chloride **9** on a wide range of electron-rich heterocycles **8** – benzothiophene, benzofuran, thiazoles, thiophene, benzothiazole, imidazoles, triazoles and caffeine.[48] Although this method was proven to be general and efficient for a wide range of substrates **10**, *NH*-containing heterocycles such as indoles or pyrroles did not give any C-H activation reactions; *N*-functionalization occurred instead.

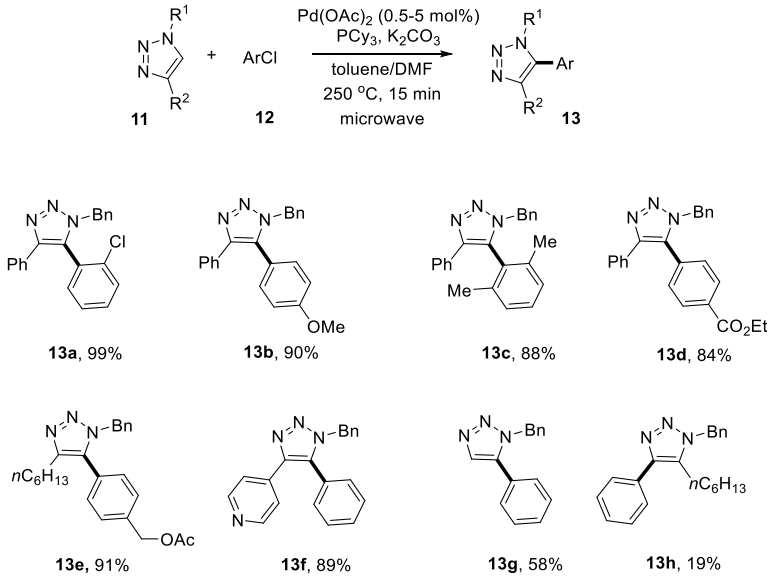


Scheme 2: General method for C(sp^2)-H arylation on various heterocycles 8

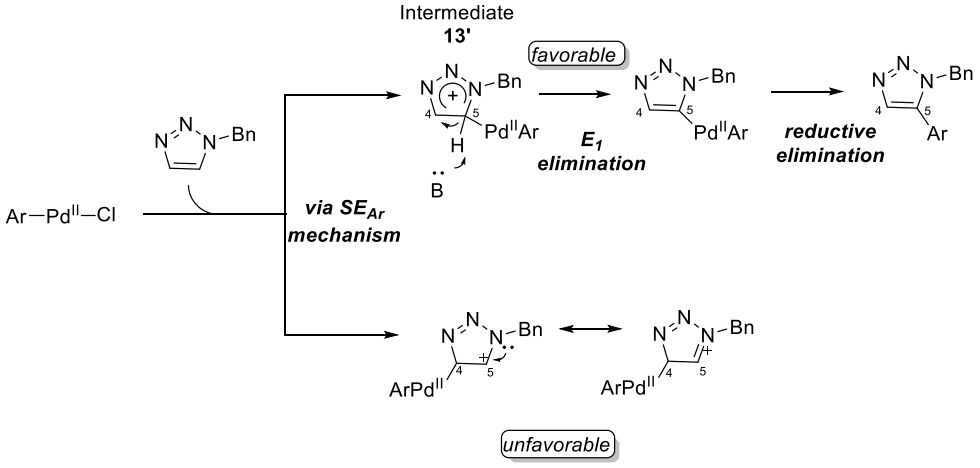
2.3.2 Oshima's C(sp^2)-H arylation of triazoles

Expansion of the scope of electron-rich heterocycles was further explored. In 2007, Oshima and co-workers demonstrated the direct arylation of 1,4-disubstituted 1,2,3-triazoles **11** at the 5-position with aryl chlorides **12** in the presence of K_2CO_3 and catalytic $Pd(OAc)_2$ under microwave radiation at high temperature (Scheme 3).[49] They obtained good to excellent yields for aryl chlorides with electron-withdrawing and electron-donating groups, as well as for a sterically hindered aryl chloride, 2,6-dimethylchlorobenzene. Unfortunately, there was a dramatic decline in efficiency for arylation to occur at the 4-position. Arylation of 1-benzyl-5-alkyltriazole with chlorobenzene only resulted in 19% of product **13h**. This low reactivity could be explained as depicted in Scheme 4. When triazole **11g** was subjected to the reaction conditions, a preference for arylation at the 5-position was observed. After the SE_{Ar} reaction of the divalent arylpalladium species (formed after oxidative addition of the palladium species with ArCl with the triazoles), the

expanded delocalization of the charge of the cationic intermediate **13'** rendered a facile arylation at the 5-position. On the other hand, arylation at the 4-position was considered unfavorable due to a more localized less-stabilized cationic charge, disfavoring its formation in the first place.



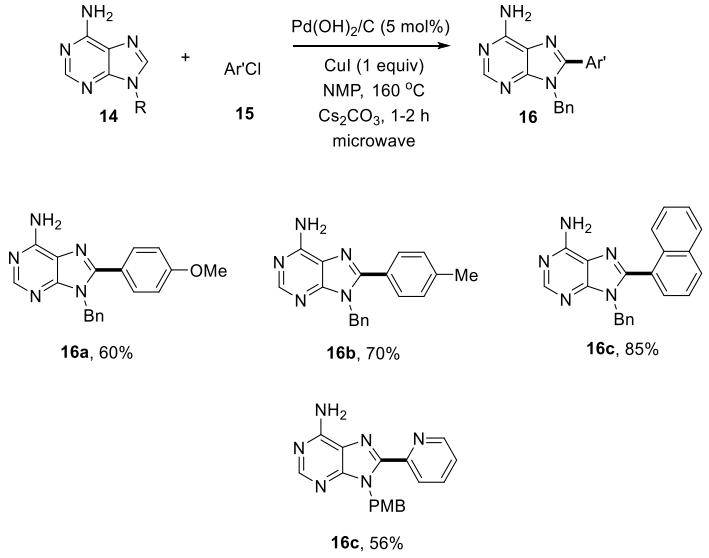
Scheme 3: C(sp^2)-H arylation on various triazole derivatives 11 under microwave radiation.



Scheme 4: Preference for arylation at the 5-position of the triazoles.

2.3.3 Alami's C(sp^2)-H arylation of adenine derivatives

Similarly, in 2008, Alami and co-workers utilized microwave radiation to activate the arylation reaction of adenine derivatives **14** with aryl chloride **15** in the presence of stoichiometric CuI and catalytic $Pd(OH)_2/C$ (Pearlman's catalyst) (Scheme 5).[50] The reaction was efficient with good to excellent yields were obtained for the arylated products **16**.



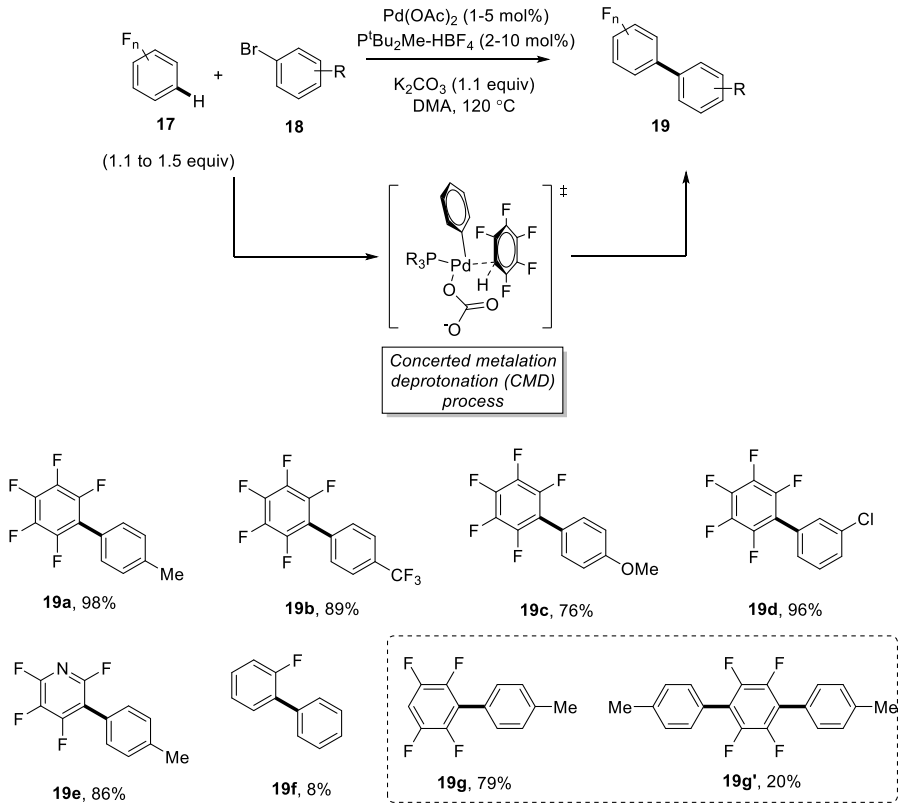
Scheme 5: C(sp^2)-H arylation on various adenine derivatives 14 under microwave radiation.

2.4 C-H Functionalization of Electron-Deficient Heterocycles

2.4.1 Fagnou's C(sp^2)-H arylation of perfluorobenzenes

Although C-H funcationalization of electron-rich heterocycles is well precedented, the mechanistic pathway for C-H activation of electron-rich heterocycles – commonly *via* electrophilic aromatic substitution (SE_{Ar}) – is fundamentally restraining since most aryl compounds are often non-nucleophilic in nature. Therefore, the discovery of new reaction pathways to address and resolve the potential constraints pertaining to electron-deficient arenes would be of great impact and importance in biaryl synthesis. Unlike C-H functionalization of electron-rich heterocycles, reactions of electron-deficient arenes such as perfluoroarenes remain challenging as they are less

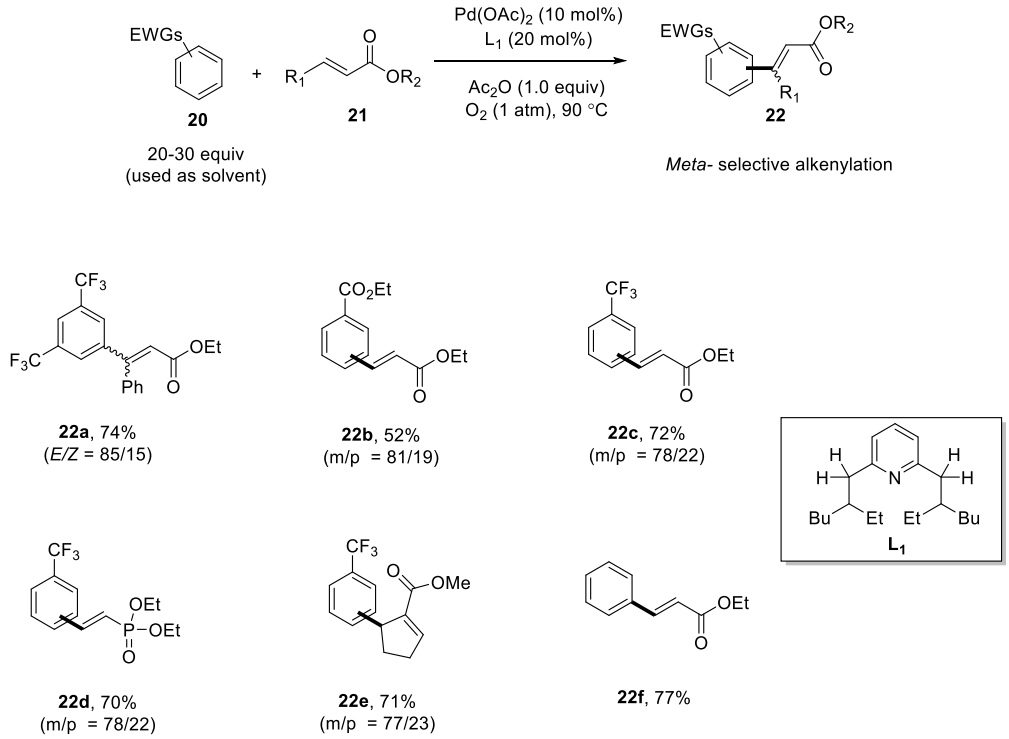
reactive due to their weak coordination with the Pd catalysts.[51] Nevertheless, in 2006, Fagnou and co-workers described an intermolecular direct C(sp^2)-H activation/arylation of electron-deficient arenes **17** with aryl halides **18** *via* a key concerted arene metalation deprotonation (CMD) to access biaryl products **19** – the reactivity was found to be dependent on the acidity of the C-H bond being activated (Scheme 6).[52] This transformation was presumed to proceed *via* an oxidative addition of aryl halide as the first step which would lower the free energy of activation for the subsequent C-H activation of electron-deficient polyfluorobenzene, followed by RE to furnish the biaryl products.[53] This reaction was found to have a broad scope with respect to both the aryl halide and the perfluroarene substrates.



Scheme 6: Fagnou's C(sp^2)-H arylation on various perflurobenzenes 17.

2.4.2 Yu's meta-selective C(sp^2)-H alkenylation of electron-deficient arenes

Later in 2009, Yu *et. al.* disclosed the first example of a regioselective *meta*-alkenylation of highly electron-deficient arenes **20**, assisted by a mutually repulsive 2,6-dialkylpyridine ligand **L_1** that allowed the synthesis of the alkenylated products **22** with the (*E*)-isomer as the major product in great yields (Scheme 7).[54] The team also replaced stoichiometric amounts of Ag salts which are typically used in such reactions with benign O_2 for the reoxidation of Pd^0 which was proven to be difficult in the absence of external ligands and co-oxidants. Since pyridyl (Py) ligands are the most efficient in promoting the reoxidation of Pd^0 with oxygen[55] and to prevent poisoning of the active Pd^{II} species due to strong Pd-N bond, they hypothesized that by increasing the steric bulk on the remote carbon atoms of the ligands (away from the the nitrogen atom) as shown in L_1, would ensure the coordination of only one ligand to the Pd^{II} thus allowing binding of any incoming electron-deficient arenes. Indeed, they observed that the ligand L_1 with the most branched side chain exhibited the highest reactivity. Despite no reaction occurred at the *ortho* position presumably attributed to steric influence from the ligand, explanation for the basis of the *meta*-selectivity over *para*-selectivity remains unclear. The group believed that the influence on the regioselectivity could be explained by the *meta* C-H bond being more acidic which would thus result in a higher tendency to undergo C-H cleavage.[56]

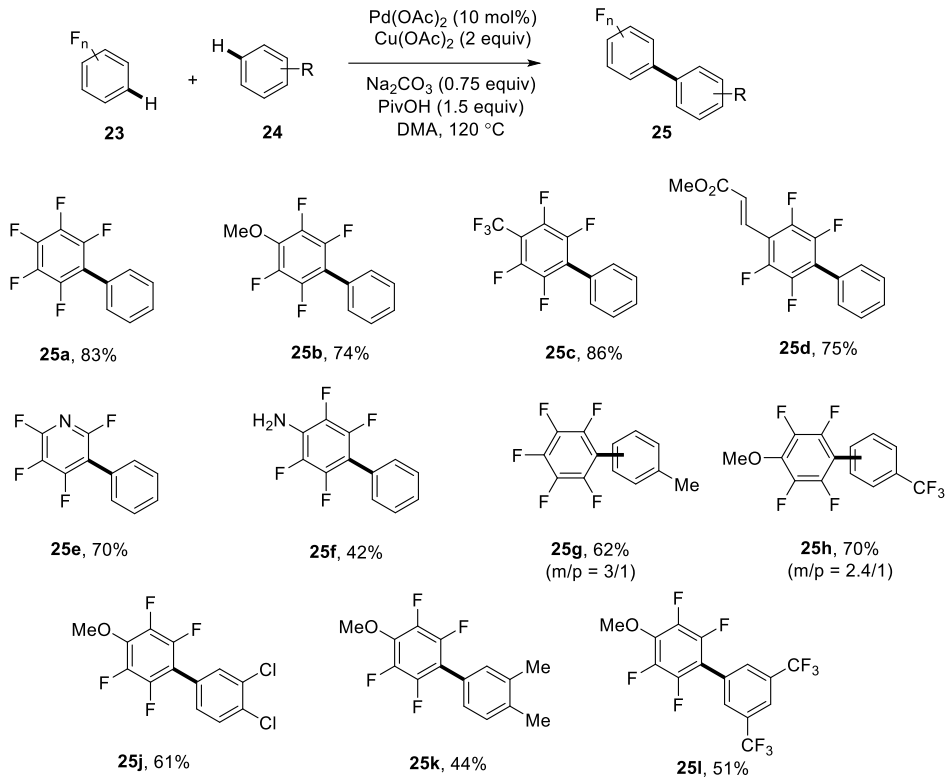


Scheme 7: Yu's C(sp^2)-H *meta*-selective alkenylation on various electron-deficient arenes 20.

2.4.3 Su's oxidative C(sp^2)-H arylation of electron-deficient polyfluoroarenes

More interestingly in 2010, Su and co-workers described the Pd^{II}-catalyzed oxidative C(sp^2)-H functionalization/arylation of a range of electron-deficient polyfluoroarenes **23** with simple arenes **24** instead of the typically used organohalides to furnish the desired biaryls **25** (Scheme 8).[57] The group envisoned that the oxidative C(sp^2)-H functionalization/arylation could be achieved by cross-coupling of two electronically distinct arenes. This premise was not unfounded. They proposed that the more electron-rich arenes would first undergo C(sp^2)-H bond cleavage due its higher affinity for electrophilic Pd^{II} catalyst. Subsequently in the concomitant palladation step, the relatively electron-rich arylpalladium complex has a greater preference for the more electron-deficient polyfluorobenzene over simple arenes.[53] Finally, the RE step would happen to produce biaryl products with high chemoselectivity. Under these reaction conditions, a range of tetrafluoroarenes containing different substituents were well-tolerated to furnish the desired biaryl

products **25** in moderate to good yields. Additionally, the scope for simple arenes was found to include mono- electron-donating (**25g**) and electron-withdrawing subsituted benzenes (**25h**), 1,2- (**25j** and **25k**) or 1,3- (**25l**) disubstituted benzenes.



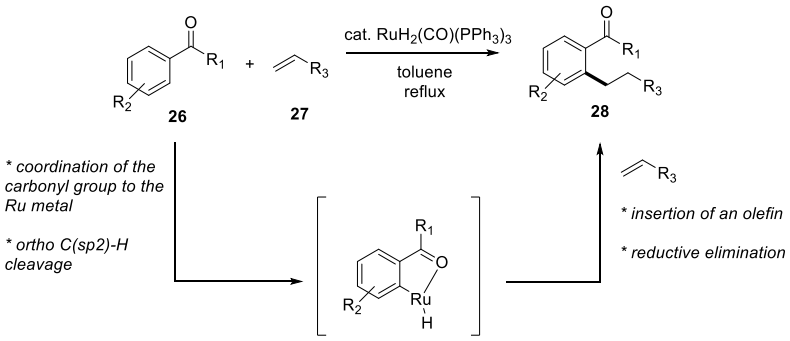
Scheme 8: Su's oxidative C(sp^2)-H arylation on various electron-deficient polyfluoroarenes 23 with simple arenes 24.

2.5 Directing Group-Promoted C-H Functionalization

Due to the ubiquity of C-H bonds present in most compounds, it is critical for C-H functionalization reactions to execute control of site selectivity thus ensuring the versatility in its application. One of the more widely used approaches to target specific unreactive C-H bonds is to use directing groups to guide the transition-metal catalysts to install new functional groups.

2.5.1 Murai's & Chatani's Ru-catalyzed C(sp^2)-H alkene addition

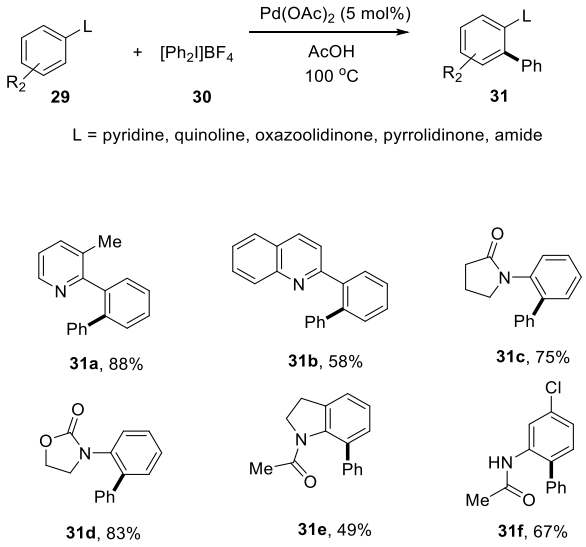
One of the pioneering works that illustrated the effectiveness of C-H functionalization *via* the directing-group promoted strategy was disclosed and popularized by Murai and Chatani.[58] The group reported an efficient approach to activate the C-H bond of the aromatic compounds **26**, *ortho* to the ketone moiety, and performed an addition to alkenes **27** in the presence of a ruthenium complex as the catalyst, $Ru(CO)_2(P(C_6H_5)_3)_3$ (Scheme 9). The ketone adducts served as an efficient directing group that provided good chelation assistance for the Ru complex to perform highly selective *ortho* C(sp^2)-H activation. This inspired the synthetic community to develop new methodologies pivoting on this approach since it demonstrated a high degree of efficiency, selectivity and generality.



Scheme 9: Murai and Chatani 's C(sp^2)-H *ortho* addition to alkenes 27 on various aromatic ketones 26.

2.5.2 Sanford's Pd-catalyzed C(sp^2)-H arylation with $[Ph_2I]BF_4$

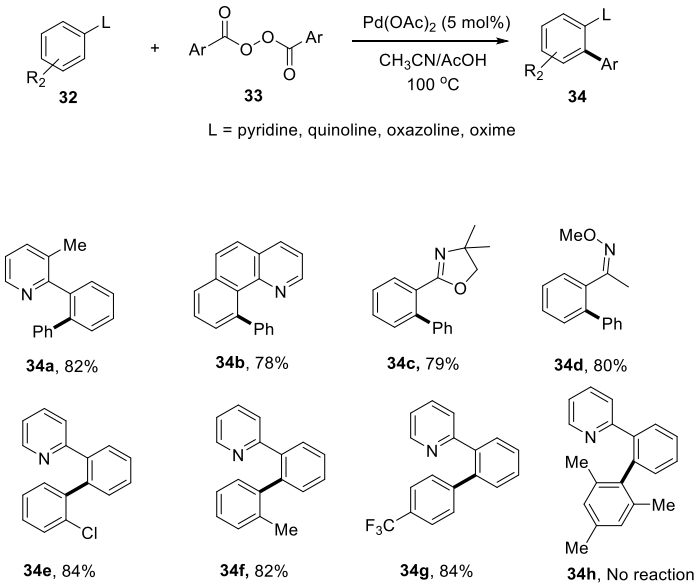
In 2005, Sanford *et. al.* reported the Pd catalyzed C(sp^2)-H activation/arylation of a diverse range of aromatic compounds **29** with the iodonium salt $[Ph_2I]BF_4$ **30** (Scheme 10).[59] The pyridine, quinoline, pyrrolidinone and oxazolidinone substituent of the arylated substrates served as an effective strong directing group to facilitate a highly regioselective *ortho* C-H activation/arylation. Furthemore, a wide variety of functionalities such as ethers, amides, aryl halides and benzylic hydrogens were found to be well-tolerated.



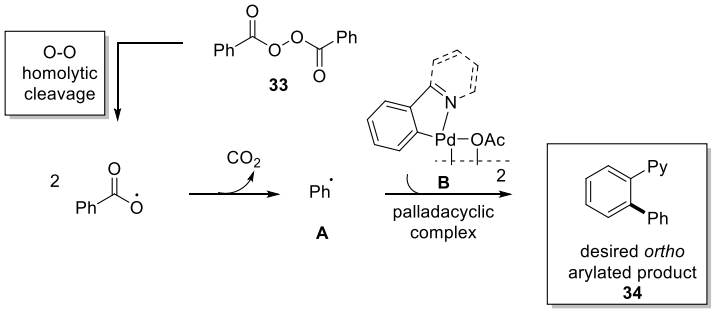
Scheme 10: Sanford's C(sp^2)-H *ortho* arylation with iodonium salt $[Ph_2I]BF_4$

2.5.3 W.-Y. Yu's Pd-catalyzed C(sp^2)-H arylation with aryl acylperoxides

Yu and co-workers also developed a similar Pd-catalyzed C(sp^2)-H arylation protocol in 2009 by using a cheaper coupling alternative, aryl acylperoxides **33** (Scheme 11).[60] The peroxides were reported to undergo a homolytic O-O cleavage, followed by decarboxylation of aryl-carboxyl radicals to generate the aryl radicals **A** (Scheme 12). Control of the site selectivity for the activation of aromatic C-H bond at the *ortho* position of **32** was accomplished by the assistance of various directing groups such as pyridyl, oxime and oxazoline to form a five-membered pallacyclic complex. Addition of the phenyl radical and subsequent reductive elimination resulted in the formation of the desired cross-coupled product **34**.



Scheme 11: W.-Y. Yu 's C(sp^2)-H *ortho* arylation of 32 with acylperoxides 33.

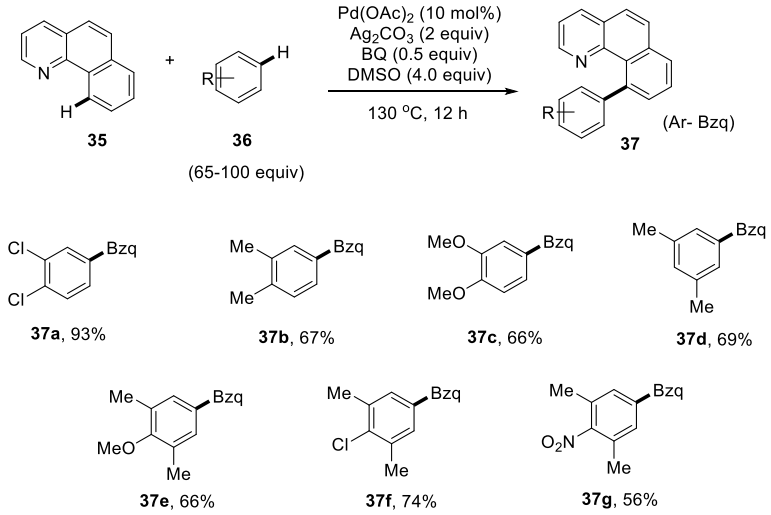


Scheme 12: Radical addition of aryl radicals with the palladacyclic complex.

2.5.4 Sanford's Pd-catalyzed oxidative C(sp^2)-H arylation of HBzq

In 2007, Sanford *et. al.* described the first example of a Pd catalyzed oxidative C(sp^2)-H activation/arylation of benzo[*h*]quinolone (HBzq) **35** with simple arenes **36** (Scheme 13).[61] The pyridinyl moiety served as a good DG for the active Pd species to perform two discrete C-H activation steps furnishing a wide range of desired arylated products **37** with excellent levels of regiocontrol. Instead of acting as an oxidant in this Pd^0/Pd^{II} reaction, 1,4- benzoquinone (BQ) is required as a coordinating ligand necessary for reductive elimination to proceed smoothly.

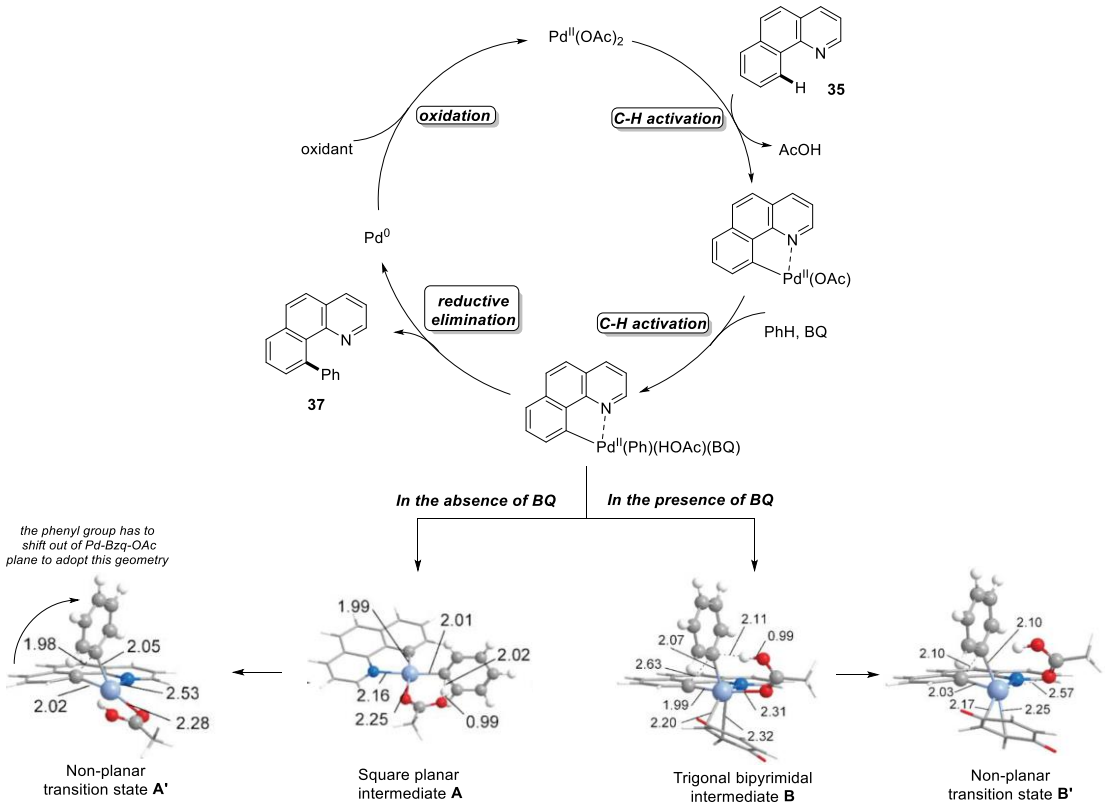
Addition of DMSO was also found to be necessary to improve the efficiency of this transformation presumably by decreasing the rate of catalyst decomposition/Pd^0 aggregation.[62]



Scheme 13: Sanford's C(sp^2)-H oxidative arylation of benzo[*h*]quinoline (Bzq) with simple arenes.

Although there are experimental findings that propose that 1,4-benzoquinone (BQ) is required to accelerate the RE step, theoretical studies to elucidate the exact role of BQ were not well established. It was not until 2010 that Sakaki and co-workers described the theoretical investigation of the stochiometric arene cross-coupling reaction between benzo[*h*]quinoline (HBzq) and benzene catalyzed by $Pd(OAc)_2$ to examine the key roles of BQ in the RE step *via* DFT, MP2 to MP4(SDQ) and CCSD(T) computations.[63] In the absence of BQ after the second C-H activation of benzene, the optimized geometry of the intermediate Pd(Bzq)(AcOH)(Ph) **A** adopts a square planar four-coordinate configuration (Scheme 14). On the other hand, the presence of BQ establishes π-back donation interactions with Pd (charge transfer from the Pd species to the electron-withdrawing BQ) resulting in BQ taking an equatorial position to stabilize the trigonal bipyramidal structure of intermediate Pd(Bzq)(AcOH)(Ph)(BQ) **B**. After the formation of the intermediates, studies of the transition states to furnish the biaryl products *via* the RE step were

then carried out. In order for the RE step to proceed smoothly, a non-planar transition state must be adopted. As a result, without BQ stabilizing the transition state, the phenyl moiety of the square planar intermediate **A** must shift considerably from the Pd-Bzq-OAc plane towards Bzq to form the non-planar structure of transition state **A'**. Whereas for trigonal bipyramidal intermediate **B**, the phenyl group is already positioned in the geometry similar to that of its transition state **B'**, thus energetically more favorable for RE.

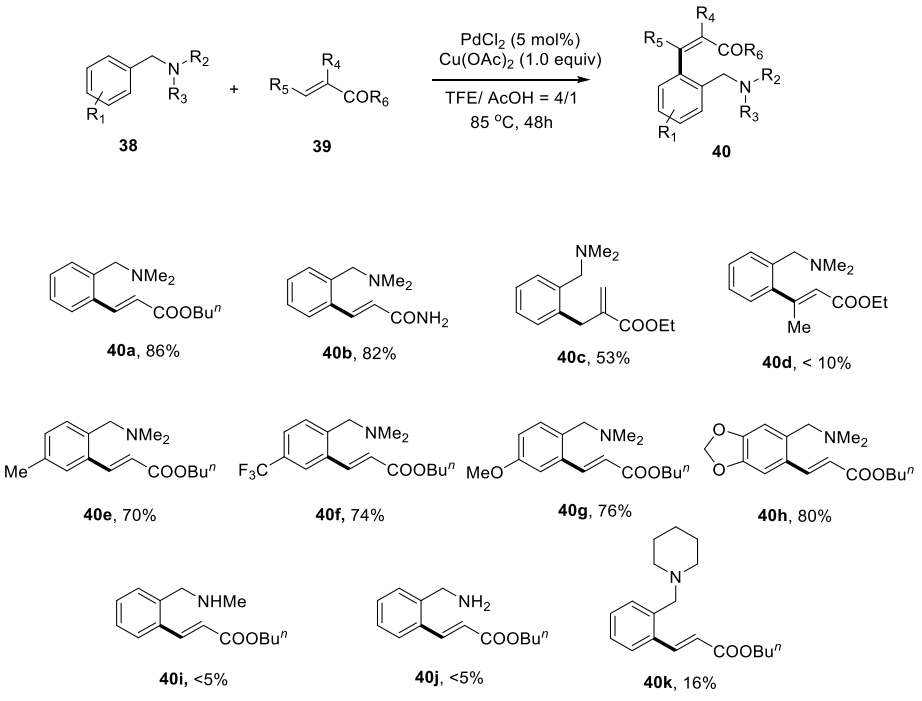


Scheme 14: Theoretical studies on the role of BQ in the RE step. Request to use the figures from Ref. 63 has been granted.

2.5.5 Shi's Pd-catalyzed C(sp^2)-H alkenylation of *N*,*N*-dimethylbenzylamine

Discovering other directing groups that include simple amine derivatives that are commonly found in natural alkaloids and biologically active compounds was highly desirable. In 2007, Shi *et. al.* developed a highly regioselective *ortho* alkenylation of *N*,*N*-dimethylbenzylamines **38** with

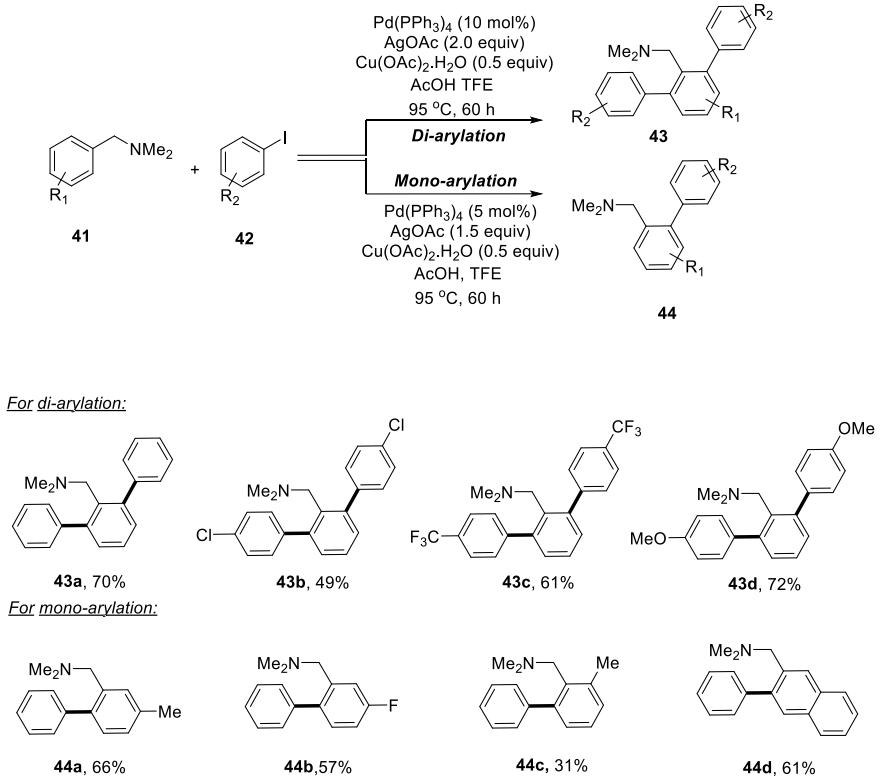
various electron-withdrawing alkenes **39** (Scheme 15).[64] The team envisaged that the *N*,*N*-dimethylaminomethyl group is a good σ-donor ligand and would provide an exemplary chelation assistance to perform *ortho* C-H activation. Nevertheless, this would ultimately increase the electron density of the metal ion, resulting in a weakening of the metal's electrophilicity.[65] Therefore, an acidic reaction medium is required to enhance the electrophilicity of the Pd^{II} species necessary for the electrophilic substitution of aromatic C-H bond.[66] Unfortunately, the efficient palladation of the benzylamines might be suppressed due to the protonation of the amino group. Therefore, the acidity of the reaction conditions had to be optimized for the reaction to proceed efficiently. Although the *ortho* olefination reaction proceeded with high yields of **40** when the *N*,*N*-dimethylaminomethyl group was used as DG, other benzylamine derivatives such as secondary, primary and cyclic, amine resulted in very low yield – **40i**, **40j** and **40k** respectively.



Scheme 15: Shi 's C(sp^2)-H alkenylation on substituted benzylamines 38.

2.5.6 Zhang's Pd-catalyzed C(sp^2)-H arylation of *N*,*N*-dimethylbenzylamine

Similarly, in 2013, Zhang and co-workers disclosed a Pd-catalyzed *ortho*-arylation of *N*,*N*-dimethylbenzylamines **41** with aryliodides **42** to give di-arylated products **43** in good yields (Scheme 16).[67] An acidic medium was essential and its acidity had to be optimized to ensure that the protonation of the amino group would not stall the reaction. Indeed, the reaction proceeded efficiently to give diarylated product when 10 equivalents of iodobenzene was used. Other aryl halide reagents such as aryl chlorides, aryl bromides and heteroaryl halides, however, did not result in any arylated products under the standard reaction conditions. The Zhang group also demonstrated the feasibility of mono-arylation at the less hindered position *ortho* to the amino directing group to furnish mono-arylated products **44**. This could be achieved by reducing the catalyst loading to 5 mol% from 10 mol% and the equivalents of the AgOAc to 1.5. Unfortunately, the scope of the reaction was limited to *N*,*N*-dimethylbenzylamines and its less than desired efficiency due to the excessive usage of iodobenzene and long reaction times were the major drawbacks of this protocol.



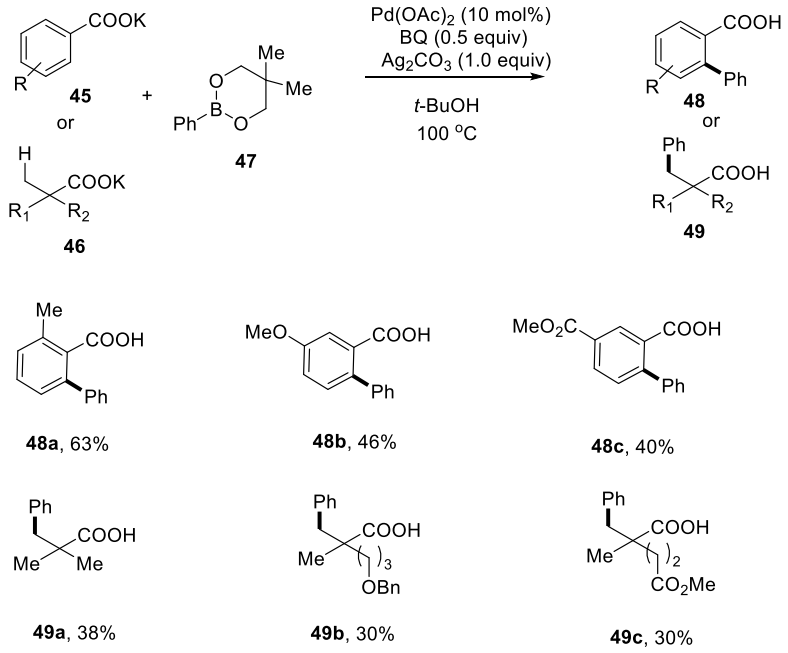
Scheme 16: Zhang 's C(sp^2)-H di- and mono- arylation on substituted benzylamines 41.

2.5.7 Yu's Pd-catalyzed C(sp^2)-H arylation of benzoic acids

As most examples discussed above required an acidic medium for C-H activation/ cross-coupling to proceed, Yu and co-workers demonstrated the *ortho* Pd-catalyzed C-H arylation of free benzoic acids (**45** & **46**) with phenylboronate **47** under basic condition in 2007 (Scheme 17).[68] They discovered that the introduction of a counterion, in this case K^+, was important for its reactivity and the electronically enriched carbonyl was hypothesized to be involved with the coordination of the Pd^{II} rather than the O-anion of the carboxylate.

For the free carboxylic acids to serve as an effective directing group proved to be challenging due to its high propensity to undergo other transformations such as decarboxylation when subjected to palladium catalyzed conditions. Nevertheless, not only did they demonstrate arylation on the *ortho*

C(sp^2)-H of aryl carboxylic acids **45**, the reaction conditions were also favourable for the activation of the C(sp^3)-H of tertiary carboxylic acids **46**.



Scheme 17: Yu 's C(sp^2)-H and C(sp^3)-H arylation of carboxylic acids 45 & 46 with phenylboronate 47.

More interestingly from a synthetic perspective, Yu and co-workers demonstrated the importance of employing intrinsic parts of the substrates that could also serve as weakly coordinating directing groups to effect C-H activation. This would render any additional steps of their installation and removal unnecessary. Often, strong donating groups (σ-donors and/or π-acceptors) that usually comprise of nitrogen, sulfur or phosphorus were not synthetically useful for subsequent transformations (Figure 5). Moreover, further functionalization of this strongly chelating, thermodynamically stable cyclometalated intermediate was restricted to a limited range of nucleophiles and electrophiles due to its low reactivity.[69]

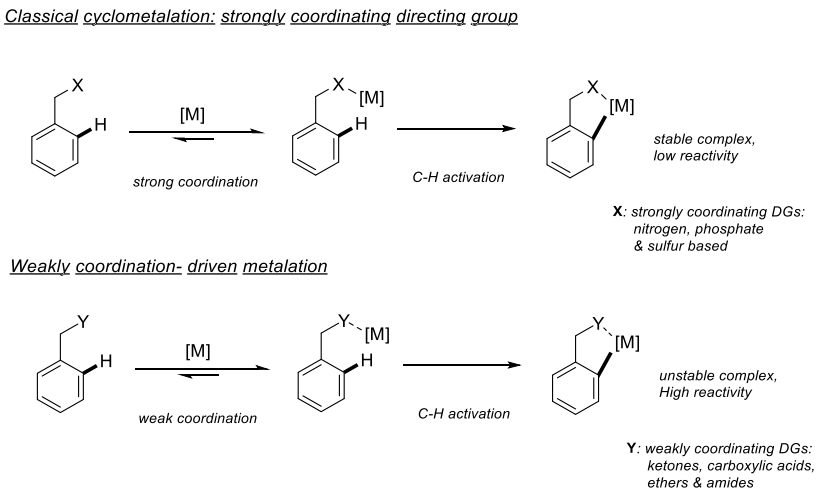


Figure 5: Classical Cyclometalation and Weak coordination-Driven Metalation

To achieve good efficiency in carboxylate-directed C-H activated cross coupling reactions, addition of a hard Lewis acidic metal was crucial. Countercations such as Na^+, K^+, NR_4^+, were hypothesized to preferentially coordinate to the carboxylate group in a κ^2 coordination mode (Figure 6). This promoted a κ^1 coordination mode of the Pd(II) with the free oxygen lone pair, which would ultimately trigger a C-H cleavage to form the complex **A** characterized by ^{1}H NMR.[69]

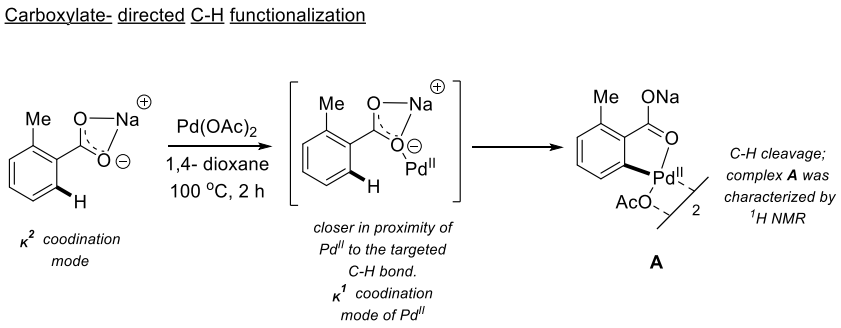
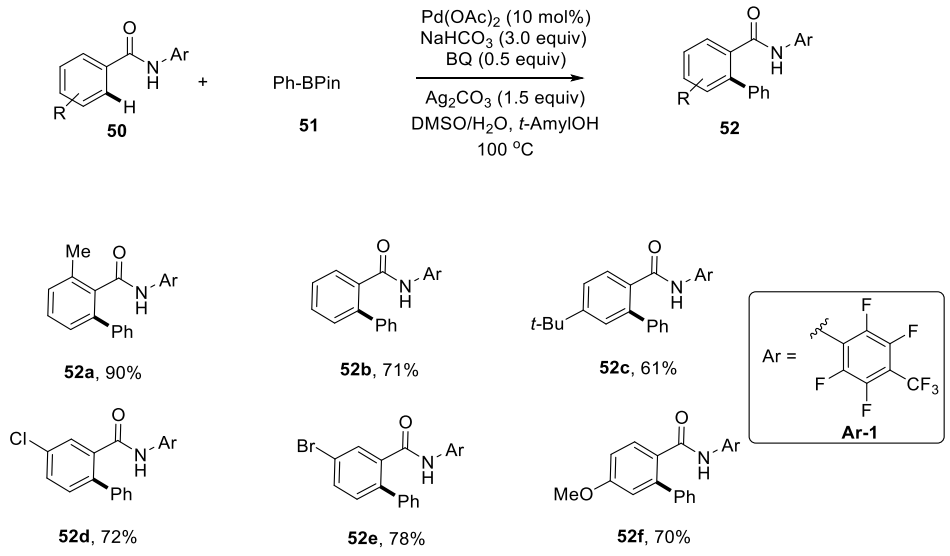


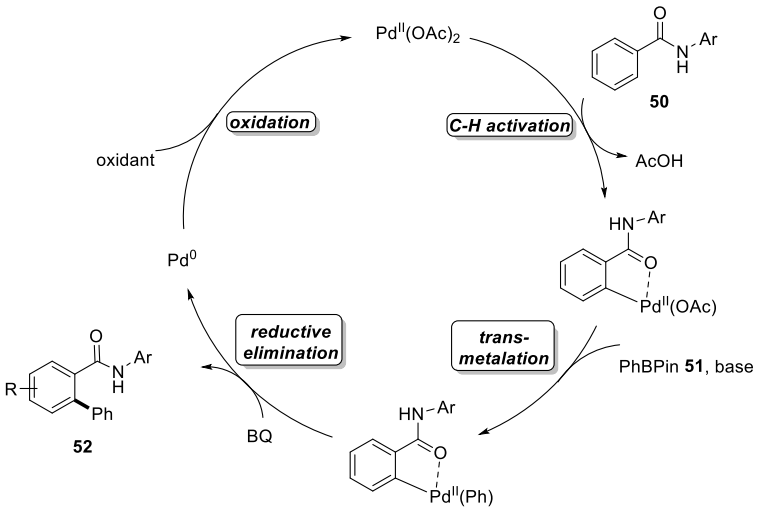
Figure 6: Proposed Coordination Structures for C-H activation promoted by Countercation and Pd^{II}

2.5.8 Yu's Pd-catalyzed C(sp^2)-H arylation of *N*-arylamide Ar-1

Later in 2011, Yu *et. al*. reported the C(sp^2)-H activated cross-coupling of **50** with arylboron reagents **51**, directed by *N*-arylamide **Ar-1** under basic conditions (Scheme 18).[70] The catalysis was proposed to undergo a Pd^{II} catalytic cycle, starting with the C-H activation of the C(sp^2)-H *ortho* to the directing group (Scheme 19). Subsequently, similar to the Suzuki's coupling reaction mechanism, transmetallation with phenylboronic acid pinacol ester (Ph-BPin) proceeded with the aid of a suitable base $NaHCO_3$. Addition of 1,4-benzoquinone (BQ) as a promoter was important for the reductive elimination to forge the new C-C bond, affording the desired cross-coupled products **52**.[63] The resultant Pd^0 was further oxidized by the terminal oxidant, Ag_2CO_3, to afford catalytically active Pd^{II} species necessary for subsequent catalysis.



Scheme 18: Yu 's C(sp^2)-H arylation of 50 with Ph-BPin 51 directed by *N*-arylamide Ar-1



Scheme 19: Yu 's proposed Pd^{II}-catalyzed cross-coupling cycle

2.6 Our Approach: Palladium(II)-catalyzed ortho-arylation of N-benzylpiperidines

2.6.1 Objective & Plan

Motivated by these findings, we envisaged that saturated *N*-containing heterocycles could serve as efficient directing groups (DGs) for C(sp^2)-H arylation under the basic reaction conditions reported by Yu and co-workers.[68,70] We first identified that the piperidine moiety could be a potentially useful directing group for C(sp^2)-H activation / arylation to proceed smoothly without the predicament that the protonation of the amino group of the piperidine would off-set its directing ability and as a result stall the reaction under acidic medium. This methodology would expand the range of DGs in the field and could be applied directly to the construction of biologically relevant motifs, for example, in known Bc1-2 antagonists[71], γ-secretase modulators[72] and 5-HT_7-antagonists[73] (Figure 7).

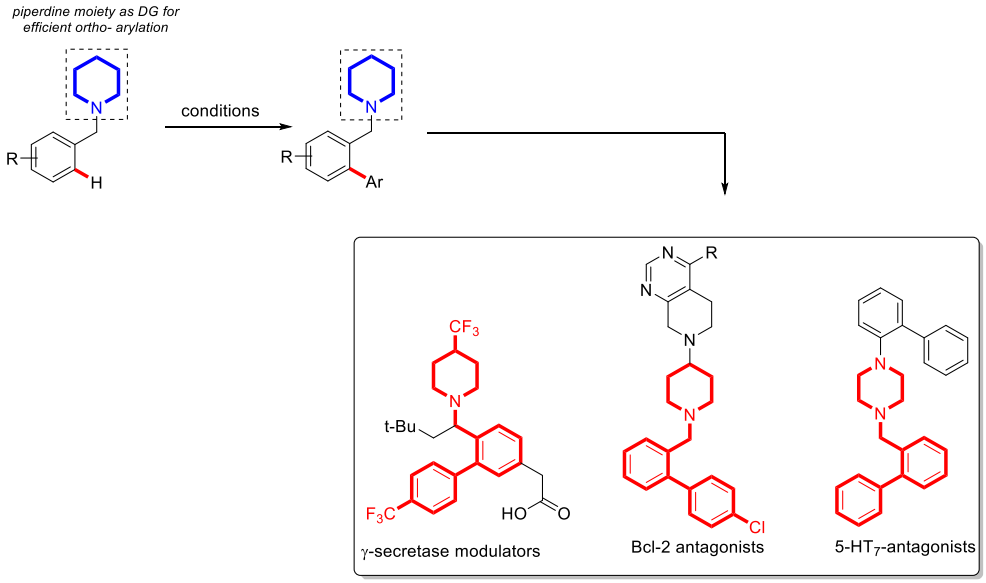
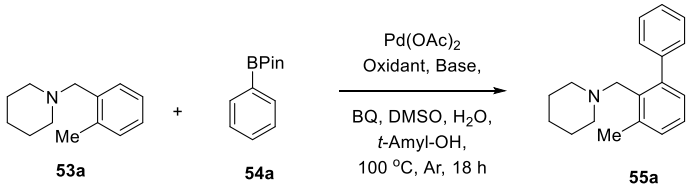


Figure 7: *Ortho*-arylation using piperidine as directing group to access biologically active compounds

2.6.2 Optimization: Base & Oxidant

Table 1: Optimization studies on various bases and oxidants.



Entry	Oxidant (equiv)	Base (equiv)	Yield[a] (%)
1	Ag_2CO_3 (2.0)	Na_2CO_3 (6.0)	55
2	Ag_2CO_3 (2.0)	KF (6.0)	25
3	Ag_2CO_3 (2.0)	K_2HPO_4 (6.0)	33
4	Ag_2CO_3 (2.0)	NaOAc (6.0)	78
5	Ag_2CO_3 (2.0)	$NaHCO_3$ (6.0)	86
6	Ag_2CO_3 (2.0)	$NaHCO_3$ (3.0)	82
7	$Cu(OAc)_2$ (1.5)	$NaHCO_3$ (3.0)	11
8	CuF_2 (1.5)	$NaHCO_3$ (3.0)	2
9	Ag_2CO_3 (1.5)	$NaHCO_3$ (4.0)	85 (77)
10	Ag_2CO_3 (0.5)	$NaHCO_3$ (4.0)	38

11[b]	Ag_2CO_3 (0.5)	$NaHCO_3$ (4.0)	37
12[c]	Ag_2CO_3 (0.8)	$NaHCO_3$ (4.0)	52
13	**Ag_2CO_3 (2.0)**	**$NaHCO_3$ (4.0)**	**88 (81)**
14	Ag_2O (2.0)	$NaHCO_3$ (4.0)	15
15	AgOAc (2.0)	$NaHCO_3$ (4.0)	81(75)
16	AgTFA (2.0)	$NaHCO_3$ (4.0)	Traces
17	AgOAc (2.0)	NaOAc (4.0)	71(64)

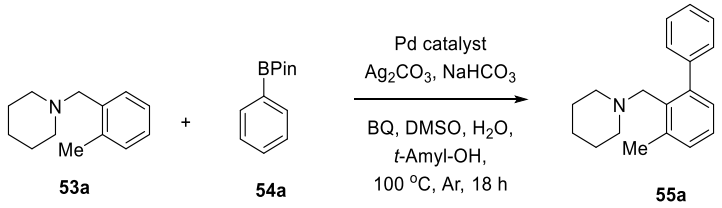
Reaction conditions: 53a (0.2 mmol), 54a (0.28 mmol), $Pd(OAc)_2$ (10 mol%), Base, Oxidant, 1,4- benzoquinone (0.5 equiv), DMSO (5 µL), H_2O (20 µL), *t*-amyl-OH (1 mL) for 18 h at 100 °C.

a. ^{1}H NMR yield with internal standard (CH_2Br_2), isolated yield in parentheses. *b.* Reaction was carried out under O_2 atmosphere. *c.* Reaction was carried out using 1,4-benzoquinone (1.0 equiv).

A preliminary experiment was conducted using the model substrate 1-(2-methylbenzyl)piperidine **53a** and phenylboronic acid pinacol ester **54a** in the presence of $Pd(OAc)_2$, Ag_2CO_3, Na_2CO_3 and 1,4-benzoquinone at 100 °C (Table 1). Encouragingly, the *ortho*-arylated product **55a** was observed in 55% yield by NMR (Table 1, entry 1). Further optimization was then carried out, starting with an investigation of the performance of different bases. Potassium bases, KF and K_2HPO_4, resulted in a reduced yield (Table 1, entry 2 & 3). Pleasingly, however, $NaHCO_3$ was found to be optimal for this transformation; full conversion of **53a** was observed and the arylated product **55a** was obtained in 86% yield by NMR after 18 hours (Table 1, entry 5). Other oxidants such as $Cu(OAc)_2$ and CuF_2 were found to give inferior yields (Table 1, entry 7 & 8) and although AgOAc was found to perform reasonably well (Table 1, entry 15), Ag_2CO_3 proved optimal (Table 1, entry 13).

2.6.3 Optimization: Catalyst

Table 2: Optimization studies on various Pd catalysts.



53a **54a** **55a**

Entry	Catalyst	Loading (mol %)	Yield[a](%)
1	$PdCl_2(CH_3CN)_2$	10	0
2	$PdCl_2$(dppf)	10	0
3	$PdCl_2(PPh_3)_2$	10	0
4	$Pd(TFA)_2$	10	44
5	$PdCl_2$	10	0
6	**$Pd(OAc)_2$**	**10**	**82**
7	$Pd(OAc)_2$	5	43

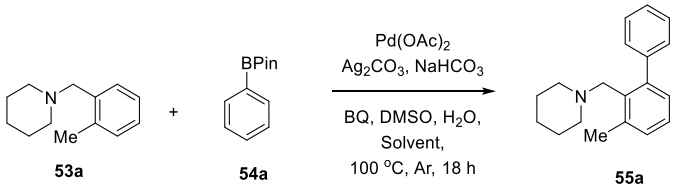
Reaction conditions: 53a (0.2 mmol), 54a (0.28 mmol), Pd catalyst, $NaHCO_3$ (3.0 equiv), Ag_2CO_3 (1.5 equiv), 1,4- benzoquinone (0.5 equiv), DMSO (5 µL), H_2O (20 µL), *t*-amyl-OH (1 mL) for 18 h at 100 °C.

a. ^1H NMR yield with internal standard (CH_2Br_2).

Various Pd(II) catalysts such as $PdCl_2$, $PdCl_2(PPh_3)_2$ and $PdCl_2(CH_3CN)_2$ – other than $Pd(OAc)_2$ – did not result in the formation of any arylated product (Table 2, entry 1, 2, 3 & 5). While $Pd(TFA)_2$ (Table, 2, entry 4) provided the arylated product with 44% yield by NMR, $Pd(Oac)_2$ was found to be the best (Table 2, entry 6). Decreasing the $Pd(OAc)_2$ loading to 5 mol% resulted in a decrease in yield and thus 10 mol% of the catalyst was deemed necessary (Table 2, entry 7).

2.6.4 Optimization: Solvent

Table 3: Optimization studies on various solvents.



53a 54a 55a

Entry	Solvent	Yield[a](%)
1	1,2-DCE	14
2	toluene	11
3	1,4-Dioxane	74
4	MeCN	56
5	PhCl	11
6	***t*-Amyl-OH**	**88 (81)**

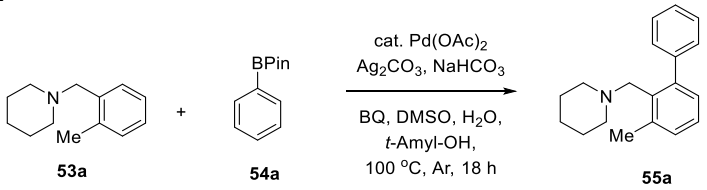
Reaction conditions: 53a (0.2 mmol), 54a (0.28 mmol), $Pd(OAc)_2$ (10 mol%), $NaHCO_3$ (3.0 equiv), Ag_2CO_3 (1.5 equiv), 1,4- benzoquinone (0.5 equiv), DMSO (5 µL), H_2O (20 µL), solvent (1 mL) for 18 h at 100 °C.

a. ^1H NMR yield with internal standard (CH_2Br_2), isolated yield in parentheses.

A solvent screen was conducted for this transformation and *t*-amyl alcohol was found to be the most suitable (Table 3, entry 6), followed by 1,4-dioxane (Table 3, entry 3) and MeCN (Table 3, entry 4). Less polar solvents such as PhCl (Table 3, entry 5) and toluene (Table 3, entry 2) both gave a poor yield of 11%.

2.6.5 Optimization: Control experiments

Table 4: Control experiments.



Entry	Oxidant	Base	Additive	Yield[a](%)
1	-	$NaHCO_3$	1,4-benzoquinone	9
2	Ag_2CO_3	-	1,4-benzoquinone	29
3	Ag_2CO_3	$NaHCO_3$	-	0
4[b]	Ag_2CO_3	$NaHCO_3$	1,4-benzoquinone	49
5[c]	Ag_2CO_3	$NaHCO_3$	1,4-benzoquinone	54

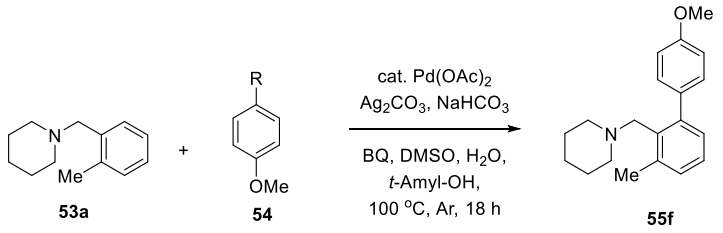
Reaction conditions: 53a (0.2 mmol), 54a (0.28 mmol), $Pd(OAc)_2$ (10 mol%), $NaHCO_3$ (3.0 equiv), Ag_2CO_3 (1.5 equiv), 1,4- benzoquinone (0.5 equiv), DMSO (5 µL), H_2O (20 µL), *t*-amyl-OH (1 mL) for 18 h at 100 °C.

a. ^1H NMR yield with internal standard (CH_2Br_2). *b.* Reaction was carried out in the absence of H_2O. *c.* Reaction was carried out in the absence of DMSO.

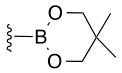
To ascertain the importance of the addition of individual components for this transformation, control experiments were conducted (Table 4). It was shown that reactions without addition of oxidant and base resulted in yields of only 9% (Table 4, entry 1) and 29% (Table 4, entry 2) respectively. 1,4-Benzoquinone (BQ) was also essential as a promoter (Table 4, entry 3); in its absence, no reaction was observed in agreement with literature findings relating to its importance in the reductive elimination step.[61,63,74,75] It was presumed that the BQ coordinates with the active Pd^{II} complex to establish the most favorable structural conformation of the pre-transition state for the concomitant RE step (Refer to section 2.5.4, Scheme 14). Furthermore, a decrease in yield was also observed without the addition of H_2O (Table 4, entry 4) and DMSO (Table 4, entry 5) – they are required to improve the efficiency of this transformation presumably by decreasing the rate of catalyst decomposition/Pd^0 aggregation.[62]

2.6.6 Optimization: Coupling reagents

Table 5: Control experiments.



53a 54 55f

Entry	R	Yield[a](%)
1	$B(OH)_2$	20
2		54
3	BPin	66

Reaction conditions: 53a (0.2 mmol), 54 (0.28 mmol), $Pd(OAc)_2$ (10 mol%), $NaHCO_3$ (3.0 equiv), Ag_2CO_3 (1.5 equiv), 1,4- benzoquinone (0.5 equiv), DMSO (5 µL), H_2O (20 µL), *t*-amyl-OH (1 mL) for 18 h at 100 °C.

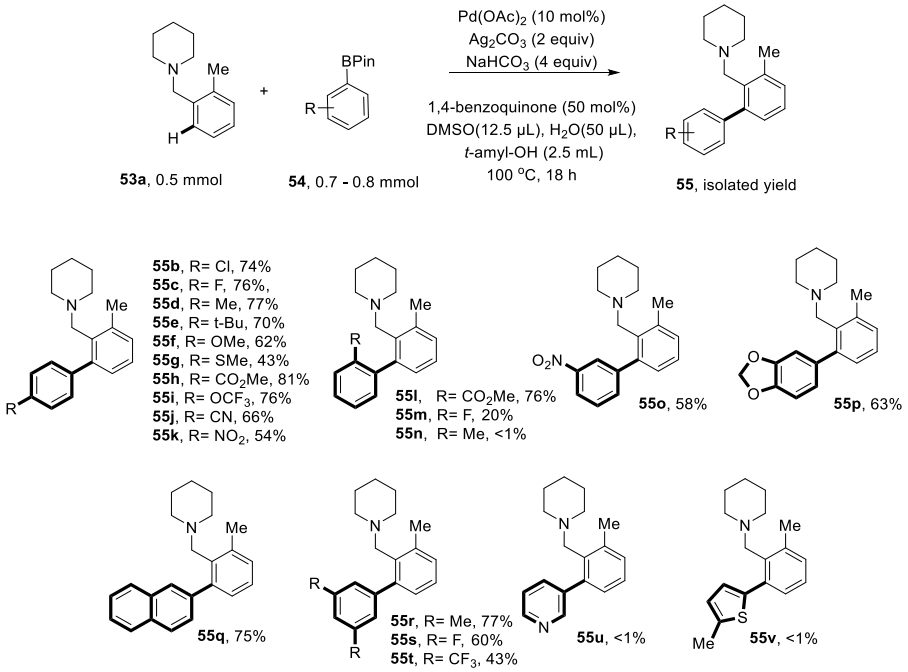
a. ^1H NMR yield with internal standard (CH_2Br_2).

Finally, other aryl boronic acid derivatives such as 4-methoxyphenylboronic acid and 4-methoxylphenylboronic acid neopentylglycol ester were also investigated (Table 5). However, 4-methoxyphenylboronic acid pinacol ester **54f** was the best coupling reagent for this reaction (Table 5, entry 3).

2.6.7 Substrate Scope: C(sp^2)-H arylation with various Ar-BPin

After identifying the optimized conditions, the scope of this methodology was evaluated using different functionalized arylboronic acid pinacol esters **54** (Ar-Pins) with 1-(2-methylbenzyl)piperidine **53a** (Scheme 20). In general, a wide range of *para*-substituted Ar-Pin substrates were tolerated and the corresponding biaryl products were obtained in modest to good yields. Substituted Ar-BPins with functional groups, such as cyano (**55j**), nitro (**55k**) and fluorine (**55c**) were suitable substrates under these reaction conditions affording the desired products in

respectable yields. Furthermore, chlorine substituted Ar-BPin (**55b**) was also well-tolerated, providing biaryl product poised for further transformations. In the case of *ortho*-substituted Ar-BPin substrates, the reaction worked well using the ester **54l** to afford the biaryl product **55l** in a yield of 76%. However, unfortunately, poor conversions were observed for other substituents such as fluoro (**55m**) and methyl (**55n**). The reaction was also amenable to *meta*-substituted and 3,5-disubstituted Ar-BPin derivatives giving rise to the corresponding products in 43-77% yield. Additionally, in agreement with related studies, heteroarylboronatees that contained pyridine – (**55u**), thiophene- (**55v**) were unreactive under these conditions.

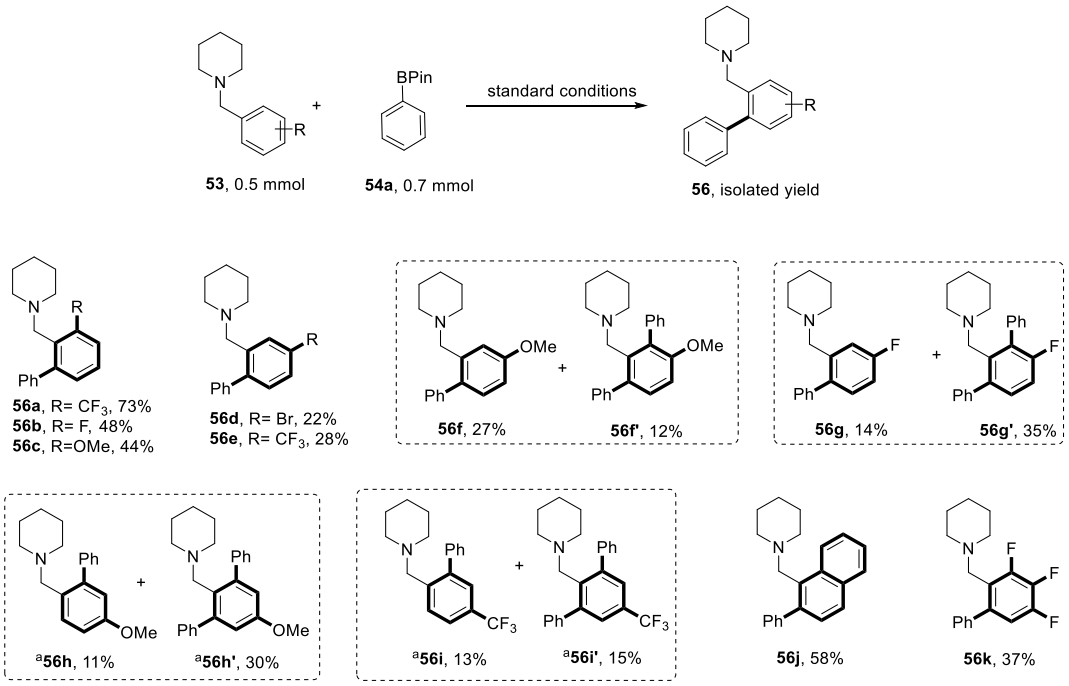


Scheme 20: C(sp^2)-H cross-coupling of 1-(2-methylbenzyl)piperidine 53a with various Ar-BPins 54.

2.6.8 Substrate Scope: C(sp^2)-H arylation with various arylbenzylpiperidines

Subsequently, the scope with respect to the substituents on the aryl portion of the benzylpiperidine with phenylboronic acid pinacol ester was investigated. *ortho*-Substituted substrates possessing electron-withdrawing (F and CF_3) and the electron-donating (OMe) substituents performed

reasonably well, with products **56a**, **56b** and **56c** being afforded in 44-73% yield (Scheme 21). *Meta*-substituted substrates with electron-withdrawing substituents that are relatively sterically bulky (Br and CF_3) underwent selective monoarylation at the less hindered *ortho* position, presumably due to steric effects, to furnish products **56d** and **56e** in 22-28% yield. On the other hand, for substrates with a less bulky electron withdrawing substituent (F), products of both mono- and di-arylation, **56g** and **56g'**, were obtained in 14% and 35% respectively. Furthermore, for an electron-donating *meta*-substituted benzylpiperidine derivative (OMe), other than monoarylation to give **56f** (27%) as the major product, diarylation was also observed to afford **56f'** in 12% yield. The reaction conditions were amenable to *para*-substituted substrates furnishing a mixture of mono- and di-arylated products. Increased reactivity was observed for electron-donating substituents (OMe) at the *para* position compared to electron-withdrawing groups, with the di-arylated compounds **56h'** and **56i'** being obtained as the major products. Naphthyl (**56j**) and tri-fluorophenyl (**56k**) derivatives were also well-tolerated.

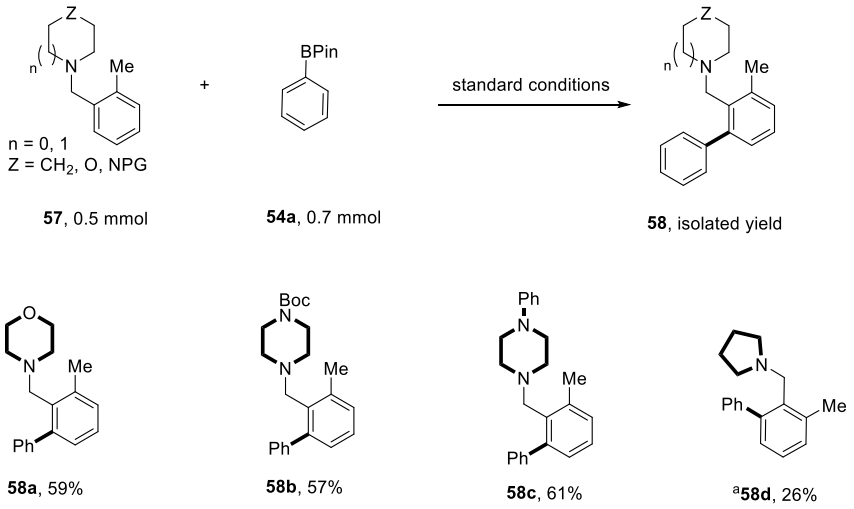


Scheme 21: C(sp^2)-H cross-coupling of phenylboronic acid ester 54a with different functionalized benzylpiperidines 53.

a. Reaction was carried out with **54a** (1.1 mmol) for 24 h.

2.6.9 Substrate Scope: C(sp^2)-H arylation with various nitrogen-containing benzylic heterocycles

After exploring arylations directed by the piperidine moiety, other possible saturated nitrogen-containing heterocyclic derivatives that could serve as effective directing groups for this methodology were then examined. Accordingly, the benzylic heterocycles **57** were subjected to our standard optimized reaction conditions (Scheme 22). Pleasingly, morpholine (**58a**) and piperazine (**58b** and **58c**) scaffolds worked well, obtaining the corresponding arylated products in good yield. Reaction with benzylic heterocycles of different ring size (**58d**) was also shown to proceed albeit the low yield obtained under the standard conditions and no further optimization was performed to improve the yield.

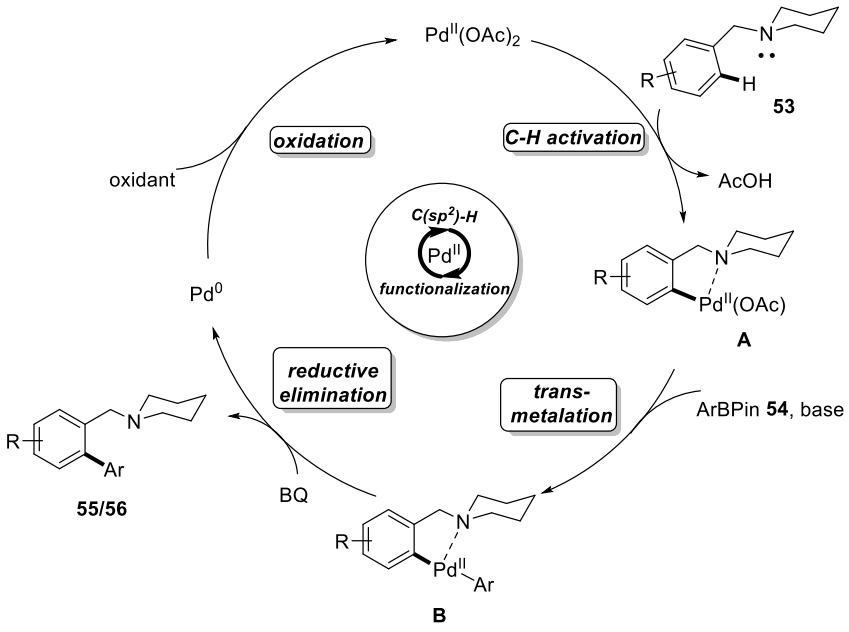


Scheme 22: C(sp^2)-H cross-coupling of phenylboronic acid ester 54a with different functionalized benzyl heterocycles 57.

a. Reaction was carried out with **54a** (1.0 mmol) for 24 h.

2.6.10 Proposed catalytic cycle

According to the previous studies[68,70], we postulate that this C-H activation cross-coupling transformation proceeds *via* a Pd^{II} / Pd^0 catalytic cycle (Scheme 23). The palladium species first activates the *ortho* C-H of **53** to form a 5-membered palladacycle intermediate **A**. Subsequently, addition of base is essential for the transmetalation of Ar-BPin **54** to proceed, generating intermediate **B**. 1,4- Benzoquinone (BQ) then facilitates reductive elimination leading to the formation of biaryl product (**55** or **56)** and the Pd^0 species.[61,63,74,75] Finally, regeneration of the active Pd^{II} species for further turnovers was achieved *via* reoxidation of Pd^0 by an oxidant, in this case Ag_2CO_3.



Scheme 23: Proposed C(sp^2)-H arylation catalytic cycle.

2.6.11 Conclusion & Future work

In conclusion, we have discovered that a range of saturated nitrogen-containing heterocycles attached to the benzylic substrates serve as effective directing groups for Pd^{II}-catalyzed C(sp^2)-H activation/arylation. Under this mild palladium catalysis, the coupling of a range of arylboronic acid pinacol esters to the *ortho* position of *N*-benzylated pyrrolidines, piperidines, morpholine and piperazine substrates providing direct access to important biaryls motifs, was demonstrated.

Although the Pd-catalyzed C-H functionalization reactions have been well documented over the last decade, there is an increasing demand to replace the use of expensive transition metals (e.g. Rh, Ir and Pd) with Earth-abundant first-row transition-metal catalysts (e.g. Ni, Co and Fe) for carbon-carbon / carbon-heteroatom transformations. Henceforth, our further work was focused on the development of new strategies for C-H functionalized transformations catalyzed by well-defined inexpensive metal complexes. Additionally, the pursuit of expanding the scope of this field

to include the site-selective C-H functionalization of the comparatively less reactive C(sp^3)-H bonds was also highly desirable and considered next.

Chapter 3: Thioamide Directed Co(III) Catalyzed Selective Amidation of C(sp^3)- H Bonds

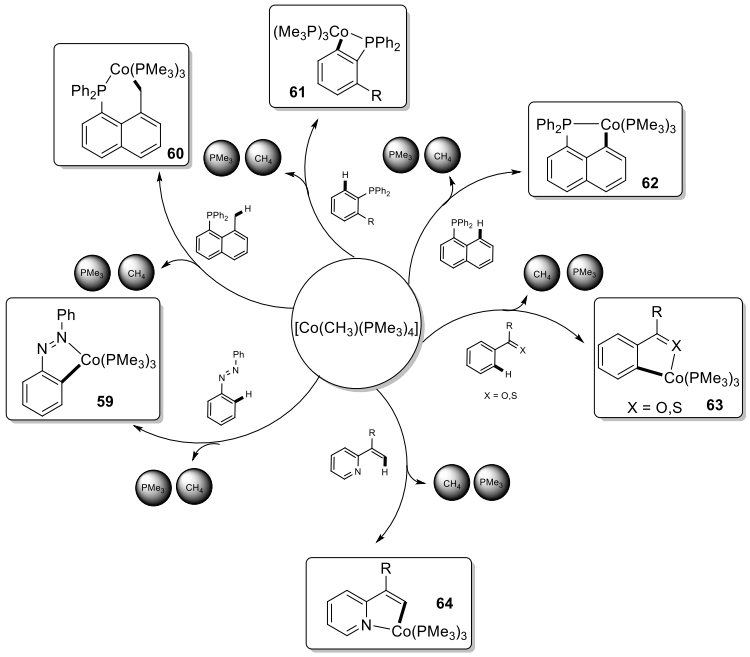
3.1 Introduction

The renaissance of C-H functionalization reactions for the formation of carbon-carbon and carbon-heteroatom bonds has proven to be an important hallmark in the history of synthetic chemistry due to its versatility and vast application in pharmaceuticals. Nevertheless, the widely used metals to achieve efficient catalyzed C-H functionalization processes, namely palladium, ruthenium, iridium and rhodium, are generally expensive albeit good for activating the inert C-H bond.[15–23] To address the issue of the over reliance on previous metals, the field of C-H functionalization has witnessed a paradigm shift towards employing cost efficient, Earth-abundant first-row metals as prospective alternatives.[76–82] Cobalt-catalyzed C-H functionalization reactions in particular have received considerable attention from the community and have been actively investigated in the recent years.[81,83–87] Despite the numerous studies that have demonstrated the great potential of cobalt complexes in homogeneous catalysis, it is important to note that they possess inherent differences from that of 4d and 5d transition metal complexes in terms of electronic properties such as electronegativity.[88] The considerably reduced electronegativity of cobalt relative to that of 4d- and 5d- transition metals allows the easy generation of more nucleophilic cobalt intermediates that are capable of achieving new reaction pathways.

3.2 Pioneering work

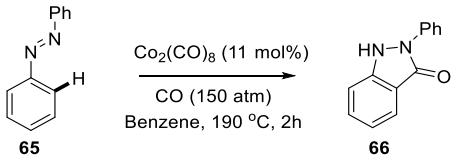
In 1993, Klein and co-workers provided the first evidence that delineated the activation of an inert C-H bond by cobalt species through the isolation of the cyclometalated cobalt complex **59**.[89] By treating azobenzene with [$Co(CH_3)(PMe_3)_4$], the active cobalt complex initiated the oxidative

addition of the C-H bond *via* the coordination of the Lewis basic directing group. Expansion of viable directing groups that would allow facile coordination of the cobalt complexes to perform cyclometalation process was further explored in their subsequent studies. Subsequently, various arenes with phosphorus, nitrogen, oxygen or sulfur based substituents were proven to be efficient directing groups for the formation of cyclocobaltated complexes **59** – **64** (Scheme 24).[90–94]



Scheme 24: Cyclometalated cobalt complex *via* stoichiometric C-H activation by [Co(CH$_3$)(PMe$_3$)$_4$].

Instead of using stoichiometric amount of Co catalysts, Murahashi and team disclosed an elegant approach that could activate the C(sp^2)-H bond *ortho* to the directing group and perform carbonylative cyclization of azobenzene to furnish indazolones in the presence of catalytic $Co_2(CO)_8$ (Scheme 25).[95,96] Nevertheless, despite its potential for other possible transformations through this cobalt-catalyzed process, harsh reaction conditions (high pressure and temperature) have made this approach less appealing.



Scheme 25: C-H activation / carbonylative cyclization of azobenzene by catalytic $Co_2(CO)_8$.

*3.3 Cp*Co^{III} catalyzed C(sp^2)-H activation / functionalization*

In the last decade, high-valent Cp*-based complexes of precious metals such as rhodium have been well-documented for their unique properties in activating inert C-H bond *via* a directing group promoted approach.[18,97–100] It was not until 2013 that Matsunaga and Kanai began their investigation to determine if the ability to cleave inert C-H bonds could be translated to relatively less expensive Cp*Co^{III} complexes.[101] To evaluate the optimal catalyst activity profile for C-H activation, a series of various Cp*Co^{III} complexes **67** – **72** was synthesized as a result (Figure 8).[102,103] Since then, a remarkable progress has been achieved in the field of Cp*Co^{III} based C-H functionalization over the past 4 years.[83–87]

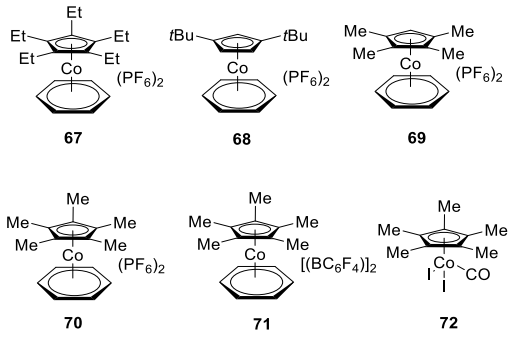
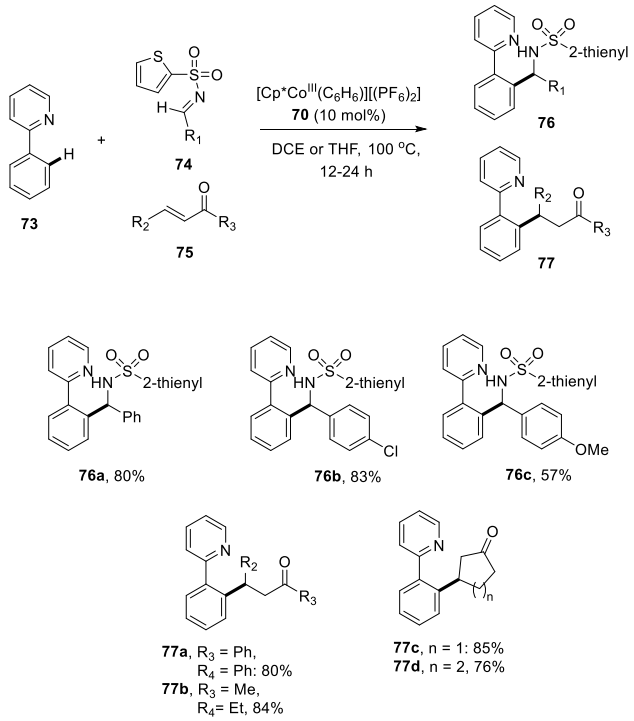


Figure 8: Cp*Co^{III} complexes and analogues 67-72 for C-H functionalization reactions.

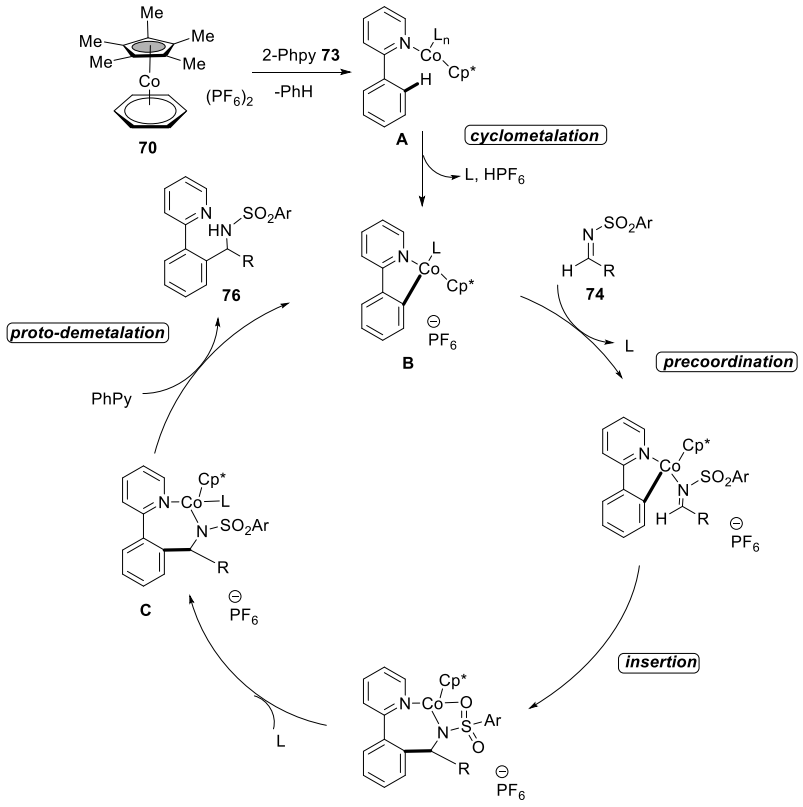
3.3.1 Hydroarylation

One of the earliest examples that established the elegant C-H activation / nucleophilic addition of 2- arylpyridines **73** to *N*-sulfonylimine **74** and enones **75** catalyzed by *in situ* generated cationic Cp^*Co^{III} complex was reported by Matsunaga/Kanai in 2013 (Scheme 26).[101] Since Cp^*Co^{III} catalyzed C-H functionalization reactions are often redox neutral, further addition of stoichiometric oxidants and σ-donating ligands were not necessary. After screening the various Co^{III} complexes **67- 72**, $[Cp^*Co^{III}(C_6H_6)][(PF_6)_2]$ **70** was found to perform the best (Figure 8). The optimized reaction was generally amenable to different substituted imines although a lower reactivity was observed for electron-rich imines. The scope of this addition reaction was also extended to other electrophiles such as α,β-unsaturated enones with excellent reactivity and great functional groups tolerance being observed.



Scheme 26: Cp^*Co^{III}-catalyzed addition reactions with aldimines 74 and enones 75.

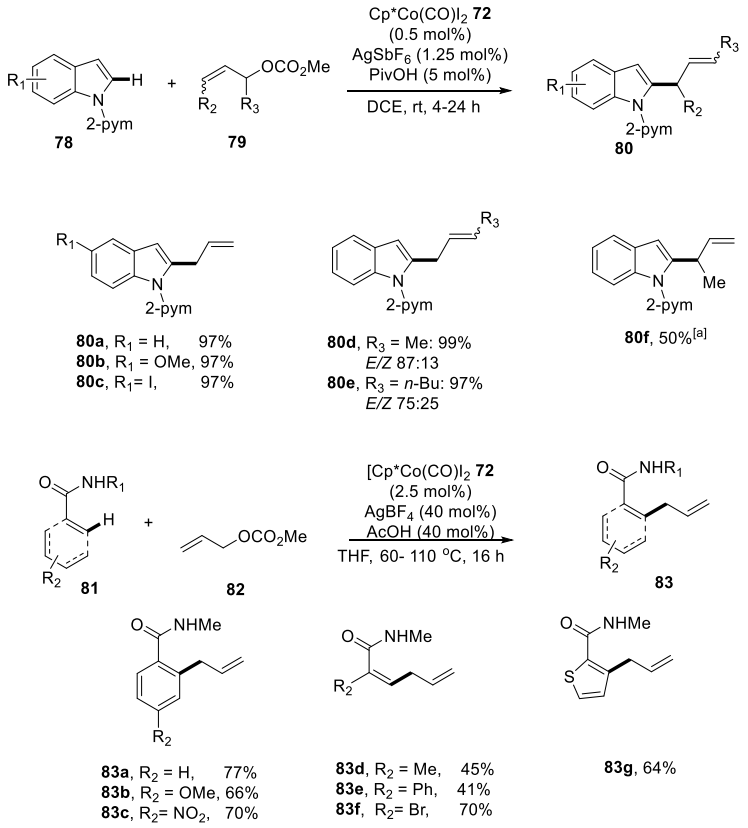
Based on the mechanistic studies carried out on analogous Rh^{III}-catalyzed reactions, the reaction was initiated by the dissociation of benzene from the complex **70** followed by the coordination of two arylpyridines **73** to generate complex **A** (Scheme 27). Subsequently, the reaction proceeded with a C-H metalation process *via* a concerted metalation-deprotonation-type (CMD) mechanism or electrophilic aromatic substitution to afford cyclometalated intermediate **B**. Coordination of intermediate **B** with electrophilic imines and successive insertion into Co-C bond resulted in the formation of the purported 7-membered-ring cobaltacycle **C**. Eventually, regeneration of the active species **B** proceeded through the coordination of an incoming arylpyridine and proto-demetalation to afford the desired addition product **76**.



Scheme 27: Proposed mechanism for Cp*Co^{III} catalyzed addition reactions (L= 2-Phpy).

3.3.2 C-H Allylation

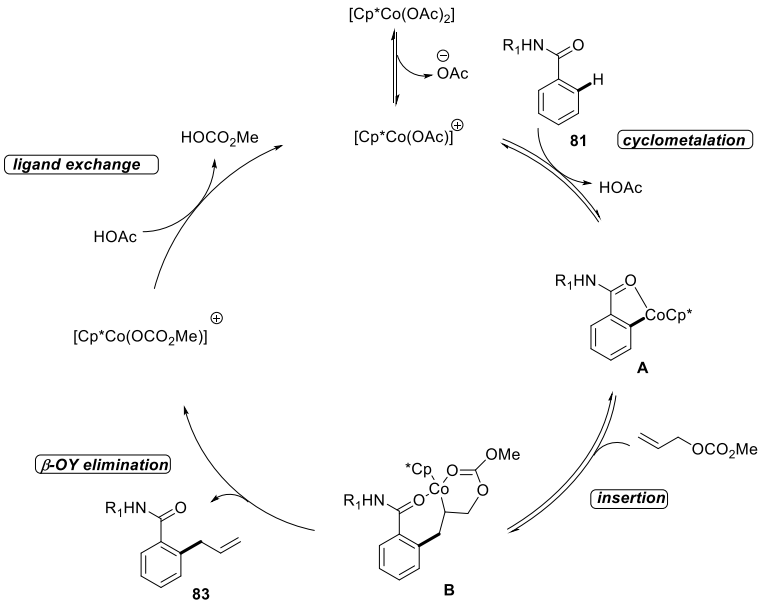
Studies on C-H allylation of aromatic compounds catalyzed by 4d transition metals have been well established due to the convenient convertibility of the allyl group into other useful functionalities.[104] Inspired by the success of their previous work demonstrating C-H allylation on the *ortho* position of di*iso*propylbenzamide using Cp^*Rh^{III} complexes,[105] Glorius and team hypothesized that C-H allylation could be realized by a Cp^*Co^{III} catalytic system. Indeed, in 2014, the group disclosed the mild allylation of 2-pyrimidyl indoles **78** with allyl methyl carbonate **79** in the presence of catalytic $[Cp^*Co(CO)I_2]$ **72**, $AgSbF_6$ and pivalic acid to deliver selectively C-2-allylated indoles **80** in excellent yields (Scheme 28).[106] More interestingly, the reaction proceeded successfully with a remarkably low catalyst loading of 0.5 mol% and TON of 2200 at ambient temperature. Meanwhile, this strategy was further extended to include the allylation of benzamides and acrylamides **81** with allyl carbonates **82**. Functional groups such as the iodo (**80c**), bromo (**83f**) and nitro (**83c**) substituents were also well-tolerated.



Scheme 28: Cp*Co^{III}-catalyzed C-H allylation of with allyl carbonates.

a. [Cp*Co(CO)I_2 (5.0 mol%), $AgSbF_6$ (40 mol%), PivOH (20 mol%), 80 °C, 16 h.

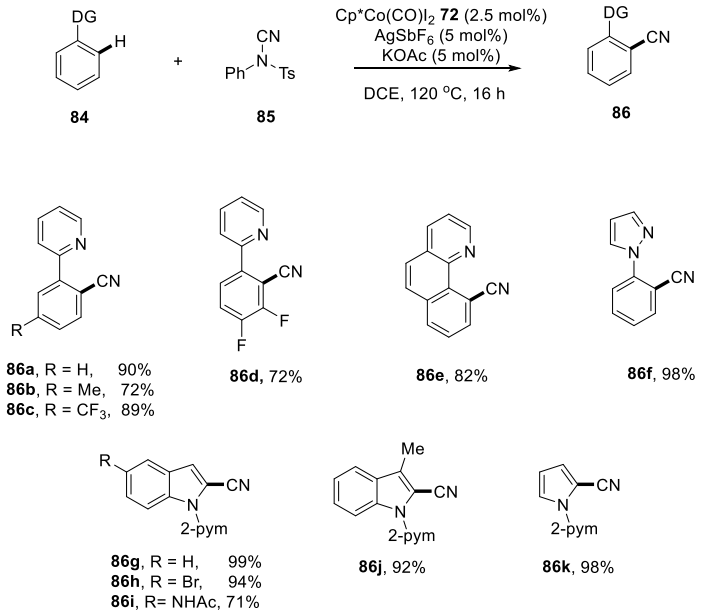
Similar to the previously reported Cp*Co^{III}-catalyzed reactions, the mechanism was proposed to undergo a CMD or electrophilic aromatic substitution mechanism to furnish the cobalt complex **A** (Scheme 29). Coordination of an incoming allyl carbonate, followed by allylic double bond migratory insertion into the Co-C bond resulted in the formation of the intermediate **B**. Thereafter, the desired product **83** was delivered through the key *β*-oxygen elimination instead of *β*-hydride elimination – Refer to section 3.4 for detailed explanation.



Scheme 29: Proposed mechanism for Cp*Co^{III}-catalyzed C-H allylation.

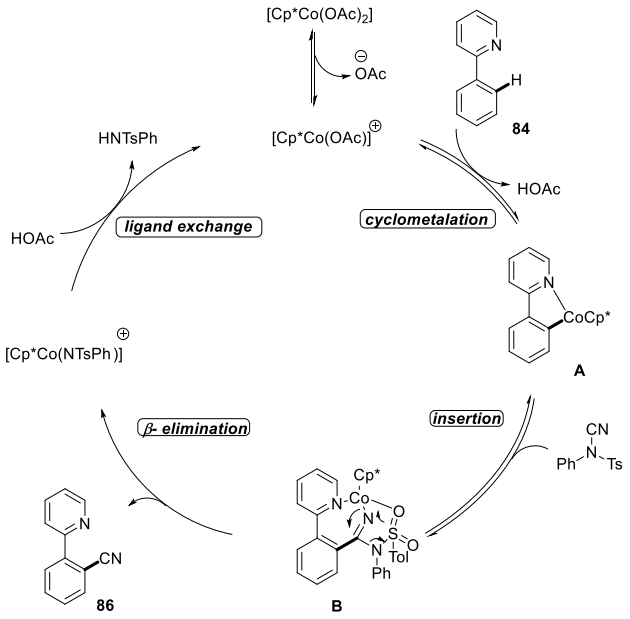
3.3.3 C-H Cyanation & Halogenation

C-H cyanation of arenes to access aromatic carbonitriles is highly attractive as such motifs are frequently found in natural alkaloids and biologically active compounds.[107] In the pursuit of discovering a method that could eliminate the use of dangerous cyanating agents such as cyanide salts and HCN, Ackermann and co-workers reported the first Cp*Co^{III}-catalyzed cyanation of hetereoarenes **84** using bench stable *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide **85** (NCTS) (Scheme 30).[108] This transformation was found to be chemo- and regioselective; only the mono-cyanated product was obtained in the presence of excess NCTS and cyanation occurred at the less hindered position for *meta* substituted arenes apart from 3,4-difluorophenylpyridine **86d** due to secondary directing-group effect. The scope with respect to the heteroarenes that were studied under the optimized conditions included indoles, pyrazoles and pyrroles and the corresponding cyanated products **86** were obtained in excellent yields.



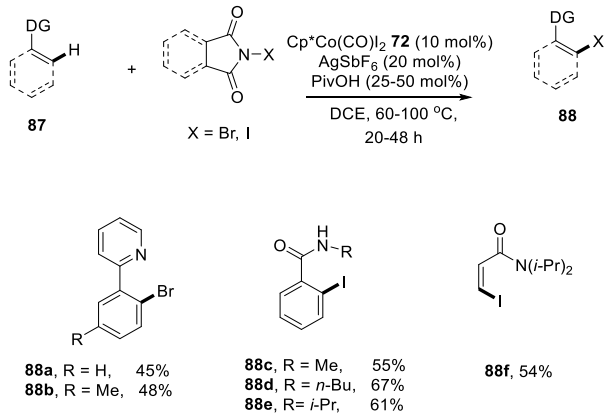
Scheme 30: Cp*Co^{III}-catalyzed C-H cyanation with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS).

The newly formed cyclometalated complex **A** underwent coordination with NCTS and subsequent migratory insertion proceeded smoothly to generate intermediate **B** (Scheme 31). To complete the catalytic cycle, β-hydride elimination and protodemetalation furnished the cyanated product **86** and at the same time, the catalytically active Co complex was regenerated for further turnovers.



Scheme 31: Proposed mechanism for Cp*Co^{III}-catalyzed C-H cyanation.

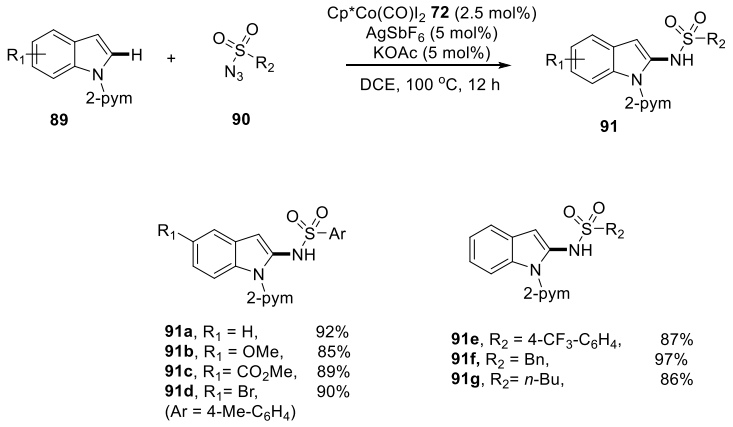
Building on the success of the cyanation of arenes, Glorius and co-workers further investigated the possibility of C-H halogenations. Thereafter in 2014, the team disclosed the Cp*Co^{III}-catalyzed bromination and iodination of arenes **87** with commonly used halogenating agents, *N*-bromophthalimide (NBS) and *N*-iodosuccinimide (NIS) respectively (Scheme 32).[106] This approach was suitable for substrates with pyridine- or benzamide – containing directing groups and their desired halogenated products were obtained in synthetically useful yields.



Scheme 32: Cp*Co^{III}-catalyzed C-H bromination and iodination of 87 with NBS and NIS respectively.

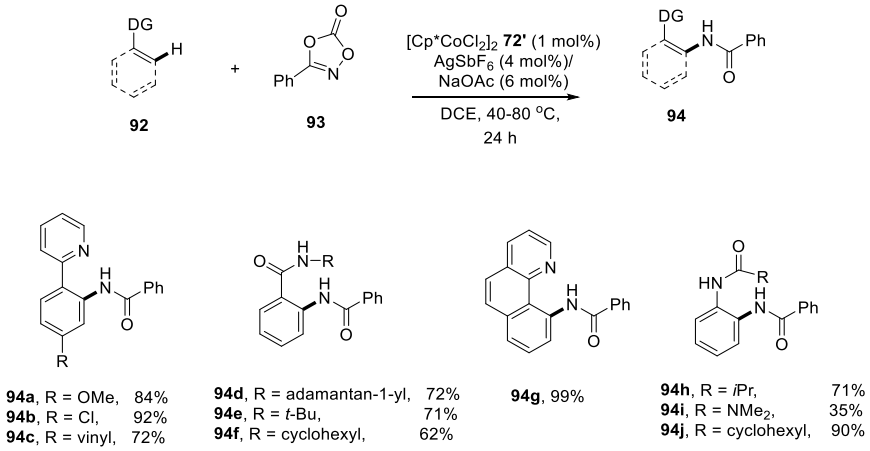
3.3.4 C-H Amidation

Owing to abundance of amide motifs in pharmaceuticals and their importance in biological processes, the development of efficient and direct C-H amidation processes is highly sought after in the synthetic community.[109,110] The earliest example that demonstrated the Cp*Co^{III}-catalyzed C-H amidation on heteroarenes was reported by Matsunaga and Kanai in 2014 (Scheme 33).[111] By treating pyrimidyl-substituted indoles **89** with sulfonyl azides **90** as the nitrogen source, an array of the desired amidated products **91** containing various functional groups was afforded in excellent yields.



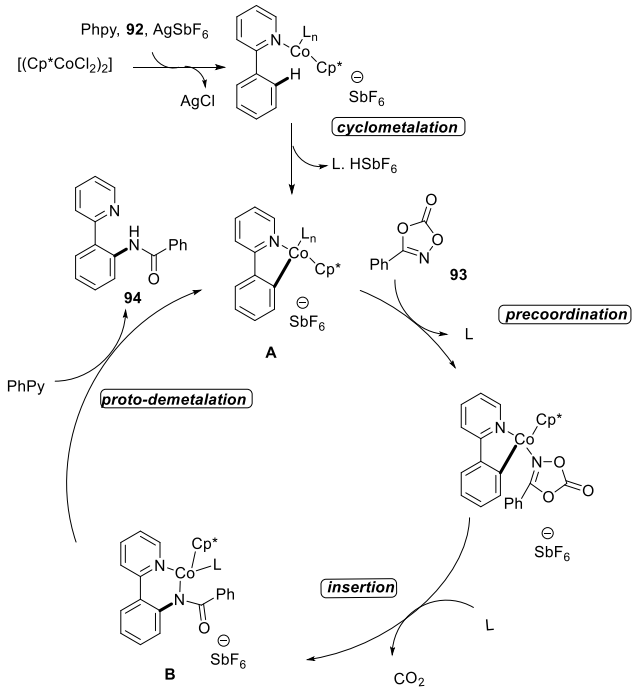
Scheme 33: Cp*Co^{III}-catalyzed C-H amidation with sulfonyl azides 90.

Despite its high efficiency, the scope of this approach was limited to the synthesis of products containing only sulfonamides. Accordingly, Chang and Park disclosed the employment of a more robust and easily accessible amidating reagent, 1,4,2-dioxazol-5-one **93**, capable of establishing stronger coordination affinity with the Cp*Co^{III} complex to drastically increase amidation efficiency in comparison to organic azides **90** (Scheme 34).[112] The reaction conditions became significantly milder and a broad range of aryl and alkyl amides **94** were prepared.



Scheme 34: Cp*Co^{III}-catalyzed C-H amidation of 92 with 1,4,2-dioxazol-5-one 93.

The team proposed that the mechanistic pathway began with the C-H cobaltation of model substrate, 2-phenylpyridine **92** to afford the intermediate cyclometalated complex **A** (Scheme 35). Coordination of the dioxazolone to the cobaltacycle **A** followed by amido insertion resulted in the formation of intermediate **B** with the synchronous release of CO_2. Finally, proto-demetalation delivered the desired amidated products **94** and concurrently regenerated the active catalyst.



Scheme 35: Proposed mechanism for Cp*Co^{III}-catalyzed amidation with 1,4,2-dioxazol-5-one 93.

3.4 Unique Reactivity and Selectivity of Cobalt

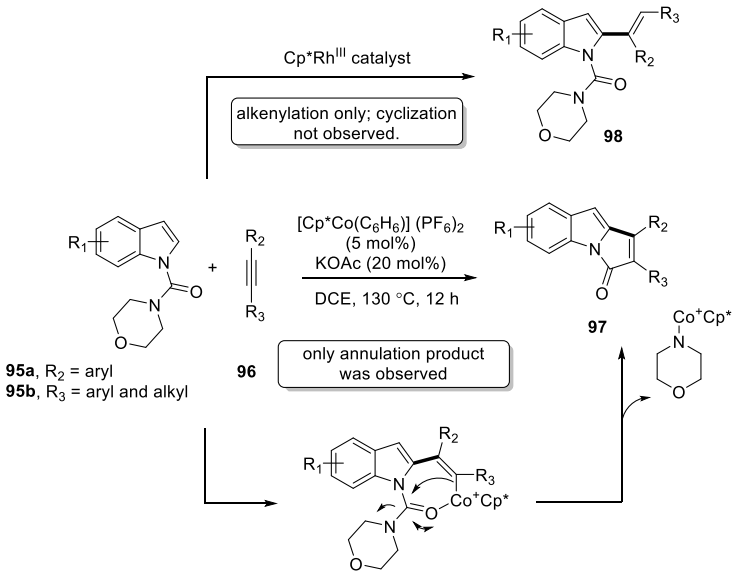
The electronic properties of the 3d transition metal cobalt are notably different to those of 4d or 5d metals (Rh and Ir):[113]

1) Higher Lewis acidity of Cp*Co^{III} compared to analogous Cp*Rh^{III} and Cp*Ir^{III}

2) Distinctively more polarized Co-carbon bonds that result in increase of nucleophilicity of organocobalt intermediates.

Henceforth, due to these inherent differences, unique transformations that were not previously observed in the 4d or 5d transition metals catalysis could be achieved with the use of Cp*Co^{III} catalysts. For instance, in 2014, Matsunaga and Kanai described a different reaction outcome in the Cp*Co^{III}-catalyzed reaction of carbamoyl- protected indoles **95** with alkynes **96** (Scheme 36).[114] While alkenylation of carbamoyl-protected indoles followed by cyclization proceeded

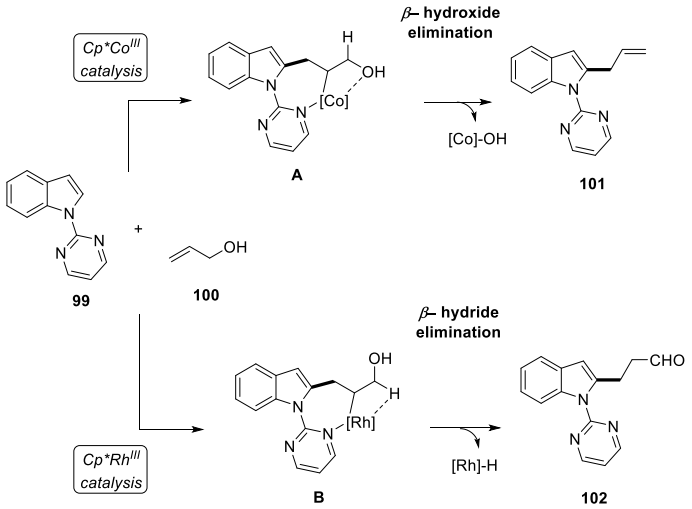
efficiently to furnish the pyrrolo[1,2-*a*]indol-3-ones **97** under Cp*Co^{III} catalyzed reaction conditions, Cp*Rh (III) catalysts only afforded the alkenylated products **98** without generating any traces of annulation products. This could be explained by the lower nucleophilicity of organorhodium species compared to that of cobalt. As such, instead of Rh-C bond insertion to the carbonyl of the carbamoyl moiety, proto-demetallation proceeded to obtain the alkenylated products **98**.



Scheme 36: Different reaction outcome for the reaction between carbamoyl-protected indoles 95 with alkynes 96.

Having a relatively higher atomic charge and an ionic radius smaller than that of rhodium, Cp*Co^{III} is considered harder than Cp*Rh^{III}.[115] Conseqeuntly cobalt has greater affinity for hard atoms such as oxygen – based on the hard and soft acids and bases (HSAB) concept.[115] This unique property of cobalt catalysts could establish a different reaction pathway in obtaining new functionalities distinct to those furnished under Cp*Rh^{III} catalysis. In 2015, Matsunaga and Kanai demonstrated this difference in the reaction outcome observed in the allylation of pyrimidine-

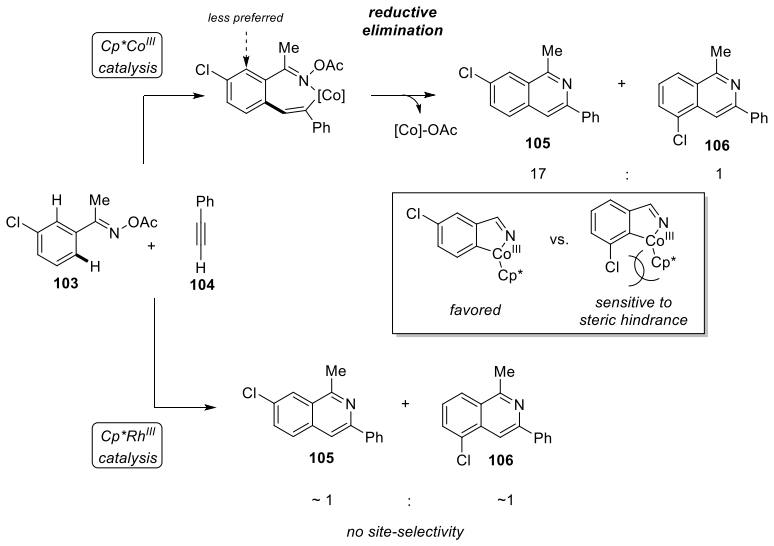
protected indole **99** with allyl alcohols **100** (Scheme 37).[116] The key difference is the *β*-elimination step: under Cp*Co^{III} catalysis, the 4-membered transition state **A** underwent the preferred *β*-hydroxy elimination instead of *β*-hydride elimination. This is due to the greater oxophillicity of Cp*Co^{III} that would facilitate the dominant *β*-hydroxy elimination to afford the corresponding alkene **101**. Relatively soft Cp*Rh^{III} prefers *β*-hydride elimination and hence provided the aldehyde **102**.



Scheme 37: Key difference in the *β*- elimination step.

Furthermore, excellent site-selectivity could be achieved in Cp*Co^{III} catalysis. This observation stemmed from the strong Lewis acidity of cobalt that resulted in the greater steric repulsion between the Cp* ligand and the substrates. In 2015, Matsunaga and Kanai reported this high regioselectivity of Cp*Co^{III} catalysis in the reaction of unsymmetrically substituted *O*-acyloximes **103** with alkynes **104** (Scheme 38).[117] In Cp*Co^{III} catalysis, the coupling of the alkynes proceeded at the less hindered position of a *meta*-Cl-substituted substrate with excellent regioselectivity whereas no selectivity was observed with Cp*Rh^{III} catalysts. High site-selectivity observed in

Cp^*Co^{III} catalysis was also realized for substrates bearing Br, I, Me and CO_2Me substituents at the *meta*-position.



Scheme 38: High site-selectivity observed in Cp^*Co^{III} catalysis.

3.5 Cp^*Co^{III}-catalyzed C(sp^3)-H activation/functionalization

Although C(sp^2)-H functionalization reactions have been well established over the last few years, reports on C(sp^3)-H functionalization catalyzed by Cp^*Co^{III} remain scarce. Efficient C(sp^3)-H activation has been inhibited by several factors.[118] They are:

1) Control of site selectivity without activating other C-H bonds that are not of interest;

2) Achieving mono-functionalization;

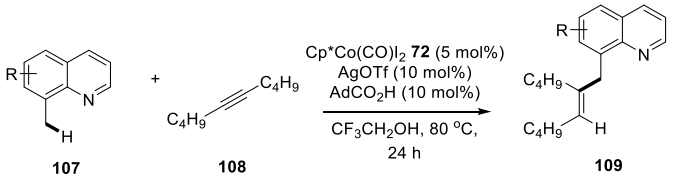
3) Ensuring products obtained are not easily susceptible to unwanted transformations and finally,

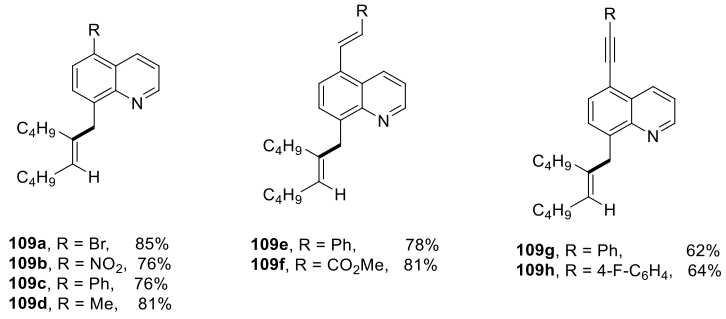
4) Preferential activation of unactivated C-H bonds over those that are more acidic/ weaker.

To date, there have been only 2 examples that demonstrated the use of bench stable cobalt catalyst, Cp^*Co^{III}, to activate inert C(sp^3)-H bonds.[119,120]

3.5.1 C-H Alkenylation

In 2016, Sundararaju and co-workers reported a mild, direct and efficient Cp*Co^{III}-catalyzed C(sp^3)-H alkenylation of 8-methylquinoline **107** with alkynes **108** (Scheme 39).[119] This approach was widely applicable to a broad range of functionalized 8-methylquinolines **107** and resulting in selective mono-alkenylation to obtain the alkenylated products **109** in excellent yields.





109a, R = Br, 85%
109b, R = NO_2, 76%
109c, R = Ph, 76%
109d, R = Me, 81%

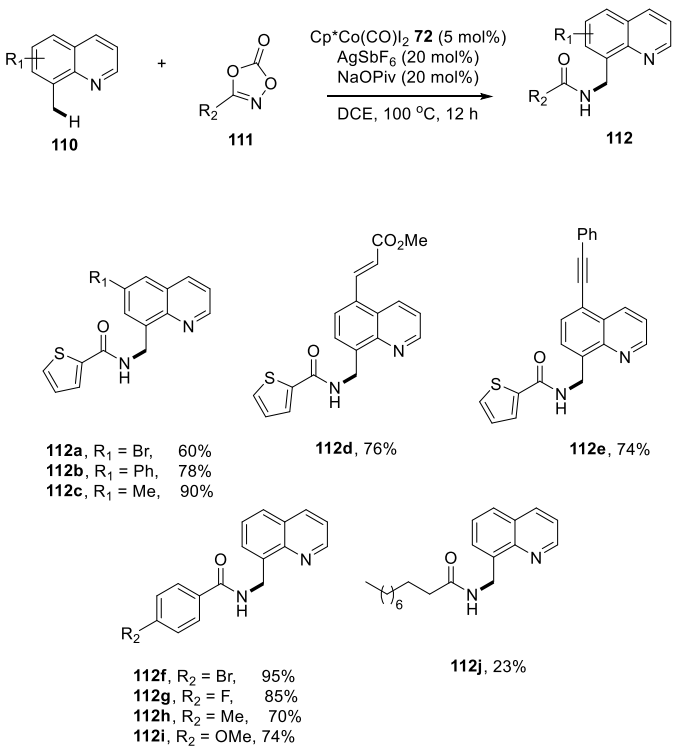
109e, R = Ph, 78%
109f, R = CO_2Me, 81%

109g, R = Ph, 62%
109h, R = 4-F-C_6H_4, 64%

Scheme 39: Cp*Co^{III}-catalyzed C(sp^3)-H alkenylation of 8-methylquinoline 107 with alkynes 108.

3.5.2 C-H Amidation

Subsequently in 2016, Sundararaju and co-workers disclosed an oxidant-free and mild amidation of 8-methylquinoline **110** with robust dioxazolones **111** to give the desired amidated products **112** in moderate to excellent yields (Scheme 40).[120] Similar to the alkenylation reaction, various functionalized 8-methylquinolines were well tolerated under the optimized reaction conditions. Through this methodology, synthesis of both aryl- and alkyl-amides **112** was found to be feasible.



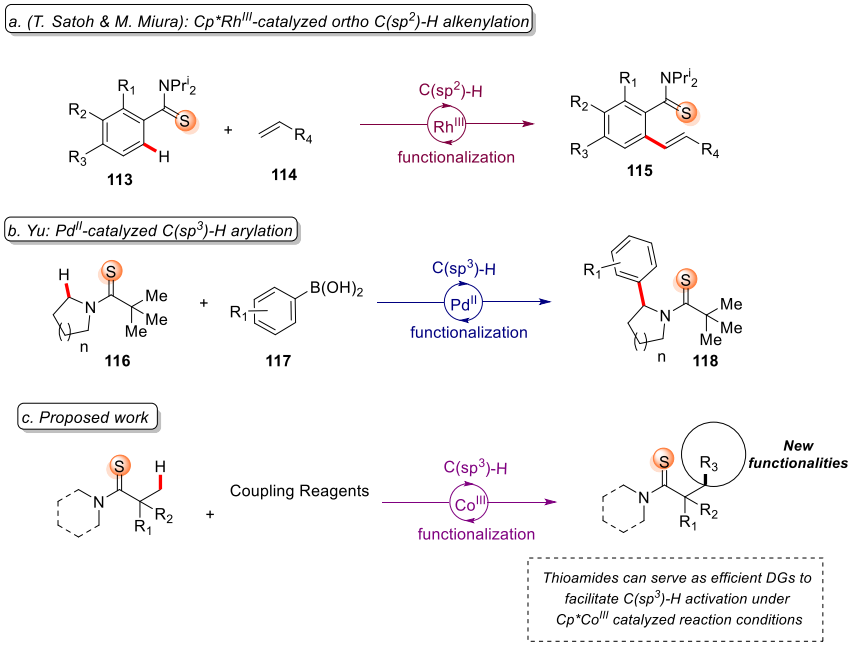
Scheme 40: Cp*Co^{III}-catalyzed C(sp^3)-H amidation of 8-methylquinoline 110 with 1,4,2-dioxazol-5-one 111.

*3.6 Our Approach: Thioamide directed Cp*Co^{III}-catalyzed selective amidation of C(sp^3)-H*

3.6.1 Objective & Plan

The scarcity of reports prompted us to explore possible transformations that could uncover and advance the potential of cobalt catalysis for the Cp*Co^{III} catalyzed C(sp^3)-H activation/functionalization reactions. We were particularly interested in employing intrinsic parts of the substrate to coordinate an incoming metal catalyst for possible C-H activation reactions without the need for any additional steps of installation and removal of directing group templates. Henceforth, our attention was drawn to thioamides, a versatile class of building blocks derived from carboxylic acids, known for their synthetic applicability to furnish heterocyclic compounds.[121–124] Thioamide motifs are also used as biologically active compounds in

pharmaceuticals and agrochemicals.[125–128] Consequently, new synthetic methods for their efficient and direct modification are sought after and to this end C-H functionalization strategies are attractive. In 2015, Miura and co-workers demonstrated that tertiary thioamide derivatives could serve as effective directing groups (DGs) to effect Cp*Rh^{III}-catalyzed *ortho* C(sp^2)-H activation/alkenylation of benzothioamides **113** (Scheme 41a).[129] Furthermore, Yu *et al.* disclosed the thioamide directed Pd^{II}-catalyzed α-C(sp^3)-H cross coupling of cyclic amines **116** with aryl- and heteroarylboronic acids **117** (Scheme 41b).[130] Inspired by and building on these recent studies we envisaged that the thioamide moiety could likely serve as an efficient DG to facilitate C(sp^3)-H activation poised for further transformations under Cp*Co^{III}-catalyzed conditions(Scheme 41c). To the best of our knowledge, this would be the first example of Cp*Co^{III}-catalyzed C(sp^3)-H functionalization using an alternative directing group to the commonly used pyridine/quinoline classes.



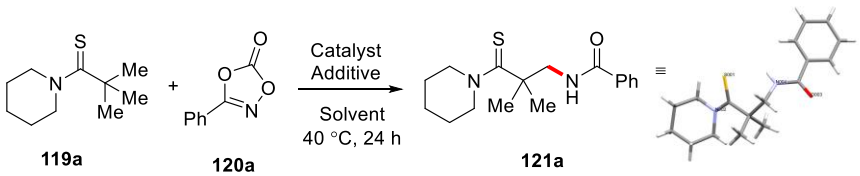
Scheme 41: Thioamide directed transition metal catalyzed C(sp^3/sp^2)-H functionalization reactions

3.6.2 Optimization

To access the potential of the Cp^*Co^{III} catalyst for any desired C(sp^3)-H functionalization, we commenced a preliminary investigation on model substrates thioamide **119a** and dioxazolone **120a** in the presence of $[Cp^*Co(MeCN)_3][SbF_6]_2$ as the catalyst in dichloroethane (DCE) at 40 °C for 24 h (Table 6, entry 1). Pleasingly, the reaction proceeded smoothly to furnish the amidated product **121a** in 56% NMR yield. The structure of which was proven by single crystal X-ray analysis. Importantly, the exclusive mono amidation was exclusively observed with selective C(sp^3)-H activation at one of the primary methyl groups of the thioamide **119a** instead of the α-methylene protons in the piperidine ring.

The yield of the reaction was optimized further by evaluating different carboxylic acids and their salts as additives. Indeed, addition of 20 mol% sodium benzoate resulted in a significant increase in yield (89%, Table 6, entry 4). The increased reactivity observed after the addition of carboxylates could be explained by its role as an intramolecular base in a rapid C-H bond metalation *via* a base-assisted deprotonation mechanism. While DCE proved to be the optimal solvent, other solvents such as trifluoroethanol, dioxane and toluene (Table 6, entries 5, 6 & 7), completely suppressed reactivity and the reactions yielded trace or no product. Catalysts such as $Cp^*Co(CO)I_2$ (Table 6, entry 8) or $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (Table 6, entry 9) other than $[Cp^*Co(MeCN)_3][SbF_6]_2$ or no transition metal catalyst at all (Table 6, entry 10) led to diminished or no reactivity. While the reaction worked at room temperature with slightly lower yield (Table 6, entry 12), higher catalyst loading (Table 6, entry 11) did not result in an improvement to the yield.

Table 6: Optimization studies on C(sp^3)- H activation/ amidation reactions of 119a & 120a and X-ray crystal structure of 121a



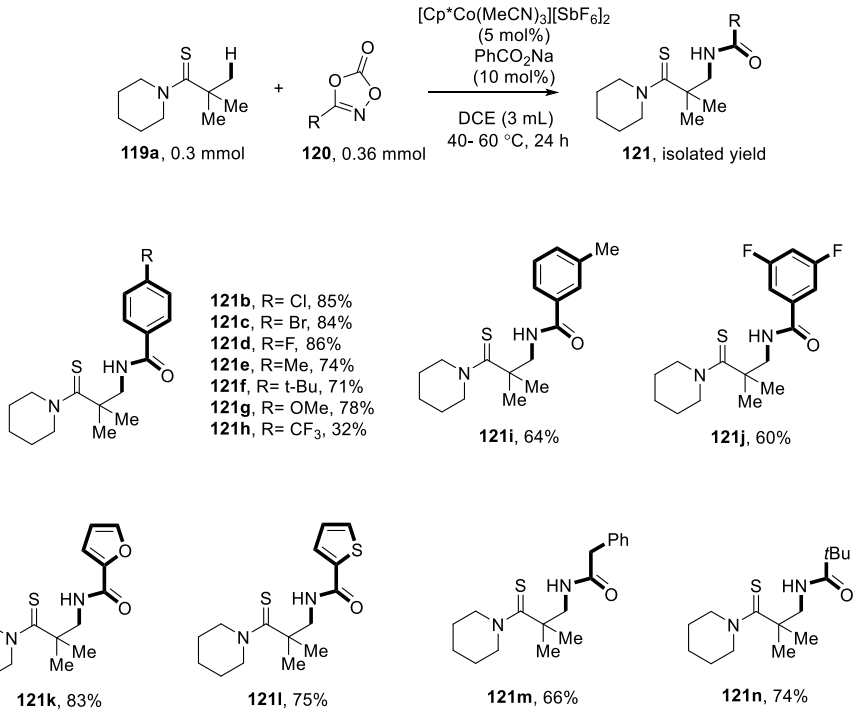
Entry	Catalyst (mol%)	Additive (mol%)	Solvent	Yield[a] (%)
1	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	-	DCE	56
2	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	PivOH (20)	DCE	79
3	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	$PhCO_2H$ (20)	DCE	85
4	**$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)**	**$PhCO_2Na$ (20)**	**DCE**	**89 (86)**
5	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	$PhCO_2Na$ (20)	TFE	-
6	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	$PhCO_2Na$ (20)	Dioxane	5
7	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	$PhCO_2Na$ (20)	Toluene	-
8	$Cp^*Co(CO)I_2$ (5)	$PhCO_2Na$ (20)	DCE	-
9	$[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5)	$PhCO_2Na$ (20)	DCE	71
10	-	$PhCO_2Na$ (20)	DCE	-
11	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (10)	$PhCO_2Na$ (20)	DCE	85
12[b]	$[Cp^*Co(MeCN)_3][SbF_6]_2$ (5)	$PhCO_2Na$ (20)	DCE	71

Reaction conditions: 1a (0.3 mmol), 2b (0.36 mmol), catalyst, additive, solvent (3 mL), T= 40 °C, 24 h.

a. ^1H NMR yield using CH_2Br_2 as internal standard; isolated yield in parenthesis. *b.* Reaction was carried out at rt.

3.6.3 Substrate scope: substituted dioxazolones

After identifying the optimal reaction conditions for the synthesis of **121a**, various substituted dioxazolones **120** were investigated to determine their influence on the overall reactivity and to establish the reaction scope (Scheme 42). In general, this C(sp^3)-H functionalization methodology was amenable to a range of aryl-substituted dioxazolones **120** consisting of various electron-withdrawing and electron-donating substituents, affording the corresponding amidated products **121** in typically good to excellent yields. Whilst a low yield was obtained in the case of reaction with *para*-CF_3-substituted 3-phenyldioxazolones (**121h**), Cl- (**121b**) and Br- (**121c**) substituents in the *para*-position were well-tolerated delivering products that are synthetically useful for downstream transformations. Moreover, reactions with heteroaryl-containing dioxazolone substrates proceeded smoothly under the optimized reaction conditions to furnish **121k** and **121l** in 83% and 75% yield, respectively. Considering the difficulty of installing an alkyl *N*-acyl amide moiety using other amidating reagents such as alkyl acyl azides,[131] it was gratifying to note that alkyl-substituted dioxazolone substrates performed well to generate **121m** and **121n** in good yields.

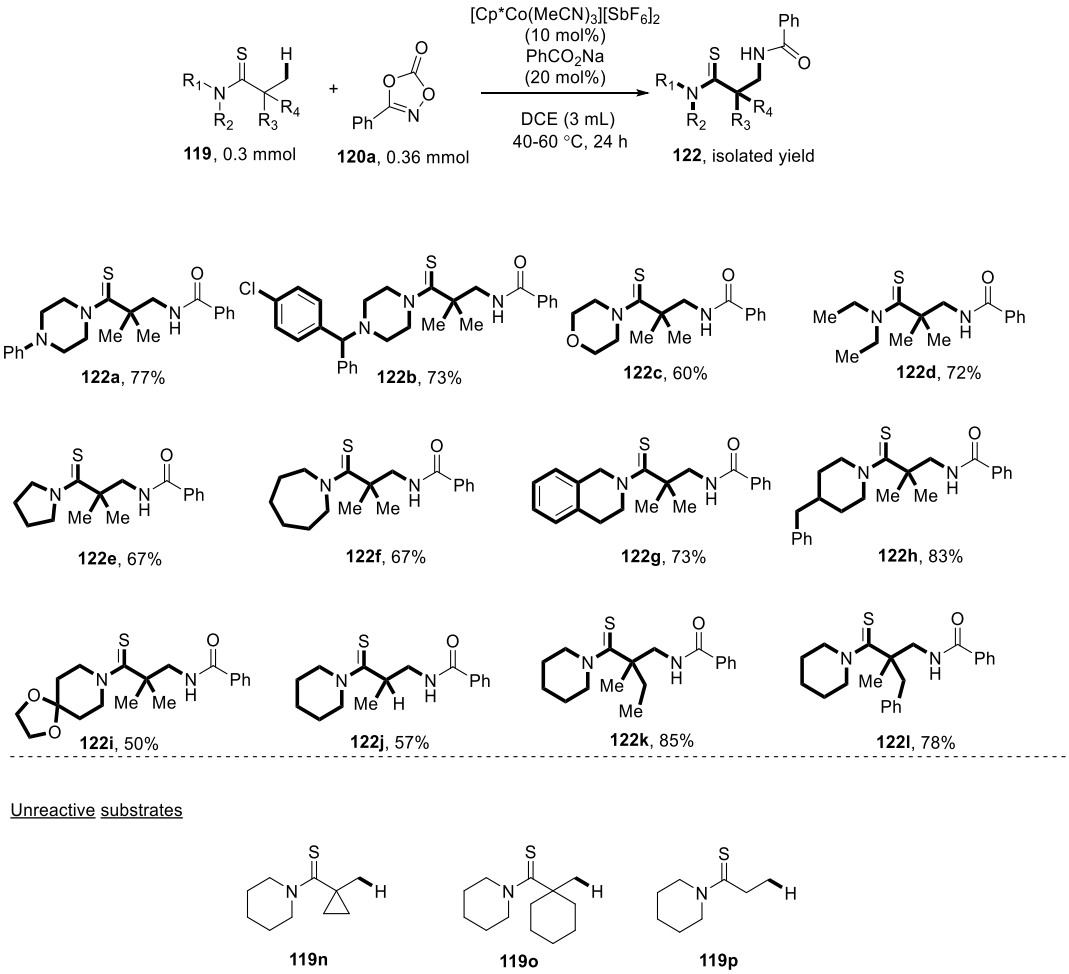


Scheme 42: C(sp^3)-H activation/amidation of thioamide 119a with various substituted dioxazolones 120.

3.6.4 Substrate scope: thioamides

To further broaden the scope of our protocol, various thioamides derived from different cyclic or acyclic amines and carboxylic acids were examined. As presented in Scheme 43, thioamides containing piperazine (**122a** and **122b**) and morpholine (**122c**) scaffolds worked well to afford the desired amidated products in synthetically useful yields of 60-77%. While simple acyclic thioamide substrate (**122d**) displayed good reactivity, reactions with thioamides containing different ring sizes of azacycles (**122e** and **122f**) were also shown to be successful. 4-Substituted piperidinyl thioamides proceeded well in this reaction to afford products **122h** and **122i** in moderate to good yields. Remarkably, primary C(sp^3)-H activation was favored even in the presence of benzylic methylene protons – as shown by reaction products **122g**, **122h** and **122l** – therefore pointing towards steric factors as overriding determinants of reactivity.[132,133]

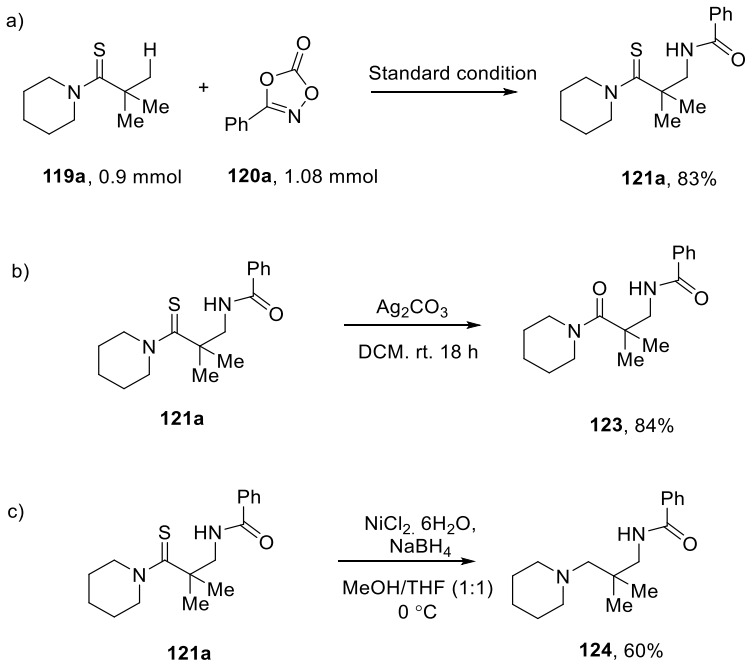
Furthermore, *iso*propyl piperidinylthioamide **119k** also reacted well under these conditions to furnish **122j** in 57% yield. Unfortunately, cyclopropanethioamide **119n**, cyclohexanethioamide **119o** and propionthioamide **119p** did not furnish any desired amidated products. The conformational rigidity of the cyclopropane moiety in **119n** presumably orientates the C(sp^3)-H in a position away from the active site, resulting in a less favorable configuration for effective C-H activation.[134] Notably, only starting material, cyclopropanethioamide **119n**, was recovered without any observation of ring-opened products after the reaction. The poor reactivity for cyclohexanethioamide **119o** could be attributed to steric hindrance; the strong Lewis acidity of the Cp^*Co^{III} catalyst due to the smaller ionic radius of cobalt would augment the steric repulsion between the Cp* ligand and the substrate.[117,135]



Scheme 43: C(sp^3)-H activation/amidation of various thioamides 119 with 3-phenyldioxazolones 120a.

3.6.5 Scale-up & derivatization

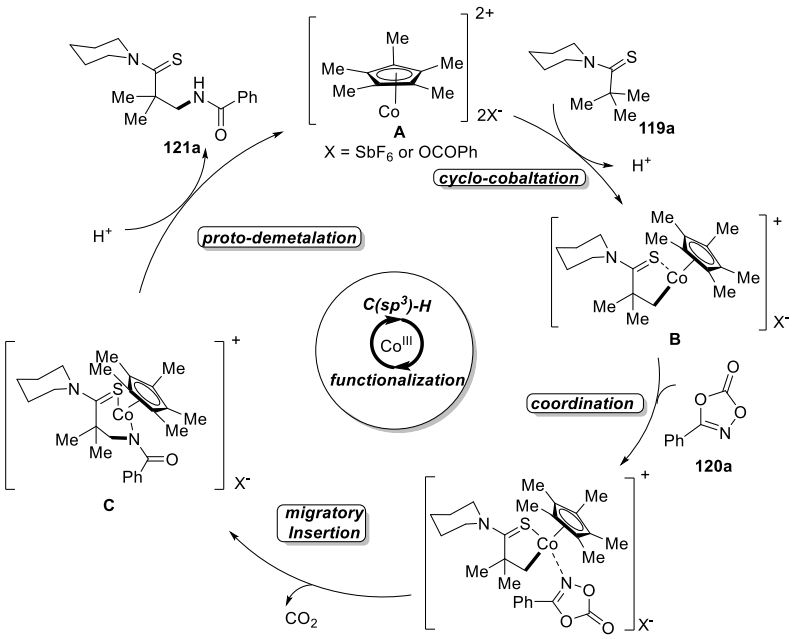
The efficiency and further applications of this transformation were next investigated (Scheme 44). A three-fold scale-up of the reaction using the standard substrates **119a** and **120a** was carried out and pleasingly, negligible deviation in the obtained yield of **121a** was observed (Scheme 44a). Additionally, access to other important functionalities *via* diversification of the amidated product was achieved through simple chemical modifications. For instance, conversion of thioamide **121a** to amide **123** was efficiently carried out with Ag(I) carbonate (Scheme 44b),[136] whilst selective reduction of the thioamide using nickel boride furnished amine **124** in 60% yield (Scheme 44c).[137]



Scheme 44: a) Three-fold scale-up reaction. B) Oxidative desulfurization of thioamide 121a. c) Reduction of thioamide 121a.

3.6.6 Proposed catalytic cycle

A redox-neutral Cp*Co^{III} catalytic cycle for the C(sp^3)-H activation/amidation of **119a** and **120a** is postulated as depicted in Scheme **45**. In the presence of sodium benzoate, the newly generated catalytically active cationic species **A**, upon coordination with the sulfur atom of **119a**, undergoes concomitant cyclo-metalation to form a 5-membered caboltacycle intermediate **B**. Subsequently, the efficient coordination of intermediate **B** with dioxazolone **120a** followed by migratory insertion of the imido group resulted in a synchronous CO_2 extrusion to afford the amido complex **C**. Proto-demetalation of **C** releases product **121a** and concurrently regenerates active species **A** for further catalytic turnovers.



Scheme 45: Postulated mechanism for C(sp^3)-H activation/amidation of thioamide 119a with dioxazolone 120a.

3.6.7 Conclusion & Future work

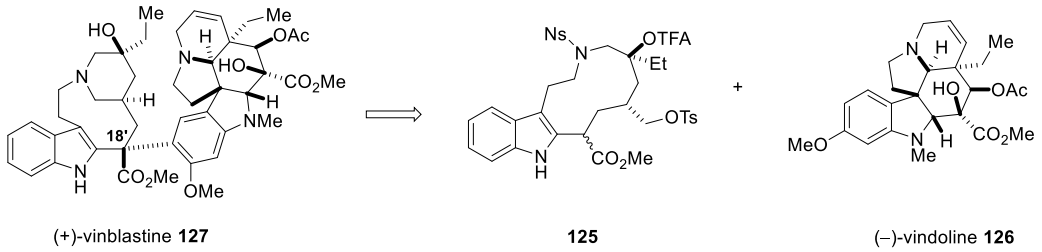
In conclusion, we have discovered and developed a mild, efficient and selective method for C(sp^3)-H bond activation / amidation employing thioamides as the directing group, with aryl-, heteroaryl- and alkyl- substituted dioxazolones under Co^{III}Cp* catalytic conditions. Furthermore, a wide range of thioamides with piperazine, morpholine, tetrahydro*iso*quinoline and other substituted *N*-containing heterocycles were well-tolerated. This work stands as a rare example of Cp*Co^{III} catalyzed C(sp^3)-H functionalization using an alternative directing group to the commonly used pyridine/quinoline classes and the first using a thioamide. Considering the unique reactivity of cobalt catalysts, we envision that novel transformations could be realized by treating thioamides with various reaction partners (e.g. alkynes, allyl carbonates etc.) under Co^{III}Cp* catalytic conditions. Since thioamide is employed as an efficient DG in the field of Cp*Co^{III}-catalyzed C(sp^3)-H functionalization for the very first time, there are potential transformations that remained unexplored. Further exciting developments and investigations into those synthetically relevant

reactions directed by thioamide moieties are currently ongoing and the results will be disclosed in due course.

Chapter 4: Expeditious & Divergent Syntheses of *Aspidosperma* Alkaloids

4.1 Introduction

Monoterpene indole alkaloids are a diverse class of natural products with well over 2000 members. Due to the inherent structural complexity (compact polycyclic architectures, labile substitution tendency and numerous stereogenic centers) and a wide array of important biological activities (ideal candidates for anti-cancer, anti-malarial and anti-arrhythmic agents),[138–142] this class of alkaloids has motivated the synthetic community to develop ingenious approaches that have engaged modern and sophisticated methodologies to facilitate their efficient synthesis. For instance, vinblastine, one of the four major vinca alkaloids isolated from *Catharanthus roseus*, exhibits anti-cancer properties by inhibiting angiogenesis – a process which involves the development of new blood vessels from pre-existing vessels.[143,144] As such, vinblastine is often administrated to treat Hodgkin's disease, breast cancer and germ cell tumors. However, over the span of four decades, accessibility to vinblastine *via* total synthesis remained limited.[145–150] Interestingly, in 2002, Fukuyama and coworkers established efficient routes to synthesize the two base indole alkaloids (**125** and (−)-vindoline **126**) which would subsequently perform stereocontrolled coupling at C18' to afford (+)- vinblastine **127** (Scheme 46).[150]



Scheme 46: Fukuyama's stereocontrolled total synthesis of (+)-vinblastine 127

Notably, a disconnection at the C18' linkage of the dimeric alkaloid, (+)-vinblastine **127**, gave two distinct alkaloids that belong to *Aspidosperma* family – one of the most abundant groups of monoterpene indole alkaloids comprising of more than 250 members.[151–153] These alkaloids are typically isolated from the plants of the genus *Aspidosperma* and are categorized into various commonly known structural classes: yohimban-type, sarpagan-type, aspidospermidine-type, aspidospermatidine-type, eburnamenine-type, quebrachamine-type and rhazinilam-type (Figure 9).[154]

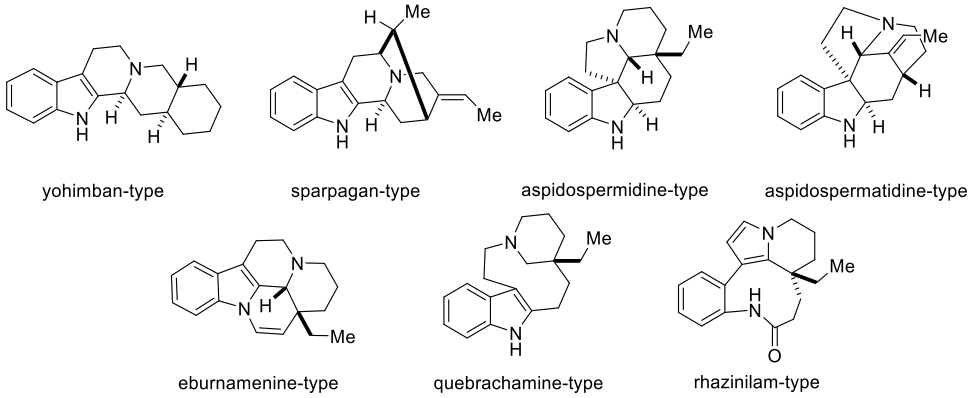


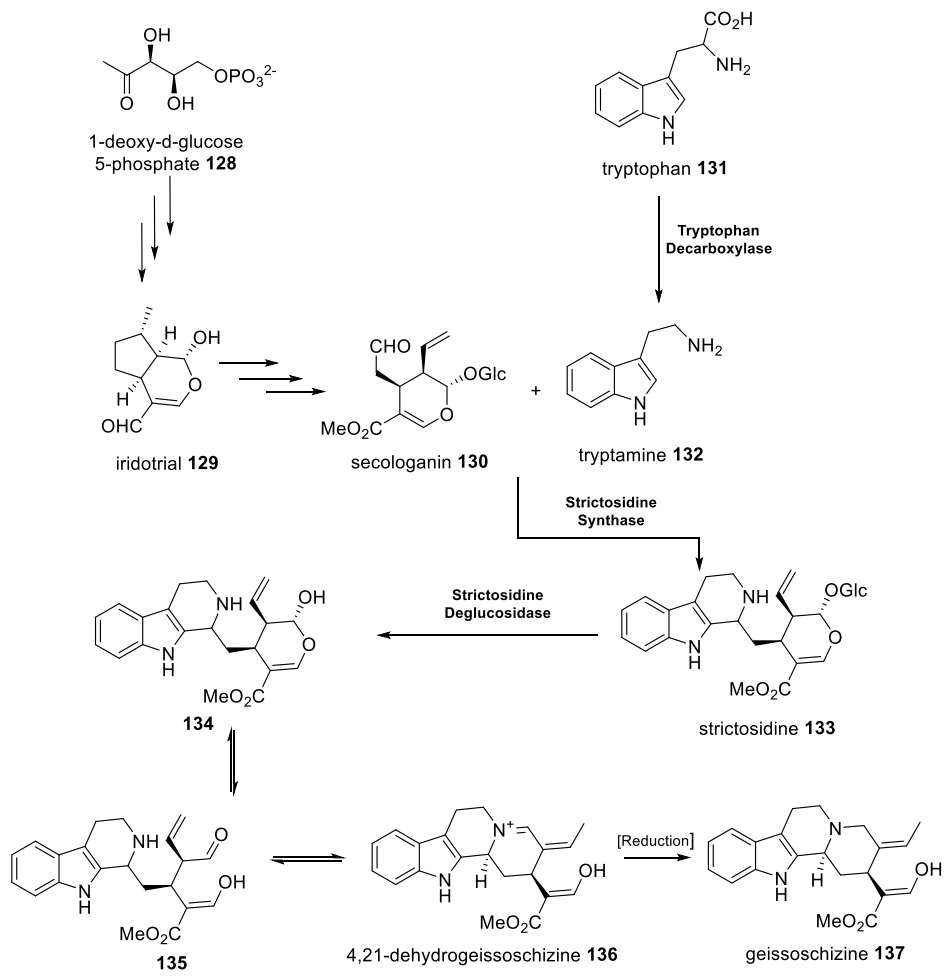
Figure 9: Base chemical structures of various types of *Aspidosperma* alkaloids

Owing to the expansive range of alkaloids in *Aspidosperma* family, the scope of discussion in this chapter will be confined to two common types of this class of natural products – aspidospermidine-type and quebrachamine-type alkaloids.

4.2 Biosynthesis of Aspidosperma alkaloids

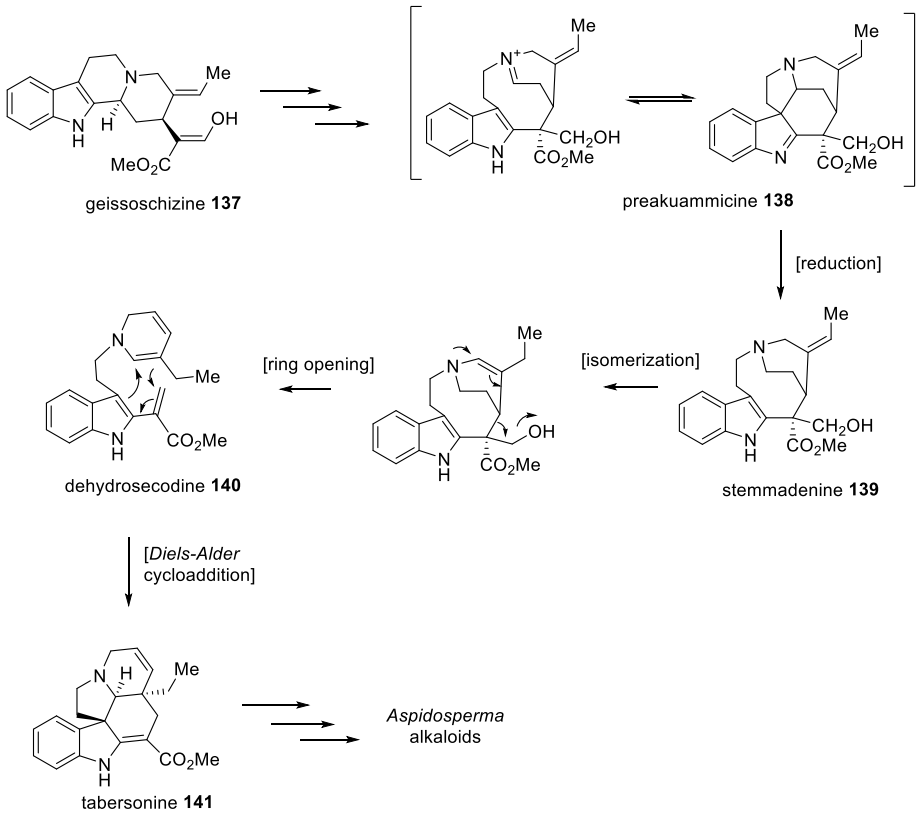
After elucidating the structural profiles of these isolated alkaloids, the synthetic community actively proposed and proved plausible theories that would explain their biosynthetic origin. Since then, the biosynthetic pathways to these terpenoid alkaloids have been well-documented and established.[155] Most, if not all of the monoterpene indole alkaloids, are derived from core building blocks, tryptamine **132** and iridoid terpene secologanin **130** (Scheme 47). The biosynthesis of

tryptamine **132** can be easily achieved by converting tryptophan **131** using a pyridoxal dependent enzyme, trytophan decarboxylase, whereas the biosynthetic pathway to attain secologanin **130** derived from 1-deoxy-d-glucose-5-phosphate is non-trivial and has not been fully understood. Subsequently, subjecting typtamine **132** and secologanin **130** with strictosidine synthase afforded strictosidine **133** *via* an enzymatic Pictet-Spengler reaction. Removal of glucose derivative of the strictosidine **133** to attain its corresponding hemiacetal **134**, followed by rearrangement resulted in the formation of 4,21-dehydrogeissoschizine **136**. This ammonium salt containing alkaloid **136** is then further reduced to obtain geissoschizine **137**, a precursor of the *Ajmalicine* family.



Scheme 47: Biosynthetic pathway leading to the synthesis of geissoschizine 137

Despite the mechanism for the transformation of geissoschizine **137** to *Aspidosperma* alkaloids remaining elusive due to the difficulties in isolating and identifying most of the participating enzymes, numerous groups in the 1960's and 1970's managed to detail a series of plausible transformations based on some isolated intermediates.[155–157]



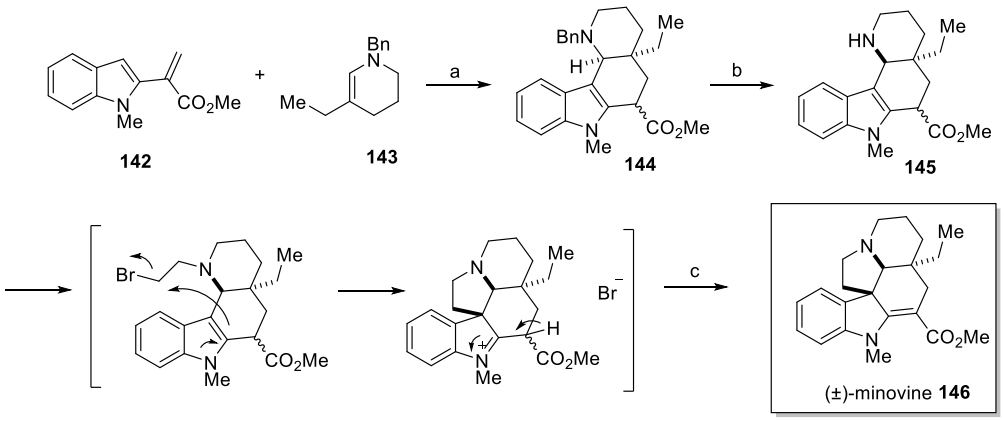
Scheme 48: Proposed biosynthetic pathway leading to the synthesis of *Aspidosperma* alkaloids

It was proposed that after a series of transformations to afford preakuammicine **138** from geissoschizine **137**, the iminium moiety of the preakuammicine **138** was subjected to reduction to obtain stemmadenine **139** (Scheme 48). [155–157] Subsequent isomerization of the double bond in stemmadenine **139** and ring opening of the macrocyclic intermediate *via* enzymatic dehydroxylation would afford the labile precursor secodine intermediate **140**. This intermediate would then undergo a *Diels-Alder* cycloaddition to form tabersonine **141** and thus access a series of *Aspidosperma* alkaloids.

4.3 Early synthetic approaches

4.3.1 Ziegler's total synthesis of (±)-minovine 146

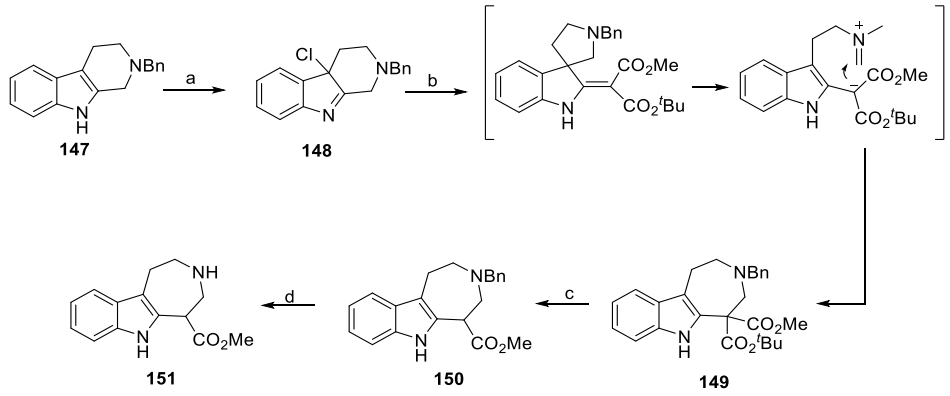
The proposed biosynthetic approach to attain the desired *Aspidosperma* and *Iboga* alkaloids had inspired chemists to develop plausible biomimetic approaches. In 1962, Wenkert and co-workers postulated that the accessibility to *Aspidosperma* and *Iboga* alkaloids could be achieved *via* an enamine (secodine) intermediate.[158] This reactive intermediate might play a pivotal role in the formation of their distinctive pentacyclic structure. Inspired by the viability to access these classes of alkaloids through this approach, Ziegler *et.al.* began the synthesis of (±)-minovine **146** with a relatively more stable endocyclic enamine **143** that would perform a formal *Diels-Alder* reaction with the corresponding indolyl acylate **142** to obtain a mixture of epimeric esters **144** (Scheme 49).[159] After constructing the C- and D-rings of (±)-minovine **146**, debenzylation of ester **144** *via* Pd-catalyzed hydrogenolysis proceeded without incident to provide secondary amine **145**. Finally, a bis-alkylation linchpin approach was employed by treating amine **145** with 1,2- dibromoethane to afford the desired (±)-minovine **146** in a modest yield of 20%.



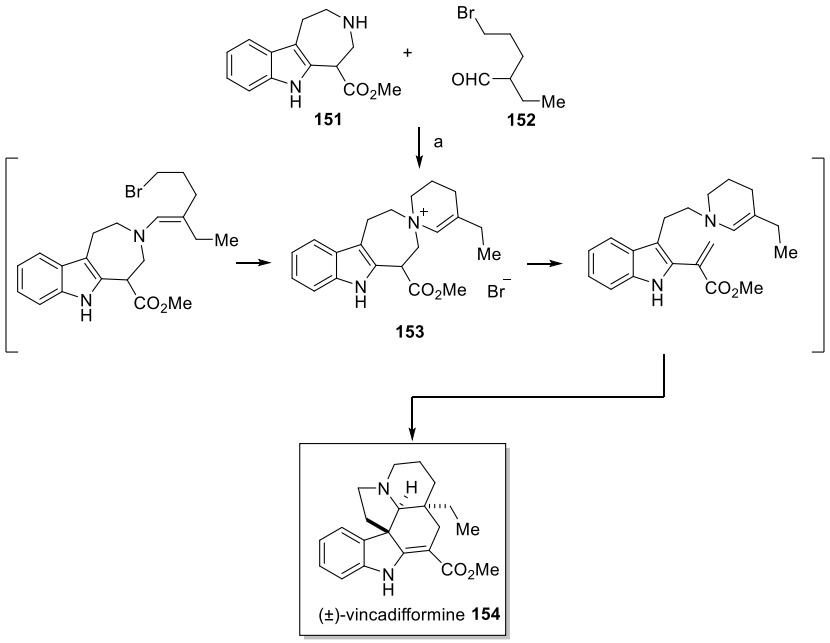
Scheme 49: Ziegler's synthesis of (±)-minovine 146. Reaction conditions: (a) reflux, 13 h, MeOH, 50%; (b) HCl, 10% Pd/C, rt, MeOH, 73%; (c) $BrCH_2CH_2Br$, reflux, 14 h, DMF, 20%.

4.3.2 Kuehne's total synthesis of (±)-vincadifformine 154

Later in 1978, Kuehne and co-workers also disclosed the first synthesis of (±)-vincadifformine **154** *via* a similar biomimetic approach (Scheme 50 and 51).[160] The synthesis began with the chlorination of tetrahydrocarbazole **147** to afford the resultant chloroindolenine **148** (Scheme 50). Subsequently, the chloroindolenine **148** was subjected to thallium *tert*-butyl methyl malonate that resulted in the formation of the desired azepinoindole **149** in 63% yield. Further heating of diester **149** with anhydrous trifluoroacetic acid in 1,2-DCE resulted in selective hydrolysis and decarboxylation of the *tert*-butyl ester moiety to afford **150** in 84% yield. Removal of the benzyl protecting group of monomethylamino ester **150** could be performed quantitatively by Pd-catalyzed hydrogenolysis in acetic acid to generate the required azepinoindole ester **151**.



Scheme 50: Kuehne's synthesis of azepinoindole ester 151. Reaction conditions: (a) NEt_3, $(CH_3)_3COCl$, rt, 1.5 h, DCM, 98%; (b) thallium *tert*-butyl methyl malonate, reflux, 36 h, benzene, 63%; (c) anhydrous TFA, reflux, 3.5 h, 1,2-DCE, 84%; (d) 5% Pd/C, rt, 1 atm, 1.5 h, AcOH, 93%.



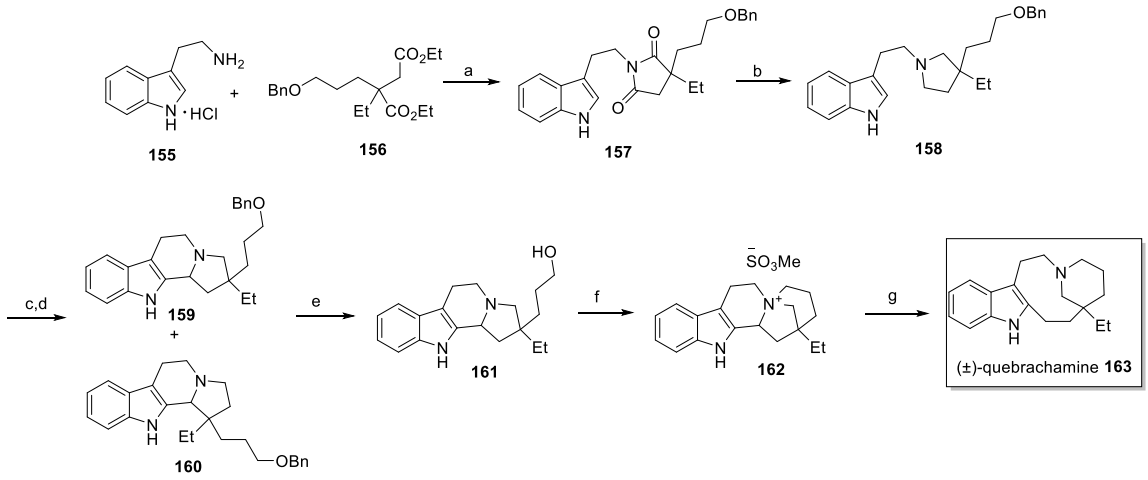
Scheme 51: Kuehne's synthesis of (±)-vincadifformine 154. Reaction conditions: (a) NEt_3, 40 °C, 12 h, MeOH, 70%.

The reaction of azepinoindole ester **151** with bromo aldehyde **152** was then performed to form the spiroenammonium salt **153** (Scheme 51). Fragmentation reaction of ammonium salt **153** generated the key secodine intermediate, which would then undergo *Diels-Alder* cycloaddition to afford the desired (±)-vincadifformine **154**.

4.3.3 Kutney's total synthesis of (±)-quebrachamine 163

Similarly, in 1970, Kutney and co-workers reported a synthetic sequence that generated (±)-quebrachamine **163** founded on the key step that involved the fragmentation of a quaternary ammonium salt (Scheme 52).[161] The synthesis began by refluxing the easily available tryptamine hydrochloric acid **155** with succinate ester **156** in glycol monoethyl ether. The isolated imide **157** was then subjected to $LiAlH_4$ reduction to form the corresponding amine **158** in 81% yield. Oxidation of amine **158** was performed with excess mercury(II) acetate to obtain the imine necessary for the subsequent intramolecular cyclization by the indole moiety. Further reduction of

the resultant imine by $NaBH_4$ was then carried out to obtain a mixture of diastereomeric components, **159** and **160**. Due to the difficulty isolating the distinctive isomers, debenzylation was performed directly on this crude mixture *via* Pd-catalyzed hydrogenolysis, and upon careful separation, alcohol **161** of both diastereomers were isolated with a combined yield of 35%. The pure alcohol **161** was then treated with methanesulfonyl chloride in triethylamine to provide cyclized quaternary ammonium salts **162** in quantitative yield. Finally, reductive cleavage of these quaternary salts occurred smoothly to afford (±)-quebrachamine **163** in 50% yield.



Scheme 52: Kutney's synthesis of (±)-quebrachamine 163. Reaction conditions: (a) tryptamine residue, reflux, 48 h, glycol monoethyl ether, 86%; (b) $LiAlH_4$, rt for 12 h followed by reflux for 4 h, THF, 81%; (c) $Hg(OAc)_2$, rt overnight followed by reflux, MeOH; (d) $NaBH_4$, rt, 2 h, MeOH, (38% for the four diastereomers over 2 steps); (e) 10% Pd/C, rt, 1 atm, 25 h, AcOH, 35% for the both diastereomers; (f) MsCl, NEt_3, rt, 42 h, $CHCl_3$, quant; (g) $LiAlH_4$, reflux, 11h, *N*-methylmorpholine, 50%.

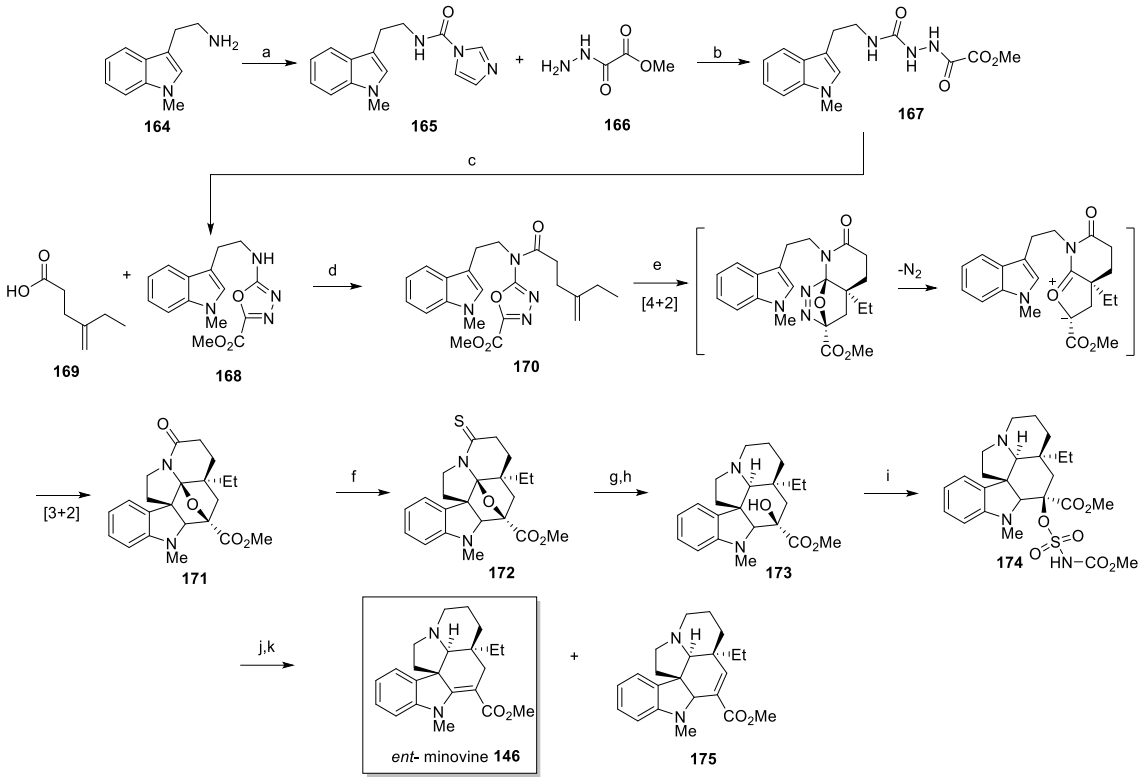
4.4 Recent Synthetic Approaches

Although these synthetic routes provided the desired alkaloids, the sequences often involved non-trivial procedures that began with difficult-to-access starting materials to obtain racemic product. As such, over the decades, the synthetic community was inspired to devise innovative and elegant

approaches that enable the efficient synthesis of these alkaloids as racemates and single enantiomers.

4.4.1 Boger's total synthesis of *ent*-minovine 146

Instead of adhering to the postulated biomimetic approach that involved the labile secodine intermediate, Boger's group had developed a concise synthetic route in 2005 to attain *ent*-minovine *via* an innovative approach that featured a novel tandem intramolecular *Diels-Alder*/ 1,3-dipolar cycloaddition reaction of 1, 3, 4-oxadiazole **168** as the key step of the sequence (Scheme 53).[162] Starting material, 1, 3, 4-oxadiazole **168**, was first prepared by treating commercially available *N*-methyl tryptamine **164** with CDI to give product **165**. Conversion of product **165** to oxadiazole precursor **167** with methyl oxalylhydrazide **166** in the presence of AcOH occurred without incident to give a yield of 93%.[163] With the aid of TsCl and NEt_3, cyclization of precursor **167** was observed to form the desired oxadiazole starting material **168**. Oxadiazole **168** was then coupled with 4-ethyl-4-pentenoic acid **169**, mediated by EDCI and DMAP, to provide substrate **170**.[150] Subsequently, the key tandem intramolecular cyclisation of **170** proceeded efficiently to furnish the cyclized product **171** as a single diastereomer. To perform a mild reduction of the amide adduct, **171** was first converted to thiolactam **172** with Lawesson's reagent.[164] Desulfurization of thiolactam **172** and subsequent reductive oxido-bridge opening was effected by S-methylation with Me_3OBF_4, followed by $NaBH_4$ reduction to afford dihydrovindorosine **173** in excellent yield of 92%.[165] In order to obtain the final product minovine **146**, **173** was first treated with Burgess reagent to provide sulfamate **174**. The isolated sulfamate **174** was then subjected to heating in toluene in the presence of NaH, resulting in the formation of *ent*-minovine **146** (39%) and its isomer **175** (53%).

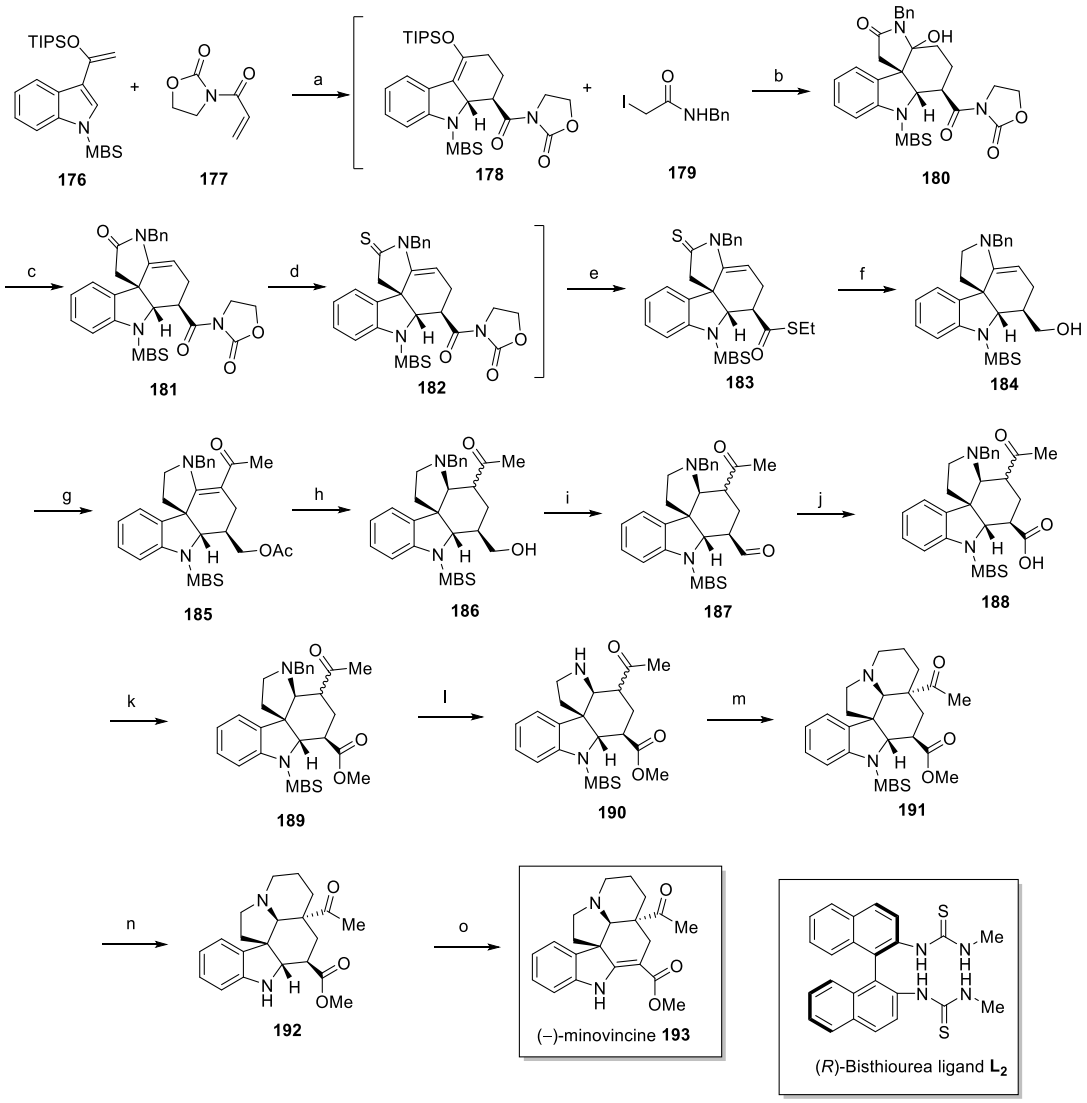


Scheme 53: Boger's synthesis of *ent*-minovine 146. Reaction conditions: (a) CDI, rt, 18 h, DCM-THF, 86%; (b) AcOH, 40 °C, 16 h, THF, 93%; (c) TsCl, NEt_3, rt, 16 h, DCM, 83% (d) EDCI, DMAP, rt, 16 h, DCM, 87%; (e) 180 °C, 24 h, *o*-dichlorobenzene, 74%; (f) Lawesson's reagent, 110 °C, 1.5 h, toluene, 85%; (g) Me_3OBF_4, 0 °C for 5 min and rt for 1.5 h, DCM; (h) $NaBH_4$, 0 °C for 5 min and rt for 2 h, MeOH, (92% over 2 steps); (i) Burgess reagent, 50 °C, 1.5 h, MeCN, 91%; (j) NaH, rt, 0.5 h, THF; (k) 100 °C, 1.5 h, toluene, yield of *ent*-minovine 146: 39%, yield of isomer 175: 53%.

4.4.2 Nishida's total synthesis of (−)-minovincine 193

More recently in 2015, Nishida's group demonstrated an elegant approach to furnish an enantio-enriched (−)-minovincine **193** *via* a highly substituted asymmetric hydrocarbazole derivative **178** (Scheme 54).[166] The synthesis of the enantioenriched hydrocarbazole derivatives was first disclosed by the group in 2013 and pivoted on an enantioselective *Diels-Alder* reaction of siloxyvinylindole **176** using a chiral holmium/bisthiourea catalyst.[167] After a series of screening of the *Diels-Alder* reaction of siloxyvinylindole **176** with **177**, it was revealed that the combination of Lewis acid $Ho(NTf_2)_3$ and bisthiourea ligand $\mathbf{L_2}$ gave the best results. Subsequently,

hydrocarbazole **178** was further subjected to a series of sequential processes in a one-pot reaction to furnish thioamide **182**. It was first treated with *N*-benzyliodoacetamide **179** [168] and TBAF to afford a single diastereoisomer tetracyclic compound **180**. This was followed by acidic dehydration to give enamide **181** and finally thiocarbonylation using Lawesson's reagent obtained the desired thioamide **182**. A single recrystallization of thioamide **182** further improved its optical purity to 94% ee. The oxazolidinone moiety of thioamide **182** was then converted to thioester by LiSEt[169] and subsequent reduction by $LiAlH_4$ gave optically pure enamine **184**. After acetylation of enamine **184**, enone **185** was successfully reduced by pinacolborance to give exclusively cis-fused pyrrolidine **186**. The hydroxyl adduct of pyrrolidine **186** was then converted to methyl ester **189** in good yields *via* a sequential IBX oxidation, Pinnick oxidation and esterification. Removal of the benzyl derivative was achieved by hydrogenation with $PdCl_2$ and a subsequent one-pot reaction of secondary amine **190** with 1,3-diiodopropane and sodium *t*-butoxide furnished the desired single diastereomer **191** of 56% yield. Lastly, the endgame of this synthesis route involved the MBS deprotection mediated by $KPPh_2$[170] and subsequently DDQ oxidation to give (−)-minovincine **193**.



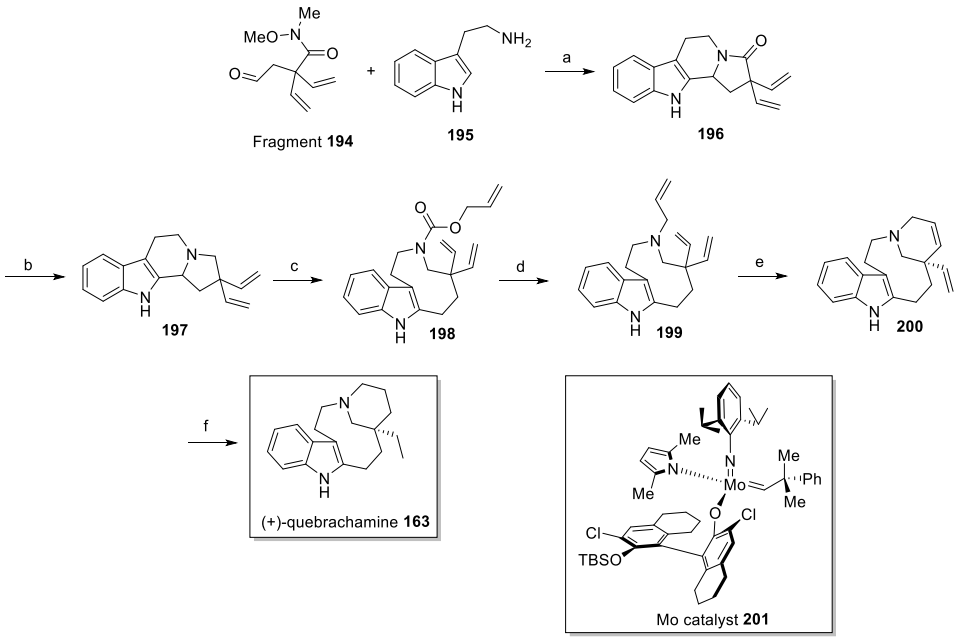
Scheme 54: Nishida's synthesis of (-)- minovincine 193. Reaction conditions: (a) $Ho(NTf_2)_3$ (0.5 mol%), L_2 (1 mol%), DBU (1 mol%), MS 4Å, 0 °C, 1 h, DCM; (b) TBAF, -78 °C to 0 °C, 0.5 h, DCM; (c) CSA, reflux, 1 h, toluene; (d) Lawesson's reagent, reflux, 1 h, toluene (one-pot reaction: 71% over 4 steps, 94% ee); (e) LiSEt, - 78 °C, 2 h, THF, 67%; (f) $LiAlH_4$, 60 °C, 2 h, THF; (g) AcCl, pyridine, DMAP, 60 °C, 4 h, DCE (76% over 2 steps); (h) PinBH, -78 °C to -40 °C, 1 h, THF, then K_2CO_3, rt, 3 h, THF/MeOH, 75%; (i) IBX, rt, 3 h, DMSO, 81%; (j) $NaClO_2$, $NaH_2PO_4.2H_2O$, 2-methyl-2-butene, rt, 1 h, *t*BuOH/H_2O; (k) $TMSCHN_2$, rt, 1 h, toluene/MeOH (86% over 2 steps); (l) $PdCl_2$, H_2 (1 atm), rt, 21.5 h, MeOH, 86%; (m) $ICH_2CH_2CH_2I$, *i*Pr_2NEt, 45 °C, 48h, MeCN, followed by NaO*t*Bu, 0 °C, 1 h, MeCN/*t*BuOH, (one-pot reaction: 56%); (n) $KPPh_2$, -40 °C to 0 °C, 1 h, THF, then $TMSCHN_2$, 46%; (o) DDQ, rt, 1 h, toluene, 41%.

4.4.3 Hoveyda's total synthesis of (+)-quebrachamine 163

Another interesting and concise approach to furnish optically active *Aspidosperma* alkaloid quebrachamine **163** was first outlined by Hoveyda's group (Scheme 55).[171] They were inspired to demonstrate the incorporation of the state-of-the-art catalytic olefin metathesis as their key step in their synthetic approach, allowing an expeditious enantioselective access to the target alkaloid quebrachamine **163**. In their plan, they envisioned that the enantioselective ring-closing metathesis of triene **199** would result in an efficient formation of the structural core of the target alkaloid. After obtaining the fragment **194**, the group carried on with the Pictet-Spengler condensation of **194** and tryptamine **195**, resulting in the formation of tetracyclic amide **196** in 79% yield. Indolyl amide **196** then underwent $LiAlH_4$ reduction, followed by acylation of amine **197** with allyl chloroformate to form its corresponding quaternary carbamate. Subsequent reductive cleavage of C-N bond at the quaternary amine resulted in the formation of **198**. Lastly, based on the Pd-catalyzed procedure developed by Tunge and co-workers, the carbamate adduct was successfully converted to allyl amine triene **199**.[172]

With the desired triene **199** in hand, the group proceeded to develop a protocol that could allow the effective selective ring-closing metathesis of triene **199** with great enantioselectivity. Initial attempts with the existing enantioenriched Ru- and Mo- based catalysts had proven futile in imparting chirality to the tetracyclic product **200**. As such, they embarked on designing the suitable Mo-based catalysts that would convert tricyclic triene **199** to the corresponding tetracyclic diene **200**, both efficiently and with great enantioselectivity. Guided by mechanical principles and theoretical studies, they postulated that by imparting chirality on the acceptor ligand will lead to the generation of products with greater enantioselectivity since the substrate most likely approaches the catalyst *syn* to the acceptor ligand. Indeed, they discovered that 1 mol% of the

newly designed Mo-based catalyst **201** resulted in the efficient formation of the desired diene **200** with 84% yield and 96% ee at 22 °C within an hour. For the final stage of the synthesis, diene **200** was subjected to catalytic PtO_2 hydrogenation, affording the desired target alkaloids, (+)-quebrachamine **163** in 97% yield.



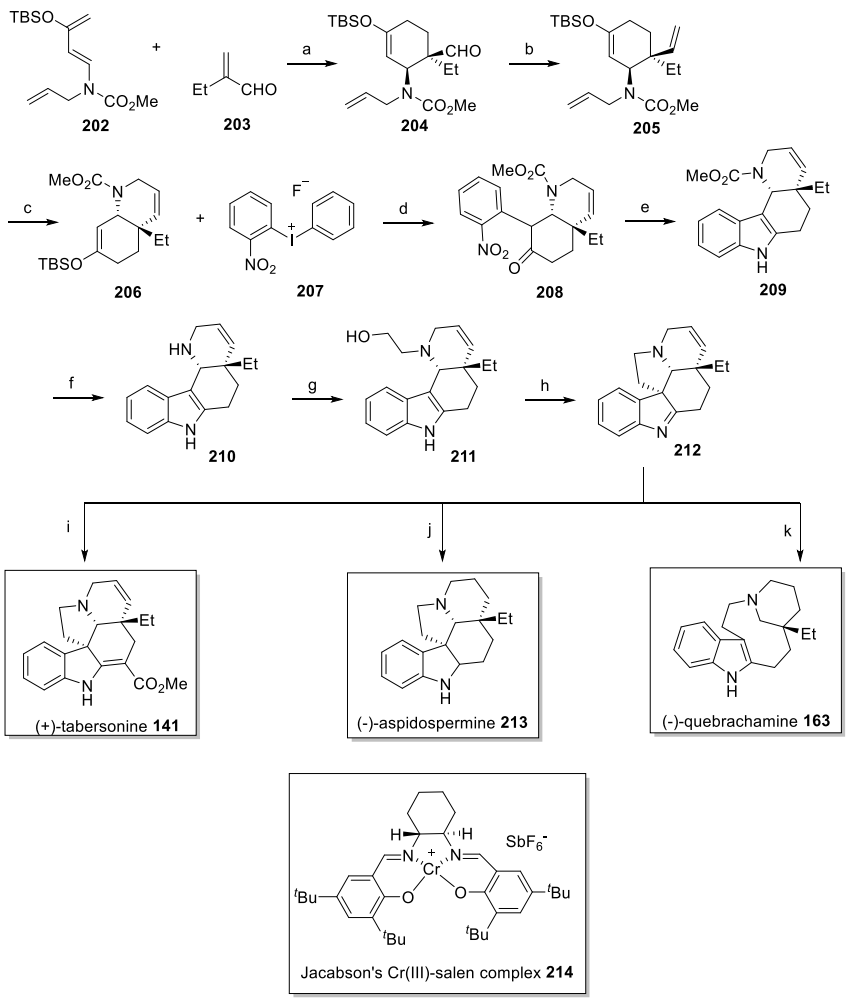
Scheme 55: Hoveyda's synthesis of (+)-quebrachamine 163. Reaction conditions: (a) AcOH, 80 °C, 2 h, toluene, 79%; (b) $LiAlH_4$, 0 °C to 65 °C, 1 h, THF, 97%; (c) allyl chloroformate, -78 °C, 1 h, then $NaCNBH_3$, -78 °C to 0 °C, 2 h, THF, 94%; (d) $Pd(PPh_3)_4$ (2.0 mol%), 22 °C, 20 min, DCM, 88%; (e) Mo catalyst 201 (1 mol%), 22 °C, 1 h, benzene, 84%, 96% ee; (f) PtO_2 (5 mol%), H_2 (1 atm), 22 °C, 1 h, EtOH, 97%.

4.5 Divergent Approaches to Indole alkaloid Syntheses

Despite many elegant synthetic approaches that have already been reported, recent efforts have shifted towards demonstrating unified, general and concise strategies that often exploit a common synthetic intermediate, and through several simple chemical transformations, furnish a collective range of structurally related natural products. Such approaches in general are more appealing in comparison to the traditional strategies that typically adhered to a customized protocol for an individual targeted alkaloid only.

4.5.1 Rawal's enantioselective syntheses of *Aspidosperma* alkaloids

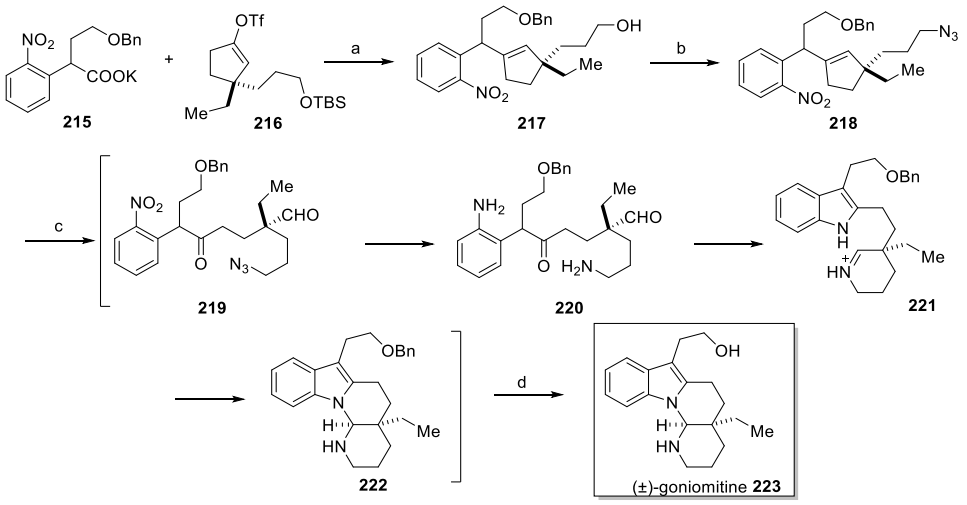
Employment of such strategies in their synthetic route was first demonstrated by Rawal and co-workers in 2002 (Scheme 56).[173] Their approach was founded on a highly regio- and stereoselective [4+2] cycloaddition of diene **202** and ethacrolein **203**, catalyzed by Jacobsen's enantioenriched Cr(III)-salen complex **214** to generate the cyclized product **204** in 84% yield and 95% ee.[174] The newly formed cycloadduct was subjected to Wittig methylenation, followed by ring-closing metathesis using Grubbs's catalyst to afford bicyclic adduct **206**.[175] Without the removal of the Grubb's catalyst, the crude mixture was treated with phenyl(*o*-nitrophenyl)iodonium fluoride **207** to attain an optically active *o*-nitrophenylated ketone **208** in 57-62% overall yield. Subsequent reduction of ketone **208** with $TiCl_3$ led to the formation of tetracyclic indole **209**.[176] Removal of the ester adduct was achieved by refluxing indole **209** with TMSI in DCM[177] and the unpurified amine **210** obtained was then reacted with bromoethanol under basic condition to furnish the *N*-alkylated indole **211.**[178] The hydroxyl adduct of the crude resultant mixture was further mesylated, facilitating the closure of the final ring of the desired scaffold with the aid of potassium *tert*-butoxide to afford **212**. By subjecting this pentacyclic scaffold **212** to various reaction conditions provided the structurally distinct aspidosperma alkaloids as desired – deprotonation with LDA followed by reaction with methyl cyanoformate furnished (+)-tabersonine **141**, reduction with $NaBH_4$ followed by hydrogenation of the alkene with Pt_2O afforded (+)-aspidospermine **213** and hydrogenation with Pt_2O in AcOH promoted the fragmentation and reduction of the olefins to provide (−)-quebrachamine **163**.



Scheme 56: Rawal's synthesis of *Aspidosperma* alkaloids. Reaction conditions: (a) Cr(III) salen catalyst 214 (5 mol%), - 40 °C, 2 days, DCM, 84%, 95% ee; (b) *n*-BuLi , Ph_3PMeBr, - 78 °C to 0 °C, 0.5 h, THF; (c) Grubbs's cat (7.2 mol%), reflux, 44 h, DCM; (d) rt, 2-4 h, THF-DMSO (1:2), (57-62% over 3 steps); (e) $TiCl_3$, NH_4OAc, rt, 0.5 h, acetone-H_2O (1.5:1); (f) TMSI, $(COCl)_2$, reflux, 1 h, DCM; (g) bromoethanol, Na_2CO_3, reflux, 15 h, ethanol; (h) NEt_3, MsCl, -15 °C, 0.5 h, DCM, then KO*t*Bu, rt, 0.75 h, THF; (i) LDA, $CNCO_2Me$, -70 °C, 1 h, THF, (33-39% over 5 steps); (j) $NaBH_4$, 0 °C to rt, 1 h, then Pt_2O, H_2 (1 atm), rt, 15 h, EtOH, 73%; (k) Pt_2O, H_2 (1 atm), rt, 2 h, AcOH, 69%.

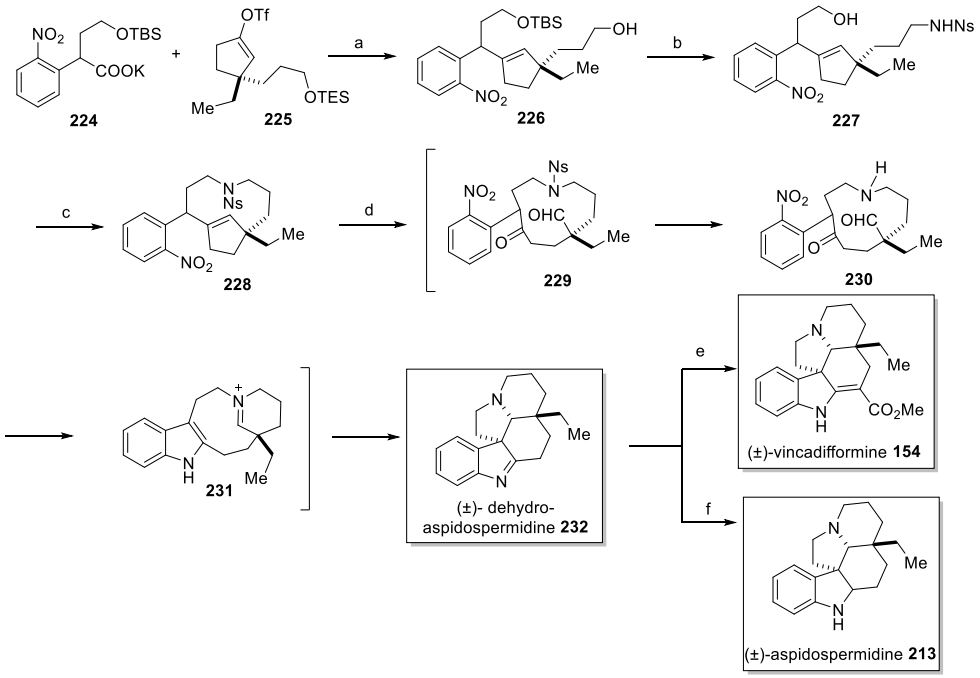
4.5.2 Zhu's unified syntheses of *Aspidosperma* alkaloids

In 2014, Zhu and co-workers disclosed an efficient and divergent strategy that was inspired by a biogenetic approach to access expediently a collective range of natural indole alkaloids from a common intermediate (Scheme 57).[179] The major highlight in their synthetic route was the construction of polycyclic indole scaffolds from cyclopentene intermediates *via* a one-pot domino cyclization process which the authors termed an *integrated oxidation/ reduction/ cyclization* (*i*ORC) sequence. The synthetic route was well-founded and started from a Pd-catalyzed decarboxylative vinylation of easy-to-access partners **215** and **216** to afford the coupling product **217** as a mixture of 2 diastereromers (dr 1/1).[180] Deprotection of the protecting group TBS by TBAF, followed by the conversion of the resulting hydroxyl moiety to azide **218** *via* Mitsunobu reaction with DDPA proceeded without incident.[181] Through the *i*ORC process, ozonolysis of the cyclopentene intermediate **218** resulted in the formation of the corresponding aldehyde adducts **219** [182] and with the subsequent addition of DMS and activated zinc and $CaCl_2$ reduction of the nitro and azido functionality to amine **220** occurred.[183] Upon refluxing the reaction mixture, the indole unit and the cyclized iminium were constructed, followed by intramolecular attack of indolyl nitrogen on the iminium species **221** that diastereoselectively generated the tetracycle **222**. Finally, (±)-goniomitine **223** was obtained in 65% yield after deprotection of the benzyl ether by sodium naphthalenide.[184,185]



Scheme 57: Zhu's synthesis of (±)-goniomitine 223. Reaction conditions: (a) $[Pd(allyl)Cl]_2$ (5 mol%), XPhos (15 mol%), 100 °C, 2 h, diglyme; TBAF, rt, 4 h, 70%; (b) DPPA, DIAD, Ph_3P, 0 °C to rt, 3 h, THF, 72%; (c) O_3, $NaHCO_3$, MeOH, -78 °C; Me_2S, -78 °C to rt; Zn, $CaCl_2$, reflux, 2 h, 80%; (d) Sodium naphthalenide, -20 °C, 15 min, 65%.

Similarly, to furnish a range of *Vinca* aspidosperma alkaloids, the synthetic route also began with the Pd-catalyzed decarboxylative vinylation of carboxylate **224** and vinyl triflate **225** forming the desired cyclopentene intermediate (Scheme 58). Removal of the TES protecting group by TBAF workup, followed by Mitsunobu reaction with nosylamine under Walker's conditions[186] and deprotection of TBS by TBAF afforded product **227**. A second intramolecular Mitsunobu reaction was realized by the nosylamine adduct to form the macrocycle **228**. Adhering to the *i*ORC protocol, the double bond of the macrocycle **228** was oxidatively cleaved by ozone, *N*-nosyl group removed[187] and the nitro group reduced by $TiCl_3$ to diastereoselectively form (±)-1,2-dehydroaspidospermidine **232**.[188] Reaction of (±)-1,2-dehydroaspidospermidine **232** with methyl cyanoformate furnished (±)- vincadifformine **154** while reduction with $NaBH_4$ provided (±)-aspidospermine **213**.

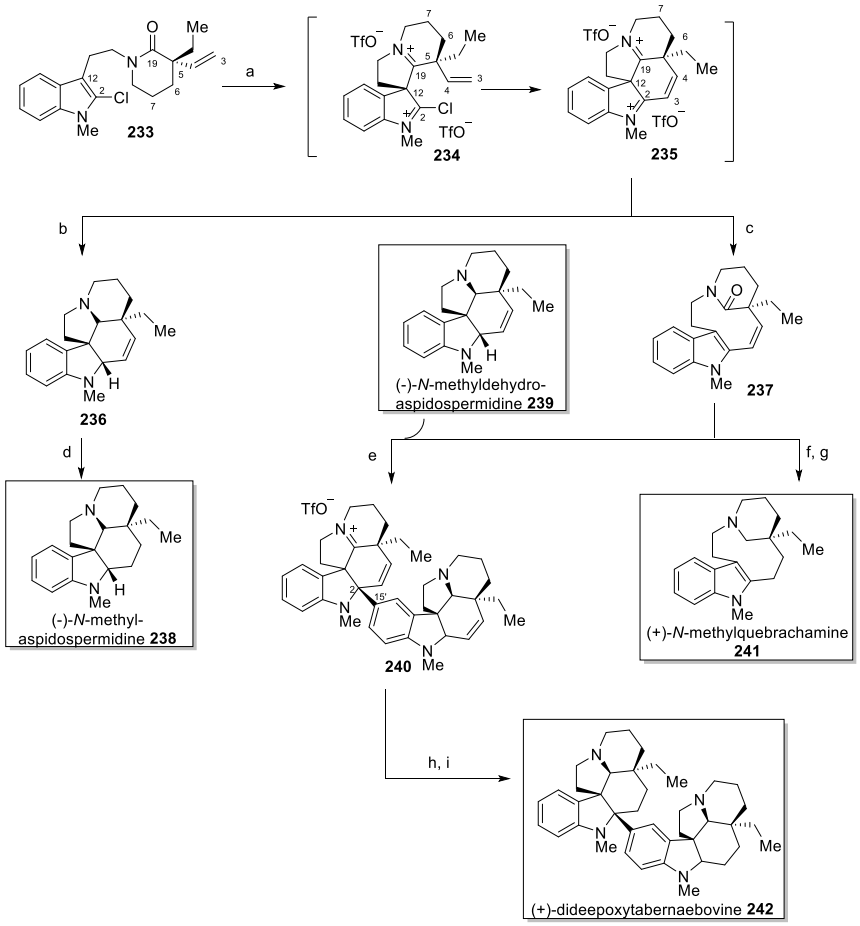


Scheme 58: Zhu's synthesis of *Vinca* alkaloids. Reaction conditions: (a) $[Pd(allyl)Cl]_2$ (5 mol%), XPhos (15 mol%), 100 °C, 2 h, diglyme; TBAF, 0 °C, 57%; (b) $NsNH_2$, PPh_3, DEAD, neopentyl alcohol (40 mol%), rt, 2 h, toluene; TBAF, rt, 75%; (c) PPh_3, DEAD, neopentyl alcohol (40 mol%), rt, 2 h, toluene, 81%; (d) O_3, -78 °C then DMS, rt, O/N, DCM, then thiophenol, Cs_2CO_3, rt, 24 h, then $TiCl_3$, NH_4OAc, MeOH, rt, 0.5 h, 50%; (e) nBuLi (1 equiv), $CNCO_2Me$, -78 °C for 0.5 h then warm to 0 °C, THF, 50%; (f) $NaBH_4$, $NaHCO_3$ (aq), rt, 2 h, (51% over step d and f).

4.5.3 Movassaghi's enantioselective syntheses of *Aspidosperma* alkaloids

In 2012, Movassaghi and co-workers were the first to demonstrate implementation of the concept of the electrophilic amide activation[189–191]in their synthetic approach to access enantioenriched *Aspidosperma* alkaloids (Scheme 59).[192] They envisioned that the generation of diiminium ion **235** from stable lactam (-)-**233** could allow divergent access to dimeric alkaloid (+)-**242** as well as monomeric aspidosperma alkaloids (-)-**238** and (+)-**241**. The team focused on the development of the unified route to access a range of *Aspidosperma* alkaloids founded on the electrophilic activation of the lactam moiety. Treatment of lactam (-)-**233** with trifluoromethanesulfonic anhydride in the presence of a basic additive 3-cyanopyridine resulted in the formation of

diiminium ion **235**.[189–191,193] This transformation began with the electrophilic activation of at the C19 position of lactam (-)-**233**, followed by rapid nucleophilic spirocyclization at C12 to furnish indoleninium intermediate **234** (an interrupted Bischler-Napieralsky reaction). Subsequently, the unactivated proximal vinyl group performed an intramolecular nucleophilic attack on the electron deficient indole at C2 to form the desired diiminium intermediate **235**. The synthetic versatility of the diiminium ion was first demonstrated for the synthesis of alkaloids (-)-**242**, (+)-**238** and (-)-**241**. *In situ* reduction of diminium ion **235** with sodium cyanoborohydride, followed by Pt-catalyzed hydrogenation of the cis-alkene afforded (-)-*N*-methylaspidospermidine **238**. Heating the diminium ion **235** in aqueous acidic solution resulted in Grob fragmentation to give tetracyclic lactam (-)-**237**.[194] Subsequent Pt- catalyzed reduction of the C3-C4 olefin carbonyl reduction of the lactam moiety furnished (+)-*N*-methylquebrachamine **241**.[195] More interestingly, the group illustrated the dimerization of two pentacyclic aspidosperma-type scaffolds at C2-C15' linkage by heating the tetracyclic lactam (-)-**237** with (-)-*N*-methyldehydroaspidospermidine **239** to afford the decacyclic alkaloid (+)-**240**. Finally, the reduction of the iminium adduct of (+)-**240** with Red-Al and the subsequent Pt-catalyzed hydrogenation provided (+)-dideepoxytabernaebovine **242** in 64% yield over 2 steps.



Scheme 59: Movassaghi's synthesis of *Aspidosperma* alkaloids. Reaction conditions: (a) Tf_2O, 3-cyanopyridine, 85 °C, 3h, MeCN; (b) $NaBH_3CN$, 23 °C, 6h, THF, 50%; (c) trifluoroacetic acid, sodium trifluoroacetate, 70 °C, 12h, H_2O, 57%; (d) H_2 (1 atm), Pt/C, 23 °C, 48h, THF, 100%; (e) Tf_2O, 2-ClPyr, 23 °C, 10 min, then (-)-239 (1.0 equiv), 85 °C, 90 min, 80%; (f) H_2 (1 atm), Pt/C, 23 °C, 48h, THF; (g) $LiAlH_4$, 60 °C, 12h, THF (82% over 2 steps); (h) Red-Al, 0 °C, 30 min, THF, 76%; (i) H_2 (1 atm), Pt/C, 23 °C, 72h, THF, 84%.

4.5.4 MacMillan's enantioselective Syntheses of *Monoterpene* alkaloids

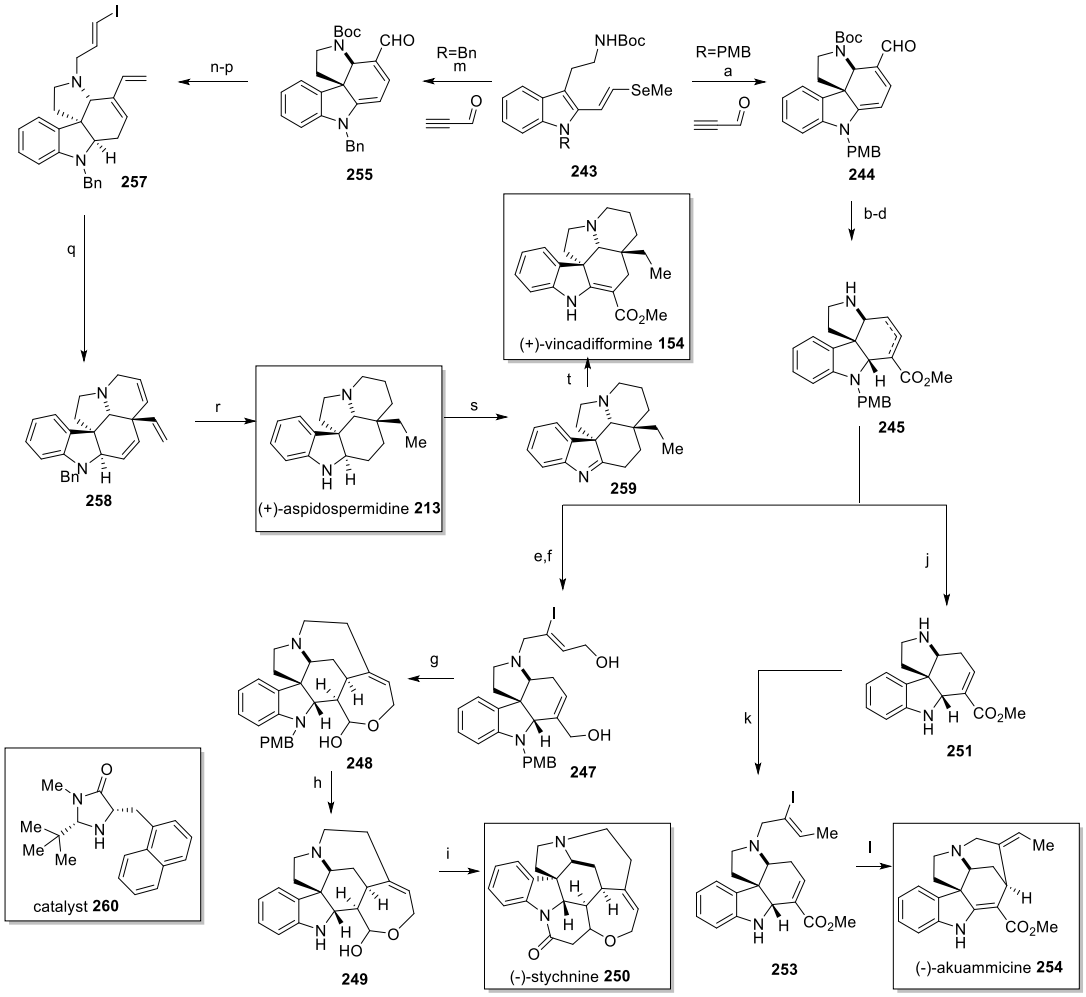
MacMillan and co-workers demonstrated a novel conglomeration of enantioselective organocascade catalysis and the strategies of collective natural alkaloids synthesis from a common intermediate to provide expedient access to a great range of optically active natural alkaloids in 2011(Scheme 60).[196] By treating 2-(vinyl-1-selenomethyl)tryptamine **243** with propynal and catalytic enantioenriched 1-naphthyl-substituted imidazolidinone catalyst **260**, an organocascade

reaction proceeded through an organocatalytic *Diels-Alder*/ β-elimination/ amine conjugate addition sequence to give the spiroindoline **244** with excellent levels of enantioinduction (97% ee).[197,198] Further advances regarding the synthesis of strychnine from the key intermediate **244** required only eight additional steps. Removal of the aldehyde moiety was first achieved by decarbonylation *via* Wilkinson's catalyst. Installment of a carbomethoxy adduct at the dienamine α-position was then performed[199], followed by DIBAL-H reduction on the unsaturated enamine provided the unsaturated ester **245** in 61% overall yield. Subsequently, the intermediate **245** was allylated with the substituted allyl bromide **246** and then treated with DIBAL-H to reduce the ester functionalities to their corresponding alcohols **247**.

The second key step of this synthesis involved the conversion of vinyl iodide **247** to the Wieland-Gumlich aldehyde **248** *via* a Jeffrey-Heck cyclization/lactol formation sequence.[200] For the endgame of this synthetic sequence, aldehyde **248** was subjected to TFA for the removal of PMB group[197] and with the subsequent heating of unprotected aldehyde **249** with a mixture of malonic acid, acetic anhydride and sodium acetate afforded the desired enantioenriched (-)-strychnine **250** in 12 steps.

The team further explored the possibility of expanding the scope of alkaloids this key intermediate might access. They demonstrated the feasibility of the construction of (-)- akuammicine[201], starting from the unsaturated ester **245**. To achieve this, intermediate **245** was first treated with TFA and thiophenol for the removal of PMB group and concomitantly isomerized the alkene into conjugation to form the spiroindoline **251**. The pyrrolidine nitrogen moiety was then allylated with allyl bromide **252**, and subsequently a Pd-catalyzed Heck cyclization[202] provided the desired (-)-akuammicine **254** in 10 steps.

Interestingly, the group could apply their cascade catalysis approach for the synthesis of *Aspidosperma* alkaloids. The synthetic route began by converting the aldehyde adduct of Bn protected **255** through Wittig olefination, followed by TFA reduction of the enamine and removal of Boc protecting group. The pyrrolidine nitrogen was then allyated with allyl bromide **256** to generate vinyl iodide **257** in this three-step sequence. A Pd-catalyzed Heck cyclization of the vinyl iodide onto the tri-substituted cyclic alkene, resulted in the formation of the aspidospermidine scaffold- triene **258**. Conversion to (+)-aspidospermidine **213** proceeded without incident by a simultaneous hydrogenation /debenzylation of triene **258**. Finally, by means of an oxidation and carbomethoxylation sequence, (+)-aspidospermidine **213** was transformed to (+)-vincadifformine **154**.[173]

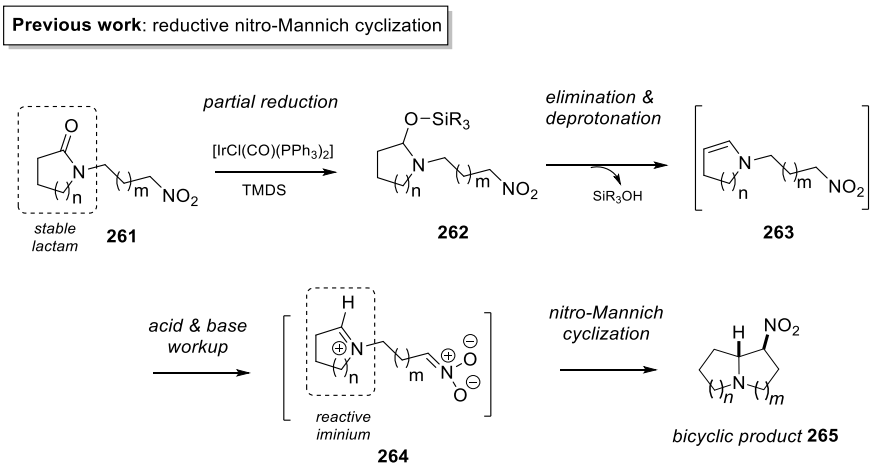


Scheme 60: Macmillan's synthesis of (-)-strychnine, (-)-akuammicine, (+)-aspidospermidine and (+)-vincadifformine. Reaction conditions: (a) 20 mol% 260·TBA, -40 °C to rt, 13 h and 10 h, toluene, 82%, 97% ee; (b) $(Ph_3P)_3RhCl$, 120 °C, 5.25 h, toluene, PhCN; (c) $COCl_2$, NEt_3, -45 °C to rt, 2.5 h, toluene, then MeOH, -30 °C to rt, 10 min; (d) DIBAL-H, -78 °C to rt, then TFA, -78 °C to rt, 3 h, DCM, (61% over 3 steps); (e) DBU, K_2CO_3, (*Z*)-4-bromo-3-iodobut-2-enyl acetate 246, rt, 50 min, DMF; (f) DIBAL-H, -78 °C, 2 h, DCM, (76% over 2 steps); (g) $Pd(OAc)_2$ (25 mol%), Bu_4NCl, $NaHCO_3$, rt, 2 h, EtOAc, 58%; (h) PhSH, TFA, 45 °C, 13 h, 66%; (i) NaOAc, Ac_2O, AcOH, malonic acid, 120 °C, 2.2 h 69%; (j) TFA, PhSH, 60 °C, 3.5 h, 91%; (k) (*Z*)- 1- bromo-2- iodobut-2-ene 252, K_2CO_3, rt, 10 min, DMF, 76%; (l) $Pd(OAc)_2$ (20 mol%), Bu_4NCl, $NaHCO_3$, 65 °C, 4.3 h, MeCN, 47%; (m) 20 mol% *ent*-260·TBA, -40 °C to RT, 12 h and 16 h, toluene, 83%, 97% ee; (n) Ph_3PCH_3I, *n*-BuLi, 0 °C, 45 min, THF, then AcOH, $NaCNBH_3$, 0 °C, 10 min; (o) TFA, rt, DCM; (p) (*Z*)-3- bromo-1-iodoprop-1-ene 256, K_2CO_3, rt, 6 h, DMF, (73% over 3 steps); (q) $(Ph_3P)_4Pd$, NEt_3, 80 °C, 24 h, toluene, 65%; (r) $Pd(OH)_2$, H_2 (200 p.s.i.), rt, 72 h, MeOH, EtOAc, 98%; (s) $(COCl)_2$, DMSO, -78 °C to rt, 20 min, DCM, 65%; (t) n-BuLi, $NCCO_2Me$, -78 °C to rt, 30 min, THF, 57%.

4.6 Our Approach: Synthetic Studies into a new Divergent Approach to access Aspidosperma Alkaloids

4.6.1 Objective & Plan

Inspired by some of the elegant and well-executed approaches descrived above, we hope to formulate a chemical strategy capable of furnishing an array of structurally diverse monoterpene alkaloids *via* an easy-to-access key intermediate. We also recognize that the implementation of a late-stage key intermediate to our divergent approach would be advantageous as it would simplify the general synthesis greatly - with the least possible number of additional transformations to access our desired alkaloids. Over the last few years, our group has been actively investigating the synthetic potential that pivoted on the rapid and chemoselective iridium (I)-catalyzed reduction of stable lactams to generate reactive enamine functionality. In 2015, relying on the aforementioned strategy, our group reported a chemoselective reductive nitro-mannich cyclization reaction sequence of nitroalkyl-tethered lactams **261** (Scheme 61).[34] Through this approach, efficient and direct access to nitrogen containing bicyclic products **265** with cores typically found in natural products was achieved. More importantly, this catalytic reductive transformation of amides to enamine approach exhibited high chemoselectivity and broad tolerance towards reducible functional groups.



Scheme 61: Dixon group's reductive nitro-Mannich cyclization

Strategies that employ enamine derivatives as synthetic intermediates to access natural alkaloids are well-founded. They were first proposed by Wenkert and Scott in the early 1960s that *Aspidosperma* and *Iboga* alkaloids, *via* the inverse electron-demand intramolecular *Diels-Alder* cycloaddition (IMDA), were biogenetically derived from enamine intermediates (Refer to section 4.2, Scheme 48).[158,203,204] This hypothesis was subsequently supported by labelling experiments and various synthetic approaches that employed the high reactivity of the enamine intermediate formed *in situ* from acyclic precursors to obtain the *Aspidosperma* alkaloids such as vincadifformine **154**.[150,159,160,205–215]However, the traditional methods of generating reactive enamine, were usually non-trivial. For instance, additional chemical steps were often required to generate aldehyde necessary to furnish labile enamine *via* Stork condensation with amines.[37] Therefore, we believed that through the chemoselective iridium(I)-catalyzed reduction of stable lactams, *in situ* generation of the putative enamine would be achieved with ease and thus provide easy access to a range of important natural alkaloids in a concise fashion (Figure 10). Furthermore, because of its high selectivity to reduce amides to enamines in the presence of other reducible functional groups, this catalytic reductive transformation would be an invaluable strategy in natural product synthesis.

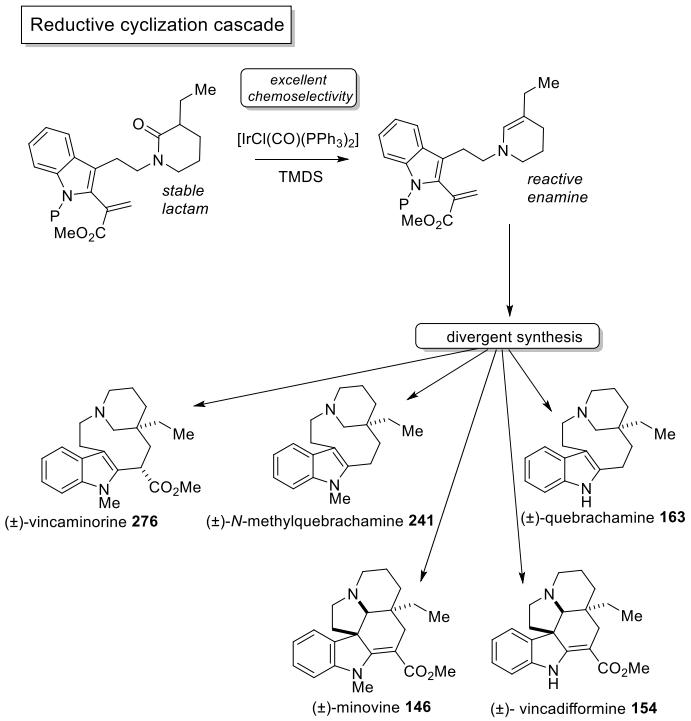
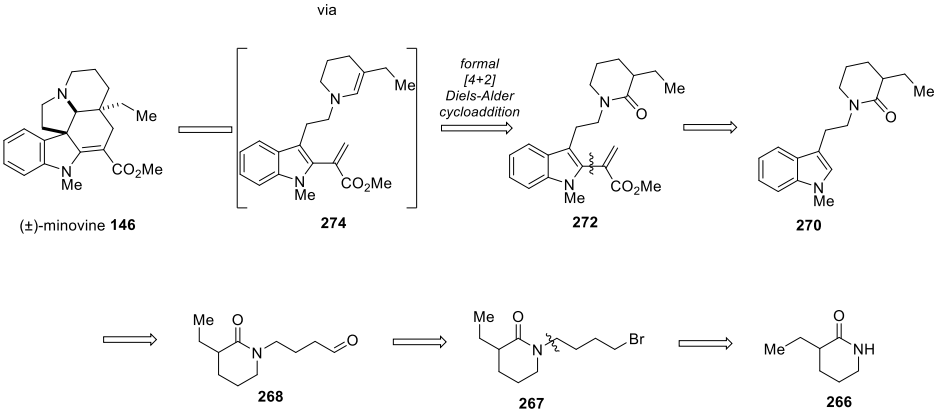


Figure 10: Proposed divergent synthesis of Aspidosperma-type alkaloids *via* Ir-catalyzed reductive cyclization cascade.

4.6.2 Retrosynthetic studies



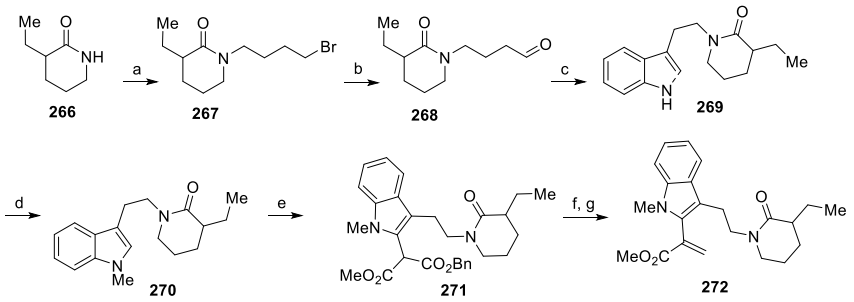
Scheme 62: Retrosynthetic analysis of (±)-minovine 146.

For our initial studies, (±)-minovine **146** was chosen as our synthetic target. To access the enamine intermediate **274** – that was primed for the inverse electron demand IMDA to furnish our desired product (±)-minovine **146** – this short and divergent route would begin with the alkylation of a

simple lactam building block **266** with 1,4-dibromobutane. The bromo functionality of **267** could easily be converted to its corresponding aldehyde **268** poised for the subsequent instalment of the indolyl moiety with phenylhydrazine. The disconnection of the acrylate moiety and the C-2 position of the indole derivative **272** could be achieved by transition metal-catalyzed direct C-H functionalization.

4.6.3 Enamine precursor formation

The route for the synthesis of the key enamine precursor **272** poised for the formation of (±)-minovine **146** was simple and straight-forward. 3-Ethyl-2-piperidone **266** was first alkylated with 1,4-dibromobutane to furnish lactam **267**. The *N*-linked alkylbromide was then treated with NMO and DMSO for the conversion to its corresponding aldehyde **268** *via* Kornblum oxidation.[216–218] Subsequently, using Stork's modification of the Fischer indole synthesis of aldehyde **268** for the construction of the indole functionality proceeded successfully with phenylhydrazine.HCl.[219–222] After the methylation of the indolyl nitrogen to afford **270**, Stephenson's photoredox-mediated direct C-H functionalization at C-2 of the indole adduct **270** with 1-benzyl 3-methyl 2-bromomalonate occurred smoothly to generate **271** in 82% yield.[223] Finally, debenzylation of the benzyl ester *via* Pd-catalyzed hydrogenolysis, followed by decarboxylative mannich reaction proceeded efficiently to generate the desired key enamine precursor – stable lactam **272**- in 55% yield over two steps.



Scheme 63: Synthesis of the key intermediate, lactam 272. Reaction conditions: (a) NaH, 1, 4-dibromobutane, THF:DMF (5:1), rt, 18 h, 80%; (b) NMO, DMSO, rt, 18 h, 60%; (c) Phenylhydrazine. HCl, 4% H_2SO_4 (aq): DMA (1:1), 110 °C, 2 h, 62%; (d) MeI, NaH, THF, rt, 2 h, 95%; (e) $[Ru(bpy)_3]Cl_2$, 1-benzyl 3-methyl 2- bromomalonate, 4-methoxyphenylamine, *blue LEDs*, DMF, rt, 12 h, 82%; (f) Pd/C, H_2, EtOH, rt, 1 h; (g) $CH_2=O$, $HNMe_2$.HCl, NaOAc, AcOH, rt, 4 h, 55% (over 2 steps).

4.6.4 Key Ir-catalyzed reduction-cycloaddition sequence

Having the desired indole-linked lactam **272** in hand, investigation into the key Ir-catalyzed reduction-cycloaddition sequence was carried out (Scheme 64). To our delight, we observed that the chemoselective Ir-catalyzed reduction of the lactam adduct in the presence of the α,β-unsaturated ester to give the desired enamine intermediate **274** was successful *via* a presumed siloxy intermediate **273**,[25,31,32,224] as confirmed by ^{1}H NMR (Figure 11) – this would be the first experimental evidence that shows the presence of the enamine derivative, a crucial precursor for the inverse electron demand IMDA. Based on the previous studies, we expected that the labile enamine (secodine) intermediate would readily undergo an inverse electron demand IMDA *via* a two-stage intramolecular enamine conjugate addition on the acrylate moiety followed by a transannular mannich reaction of the putative iminium species to form (±)-minovine **146** (concerted reaction pathway cannot be ruled out at this stage of investigation). However, during our initial attempts, we did not observe the formation of (±)-minovine **146** under ambient reaction conditions. To resolve this issue, we anticipated that the addition of a Lewis acid or hydrogen

bond-donor additives would enhance the electrophilicity of the acrylate moiety to facilitate the nucleophilic addition step by the enamine intermediate.

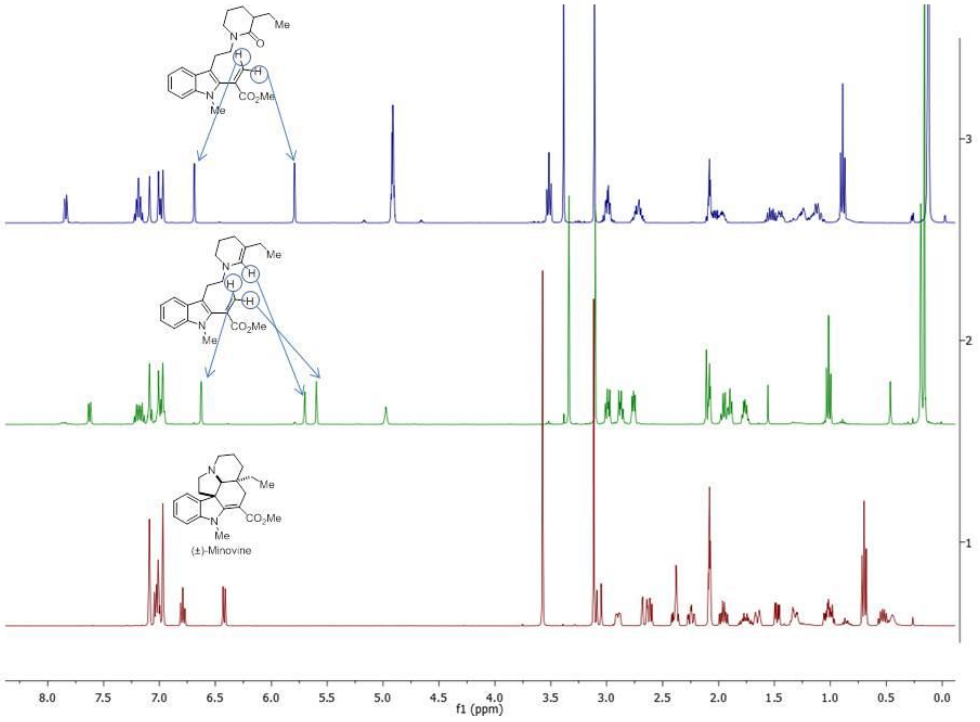
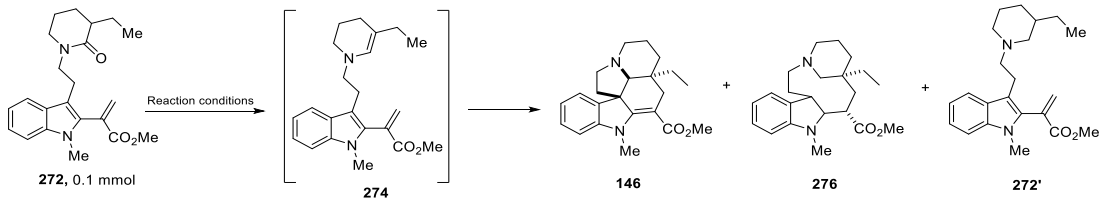


Figure 11: ^{1}H NMR analysis on the formation of enamine (secodine) intermediate

It was whilst surveying various acidic additives and other reaction parameters, we began to appreciate the intricacy of this transformation – the enamine intermediate has the propensity to either undergo further reduction to afford the fully saturated piperidine product, thus rendering subsequent cyclization futile (Table 7, entry 1 & 6), or decompose to give a complex mixture (Table 7, entry 7). Pleasingly, the addition of an optimal amount of silica gel[225–229] after the formation of the enamine intermediate resulted in the direct formation of the target alkaloid, (±)-minovine **146** with a trace amount of piperidine side product **272'** observed (Table 7, entry 3). Interestingly, it was noteworthy to mention that another skeletally distinct alkaloid, (±)-

vincaminorine **276** was also formed as a single diastereomer in the reaction vessel (**146**:**276** = 1.7: 1.0. combined yield = 83%).

Table 7: Optimization studies on key Ir-catalyzed reduction-cycloaddition sequence



Entry	Vaska's complex (mol %)	TMDS (equiv)	Additive	Solvent	Temp	Minovine 146 (%)	Vincaminorine 276 (%)	Over-reduced 272' (%)	Combined yield of 146 & 276 (%)
1[a]	1	2	Silica gel (10 x wt of **272**)	Toluene (1 mL)	25 °C	20	25	26	45
2[a]	1	2	Silica gel (5 x wt of **272**)	Toluene (1 mL)	25°C	43	29	Trace	72
3[b]	1	2	Silica gel (5 x wt of **272**)	Toluene (1 mL)	Reduction of amide: 25°C Addition of additive: -78 °C → 25 °C	52	31	Trace	83
4[c]	1	2 + 1	Silica gel (5 x wt of **272**)	Toluene (1 mL)	Reduction of amide: 25°C Addition of additive: -78 °C → 25 °C	7	17	46	24
5[c]	1	2 + 0.5	Silica gel (5 x wt of **272**)	Toluene (1 mL)	Reduction of amide: 25°C Addition of additive: -78 °C → 25 °C	8	15	52	23

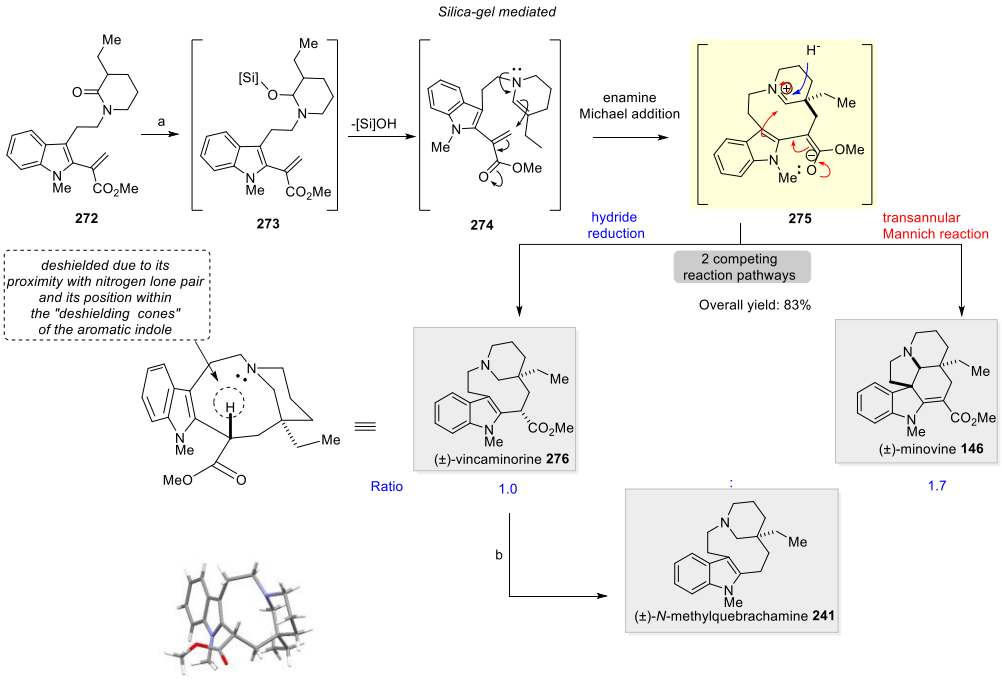
6[b]	1	2	AcOH (1 equiv) in toluene (2.5 mL)	Toluene (1 mL)	Reduction of amide: 25°C Addition of additive: -78 °C → 25 °C	13	Trace	39	13
7[b]	1	2	pTsOH (1 equiv)	Toluene (1 mL)	Reduction of amide: 25°C Addition of additive: -78 °C → 25 °C	Reaction gives a complex mixture			-
8[d]	1	2	MeOH (1 mL)	Toluene (1 mL)	Reduction of amide: 25°C Addition of additive: -78 °C → 25 °C	20	6	27	26

a. Reduction of amide to its corresponding enamine was carried out at 25 °C for 10 min. Additive was added at 25 °C and the reaction was stirred at 25 °C for 30 min.

b. Reduction of amide to its corresponding enamine was carried out at 25 °C for 10 min. Additive was added at -78 °C. Reaction mixture was warmed to 25 °C and stirred for 30 min.

c. Reduction of amide to its corresponding enamine was carried out at 25 °C for 10 min. Additive, followed by TMDS were added at -78 °C. Reaction mixture was warmed to 25 °C and stirred for 30 min.

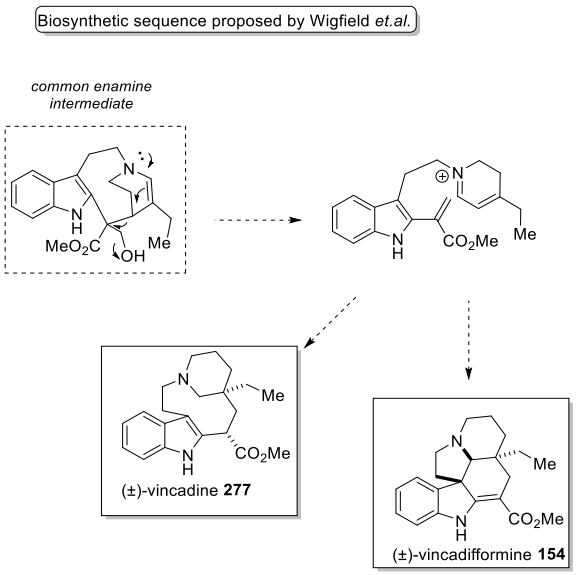
d. Reduction of amide to its corresponding enamine was carried out at 25 °C for 10 min. Additive was added at -78 °C. Reaction mixture was warmed to 25 °C and stirred for 16 h.



Scheme 64: Divergent synthesis of (±)-vincaminorine 276, (±)-minovine 146 and (±)-*N*-methylquebrachamine 241 and X-ray crystal structure of 276. Reaction conditions: (a) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS (2 eq), toluene, rt, 10 min, subsequent addition of SiO_2, -78 °C to rt, 1h, 146: 52%, 276: 31%; (b) 6*N* HCl, 90 °C, 2h, 61%.

(±)-Vincaminorine **276** was presumably formed by a competing Ir-catalyzed reduction of the iminium intermediate **275** after the initial Michael addition of the enamine intermediate to the α,β-unsaturated ester (Scheme 64). While the results of this intriguing one-pot reaction sequence supported the hypothesis of the enamine (secodine) intermediate undergoing an inverse electron demand IMDA reaction pathway, they also provided invaluable insights into its stepwise nature and the potential biogenesis of skeletally distinct quebrachamine-type alkaloids. The lack of full characterization data available in the literature prompted us to determine the relative configuration of the (±)-vincaminorine **276** by single crystal X-ray diffraction. It is also important to note that the proton adjacent to the ester functionality has a chemical shift of δ 6.22 ppm. As the overall structural rigidity of the (±)-vincaminorine **276** prevented the proton to undergo conformational inversion, the proton was found to resonate farther downfield due to its proximity with the nitrogen

lone pair and is in the "deshielding cones" of the aromatic indole. This observation could aid in determining the stereochemical configuration at the carbon center adjacent to the ester and the indole of (±)-vincaminorine **276**. In 1968, Wigfield and co-workers had postulated a biosynthetic sequence that involved a common enamine intermediate which eventually led to quebrachamine-type and vincadifformine-type alkaloids *via* independent pathways (Scheme 65).[230] To the best of our knowledge, this is the first evidence demonstrating the feasibility of such a sequence to divergently form these alkaloids from a common enamine intermediate.



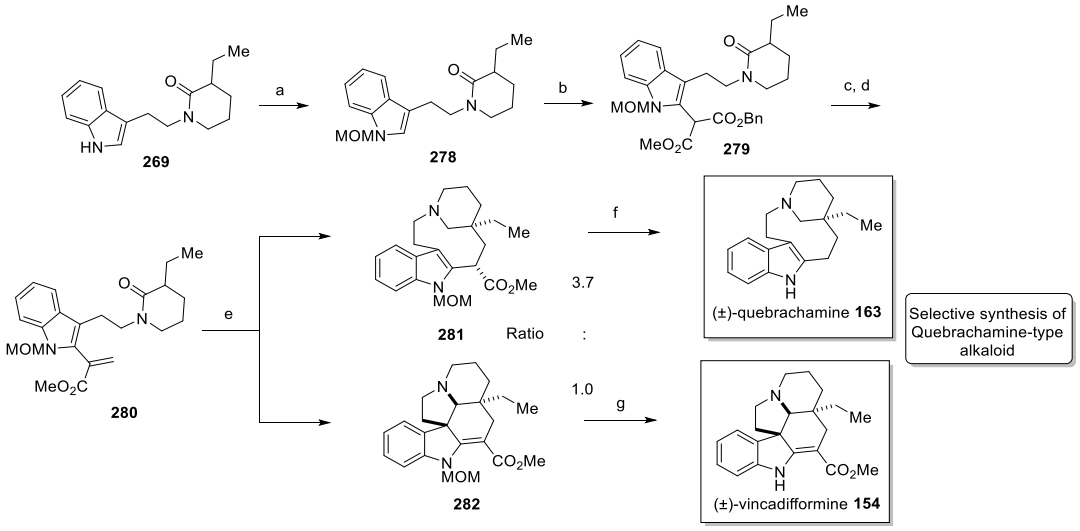
Scheme 65: Wigfield's biosynthetic sequence to form quebrachamine-type and vincadifformine-type alkaloids *via* enamine intermediate.

Further treatment of (±)-vincaminorine **276** with 6*N* HCl (aq) resulted in the formation of (±)-*N*-methylquebrachamine **241** *via* acid hydrolysis/ decarboxylation.

4.6.5 Syntheses of non-*N*-methylated *Aspidosperma*-type alkaloids

Given the success of furnishing the natural alkaloids (±)-minovine **146**, (±)-vincaminorine **276** and (±)-*N*-methylquebrachamine **241**, we began to explore and investigate the synthetic potential and versatility of this strategy to generate non-*N*-methylated *Aspidosperma* type alkaloids (Scheme

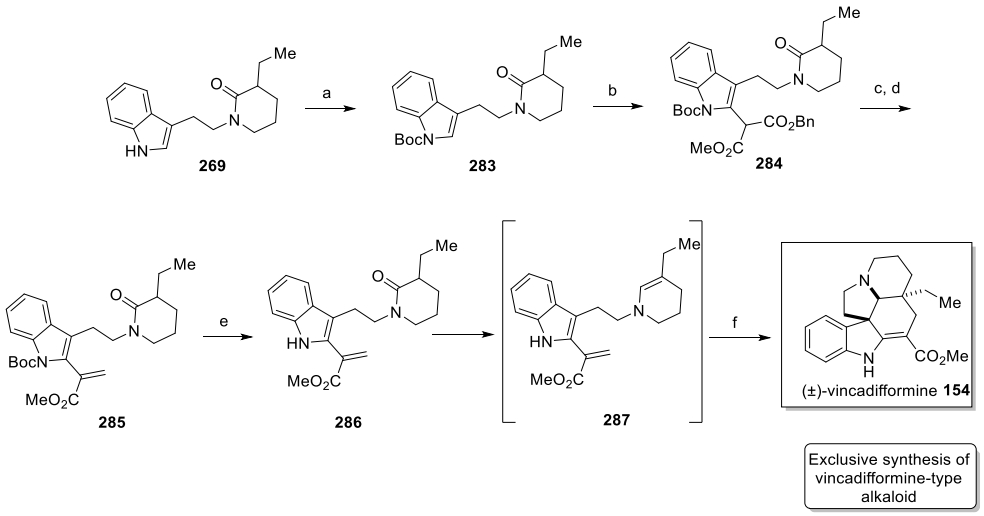
66). MOM protected lactam **280** was first chosen to be the key enamine precursor for this study and its synthesis was straightforward. Thereafter, the key transformation, the Ir-catalyzed reduction of lactam **280** to attain the key enamine (secodine) intermediate, proceeded without incident. However, it was interesting to note the difference in the product distribution; the Michael addition / iminium reduction product **281** was obtained in larger proportion than the formal *Diels-Alder* cycloaddition product **282** (**281**:**282** = 3.7: 1.0) (Scheme 66). Subsequent treatment of product **281** and **282** with dilute hydrochloric acid generated (±)-quebrachamine **163** and (±)-vincadifformine **154** in 71% and 84% yields respectively.



Scheme 66: Divergent synthesis of (±)-quebrachamine 163 and (±)-vincadifformine 154. Reaction conditions: (a) MOMCl, NaH, THF:DMF (1:1), 0 °C, 2 h, 89%; (b) $[Ru(bpy)_3]Cl_2$, 1-benzyl 3-methyl 2- bromomalonate, 4- methoxyphenylamine, *blue LEDs*, DMF, rt, 12 h, 66%; (c) Pd/C, H_2, EtOH, rt, 1 h; (d) CH_2=O, $HNMe_2$.HCl, NaOAc, AcOH, rt, 4 h, 55% (over 2 steps); (e) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS (2 eq), toluene, rt, 10 min, subsequent addition of SiO_2, -78 °C to rt, 2 h, 282: 14%, 281: 52%; (f) 3*N* HCl, MeOH, 55 °C, 48 h, 71%; (g) 1*N* HCl, MeOH, rt, 20 min, 84%.

This observation of changing selectivity between the formal *Diels-Alder* product and the Michael addition / reduction product as a result of the nature of substituent on the indolyl nitrogen is interesting and synthetically relevant. This suggested that the decrease in the electron density of the indole moiety reduced the rate of second cyclization relative to reduction by hydride. Intrigued

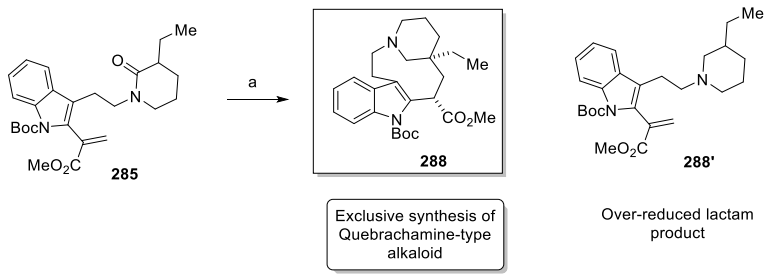
by these results, we proceeded to investigate if the absence of a protecting group on the indolyl nitrogen would influence the outcome too (Scheme 67). Consequently, the unprotected precursor **286** was synthesized and due to its instability towards attempted purification, it was immediately subjected to the Ir-catalyzed reduction conditions. Interestingly in this case, the reaction proceeded directly – without the addition of any silica gel mediator – to afford exclusively the formal *Diels-Alder* product, (±)-vincadifformine **154**, with a yield of 44% over 2 steps. Generally, this study demonstrated the control to attain selectively either the vincadifformine-type alkaloids or quebrachamine-type alkaloids could be achieved by manipulating the intrinsic electron density of the indole core through varying the distinct electronic nature of the protecting group attached to the indolyl nitrogen.



Scheme 67: Exclusive synthesis of (±)-vincadifformine 154. Reaction conditions: (a) Boc_2O, NEt_3, DMAP, DCM, rt, 1.5 h, 95%; (b) $[Ru(bpy)_3]Cl_2$, 1-benzyl 3-methyl 2- bromomalonate, 4-methoxyphenylamine, *blue LEDs*, DMF, rt, 12 h, 89%; (c) Pd/C, H_2, EtOH, rt, 1 h; (d) $CH_2=O$, $HNMe_2$.HCl, NaOAc, AcOH, rt, 4 h, 82% (over 2 steps); (e) TFA, Me_2S, DCM, rt, 1 h; (f) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS (2 eq), toluene, rt, 1 h, 44% (over 2 steps).

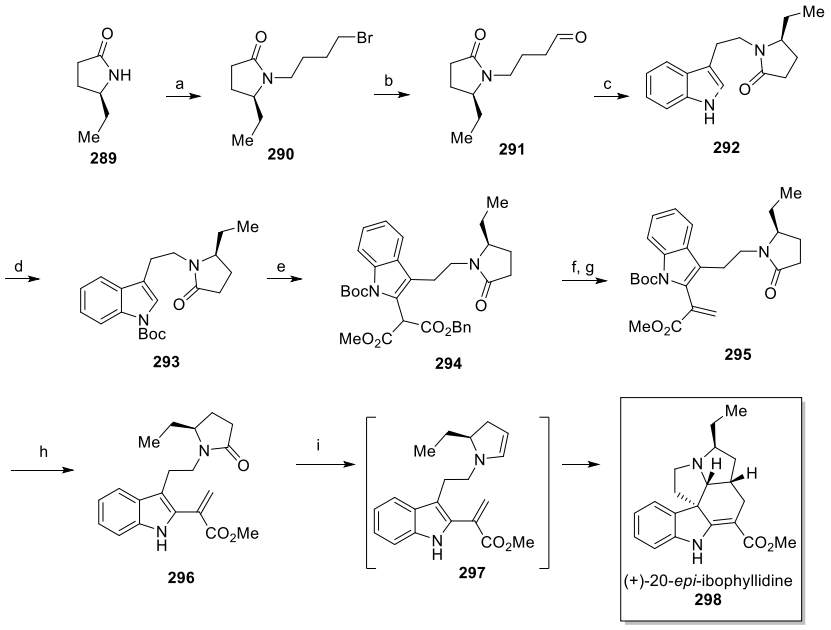
To further substantiate the evidence that the decrease in the electron density of the indole moiety could reduce the rate of second cyclization relative to reduction by hydride, we postulated that the Boc-protected lactam **285** could selectively furnish the quebrachamine-type alkaloids under this Ir

(I)-catalyzed reductive conditions (Scheme 68). Unfortunately, although no formal *Diels-Alder* product was observed, reductive cyclization product **288** was obtained only in 13% yield with the remainder of the mass largely attributed to over-reduced lactam product **288'**.



Scheme 68: Exclusive synthesis of 288. Reaction conditions: (a) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS (2 eq), toluene, rt, 10 min, subsequent addition of SiO_2, -78 °C to rt, 4 h, 13%.

Finally, the versatility of our synthetic strategy was further established by expanding its scope towards the synthesis of enantiomerically pure monoterpene indole alkaloid, (+)-20-*epi*-ibophyllidine **298**, starting from simple γ-lactam building block (*S*)-5-ethylpyrrolidin-2-one, **289** (Scheme 69). Lactam **289** was first converted to the stable lactam derivative **295** by the similar synthetic steps to those described in Scheme 63. Subsequent Boc deprotection of **295** with TFA in the presence of dimethyl sulfide furnished precursor **296**. Ir-catalyzed reduction of precursor **296** proceeded smoothly without the aid of any silica gel promoter, to generate the formal *Diels-Alder* product, (±)-20-*epi*-ibophyllidine **298** as a single diastereomer.



Scheme 69: Synthesis of (±)-20-*epi*-ibophyllidine 298. Reaction conditions: (a) NaH, 1,4-dibromobutane, THF:DMF (5:1), rt, 18 h, 71%; (b) NMO, DMSO, rt, 18 h, 55%; (c) Phenylhydrazine. HCl, 4% H_2SO_4 (aq): DMA (1:1), 110 °C, 2 h, 68%; (d) Boc_2O, NEt_3, DMAP, DCM, rt, 1.5 h, 92%; (e) $[Ru(bpy)_3]Cl_2$, 1-benzyl 3-methyl 2- bromomalonate, 4-methoxyphenylamine, *blue LEDs*, DMF, rt, 12 h, 81%; (f) Pd/C, H_2, EtOH, rt, 1 h; (g) CH_2=O, $HNMe_2$.HCl, NaOAc, AcOH, rt, 4 h, 88% (over 2 steps); (h) TFA, Me_2S, DCM, rt, 1 h; (i) $IrCl(CO)(PPh_3)_2$ (1 mol%), TMDS (2 eq), toluene, rt, 1 h, 40% (over 2 steps).

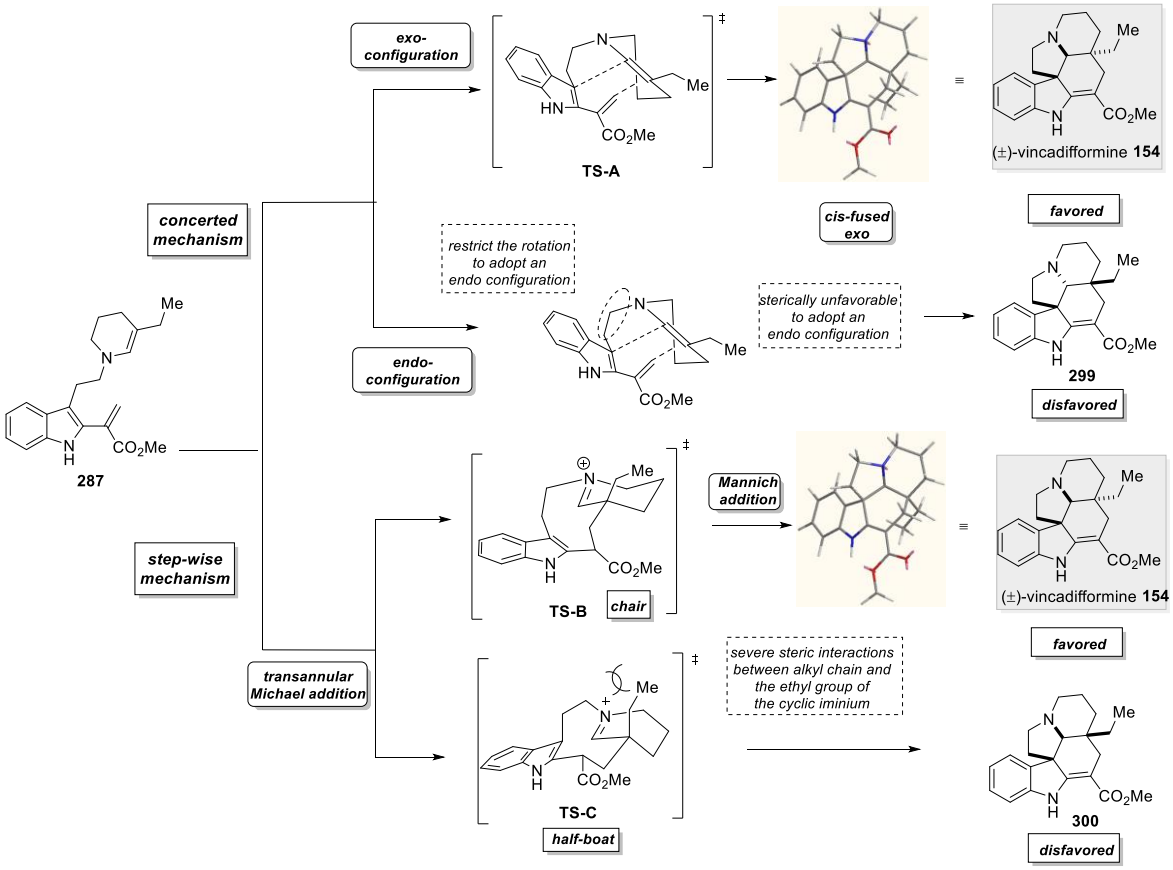
4.6.6 Stereochemical Aspects of the Inverse electron demand Intramolecular *Diels-Alder* Reaction (IMDA)

Since there are no obvious experimental methods to determine the mechanism of the inverse electron demand IMDA, we presumed that the enamine precursor **287** would either proceed *via* a stepwise Michael addition / Mannich addition cascade or a concerted pericyclic process to furnish the desired (±)-vincadifformine **154** as a single diastereomer (Scheme 70).

Through a concerted cycloaddition, the enamine precursor **287** would preferentially and selectively adopt an *exo*-transition-state **TS-A** towards the synthesis of *cis*-fused (±)-vincadifformine **154**. An *endo*-transition-state is highly disfavored due to the greater degree of steric buttressing between the incipient indole and the ethyl group. Moreover, the alkyl chain

(linking C2 of the indole moiety and the piperidine ring) restricts the rotation of the cyclic enamine adduct to adopt an *endo*-transition-state configuration. Therefore, the formation of the diasteromer **299** is highly unlikely.

On the other hand, it is also reasonable that the enamine precursor **287** could undergo a stepwise process to furnish the cis-fused (±)-vincadifformine **154**.[159] After the intramolecular Michael conjugate addition of the acrylate adduct, the cyclic iminium would either adopt a chair-like **TS-B** or a half-boat **TS-C** conformation to maintain a favorable orbital overlap (between the indole and the iminium) in the transition state during the Mannich closure. However, due to the severe steric interactions between the alkyl chain (linking C2 of the indole moiety and the piperidine ring) and the ethyl group, the formation of the half-boat conformation **TS-C** of the cyclic iminium in the transition state is highly disfavored. As such, formation of diastereomer **300** was not observed.



Scheme 70: Inverse electron demand IMDA *via* either a concerted or step-wise process. Chem3D minimized structure of 154 was provided.

4.6.7 Conclusion and Future work

In conclusion, a new and expeditious approach, for the divergent syntheses of a series of *Aspidosperma* alkaloids, namely (±)-vincaminorine **276**, (±)-*N*-methylquebrachamine **241**, (±)-quebrachamine **163**, (±)-minovine **146** and (±)-vincadifformine **154** that pivoted on the late-stage generation of reactive enamine functionality from the stable indole-linked lactam *via* an efficient and highly chemoselective iridium (I) catalyzed reduction, has been developed. This work built on our previous paper where it serves as an expansion of the concept of the reductive cyclisation to provide access to a range of important natural alkaloids with excellent diastereoselectivities. In this chapter, we demonstrated an intriguing one-pot reaction sequence that not only underscored the hypothesis of the newly formed labile secodine intermediate undergoing an inverse electron

demand IMDA to generate vincadifformine-type alkaloids but also provided invaluable insights into its stepwise nature and the potential biogenesis of skeletally distinct quebrachamine-type alkaloids *via* a competitive Michael addition/reduction of the secodine intermediate. To the best of our knowledge, this cascading series of reactions proceeding through an enamine Michael addition/reduction sequence in a single pot is the first example of its kind to provide efficient access to the quebrachamine-type alkaloids. Due to the insufficient full characterisation data available in the literature, we also elucidated the stereochemical configuration of the (±)-vincaminorine **276** by single crystal X-ray analysis. Control of the preference of the secodine intermediate to undergo either of the two reaction pathways was achieved through subtle modifications of the lactam indole precursors. To further delineate the versatility of our synthetic approach, an asymmetric synthesis of (+)-20-*epi*-ibophyllidine **298** is also described.

Since these alkaloids were synthesized as racemates, it will be important to develop strategies that could synthesize enantio-enriched natural products in a concise and direct manner. In the case of our method in accessing (±)-minovine **146**, addition of silica gel enhanced the electrophilicity of the acrylate moiety to facilitate the nucleophilic addition step by the enamine intermediate. As such, we postulate that the replacement of silica gel with the suitable chiral hydrogen-bond donor organocatalysts would allow the facile formal [4+2] *Diels-Alder* cycloaddition to proceed smoothly and at the same time, impart chirality in the final products. Investigations into the development of an enantioselective variant of this Ir(I)-catalyzed reductive cyclization sequence are currently ongoing and will be disclosed in due course.

Chapter 5: Experimental

5.1 General experimental

5.1.1 General techniques

Reactions were carried out under a nitrogen atmosphere in oven-dried glassware at room temperature (rt = 20-25 °C) unless otherwise stated. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Temperatures of 0 °C and −78 °C were obtained using an ice-bath and a dry-ice/acetone bath respectively. Reflux conditions were obtained using an oil-bath equipped with a thermometer. When reaction temperatures are quoted, these refer to the temperature of the oil-bath.

5.1.2 Compound naming

Compound names are those generated by ChemDraw Professional 16.0 software following IUPAC nomenclature.

5.1.3 Solvents & Reagents

All reagents purchased from commercial sources were used as received. Organic solvents were evaporated under reduced pressure using a Büchi rotary evaporator. All solvents were used directly as received from commercial suppliers. Petroleum ether (PE) refers to the 40 - 60 °C fraction of distilled light petroleum. Anhydrous solvents were dried by passing through a Glass Contour Solvent Purification System Model-AOCSOLCOL. Brine refers to a saturated aqueous solution of NaCl. Reagents used were obtained from commercial suppliers and used without purification. Na_2SO_4 refers to anhydrous sodium sulphate.

5.1.4 Chromatography

Thin layer chromatography (TLC) analyses were performed using Merck silica gel 60 F_{254} (230-400 mesh) fluorescent treated silica plates and visualised under UV light and/or stained with aqueous potassium permanganate solutions as appropriate. Flash column chromatography (FCC) was carried out on Merck Kieselgel (230-400 mesh) and Macheney-nagel silica 60M (0.04 – 0.063 mm).

5.1.5 Spectroscopy & Instrument

All ^{1}H and ^{13}C NMR spectra were recorded using a Bruker 500 MHz and Bruker 400 MHz spectrometers against a residual solvent peak as an internal standard. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz).

^{1}H NMR spectra are reported as follows: δ/ppm (multiplicity, coupling constant(s) *J*/Hz, number of protons, assignment). Multiplicity is abbreviated as follows: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, dt = doublet of triplets, q = quartet, dq = doublet of quartets, quin = quintet, sept = septet m = multiplet; "app" is used to denote the apparent splitting of a signal. ^{13}C NMR spectra are reported in δ/ppm. Two-dimensional NMR spectroscopy experiments (COSY, HSQC, HMBC) were used to assist in the assignment of signals in ^{1}H and ^{13}C NMR spectra.

IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer from a thin film or from a compressed sample of the solid, and only selected maximum absorbances (ν_{max}) of the most intense peaks are reported (cm^{-1}).

High resolution mass spectra were recorded on a Bruker MicroTof mass spectrometer (equipped with an ESI source unless otherwise stated).

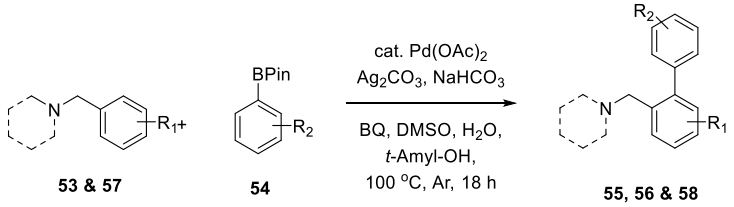
Melting points were recorded using a Leica Galen III hot-stage microscope apparatus or Büchi Melting Point B-540 apparatus and are reported uncorrected in degrees Celsius (°C).

Photoredox reactions for the synthesis of **10**, **11**, **12** and **28** were carried out with the use of blue leds strips. (EC Technology® 12V/ 5A 60W Waterproof LED Flexible Light Strip)

Specific rotations were recorded using an Optical Activity AA-1000 polarimeter; $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentration (c) is given in g/100 ml; measured at 589 nm.

5.2 Experimental Chapter 2

5.2.1 General Procedure A: Synthesis of Compounds 55, 56 & 58

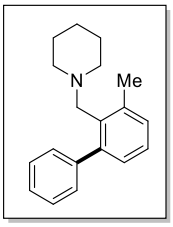


A microwave vial (10 mL) containing a stir bar was charged with benzylpiperidine (**53** and **57)** (0.5 mmol, 1 equiv), Ag_2CO_3 (275.0 mg, 1.0 mmol, 2 equiv), $NaHCO_3$ (168.0 mg, 2.0 mmol, 4 equiv), 1,4 benzoquinone (27.0 mg, 0.25 mmol, 0.5 equiv), aryl-BPin **54** (0.7 mmol, 1.4 equiv) and $Pd(OAc)_2$ (11.3 mg, 0.05 mmol, 10 mol%). The vial was evacuated and backfilled with Ar thrice and a solution mixture of DMSO (12.5 µL), H_2O (50 µL) and *t*-amylOH (2.5 mL) was then added. The vial was then sealed and the reaction mixture was allowed to stir at 100 ^oC for 18 hours. The reaction mixture was allowed to cool down to room temperature, then diluted with EtOAc and filtered through a pad of Celite, washing with EtOAc. The solvent was removed *in vacuo* and crude mixture was then filtered over basic alumina with 1:9 mixture of ethyl acetate and petroleum ether (200 mL) and filtrate was concentrated *in vacuo*, and the resulting mixture was purified *via* basified flash column chromatography (DCM/NEt_3 = 100/0 to 99/1). TLC analysis ($DCM/MeOH/NEt_3$= 94/5/1): R_f was reported within the range of 0.35 – 0.45.

Starting materials (Ar-Pin & benzylic heterocycles) were synthesised by Maxwell Haughley and their synthesis and characterization will not be disclosed in this chapter.

5.2.2 Synthesis & Characterization of Compounds 55.

55a: 1-((3-Methyl-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **55a** was isolated as a white solid (107 mg, 81%).

MP 56-57 ^{o}C

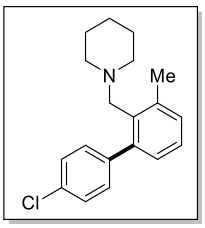
IR (film) 2931, 1498, 1092, 831, 785 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 3H, Ar-H), 7.39 – 7.34 (m, 2H, Ar-H), 7.28 – 7.24 (m, 2H, Ar-H), 7.12 (dd, *J* = 6.0, 3.0 Hz, 1H, Ar-H), 3.45 (s, 2H, NCH_2Ar), 2.59 (s, 3H, Ar-CH_3), 2.20 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.52 – 1.43 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.42 – 1.33 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 142.5, 139.2, 134.8, 129.9, 129.6, 127.6, 127.5, 126.4, 126.3, 56.9, 53.9, 26.2, 24.4, 20.2.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{24}N$) requires *m/z* 266.1903, found *m/z* 266.1899.

55b: 1-((4'-Chloro-3-methyl-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 4-chlorophenylboronic acid pinacol ester **54b** (166.7 mg, 0.7 mmol). **55b** was isolated as a colourless oil (111 mg, 74%).

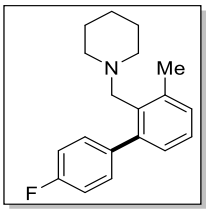
IR (film) 2932, 1492, 1090, 834, 782 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.36 (m, 2H, Ar-H), 7.33–7.28 (m, 2H, Ar-H), 7.25–7.21 (m, 2H, Ar-H), 7.07–7.01 (m, 1H, Ar-H), 3.36 (s, 2H, NCH_2Ar), 2.54 (s, 3H, Ar-CH_3), 2.18 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.50–1.40 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.39-1.32 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 142.6, 141.0, 139.2, 134.8, 132.5, 131.2, 129.8, 127.6, 127.5, 126.4, 56.8, 53.9, 26.2, 24.4, 20.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}ClN$) requires *m/z* 300.1514, found *m/z* 300.1507.

55c: 1-((4'-Fluoro-3-methyl-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 4-fluorophenylboronic acid pinacol ester **54c** (155.5 mg, 0.7 mmol). **55c** was isolated as a colourless oil (108 mg, 76%).

IR (film) 2933, 1510, 1464, 839, 783 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.28 (m, 2H, Ar-H), 7.26 – 7.19 (m, 2H, Ar-H), 7.16 – 7.01 (m, 3H, Ar-H), 3.37 (s, 2H, NCH_2Ar), 2.55 (s, 3H, Ar-CH_3), 2.18 (br. m, 4H,

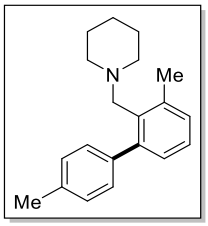
$CH_2CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 1.52–1.41 (m, 4H, $CH_2C\underline{H_2}CH_2NCH_2C\underline{H_2}$), 1.40-1.32 (m, 2H, $C\underline{H_2}CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.8 (d, J_{C-F} = 245.0 Hz), 142.8, 139.1, 138.4 (d, J_{C-F} = 3.4 Hz), 135.0, 131.4 (d, J_{C-F} = 7.8 Hz), 129.7, 127.7, 126.4, 114.3 (d, J_{C-F} = 21.1 Hz), 56.8, 53.9, 26.2, 24.5, 20.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ -116.63.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}FN$) requires *m/z* 284.1809, found *m/z* 284.1803.

55d: 1-((3,4'-Dimethyl-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 4-methylphenylboronic acid pinacol ester **54d** (152.7 mg, 0.7 mmol). **55d** was isolated as a colourless oil (108 mg, 77%).

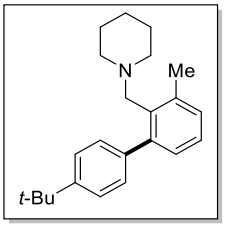
IR (film) 2933, 1514, 1264, 1099, 728 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.16 (m, 6H, Ar-H), 7.03 (dd, *J* = 5.5, 3.0 Hz, 1H, Ar-H), 3.38 (s, 2H, $NC\underline{H_2}Ar$), 2.51 (s, 3H, Ar-$C\underline{H_3}$), 2.42 (s, 3H, Ar-$C\underline{H_3}$), 2.15 (br. m, 4H, $CH_2CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 1.50–1.36 (m, 4H, $CH_2C\underline{H_2}CH_2NCH_2C\underline{H_2}$), 1.35-1.25 (m, 2H, $C\underline{H_2}CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.7, 139.6, 139.2, 136.0, 134.9, 129.8, 129.4, 128.2, 127.7, 126.3, 57.0, 53.9, 26.2, 24.5, 21.2, 20.2.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{26}N$) requires *m/z* 280.2060, found *m/z* 280.2055.

55e: 1-((4'-(*t*-Butyl)-3-methyl-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 4-*t*-butylphenylboronic acid pinacol ester **54e** (182.1 mg, 0.7 mmol). **55e** was isolated as a white solid (112 mg, 70%).

MP 107-108 ^oC.

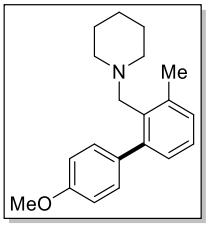
IR (film) 2932, 1511, 1463, 862, 782 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.22 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.19 – 7.14 (m, 2H, Ar-H), 7.05 (dd, *J* = 6.5, 2.5 Hz, 1H, Ar-H), 3.38 (s, 2H, NCH_2Ar), 2.51 (s, 3H, Ar-CH_3), 2.14 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.44 – 1.36 (m, 13H, $CH_2CH_2CH_2NCH_2CH_2$, $ArC(CH_3)_3$), 1.36 – 1.24 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.2, 143.7, 139.5, 139.1, 135.1, 129.5, 129.4, 127.7, 126.2, 124.3, 56.9, 53.9, 34.5, 31.5, 26.2, 24.5, 20.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{32}N$) requires *m/z* 322.2529, found *m/z* 322.2524.

55f: 1-((4'-Methoxy-3-methyl-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 4-methoxyphenylboronic acid pinacol ester **54f** (187.3 mg, 0.8 mmol). **55f** was isolated as a white solid (91 mg, 62 %).

MP 80-81 ^{o}C.

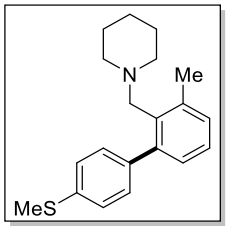
IR (film) 2932, 1610, 1463, 852, 783 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.20 (m, 2H, Ar-H), 7.19 – 7.14 (m, 2H, Ar-H), 7.03 (dd, *J* = 6.5, 2.5 Hz, 1H, Ar-H), 6.95 – 6.89 (m, 2H, Ar-H), 3.87 (s, 3H, Ar-OCH_3), 3.36 (s, 2H, NCH_2Ar), 2.50 (s, 3H, Ar-CH_3), 2.14 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.47 – 1.36 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.35 – 1.25 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.2, 143.4, 139.2, 135.1, 135.0, 131.0, 129.4, 127.8, 126.3, 112.9, 56.9, 55.2, 53.9, 26.2, 24.5, 20.2.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{26}NO$) requires *m/z* 296.2009, found *m/z* 296.2004.

55g: 1-((3-methyl-4'-(methylthio)-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 4-thiomethylphenylboronic acid pinacol ester **54g** (175.1 mg, 0.7 mmol). **55g** was isolated as a white solid (67 mg, 43 %).

MP 84 – 85 ^{o}C.

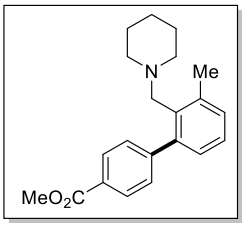
IR (film) 2930, 1600, 1495, 1117, 781 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.21 (m, 4H, Ar-H), 7.21 – 7.15 (m, 2H, Ar-H), 7.02 (dd, *J* = 6.0, 3.0 Hz, 1H, Ar-H), 3.36 (s, 2H, NCH_2Ar), 2.54 (s, 3H, Ar-SCH_3), 2.50 (s, 3H, Ar-CH_3), 2.14 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.47 – 1.35 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.35 – 1.26 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.2, 139.4, 139.2, 136.3, 134.9, 130.4, 129.6, 127.6, 126.4, 125.7, 56.9, 53.9, 26.2 24.4, 20.2, 15.9.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{26}NS$) requires *m/z* 312.1781, found *m/z* 312.1777.

55h: Methyl 3'-methyl-2'-(piperidin-1-ylmethyl)-[1,1'-biphenyl]-4-carboxylate



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 4-methoxycarbonylphenylboronic acid pinacol ester **54h** (183.5 mg, 0.7 mmol). **55h** was isolated as a white solid (131 mg, 81%)

MP 56 – 58 ^{o}C.

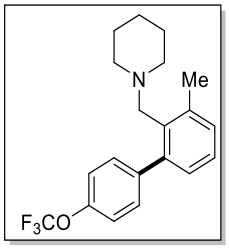
IR (film) 2933, 1723, 1609, 1435, 861, 770 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.38 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.23 – 7.15 (m, 2H, Ar-H), 7.05 – 6.95 (m, 1H, Ar-H), 3.95 (s, 3H, Ar-CO_2CH_3), 3.32 (s, 2H, NCH_2Ar), 2.49 (s, 3H, Ar-CH_3), 2.10 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.42 - 1.33 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.32 – 1.23 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.2, 147.6, 142.8, 139.2, 134.7, 130.0, 129.9, 128.8, 128.2, 127.3, 126.5, 56.8, 53.8, 52.1, 26.1, 24.4, 20.2.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{26}NO_2$) requires *m/z* 324.1958, found *m/z* 324.1949.

55i: 1-((3-Methyl-4'-(trifluoromethoxy)-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 4-trifluoroetherphenylboronic acid pinacol ester **54j** (201.7 mg, 0.7 mmol). **55i** was isolated as a colourless oil (132 mg, 76%).

IR (film) 2934, 1510, 1465, 851, 782 cm^{-1}.

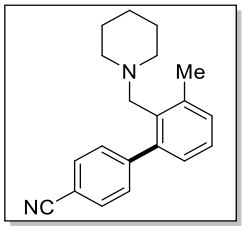
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, 2H, *J* = 9.0 Hz, Ar-H), 7.25 – 7.16 (m, 4H, Ar-H), 7.04 – 7.00 (m, 1H, Ar-H), 3.31 (s, 2H, NCH_2Ar), 2.49 (s, 3H, Ar-CH_3), 2.12 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.46 – 1.21 (m, 6H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 148.0, 142.5, 141.3, 139.1, 134.9, 131.2, 129.9, 127.6, 126.5, 120.6 (q, J_{C-F} = 21.1 Hz), 119.9, 56.7, 53.8, 26.1, 24.4, 20.3.

^{19}F NMR (377 MHz, $CDCl_3$): -57.76

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{23}F_3NO$) requires *m/z* 350.1726, found *m/z* 350.1720.

55j: 3'-Methyl-2'-(piperidin-1-ylmethyl)-[1,1'-biphenyl]-4-carbonitrile



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 4-cyanophenylboronic acid pinacol ester **54j** (160.4 mg, 0.7 mmol). **55j** was isolated as a white solid (96 mg, 66%).

MP 80-81 ºC.

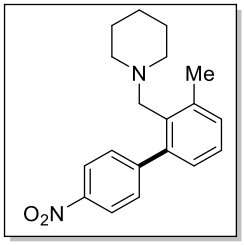
IR (film) 2932, 2227, 1606, 1505, 1465, 844, 783 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.44 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.21 (d, *J* = 4.5 Hz, 2H, Ar-H), 6.98 (t, *J* = 4.5 Hz, 1H, Ar-H), 3.28 (s, 2H, NCH_2Ar), 2.48 (s, 3H, Ar-CH_3), 2.10 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.40 – 1.23 (m, 6H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.7, 142.1, 139.1, 134.6, 131.3, 130.5, 130.4, 127.2, 126.6, 119.2, 110.3, 56.6, 53.8, 26.1, 24.3, 20.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{23}N_2$) requires *m/z* 291.1856, found *m/z* 291.1851.

55k: 1-((3-Methyl-4'-nitro-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 4-nitrophenylboronic acid pinacol ester **54k** (174.4 mg, 0.7 mmol). **55k** was isolated as a solid (84 mg, 54%).

MP 90 - 92 ^{o}C.

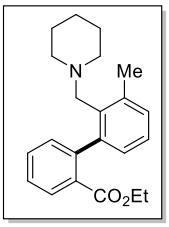
IR (film) 2933, 1598, 1459, 857, 785 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.51 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.23 (d, *J* = 4.5 Hz, 2H, Ar-H), 7.00 (t, *J* = 4.5 Hz, 1H, Ar-H), 3.30 (s, 2H, NCH_2Ar), 2.48 (s, 3H, Ar-CH_3), 2.11 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.51 – 1.17 (m, 6H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.9, 146.6, 141.7, 139.1, 134.6, 130.6, 130.5, 127.3, 126.7, 122.7, 56.7, 53.8, 26.1, 24.3, 20.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}N_2O_2$) requires *m/z* 311.1754, found *m/z* 311.1750.

55l: Ethyl 3'-methyl-2'-(piperidin-1-ylmethyl)-[1,1'-biphenyl]-2-carboxylate



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 2-ethoxycarbonylphenylboronic acid pinacol ester **54l** (193.3 mg, 0.7 mmol). **55l** was isolated as a colourless oil (128 mg, 76%).

IR (film) 2933, 1719, 1465, 862, 784 cm^{-1}.

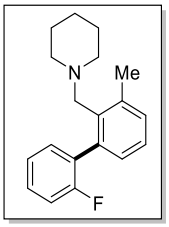
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 – 7.98 (m, 2H, Ar-H), 7.51 (dt, *J* = 7.5, 1.5 Hz, 1 H, Ar-H), 7.44 (t, *J* = 8.0, 1H), 7.22 – 7.17 (m, 2H), 7.03 (dd, *J* = 5.5, 3.5 Hz, 1H), 4.38 (q, *J* = 7.0Hz, 2H, Ar-$CO_2CH_2CH_3$), 3.30 (s, 2H, NCH_2Ar), 2.49 (s, 3H, Ar-CH_3), 2.12 (br. m, 4H,

$CH_2CH_2C\underline{H_2}N\underline{CH_2}CH_2$), 1.48 – 1.33 (m, 4H, $CH_2C\underline{H_2}CH_2NCH_2C\underline{H_2}$), 1.39 (t, 7.0 Hz, 3H, Ar-$CO_2CH_2C\underline{H_3}$), 1.34 – 1.24 (m, 2H, $C\underline{H_2}CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 142.9, 142.7, 139.0, 134.9, 134.2, 131.0, 129.9, 129.6, 127.7, 127.6, 127.5, 126.4, 60.9, 56.8, 53.8, 26.1, 24.4, 20.3, 14.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{28}NO_2$) requires *m/z* 338.2115, found *m/z* 338.2105.

55m: 1-((2'-Fluoro-3-methyl-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 2-fluorophenylboronic acid pinacol ester **54m** (155.5 mg, 0.7 mmol). **55m** was isolated as a white solid (28 mg, 20%).

MP 74 - 76 ^oC.

IR (film) 2931, 1512, 838, 782 cm^{-1}.

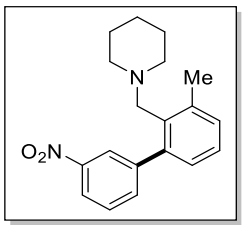
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.29 (m, 1H, Ar-H), 7.26 – 7.19 (m, 3H, Ar-H), 7.16 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.10 (t, *J* = 9.0 Hz, 1H, Ar-H), 7.05 – 6.99 (m, 1H, Ar-H), 3.40 (d, *J* = 12.5 Hz, 1H, NCH_ACH_BAr), 3.19 (d, *J* = 12.5 Hz, 1H, NCH_ACH_BAr), 2.50 (s, 3H, Ar-CH_3), 2.08 (br. m, 4H, $CH_2CH_2C\underline{H_2}N\underline{CH_2}CH_2$), 1.41 – 1.32 (m, 4H, $CH_2C\underline{H_2}CH_2NCH_2C\underline{H_2}$), 1.31 - 1.24 (m, 2H, $C\underline{H_2}CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.7 (d, J_{C-F} = 244.3 Hz), 139.0, 136.9, 135.8, 131.9 (d, J_{C-F} = 3.5 Hz), 130.3, 130.0 (d, J_{C-F} = 16.7 Hz), 128.7 (d, J_{C-F} = 8.0 Hz), 127.7, 126.4, 123.4 (d, J_{C-F} = 3.4 Hz), 115.0 (d, J_{C-F} = 22.5 Hz), 57.5, 53.9, 26.1, 24.4, 20.1.

^{19}F NMR (377 MHz, $CDCl_3$): δ -114.40.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}NF$) requires *m/z* 284.1809, found *m/z* 284.1803.

55o: 1-((3-Methyl-3'-nitro-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 3-nitrophenylboronic acid pinacol ester **54o** (174.4 mg, 0.7 mmol). **55o** was isolated as a yellow solid (90 mg, 58%).

MP 88 – 90 ºC.

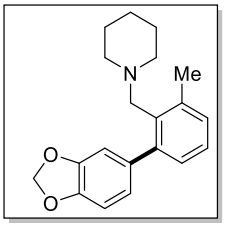
IR (film) 2933, 1526, 1459, 886, 783 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (t, *J* = 2.0 Hz, 1H, Ar-H), 8.20 (ddd, *J* = 8.0, 2.5, 1.0 Hz, 1H, Ar-H), 7.67 (dt, *J* =7.5, 1.2 Hz, 1H, Ar-H), 7.53 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.24 – 7.20 (m, 2H, Ar-H), 7.04 (t, *J* = 4.5 Hz, 1 H, Ar-H), 3.27 (s, 2H, NCH_2Ar), 2.48 (s, 3H, Ar-CH_3), 2.14 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.44 – 1.23 (m, 6H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.4, 144.2, 141.6, 138.9, 135.9, 134.8, 130.4, 128.2, 127.7, 126.8, 125.0, 121.6, 56.6, 53.7, 26.1, 24.4, 20.4.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{23}N_2O_2$) requires *m/z* 311.1754, found *m/z* 311.1748.

55p: 1-(2-(Benzo[*d*][1,3]dioxol-5-yl)-6-methylbenzyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 3,4-methylenedioxyphenylboronic acid pinacol ester **54p** (173.7 mg, 0.7 mmol). **55p** was isolated as a white solid (97 mg, 63 %).

MP 56 – 58 ^{o}C**.**

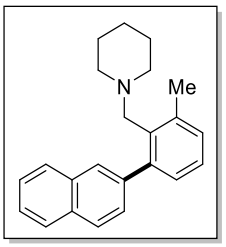
IR (film) 2933, 1490, 1223, 1038, 815, 738 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 – 7.14 (m, 2H, Ar-H), 7.04 – 7.00 (m, 1H, Ar-H), 6.85 (d, *J* = 1.5 Hz, 1H, Ar-H), 6.83 (d, *J* = 8.0 Hz, 1H, Ar-H), 6.73 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-H), 6.01 (s, 1H, OCH_2O), 3.36 (s, 2H, NCH_2Ar), 2.49 (s, 3H, Ar-CH_3), 2.16 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.49 – 1.38 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.36 – 1.28 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.8, 146.1, 143.3, 139.2, 136.4, 135.1, 129.5, 127.7, 126.3, 123.2, 110.7, 107.5, 100.9, 56.9, 53.9, 26.2, 24.5, 20.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{24}O_2N$) requires *m/z* 310.1802, found *m/z* 310.1798.

55q: 1-(2-Methyl-6-(naphthalen-2-yl)benzyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 2-naphthylboronic acid pinacol ester **54q** (203.3 mg, 0.8 mmol). **55q** was isolated as a white solid (118 mg, 75%)

MP 96 – 98 ^{o}C.

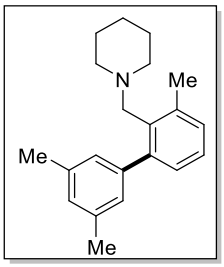
IR (film) 3053, 2931, 1503, 1456, 894, 783 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.83 (m, 3H, Ar-H), 7.80 (s, 1H, Ar-H), 7.58 – 7.43 (m, 3H, Ar-H), 7.25 – 7.19 (m, 2H, Ar-H), 7.17 – 7.10 (m, 1H, Ar-H), 3.41 (s, 2H, NCH_2Ar), 2.54 (s, 3H, Ar-CH_3), 2.13 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.49 – 1.34 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.33 – 1.19 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.7, 140.1, 139.2, 135.0, 133.0, 132.1, 129.7, 128.7, 128.4, 128.0, 127.8, 127.6, 126.8, 126.4, 126.0, 125.7, 57.1, 53.8, 26.2, 24.4, 20.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{26}N$) requires *m/z* 316.2060, found *m/z* 316.2052.

55r: 1-((3,3',5'-trimethyl-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 3,5-dimethylphenylboronic acid pinacol ester **54r** (162.5 mg, 0.7 mmol). **55r** was isolated as a colourless oil (113 mg, 77%).

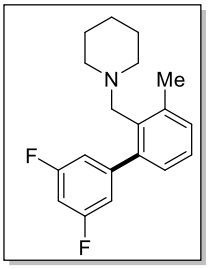
IR (film) 2931, 1602, 1466, 851, 782 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 – 7.12 (m, 2H, Ar-H), 7.03 (dd, *J* = 6.5, 2.5 Hz, 1H, Ar-H), 6.99 – 6.96 (m, 1H, Ar-H), 6.94 (s, 2H, Ar-H), 3.36 (s, 2H, NCH_2Ar), 2.50 (s, 3H, Ar-CH_3), 2.36 (s, 6H, Ar-CH_3, Ar-CH_3), 2.17 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.48 – 1.38 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.36 – 1.28 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.0, 142.4, 139.1, 136.8, 134.8, 129.4, 128.0, 127.8, 127.5, 126.2, 57.0, 53.9, 26.3, 24.5, 21.4, 20.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{28}N$) requires *m/z* 294.2216, *m/z* found 294.2210.

55s: 1-((3',5'-Difluoro-3-methyl-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 3,5-difluorophenylboronic acid pinacol ester **54s** (168.1 mg, 0.7 mmol). **55s** was isolated as a colourless oil (91 mg, 60 %)

IR (film) 2933, 1623, 1454, 859, 783 cm^{-1}.

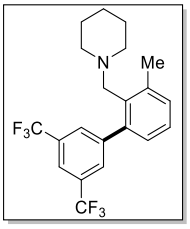
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.15 (m, 2H, Ar-H), 7.01 (t, *J* = 4.5 Hz, 1H, Ar-H), 6.95 – 6.89 (m, 2H, Ar-H), 6.78 (tt, *J* = 9.0, 2.5 Hz, 1H, Ar-H), 3.31 (s, 2H, NCH_2Ar), 2.48 (s, 3H, Ar-CH_3), 2.17 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.48 – 1.39 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.38 – 1.28 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.2 (dd, J_{C-F} = 247.5, 13.0 Hz), 145.9 (t, J_{C-F} = 9.7 Hz), 141.7 (t, J_{C-F} = 1.9 Hz), 139.1, 134.7, 130.2, 127.3, 126.6, 113.6 – 112.4 (m), 101.9 (t, J_{C-F} = 25.3 Hz), 56.7, 53.8, 26.2, 24.4, 20.3.

^{19}F NMR (377 MHz, $CDCl_3$): -111.42.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{22}NF_2$) requires *m/z* 302.1715, found *m/z* 302.1710.

55t: 1-((3-Methyl-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)piperidine **53a** (95.0 mg, 0.5 mmol) and 3,5-bis(trifluoromethylphenyl)boronic acid pinacol ester **54t** (238.1 mg, 0.7 mmol). **55t** was isolated as a colourless oil (86 mg, 43%).

IR (film) 2937, 1379, 1275, 1128, 896, 783 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 2H, Ar-H), 7.84 (s, 1H, Ar-H), 7.28 – 7.20 (m, 2H, Ar-H), 7.09 – 6.99 (m, 1H, Ar-H), 3.24 (s, 2H, NCH_2Ar), 2.46 (s, 3H, Ar-CH_3), 2.17 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.42 – 1.27 (m, 6H, $CH_2CH_2CH_2NCH_2CH_2$).

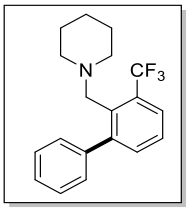
^{13}C NMR (101 MHz, $CDCl_3$): δ 144.7, 141.3, 138.7, 134.8, 130.6, 130.5 (q, J_{C-F} = 36.3 Hz), 129.9 (d, J_{C-F} = 3.1 Hz), 128.0, 126.9, 123.6 (q, J_{C-F} = 273.7 Hz), 120.3, 56.5, 53.6, 25.9, 24.4, 20.6.

^{19}F NMR (377 MHz, $CDCl_3$): -62.62.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{22}NF_6$) requires *m/z* 402.1651, found *m/z* 402.1645.

5.2.3 Synthesis & Characterization of Compounds 56

56a: 1-((3-(Trifluoromethyl)-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-(trifluoromethyl)benzyl)piperidine **53b** (121.6 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **56a** was isolated as a pale yellow oil (117 mg, 73 %)

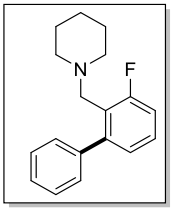
IR (film) 2934, 1320, 1119, 760, 646 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 – 7.52 (m, 1H, Ar-H), 7.35 – 7.25 (m, 5H, Ar-H), 7.23 – 7.17 (m, 2H, Ar-H), 3.44 (d, J = 1.0 Hz, 2H, NCH_2Ar), 1.96 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.16 (m, 6H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.9, 142.0, 136.7, 133.8, 130.0 (q, J_{C-F} = 29.4 Hz), 129.0, 127.6, 126.7, 126.5, 125.2, 124.7 (q, J_{C-F} = 273.3 Hz), 55.7, 53.6, 25.9, 24.3. **^{19}F NMR** (377 MHz, $CDCl_3$): -57.18.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{21}NF_3$) requires *m/z* 320.1621, *m/z* found 320.1614.

56b: 1-((3-Fluoro-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-fluorobenzyl)piperidine **53c** (96.6 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **56b** was isolated as a yellow oil (64 mg, 48%).

IR (film) 2932, 1464, 1153, 759, 700 cm^{-1}.

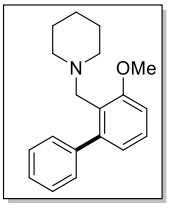
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 8.0, 1.5 Hz, 2H, Ar-H), 7.39 – 7.28 (m, 3H, Ar-H), 7.22 (dt, *J* = 5.5, 2.0 Hz, 1H, Ar-H), 7.05 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar-H), 6.99 (ddd, *J* = 9.5, 8.0, 1.0 Hz, 1H, Ar-H), 3.31 (d, *J* = 2.5 Hz, 2H, NCH_2Ar), 2.23 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.48 – 1.37 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.36 – 1.25 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.9 (d, J_{C-F} = 245.5 Hz), 146.1 (d, J_{C-F} = 4.0 Hz), 140.6 (d, J_{C-F} = 2.7 Hz), 129.9, 128.1 (d, J_{C-F} = 9.5 Hz), 127.6, 127.1, 125.9 (d, J_{C-F} = 3.0 Hz), 123.8 (d, J_{C-F} = 14.5 Hz), 113.9 (d, J_{C-F} = 23.9 Hz), 53.7, 52.7, 26.1, 24.3.

^{19}F NMR (377 MHz, $CDCl_3$): -114.87.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{21}NF$) requires *m/z* 270.1653, found *m/z* 270.1647.

56c: 1-((3-Methoxy-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2-methoxybenzyl)piperidine **53d** (102.6 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **56c** was isolated as a yellow oil (62 mg, 44%).

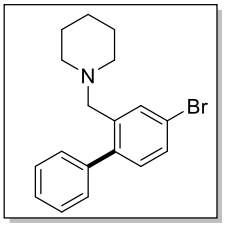
IR (film) 2930, 1581, 1498, 1205, 759, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.39 – 7.21 (m, 4H, Ar-H), 6.94 – 6.84 (m, 2H, Ar-H), 3.84 (s, 3H, Ar-OCH_3), 3.35 (s, 2H, NCH_2Ar), 2.23 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.49 – 1.37 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.36 – 1.27 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.6, 145.5, 141.9, 130.0, 127.6, 127.4, 126.6, 125.3, 122.9, 113.9, 55.8, 53.7, 52.8, 26.2, 24.5.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{24}NO$) requires *m/z* 282.1852, found *m/z* 282.1844.

56d: 1-((4-Bromo-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(3-bromobenzyl)piperidine **53e** (126.5 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **56d** was isolated as a yellow oil (36 mg, 22%).

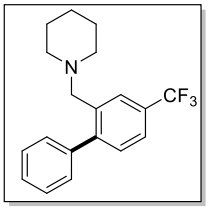
IR (film) 2933, 1468, 1123, 763, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 2.0 Hz, 1H, Ar-H), 7.44 – 7.30 (m, 6H, Ar-H), 7.10 (d, *J* = 8.0 Hz, 1H, Ar-H), 3.32 (s, 2H, NCH_2Ar), 2.28 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.60 – 1.49 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.44 – 1.36 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 141.2, 140.4, 138.9, 132.3, 131.5, 129.5, 129.3, 127.9, 127.1, 121.3, 60.1, 54.3, 26.0, 24.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{21}NBr$) requires *m/z* 330.0852, 332.0831, found *m/z* 330.0846, 332.0822.

56e: 1-((4-(Trifluoromethyl)-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(3-trifluorobenzyl)piperidine **53f** (121.6 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **56e** was isolated as a yellow oil (44 mg, 28%).

IR (film) 2935, 1327, 1163, 1120, 768, 701 cm^{-1}.

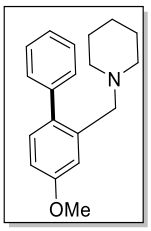
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1H, Ar-H), 7.54 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.48 – 7.31 (m, 6H, Ar-H), 3.37 (s, 2H, NCH_2Ar), 2.28 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.61 – 1.48 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.44 – 1.32 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 145.8, 140.2 137.6, 130.3, 129.3 (q, J_{C-F} = 32.4 Hz), 129.2, 128.0, 127.4, 126.4 (q, J_{C-F} = 3.7 Hz), 124.4 (q, J_{C-F} = 272.6 Hz), 123.6 (q, J_{C-F} = 3.8 Hz), 60.1, 54.3, 26.0, 24.3.

^{19}F NMR (377 MHz, $CDCl_3$): - 62.26.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{21}NF_3$) requires *m/z* 320.1621, found *m/z* 320.1613.

56f: 1-((4-Methoxy-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(3-methoxybenzyl)piperidine **53g** (102.6 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **56f** was isolated as a yellow oil (38 mg, 27%); **56f'** was isolated as a white solid (22 mg, 12 %). **56f** was separated from a mixture of **56f** and SM **53g** using prep HPLC (Hexane/IPA= 95/5), 15 mL/ min, 60 mins.

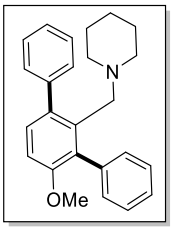
IR (film) 2933, 1607, 1492, 1274, 1051, 766, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.29 (m, 5H, Ar-H), 7.18 (d, *J* = 2.5 Hz, 1H, Ar-H), 7.16 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.84 (dd, *J* = 8.5, 3.0 Hz, 1H, Ar-H), 3.86 (s, 3H, Ar-OCH_3), 3.34 (s, 2H, NCH_2Ar), 2.29 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.57 – 1.45 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.42 - 1.31 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): 158.7, 141.3, 137.9, 135.0, 130.9, 129.7, 127.8, 126.4, 114.7, 111.9, 60.6, 55.3, 54.3, 26.1, 24.4.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{24}NO$) requires *m/z* 282.1852, found *m/z* 282.1845.

56f': 1-((4'-Methoxy-[1,1':3',1"-terphenyl]-2'-yl)methyl)piperidine



MP 86 – 87 ºC.

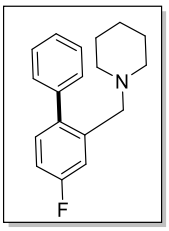
IR (film) 2931, 1593, 1493, 1337, 1204, 859, 771, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.27 (m, 10H, Ar-H), 7.21 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.95 (d, *J* = 8.5 Hz, 1H, Ar-H), 3.75 (s, 3H, Ar-OCH_3), 3.14 (s, 2H, NCH_2Ar), 1.79 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.22 – 1.07 (m, 6H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): 156.0, 142.7, 137.7, 136.6, 136.6, 132.6, 130.7, 129.9, 129.8, 127.4, 127.3, 126.4, 126.1, 109.1, 56.3, 55.8, 53.3, 25.9, 24.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{25}H_{28}NO$) requires *m/z* 358.2165, found *m/z* 358.2157.

56g: 1-((4-Fluoro-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(3-fluorobenzyl)piperidine **53h** (96.6 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **56g** was isolated as a yellow oil (19 mg, 14%); **56g'** was isolated as a white solid (60 mg, 35 %). **56g** was separated from a mixture of **56g** and SM **53h** using prep TLC (EA/PE = 1/19).

IR (film) 2934, 1610, 1480, 1266, 765, 700 cm^{-1}.

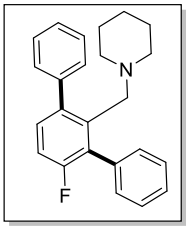
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 – 7.27 (m, 6H, Ar-H), 7.18 (dd, *J* = 8.5, 6.0 Hz, 1H, Ar-H), 6.96 (td, *J* = 8.5, 3.0 Hz, 1H, Ar-H), 3.33 (s, 2H, NCH_2Ar), 2.28 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.58 – 1.46 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.44 - 1.33 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.2 (d, J_{C-F} = 245.0 Hz), 140.6, 139.2 (d, J_{C-F} = 5.2 Hz), 138.1 (d, J_{C-F} = 3.0 Hz), 131.3 (d, J_{C-F} = 7.9 Hz), 129.6, 127.9, 126.9, 115.8 (d, J_{C-F} = 21.9 Hz), 113.2 (d, J_{C-F} = 21.3 Hz), 60.3, 54.4, 26.1, 24.3.

^{19}F NMR (377 MHz, $CDCl_3$): -115.76.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{21}NF$) requires *m/z* 270.1653, found *m/z* 270.1645.

56g': 1-((4'-Fluoro-[1,1':3',1"-terphenyl]-2'-yl)methyl)piperidine



MP 110 – 111 °C.

IR (film) 2932, 1603, 1465, 1251, 763, 700 cm^{-1}.

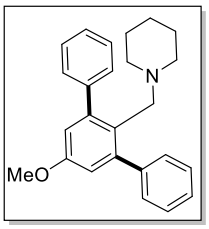
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 – 7.30 (m, 10H, Ar-H), 7.19 (dd, *J* = 8.5, 6.0 Hz, 1H, Ar-H), 7.08 (dd, *J* = 8.5, 6.0 Hz, 1H, Ar-H), 3.18 (s, 2H, NCH_2Ar), 1.80 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.22 – 1.07 (m, 6H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.0 (d, J_{C-F} = 243.4 Hz), 141.9, 139.8 (d, J_{C-F} = 3.4 Hz), 137.5 (d, J_{C-F} = 2.2 Hz), 135.1, 131.0 (d, J_{C-F} = 16.0 Hz), 130.4, 130.2 (d, J_{C-F} = 8.3 Hz), 129.8, 127.6, 127.5, 127.1, 126.6, 113.5 (d, J_{C-F} = 23.2 Hz), 56.1, 53.3, 25.9, 24.2.

^{19}F NMR (377 MHz, $CDCl_3$): -115.50.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{24}H_{25}NF$) requires *m/z* 346.1966, found *m/z* 346.1959.

56h': 1-((5'-Methoxy-[1,1':3',1"-terphenyl]-2'-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(4-methoxybenzyl)piperidine **53i** (102.6 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (224.7 mg, 1.1 mmol). **56h'** was isolated as

a colourless oil (53 mg, 30 %); yield of **56h** was calculated from an isolated mixture of **56h** and SM **53i** *via* ^{1}H NMR (11%).

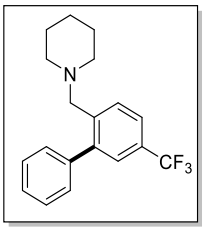
IR (film) 2932, 1603, 1465, 1251, 763, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.29 (m, 10H, Ar-H), 6.79 (s, 2H, Ar-H), 3.82 (s, 3H, Ar-OCH_3), 3.21 (s, 2H, NCH_2Ar), 1.86 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.22 – 1.09 (m, 6H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.2, 145.4, 142.7, 129.6, 127.4, 127.0, 126.5, 114.7, 55.6, 55.3, 53.2, 26.0, 24.4.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{25}H_{28}NO$) requires *m/z* 358.2165, found *m/z* 358.2157.

56i: 1-((5-(Trifluoromethyl)-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(4-(trifluoromethyl)benzyl)piperidine **53j** (121.6 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (224.7 mg, 1.1 mmol). **56i** was isolated as a pale yellow oil (21 mg, 13%); **56i'** was isolated as a yellow oil (30 mg, 15%). **56i** was separated from a mixture of **56i** and SM **53j** using prep HPLC (Hexane/IPA= 98/2), 15 mL/ min), 60 mins.

IR (film) 2934, 1333, 1121, 837, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.58 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.49 (s, 1H, Ar-H), 7.45 – 7.32 (m, 5H, Ar-H), 3.39 (s, 2H, NCH_2Ar), 2.28 (br. m, 4H,

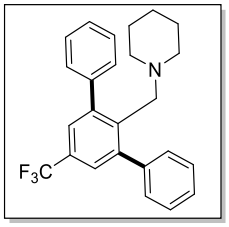
$CH_2CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 1.57 – 1.47 (m, 4H, $CH_2C\underline{H_2}CH_2NCH_2C\underline{H_2}$), 1.43 – 1.34 (m, 2H, $C\underline{H_2}CH_2CH_2NCH_2CH_2$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 142.8, 140.7, 140.1, 130.0, 129.3, 128.7 (q, J_{C-F} = 32.4 Hz), 128.1, 126.7 (q, J_{C-F} = 3.3 Hz), 125.4, 124.3 (q, J_{C-F} = 272.3 Hz), 123.8 (d, J_{C-F} = 3.6 Hz), 60.2, 54.4, 26.0, 24.3.

^{19}F NMR (377 MHz, $CDCl_3$): δ –62.28.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{21}NF_3$) requires *m/z* 320.1621, found *m/z* 320.1613.

56i': 1-((5'-(Trifluoromethyl)-[1,1':3',1''-terphenyl]-2'-yl)methyl)piperidine



IR (film) 2933, 1359, 1263, 1121, 748, 701 cm^{-1}.

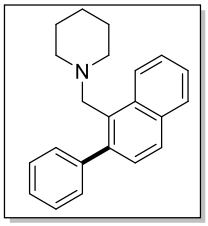
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (s, 2H, Ar-H), 7.44 – 7.31 (m, 10H, Ar-H), 3.34 (s, 2H, $NC\underline{H_2}Ar$), 1.82 (br. m, 4H, $CH_2CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 1.12 – 1.07 (m, 6H, $C\underline{H_2}C\underline{H_2}CH_2NCH_2C\underline{H_2}$).

^{13}C NMR (126 MHz, $CDCl_3$): δ 144.8, 141.4 (2XC), 138.8, 129.5, 128.4 (q, J_{C-F} = 32.5 Hz), 127.7, 127.0, 125.9 (q, J_{C-F} = 3.5 Hz), 124.2 (q, J_{C-F} = 272.3 Hz), 123.6 (q, J_{C-F} = 3.8 Hz), 55.9, 53.3, 25.9, 24.2.

^{19}F NMR (377 MHz, $CDCl_3$): -62.29.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{25}H_{25}NF_3$) requires *m/z* 396.1934, found *m/z* 396.1916.

56j: 1-((2-Phenylnaphthalen-1-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(naphthalen-1-ylmethyl)piperidine **53k** (112.6 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **56j** was isolated as a white solid (88 mg, 58%).

MP 116 – 118 ^{o}C

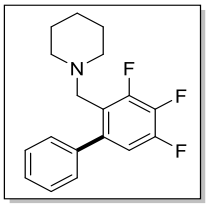
IR (film) 2932, 1494, 1442, 864, 762, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.85 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.78 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.59 – 7.29 (m, 8H, Ar-H), 3.81 (s, 2H, NCH_2Ar), 2.26 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.47 – 1.38 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.36 – 1.28 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.6, 140.9, 133.3, 133.1, 131.6, 130.0, 128.1, 128.0, 127.7, 127.0, 126.7, 126.6, 125.7, 125.5, 56.8, 54.1, 26.1, 24.4.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{24}N$) requires *m/z* 302.1903, found *m/z* 302.1900.

56k:1-((3,4,5-Trifluoro-[1,1'-biphenyl]-2-yl)methyl)piperidine



Prepared according to general procedure A, using 1-(2,3,4-trifluorobenzyl)piperidine **53e** (114.6 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **56k** was isolated as a white solid (57 mg, 37%).

MP 60 – 62 ^{o}C.

IR (film) 2935, 1607, 1516, 1493, 767, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 – 7.47 (m, 2H, Ar-H), 7.44 – 7.34 (m, 3H, Ar-H), 6.94 (ddd, *J* = 10.5, 7.0, 2.0 Hz, 1H, Ar-H), 3.31 (d, *J* = 3.0 Hz, 2H, NCH_2Ar), 2.27 (br. m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.54 – 1.42 (m, 4H, $CH_2CH_2CH_2NCH_2CH_2$), 1.42 – 1.31 (m, 2H, $CH_2CH_2CH_2NCH_2CH_2$).

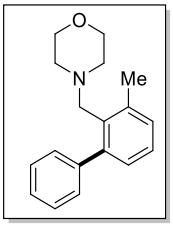
^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0 (ddd, $J_{C\text{-}F}$ = 245.4, 103.5, 3.0 Hz), 149.9 (ddd, $J_{C\text{-}F}$ = 249.5, 104.0, 4.0 Hz), 139.9 – 139.8 (m), 139.0, 138.7 (ddd, $J_{C\text{-}F}$ = 251.5, 17.2, 15.2 Hz), 129.7, 127.9, 127.7, 121.5 (dd, $J_{C\text{-}F}$ = 11.4, 2.9 Hz), 113.6 (dd, $J_{C\text{-}F}$ = 17.2, 3.3 Hz), 53.6, 52.6, 26.1, 24.2.

^{19}F NMR (377 MHz, $CDCl_3$): -135.06 (dd, $J_{F\text{-}F}$= 20.9, 4.1 Hz), -136.66 (ddd, $J_{F\text{-}F}$ = 20.8, 10.6, 7.4 Hz), -162.40 (td, $J_{F\text{-}F}$ = 21.1, 7.2 Hz).

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{19}NF_3$) requires *m/z* 306.1464, found *m/z* 306.1457.

5.2.4 Synthesis & Characterization of Compounds 58

58a: 4-((3-Methyl-[1,1'-biphenyl]-2-yl)methyl)morpholine



Prepared according to general procedure A, using 4-(2-methylbenzyl)morpholine **57a** (95.6 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **58a** was isolated as a pale yellow oil (79 mg, 59%).

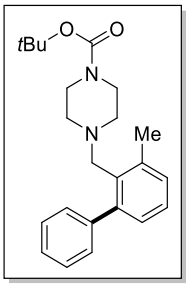
IR (film) 2851, 1461, 1004, 760, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.38 (m, 3H, Ar-H), 7.35 – 7.30 (m, 2H, Ar-H), 7.29 – 7.23 (m, 2H, Ar-H), 7.12 (dd, *J* = 6.5, 2.5 Hz, 1H, Ar-H), 3.64 – 3.55 (m, 4H, $CH_2CH_2OCH_2CH_2N$), 3.50 (s, 2H, NCH_2Ar), 2.57 (s, 3H, Ar-CH_3), 2.29 – 2.19 (m, 4H, $CH_2CH_2OCH_2CH_2N$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.9, 142.3, 139.0, 133.6, 129.7, 129.7, 127.7, 127.6, 126.7, 126.6, 67.1, 56.4, 52.9, 20.2.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{22}NO$) requires *m/z* 268.1696, found *m/z* 268.1689.

58b: *tert*-Butyl 4-((3-methyl-[1,1'-biphenyl]-2-yl)methyl)piperazine-1-carboxylate



Prepared according to general procedure A, using *t*-butyl 4-(2-methylbenzyl)piperazine-1-carboxylate **57b** (145.1 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **58b** was isolated as a white solid (104 mg, 57%).

MP 78 – 79 °C.

IR (film) 2976, 1692, 1420, 1168, 1124, 1002, 788, 703 cm^{-1}.

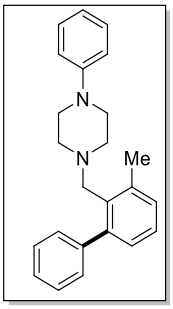
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.35 (m, 3H, Ar-H), 7.33 – 7.21 (m, 4H, Ar-H) 7.10 (dd, *J* = 6.5, 2.0 Hz, 1H, Ar-H), 3.48 (s, 2H, NCH_2Ar), 3.35 – 3.23 (m, 4H,

C$\underline{H_2}$CH$_2$N(CH$_2$Ar)CH$_2$C$\underline{H_2}$N(CO$_2$*t*Bu)), 2.54 (s, 3H, Ar-C$\underline{H_3}$), 2.22 – 2.08 (m, 4H, CH$_2$C$\underline{H_2}$N(CH$_2$Ar)C$\underline{H_2}$CH$_2$N(CO$_2$*t*Bu)), 1.46 (s, 9H, NCO$_2$C(C$\underline{H_3}$)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.7, 143.9, 142.2, 139.0, 133.7, 129.7, 129.7, 127.7, 127.6, 126.7, 126.6, 79.4, 56.1, 52.2, 43.5, 28.4, 20.2.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{31}N_2O_2$) requires *m/z* 367.2380, found *m/z* 367.2373.

58c: 1-((3-Methyl-[1,1'-biphenyl]-2-yl)methyl)-4-phenylpiperazine



Prepared according to general procedure A, using 1-(2-methylbenzyl)-4-phenylpiperazine **57c** (133.1 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (143.0 mg, 0.7 mmol). **58c** was isolated as a white solid (105 mg, 61%).

MP 79 – 80 ºC

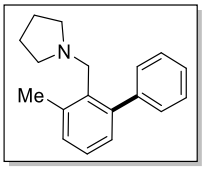
IR (film) 2816, 1599, 1495, 1228, 1005, 758, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 – 7.31 (m, 5H, Ar-$\underline{H}$), 7.30 – 7.23 (m, 4H, Ar-$\underline{H}$), 7.13 (dd, *J* = 6.5, 2.5 Hz, 1H, Ar-$\underline{H}$), 6.97 – 6.81 (m, 3H, Ar-$\underline{H}$), 3.55 (s, 2H, NC$\underline{H_2}$Ar), 3.11 – 3.03 (m, 4H, C$\underline{H_2}$CH$_2$N(CH$_2$Ar)CH$_2$C$\underline{H_2}$N(Ar)), 2.58 (s, 3H, Ar-C$\underline{H_3}$), 2.45 – 2.34 (m, 4H, CH$_2$C$\underline{H_2}$N(CH$_2$Ar)C$\underline{H_2}$CH$_2$N(Ar)).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.4, 143.9, 142.3, 139.0, 133.9, 129.8, 129.7, 129.0, 127.7, 127.6, 126.6 (2xC), 119.4, 115.9, 56.1, 52.5, 49.3, 20.2.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{24}H_{27}N_2$) requires *m/z* 343.2169, found *m/z* 343.2166.

58d: 1-((3-Methyl-[1,1'-biphenyl]-2-yl)methyl)pyrrolidine



Prepared according to general procedure A, using 1-(2-methylbenzyl)pyrrolidine **57d** (87.6 mg, 0.5 mmol) and phenylboronic acid pinacol ester **54a** (224.7 mg, 1.1 mmol). **58d** was isolated as a yellow oil (33 mg, 26%)

IR (film) 3057, 2961, 1495, 759, 702 cm^{-1}.

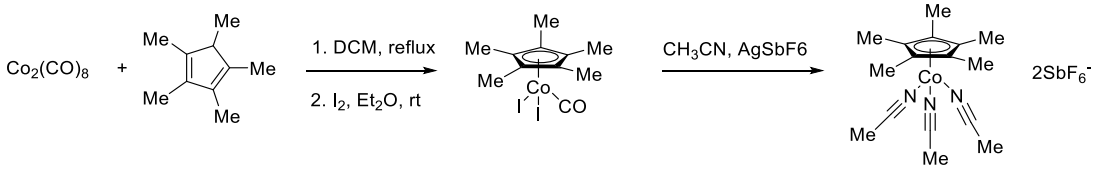
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (m, 5H, Ar-H), 7.22 – 7.17 (m, 2H, Ar-H), 7.09 – 7.03 (m, 1H, Ar-H), 3.59 (s, 2H, NCH_2Ar), 2.53 (s, 3H, Ar-CH_3), 2.25 (br. m, 4H, $CH_2CH_2NCH_2CH_2$), 1.67 – 1.52 (m, 4H, $CH_2CH_2NCH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.0, 142.5, 138.8, 135.4, 130.0, 129.6, 127.7, 127.6, 126.5, 126.3, 53.7, 53.3, 23.5, 20.0.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{22}N$) requires *m/z* 252.1747, found *m/z* 252.1742.

5.3 Experimental Chapter 3

5.3.1 Synthesis & Characterization of catalyst $[Cp^*Co(MeCN)_3][SbF_6]_2$



To an oven-dried 2-necked 500 mL flask were added $Co_2(CO)_8$ (5.0 g, 14.6 mmol), degassed DCM (100 mL) and pentamethylcyclopentadiene (5.55 mL, 35.4 mmol). The reaction mixture was heated under reflux at 48 °C under argon for 6 h and then cooled to rt. After the solvent was removed in vacuo, the residue was dissolved Et_2O (50 mL) and subsequently iodine (9.0 g, 35.5 mmol) in degassed Et_2O (50 mL) was added dropwise at rt with stirring. The reaction mixture was then allowed to stir at room temperature for 1 h and solvent was evaporated. The crude mixture was purified by silica gel flash column chromatography (hexane then CH_2Cl_2/hexane=4/1) to afford deep purple crystalline solid. (12.0 g, 86% based on Co)

IR (film) 2080 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 15H, Cp*-C<u>H</u>$_3$)

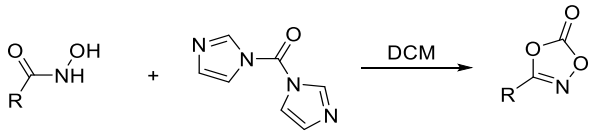
^{13}C NMR (101 MHz, $CDCl_3$): δ 100.9, 11.4.

To a suspension of $[Cp^*Co(CO)I_2]$ (220 mg, 0.46 mmol) in anhydrous CH_3CN (3.6 mL), a solution of $AgSbF_6$ (600 mg, 1.75 mmol) in anhydrous CH_3CN (4.6 mL) was added within 2 min. A solid precipitation was immediately observed and the reaction mixture was stirred at rt for 3h. After the completion of the reaction, the solid was filtered over a pad of Celite and washed with CH_3CN (20 mL x 3). The fitrate was evaporated in vacuo to 15 mL, Et_2O (50 mL) was added dropwise and precipitation of a purple solid was observed. The purple solid was then collected by filtration, washed with Et_2O (50 mL), dried in vacuo to afford $[Cp^*Co(MeCN)_3][SbF_6]_2$ (315 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (s, 9H, $C\underline{H_3}CN$), 1.44 (s, 15H, Cp*-$C\underline{H_3}$)

Analytical data are in accordance with those previously reported for this compound.[106,111]

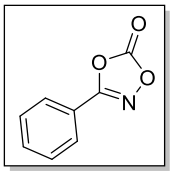
5.3.2 General Procedure B: Synthesis of Dioxazolones 120



To a stirred suspension of hydroxamic acid (1 equiv) in DCM (0.1 M) was added 1,1'-carbonyldiimidazole (1 equiv) in one portion at rt. After stirring for 1 h, the reaction was quenched with 1.0 M HCl, extracted with DCM and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to afford the crude product. The product was then redissolved in toluene and filtered to obtain the filtrate and subsequently toluene was removed in vacuo to obtain 3-substituted 1,4,2-dioxazol-5-ones.[231–234]

5.3.3 Synthesis & Characterization of Dioxazolones 120

120a: 3-phenyl-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.40 g, 86%)

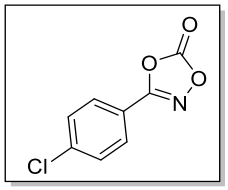
IR (film) 3293, 1860, 1816, 1610, 1358, 1172, 966 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 – 7.82 (m, 2H, Ar-$\underline{H}$), 7.67 – 7.63 (m, 1H, Ar-$\underline{H}$), 7.56- 7.53 (m, 2H, Ar-$\underline{H}$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.6, 153.9, 133.9, 129.3, 126.6, 120.1.

Analytical data are in accordance with those previously reported for this compound.[231–234]

120b: 3-(4-chlorophenyl)-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.62 g, 82% yield)

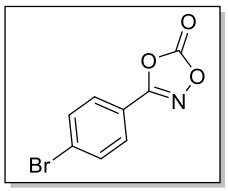
IR (film) 3293, 1859, 1815, 1615, 1359, 829 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.54 (d, *J* = 8.0 Hz, 2H, Ar-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.0, 153.7, 140.5, 130.0, 128.1, 118.7.

Analytical data are in accordance with those previously reported for this compound.[231–234]

120c: 3-(4-bromophenyl)-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.87 g, 78%)

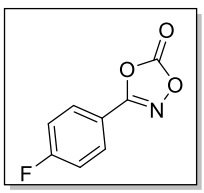
IR (film) 3293, 1858, 1615, 1359, 827 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 - 7.70 (m, 4H, Ar-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.1, 153.7, 133.0, 129.1, 128.1, 119.2.

Analytical data are in accordance with those previously reported for this compound.[231–234]

120d: 3-(4-fluorophenyl)-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.35 g, 75%)

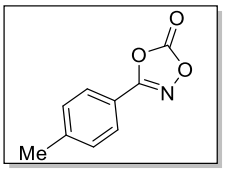
IR (film) 1864, 1835, 1604, 1246, 971, 845, 763, 738, 602 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 - 7.85 (m, 2H, Ar-H), 7.30 - 7.22 (m, 2H, Ar-H),

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.1 (d, J_{C-F} = 257.0 Hz), 162.9, 153.8, 129.3 (d, J_{C-F} = 9.5 Hz), 117.1 (d, J_{C-F} = 22.5 Hz), 116.6 (d, J_{C-F} = 3.5 Hz).

Analytical data are in accordance with those previously reported for this compound.[231–234]

120e: 3-(*p*-tolyl)-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.58 g, 89%)

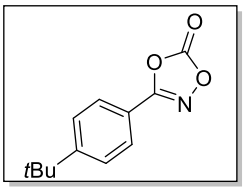
IR (film) 1856, 1612, 1360, 1158, 1013, 826, 746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.34 (d, *J* = 8.0 Hz, 2H, Ar-H), 2.45 (s, 3H, Ar-CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.8, 154.1, 145.0, 130.1, 126.8, 117.4, 22.0.

Analytical data are in accordance with those previously reported for this compound.[231–234]

120f: 3-(4-(*tert*-butyl)phenyl)-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.86 g, 85%)

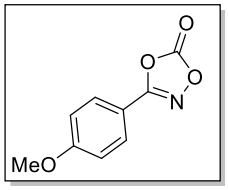
MP 69 °C

IR (film) 2967, 1861, 1831, 1617, 1416, 1372, 1364, 1167, 970, 841, 757 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 - 7.76 (m, 2H, Ar-H), 7.59 - 7.54 (m, 2H, Ar-H), 1.36 (s, 9H. Ar-C(CH_3)$_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.8, 158.0, 154.2, 126.7, 126.6, 117.3, 35.5, 31.1.

120g: 3-(4-methoxyphenyl)-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.35 g, 70%)

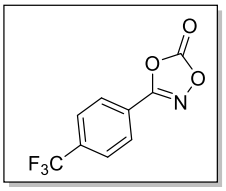
IR (film) 1857, 1608, 1515, 1363, 1170, 971 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.02 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.90 (s, 3H, Ar-OCH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.0, 163.5, 154.2, 128.7, 115.1, 112.2, 55.7.

Analytical data are in accordance with those previously reported for this compound.[231–234]

120h: 3-(4-(trifluoromethyl)phenyl)-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.67 g, 72%)

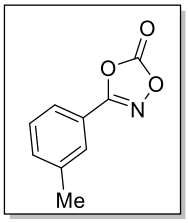
IR (film) 1877, 1323, 1166, 1125, 1080, 860, 763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.83 (d, *J* = 8.0 Hz, 2H, Ar-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.7, 153.4, 135.1 (q, J_{C-F} = 33.3 Hz), 127.3, 126.6 (q, J_{C-F} = 3.5 Hz), 123.7 (d, J_{C-F} = 1.5 Hz), 123.3 (q, J_{C-F} = 273.0 Hz).

Analytical data are in accordance with those previously reported for this compound. [231–234]

120i: 3-(*m*-tolyl)-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.39 g, 79%)

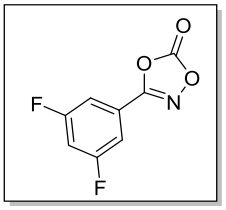
IR (film) 1870, 1837, 1368, 1158, 1073, 972, 759, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 – 7.61 (m, 2H, Ar-H), 7.47 – 7.39 (m, 2H, Ar-H), 2.44 (s, 3H, Ar-CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.8, 154.0, 139.6, 134.7, 129.4, 127.1, 124.0, 120.1, 21.4.

Analytical data are in accordance with those previously reported for this compound.[231–234]

120j: 3-(3,5-difluorophenyl)-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.50 g, 75%)

MP 57 °C

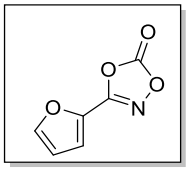
IR (film) 1857, 1597, 1442, 1379, 1130, 987, 868, 760 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 – 7.39 (m, 2H, Ar-H), 7.11 (tt, J = 8.5, 2.5 Hz, 1H, Ar-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.5 (dd, J_{C-F} = 253.0, 12.5 Hz), 162.0 (t, J_{C-F} = 4.0 Hz), 153.2, 123.0 (t, J_{C-F} = 10.5 Hz), 110.6 – 110.0 (m), 109.6 (t, J_{C-F} = 25.0 Hz).

^{19}F NMR (377 MHz, $CDCl_3$): -105.29.

120k: 3-(furan-2-yl)-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (690 mg, 45%)

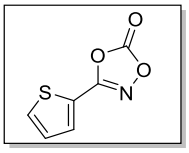
IR (film) 1828, 1640, 1474, 1418, 1190, 970 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.72 (m, 1H, Ar-H), 7.20 – 7.19 (m, 1H, Ar-H), 6.67-6.65 (m, 1H, Ar-H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.7, 153.1, 147.9, 135.1, 117.9, 112.7.

Analytical data are in accordance with those previously reported for this compound.[231–234]

120l: 3-(thiophen-2-yl)-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.47 g, 87%)

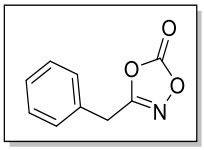
IR (film) 1836, 1609, 1430, 1157, 955 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.70 (m, 2H, Ar-H), 7.24 – 7.20 (m, 1H, Ar-H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.3, 153.5, 132.9, 132.4, 128.6, 120.4.

Analytical data are in accordance with those previously reported for this compound.[231–234]

120m: 3-benzyl-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.47 g, 83%)

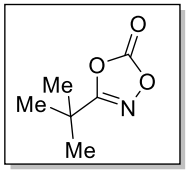
IR (film) 3446, 1836, 1456, 1385, 1149, 1025, 990 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.34 (m, 3H, Ar-H), 7.32 – 7.29 (m, 2H, Ar-H), 3.93 (s, 2H, $ArCH_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.4, 154.0, 130.5, 129.3, 129.1, 128.5, 31.3.

Analytical data are in accordance with those previously reported for this compound.[231–234]

120n: 3-(*tert*-butyl)-1,4,2-dioxazol-5-one



Prepared according to general procedure B on 10 mmol scale. (1.06 g, 74%)

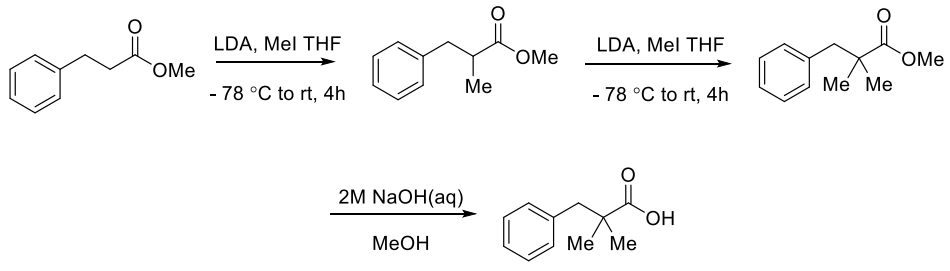
IR (film) 3440, 1840, 1464, 1340, 1123, 978 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4, 154.4, 32.6, 26.3.

Analytical data are in accordance with those previously reported for this compound.[231–234]

5.3.4 Synthesis & Characterization of 2,2-dimethyl-3-phenylpropanoic acid



To a stirred solution of diisopropylamine (1.40 mL, 10.0 mmol) in THF (25 mL) at -78 ºC was added dropwise a solution of 2.5 M *n*-butyllithium (4.02 mL, 10.0 mmol) in hexane. The reaction mixture was stirred for 1 h, and methyl 3-phenyl propionate (1.05 mL, 6.67 mmol) was added subsequently. The reaction mixture was stirred for 1 h, and then methyl iodide (1.11 mL, 17.8

mmol) was added, stirred for a further 2 h, and the reaction mixture was poured into a 1.0 M HCl solution (10 mL) and extracted with ether (2 x 10 mL). The combined extracts were dried over anhydrous Na_2SO_4 and solvent was removed in vacuo to give the crude monomethylated product, which was then subjected to a second methylation cycle repeating the procedure described above. The resulting residue was purified by silica gel flash column chromatography (2% EtOAc/Hexane) to afford the pure ester (706 mg, 55%) as a colorless oil.

IR (film) 2973, 1732, 1192, 1124, 741, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.19 (m, 3H, Ar-H), 7.09 (d, *J* = 7.5 Hz, 2H, Ar-H), 3.66 (s, 3H, CO_2CH_3), 2.85 (s, 2H, $ArCH_2C(CH_3)_2$), 1.18 (s, 6H, $ArCH_2C(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.2, 138.1, 130.4, 128.3, 126.7, 51.9, 46.6, 43.9, 25.2.

To a solution of dimethyl-3-phenylpropionic acid methyl ester (600 mg, 3.12 mmol) in MeOH (10 mL) was added a solution of aq. 2.0 M NaOH (8 mL). The reaction mixture was then stirred overnight at 60 °C. After the removal of MeOH in vacuo, the pH of mixture was adjusted to 2 with the addition of 1.0 M HCl. After the solution was then extracted with Et_2O and brine, the combined extracts were then dried over Na_2SO_4 and evaporated in vacuo to give the carboxylic acid, which was used directly for the next step without purification.

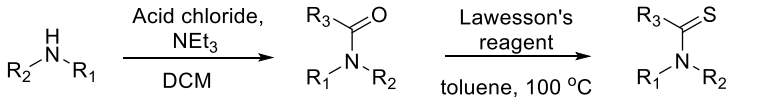
IR (film) 2972, 1685, 1135, 939, 741, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.13 (m, 5H, Ar-H), 2.88 (s, 2H, $ArCH_2C(CH_3)_2$), 1.20 (s, 6H, $ArCH_2C(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$): δ 184.8, 137.8, 130.4, 128.2, 126.7, 46.0, 43.6, 24.8.

Analytical data are in accordance with those previously reported for this compound.[235,236]

5.3.5 General Procedure C: Synthesis of thioamides 119a-119k, 119q

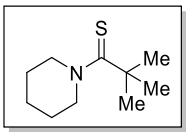


119a - 119k, **119q**

To a stirred mixture of an *N*,*N*-disubstituted amine (1.0 equiv) and NEt_3 (2.0 equiv) in DCM (0.2 M) at 0 °C, acid chloride (1.1 equiv) was added dropwise. The reaction mixture was then warmed to rt and stirred for 2 h. Upon completion of the reaction, the crude mixture was quenched with sat. $NaHCO_3$ and extracted with DCM. The combined organic layers were washed with brine, dried with Na_2SO_4, evaporated *in vacuo* and the resultant crude amide was added with toluene (0.2 M). Lawesson's reagent (1.1 equiv) was subsequently added and stirred reaction mixture was heated to 100 °C overnight. The reaction was cooled to rt and solvent was removed *in vacuo.* The crude residue was then purified *via* FCC (EtOAc/ PE) twice to afford the resultant thioamide products.[130]

5.3.6 Synthesis & Characterization of thioamides 119a-119k, 119q

119a: 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione



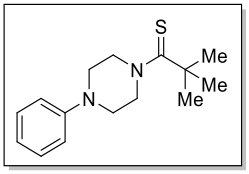
Prepared according to the general procedure C, using piperidine (5.0 mmol, 494 µL), pivaloyl chloride (5.5 mmol, 677 µL) and Lawesson's reagent (5.5 mmol, 2.23 g). **119a** was isolated as a white solid (571mg, 62%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 – 4.07 (m, 4H, $CH_2CH_2NCH_2CH_2$), 1.74 – 1.64 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.42 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 54.2, 43.7, 31.6, 26.3, 24.5.

Analytical data are in accordance with those previously reported for this compound.[130,237]

119b: 2,2-dimethyl-1-(4-phenylpiperazin-1-yl)propane-1-thione



Prepared according to the general procedure C, using 1-phenylpiperazine (5.0 mmol, 764 μL), pivaloyl chloride (5.5 mmol, 677 μL) and Lawesson's reagent (5.5 mmol, 2.23 g). **119b** was isolated as a yellow solid (617 mg, 47%).

MP 72-73 °C

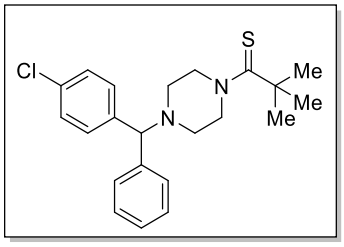
IR (film) 2912, 1599, 1419, 1231, 1199, 1011 (C=S), 758, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H, Ar-H), 6.98 – 6.89 (m, 3H, Ar-H), 4.45 – 4.33 (m, 4H, $CH_2CH_2NCH_2CH_2N$(Ar)), 3.35 – 3.26 (m, 4H, $CH_2CH_2NCH_2CH_2N$(Ar)), 1.47 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.0, 150.2, 129.4, 120.8, 116.3, 52.3, 49.3, 43.8, 31.7.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{22}N_2S$) requires *m/z* 263.1576, found *m/z* 263.1579.

119c: 1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2,2-dimethylpropane-1-thione



Prepared according to the general procedure C, using 1-((4-chlorophenyl)(phenyl)methyl)piperazine (5.0 mmol, 1.43 g), pivaloyl chloride (5.5 mmol, 677

μL) and Lawesson's reagent (5.5 mmol, 2.23 g). **119c** was isolated as a white powder (541 mg, 28%).

MP 139 °C

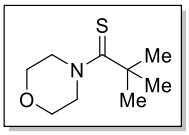
IR (film) 2914, 1487, 1421, 1242, 1199, 1014 (C=S), 758, 719 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.33 (m, 4H, Ar-H), 7.33 – 7.17 (m, 5H, Ar-H), 4.40 – 4.02 (m, 4H, $CH_2CH_2NCH_2CH_2N(CH)$), 4.21 (s, 1H, Ar(CH)Ar), 2.61 – 2.34 (m, 4H, $CH_2CH_2NCH_2CH_2N(CH)$), 1.39 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.5, 141.5, 140.7, 133.1, 129.2, 129.1, 129.0, 127.9, 127.7, 75.4, 52.6, 52.1, 43.6, 31.6.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{27}N_2SCl$) requires *m/z* 387.1656, 389.1633 found *m/z* 387.1667, 389.1644.

119d: 2,2-dimethyl-1-morpholinopropane-1-thione



Prepared according to the general procedure C, using morpholine (5.0 mmol, 437 μL) pivaloyl chloride (5.5 mmol, 677 μL) and Lawesson's reagent (5.5 mmol, 2.23 g). **119d** was isolated as a white solid (601 mg, 64%).

MP 83 °C

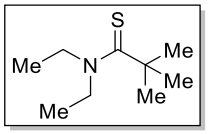
IR (film) 2924, 1423, 1269, 1114, 1016 (C=S), 884, 843 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 – 4.17 (m, 4H, $CH_2CH_2NCH_2CH_2O$), 3.79 – 3.72 (m, 4H, $CH_2CH_2NCH_2CH_2O$), 1.43 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 213.1, 66.8, 53.4, 43.7, 31.6.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_9H_{17}NOS$) requires *m/z* 188.1104, found *m/z* 188.1102.

119e: *N*,*N*-Diethyl-2,2-dimethylpropanethioamide



Prepared according to general procedure C, using diethylamine. HCl (5.0 mmol, 548 mg), pivaloyl chloride (5.5 mmol, 677 μL) and Lawesson's reagent (5.5 mmol, 2.23 g). **119e** was isolated as a yellow oil (575 mg, 66%).

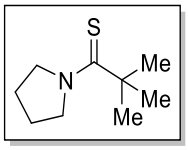
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 – 3.66 (m, 4H, $CH_3CH_2NCH_2CH_3$), 1.41 (s, 9H, $C(CH_3)_3$), 1.32 – 1.19 (m, 6H, $CH_3CH_2NCH_2CH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0, *49.3, *47.4, 43.7, 31.7, *13.9, *10.9.

*Rotamers observed.

Analytical data are in accordance with those previously reported for this compound.[238]

119f: 2,2-Dimethyl-1-(pyrrolidin-1-yl)propane-1-thione



Prepared according to general procedure C, using pyrrolidine (5.0 mmol, 417 μL), pivaloyl chloride (5.5 mmol, 677 μL) and Lawesson's reagent (5.5 mmol, 2.23 g). **119f** was isolated as a pale yellow solid (576 mg, 67%).

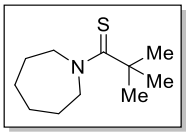
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 – 3.75 (m, 4H, $CH_2CH_2NCH_2CH_2$), 2.10 – 1.79 (m, 4H, $CH_2CH_2NCH_2CH_2$), 1.42 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 290.1, *57.9, *53.1, 43.9, 30.6, *27.6, *23.3.

*Rotamers observed.

Analytical data are in accordance with those previously reported for this compound.[130]

119g: 1-(azepan-1-yl)-2,2-dimethylpropane-1-thione



Prepared according to general procedure C, using hexamethyleneimine (5.0 mmol, 563 μL), pivaloyl chloride (5.5 mmol, 677 μL) and Lawesson's reagent (5.5 mmol, 2.23 g). **119g** was isolated as a pale yellow oil (690 mg, 69%).

IR (film) 2925, 1470, 1419, 1270, 1174, 1011 (C=S), 880 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 – 3.85 (m, 4H, $CH_2CH_2C\underline{H_2}NC\underline{H_2}CH_2CH_2$), 1.93 – 1.78 (m, 4H, $CH_2C\underline{H_2}CH_2NCH_2C\underline{H_2}CH_2$), 1.62 – 1.51 (m, 4H, $C\underline{H_2}CH_2CH_2NCH_2CH_2C\underline{H_2}$), 1.42 (s, 9H, $C(C\underline{H_3})_3$).

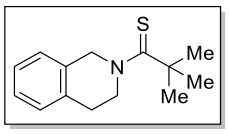
^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1, *57.4, *54.1, 43.8, 31.8, 30.9 – 23.8 (br. m, $\underline{C}H_2\underline{C}H_2CH_2NCH_2\underline{C}H_2\underline{C}H_2$).

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{21}NS$) requires *m/z* 200.1473, found *m/z* 200.1470.

*Rotamers observed.

119g prepared according to the literature procedure.[130]

119h: 1-(3,4-dihydroisoquinolin-2(1H)-yl)-2,2-dimethylpropane-1-thione



Prepared according to the general procedure C, using 1,2,3,4-tetrahydroisoquinoline (5.0 mmol, 626 μL), pivaloyl chloride (5.5 mmol, 677 μL) and Lawesson's reagent (5.5 mmol, 2.23 g). **119h** was isolated as a yellow oil (781 mg, 67%).

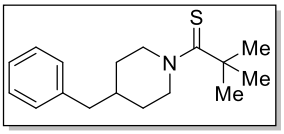
IR (film) 2923, 1475, 1418, 1282, 1182, 1017 (C=S), 748, 673 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.12 (m, 4H, Ar-H), 5.20 (s, 2H, $ArCH_2N$), 4.31 (t, *J* = 5.5 Hz, 2H, $ArCH_2NCH_2CH_2$), 3.02 (t, *J* = 5.5 Hz, 2H, $ArCH_2NCH_2CH_2$), 1.48 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.0, 134.4, 133.0, 128.5, 127.2, 126.7, 126.3, 55.3, 51.0, 43.8, 31.6, 28.8.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{14}H_{19}NS$) requires *m/z* 234.1311, found *m/z* 234.1310.

119i: 1-(4-benzylpiperidin-1-yl)-2,2-dimethylpropane-1-thione



Prepared according to the general procedure C, using 4-benzylpiperidine (2.5 mmol, 439 μL), pivaloyl chloride (2.75 mmol, 339 μL) and Lawesson's reagent (2.75 mmol, 1.11 g). **119i** was isolated as a yellow oil (394 mg, 57%).

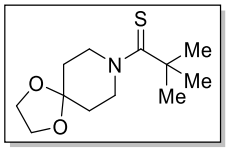
IR (film) 2919, 1484, 1423, 1270, 1174, 1009 (C=S), 746, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H, Ar-H), 7.24 – 7.18 (m, 1H, Ar-H), 7.16 – 7.11(m, 2H, Ar-H), 5.46 – 4.81 (m, 2H, $CH_2CH_AH_BNCH_AH_BCH_2$), 3.05 (app t, *J* = 12.5 Hz, 2H, $CH_2CH_AH_BNCH_AH_BCH_2$), 2.56 (d, *J* = 7.0 Hz, 2H, $ArCH_2$), 2.00 – 1.85 (m, 1H, $CHCH_2CH_2NCH_2CH_2$), 1.84 – 1.72 (m, 2H, $CH_AH_BCH_2NCH_2CH_AH_B$), 1.42 (s, 9H, $C(CH_3)_3$), 1.40 – 1.29 (m, 2H, $CH_AH_BCH_2NCH_2CH_AH_B$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.5, 139.9, 129.1, 128.5, 126.3, 53.3, 43.7, 42.7, 38.3, 32.4, 31.6.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{25}NS$) requires *m/z* 276.1780, found *m/z* 276.1785.

119j: 2,2-dimethyl-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)propane-1-thione



Prepared according to the general procedure C, using 1,4-dioxa-8-azaspiro[4.5]decane (2.5 mmol, 320 μL), pivaloyl chloride (2.75 mmol, 339 μL) and Lawesson's reagent (2.75 mmol, 1.11 g). **119j** was isolated as a white solid (56.6 mg, 9%)

MP 109 °C

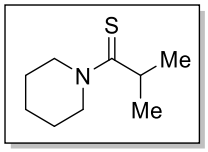
IR (film) 2921, 1428, 1244, 1094, 1024 (C=S), 943, 917 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 – 4.19 (m, 4H, $CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 4.00 (s, 4H, $OC\underline{H_2}C\underline{H_2}O$), 1.85 – 1.76 (m, 4H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}$), 1.43 (s, 9H, $C(C\underline{H_3})_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.4, 106.8, 64.7, 50.7, 43.8, 35.4, 31.7.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{12}H_{21}NO_2S$) requires *m/z* 244.1366, found *m/z* 244.1364.

119k: 2-methyl-1-(piperidin-1-yl)propane-1-thione



Prepared according to general the procedure C, using piperidine (10.0 mmol, 885 μL), isobutyryl chloride (11.0 mmol, 1.15 mL) and Lawesson's reagent (11.0 mmol, 4.45 g). **119k** was isolated as a yellow oil (1.02 g, 60%).

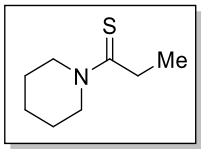
^{1}H NMR (400 MHz, $CDCl_3$) δ *4.52 – 4.11 (m, 2H, $CH_2C\underline{H_2}NCH_2CH_2$), *3.94 – 3.64 (m, 2H, $CH_2CH_2NC\underline{H_2}CH_2$), 3.13 (sept, *J* = 6.5 Hz, 1H, $CH_3C\underline{H}CH_3$), 1.77 – 1.59 (m, 6H, $C\underline{H_2}CH_2NC\underline{H_2}C\underline{H_2}$), 1.22 (d, *J* = 6.5 Hz, 6H, $C\underline{H_3}CHC\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9, *51.8, *50.3, 36.5, *27.3, *25.5, 24.6, 23.2.

* Rotamers observed.

Analytical data are in accordance with those previously reported for this compound.[239]

119p: 1-(piperidin-1-yl)propane-1-thione



Prepared according to general the procedure C, using piperidine (10.0 mmol, 885 μL), propionyl chloride (11.0 mmol, 961 μL) and Lawesson's reagent (11.0 mmol, 4.45 g). **119p** was isolated as a yellow oil (881 mg, 56%).

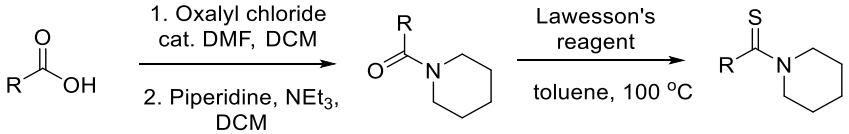
^{1}H NMR (400 MHz, $CDCl_3$) δ *4.35 – 4.16 (m, 2H, $CH_2C\underline{H_2}NCH_2CH_2$), *3.86 – 3.56 (m, 2H, $CH_2CH_2NC\underline{H_2}CH_2$), 2.87 (q, *J* = 7.5 Hz, 2H, $C(S)C\underline{H_2}CH_3$), 1.83 – 1.56 (m, 6H, $C\underline{H_2}CH_2NC\underline{H_2}C\underline{H_2}$), 1.26 (t, *J* = 7.5 Hz, 3H, $C(S)CH_2C\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6, *51.6, *50.8, 37.3, *27.0, *25.4, 24.2, 13.6.

* Rotamers observed.

Analytical data are in accordance with those previously reported for this compound.[240]

5.3.7 General Procedure D: Synthesis of thioamides 119l-119p



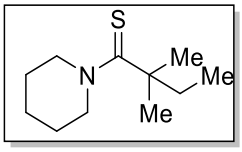
119l-119p

To a stirred solution of the carboxylic acid (1.1 equiv) in DCM (0.5 M) at 0 °C, oxalyl chloride (2.2 equiv) was added dropwise. 1-2 drops of DMF was subsequently added and the reaction mixture was then stirred at rt for 2 h. Upon completion of the reaction, the solvent of the crude

mixture was removed *in vacuo* to give the corresponding acid chloride. The crude acid chloride was then added dropwise to a stirred mixture of piperidine (1.0 equiv) and NEt_3 (2.0 equiv) in DCM (0.2 M) at 0 °C. The reaction mixture was then warmed to rt and stirred for 2 h. Upon completion of the reaction, the crude mixture was quenched with sat. $NaHCO_3$ and extracted with DCM. The combined organic layers were washed with brine, dried with Na_2SO_4, evaporated *in vacuo* and the resultant crude amide was added with toluene (0.2 M). Lawesson's reagent (1.1 equiv) was subsequently added and the stirred reaction mixture was heated to 100 °C overnight. The reaction was cooled to rt and solvent was removed *in vacuo.* The crude residue was then purified *via* FCC (EtOAc/ PE) twice to afford the resultant thioamide products.

5.3.8 Synthesis & Characterization of thioamides 119l-119o

119l: 2,2-Dimethyl-1-(piperidin-1-yl)butane-1-thione



Prepared according to the general procedure D, using piperidine (5.0 mmol, 443 μL), 2,2-dimethylbutanoic acid (5.5 mmol, 688 μL), oxalyl chloride (11.0 mmol, 931 μL) and Lawesson's reagent (5.5 mmol, 2.23 g). **119l** was isolated as a yellow oil (535 mg, 54%).

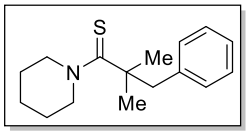
IR (film) 2937, 1420, 1249, 1232, 1130, 1009 (C=S) cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 – 4.03 (m, 4H, $CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 1.74 (q, *J* = 7.5 Hz, 2H, $CC\underline{H_2}CH_3$), 1.74 – 1.64 (m, 6H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}C\underline{H_2}$), 1.41 (s, 6H, $C\underline{H_3}CC\underline{H_3}$), 0.90 (t, *J* = 7.5 Hz, 3H, $CCH_2C\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.5, 54.2, 47.5, 34.2, 30.4, 26.3, 24.5, 9.6.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{21}NS$) requires *m/z* 200.1467, found *m/z* 200.1468.

119m: 2,2-Dimethyl-3-phenyl-1-(piperidin-1-yl)propane-1-thione



Prepared according to general procedure D, using piperidine (2.5 mmol, 247 μL), 2,2-dimethyl-3-phenylpropanoic acid (2.75 mmol, 490 mg), oxalyl chloride (5.5 mmol, 465 μL) and Lawesson's reagent (2.75 mmol, 1.11 g). **119m** was isolated as a pale-yellow solid (196 mg, 30%).

MP 79 °C

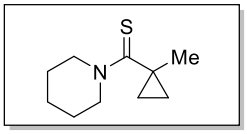
IR (film) 2935, 1419, 1223, 1019, 1002 (C=S), 742, 701 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 3H, Ar-H), 7.18 – 7.12 (m, 2H, Ar-H), 4.21 – 4.08 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.05 (s, 2H, CCH_2Ar), 1.82 – 1.68 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.40 (s, 6H, CH_3CCH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0, 138.1, 130.6, 128.1, 126.6, 54.5, 48.0, 46.6, 30.2, 26.3, 24.5.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{23}NS$) requires *m/z* 262.1624, found *m/z* 262.1626.

119n: (1-Methylcyclopropyl)(piperidin-1-yl)methanethione



Prepared according to general procedure D, using piperidine (2.5 mmol, 247 μL), 1-methylcyclopropanecarboxylic acid (2.75 mmol, 275 mg), oxalyl chloride (5.5 mmol, 465 μL) and Lawesson's reagent (2.75 mmol, 1.11 g). **119n** was isolated as a pale-yellow solid (203 mg, 44%).

MP 56 °C

IR (film) 2937, 2858, 1481, 1437, 1245, 1228, 1136, 1008 (C=S) cm^{-1}.

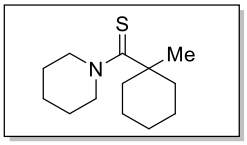
^{1}H NMR (400 MHz, $CDCl_3$) δ *4.24 – 4.13 (m, 2H, $CH_2C\underline{H_2}NCH_2CH_2$), *4.02 – 3.92 (m, 2H, $CH_2CH_2NC\underline{H_2}CH_2$), 1.75 – 1.62 (m, 6H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}C\underline{H_2}$), 1.33 (s, 3H, $(CH_2CH_2)CC\underline{H_3}$), 1.09 (app q, *J* = 4.5 Hz, 2H, $(C\underline{H_2}CH_2)CCH_3$), 0.80 (app q, *J* = 4.5 Hz, 2H, $(CH_2C\underline{H_2})CCH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 205.0, *52.1, *51.2, 28.2, *26.7, *25.4, 24.4, 24.1, 17.2.

* Rotamers observed.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{17}NS$) requires *m/z* 184.1154, found *m/z* 184.1158.

119o: (1-methylcyclohexyl)(piperidin-1-yl)methanethione



Prepared according to general procedure D, using piperidine (2.5 mmol, 247 μL), 1-methyl-1-cyclohexanecarboxylic acid (2.75 mmol, 391 mg), oxalyl chloride (5.5 mmol, 465 μL) and Lawesson's reagent (2.75 mmol, 1.11 g). **119o** was isolated as a yellow oil (231 mg, 41%).

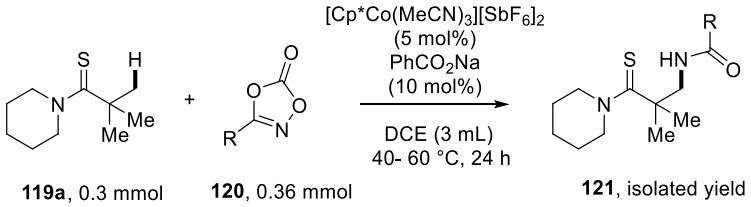
IR (film) 2933, 2856, 1442, 1416, 1245, 1230, 1126, 1018, 1007 (C=S), 855 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 – 4.02 (m, 4H, $CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 2.19 – 2.04 (m, 2H, $C(S)C(CH_3)C\underline{H_A}H_BCH_2CH_2CH_2C\underline{H_A}H_B$) 1.76 – 1.59 (m, 10 H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}C\underline{H_2}$, $C(S)C(CH_3)CH_A\underline{H_B}C\underline{H_A}H_BCH_2C\underline{H_A}H_BCH_A\underline{H_B}$), 1.54 – 1.40 (m, 3H, $C(S)C(CH_3)CH_2CH_A\underline{H_B}C\underline{H_A}H_BCH_A\underline{H_B}CH_2$), 1.36 – 1.26 (m, 4H, $C(S)C(C\underline{H_3})CH_2CH_2CH_A\underline{H_B}CH_2CH_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.7, 54.5, 46.9, 39.6, 26.3, 25.8, 24.5, 24.2, 23.1.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{13}H_{23}NS$) requires *m/z* 226.1624, found *m/z* 226.1625.

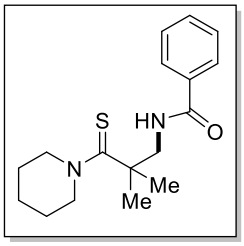
5.3.9 General Procedure E: Synthesis of Compound 121



In a N_2-filled glovebox, a 8 mL microwave vial was charged with thioamide **119a** (0.30 mmol, 1 equiv), dioxazolone **120** (0.36 mmol, 1.2 equiv), PhCOONa (0.03 mmol, 4.32 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.015 mmol, 11.8 mg) in DCE (3 mL). The vial was then brought out of the glovebox and reaction was run under inert atmosphere at 40-60 °C. After 24 h, the reaction mixture was cooled to room temperature and solvent was removed *in vacuo*. The crude reaction mixture was then purified and pure products were isolated by flash silica gel column chromatography (EtOAc/ PE = 1/9 to 2/3).

5.3.10 Synthesis & Characterization of Compound 121

121a: *N*-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)benzamide



Prepared according to the general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55.5 mg) and 3-phenyl-1,4,2-dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **121a** was isolated as a white solid (78.6 mg, 86%). Reaction was carried out at 40 °C.

MP 112 °C

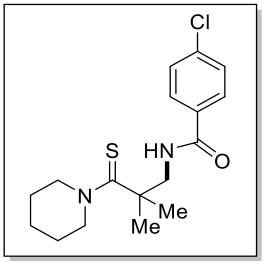
IR (film) 2937, 1630 (C=O), 1483, 1430, 1017 (C=S), 712, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (br. s, 1H, NHC(O)Ar), 7.84 – 7.77 (m, 2H, Ar-H), 7.50 – 7.37 (m, 3H, Ar-H), 4.35 – 3.91 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.87 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), 1.81- 1.64 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.41 (s, 6H, CCH_3CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 167.4, 134.8, 131.3, 128.5, 127.1, 54.2, 53.2, 49.0, 26.3, 24.6, 24.2.

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{24}ON_2S$) requires *m/z* 327.1502, found *m/z* 327.1502.

121b: 4-chloro-*N*-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)benzamide



Prepared according to the general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55.5 mg) and 3-(4-chlorophenyl)-1,4,2-dioxazol-5-one **120b** (0.36 mmol, 70.9 mg). **121b** was isolated as a white solid (86.1 mg, 85%). Reaction was carried out at 40 °C.

MP 128 °C

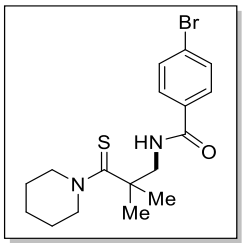
IR (film) 2939, 1660 (C=O), 1480, 1430, 1013 (C=S), 756, 735 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br. s, 1H, NHC(O)Ar), 7.74 (app d, *J* = 8.5 Hz, 2H, Ar-H), 7.38 (app d, *J* = 8.5 Hz, 2H, Ar-H), 4.35 – 3.91 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.84 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), 1.79- 1.65 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.40 (s, 6H, CCH_3CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 166.3, 137.6, 133.3, 128.8, 128.6, 54.3, 53.3, 49.0, 26.3, 24.6, 24.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{23}ClN_2OS$) requires *m/z* 339.1298, found *m/z* 339.1303.

121c: 4-bromo-*N*-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)benzamide



Prepared according to the general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55.5 mg) and 3-(4-bromophenyl)-1,4,2-dioxazol-5-one **120c** (0.36 mmol, 87.5 mg). **121c** was isolated as a white solid (96.7 mg, 84%). Reaction was carried out at 40 °C.

MP 150 °C

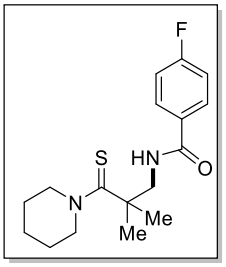
IR (film) 2938, 1660 (C=O), 1478, 1430, 1009 (C=S), 844 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br. s, 1H, N<u>H</u>C(O)Ar), 7.67 (app d, *J* = 8.5 Hz, 2H, Ar-<u>H</u>), 7.55 (app d, *J* = 8.5 Hz, 2H, Ar-<u>H</u>), 4.38 – 3.93 (m, 4H, $CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 3.84 (d, *J* = 6.5 Hz, 2H, $CC\underline{H_2}NHC(CO)$), 1.78- 1.65 (m, 6H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}C\underline{H_2}$), 1.40 (s, 6H, $CC\underline{H_3}C\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9, 166.2, 137.4, 133.1, 128.7, 128.4, 54.2, 53.1, 48.9, 26.2, 24.4, 24.1.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{23}BrN_2OS$) requires *m/z* 383.0793, found *m/z* 383.0795.

121d: 4-fluoro-*N*-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)benzamide



Prepared according to the general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55. 5 mg) and 3-(4-fluorophenyl)-1,4,2-dioxazol-5-one **120d** (0.36 mmol, 65.2 mg). **121d** was isolated as a white solid (83.2 mg, 86%). Reaction was carried out at 40 °C.

MP 104 - 105 °C

IR (film) 2938, 1659 (C=O), 1492, 1431, 1015 (C=S), 851 cm^{-1}.

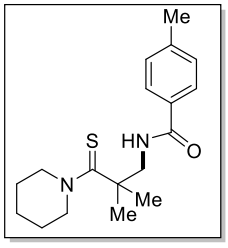
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br. s, 1H, NHC(O)Ar), 7.84 – 7.77 (m, 2H, Ar-H), 7.12 – 7.05 (m, 2H, Ar-H), 4.42 – 3.93 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.84 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), 1.80- 1.64 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.40 (s, 6H, CCH_3CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.1, 166.3, 164.8 (d, J_{C-F} = 251.5 Hz), 131.0 (d, J_{C-F} = 3.0 Hz), 129.4 (d, J_{C-F} = 9.0 Hz), 115.6 (d, J_{C-F} = 21.8 Hz), 54.3, 53.3, 49.0, 26.3, 24.6, 24.3.

^{19}F NMR (377 MHz, $CDCl_3$): -108.78.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{23}FN_2OS$) requires *m/z* 323.1593, found *m/z* 323.1597.

121e: *N*-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)-4-methylbenzamide



Prepared according to the general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55. 5 mg) and 3-(*p*-tolyl)-1,4,2-dioxazol-5-one **120e** (0.36 mmol, 63.7 mg). **121e** was isolated as a white solid (70.6 mg, 74%). Reaction was carried out at 60 °C.

MP 124 °C

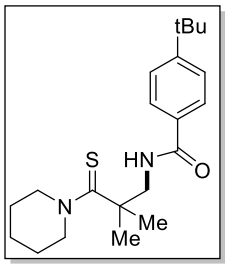
IR (film) 2938, 1649 (C=O), 1492, 1430, 1018 (C=S), 751 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (br. s, 1H, NHC(O)Ar), 7.70 (app d, *J* = 8.0 Hz, 2H, Ar-H), 7.21 (app d, *J* = 8.0 Hz, 2H, Ar-H), 4.40 – 3.94 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.86 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), 2.38 (s, 3H, Ar-CH_3), 1.80- 1.63 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.40 (s, 6H, CCH_3CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3, 167.4, 141.8, 132.0, 129.2, 127.1, 54.3, 53.1, 49.0, 26.4, 24.7, 24.3, 21.6.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{26}N_2OS$) requires *m/z* 319.1844, found *m/z* 319.1848.

121f: 4-(*tert*-butyl)-*N*-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)benzamide



Prepared according to general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55. 5 mg) and 3-(4-(*tert*-butyl)phenyl)-1,4,2-dioxazol-5-one **120f** (0.36 mmol, 78.9 mg). **121f** was isolated as a pale yellow oil (77.2 mg, 71%). Reaction was carried out at 60 °C.

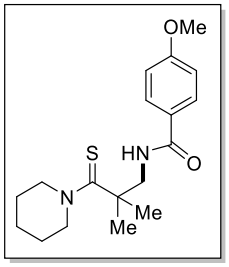
IR (film) 2940, 1657 (C=O), 1490, 1429, 1016 (C=S), 735 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br. s, 1H, NHC(O)Ar), 7.74 (app d, *J* = 8.5 Hz, 2H, Ar-H), 7.43 (app d, *J* = 8.5 Hz, 2H, Ar-H), 4.35 – 3.96 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.85 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), 1.78- 1.63 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.40 (s, 6H, CCH_3CH_3), 1.31 (s, 9H, $Ar(CH_3)_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3, 167.3, 154.8, 132.0, 126.9, 125.5, 54.3, 53.1, 49.0, 35.0, 31.3, 26.3, 24.6, 24.3.

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{21}H_{32}N_2OS$) requires *m/z* 383.2128, found *m/z* 383.2131.

121g: *N*-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)-4-methoxybenzamide



Prepared according to the general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55. 5 mg) and 3-(4-methoxyphenyl)-1,4,2-dioxazol-5-one **120g** (0.36 mmol, 69.5 mg). **121g** was isolated as a pale yellow oil (77.7 mg, 78%). Reaction was carried out at 60 °C.

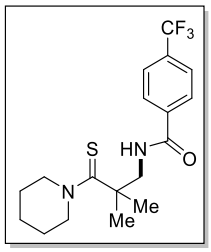
IR (film) 2938, 1650 (C=O), 1492, 1431, 1252, 1020 (C=S), 844 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br. s, 1H, NHC(O)Ar), 7.76 (app d, *J* = 9.0 Hz, 2H, Ar-H), 6.90 (app d, *J* = 9.0 Hz, 2H, Ar-H), 4.31 – 3.94 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.83 (d, *J* = 7.0 Hz, 2H, $CCH_2NHC(CO)$), 3.82 (s, 3H, Ar-OCH_3), 1.77- 1.64 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.40 (s, 6H, CCH_3CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3, 166.9, 162.1, 128.8, 127.2, 113.7, 55.5, 54.2, 53.1, 49.0, 26.3, 24.6, 24.3.

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{26}N_2O_2S$) requires *m/z* 357.1607, found *m/z* 357.1622.

121h: *N*-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)-4-(trifluoromethyl)benzamide



Prepared according to the general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55. 5 mg) and 3-(4-(trifluoromethyl)phenyl)-1,4,2-dioxazol-5-one **120h** (0.36 mmol, 83.2 mg). **121h** was isolated as a white solid (35.2 mg, 32%). Reaction was carried out at 60 °C.

MP 118 °C

IR (film) 2940, 1667 (C=O), 1497, 1431, 1326, 1016 (C=S), 838 cm^{-1}.

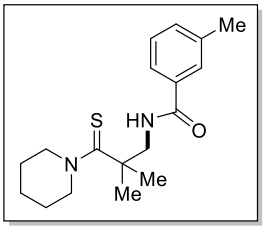
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br. s, 1H, NHC(O)Ar), 7.91 (app d, *J* = 8.0 Hz, 2H, Ar-H), 7.68 (app d, *J* = 8.0 Hz, 2H, Ar-H), 4.41 – 3.94 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.87 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), 1.80- 1.66 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.41 (s, 6H, CCH_3CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.0, 166.1, 138.2 (d, J_{C-F} = 0.5 Hz), 133.1 (q, J_{C-F} = 32.5 Hz), 127.6, 125.7 (q, J_{C-F} = 3.5 Hz), 123.9 (q, J_{C-F} = 272.5 Hz), 54.4, 53.4, 49.0, 26.4, 24.6, 24.3.

^{19}F NMR (377 MHz, $CDCl_3$): -62.89.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{23}F_3N_2OS$) requires *m/z* 373.1556, found *m/z* 373.1554.

121i: *N*-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)-3-methylbenzamide



Prepared according to the general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55. 5 mg) and 3-(m-tolyl)-1,4,2-dioxazol-5-one **120i** (0.36 mmol, 63.7 mg). **121i** was isolated as a white solid (60.7 mg, 64%). Reaction was carried out at 60 °C.

MP 105 - 106 °C

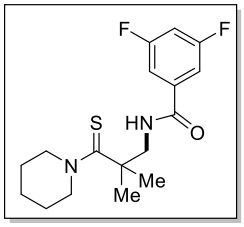
IR (film) 2939, 1656 (C=O), 1482, 1430, 1018 (C=S), 736 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br. s, 1H, NHC(O)Ar), 7.63 (s, 1H, Ar-H), 7.59 - 7.54 (m, 1H, Ar-H), 7.33 – 7.25 (m, 2H, Ar-H), 4.33 – 3.91 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.86 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), 2.39 (s, 3H, Ar-CH_3), 1.77- 1.65 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.41 (s, 6H, CCH_3CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3, 167.6, 138.4, 134.9, 132.1, 128.5, 127.9, 124.0, 54.3, 53.2, 49.0, 26.4, 24.6, 24.3, 21.5.

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{26}N_2OS$) requires *m/z* 341.1658, found *m/z* 341.1666.

121j: *N*-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)-3,5-difluorobenzamide



Prepared according to general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55. 5 mg) and 3-(3,5-difluorophenyl)-1,4,2-dioxazol-5-one **120j** (0.36 mmol, 71.6 mg). **121j** was isolated as a white solid (61.2 mg, 60%). Reaction was carried out at 40 °C.

MP 137 °C

IR (film) 2939, 1667 (C=O), 1436, 1323, 1123, 1018 (C=S), 987, 856 cm^{-1}.

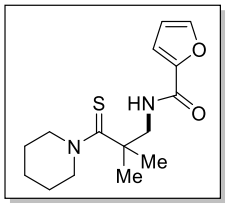
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (br. s, 1H, NHC(O)Ar), 7.35 - 7.27 (m, 2H, Ar-H), 6.91 (tt, *J* = 8.5, 2.5 Hz, 1H, Ar-H), 4.46 – 3.88 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.84 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), 1.80 - 1.67 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.40 (s, 6H, CCH_3CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.8, 166.1(app t, J_{C-F} = 3.0 Hz), 163.1 (dd, J_{C-F} = 250.0, 12.0 Hz), 138.4 (t, J_{C-F} = 8.0 Hz), 110.5- 110.2 (m), 106.7 (t, J_{C-F} = 25.5 Hz), 54.3, 53.5, 49.0, 26.3, 24.5, 24.3.

^{19}F NMR (377 MHz, $CDCl_3$): -108.44.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{22}F_2N_2OS$) requires *m/z* 341.1494, found *m/z* 341.1506.

121k: *N*-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)furan-2-carboxamide



Prepared according to the general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55. 5 mg) and 3-(furan-2-yl)-1,4,2-dioxazol-5-one **120k** (0.36 mmol, 55.1 mg). **121k** was isolated as a white solid (73.5 mg, 83%). Reaction was carried out at 60 °C.

MP 107 °C

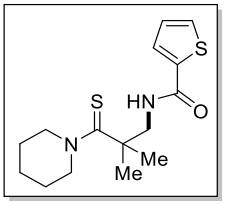
IR (film) 2940, 1660 (C=O), 1513, 1474, 1431, 1010 (C=S), 735 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (br. s, 1H, N<u>H</u>C(O)Ar), 7.44 (dd, *J* = 1.5, 1.0 Hz, 1H, Ar-<u>H</u>), 7.07 (dd, *J* = 3.5, 1.0 Hz, 1H, Ar-<u>H</u>), 6.46 (dd, *J* = 3.5, 2.0 Hz, 1H, Ar-<u>H</u>), 4.42 – 3.91 (m, 4H, $CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 3.83 (d, *J* = 7.0 Hz, 2H, $CC\underline{H_2}$NHC(CO)), 1.79 - 1.65 (m, 6H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}C\underline{H_2}$), 1.39 (s, 6H, $CC\underline{H_3}C\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 158.8, 148.4, 144.1, 113.9, 112.0, 54.3, 52.5, 49.0, 26.3, 24.6, 24.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{22}N_2O_2S$) requires *m/z* 295.1475, found *m/z* 295.1468.

<u>121l</u><u>: *N*-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)thiophene-2-carboxamide</u>



Prepared according to the general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55. 5 mg) and 3-(thiophen-2-yl)-1,4,2-dioxazol-5-one **120l** (0.36 mmol, 60.8 mg). **121l** was isolated as a white solid (69.6 mg, 75%). Reaction was carried out at 60 °C.

MP 115 - 116 °C

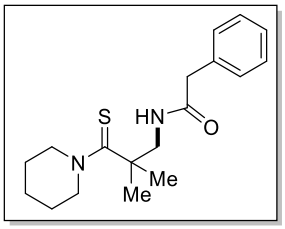
IR (film) 2938, 1645 (C=O), 1498, 1430, 1007 (C=S), 733 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br. s, 1H, N<u>H</u>C(O)Ar), 7.48 (dd, *J* = 3.5, 1.0 Hz, 1H, Ar-<u>H</u>), 7.44 (dd, *J* = 5.0, 1.0 Hz, 1H, Ar-<u>H</u>), 7.05 (dd, *J* = 5.0, 3.5 Hz, 1H, Ar-<u>H</u>), 4.43 – 3.93 (m, 4H, $CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 3.81 (d, *J* = 6.5 Hz, 2H, $CC\underline{H_2}$NHC(CO)), 1.79 - 1.62 (m, 6H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}C\underline{H_2}$), 1.40 (s, 6H, $CC\underline{H_3}C\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 162.0, 139.9, 129.8, 127.7, 127.6, 54.3, 53.2, 49.0, 26.3, 24.6, 24.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{22}N_2OS_2$) requires *m/z* 311.1246, found *m/z* 311.1245.

121m: *N*-(2,2-Dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)-2-phenylacetamide



Prepared according to the general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55. 5 mg) and 3-benzyl-1,4,2-dioxazol-5-one **120m** (0.36 mmol, 63.7 mg). **121m** was isolated as a pale yellow oil (63.2 mg, 66%). Reaction was carried out at 60 °C.

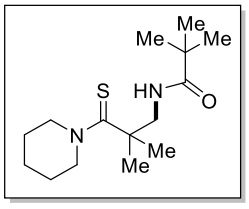
IR (film) 2938, 1655 (C=O), 1494, 1427, 1019 (C=S), 729, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 2H, Ar-H), 7.27 – 7.23 (m, 3H, Ar-H), 7.05 (br. s, 1H, NHC(O)CH_2Ar), 4.16 – 3.84 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.61 (d, *J* = 6.5 Hz, 2H, CCH_2NHC(CO)), 3.55 (s, 2H, C(O)CH_2Ar), 1.76 - 1.60 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.28 (s, 6H, $C(CH_3)_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1, 171.6, 135.3, 129.6, 129.0, 127.3, 54.3, 52.9, 48.9, 44.4, 26.4, 24.8, 24.4.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{26}N_2OS$) requires *m/z* 319.1839, found *m/z* 319.1836.

121n: *N*-(2,2-Dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)pivalamide



Prepared according to the general procedure E, using 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **119a** (0.30 mmol, 55. 5 mg) and 3-(*tert*-butyl)-1,4,2-dioxazol-5-one **120n** (0.36 mmol, 51.5 mg). **121n** was isolated as a pale yellow oil (62.7 mg, 74%). Reaction was carried out at 60 °C.

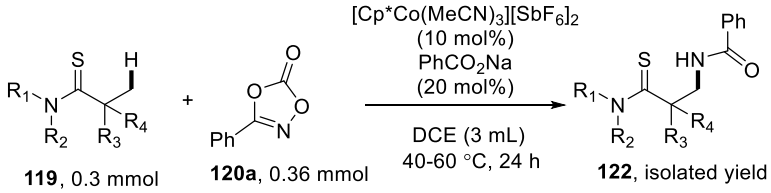
IR (film) 2938, 1658 (C=O), 1508, 1428, 1248, 1195, 1019 (C=S), 856 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (br. s, 1H, N<u>H</u>C(O)C), 4.35 – 3.92 (m, 4H, $CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 3.63 (d, *J* = 6.5 Hz, 2H, $CC\underline{H_2}NHC(CO)$), 1.77 – 1.62 (m, 6H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}C\underline{H_2}$), 1.32 (s, 6H, $CC\underline{H_3}C\underline{H_3}$), 1.17 (s, 9H, $C(O)C(C\underline{H_3})_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4, 178.8, 54.2, 52.4, 48.8, 38.9, 27.8, 26.3, 24.7, 24.3.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{15}H_{28}N_2OS$) requires *m/z* 285.1995, found *m/z* 285.1992.

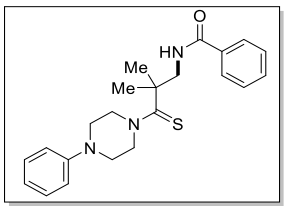
5.3.11 General Procedure F: Synthesis of Compound 122



In a N_2-filled glovebox, a 8 mL microwave vial was charged with thioamide **119** (0.30 mmol, 1 equiv), dioxazolone **120a** (0.36 mmol, 1.2 equiv), PhCOONa (0.06 mmol, 8.64 mg), $[Cp^*Co(MeCN)_3][SbF_6]_2$ (0.030 mmol, 23.6 mg) in DCE (3 mL). The vial was then brought out of the glovebox and reaction was run under inert atmosphere at 40-60 °C. After 24 h, the reaction mixture was cooled to room temperature and solvent was removed *in vacuo*. The crude reaction mixture was then purified and pure products were isolated by flash silica gel column chromatography (EtOAc/ PE = 1/9 to 2/3).

5.3.12 Synthesis & Characterization of Compound 122

122a: *N*-(2,2-dimethyl-3-(4-phenylpiperazin-1-yl)-3-thioxopropyl)benzamide



Prepared according to the general procedure F, using 2,2-dimethyl-1-(4-phenylpiperazin-1-yl)propane-1-thione **119b** (0.30 mmol, 78.6 mg) and 3-phenyl-1,4,2-dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **122a** was isolated as a white solid (87.7 mg, 77%). Reaction was carried out at 40 °C.

MP 133 °C

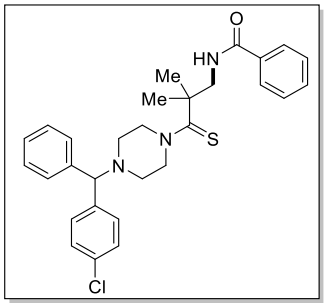
IR (film) 2922, 1655 (C=O), 1483, 1425, 1020, 734, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (br. s, 1H, N<u>H</u>C(O)Ar), 7.82 – 7.78 (m, 2H, Ar-<u>H</u>), 7.52 – 7.40 (m, 3H, Ar-<u>H</u>), 7.33 – 7.27 (m, 2H, Ar-<u>H</u>), 6.96 – 6.89 (m, 3H, Ar-<u>H</u>), 4.47 – 4.25 (m, 4H, $CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 3.90 (d, *J* = 6.5 Hz, 2H, $CC\underline{H_2}NHC(CO)$), 3.34 – 3.22 (m, 4H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}N$), 1.46 (s, 6H, $CC\underline{H_3}C\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.0, 167.5, 134.8, 131.5, 130.2, 129.5, 128.7, 127.1, 121.1, 116.5, 53.0, 52.4, 49.3, 49.2, 24.9.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{27}N_3OS$) requires *m/z* 382.1948, found *m/z* 382.1938.

122b: *N*-(3-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2,2-dimethyl-3-thioxopropyl)benzamide



Prepared according to general procedure F, using 1-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-2,2-dimethylpropane-1-thione **119c** (0.30 mmol, 115.8 mg) and 3-phenyl-1,4,2-dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **122b** was isolated as a white solid (110.7 mg, 73%). Reaction was carried out at 40 °C.

MP 94 °C

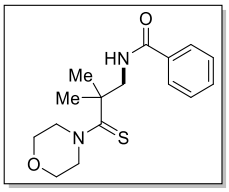
IR (film) 2927, 1658 (C=O), 1485, 1427, 1014 (C=S), 736, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (br. s, 1H, NHC(O)Ar), 7.82 – 7.33 (m, 2H, Ar-H), 7.51 – 7.34 (m, 7H, Ar-H), 7.33 – 7.18 (m, 5H, Ar-H), 4.71 – 3.91 (m, 4H, $CH_2CH_2NCH_2CH_2$), 4.20 (s, 1H, Ar-CH-Ar), 3.84 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), 2.64 – 2.37 (m, 4H, $CH_2CH_2NCH_2CH_2N$), 1.37 (s, 6H, CCH_3CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6, 167.4, 141.2, 140.3, 134.8, 133.4, 131.5, 129.2, 129.2, 129.1, 128.6, 128.0, 127.9, 127.1, 75.5, 52.9, 52.4, 52.0, 49.0, 24.9.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{29}H_{32}ClN_3OS$) requires *m/z* 506.2027, found *m/z* 506.2010.

122c: *N*-(2,2-dimethyl-3-morpholino-3-thioxopropyl)benzamide



Prepared according to general procedure F, using 2,2-dimethyl-1-morpholinopropane-1-thione **119d** (0.30 mmol, 56.1 mg) and 3-phenyl-1,4,2-dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **122c** was isolated as a pale yellow oil (55.3 mg, 60%). Reaction was carried out at 40 °C.

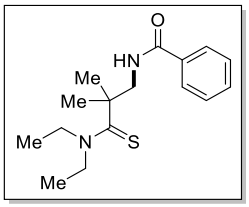
IR (film) 2928, 1655 (C=O), 1484, 1424, 1036, 734, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (br. s, 1H, NHC(O)Ar), 7.81 – 7.76 (m, 2H, Ar-H), 7.51 – 7.39 (m, 3H, Ar-H), 4.32 – 4.14 (m, 4H, $CH_2CH_2NCH_2CH_2$), 3.87 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), 3.79- 3.74 (m, 4H, $CH_2CH_2NCH_2CH_2O$), 1.41 (s, 6H, CCH_3CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.0, 167.5, 134.7, 131.5, 128.6, 127.1, 66.7, 53.4, 53.0, 49.0, 24.8.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{22}N_2O_2S$) requires *m/z* 307.1475, found *m/z* 307.1475.

122d: *N*-(3-(diethylamino)-2,2-dimethyl-3-thioxopropyl)benzamide



Prepared according to general procedure F, using *N*,*N*-diethyl-2,2-dimethylpropanethioamide **119e** (0.30 mmol, 51.9 mg) and 3-phenyl-1,4,2-dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **122d** was isolated as a white solid (62.8 mg, 72%). Reaction was carried out at 40 °C.

MP 74 °C

IR (film) 2935, 1660 (C=O), 1484, 1420, 1026, 712, 693 cm^{-1}.

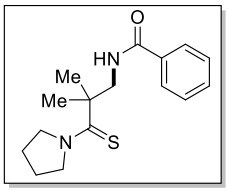
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (br. s, 1H, NHC(O)Ar), 7.83 – 7.77 (m, 2H, Ar-H), 7.50 – 7.38 (m, 3H, Ar-H), *4.08 – 3.97 (m, 2H, $CH_3CH_2NCH_2CH_3$), 3.87 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), *3.85 - 3.74 (m, 2H, $CH_3CH_2NCH_2CH_3$), 1.40 (s, 6H, CCH_3CH_3), 1.33 – 1.22 (m, 6H, $CH_3CH_2NCH_2CH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3, 167.4, 134.9, 131.4, 128.6, 127.1, 53.5, *49.3, 49.1, *47.5, 24.8, *13.9, *10.8.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{24}N_2OS$) requires *m/z* 293.1682, found *m/z* 293.1695.

* Rotamers observed.

122e: *N*-(2,2-dimethyl-3-(pyrrolidin-1-yl)-3-thioxopropyl)benzamide



Prepared according to the general procedure F, using 2,2-dimethyl-1-(pyrrolidin-1-yl)propane-1-thione **119f** (0.30 mmol, 51.3 mg) and 3-phenyl-1,4,2-dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **122e** was isolated as a pale yellow oil (58.6 mg, 67%). Reaction was carried out at 40 °C.

IR (film) 2972, 1658 (C=O), 1485, 1434, 1035, 713, 693 cm^{-1}.

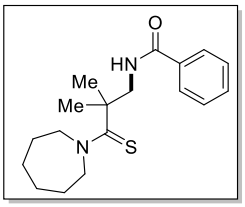
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (br. s, 1H, NHC(O)Ar), 7.83 – 7.78 (m, 2H, Ar-H), 7.51 – 7.38 (m, 3H, Ar-H), *3.95 (t, *J* = 7.0 Hz, 2H, $CH_2CH_2NCH_2CH_2$), 3.90 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), *3.82 (t, *J* = 7.0 Hz, 2H, $CH_2CH_2NCH_2CH_2$), *2.05 (p, *J* = 7.0 Hz, 2H, $CH_2CH_2NCH_2CH_2$), *1.92 (p, *J* = 7.0 Hz, 2H, $CH_2CH_2NCH_2CH_2$), 1.41 (s, 6H, CCH_3CH_3). **^{13}C**

NMR (101 MHz, $CDCl_3$) δ 206.1, 167.3, 135.0, 131.4, 128.6, 127.1, *58.0, *53.1, 52.8, 49.3, *27.5, 23.9, *23.2.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{22}N_2OS$) requires *m/z* 291.1526, found *m/z* 291.1530.

* Rotamers observed.

122f: *N*-(3-(azepan-1-yl)-2,2-dimethyl-3-thioxopropyl)benzamide



Prepared according to general procedure F, using 1-(azepan-1-yl)-2,2-dimethylpropane-1-thione **119g** (0.30 mmol, 59.7 mg) and 3-phenyl-1,4,2-dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **122f** was isolated as a pale yellow oil (63.7 mg, 67%). Reaction was carried out at 40 °C.

IR (film) 2933, 1659 (C=O), 1484, 1417, 1019 (C=S), 712, 693 cm^{-1}.

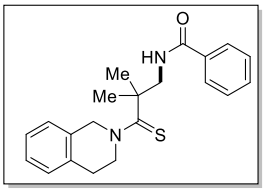
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br. s, 1H, N<u>H</u>C(O)Ar), 7.83 – 7.76 (m, 2H, Ar-<u>H</u>), 7.50 – 7.38 (m, 3H, Ar-<u>H</u>), *4.16 – 4.04 (m, 2H, $CH_2CH_2C\underline{H_2}NCH_2CH_2CH_2$), *4.02 – 3.90 (m, 2H, $CH_2CH_2CH_2NC\underline{H_2}CH_2CH_2$), 3.87 (d, *J* = 6.5 Hz, 2H, $CC\underline{H_2}$NHC(CO)), 1.97 – 1.78 (m, 4H, $CH_2C\underline{H_2}CH_2NCH_2C\underline{H_2}CH_2$), 1.62 – 1.55 (m, 4H, $C\underline{H_2}CH_2CH_2NCH_2CH_2C\underline{H_2}$), 1.42 (s, 6H, $CC\underline{H_3}C\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4, 167.4, 134.9, 131.4, 128.6, 127.1, *57.5, *54.2, 53.5, 49.2, *29.7, *27.8, *25.4, *24.8(2 x C).

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{26}N_2OS$) requires *m/z* 319.1839, found *m/z* 319.1843.

* Rotamers observed.

122g: *N*-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2,2-dimethyl-3-thioxopropyl)benzamide



Prepared according to general procedure F, using 1-(3,4-dihydroisoquinolin-2(1H)-yl)-2,2-dimethylpropane-1-thione **119h** (0.30 mmol, 69.9 mg) and 3-phenyl-1,4,2-dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **122g** was isolated as a yellow oil (77.1 mg, 73%). Reaction was carried out at 40 °C.

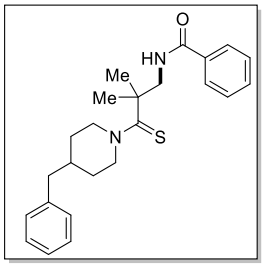
IR (film) 2932, 1655 (C=O), 1483, 1425, 1026, 712, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (br. s, 1H, NHC(O)Ar), 7.81 – 7.76 (m, 2H, Ar-H), 7.50 – 7.44 (m, 1H, Ar-H), 7.44 – 7.38 (m, 2H, Ar-H), 7.25 – 7.20 (m, 2H, Ar-H), 7.20 – 7.13 (m, 2H, Ar-H), 5.35 – 5.01 (m, 2H, $ArCH_2NCH_2CH_2$), 4.44 – 4.16 (m, 2H, $ArCH_2NCH_2CH_2$), 3.91 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), 3.03 (t, *J* = 5.5 Hz, 2H, $ArCH_2NCH_2CH_2$), 1.47 (s, 6H, CCH_3CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9, 167.4, 134.7, 134.1, 132.4, 131.4, 128.6, 128.5, 127.4, 127.0, 126.9, 126.3, 55.3, 53.0, 51.1, 49.1, 28.7, 24.7.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{24}N_2OS$) requires *m/z* 353.1682, found *m/z* 353.1691.

122h: *N*-(3-(4-benzylpiperidin-1-yl)-2,2-dimethyl-3-thioxopropyl)benzamide



Prepared according to the general procedure F, using 1-(4-benzylpiperidin-1-yl)-2,2-dimethylpropane-1-thione **119i** (0.30 mmol, 82.6 mg) and 3-phenyl-1,4,2-dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **122h** was isolated as a yellow gum (97.8 mg, 83%). Reaction was carried out at 40 °C.

IR (film) 2930, 1658 (C=O), 1483, 1431, 1028, 735, 700 cm^{-1}.

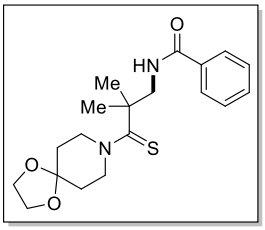
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (br. s, 1H, NHC(O)Ar), 7.84 – 7.79 (m, 2H, Ar-H), 7.50 – 7.39 (m, 3H, Ar-H), 7.31 – 7.27 (m, 2H, Ar-H), 7.24 – 7.18 (m, 1H, Ar-H), 7.15 – 7.11 (m, 2H, Ar-H), 3.87 (d, *J* = 6.5 Hz, 2H, $CCH_2NHC(CO)$), *3.33 – 2.81 (m, 4H, $CH_2CH_2NCH_2CH_2$), 2.56 (d, *J* = 7.0 Hz, 2H, $ArCH_2CH$), 1.99 – 1.88 (m, $ArCH_2CH$), 1.86 – 1.76 (m, 2H, $CH_AH_BCH_2NCH_2CH_AH_B$), 1.40 (s, 6H, CCH_3CH_3), 1.38 – 1.28 (m, 2H, $CH_AH_BCH_2NCH_2CH_AH_B$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5, 167.4, 139.7, 134.8, 131.4, 129.1, 128.6, 128.5, 127.1, 126.4, 53.4, 53.2, 49.1, 42.6, 38.2, 32.4, 24.7.

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{24}H_{30}N_2OS$) requires *m/z* 417.1971, found *m/z* 417.1981.

*Due to the broadening of this signal, its integral is not accurate.

122i: *N*-(2,2-dimethyl-3-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3-thioxopropyl)benzamide



Prepared according to the general procedure F, using 2,2-dimethyl-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)propane-1-thione **119j** (0.30 mmol, 72.9 mg) and 3-phenyl-1,4,2-

dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **122i** was isolated as a white solid (54.3 mg, 50%). Reaction was carried out at 40 °C.

MP 85 °C

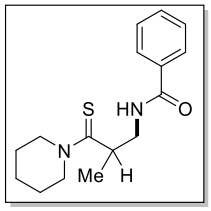
IR (film) 2964, 1658 (C=O), 1483, 1426, 1100, 1034, 713, 692 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br. s, 1H, N<u>H</u>C(O)Ar), 7.83 – 7.77 (m, 2H, Ar-<u>H</u>), 7.50 – 7.38 (m, 3H, Ar-<u>H</u>), 4.41 – 4.09 (m, 4H, $CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 3.99 (s, 4H, $OC\underline{H_2}C\underline{H_2}O$), 3.87 (d, *J* = 6.5 Hz, 2H, $CC\underline{H_2}NHC(CO)$), 1.86 – 1.77 (m, $C\underline{H_2}CH_2NCH_2C\underline{H_2}$), 1.41 (s, 6H, $CC\underline{H_3}C\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5, 167.5, 134.8, 131.4, 128.6, 127.1, 106.5, 64.8, 53.2, 50.8, 49.2, 35.4, 24.7.

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{19}H_{26}N_2O_3S$) requires *m/z* 385.1556, found *m/z* 385.1570.

122j: *N*-(2-methyl-3-(piperidin-1-yl)-3-thioxopropyl)benzamide



Prepared according to general procedure F, using 2-methyl-1-(piperidin-1-yl)propane-1-thione **119k** (0.30 mmol, 51.3 mg) and 3-phenyl-1,4,2-dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **122j** was isolated as a white solid (49.4 mg, 57%). Reaction was carried out at 60 °C.

MP 89 °C

IR (film) 2937, 1639 (C=O), 1486, 1442, 1021, 713, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 2H, Ar-<u>H</u>), 7.51 – 7.45 (m, 1H, Ar-<u>H</u>), 7.44 – 7.38 (m, 2H, Ar-<u>H</u>), 7.18 (br. s, 1H, N<u>H</u>C(O)Ar), *4.37 – 4.27 (m, 2H, $CH_2C\underline{H_2}NCH_2CH_2$), 3.90 – 3.80 (m, 1H, $CHC\underline{H_A}H_BNHC(CO)$), *3.78 – 3.73 (m, 2H, $CH_2CH_2NC\underline{H_2}CH_2$), 3.76 – 3.66 (m, 1H,

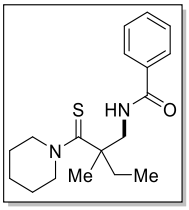
$CHCH_A\underline{H_B}NHC(CO)$), 3.53 – 3.43 (m, 1H, $C\underline{H}CH_2NHC(CO)$), 1.77- 1.54 (m, 6H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}C\underline{H_2}$), 1.21 (d, *J* = 7.0 Hz, 3H, $CHC\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.8, 167.5, 134.6, 131.6, 128.7, 127.0, *52.1, *50.8, 45.3, 41.8, 27.4, *25.7, *24.4, 18.4.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{22}N_2OS$) requires *m/z* 291.1526, found *m/z* 291.1530.

* Rotamers observed.

122k: *N*-(2-methyl-2-(piperidine-1-carbonothioyl)butyl)benzamide



Prepared according to general procedure F, using 2-methyl-1-(piperidin-1-yl)butane-1-thione **119l** (0.30 mmol, 59.7 mg) and 3-phenyl-1,4,2-dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **122k** was isolated as a pale yellow oil (81.2 mg, 85%). Reaction was carried out at 40 °C.

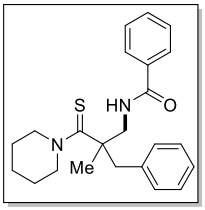
IR (film) 2939, 1658 (C=O), 1484, 1427, 1009 (C=S), 712, 693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (br. s, 1H, $N\underline{H}C(O)Ar$), 7.84 – 7.77 (m, 2H, Ar-$\underline{H}$), 7.50 – 7.37 (m, 3H, Ar-$\underline{H}$), 4.33 – 4.01 (m, 4H, $CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 3.98 (dd, *J* = 13.5, 5.0 Hz, 1H, $CC\underline{H_A}H_BNHC(O)$), 3.87 (dd, *J* = 13.5, 8.0 Hz, 1H, $CCH_A\underline{H_B}NHC(O)$), 1.86 (dq, *J* = 15.0, 7.5 Hz, 1H, $CC\underline{H_A}H_BCH_3$), 1.81- 1.68 (m, 1H, $CCH_A\underline{H_B}CH_3$), 1.77 – 1.65 (m, 6H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}C\underline{H_2}$), 1.37 (s, 3H, $CC\underline{H_3}$), 1.00 (t, *J* = 7.5 Hz, 3H, $CCH_2C\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 167.4, 134.9, 131.3, 128.6, 127.1, 54.2, 52.7, 50.9, 30.7, 26.3, 24.3, 22.3, 9.4.

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{26}N_2OS$) requires *m/z* 341.1658, found *m/z* 341.1643.

122l: *N*-(2-benzyl-2-methyl-3-(piperidin-1-yl)-3-thioxopropyl)benzamide



Prepared according to general procedure F, using 2,2-dimethyl-3-phenyl-1-(piperidin-1-yl)propane-1-thione **119m** (0.30 mmol, 78.3 mg) and 3-phenyl-1,4,2-dioxazol-5-one **120a** (0.36 mmol, 58.7 mg). **122l** was isolated as a pale yellow oil (88.6 mg, 78%). Reaction was carried out at 40 °C.

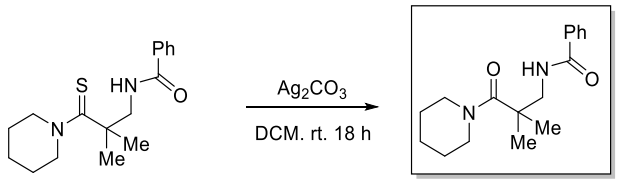
IR (film) 2940, 1659 (C=O), 1482, 1427, 1009 (C=S), 735, 702 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br. s, 1H, N<u>H</u>C(O)Ar), 7.81 – 7.74 (m, 2H, Ar-<u>H</u>), 7.50 – 7.37 (m, 3H, Ar-<u>H</u>), 7.33 – 7.27 (m, 2H, Ar-<u>H</u>), 7.26 – 7.19 (m, 3H, Ar-<u>H</u>), 4.45 – 4.02 (m, 4H, $CH_2C\underline{H_2}NC\underline{H_2}CH_2$), 4.01 – 3.85 (m, 2H, $CC\underline{H_2}NHC(CO)$), 3.20 (d, *J* = 14.0 Hz, 1H, $CC\underline{H_A}H_BAr$), 2.98 (d, *J* = 14.0 Hz, 1H, $CCH_A\underline{H_B}Ar$), 1.81 – 1.65 (m, 6H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}C\underline{H_2}$), 1.40 (s, 3H, $C(CH_2Ar)C\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6, 167.5, 136.4, 134.8, 131.4, 130.4, 128.6, 128.5, 127.1 (2xC), 54.5, 53.1, 51.6, 43.7, 26.3, 24.3, 22.5.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{28}N_2OS$) requires *m/z* 381.1995, found *m/z* 381.1996.

5.3.13 Synthesis & Characterization of N-(2,2-dimethyl-3-oxo-3-(piperidin-1-yl)propyl)benzamide 123



121a **123**

To a solution of thioamide **121a** (49 mg, 0.161 mmol) in DCM (2 mL) was added Ag_2CO_3 (133 mg, 0.483 mmol). The reaction was then stirred at rt for 18h, filtered over a pad of Celite, and concentrated *in vacuo.* The crude mixture was purified by FCC (PE/EtOAc: 4: 1 → 2:3) to obtain **123** as a white solid (38.9 mg, 84%).

MP 93 °C

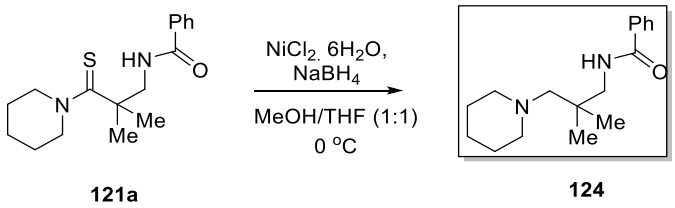
IR (film) 2936, 1655 (C=O), 1609, 1485, 1433, 713, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.77 (m, 2H, Ar-H), 7.50 – 7.34 (m, 4H, Ar-H, NHC(O)Ar), 3.60 – 3.54 (m, 6H, $CCH_2NHC(CO)$, $CH_2CH_2NCH_2CH_2$), 1.69- 1.54 (m, 6H, $CH_2CH_2NCH_2CH_2CH_2$), 1.34 (s, 6H, CCH_3CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 167.6, 135.0, 131.3, 128.6, 127.2, 50.8, 46.2, 43.8, 26.2, 24.7, 23.0.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{24}N_2O_2$) requires *m/z* 289.1911, found *m/z* 289.1911.

5.3.14 Synthesis & Characterization of N-(2,2-dimethyl-3-(piperidin-1-yl)propyl)benzamide 124



121a **124**

To a solution of thioamide **121a** (50 mg, 0.164 mmol) and $NiCl_2.6H_2O$ (304 mg, 1.28 mmol) in MeOH-THF (1:1, 40 ml) at 0 °C was added $NaBH_4$ (142 mg, 3.84 mmol) slowly in portion-wise. The reaction mixture was then stirred at 0 °C for 1 h. Upon completion, the mixture was warmed to rt and concentrated *in vacuo.* DCM was subsequently added to the black crude residue and filtered over a pad of celite. The filtrate was collected and solvent was removed *in vacuo*. The crude gum was purified *via* FCC (MeOH/DCM/NEt_3: 0: 99.5: 0.5 →1: 98.5: 0.5) to give **124** as a white solid (26.7 mg, 60%).[7]

MP 72 °C

IR (film) 2933, 1645 (C=O), 1535, 1609, 1489, 1294, 700 cm^{-1}.

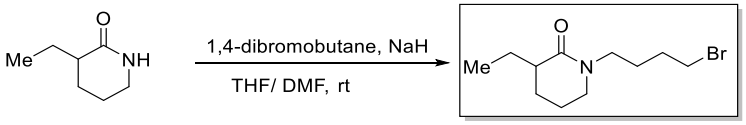
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (br. s, 1H, N<u>H</u>C(O)Ar), 7.90 – 7.83 (m, 2H, Ar-<u>H</u>), 7.51 – 7.39 (m, 3H, Ar-<u>H</u>), 3.36 (d, *J* = 4.5 Hz, 2H, CC<u>H$_2$</u>NHC(CO)), 2.66 – 2.39 (m, 4H, $CH_2C\underline{H_2}N\underline{CH_2}CH_2$), 2.32 (s, 2H, $NC\underline{H_2}C(CH_3)_2$), 1.57 – 1.46 (m, 4H, $C\underline{H_2}CH_2NCH_2C\underline{H_2}CH_2$), 1.44 – 1.35 (m, 2H, $CH_2CH_2NCH_2CH_2C\underline{H_2}$), 0.99 (s, 6H, $CC\underline{H_3}C\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 135.5, 131.2, 128.4, 127.3, 71.6, 57.5, 52.1, 34.4, 26.6, 25.3, 23.8.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{17}H_{26}N_2O$) requires *m/z* 275.2118, found *m/z* 275.2122.

5.4 Experimental Chapter 4

5.4.1 Synthesis & Characterization of 1-(4-bromobutyl)-3-ethylpiperidin-2-one 267



266 **267**

To a stirred mixture of THF (90 mL), DMF (18 mL) and NaH (942 mg, 23.6 mmol, 60% in mineral oil), 3-ethyl-2-piperidone, **266** (2.00 g, 15.7 mmol), was added at 0 ^{o}C. After the reaction mixture was stirred for 1 h at 0 ^{o}C, 1,4-dibromobutane (9.37 mL, 78.5 mmol) was added subsequently. The mixture was then warmed to rt and stirred for 18 h. Upon the completion of the reaction, the crude mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried with Na_2SO_4, and evaporated *in vacuo*. The crude mixture was then purified by FCC (PE:EtOAc 7:3 → 5:3) to give a pale yellow oil **267** (3.30g, 80%).

IR (film) 2933, 2867, 1630 (C=O), 1490, 1462, 676, 645 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 – 3.30 (m, 4H, $NCH_2CH_2CH_2$ $C\underline{H_2}Br$, $CHC(O)NC\underline{H_2}$), 3.28-3.21 (m, 2H, $NC\underline{H_2}CH_2CH_2$ CH_2Br), 2.28- 2.15 (m, 1H, $CH_2C\underline{H}(CH_2CH_3)C(O)N$), 1.99- 1.79 (m, 5H, $NCH_2CH_2C\underline{H_2}CH_2Br$, $C\underline{H_2}C\underline{H_A}H_BCH(CH_2CH_3)C(O)N$), 1.78- 1.62 (m, 3H, $CH_2CH_A\underline{H_B}CH(CH_2CH_3)C(O)N$, $CH(C\underline{H_2}CH_3)C(O)N$), 1.59- 1.44 (m, 2H, $NCH_2C\underline{H_2}CH_2CH_2Br$), 0.91 (t, *J* = 7.5 Hz, 3H, $CH(CH_2C\underline{H_3})C(O)N$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 47.9, 46.0, 42.8, 33.6, 29.9, 25.8, 25.6, 24.8, 21.8, 11.4.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{20}ONBr$) requires *m/z* 262.0803, 264.0781, found *m/z* 262.0801, 264.0781.

5.4.2 Synthesis & Characterization of 4-(3-ethyl-2-oxopiperidin-1-yl)butanal 268



267 **268**

To a solution of lactam **267** (3.00 g, 11.4 mmol) in DMSO (11 mL) was added NMO (5.35 g, 45.6 mmol). The reaction mixture was then left to stir at rt for 18h. Upon completion, the mixture was diluted with CH_2Cl_2 and washed with H_2O. The aqueous layer was then extracted and washed with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried with Na_2SO_4 and concentrated. The crude mixture was purified by FCC (PE:EtOAc 1:1 → 3:7 →0:1) to afford the desired colourless oil **268**. (1.34g, 60 %)

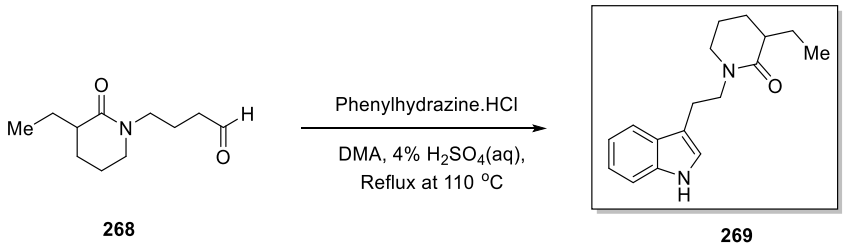
IR (film) 2935, 2870, 1720, 1628, 1492, 753, 676 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H, $NCH_2CH_2CH_2C(O)\underline{H}$), 3.40- 3.33 (m, 2H, $NC\underline{H_2}CH_2CH_2C(O)H$), 3.29- 3.21 (m, 2H, $CHC(O)NC\underline{H_2}$), 2.47 (t, *J* = 7.0 Hz, 2H, $NCH_2CH_2C\underline{H_2}C(O)H$), 2.18 (dq, *J* = 13.5, 4.5 Hz, 1H, $CH_2C\underline{H}(CH_2CH_3)C(O)N$), 2.00 – 1.80 (m, 5H, $NCH_2C\underline{H_2}CH_2C(O)H$, $C\underline{H_2}C\underline{H_A}H_BCH(CH_2CH_3)C(O)N$), 1.78 – 1.65 (m, 1H, $CH_2CH_A\underline{H_B}CH(CH_2CH_3)C(O)N$), 1.59 – 1.41 (m, 2H, $CH(C\underline{H_2}CH_3)C(O)N$), 0.91 (t, *J* = 7.5 Hz, 3H, $CH(CH_2C\underline{H_3})C(O)N$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 172.7, 48.0, 46.4, 42.8, 41.2, 25.7, 24.7, 21.7, 19.6, 11.4.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{11}H_{19}O_2N$) requires *m/z* 198.1489, found *m/z* 198.1489.

5.4.3 Synthesis & Characterization of 1-(2-(1*H*-indol-3-yl)ethyl)-3-ethylpiperidin-2-one 269



268 **269**

N_2 was bubbled through the solution of 4% H_2SO_4 (aq, 5 mL) at 50 °C for 20 min. Phenylhydrazine.HCl (217 mg, 1.50 mmol) was added subsequently and allowed to dissolve over 10 min. Aldehyde **268** (197 mg, 1.00 mmol) in degassed DMA (5 mL) was then added and the reaction mixture was heated under reflux at 110 °C for 2 h. After completion, the reaction was cooled to rt and washed with EtOAc and H_2O. The organic layer was removed and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried with Na_2SO_4, and evaporated *in vacuo*. The crude mixture was purified by FCC (PE:EtOAc 1:1 → 3:7 →0:1) to give a pale yellow solid **269**. (168 mg, 62%)

MP 122 -124 °C

IR (film) 2934, 2868, 1612, 1494, 1458, 740 cm^{-1}.

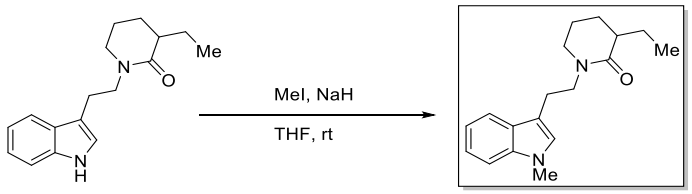
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (br.s, 1H, ArN<u>H</u>), 7.68 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.36 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.20 (dd, *J* = 11.0, 4.0 Hz, 1H, Ar<u>H</u>), 7.13 (dd, *J* = 11.0, 4.0 Hz, 1H, Ar<u>H</u>), 7.05 (d, *J* = 2.0 Hz, 1H, Ar<u>H</u>), 3.70 – 3.59 (m, 2H, $ArCH_2C\underline{H_2}N$), 3.21 – 3.13 (m, 2H, $C\underline{H_2}NC(O)CH(CH_2CH_3)$), 3.06 – 2.99 (m, 2H, $ArC\underline{H_2}CH_2N$), 2.32 – 2.16 (m, 1H, $CH_2NC(O)C\underline{H}(CH_2CH_3)$), 2.04 – 1.93 (m, 1H, $CH_2NC(O)CH(C\underline{H_A}H_BCH_3)CH_2CH_2$), 1.92 – 1.82 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)C\underline{H_A}H_BCH_2$), 1.82 – 1.73 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)CH_2C\underline{H_A}H_B$), 1.67 – 1.62 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)CH_2CH_A\underline{H_B}$),

1.59 – 1.42 (m, 2H, $CH_2NC(O)CH(CH_A\underline{H_B}CH_3)CH_2CH_2$, $CH_2NC(O)CH(CH_2CH_3)CH_A\underline{H_B}CH_2$), 0.94 (t, *J* = 7.5 Hz, 3H, $CH_2NC(O)CH(CH_2C\underline{H_3})$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 136.2, 127.5, 121.9 (2XC), 119.3, 118.8, 113.4, 111.1, 48.7, 48.6, 42.9, 25.8, 24.8, 23.0, 21.8, 11.5.

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{17}H_{22}ON_2$) requires *m/z* 293.1623, found *m/z* 293.1624.

5.4.4 Synthesis & Characterization of 3-ethyl-1-(2-(1-methyl-1*H*-indol-3-yl)ethyl)piperidin-2-one 270



269 **270**

To a stirred solution of indole **269** (340 mg, 1.26 mmol) in THF (5 mL) at 0 ^oC was added NaH (75.6 mg, 1.89 mmol, 60% in mineral oil). The reaction mixture was stirred at 0 ^oC for 15 min and subsequently at rt for 1 h. The mixture was then cooled to 0 ^oC, treated with MeI (0.157 mL, 2.52 mmol) and was allowed to warm up to rt. After stirring at rt for 3 h, the reaction mixture was cooled to 0 ^oC, quenched with std. NH_4Cl and extracted with EtOAc. The organic layes were combined, washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The crude residue was then purified by FCC (PE:EtOAc 1:1 → 3:7 →0:1) to afford a white solid **270**. (339 mg, 95%)

MP 82 -83 °C

IR (film) 2933, 2870, 1629, 1488, 1466, 740 cm^{-1}.

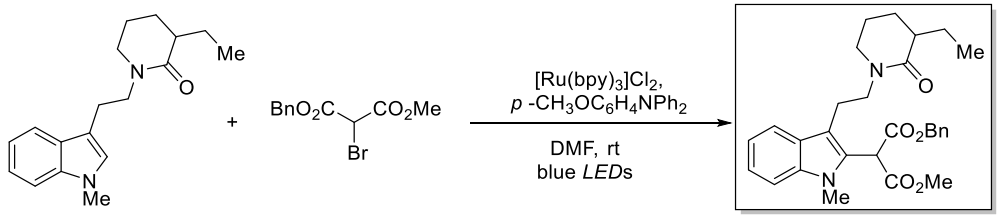
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 1H, Ar$\underline{H}$), 7.32 – 7.25 (m, 1H, Ar$\underline{H}$), 7.22 (t, *J* = 7.5 Hz, 1H, Ar$\underline{H}$), 7.11 (t, *J* = 7.5 Hz, 1H, Ar$\underline{H}$), 6.90 (s, 1H, Ar$\underline{H}$), 3.74 (s, 3H, $ArNC\underline{H_3}$), 3.62

(td, *J* = 8.0, 2.5 Hz, 2H, ArCH$_2$C<u>H$_2$</u>N), 3.19 (dt, *J* = 9.5, 5.0 Hz, 2H, C<u>H$_2$</u>NC(O)CH(CH$_2$CH$_3$)), 3.01 (t, *J* = 7.5 Hz, 2H, ArC<u>H$_2$</u>CH$_2$N), 2.28 – 2.18 (m, 1H, CH$_2$NC(O)C<u>H</u>(CH$_2$CH$_3$)), 2.04 – 1.93 (m, 1H, CH$_2$NC(O)CH(CH$_2$CH$_3$)C<u>H$_A$</u>H$_B$CH$_2$), 1.92 – 1.83 (m, 1H, CH$_2$NC(O)CH(C<u>H$_A$</u>H$_B$CH$_3$)CH$_2$CH$_2$), 1.82 – 1.74 (m, 1H, CH$_2$NC(O)CH(CH$_2$CH$_3$)CH$_2$C<u>H$_A$</u>H$_B$), 1.70-1.59 (m, 1H, CH$_2$NC(O)CH(CH$_2$CH$_3$)CH$_2$CH$_A$<u>H$_B$</u>), 1.54 – 1.41 (m, 2H, CH$_2$NC(O)CH(CH$_2$CH$_3$)CH$_A$<u>H$_B$</u>CH$_2$, CH$_2$NC(O)CH(CH$_A$<u>H$_B$</u>CH$_3$)CH$_2$CH$_2$), 0.94 (t, *J* = 7.5 Hz, 3H, CH$_2$NC(O)CH(CH$_2$C<u>H$_3$</u>)).

^{13}C NMR (125 MHz, CDCl$_3$) δ 172.4, 136.9, 127.9, 126.7, 121.5, 119.0, 118.7, 111.9, 109.1, 48.7 (2XC), 42.9, 32.6, 25.8, 24.8, 22.9, 21.8, 11.5.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{18}H_{24}ON_2$) requires *m/z* 285.1961, found *m/z* 285.1959.

5.4.5 Synthesis & Characterization of 1-benzyl 3-methyl 2-(3-(2-(3-ethyl-2-oxopiperidin-1-yl)ethyl)-1-methyl-1*H*-indol-2-yl)malonate 271



270 **271**

To a 10 mL vial, tris(2,2'-bipyridyl)ruthenium(II) chloride hexahydrate (3.95 mg, 5.28 µmol), indole **270** (150 mg, 0.528 mmol), 1-benzyl 3-methyl 2-bromomalonate (304 mg, 1.06 mmol), 4-methoxytriphenylamine (292 mg, 1.06 mmol) and DMF (5 mL) were added. The mixture was then placed at a distance of ~ 2.5 cm from blue light emitting diodes (LEDs) and stirred at rt for 12 h. Upon completion of the reaction, the mixture was extracted with EtOAc and H_2O. The organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic

layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by FCC (PE:EtOAc 7:3 → 1:1 →3:7), affording product **271** as a pale yellow oil. (213 mg, 82%) Product was obtained as a mixture of 2 diastereomers.

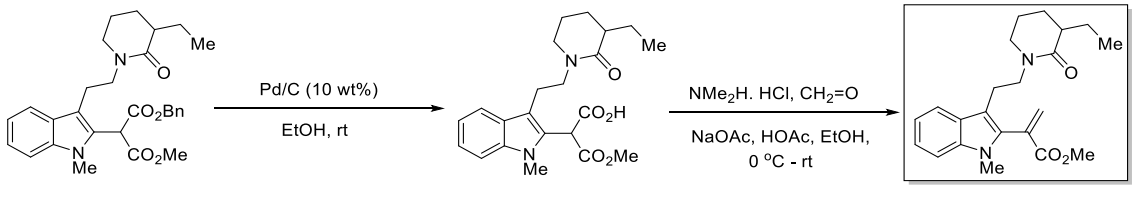
IR (film) 2938, 1736, 1626, 1491, 1144, 737, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.0, 2.5 Hz, 1H, Ar$\underline{H}$), 7.36 – 7.21 (m, 7H, Ar$\underline{H}$), 7.11 (t, *J* = 7.0 Hz, 1H, Ar$\underline{H}$), 5.24 (s, 1H, ArC$\underline{H}$(CO_2CH_2Ar)(CO_2CH_3)), 5.22 (s, 2H, ArCH($CO_2C\underline{H_2}Ar$)(CO_2CH_3)), 3.77 (s, 3H, ArNC$\underline{H_3}$), 3.65 (s, 3H, ArCH(CO_2CH_2Ar)($CO_2C\underline{H_3}$)), 3.60 – 3.47 (m, 1H, $ArCH_2C\underline{H_A}H_BN$), 3.41 – 3.27 (m, 1H, $ArCH_2CH_A\underline{H_B}N$), 3.12 – 2.93 (m, 4H, $ArC\underline{H_2}CH_2N$, $C\underline{H_2}NC(O)CH(CH_2CH_3)$), 2.24 – 2.12 (m, 1H, $CH_2NC(O)C\underline{H}(CH_2CH_3)$), 2.06 – 1.94 (m, 1H, $CH_2NC(O)CH(C\underline{H_A}H_BCH_3)CH_2CH_2$), 1.88 – 1.79 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)C\underline{H_A}H_BCH_2$), 1.74 – 1.65 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)CH_2C\underline{H_A}H_B$), 1.58 – 1.34 (m, 3H, $CH_2NC(O)CH(CH_2CH_3)CH_A\underline{H_B}CH_2$, $CH_2NC(O)CH(CH_A\underline{H_B}CH_3)CH_2CH_2$, $CH_2NC(O)CH(CH_2CH_3)CH_2CH_A\underline{H_B}$), 0.94 (t, *J* = 7.5 Hz, 3H, $CH_2NC(O)CH(CH_2C\underline{H_3})$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 167.7, 167.1, 137.5, 135.0, 128.5 (3xC), 128.3 (2xC), 127.3, 127.2, 127.1, 122.4, 119.3, 113.0, 109.2, 67.8, 53.0, 49.3, 49.1, 49.0, 42.9, 31.0, 25.7, 24.7, 22.4, 21.7, 11.6.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{29}H_{34}O_5N_2$) requires *m/z* 491.2541, found *m/z* 491.2539.

5.4.6 Synthesis & Characterization of methyl 2-(3-(2-(3-ethyl-2-oxopiperidin-1-yl)ethyl)-1-methyl-1*H*-indol-2-yl)acrylate 272



Palladium on carbon (10 wt%, 43.4 mg, 0.0408 mmol) was added to a stirred solution of indole **271** (200 mg, 0.408 mmol) in EtOH (10 mL). The reaction mixture was subsequently purged with H_2 and was allowed to stir at rt for 1 h. After the reaction was completed, the suspension was filtered over a pad of Celite and washed with EtOH. Excess EtOH was removed in *vacuo* to afford a solution of carboxylic acid **271a** in EtOH (4 mL). To the solution of carboxylic acid **271a** in EtOH (4 mL) was added dimethylamine chloride. HCl (332 mg, 4.07 mmol) and formaldehyde (37 wt% in water, 0.6 mL) at 0 ^oC. NaOAc (457 mg, 5.57 mmol) and acetic acid (0.170 mL, 2.97 mmol) were subsequently added and the reaction mixture was warmed to rt and stirred for 4 h. After the completion of the reaction, the suspension was then washed with H_2O and EtOAc. The aqueous phase was separated and washed with EtOAc. The combined organic layers were washed with satd. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was then purified by FCC (PE:EtOAc 7:3 → 1:1 →3:7) to afford a colourless foam **272**. (82 mg, 55 %)

IR (film) 2935, 2869, 1722, 1629, 1490, 1199, 746 cm^{-1}.

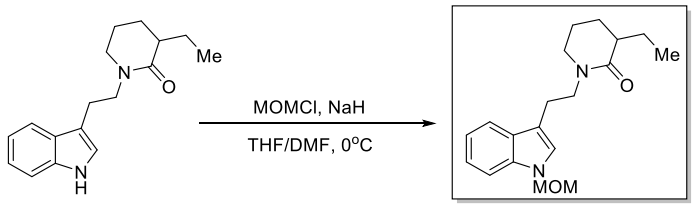
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1H, Ar$\underline{H}$), 7.29 – 7.19 (m, 2H, Ar$\underline{H}$), 7.11 (t, *J* = 7.5 Hz, 1H, Ar$\underline{H}$), 6.83 (d, *J* = 1.5 Hz, 1H, ArC=C$\underline{H_A}H_B(CO_2CH_3)$), 6.01 (d, *J* = 1.5 Hz, 1H, ArC=C$H_A\underline{H_B}(CO_2CH_3)$), 3.78 (s, 3H, ArNC$\underline{H_3}$), 3.63 – 3.56 (m, 1H, ArCH_2C$\underline{H_A}H_B$N), 3.54 (s, 3H, ArC=C$H_AH_B(CO_2C\underline{H_3})$), 3.47 – 3.35 (m, 1H, ArCH_2C$H_A\underline{H_B}$N), 3.24 – 3.10 (m, 2H, C$\underline{H_2}$NC(O)CH(CH_2CH_3)), 2.94 (t, *J* = 7.5 Hz, 2H, ArC$\underline{H_2}$CH_2N), 2.24 – 2.12 (m, 1H, CH_2NC(O)C$\underline{H}$(CH_2CH_3)), 2.03 – 1.91 (m, 1H, CH_2NC(O)CH(C$\underline{H_A}H_BCH_3$)CH_2CH_2), 1.90 – 1.80 (m, 1H, CH_2NC(O)CH(CH_2CH_3)C$\underline{H_A}H_BCH_2$), 1.79 – 1.70 (m, 1H, CH_2NC(O)CH(CH_2CH_3)CH_2C$\underline{H_A}H_B$), 1.64 – 1.55 (m, 1H, CH_2NC(O)CH(CH_2CH_3)$CH_2CH_A\underline{H_B}$),

1.54 – 1.38 (m, 2H, $CH_2NC(O)CH(CH_A\underline{H_B}CH_3)CH_2CH_2$, $CH_2NC(O)CH(CH_2CH_3)CH_A\underline{H_B}CH_2$), 0.92 (t, *J* = 7.5 Hz, 3H, $CH_2NC(O)CH(CH_2C\underline{H_3})$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 166.4, 136.8, 133.5, 133.3, 131.8, 127.4, 122.2, 119.5, 119.2, 111.8, 109.1, 52.4, 49.2, 48.8, 42.9, 30.6, 25.7, 24.7, 22.7, 21.8, 11.5.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{28}O_3N_2$) requires *m/z* 369.2173, found *m/z* 369.2180.

5.4.7 Synthesis & Characterization of 3-ethyl-1-(2-(1-(methoxymethyl)-1*H*-indol-3-yl)ethyl)piperidin-2-one 278



269 **278**

To a suspension of NaH (44.4 mg, 1.11 mmol, 60% in mineral oil) in THF (2.0 mL) and DMF (1.0 mL) at 0 °C was added a solution of indole **269** (200 mg, 0.74 mmol) in THF (1.0 mL) dropwise. After stirring at 0 °C for 1 h, MOMCl (84.3 µL, 1.11 mmol) was added dropwise. The reaction mixture was then stirred at 0 °C for another 1 h. Upon completion, the reaction was quenched with H_2O and extracted with EtOAc. The organic layers were combined, washed with brine and dried over Na_2SO_4. The crude residue was then purified by FCC (PE:EtOAc 7:3 → 1:1) to afford a white solid **278**. (206.3 mg, 89%)

MP 79 -80 °C

IR (film) 2937, 2873, 1629, 1492, 1465, 1352, 1331, 1240, 1184, 1130, 1084, 912, 744 cm^{-1}.

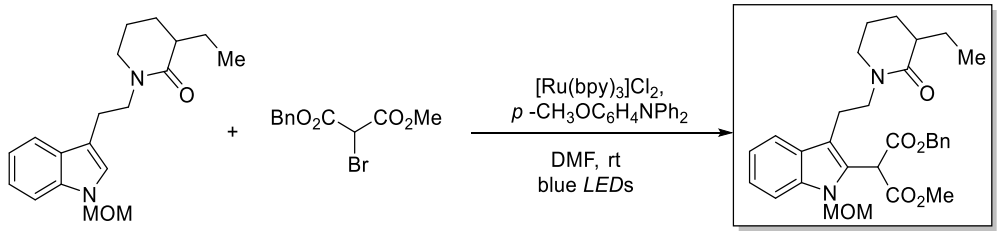
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 1H, Ar$\underline{H}$), 7.45 (d, *J* = 8.0 Hz, 1H, Ar$\underline{H}$), 7.23 (app t, *J* = 8.0 Hz, 1H, Ar$\underline{H}$), 7.15 (app t, *J* = 8.0 Hz, 1H, Ar$\underline{H}$), 7.02 (s, 1H, Ar$\underline{H}$), 5.40 (s, 2H,

NC$\underline{H_2}$O), 3.67 – 3.61 (m, 2H, ArCH$_2$C$\underline{H_2}$N), 3.23 (s, 3H, NCH$_2$OC$\underline{H_3}$), 3.21 – 3.13 (m, 2H C$\underline{H_2}$NC(O)CH(CH$_2$CH$_3$)), 3.04 – 2.98 (m, 2H, ArC$\underline{H_2}$CH$_2$N), 2.27 – 2.18 (m, 1H CH$_2$NC(O)C$\underline{H}$(CH$_2$CH$_3$)), 2.03 – 1.93 (m, 1H, CH$_2$NC(O)CH(CH$_2$CH$_3$)C$\underline{H_A}$H$_B$CH$_2$), 1.93 - 1.84 (m, 1H, CH$_2$NC(O)CH(C$\underline{H_A}$H$_B$CH$_3$)CH$_2$CH$_2$), 1.82 – 1.74 (m, 1H, CH$_2$NC(O)CH(CH$_2$CH$_3$)CH$_2$C$\underline{H_A}$H$_B$), 1.70 – 1.61 (m, 1H, CH$_2$NC(O)CH(CH$_2$CH$_3$)CH$_2$CH$_A$$\underline{H_B}$), 1.56 – 1.41 (m, 2H, CH$_2$NC(O)CH(CH$_2$CH$_3$)CH$_A$$\underline{H_B}CH_2$, CH$_2$NC(O)CH(CH$_A$$\underline{H_B}CH_3$)CH$_2CH_2$), 0.95 (t, *J* = 7.5 Hz, 3H, CH$_2$NC(O)CH(CH$_2$C$\underline{H_3}$)).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 136.8, 128.8, 125.8, 122.3, 119.9, 119.2, 113.7, 109.8, 77.3, 55.8, 48.8, 48.5, 43.0, 25.8, 24.8, 23.0, 21.8, 11.5.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{26}O_2N_2$) requires *m/z* 315.2069, found *m/z* 315.2067.

5.4.8 Synthesis & Characterization of 1-benzyl 3-methyl 2-(3-(2-(3-ethyl-2-oxopiperidin-1-yl)ethyl)-1-(methoxymethyl)-1*H*-indol-2-yl)malonate 279



278 **279**

To a 10 mL vial, tris(2,2'-bipyridyl)ruthenium(II) chloride hexahydrate (4.77 mg, 6.37 µmol), indole **278** (200 mg, 0.637 mmol), 1-benzyl 3-methyl 2-bromomalonate (364 mg, 1.27 mmol), 4-methoxytriphenylamine (351 mg, 1.27 mmol) and DMF (6 mL) were added. The mixture was then placed at a distance of ~ 2.5 cm from blue light emitting diodes (LEDs) and stirred at rt for 12 h. Upon completion of the reaction, the mixture was extracted with EtOAc and H_2O. The organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic

layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by FCC (PE:EtOAc 7:3 → 1:1 →3:7), affording product **279** as a pale yellow oil. (220 mg, 66 %) Product was obtained as a mixture of 2 diastereomers.

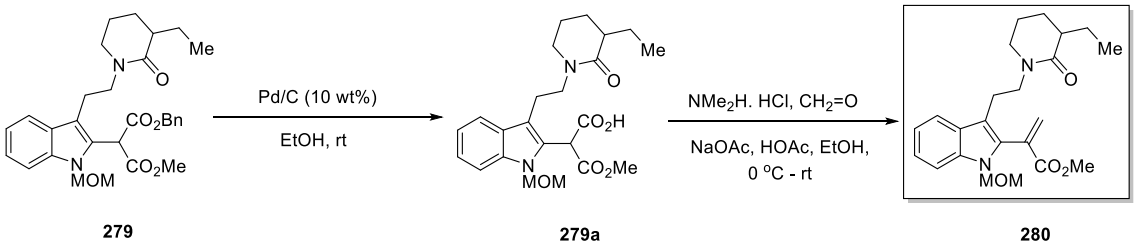
IR (film) 2946, 2868, 1752, 1739, 1631, 1492, 1465, 1335, 1298, 1185, 1146, 912, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (app d, *J* = 8.0 Hz, 1H, ArH), 7.40 (d, *J* = 8.0 Hz, 1H, ArH), 7.35 – 7.29 (m, 5H, ArH), 7.25 – 7.22 (m, 1H, ArH), 7.15 (app t, *J* = 7.5, 1H, ArH), 5.56 – 5.44 (m, 2H, NCH_2OCH_3), 5.28 – 5.14 (m, 3H, $ArCH(CO_2CH_2Ar)(CO_2CH_3)$, $ArCH(CO_2CH_2Ar)(CO_2CH_3)$), 3.76 (s, 3H, $ArCH(CO_2CH_2Ar)(CO_2CH_3)$), 3.64 – 3.52 (m, 1H, $ArCH_2CH_AH_BN$), 3.42 – 3.32 (m, 1H, $ArCH_2CH_AH_BN$), 3.15 (s, 3H, NCH_2OCH_3), 3.10 – 3.03 (m, 2H, $CH_2NC(O)CH(CH_2CH_3)$), 3.01 – 2.94 (m, 2H, $ArCH_2CH_2N$), 2.24 – 2.14 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)$), 2.06 – 1.94 (m, 1H, $CH_2NC(O)CH(CH_AH_BCH_3)CH_2CH_2$), 1.87 – 1.79 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)CH_AH_BCH_2$), 1.74 – 1.64 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)CH_2CH_AH_B$), 1.55 – 1.37 (m, 3H, $CH_2NC(O)CH(CH_2CH_3)CH_AH_BCH_2$, $CH_2NC(O)CH(CH_AH_BCH_3)CH_2CH_2$, $CH_2NC(O)CH(CH_2CH_3)CH_2CH_AH_B$), 0.95 (t, *J* = 7.5 Hz, 3H, $CH_2NC(O)CH(CH_2CH_3)$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 167.6, 167.0, 137.6, 135.1, 128.5 (3XC), 128.4, 128.3 (2XC), 128.0, 126.8, 120.3, 119.8, 115.3, 109.4, 74.6, 67.8, 55.5, 53.0, 49.0, 48.9, 48.6, 43.0, 25.8, 24.7, 22.3, 21.8, 11.6.

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{30}H_{36}O_6N_2$) requires *m/z* 543.2466, found *m/z* 543.2463.

5.4.9 Synthesis & Characterization of methyl 2-(3-(2-(3-ethyl-2-oxopiperidin-1-yl)ethyl)-1-(methoxymethyl)-1*H*-indol-2-yl)acrylate 280



279 279a 280

Palladium on carbon (10 wt%, 24.6 mg, 0.0231 mmol) was added to a stirred solution of indole **279** (120 mg, 0.231 mmol) in EtOH (6 mL). The reaction mixture was subsequently purged with H_2 and was allowed to stir at rt for 1 h. After the reaction was completed, the suspension was filtered over a pad of Celite and washed with EtOH. Excess EtOH was removed in *vacuo* to afford a solution of carboxylic acid **279a** in EtOH (2.5 mL). To the solution of carboxylic acid **279a** in EtOH (2.5 mL) was added dimethylamine chloride. HCl (188 mg, 2.31 mmol) and formaldehyde (37 wt% in water, 0.34 mL) at 0 °C. NaOAc (260 mg, 3.16 mmol) and acetic acid (96.7 µL, 1.69 mmol) were subsequently added and the reaction mixture was warmed to rt and stirred for 4 h. After the completion of the reaction, the suspension was then washed with H_2O and EtOAc. The aqueous phase was separated and washed with EtOAc. The combined organic layers were washed with satd. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was then purified by FCC (PE:EtOAc 7:3 → 1:1 →3:7) to afford a pale yellow oil **280**. (50.7 mg, 55 %)

IR (film) 2940, 2868, 1725, 1624, 1494, 1466, 1337, 1298, 1284, 1202, 1102, 913, 733 cm^{-1}.

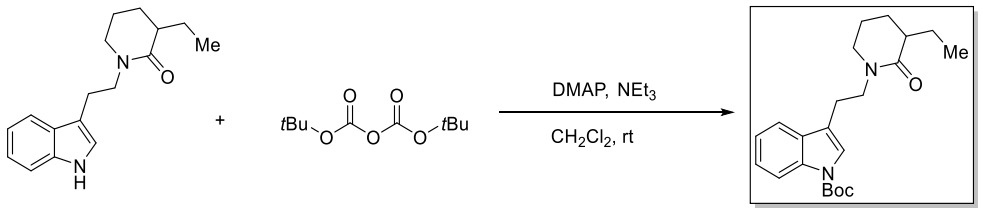
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.44 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.25 (app t (masked by $CDCl_3$), *J* = 7.5 Hz, 1H, Ar<u>H</u>), 7.16 (dd, *J* = 8.0, 6.5 Hz, 1H, Ar<u>H</u>), 6.84 (d, *J* = 1.5 Hz, 1H, ArC=C<u>H$_A$</u>H$_B$(CO_2CH_3)), 6.05 (d, *J* = 1.5 Hz, 1H, ArC=CH$_A$<u>H$_B$</u>(CO_2CH_3)), 5.31 (s, 2H, NC<u>H$_2$</u>O), 3.77 (s, 3H, ArC=CH$_A$H$_B$(CO_2C<u>H$_3$</u>)), 3.65 – 3.56 (m, 1H, ArCH$_2$C<u>H$_A$</u>H$_B$N), 3.49 –

3.39 (m, 1H, $ArCH_2CH_A\underline{H_B}N$), 3.23 – 3.11 (m, 5H, $C\underline{H_2}NC(O)CH(CH_2CH_3)$, $NCH_2OC\underline{H_3}$), 2.93 (app t, *J* = 7.5 Hz, 2H, $ArC\underline{H_2}CH_2N$), 2.24 – 2.14 (m, 1H, $CH_2NC(O)C\underline{H}(CH_2CH_3)$), 2.03 – 1.91 (m, 1H, $CH_2NC(O)CH(C\underline{H_A}H_BCH_3)CH_2CH_2$), 1.91 – 1.82 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)C\underline{H_A}H_BCH_2$), 1.80 – 1.72 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)CH_2C\underline{H_A}H_B$), 1.61 – 1.38 (m, 3H, $CH_2NC(O)CH(CH_2CH_3)CH_2CH_A\underline{H_B}$, $CH_2NC(O)CH(CH_A\underline{H_B}CH_3)CH_2CH_2$, $CH_2NC(O)CH(CH_2CH_3)CH_A\underline{H_B}CH_2$), 0.94 (t, *J* = 7.5 Hz, 3H, $CH_2NC(O)CH(CH_2C\underline{H_3})$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 166.5, 137.0, 133.7, 132.7, 131.9, 128.1, 122.9, 120.3, 119.7, 113.7, 109.9, 75.0, 55.6, 52.4, 48.9 (2XC), 42.9, 25.8, 24.7, 22.6, 21.8, 11.5.

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{23}H_{30}O_4N_2$) requires *m/z* 421.2098, found *m/z* 421.2089.

5.4.10 Synthesis & Characterization of tert-butyl 3-(2-(3-ethyl-2-oxopiperidin-1-yl)ethyl)-1*H*-indole-1-carboxylate 283



269 **283**

To a stirred solution of indole **269** (700 mg, 2.59 mmol) and di-*tert*-butyl dicarbonate (849 mg, 3.89 mmol) in CH_2Cl_2 (9 mL) were added DMAP (31.6 mg, 0.259 mmol) and NEt_3 (0.615 mL, 4.41 mmol) at 0 °C. The reaction mixture was allowed to warm to rt and stir for 1.5 h. Upon completion, the reaction was quenched with satd. $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. FCC (PE:EtOAc 1:1 → 3:7 →0:1) was performed to give product **283** as an off-white solid. (913 mg, 95 %)

MP 79-80 °C

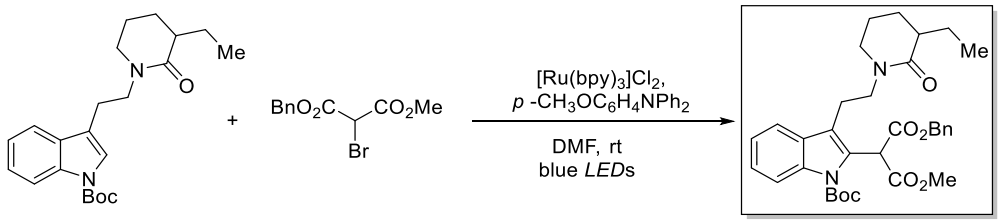
IR (film) 2934, 2870, 1728, 1633, 1490, 1453, 747 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br.s, 1H, Ar<u>H</u>), 7.63 (d, *J* = 7.5 Hz, 1H, Ar<u>H</u>), 7.40 (s, 1H, Ar<u>H</u>), 7.31 (t, *J* = 7.5 Hz, 1H, Ar<u>H</u>), 7.24 (t, *J* = 7.5 Hz, 1H, Ar<u>H</u>), 3.66 – 3.57 (m, 2H, $ArCH_2C\underline{H_2}N$), 3.23 – 3.15 (m, 2H, $C\underline{H_2}NC(O)CH(CH_2CH_3)$), 2.99 – 2.93 (m, 2H, $ArC\underline{H_2}CH_2N$), 2.32 – 2.18 (m, 1H, $CH_2NC(O)C\underline{H}(CH_2CH_3)$), 2.04 – 1.94 (m, 1H, $CH_2NC(O)CH(C\underline{H_A}H_BCH_3)CH_2CH_2$), 1.93 – 1.84 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)C\underline{H_A}H_BCH_2$), 1.84 – 1.76 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)CH_2C\underline{H_A}H_B$), 1.70 – 1.60 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)CH_2CH_A\underline{H_B}$), 1.65 (s, 9H, $NCO_2C(C\underline{H_3})_3$), 1.60 – 1.45 (m, 2H, $CH_2NC(O)CH(CH_A\underline{H_B}CH_3)CH_2CH_2$, $CH_2NC(O)CH(CH_2CH_3)CH_A\underline{H_B}CH_2$), 0.95 (t, *J* = 7.5 Hz, 3H, $CH_2NC(O)CH(CH_2C\underline{H_3})$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 149.7, 135.5, 130.5, 124.4, 123.1, 122.5, 119.1, 118.1, 115.2, 83.4, 48.9, 48.1, 42.9, 28.2 (3XC), 25.8, 24.8, 22.8, 21.8, 11.5.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{30}O_3N_2$) requires *m/z* 371.2325, found *m/z* 371.2329.

5.4.11 Synthesis & Characterization of 1-benzyl 3-methyl 2-(1-(*tert*-butoxycarbonyl)-3-(2-(3-ethyl-2-oxopiperidin-1-yl)ethyl)-1*H*-indol-2-yl)malonate 284



283 **284**

To a 10 mL vial, tris(2,2'-bipyridyl)ruthenium(II) chloride hexahydrate (4.05 mg, 5.41 µmol), indole **283** (200 mg, 0.541 mmol), 1-benzyl 3-methyl 2-bromomalonate (309 mg, 1.08 mmol), 4-methoxytriphenylamine (297 mg, 1.08 mmol) and DMF (5 mL) were added. The mixture was then placed at a distance of ~ 2.5 cm from blue light emitting diodes (LEDs) and stirred at rt for 12 h. Upon completion of the reaction, the mixture was transferred to a separating funnel and extracted with EtOAc and H_2O. The organic phase was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by FCC (PE:EtOAc 7:3 → 1:1 →3:7), affording product **284** as a pale yellow foam. (278 mg, 89 %) Product **284** was obtained as a mixture of 2 diastereomers.

IR (film) 2937, 1726, 1629, 1455, 1328, 745 cm^{-1}.

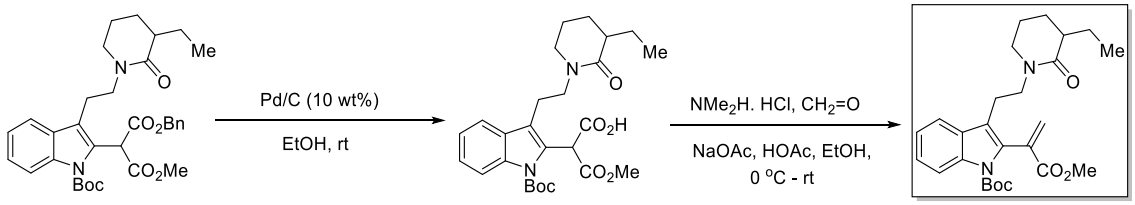
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.5 Hz, 1H, Ar<u>H</u>), 7.75 (d, *J* = 7.5 Hz, 1H, Ar<u>H</u>), 7.39 – 7.21 (m, 7H, Ar<u>H</u>), 5.51 (s, 1H, ArC<u>H</u>(CO_2CH_2Ar)(CO_2CH_3)), 5.22 (s, 2H, ArCH($CO_2C\underline{H_2}Ar$)(CO_2CH_3)), 3.75 (s, 3H, ArCH(CO_2CH_2Ar)($CO_2C\underline{H_3}$)), 3.60 – 3.48 (m, 1H, $ArCH_2C\underline{H_A}H_BN$), 3.37 – 3.28 (m, 1H, $ArCH_2CH_A\underline{H_B}N$), 3.08 – 2.97 (m, 2H, $C\underline{H_2}NC(O)CH(CH_2CH_3)$), 2.96 – 2.83 (m, 2H, $ArC\underline{H_2}CH_2N$), 2.21 – 2.12 (m, 1H, $CH_2NC(O)C\underline{H}(CH_2CH_3)$), 2.04 – 1.94 (m, 1H, $CH_2NC(O)CH(C\underline{H_A}H_BCH_3)CH_2CH_2$), 1.85 – 1.77

(m, 1H, $CH_2NC(O)CH(CH_2CH_3)C\underline{H_A}H_BCH_2$), 1.69 – 1.59 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)CH_2C\underline{H_A}H_B$), 1.63 (s, 9H, $NCO_2C(C\underline{H_3})_3$), 1.56 – 1.46 (m, 2H, $CH_2NC(O)CH(CH_A\underline{H_B}CH_3)CH_2CH_2$, $CH_2NC(O)CH(CH_2CH_3)CH_2CH_A\underline{H_B}$), 1.44 – 1.35 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)CH_A\underline{H_B}CH_2$), 0.95 (t, *J* = 7.5 Hz, 3H, $CH_2NC(O)CH(CH_2C\underline{H_3})$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 167.2, 166.7, 150.6, 135.4, 129.6, 128.4 (3XC), 128.2, 128.0(2XC), 127.7, 124.8, 122.8, 120.4, 119.5, 115.6, 84.5, 67.4, 52.7, 49.9, 49.1, 48.4, 42.9, 28.1(3XC), 25.7, 24.7, 22.0, 21.7, 11.6.

HRMS (ES+) exact mass calculated for $[M+Na]^+$ ($C_{33}H_{40}O_7N_2$) requires *m/z* 599.2726, found *m/z* 599.2728.

5.4.12 Synthesis & Characterization of *tert*-butyl 3-(2-(3-ethyl-2-oxopiperidin-1-yl)ethyl)-2-(3-methoxy-3-oxoprop-1-en-2-yl)-1*H*-indole-1-carboxylate 285



284 **284a** **285**

Palladium on carbon (10 wt%, wet, 63.5 mg, 0.0597 mmol) was added to a stirred solution of indole **284** (344 mg, 0.597 mmol) in EtOH (15 mL). The reaction mixture was subsequently purged with H_2 and was allowed to stir at rt for 1 h. After the reaction was completed, the suspension was filtered over a pad of Celite and washed with EtOH. Excess EtOH was removed *in vacuo* to afford a solution of carboxylic acid **284a** in EtOH (6 mL). To the solution of carboxylic acid **284a** in EtOH (6 mL) was added dimethylamine. HCl (487 mg, 5.97 mmol) and formaldehyde (37 wt% in water, 0.6 mL) at 0 °C. NaOAc (669 mg, 8.16 mmol) and acetic acid (0.25 mL, 4.37 mmol) were subsequently added and the reaction mixture was warmed to rt and stirred for 4 h. After the

completion of the reaction, the suspension was then washed with H_2O and EtOAc. The aqueous phase was separated and washed with EtOAc. The combined organic layers were washed with satd. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was then purified by FCC (PE:EtOAc 7:3 → 1:1 →3:7) to afford a colourless oil **285**. (221mg, 82%)

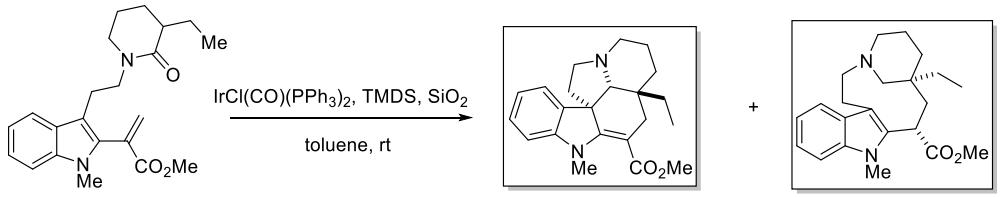
IR (film) 2936, 1726, 1631, 1491, 1152, 834 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.5 Hz, 1H, ArH), 7.74 (d, *J* = 7.5 Hz, 1H, ArH), 7.33 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H, ArH), 7.29 – 7.24 (m, 1H, ArH), 6.63 (d, *J* = 1.5 Hz, 1H, ArC=CH_AH_B(CO_2CH_3)), 5.87 (d, *J* = 1.5 Hz, 1H, ArC=CH_AH_B(CO_2CH_3)), 3.73 (s, 3H, ArCH(CO_2CH_2Ar)(CO_2CH_3)), 3.59 (br. s, 1H, $ArCH_2CH_AH_BN$), 3.39 (br. s, 1H, $ArCH_2CH_AH_BN$), 3.25 – 3.12 (m, 2H, $CH_2NC(O)CH(CH_2CH_3)$), 2.94 (t, *J* = 7.5 Hz, 2H, $ArCH_2CH_2N$), 2.23 – 2.14 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)$), 2.03-1.93 (m, 1H, $CH_2NC(O)CH(CH_AH_BCH_3)CH_2CH_2$), 1.90-1.82 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)CH_AH_BCH_2$), 1.82 – 1.74 (m, 1H, $CH_2NC(O)CH(CH_2CH_3)CH_2CH_AH_B$), 1.65 – 1.42 (m, 12H, $CH_2NC(O)CH(CH_2CH_3)CH_2CH_AH_B$, $CH_2NC(O)CH(CH_AH_BCH_3)CH_2CH_2$, $CH_2NC(O)CH(CH_2CH_3)CH_AH_BCH_2$, $NCO_2C(CH_3)_3$), 0.94 (t, *J* = 7.5 Hz, 3H, $CH_2NC(O)CH(CH_2CH_3)$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 166.4, 150.2, 135.5, 133.8, 132.0, 129.6, 127.9, 125.0, 122.8, 119.6, 119.0, 115.5, 84.3, 52.1, 49.0, 48.7, 42.9, 28.0 (3XC), 25.7, 24.7, 22.4, 21.8, 11.5.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{26}H_{34}O_5N_2$) requires *m/z* 455.2540, found *m/z* 455.2541.

5.4.13 Synthesis & Characterization of (±)-minovine 146 & (±)-vincaminorine 276



272 (±)-minovine **146** (±)-vincaminorine **276**

To a stirred solution of indole **272** (36.3 mg, 0.0986 mmol) in toluene (1 mL), TMDS (34.9 µL, 0.197 mmol) and the Vaska's complex (0.77 mg, 9.86 x 10^{-4} mmol) were added at rt. After 10 -15 min (until no bubbling was observed), the reaction mixture was cooled down to -78 ^{o}C. Silica gel (182 mg) was then added and the reaction was warmed up to rt. Upon the completion of the reaction after 0.5 h, SiO_2 was filtered and washed with EtOAc. The organic extract was then concentrated *in vacuo* and purified by FCC (Pentane:EtOAc 1:0 → 9.5: 0.5 → 9:1) to afford (±)-minovine **146** (18.2 mg, 52%) and (±)-vincaminorine **276** (10.9 mg, 31%). Overall yield was obtained in 83%.

(±)-Minovine **146**

MP 120 -122 °C (lit. m.p. 119 – 121 °C)[3a]

IR (film) 2930, 2776, 1679, 1582, 1472, 1443, 1206, 1136, 1104, 744 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 2H, ArH), 6.91 (t, *J* = 7.5 Hz, 1H, ArH), 6.81 (d, *J* = 8.0 Hz, 1H, ArH), 3.75 (s, 3H, CO_2CH_3), 3.25 (s, 1H, $ArNCH_3$), 3.16 – 3.08 (m, 1H, $CCH_2CH_AH_BN$), 2.96 – 2.92 (m, 1H, $NCH_AH_BCH_2CH_2C$), 2.90 (d, *J* = 16.0 Hz, 1H, $C{=}CCH_AH_B$), 2.63 – 2.57 (m, 1H, $NCH_AH_BCH_2CH_2C$), 2.49 (s, 1H, NCHC), 2.46 (d, 1H, *J* = 16.0 Hz, $C{=}CCH_AH_B$), 2.44 – 2.36 (m, 1H, $CCH_2CH_AH_BN$), 2.03 – 1.94 (m, 1H, CCH_AH_BCH2N), 1.91 – 1.76 (m, 2H, $CCH_AH_BCH_2CH_2N$, $NCH_2CH_AH_BCH_2C$), 1.64 (dd, *J* = 11.5, 4.5 Hz, 1H,

$CCH_A\underline{H_B}CH2N$), 1.54 – 1.49 (m, 1H, $NCH_2CH_A\underline{H_B}CH_2C$), 1.23 – 1.15 (m, 1H, $CCH_A\underline{H_B}CH_2CH_2N$), 0.92 – 0.84 (m, 1H, $C\underline{H_A}H_BCH_3$), 0.68 – 0.58 (m, 4H, $CH_A\underline{H_B}CH_3$, $CH_2C\underline{H_3}$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 167.1, 146.9, 138.8, 127.4, 120.8, 120.7, 108.5, 92.7, 75.4, 56.6, 51.9, 50.9, 50.5, 47.1, 37.4, 36.1, 32.5, 30.0, 29.3, 22.1, 7.1.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{28}O_2N_2$) requires *m/z* 353.2224, found *m/z* 353.2225.

Analytical data are in accordance with those previously reported for this compound.[206,241]

(±)-Vincaminorine **276**

MP 130 -132 °C

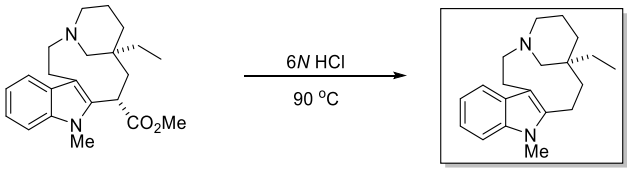
IR (film) 2923, 1729, 1472, 1434, 1330, 1293, 1245, 1164, 741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.5 Hz, 1H, Ar$\underline{H}$), 7.27 (app d (masked by $CDCl_3$), *J* = 7.5 Hz, 1H, Ar$\underline{H}$), 7.19 (app t, *J* = 8.0 Hz, 1H, Ar$\underline{H}$), 7.10 (app t, *J* = 8.0 Hz, 1H, Ar$\underline{H}$), 6.22 (dd, *J* = 10.5, 1.5 Hz, 1H, $CC\underline{H}(CO_2Me)CH_2C$), 3.66 (s, 3H, $CO_2C\underline{H_3}$), 3.62 (s, 3H, $ArNC\underline{H_3}$), 3.02 – 2.86 (m, 3H, $NC\underline{H_A}H_BCH_2CH_2C$, $CC\underline{H_2}CH_2N$), 2.69 – 2.61 (m, 1H, $CCH_2C\underline{H_A}H_BN$), 2.51 – 2.31 (m, 3H, $NCH_A\underline{H_B}CH_2CH_2C$, $CCH_2CH_A\underline{H_B}N$, $CCH(CO_2Me)C\underline{H_A}H_BC$), 2.23 (d, *J* = 12.0 Hz, 1H, $NC\underline{H_A}H_BC$), 2.07 – 1.94 (m, 1H, $CCH(CO_2Me)CH_A\underline{H_B}C$), 1.85 (d, *J* = 12.0 Hz, 1H, $NCH_A\underline{H_B}C$), 1.82 – 1.73 (m, 1H, $NCH_2C\underline{H_A}H_BCH_2C$), 1.69 – 1.61 (m, 1H, $NCH_2CH_2C\underline{H_A}H_BC$), 1.58 – 1.49 (m, 1H, $NCH_2CH_A\underline{H_B}CH_2C$), 1.16 – 0.92 (m, 3H, $NCH_2CH_2CH_A\underline{H_B}C$, $C\underline{H_2}CH_3$), 0.68 (t, *J* = 7.5 Hz, 3H, $CH_2C\underline{H_3}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 137.4, 136.9, 127.4, 121.0, 118.8, 118.2, 112.0, 108.7, 60.9, 54.2, 53.6, 52.1, 39.0 (2 x C), 35.8, 35.1 (2xC), 30.9, 26.7, 23.1, 7.4.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{22}H_{30}O_2N_2$) requires *m/z* 355.2380, found *m/z* 355.2373.

5.4.14 Synthesis & Characterization of (±)-*N*-methylquebrachamine 241



(±)-vincaminorine **276** (±)-*N*-methylquebrachamine **241**

To a 8 mL vial was charged with (±)-vincaminorine **276** (10 mg, 0.0282mmol) and 6*N* HCl (aq., 2 mL). The reaction mixture was then stirred and heated at 90 °C for 2h. Upon completion, the reaction mixture was cooled down to rt and its pH was subsequently adjusted to pH 12 by the addition of 1*N* NaOH. The mixture was then extracted with EtOAc and brine. The extracted organic layers were then concentrated under reduced pressure and the residue was purified by FCC (Pentane:EtOAc 1:0 → 9.5: 0.5) to afford (±)-*N*-methylquebrachamine **241** as a white solid. (5.1 mg, 61%)

MP 72 -76 °C

IR (film) 2930, 2780, 1475, 1371, 1299, 1191, 1139, 1014, 736 cm^{-1}.

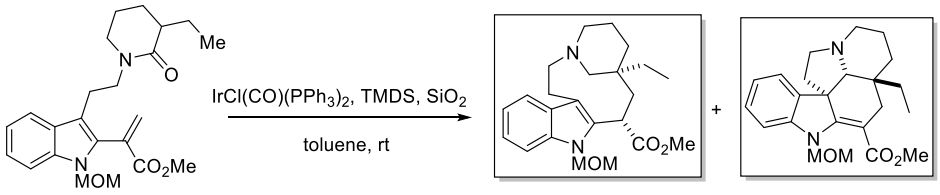
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 1H, ArH), 7.25 (d, *J* = 8.0 Hz, 1H, ArH), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, ArH), 7.05 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, ArH), 3.67 (s, 3H, ArNCH_3), 3.33 (d, *J* = 12.0 Hz, 1H, NCH_AH_BC), 2.99 – 2.83 (m, 2H, CCH_2CH_2N), 2.79 (ddd, *J* = 15.5, 10.5, 2.0 Hz, 1H, CCH_AH_BCH_2C), 2.63 (ddd, *J* = 15.5, 7.0, 2.0 Hz, 1H, CCH_AH_BCH_2C), 2.48 – 2.37 (m, 2H, CCH_2CH_AH_BN, NCH_AH_BCH_2CH_2C), 2.33 – 2.21 (m, 2H, CCH_2CH_AH_BN, NCH_AH_BCH_2CH_2C), 1.80 (ddd, *J* = 13.5, 7.0, 1.5 Hz, 1H, CCH_2CH_AH_BC), 1.67 – 1.55 (m, 2H, CCH_2CH_AH_BC, NCH_2CH_AH_BCH_2C), 1.50 (d, *J* = 12.0 Hz, 1H, NCH_AH_BC), 1.33 – 1.24 (m, 3H, NCH_2CH_AH_BCH_2C, NCH_2CH_2CH_AH_BC, CH_AH_BCH_3), 1.24 – 1.08 (m, 2H, NCH_2CH_2CH_AH_BC, CH_AH_BCH_3), 0.88 (t, *J* = 7.5 Hz, 3H, CH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 136.2, 127.7, 119.7, 118.2, 117.3, 108.5, 108.3, 56.7, 55.2, 53.5, 37.6, 34.9, 32.4, 32.1, 29.5, 22.6, 22.5, 19.1, 7.9.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{28}N_2$) requires *m/z* 297.2325, found *m/z* 297.2329.

Analytical data are in accordance with those previously reported for this compound.[192]

5.4.15 Synthesis & Characterization of product 281 & 282



280 **281** **282**

To a stirred solution of indole **280** (33.3 mg, 0.0837 mmol) in toluene (1 mL), TMDS (29.5 µL, 0.167 mmol) and the Vaska's complex (0.65 mg, 8.37 x 10^{-4} mmol) were added at rt. After 10 -15 min (until no bubbling was observed), the reaction mixture was cooled down to -78 °C. Silica gel (83.3 mg) was then added and the reaction was warmed up to 0 °C. After stirring at 0 °C for 15 min, the reaction was then warmed up to rt and stirred for 45 min. Subsequently, another potion of silica gel (83.3 mg) was added and the reaction mixture was allowed to stir at RT for another 1 h. Upon the completion of the reaction, silica gel was filtered and washed with EtOAc. The organic extract was then concentrated *in vacuo* and purified by FCC (Pentane:EtOAc 1:0 → 9.5: 0.5 → 8:2) to afford colourless oil **281** (16.6 mg, 52%) and pale yellow oil **282** (4.4 mg, 14%). Overall yield was obtained in 66%.

Product **281**

IR (film) 2924, 2847, 2787, 1731, 1586, 1562, 1409, 1364, 1316, 1250, 1175, 1078, 742 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.40 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.19 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar<u>H</u>), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, Ar<u>H</u>), 6.24 (dd, *J* = 10.5, 2.0 Hz, 1H, CC<u>H</u>(CO_2Me)CH_2C), 5.37 (q, *J* = 10.5 Hz, 2H, NC<u>H_2</u>OCH_3), 3.63 (s, 3H, CO_2C<u>H_3</u>), 3.27 (s, 3H, NCH_2OC<u>H_3</u>), 3.03 – 2.84 (m, 3H, NC<u>H_A</u>$H_B$$CH_2CH_2$C, CC<u>$H_2$</u>$CH_2$N), 2.66 (ddd, *J* = 13.5, 4.0, 3.0 Hz, 1H, CCH_2C<u>H_A</u>H_BN), 2.46 (ddd, *J* = 10.0, 8.5, 5.0 Hz, 1H, NCH_A<u>H_B</u>CH_2CH_2C), 2.42 – 2.29 (m, 2H, CCH_2CH_A<u>H_B</u>N, CCH(CO_2Me)C<u>H_A</u>H_BC), 2.24 (d, *J* = 12.0 Hz, 1H, NC<u>H_A</u>H_BC), 2.09 (dd, *J* = 15.0, 10.5 Hz, 1H, CCH(CO_2Me)CH_A<u>H_B</u>C), 1.87 (d, *J* = 12.0 Hz, 1H, NCH_A<u>H_B</u>C), 1.82 – 1.70 (m, 1H, NCH_2C<u>H_A</u>$H_B$$CH_2$C), 1.66 – 1.58 (m, 1H, NCH_2CH_2C<u>H_A</u>H_BC), 1.54 – 1.48 (m, 1H, NCH_2CH_A<u>H_B</u>CH_2C), 1.12 – 0.94 (m, 3H, $NCH_2CH_2CH_A$<u>H_B</u>C, C<u>H_2</u>CH_3), 0.69 (t, *J* = 7.5 Hz, 3H, CH_2C<u>H_3</u>).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 137.7, 136.5, 128.0, 121.8, 119.7, 118.3, 114.2, 109.6, 74.8, 60.9, 55.6, 53.8, 53.6, 52.1, 38.7, 38.6, 35.5, 35.1, 35.0, 26.7, 23.1, 7.4.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{32}N_2O_3$) requires *m/z* 385.2486, found *m/z* 385.2477.

<u>Product **282**</u>

IR (film) 2933, 2854, 2776, 1693, 1626, 1603, 1592, 1481, 1461, 1435, 1326, 1251, 1208, 1177, 1148, 1128, 1109, 1076, 1037, 743 cm^{-1}.

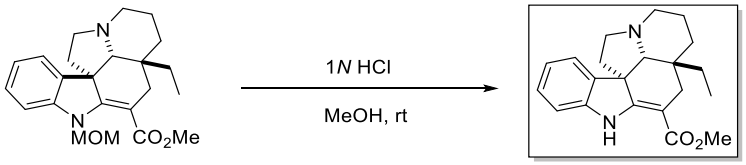
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.13 (m, 2H, Ar<u>H</u>), 6.93 – 6.86 (m, 2H, Ar<u>H</u>), 5.51 (d, *J* = 10.5 Hz, 1H, NC<u>H_A</u>$H_B$$OCH_3$), 5.19 (d, *J* = 10.5 Hz, 1H, NCH_A<u>H_B</u>OCH_3), 3.75 (s, 3H, CO_2C<u>H_3</u>), 3.20 (s, 3H, NCH_2OC<u>H_3</u>), 3.14 – 3.07 (m, 1H, CCH_2C<u>H_A</u>H_BN), 2.94 – 2.82 (m, 2H, NC<u>H_A</u>$H_B$$CH_2CH_2$C, C=CC<u>$H_A$</u>$H_B$), 2.60 – 2.50 (m, 1H, NCH_A<u>H_B</u>CH_2CH_2C), 2.48 (d, *J* = 2.0 Hz, 1H, NC<u>H</u>C), 2.46 – 2.35 (m, 2H, C=CCH_A<u>H_B</u>, CCH_2CH_A<u>H_B</u>N), 2.04 (td, *J* = 11.5, 6.5 Hz, 1H, CC<u>H_A</u>H_BCH2N), 1.90 – 1.75 (m, 2H, CC<u>H_A</u>$H_B$$CH_2CH_2$N, NCH_2C<u>H_A</u>$H_B$$CH_2$C), 1.65 (dd, *J* = 11.5,

4.5 Hz, 1H, $CCH_A\underline{H_B}CH2N$), 1.54 – 1.49 (m, 1H, $NCH_2CH_A\underline{H_B}CH_2C$), 1.30 – 1.18 (m, 1H, $CCH_A\underline{H_B}CH_2CH_2N$), 1.17 – 1.06 (m, 1H, $C\underline{H_A}H_BCH_3$), 0.74 – 0.64 (m, 4H, $CH_A\underline{H_B}CH_3$, $CH_2C\underline{H_3}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 159.2, 145.5, 137.6, 127.3, 120.9, 120.7, 108.6, 98.3, 76.3, 73.7, 56.1, 55.5, 51.6, 51.2, 50.6, 47.0, 37.3, 32.5, 29.8, 29.2, 22.2, 7.0.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{23}H_{30}N_2O_3$) requires *m/z* 383.2329, found *m/z* 383.2326.

5.4.16 Synthesis & Characterization of (±)-vincadifformine 154



282 (±)-vincadifformine **154**

To a solution of **282** (2.3 mg, 6.02 µmol) in MeOH (1 mL) was added 1*N* HCl (aq., 0.2 mL). The reaction mixture was then stirred at rt for 20 min. Upon completion, the reaction mixture's pH was adjusted to pH 12 by the addition of 1*N* NaOH. The mixture was then extracted with EtOAc and brine. The extracted organic layers were concentrated under reduced pressure and the residue was purified by FCC (Pentane:EtOAc 1:0 → 9.5: 0.5) to afford (±)-vincadifformine **154** as a white solid. (1.7 mg, 84%)

MP 124-125 °C (lit. m.p. 124 – 125 °C)[5a]

IR (film) 3366, 2932, 2776, 1674, 1606, 1467, 1159, 744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) 8.90 (br.s, 1H, ArN$\underline{H}$), 7.19 (d, *J* = 7.5 Hz, 1H, Ar$\underline{H}$), 7.12 (td, *J* = 7.5, 1.0 Hz, 1H, Ar$\underline{H}$), 6.86 (t, *J* = 7.5 Hz, 1H, Ar$\underline{H}$), 6.79 (d, *J* = 7.5 Hz, 1H, Ar$\underline{H}$), 3.76 (s, 3H, $CO_2C\underline{H_3}$), 3.16 – 3.08 (m, 1H, $CCH_2C\underline{H_A}H_BN$), 2.95 – 2.88 (m, 1H, $NC\underline{H_A}H_BCH_2CH_2C$), 2.72 (d, *J* = 15.0 Hz, 1H, C=CC$\underline{H_A}H_B$), 2.59 – 2.50 (m, 1H, $NCH_A\underline{H_B}CH_2CH_2C$), 2.44 (s, 1H, NC$\underline{H}$C), 2.43 – 2.36 (m, 1H, $CCH_2CH_A\underline{H_B}N$), 2.27 (d, *J* = 15.0, 1H, C=$CCH_A\underline{H_B}$), 2.11 – 1.98 (m, 1H,

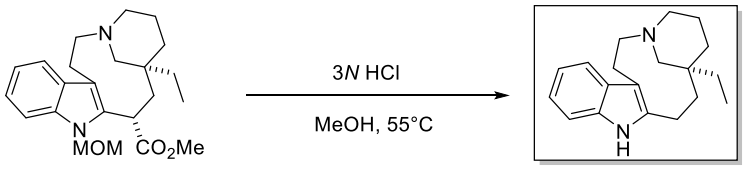
CC$\underline{H_A}H_B$CH2N), 1.90 – 1.76 (m, 2H, CC$\underline{H_A}H_B$CH$_2$CH$_2$N, NCH$_2$C$\underline{H_A}H_B$CH$_2$C), 1.70 (dd, *J* = 11.5, 4.5 Hz, 1H, CCH$_A\underline{H_B}$CH2N), 1.60 – 1.50 (m, 1H, NCH$_2$CH$_A\underline{H_B}$CH$_2$C), 1.29 – 1.23 (m, 1H, CCH$_A\underline{H_B}$CH$_2$CH$_2$N), 1.03 – 0.92 (m, 1H, C$\underline{H_A}H_B$CH$_3$), 0.63 – 0.53 (m, 4H, CH$_A\underline{H_B}$CH$_3$, CH$_2$C$\underline{H_3}$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 167.9, 143.3, 138.0, 127.4, 121.0, 120.5, 109.3, 92.7, 72.7, 55.5, 51.7, 51.0, 50.7, 45.2, 38.2, 32.8, 29.3, 25.5, 22.2, 7.1.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{26}O_2N_2$) requires *m/z* 339.20670, found *m/z* 339.2069.

Analytical data are in accordance with those previously reported for this compound.[196,242]

5.4.17 Synthesis & Characterization of (±)-quebrachamine 163



281 (±)-quebrachamine **163**

To a solution of **281** (23.3 mg, 0.0607 mmol) in MeOH (2 mL) was added 3*N* HCl (aq., 1.2 mL). The reaction mixture was then stirred at 55 °C for 48 h. Upon completion, the reaction mixture was cooled down to rt and subsequently quenched with satd. $NaHCO_3$(aq). The mixture was then extracted with EtOAc and brine. The extracted organic layers were concentrated under reduced pressure and the residue was purified by FCC (Pentane:EtOAc 1:0 → 9.5: 0.5) to afford (±)-quebrachamine **163** as a white solid. (12.2 mg, 71%)

MP 107-110 °C (lit. m.p. 112 – 115 °C)[6a]

IR (film) 3404, 2922, 2785, 2726, 1462, 1440, 1370, 1334, 1303, 1248, 1131, 1067, 1008, 740 cm^{-1}.

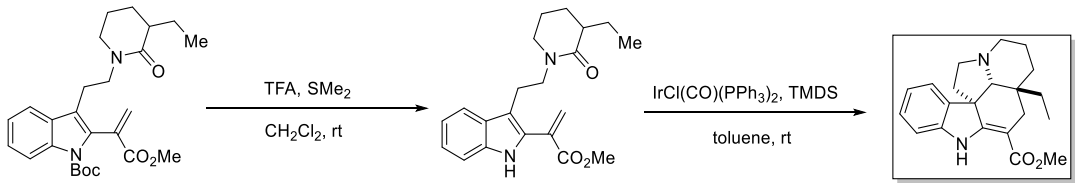
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (br. s, 1H, ArN<u>H</u>), 7.49 – 7.46 (m, 1H, Ar<u>H</u>), 7.29 – 7.26 (m, 1H, Ar<u>H</u>), 7.10 – 7.04 (m, 2H, Ar<u>H</u>), 3.24 (br. d, *J* = 12.0 Hz, 1H, NC<u>H_A</u>H_BC), 2.94 (ddd, *J* = 15.0, 11.5, 4.5 Hz, 1H, CC<u>H_A</u>$H_B$$CH_2$N), 2.84 (ddd, *J* = 15.0, 4.5, 3.0 Hz, 1H, CCH_A<u>H_B</u>CH_2N), 2.76 (ddd, *J* = 15.5, 10.5, 2.0 Hz, 1H, CC<u>H_A</u>$H_B$$CH_2$C), 2.68 (ddd, *J* = 15.0, 7.0, 2.0 Hz, 1H, CCH_A<u>H_B</u>CH_2C), 2.51 – 2.44 (m, 1H, CCH_2C<u>H_A</u>H_BN), 2.42 (dd, *J* = 4.5, 2.5 Hz, 1H, NC<u>H_A</u>$H_B$$CH_2CH_2$C), 2.34 (td, *J* = 11.5, 4.5 Hz, 1H, CCH_2CH_A<u>H_B</u>N), 2.25 (td, *J* = 11.5, 3.0 Hz, 1H, NCH_A<u>H_B</u>CH_2CH_2C), 1.97 – 1.88 (m, 1H, CCH_2C<u>H_A</u>H_BC), 1.66 – 1.58 (m, 2H, CCH_2CH_A<u>H_B</u>C, NCH_2C<u>H_A</u>$H_B$$CH_2$C), 1.51 (d, *J* = 12.0 Hz, 1H, NCH_A<u>H_B</u>C), 1.35 – 1.06 (m, 5H, NCH_2CH_A<u>H_B</u>CH_2C, NCH_2CH_2C<u>H_A</u>H_BC, C<u>H_A</u>$H_B$$CH_3$, $NCH_2CH_2CH_A$<u>H_B</u>C, CH_A<u>H_B</u>CH_3), 0.85 (t, *J* = 7.5 Hz, 3H, CH_2C<u>H_3</u>).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 134.9, 129.0, 120.2, 118.7, 117.4, 110.0, 108.8, 56.8, 55.1, 53.3, 37.1, 34.8, 33.6, 32.2, 22.7, 22.5, 22.1, 7.8.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{19}H_{26}N_2$) requires *m/z* 283.2169, found *m/z* 283.2463.

Analytical data are in accordance with those previously reported for this compound.[171]

5.4.18 Synthesis of (±)-vincadifformine 154



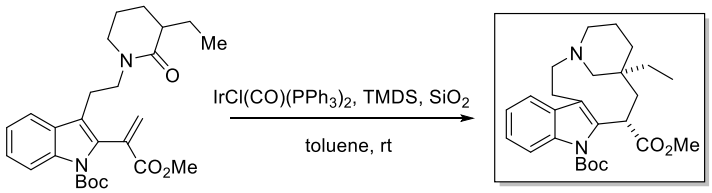
285 **286** (±)-vincadifformine **154**

Trifluoroacetic acid (2.80 mL, 36.6 mmol) was added to a stirred solution of indole **285** (80 mg, 0.176 mmol) and dimethylsulfide (129 µL, 1.76 mmol) in CH_2Cl_2 (4 mL) at rt. After stirring for 1 h, the reaction mixture was transferred carefully into a vigorously stirred suspension of EtOAc and

$NaHCO_3$ at 0 °C. The suspension was subsequently warmed to rt and further stirred for 10 min. After the organic phase was extracted, the aqueous extract was washed with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was then quickly dissolved in a small amount of EtOAc and filtered through a short pad of silica (with eluent system of 1:1; EtOAc: P.E.). Solvent was then removed *in vacuo* and the resulting mixture was immediately added with toluene (4 mL). The stirred reaction mixture was then added TMDS (62 µL, 0.352 mmol) and the Vaska's complex (1.4 mg, 1.76 x 10^{-3} mmol). After stirring at rt for 1 h, the crude mixture was extracted with satd. $NaHCO_3$ and EtOAc. The organic extract was then washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was then purified by FCC (PE:EtOAc 19:1 → 9:1) to afford (±)-vincadifformine **154**. (26.1 mg, 44%)

Analytical data are in accordance with those previously reported for this compound.[196,242]

5.4.19 Synthesis & Characterization of product 288



285 **288**

To a stirred solution of indole **285** (50.0 mg, 0.110 mmol) in toluene (1.3 mL), TMDS (38.9 µL, 0.220 mmol) and the Vaska's complex (0.86 mg, 1.10 x 10^{-3} mmol) were added at rt. After 10 -15 min (until no bubbling was observed), the reaction mixture was cooled down to -78 °C. Silica gel (125 mg) was then added and the reaction was warmed up to 0 °C. After stirring at 0 °C for 15 min, the reaction was then warmed up to rt and stirred for 1h. Subsequently, another potion of silica gel (125 mg) was added and the reaction mixture was allowed to stir at rt for another 3 h.

Upon the completion of the reaction, silica gel was filtered and washed with EtOAc. The organic extract was then concentrated *in vacuo* and purified by FCC (Pentane:EtOAc 1:0 → 9.5: 0.5 → 8:2) to afford colourless oil **288**. (6.1 mg, 13%)

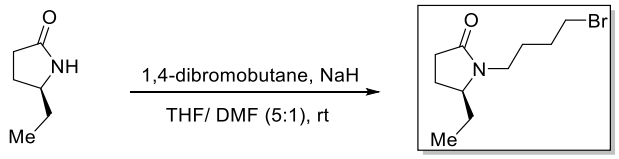
IR (film) 2971, 2932, 2854, 1729, 1459, 1370, 1325, 1235, 1167, 1132, 1068, 738 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (app d, *J* = 8.0 Hz, 1H, ArH), 7.45 (app d, *J* = 8.0 Hz, 1H, ArH), 7.30 – 7.20 (m, 2H, ArH), 6.24 (dd, *J* = 9.0, 2.0 Hz, 1H, CCH(CO$_2$Me)CH$_2$C), 3.60 (s, 3H, CO$_2$CH$_3$), 2.97- 2.77 (m, 3H, NCH$_A$H$_B$CH$_2$CH$_2$C, CCH$_2$CH$_2$N), 2.68 (ddd, *J* = 13.5, 4.0, 3.0 Hz, 1H, CCH$_2$CH$_A$H$_B$N), 2.57- 2.36 (m, 3H, NCH$_A$H$_B$CH$_2$CH$_2$C, CCH$_2$CH$_A$H$_B$N, CCH(CO$_2$Me)CH$_A$H$_B$C), 2.21 (d, *J* = 12.0, 1H, NH$_A$H$_B$C), 1.97 (dd, *J* = 15.5, 9.0 Hz, 1H, CCH(CO$_2$Me)CH$_A$H$_B$C), 1.91 (d, *J* = 12.0, 1.5 Hz, 1H, NH$_A$H$_B$C), 1.84 – 1.73 (m, 1H, NCH$_2$CH$_A$H$_B$CH$_2$C), 1.72- 1.63 (m, 10H, NCH$_2$CH$_2$CH$_A$H$_B$C, NCO$_2$C(CH$_3$)$_3$), 1.52 – 1.48 (m, 1H, NCH$_2$CH$_A$H$_B$CH$_2$C), 1.14 – 0.87 (m, 3H, NCH$_2$CH$_2$CH$_A$H$_B$C, CH$_2$CH$_3$), 0.65 (t, *J* = 7.5 Hz, 3H, CH$_2$CH$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 150.4, 137.6, 135.9, 129.7, 123.8, 122.3, 118.8, 118.1, 116.0, 83.9, 60.7, 53.3, 53.2, 51.7, 39.9, 39.3, 35.3, 35.0 (2XC), 28.2 (3XC), 26.7, 22.9, 7.4.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{26}H_{36}N_2O_4$) requires *m/z* 441.2748, found *m/z* 441.2743.

5.4.20 Synthesis & Characterization of (*S*)-1-(4-bromobutyl)-5-ethylpyrrolidin-2-one 290



289 **290**

To a stirred mixture of THF (30 mL), DMF (6 mL) and NaH (265 mg, 6.63 mmol, 60% in mineral oil), (*S*)-5-ethylpyrrolidin-2-one, **289** (500 mg, 4.42 mmol), was added at 0 ^{o}C. After the reaction mixture was stirred for 1 h at 0 ^{o}C, 1,4-dibromobutane (2.64 mL, 22.1 mmol) was added subsequently. The mixture was then warmed to rt and stirred for 18 h. Upon the completion of the reaction, the crude mixture was quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried with Na_2SO_4, and evaporated *in vacuo*. The crude mixture was then purified by FCC (PE:EtOAc 7:3 → 5:3) to give a pale yellow oil **290**. (776 mg, 71%)

$[\alpha]_D^{25.1}$ = + 13.2 (c = 1.00, $CHCl_3$)

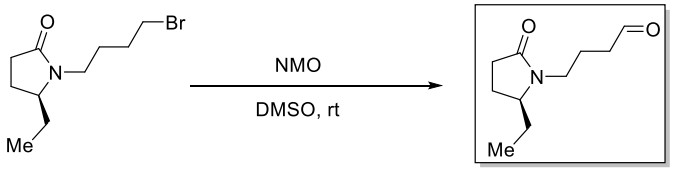
IR (film) 2964, 2932, 1673, 1423, 1371, 1260, 650 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (dt, *J* = 14.0, 8.0 Hz, 1H, NC$\underline{H_A}H_BCH_2CH_2CH_2Br$), 3.58 – 3.52 (m, 1H, C(O)NC$\underline{H}(CH_2CH_3)$), 3.43 (t, *J* = 6.5 Hz, 2H, $NCH_2CH_2CH_2C\underline{H_2}Br$), 2.98 – 2.91 (m, 1H, $NCH_A\underline{H_B}CH_2CH_2CH_2Br$), 2.44 – 2.24 (m, 2H, $C\underline{H_2}C(O)NCH(CH_2CH_3)$), 2.17 – 2.07 (m, 1H, $C\underline{H_A}H_BCH_2C(O)NCH(CH_2CH_3)$), 1.84 (dq, *J* = 8.0, 7.0 Hz, 2H, $NCH_2CH_2C\underline{H_2}CH_2Br$), 1.80 – 1.73 (m, 1H, $C(O)NCH(C\underline{H_A}H_BCH_3)$), 1.72 – 1.56 (m, 3H, $NCH_2C\underline{H_2}CH_2CH_2Br$, $CH_A\underline{H_B}CH_2C(O)NCH(CH_2CH_3)$), 1.45- 1.32 (m, 1H, $C(O)NCH(CH_A\underline{H_B}CH_3)$), 0.89 (t, *J* = 7.5 Hz, 3H, $C(O)NCH(CH_2C\underline{H_3})$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 58.4, 39.0, 33.4, 30.3, 29.9, 25.8 (2XC), 23.4, 8.6.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{18}ONBr$) requires *m/z* 248.0645, 250.0624, found *m/z* 248.0646, 250.0624.

5.4.21 Synthesis & Characterization of (*S*)-4-(2-ethyl-5-oxopyrrolidin-1-yl)butanal 291



290 **291**

To a solution of lactam **290** (700 mg, 2.82 mmol) in DMSO (3 mL) was added NMO (1.33g, 11.3 mmol). The reaction mixture was then left to stir at rt for 18h. Upon completion, the mixture was diluted with CH_2Cl_2 and washed with H_2O. The aqueous layer was then extracted and washed with CH_2Cl_2. The combined organic layers were washed with H_2O and brine, dried with Na_2SO_4 and concentrated. The crude mixture was purified by FCC (PE:EtOAc 1:1 → 3:7 →0:1) to afford the desired colourless oil **291**. (285 mg, 55%)

$[\alpha]_D^{25.1}$ = + 19.2 (c = 1.00, $CHCl_3$)

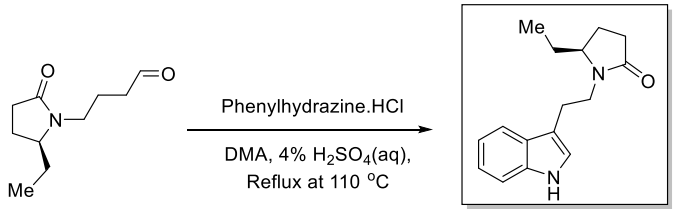
IR (film) 2966, 2935, 1721, 1641, 1461, 1423, 622 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H, $NCH_2CH_2CH_2C(O)\underline{H}$), 3.63 – 3.49 (m, 2H, $NC\underline{H_A}H_BCH_2CH_2C(O)H$, $C(O)NC\underline{H}(CH_2CH_3)$), 3.02 – 2.93 (m, 1H, $NCH_A\underline{H_B}CH_2CH_2C(O)H$), 2.49 (t, *J* = 7.0 Hz, 2H, $NCH_2CH_2C\underline{H_2}C(O)H$), 2.42 – 2.25 (m, 2H, $C\underline{H_2}C(O)NCH(CH_2CH_3)$), 2.15- 2.05 (m, 1H, $C\underline{H_A}H_BCH_2C(O)NCH(CH_2CH_3)$), 1.91 – 1.81 (m, 1H, $NCH_2C\underline{H_A}H_BCH_2C(O)H$), 1.81 – 1.72 (m, 2H, $C(O)NCH(C\underline{H_A}H_BCH_3)$, $NCH_2CH_A\underline{H_B}CH_2C(O)H$), 1.69 – 1.60 (m, 1H, $CH_A\underline{H_B}CH_2C(O)NCH(CH_2CH_3)$), 1.44 - 1.32 (m, 1H, $C(O)NCH(CH_A\underline{H_B}CH_3)$), 0.88 (t, *J* = 7.5 Hz, 3H, $C(O)NCH(CH_2C\underline{H_3})$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 175.3, 58.6, 41.3, 39.4, 30.2, 25.8, 23.4, 19.9, 8.6.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{10}H_{17}O_2N$) requires *m/z* 184.1332, found *m/z* 184.1332.

5.4.22 Synthesis & Characterization of (*S*)-1-(2-(1*H*-indol-3-yl)ethyl)-5-ethylpyrrolidin-2-one 292



291 **292**

N_2 was bubbled through the solution of 4% H_2SO_4 (aq, 6 mL) at 50 °C for 20 min. Phenylhydrazine.HCl (272 mg, 1.88 mmol) was added subsequently and allowed to dissolve over 10 min. Aldehyde **291** (229 mg, 1.25 mmol) in degassed DMA (6 mL) was then added and the reaction mixture was heated under reflux at 110 °C for 2 h. After completion, the reaction was cooled to rt and washed with EtOAc and H_2O. The organic layer was removed and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried with Na_2SO_4, and evaporated *in vacuo*. The crude mixture was purified by FCC (PE:EtOAc 1:1 → 3:7 →0:1) to give a white solid **292**. (218 mg, 68%)

$[\alpha]_D^{25.1}$ = - 21.2 (c = 1.00, $CHCl_3$)

IR (film) 3260, 2965, 2930, 1658, 1457, 1422, 740 cm^{-1}.

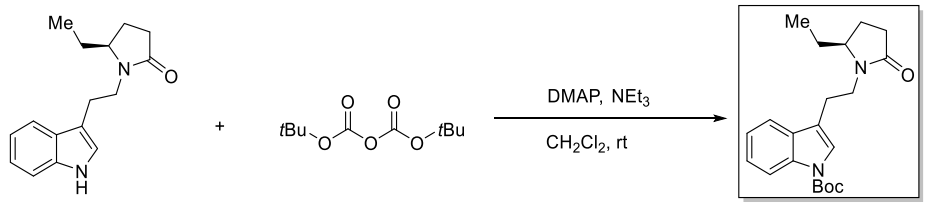
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (br.s, 1H, ArN<u>H</u>), 7.63 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.36 (d, *J* = 8.0 Hz, 1H, Ar<u>H</u>), 7.19 (dd, *J* = 8.0, 7.0 Hz, 1H, Ar<u>H</u>), 7.13 (dd, *J* = 8.0, 7.0 Hz, 1H, Ar<u>H</u>), 7.08 – 7.03 (m, 1H, Ar<u>H</u>), 4.01- 3.92 (m, 1H, $ArCH_2C\underline{H_A}H_BN$), 3.51- 3.42 (m, 1H, $C(O)NC\underline{H}(CH_2CH_3)$), 3.28 – 3.19 (m, 1H, $ArCH_2CH_A\underline{H_B}N$), 3.09- 3.00 (m, 1H, $ArC\underline{H_A}H_BCH_2N$), 2.98- 2.88 (m, 1H, $ArCH_A\underline{H_B}CH_2N$), 2.45- 2.35 (m, 1H, $C\underline{H_A}H_BC(O)NCH(CH_2CH_3)$), 2.35- 2.27 (m, 1H,

$CH_AH_BC(O)NCH(CH_2CH_3)$), 2.09- 2.00 (m, 1H, $CH_AH_BCH_2C(O)NCH(CH_2CH_3)$), 1.81- 1.71 (m, 1H, $C(O)NCH(CH_AH_BCH_3)$), 1.67- 1.58 (m, 1H, $CH_AH_BCH_2C(O)NCH(CH_2CH_3)$), 1.45- 1.36 (m, 1H, $C(O)NCH(CH_AH_BCH_3)$), 0.86 (t, *J* = 7.5 Hz, 3H, $C(O)NCH(CH_2CH_3)$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 136.2, 127.4, 122.0, 121.8, 119.3, 118.6, 113.0, 111.2, 58.8, 40.7, 30.4, 25.9, 23.4, 23.2, 8.6.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{16}H_{20}ON_2$) requires *m/z* 257.1648, found *m/z* 257.1652.

5.4.23 Synthesis & Characterization of *tert*-butyl (*S*)-3-(2-(2-ethyl-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indole-1-carboxylate 293



292 **293**

To a stirred solution of indole **292** (172 mg, 0.672 mmol) and di-*tert*-butyl dicarbonate (220 mg, 1.01 mmol) in CH_2Cl_2 were added DMAP (8.21 mg, 0.0672 mmol) and NEt_3 (0.159 mL, 1.14 mmol) at 0 ^oC. The reaction mixture was allowed to warm to rt and stir for 1.5 h. Upon completion, the reaction was quenched with satd. $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. FCC (PE:EtOAc 1:1 → 3:7 →0:1) was performed to give product **293** as a pale yellow oil. (220 mg, 92%)

$[\alpha]_D^{25.1}$ = - 0.3 (c = 1.00, $CHCl_3$)

IR (film) 2970, 2932, 1728, 1680, 1453, 1370, 1255, 1155, 1089, 746 cm^{-1}.

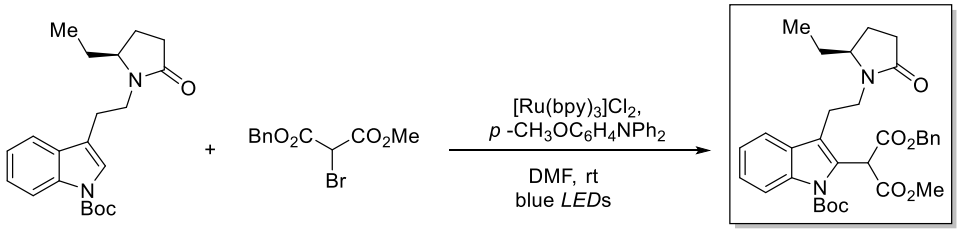
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br.s, 1H, ArH), 7.59 (d, *J* = 7.5 Hz, 1H, ArH), 7.43 (s, 1H, ArH), 7.31 (dd, *J* = 8.5, 7.0 Hz, 1H, ArH), 7.27 – 7.23 (m, 1H, ArH), 3.94- 3.84 (m, 1H,

$ArCH_2C\underline{H_A}H_BN$), 3.54- 3.45 (m, 1H, $C(O)NC\underline{H}(CH_2CH_3)$), 3.28- 3.19 (m, 1H, $ArCH_2CH_A\underline{H_B}N$), 3.04- 2.94 (m, 1H, $ArC\underline{H_A}H_BCH_2N$), 2.88- 2.79 (m, 1H, $ArCH_A\underline{H_B}CH_2N$), 2.49 – 2.27 (m, 2H, $C\underline{H_2}C(O)NCH(CH_2CH_3)$), 2.14- 2.02 (m, 1H, $C\underline{H_A}H_BCH_2C(O)NCH(CH_2CH_3)$), 1.80 – 1.72 (m, 1H, $C(O)NCH(C\underline{H_A}H_BCH_3)$), 1.70- 1.61 (m, 10H, $NCO_2C(C\underline{H_3})_3$, $CH_A\underline{H_B}CH_2C(O)NCH(CH_2CH_3)$), 1.47- 1.35 (m, 1H, $C(O)NCH(CH_A\underline{H_B}CH_3)$), 0.87 (t, J = 7.5 Hz, 3H, $C(O)NCH(CH_2C\underline{H_3})$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 149.7, 135.5, 130.4, 124.4, 123.0, 122.5, 118.9, 117.7, 115.3, 83.5, 59.0, 40.4, 30.3, 28.2 (3XC), 26.0, 23.5, 23.2, 8.7.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{21}H_{28}O_3N_2$) requires *m/z* 357.2173, found *m/z* 357.2169.

5.4.24 Synthesis & Characterization of 1-benzyl 3-methyl 2-(1-(*tert*-butoxycarbonyl)-3-(2-((*S*)-2-ethyl-5-oxopyrrolidin-1-yl)ethyl)-1*H*-indol-2-yl)malonate 294



To a 10 mL vial, tris(2,2'-bipyridyl)ruthenium(II) chloride hexahydrate (4.21 mg, 5.62 µmol), indole **293** (200 mg, 0.562 mmol), 1-benzyl 3-methyl 2-bromomalonate (320 mg, 1.12 mmol), 4-methoxytriphenylamine (308 mg, 1.12 mmol) and DMF (5 mL) were added. The mixture was then placed at a distance of ~ 2.5 cm from blue light emitting diodes (LEDs) and stirred at rt for 12 h. Upon completion of the reaction, the mixture was transferred to a separating funnel and extracted with EtOAc and H_2O. The organic phase was separated and the aqueous layer was extracted with

EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by FCC (PE:EtOAc 7:3 → 1:1 →3:7), affording product **294** as a pale yellow foam. (256 mg, 81%) Product **294** was obtained as a mixture of 2 diastereomers.

$[\alpha]_D^{25.1}$ = - 19.5 (c = 1.00, $CHCl_3$)

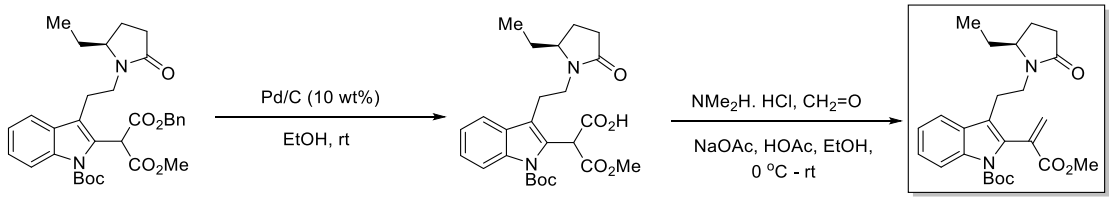
IR (film) 2970, 2936, 1728, 1676, 1455, 1365, 1326, 1230, 1131, 1029, 740, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 1H, ArH), 7.69 (d, *J* = 7.5 Hz, 1H, ArH), 7.31-7.21 (m, 7H, ArH), 5.47 (d, *J* = 7.5 Hz, 1H, ArCH(CO_2CH_2Ar)(CO_2CH_3)), 5.25 – 5.13 (m, 2H, ArCH(CO_2CH_2Ar)(CO_2CH_3)), 3.72 (s, 3H, ArCH(CO_2CH_2Ar)(CO_2CH_3)), 3.69- 3.55 (m, 1H, $ArCH_2CH_AH_BN$), 3.32 – 3.26 (m, 1H, C(O)NCH(CH_2CH_3)), 3.15 – 3.04 (m, 1H, $ArCH_2CH_AH_BN$), 3.01- 2.91(m, 1H, $ArCH_AH_BCH_2N$), 2.78- 2.66 (m, 1H, $ArCH_AH_BCH_2N$), 2.38-2.28 (m, 1H, $CH_AH_BC(O)NCH(CH_2CH_3)$), 2.29- 2.18 (m, 1H, $CH_AH_BC(O)NCH(CH_2CH_3)$), 1.94-1.84 (m, 1H, $CH_AH_BCH_2C(O)NCH(CH_2CH_3)$), 1.63 – 1.47 (m, 11H, $NCO_2C(CH_3)_3$, $CH_AH_BCH_2C(O)NCH(CH_2CH_3)$, C(O)NCH($CH_AH_BCH_3$)), 1.32 – 1.19 (m, 1H, C(O)NCH($CH_AH_BCH_3$)), 0.76 (td, *J* = 7.5, 3.0 Hz, 3H, C(O)NCH(CH_2CH_3)).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 167.2, 166.6, 150.6, 135.5 (2XC), 129.3, 128.4(2XC), 128.1, 128.0 (2XC), 127.9, 124.8, 122.8, 119.9, 119.2, 115.7, 84.6, 67.4, 59.5, 52.8, 49.8, 40.7, 30.2, 28.1 (3XC), 26.0, 23.4, 22.6, 8.5.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{32}H_{38}O_7N_2$) requires *m/z* 563.2752, found *m/z* 563.2750.

5.4.25 Synthesis & Characterization of tert-butyl (*S*)-3-(2-(2-ethyl-5-oxopyrrolidin-1-yl)ethyl)-2-(3-methoxy-3-oxoprop-1-en-2-yl)-1*H*-indole-1-carboxylate 295



294 **294a** **295**

Palladium on carbon (10 wt%, wet, 43.0 mg, 0.0404 mmol) was added to a stirred solution of indole **294** (227 mg, 0.404 mmol) in EtOH (10 mL). The reaction mixture was subsequently purged with H_2 and was allowed to stir at rt for 1 h. After the reaction was completed, the suspension was filtered over a pad of Celite and washed with EtOH. Excess EtOH was removed in *vacuo* to afford a solution of carboxylic acid **294a** in EtOH (4 mL). To the solution of carboxylic acid **294a** in EtOH (4 mL) was added dimethylamine chloride. HCl (329 mg, 4.04 mmol) and formaldehyde (37 wt% in water, 0.6 mL) at 0 ^oC. NaOAc (457 mg, 5.57 mmol) and acetic acid (0.170 mL, 2.97 mmol) were subsequently added and the reaction mixture was warmed to rt and stirred for 4 h. After the completion of the reaction, the suspension was then washed with H_2O and EtOAc. The aqueous phase was separated and washed with EtOAc. The combined organic layers were washed with satd. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was then purified by FCC (PE:EtOAc 7:3 → 1:1 →3:7) to afford a colourless foam **295**. (157 mg, 88%)

$[\alpha]_D^{25.0}$ = - 21.1 (c = 1.00, $CHCl_3$)

IR (film) 2972, 2929, 1726, 1676, 1455, 1363, 1325, 1152, 1099, 915, 730 cm^{-1}.

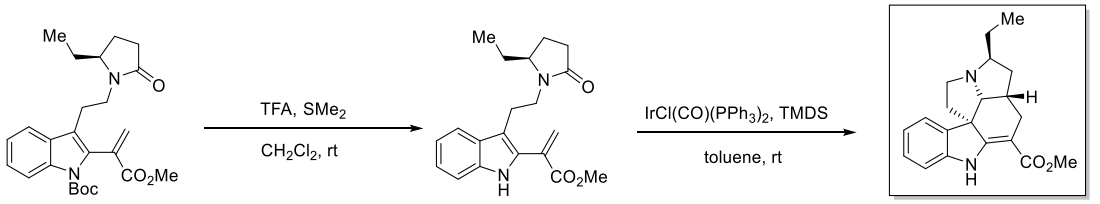
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 1H, Ar<u>H</u>), 7.70 (d, *J* = 7.5Hz, 1H, Ar<u>H</u>), 7.34 (dd, *J* = 8.5, 7.0 Hz, 1H, Ar<u>H</u>), 7.30 – 7.26 (m, 1H, Ar<u>H</u>), 6.64 (d, *J* = 1.5 Hz, 1H, ArC=C<u>H_A</u>H_B(CO_2CH_3)), 5.86 (d, *J* = 1.5 Hz, 1H, ArC=CH_A<u>H_B</u>(CO_2CH_3)), 3.79- 3.68 (m, 4H,

ArC(=CH_2)$CO_2C\underline{H_3}$, $ArCH_2C\underline{H_A}H_BN$), 3.40 (br.s, 1H, C(O)NC<u>H</u>(CH_2CH_3)), 3.13 (br.s, 1H, $ArCH_2CH_A\underline{H_B}N$), 3.07 – 2.96 (m, 1H, $ArC\underline{H_A}H_BCH_2N$), 2.80 (br.s, 1H, $ArCH_A\underline{H_B}CH_2N$), 2.43-2.33 (m, 1H, $C\underline{H_A}H_BC(O)NCH(CH_2CH_3)$), 2.33- 2.23 (m, 1H, $CH_A\underline{H_B}C(O)NCH(CH_2CH_3)$), 1.98 (br.s, 1H, $C\underline{H_A}H_BCH_2C(O)NCH(CH_2CH_3)$), 1.69 – 1.63 (m, 1H, C(O)NCH($C\underline{H_A}H_BCH_3$)), 1.62-1.56 (m, 10H, $NCO_2C(C\underline{H_3})_3$, $CH_A\underline{H_B}CH_2C(O)NCH(CH_2CH_3)$), 1.40-1.30 (m, 1H, C(O)NCH($CH_A\underline{H_B}CH_3$)), 0.84 (t, *J* = 7.5 Hz, 3H, C(O)NCH($CH_2C\underline{H_3}$)).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 166.3, 150.2, 135.6, 133.8, 132.2, 129.4, 128.0, 125.0, 122.8, 119.3, 118.7, 115.6, 84.4, 59.2, 52.1, 40.9, 30.2, 28.0 (3XC), 26.1, 23.4, 22.9, 8.5.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{25}H_{32}O_5N_2$) requires *m/z* 441.2384, found *m/z* 441.2376.

5.4.26 Synthesis & Characterization of (+)-20- *epi*- ibophyllidine 298



295 **296** (+)- 20-*epi*-ibophyllidine **298**

Trifluoroacetic acid (2.50 mL, 32.7 mmol) was added to a stirred solution of indole **295** (69.2 mg, 0.157 mmol) and dimethylsulfide (115 µL, 1.57 mmol) in CH_2Cl_2 (4 mL) at rt. After stirring for 1 h, the reaction mixture was transferred carefully into a vigorously stirred suspension of EtOAc and $NaHCO_3$ at 0 ^oC. The suspension was subsequently warmed to rt and further stirred for 10 min. After the organic phase was extracted, the aqueous extract was washed with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was then quickly dissolved in a small amount of EtOAc and filtered through a short pad of silica (with eluent system of 1:1; EtOAc: P.E → 1:0; EtOAc: P.E). Solvent was then removed *in*

vacuo and the resulting mixture was immediately added with toluene (4 mL). The stirred reaction mixture was then added TMDS (55.5 µL, 0.314 mmol) and the Vaska's complex (1.2 mg, 1.57 x 10^{-3} mmol). After stirring at rt for 1 h, the crude mixture was extracted with satd. $NaHCO_3$ and EtOAc. The organic extract was then washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was then purified by FCC (100% EtOAc) to afford (+)-20 –*epi*-ibophyllidine **298**. (20.1 mg, 40%)

$[\alpha]_D^{25.0}$ = + 292 (c = 1.00, $CHCl_3$) (lit. **$[\alpha]_D$** = + 268 (c = 1.00, $CHCl_3$))

IR (film) 3377, 3025, 2947, 2863, 1676, 1609, 1469, 1379, 1290, 1244, 1200, 1112, 1039, 878, 747 cm^{-1}.

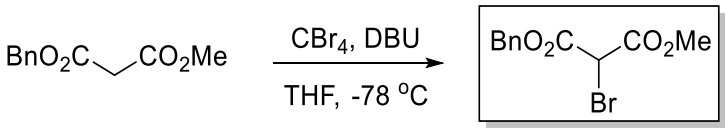
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.08 (s, 1H, ArN<u>H</u>), 7.40 (d, *J* = 7.5 Hz, 1H, Ar<u>H</u>), 7.17 (td, *J* = 7.5, 1.0 Hz, 1H, Ar<u>H</u>), 6.88 (td, *J* = 7.5, 1.0 Hz, 1H, Ar<u>H</u>), 6.83 (d, *J* = 7.5 Hz, 1H, Ar<u>H</u>), 3.90 (d, *J* = 7.0 Hz, 1H, NC<u>H</u>C), 3.77 (s, 3H, $CO_2C\underline{H_3}$), 3.37 (td, *J* = 12.5, 5.0 Hz, 1H, $CCH_2C\underline{H_A}H_BN$), 2.98 (dd, *J* = 12.5, 7.0 Hz, 1H, $CCH_2CH_A\underline{H_B}N$), 2.84 - 2.72 (m, 2H, $C{=}CC\underline{H_A}H_BCH$, $NC\underline{H}(CH_2CH_3)CH_2C$)), 2.11- 2.00 (m, 2H, $CC\underline{H_A}H_BCH2N$, $C{=}CCH_2C\underline{H}$), 1.97 – 1.87 (m, 2H, $NCH(CH_2CH_3)C\underline{H_A}H_BCH$, $C{=}CCH_A\underline{H_B}CH$), 1.77 – 1.68 (m, 2H, $NCH(CH_2CH_3)CH_A\underline{H_B}CH$, $NCH(C\underline{H_A}H_BCH_3)CH_2CH$), 1.64 (dd, *J* = 12.0, 5.0 Hz, 1H, $CCH_A\underline{H_B}CH2N$), 1.51 – 1.40 (m, 1H, $NCH(CH_A\underline{H_B}CH_3)CH_2CH$), 0.96 (t, *J* = 7.5 Hz, 3H, $NCH(CH_2C\underline{H_3})CH_2CH$).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 164.3, 143.5, 136.6, 128.0, 122.7, 120.8, 109.1, 91.6, 73.5, 68.4, 57.9, 51.7, 50.9, 38.8, 38.6, 37.6, 30.1, 26.8, 11.7.

HRMS (ES+) exact mass calculated for $[M+H]^+$ ($C_{20}H_{24}O_2N_2$) requires *m/z* 325.1911, found *m/z* 325.1911.

Analytical data are in accordance with those previously reported for this compound.[213,243]

5.4.27 Synthesis & Characterization of 1-benzyl 3-methyl 2-bromomalonate



To a solution of benzyl methyl malonate (1.09 mL, 6.0 mmol) in THF anhydrous (100 mL) was added DBU (0.90 mL, 6.0 mmol) at 0 °C under N_2. The reaction mixture was then stirred at RT for 1 h and cooled to -78 °C. CBr_4 (3.42g, 10.3 mmol) was subsequently added and the solution mixture was stirred at -78 °C for 3 h and quenched with satd. NH_4Cl (aq). Hexane was then added and the organic layer was collected and washed with brine. The aqueous layer was washed twice with DCM and the combined organic extract was then concentrated *in vacuo* and purified by FCC (PE:EtOAc 1:0 → 9.5: 0.5 → 8:2) to afford colourless oil 1-benzyl 3-methyl 2-bromomalonate (1.03g, 60%) .

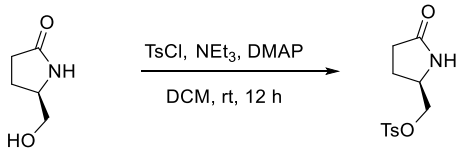
IR (film) 2956, 1738, 1499, 1455, 1264, 1140, 1014, 748, 697.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38- 7.34 (m, 5H, Ar<u>H</u>), 5.26 (s, 2H, ArC<u>H</u>$_2$$CO_2$), 4.89 (s, 1H, CO_2C<u>H</u>$BrCO_2$), 3.80 (s, 3H, CO_2C<u>H</u>$_3$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 164.3, 134.5, 128.6 (3XC), 128.2 (2XC), 68.7, 53.8, 41.8.

Analytical data are in accordance with those previously reported for this compound.[244]

5.4.28 Synthesis & Characterization of (*R*)-(5-oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate



To a stirred solution of (*R*)-5-(hydroxymethyl)-2- pyrrolidinone (500 mg, 4.34 mmol) and *p*-toluenesulfonyl chloride (1.08 g, 5.6 mmol) in DCM (10 mL) at 0 °C were added DMAP (106 mg,

0.87 mmol) and Et_3N (780 µL, 5.6 mmol). The reaction mixture was allowed to warm to rt and stirred for 12 h. The reaction was then quenched with water (10 mL) and the aqueous layer was extracted with DCM. The combined organic extracts were washed with 1*N* HCl and dried over anhydrous Na_2SO_4. Solvent was removed in vacuo, followed by purification *via* FCC (2.5% MeOH in $CHCl_3$) to afford the (*R*)-(5-oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate (1.05 g, 90%) as a yellow solid.

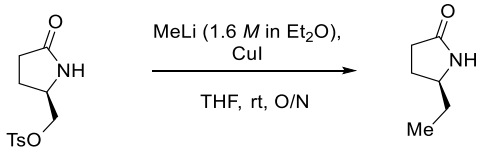
$[\alpha]_D^{25.0}$ = - 23.6 (c = 1.00, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.54 (s, 1H, C(O)NH), 4.07 – 3.97 (m, 1H, C(O)NHCH(CH_AH_BO-Ts)), 3.93 – 3.80 (m, 2H, C(O)NHCH(CH_AH_BO-Ts)), 2.44 (s, 3H, Ar-CH_3), 2.35 – 2.14 (m, 3H, $CH_ACH_BCH_2C(O)NH$), 1.83 - 1.70 (m, 1H, $CH_ACH_BCH_2C(O)NH$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 145.4, 132.4, 130.2, 128.0, 72.1, 52.7, 29.4, 22.9, 21.8.

Analytical data are in accordance with those previously reported for this compound.[245]

5.4.29 Synthesis & Characterization of (*S*)-5-ethylpyrrolidin-2-one 289



289

To a suspension of CuI (1.77 g, 9.30 mmol) in anhydrous THF (10 mL) was added MeLi (11.6 mL, 1.6 *M* in ether, 18.6 mmol) at 0 ° C. A solution of (*R*)-(5-oxopyrrolidin-2-yl)methyl 4-methylbenzenesulfonate (1.0 g, 3.72 mmol) in anhydrous THF (20 mL) was then added dropwise to the reaction mixture at 0 ° C. The resulting mixture was warmed to rt and stir overnight. Upon completion of reaction, the mixture was quenched at 0 ° C with NH_4Cl-NH_3 buffer solution (9:1), washed with brine and extracted with Et_2O. The combined organic layers were then dried over

anhydrous Na_2SO_4, solvent was removed in vacuo and crude mixture was purified by FCC to afford (*S*)-5-ethylpyrrolidin-2-one **289** as a colourless oil. (257 mg, 61%)

$[\alpha]_D^{25.0}$ = - 3.08 (c = 1.00, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H, C(O)N<u>H</u>), 3.55 (p, *J* = 6.5 Hz, 1H, C(O)NHC<u>H</u>(CH_2CH_3)), 2.41 – 2.13 (m, 3H, C<u>H_A</u>CH_BC<u>H_2</u>C(O)NH), 1.73 – 1.62 (m, 1H, CH_AC<u>H_B</u>CH_2C(O)NH), 1.60 – 1.41 (m, 2H, C(O)NHCH(C<u>H_2</u>CH_3)), 0.92 (t, *J* = 7.5 Hz, 3H, C(O)NHCH(CH_2C<u>H_3</u>)).

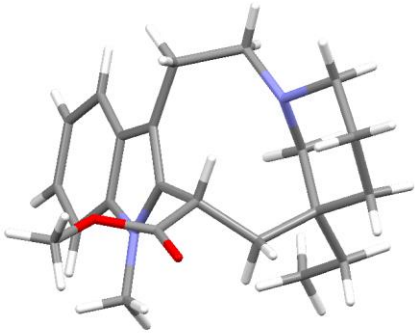
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 56.2, 30.5, 29.6, 26.9, 10.1.

Analytical data are in accordance with those previously reported for this compound.[246]

Chapter 6: Appendices

6.1 X-ray Diffraction Data

6.1.1 X-ray Diffraction Data for (±)-Vincaminorine 276



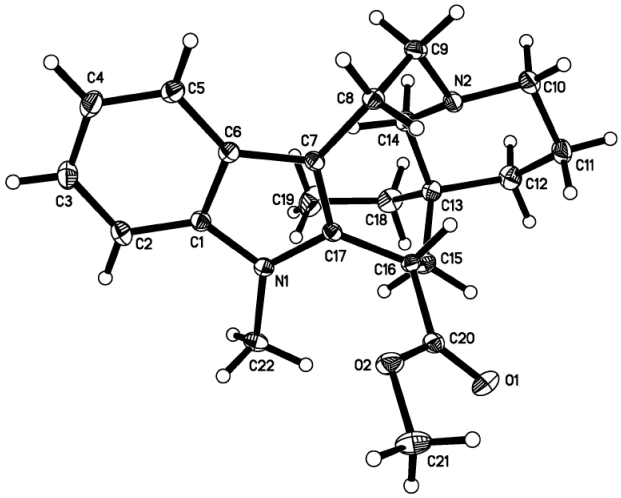


Table 1. Sample and crystal data

Identification code	ices14s
Chemical formula	$C_{22}H_{30}N_2O_2$
Formula weight	354.48 g/mol
Temperature	103(2) K

Wavelength	0.71073 Å	
Crystal size	0.180 x 0.220 x 0.420 mm	
Crystal habit	colorless plate	
Crystal system	monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 11.2859(12) Å	α = 90°
	b = 9.2140(10) Å	β = 96.066(3)°
	c = 18.255(2) Å	γ = 90°
Volume	1887.7(4) $Å^3$	
Z	4	
Density (calculated)	1.247 g/cm^3	
Absorption coefficient	0.080 mm^{-1}	
F(000)	768	

Table 2. Data collection and structure refinement

Theta range for data collection	2.03 to 31.10°
Index ranges	-16<=h<=15, -13<=k<=13, -25<=l<=26
Reflections collected	20214
Independent reflections	5989 [R(int) = 0.0458]
Coverage of independent reflections	98.5%
Absorption correction	Multi-Scan
Max. and min. transmission	0.9860 and 0.9670
Structure solution technique	direct methods
Structure solution program	XS, VERSION 2013/1
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$

Data / restraints / parameters	5989 / 0 / 238	
Goodness-of-fit on F^2	1.022	
Final R indices	4316 data; $I>2\sigma(I)$	R1 = 0.0493, wR2 = 0.1131
	all data	R1 = 0.0769, wR2 = 0.1273
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0599P)^2+0.3596P]$ where $P=(F_o^2+2F_c^2)/3$	
Largest diff. peak and hole	0.382 and -0.248 eÅ^{-3}	
R.M.S. deviation from mean	0.057 eÅ^{-3}	

Table 3. Atomic coordinates and equivalent isotropic atomic displacement parameters (Å²)

U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x/a	y/b	z/c	U(eq)
C1	0.26570(11)	0.29568(13)	0.35204(6)	0.0126(2)
C2	0.15001(12)	0.30548(14)	0.37189(7)	0.0171(3)
C3	0.12197(12)	0.22018(15)	0.43003(8)	0.0201(3)
C4	0.20599(12)	0.12696(14)	0.46755(7)	0.0190(3)
C5	0.32013(12)	0.11590(13)	0.44707(7)	0.0151(2)
C6	0.35164(11)	0.20030(12)	0.38800(6)	0.0118(2)
C7	0.45741(11)	0.21328(12)	0.35143(6)	0.0108(2)
C8	0.57192(11)	0.13131(12)	0.37147(7)	0.0126(2)
C9	0.67170(11)	0.21702(13)	0.41534(7)	0.0142(2)
C10	0.82183(12)	0.38474(14)	0.37092(7)	0.0174(3)
C11	0.82727(12)	0.49481(14)	0.30897(7)	0.0187(3)
C12	0.75183(12)	0.62800(14)	0.32167(8)	0.0186(3)
C13	0.62250(11)	0.59031(13)	0.33474(7)	0.0137(2)
C14	0.63093(11)	0.47673(13)	0.39659(6)	0.0140(2)
C15	0.54989(12)	0.54084(13)	0.26131(7)	0.0143(2)
C16	0.51984(11)	0.37789(12)	0.24785(6)	0.0113(2)
C17	0.43410(11)	0.31542(12)	0.29666(6)	0.0107(2)

	x/a	y/b	z/c	U(eq)
C18	0.56465(13)	0.72986(14)	0.36140(8)	0.0198(3)
C19	0.44400(15)	0.70935(16)	0.39036(9)	0.0283(3)
C20	0.48931(11)	0.34966(13)	0.16596(6)	0.0134(2)
C21	0.38740(14)	0.19737(17)	0.07689(7)	0.0255(3)
C22	0.25170(12)	0.46046(14)	0.24324(7)	0.0168(3)
N1	0.31771(9)	0.36605(11)	0.29688(5)	0.0123(2)
N2	0.69745(9)	0.34968(11)	0.37614(6)	0.0132(2)
O1	0.53231(9)	0.41286(11)	0.11753(5)	0.0218(2)
O2	0.41274(8)	0.23760(10)	0.15333(5)	0.0180(2)

Table 4. Bond lengths (Å)

C1-N1	1.3798(15)	C1-C2	1.3943(18)
C1-C6	1.4175(17)	C2-C3	1.3840(18)
C3-C4	1.4032(19)	C4-C5	1.3825(18)
C5-C6	1.4054(16)	C6-C7	1.4329(17)
C7-C17	1.3781(16)	C7-C8	1.5082(17)
C8-C9	1.5306(17)	C9-N2	1.4611(15)
C10-N2	1.4533(16)	C10-C11	1.5251(18)
C11-C12	1.5253(19)	C12-C13	1.5432(18)
C13-C14	1.5351(17)	C13-C18	1.5440(17)
C13-C15	1.5634(17)	C14-N2	1.4604(16)
C15-C16	1.5531(16)	C16-C17	1.4980(16)
C16-C20	1.5207(16)	C17-N1	1.3942(15)
C18-C19	1.524(2)	C20-O1	1.2028(15)
C20-O2	1.3506(15)	C21-O2	1.4430(15)
C22-N1	1.4549(15)		

Table 5. Bond angles (°)

N1-C1-C2	129.90(11)	N1-C1-C6	107.83(10)
C2-C1-C6	122.24(11)	C3-C2-C1	117.31(12)
C2-C3-C4	121.63(12)	C5-C4-C3	120.93(12)

C4-C5-C6	119.03(12)	C5-C6-C1	118.82(11)
C5-C6-C7	133.98(11)	C1-C6-C7	107.18(10)
C17-C7-C6	106.89(10)	C17-C7-C8	127.66(11)
C6-C7-C8	125.44(10)	C7-C8-C9	115.64(10)
N2-C9-C8	110.41(10)	N2-C10-C11	108.13(10)
C10-C11-C12	110.82(11)	C11-C12-C13	113.25(10)
C14-C13-C12	106.32(10)	C14-C13-C18	109.35(10)
C12-C13-C18	107.44(10)	C14-C13-C15	114.71(10)
C12-C13-C15	110.59(10)	C18-C13-C15	108.20(10)
N2-C14-C13	110.61(9)	C16-C15-C13	120.23(10)
C17-C16-C20	115.19(10)	C17-C16-C15	114.92(10)
C20-C16-C15	110.11(9)	C7-C17-N1	109.51(10)
C7-C17-C16	127.46(11)	N1-C17-C16	122.76(10)
C19-C18-C13	115.42(11)	O1-C20-O2	123.05(11)
O1-C20-C16	124.94(12)	O2-C20-C16	111.89(10)
C1-N1-C17	108.57(10)	C1-N1-C22	123.04(10)
C17-N1-C22	127.85(10)	C10-N2-C14	111.40(10)
C10-N2-C9	117.49(10)	C14-N2-C9	114.27(9)
C20-O2-C21	114.79(10)		

Table 6. Anisotropic atomic displacement parameters (Å^2)

The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

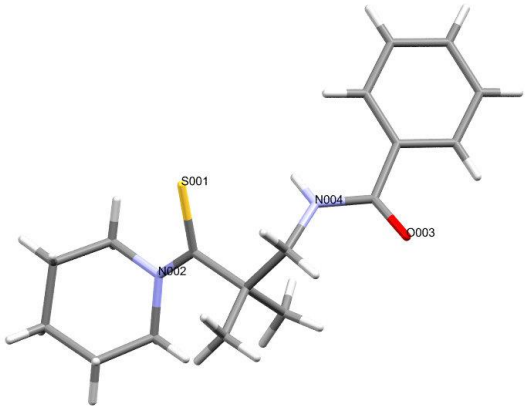
	U_{11}	**U_{22}**	**U_{33}**	**U_{23}**	**U_{13}**	**U_{12}**
C1	0.0121(6)	0.0133(5)	0.0123(5)	-0.0008(4)	0.0008(4)	-0.0008(4)
C2	0.0117(6)	0.0194(6)	0.0202(6)	-0.0003(5)	0.0017(5)	0.0018(5)
C3	0.0144(7)	0.0252(7)	0.0217(6)	0.0002(5)	0.0061(5)	-0.0017(5)
C4	0.0200(7)	0.0201(6)	0.0176(6)	0.0024(5)	0.0058(5)	-0.0040(5)
C5	0.0169(7)	0.0147(5)	0.0136(5)	0.0011(4)	0.0012(5)	-0.0013(5)
C6	0.0127(6)	0.0112(5)	0.0114(5)	-0.0017(4)	0.0005(4)	-0.0021(4)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C7	0.0104(6)	0.0105(5)	0.0113(5)	-0.0010(4)	-0.0001(4)	-0.0003(4)
C8	0.0139(6)	0.0106(5)	0.0134(5)	0.0016(4)	0.0016(4)	0.0019(4)
C9	0.0135(6)	0.0147(5)	0.0139(5)	0.0031(4)	-0.0009(5)	0.0011(5)
C10	0.0123(6)	0.0205(6)	0.0193(6)	0.0016(5)	0.0005(5)	-0.0004(5)
C11	0.0129(7)	0.0211(6)	0.0225(6)	0.0026(5)	0.0035(5)	-0.0027(5)
C12	0.0172(7)	0.0159(6)	0.0229(6)	0.0011(5)	0.0019(5)	-0.0054(5)
C13	0.0148(6)	0.0116(5)	0.0150(5)	0.0001(4)	0.0028(5)	-0.0013(4)
C14	0.0145(6)	0.0142(5)	0.0130(5)	-0.0011(4)	0.0006(4)	-0.0009(5)
C15	0.0179(6)	0.0118(5)	0.0134(5)	0.0018(4)	0.0017(5)	-0.0007(5)
C16	0.0124(6)	0.0120(5)	0.0094(5)	0.0013(4)	0.0012(4)	0.0011(4)
C17	0.0104(6)	0.0106(5)	0.0109(5)	-0.0010(4)	0.0003(4)	0.0003(4)
C18	0.0268(8)	0.0123(5)	0.0206(6)	-0.0022(5)	0.0037(5)	0.0015(5)
C19	0.0359(9)	0.0213(7)	0.0304(8)	0.0010(6)	0.0166(7)	0.0089(6)
C20	0.0133(6)	0.0138(5)	0.0131(5)	0.0007(4)	0.0009(4)	0.0044(4)
C21	0.0321(8)	0.0297(7)	0.0133(6)	-0.0050(5)	-0.0044(6)	-0.0020(6)
C22	0.0154(6)	0.0175(6)	0.0166(6)	0.0047(5)	-0.0021(5)	0.0046(5)
N1	0.0117(5)	0.0129(5)	0.0122(4)	0.0019(4)	0.0008(4)	0.0017(4)
N2	0.0108(5)	0.0132(5)	0.0157(5)	0.0024(4)	0.0015(4)	0.0003(4)
O1	0.0276(6)	0.0249(5)	0.0138(4)	0.0033(4)	0.0059(4)	-0.0007(4)
O2	0.0212(5)	0.0200(4)	0.0121(4)	-0.0022(3)	-0.0008(4)	-0.0026(4)

Table 7. Hydrogen atomic coordinates and isotropic atomic displacement parameters ($Å^2$).

	x/a	y/b	z/c	U(eq)
H2	0.0928	0.3682	0.3465	0.021
H3	0.0439	0.2249	0.4449	0.024
H4	0.1841	0.0707	0.5076	0.023
H5	0.3764	0.0522	0.4726	0.018
H8A	0.6016	0.0964	0.3255	0.015
H8B	0.5540	0.0448	0.4005	0.015
H9A	0.6474	0.2422	0.4643	0.017
H9B	0.7444	0.1564	0.4229	0.017
H10A	0.8664	0.2960	0.3603	0.021
H10B	0.8582	0.4261	0.4181	0.021
H11A	0.7979	0.4493	0.2614	0.022
H11B	0.9110	0.5248	0.3064	0.022
H12A	0.7505	0.6927	0.2783	0.022
H12B	0.7896	0.6819	0.3649	0.022
H14A	0.6712	0.5198	0.4423	0.017
H14B	0.5498	0.4470	0.4063	0.017
H15A	0.4735	0.5946	0.2569	0.017
H15B	0.5942	0.5738	0.2204	0.017
H16	0.5965	0.3252	0.2615	0.014
H18A	0.6200	0.7739	0.4009	0.024
H18B	0.5550	0.7997	0.3200	0.024
H19A	0.3899	0.6589	0.3532	0.042
H19B	0.4106	0.8044	0.4008	0.042
H19C	0.4539	0.6516	0.4357	0.042
H21A	0.3574	0.2821	0.0482	0.038
H21B	0.3272	0.1204	0.0723	0.038
H21C	0.4605	0.1623	0.0582	0.038
H22A	0.1838	0.4073	0.2183	0.025
H22B	0.3041	0.4924	0.2068	0.025
H22C	0.2228	0.5453	0.2684	0.025

6.1.2 X-ray Diffraction Data for Compound 121a



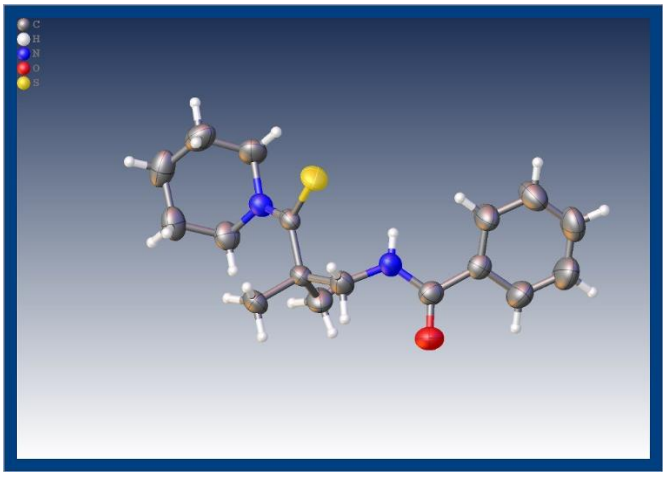


Table 1 Crystal data and structure refinement

Identification code	PW-TH-01
Empirical formula	$C_{17}H_{24}N_2OS$
Formula weight	304.44
Temperature/K	296.91(14)
Crystal system	triclinic
Space group	P-1
a/Å	6.9736(3)
b/Å	9.4387(6)

c/Å	13.6145(7)
α/°	86.443(5)
β/°	88.638(4)
γ/°	69.185(5)
Volume/Å^3	836.03(8)
Z	2
ρ_{calc}g/cm^3	1.209
μ/mm^{-1}	0.195
F(000)	328.0
Crystal size/mm^3	? × ? × ?
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.878 to 60.746
Index ranges	-6 ≤ h ≤ 9, -12 ≤ k ≤ 12, -18 ≤ l ≤ 18
Reflections collected	7916
Independent reflections	4287 [R_{int} = 0.0159, R_{sigma} = 0.0291]
Data/restraints/parameters	4287/0/192
Goodness-of-fit on F^2	1.012
Final R indexes [I>=2σ (I)]	R_1 = 0.0506, wR_2 = 0.1288
Final R indexes [all data]	R_1 = 0.0696, wR_2 = 0.1432
Largest diff. peak/hole / e Å^{-3}	0.23/-0.19

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S001	4593.8(7)	7619.1(6)	1671.7(4)	57.97(17)
N002	6620(2)	9386.3(16)	2063.1(11)	46.4(3)
O003	10330(2)	2630.3(18)	3213.5(13)	77.9(5)
N004	7620(2)	4689.7(17)	2736.0(12)	53.7(4)
C005	6724(2)	7987.5(18)	1894.3(11)	38.9(3)
C006	8838(2)	6679.0(19)	1904.7(12)	43.7(4)
C007	7213(3)	3022.5(19)	4085.0(13)	46.3(4)
C008	8531(3)	3434(2)	3320.0(14)	50.3(4)
C009	8584(3)	5127(2)	1873.6(15)	55.5(5)
C00A	10018(3)	6816(2)	951.6(15)	58.4(5)
C00B	8309(3)	9991(2)	2027.8(15)	57.9(5)
C00C	10079(3)	6618(3)	2839.8(15)	61.8(5)
C00D	5107(3)	3575(3)	4065.5(16)	65.8(6)

C00E	4635(3)	10641(2)	2145.7(17)	64.5(5)
C00F	8057(4)	11098(3)	1142.9(17)	69.8(6)
C00G	8184(4)	1959(3)	4825.9(17)	74.1(6)
C00H	4281(4)	11719(2)	1241.1(17)	71.3(6)
C00I	3981(4)	3061(3)	4752.9(18)	77.8(7)
C00J	5987(4)	12370(3)	1122.3(18)	76.9(7)
C00K	4964(4)	1994(3)	5472.1(17)	79.4(7)
C00L	7064(5)	1459(3)	5515.3(19)	94.4(9)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) . The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S001	38.1(2)	69.8(3)	71.7(3)	5.1(2)	-7.4(2)	-27.1(2)
N002	42.7(7)	45.4(8)	51.9(8)	-4.0(6)	6.6(6)	-16.7(6)
O003	47.4(8)	71.2(10)	98.0(12)	15.6(9)	9.5(7)	-4.0(7)
N004	47.4(8)	42.7(8)	66.3(10)	3.5(7)	13.3(7)	-12.2(6)
C005	33.7(7)	48.4(9)	35.6(7)	1.8(6)	2.0(5)	-16.5(6)
C006	33.7(8)	47.5(9)	48.9(9)	2.3(7)	4.8(6)	-14.2(6)
C007	51.3(9)	42.8(9)	45.6(9)	-3.5(7)	-2.5(7)	-17.4(7)
C008	46.3(9)	44.4(9)	59.4(11)	-2.3(8)	-0.8(7)	-15.1(7)
C009	54.6(10)	46.7(10)	61.3(11)	-2.9(8)	16.2(8)	-14.2(8)
C00A	45.7(10)	64.1(12)	63.3(12)	0.9(9)	16.3(8)	-18.5(8)
C00B	62.3(11)	59.0(11)	63.0(12)	-4.4(9)	-1.1(9)	-34.4(9)
C00C	43.6(10)	74.7(13)	66.1(12)	15.4(10)	-11.5(8)	-22.3(9)
C00D	52.9(11)	83.5(15)	58.7(12)	17.7(10)	-4.7(9)	-24.6(10)
C00E	59.8(12)	51.9(11)	71.9(13)	-9.9(10)	18.1(10)	-7.6(9)
C00F	86.8(15)	68.5(13)	69.1(14)	0.4(11)	6.6(11)	-46.9(12)
C00G	63.5(13)	74.9(14)	68.7(14)	17.8(11)	-1.4(10)	-9.5(11)
C00H	72.2(14)	53.0(11)	71.7(14)	-5.4(10)	2.8(10)	-1.1(10)
C00I	60.1(13)	111(2)	66.2(14)	6.0(13)	6.4(10)	-36.9(13)
C00J	118(2)	53.7(12)	60.8(13)	1.8(10)	2.2(12)	-33.1(13)
C00K	95.8(18)	89.2(17)	57.2(13)	6.7(12)	18.4(12)	-40.7(14)
C00L	95(2)	97(2)	71.0(16)	32.6(14)	5.9(13)	-15.9(15)

Table 4 Bond Lengths

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S001	C005	1.6793(15)	C007	C008	1.496(3)
N002	C005	1.330(2)	C007	C00D	1.374(3)
N002	C00B	1.479(2)	C007	C00G	1.381(3)

N002	C00E	1.475(2)	C00B	C00F	1.516(3)
O003	C008	1.224(2)	C00D	C00I	1.381(3)
N004	C008	1.346(2)	C00E	C00H	1.515(3)
N004	C009	1.450(2)	C00F	C00J	1.514(3)
C005	C006	1.551(2)	C00G	C00L	1.373(3)
C006	C009	1.540(3)	C00H	C00J	1.522(3)
C006	C00A	1.543(2)	C00I	C00K	1.364(3)
C006	C00C	1.543(2)	C00K	C00L	1.370(4)

Table 5 Bond Angles

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C005	N002	C00B	127.79(14)	C00G	C007	C008	117.66(17)
C005	N002	C00E	121.59(15)	O003	C008	N004	122.08(17)
C00E	N002	C00B	109.84(15)	O003	C008	C007	121.10(17)
C008	N004	C009	123.77(15)	N004	C008	C007	116.77(15)
N002	C005	S001	120.87(12)	N004	C009	C006	114.93(15)
N002	C005	C006	119.60(13)	N002	C00B	C00F	110.10(16)
C006	C005	S001	119.53(12)	C007	C00D	C00I	121.2(2)
C009	C006	C005	111.06(13)	N002	C00E	C00H	109.90(16)
C009	C006	C00A	104.49(14)	C00J	C00F	C00B	112.57(19)
C009	C006	C00C	106.92(15)	C00L	C00G	C007	120.6(2)
C00A	C006	C005	109.42(13)	C00E	C00H	C00J	110.74(19)
C00C	C006	C005	112.16(14)	C00K	C00I	C00D	119.9(2)
C00C	C006	C00A	112.51(15)	C00F	C00J	C00H	110.09(18)
C00D	C007	C008	124.05(16)	C00I	C00K	C00L	119.6(2)
C00D	C007	C00G	118.20(19)	C00K	C00L	C00G	120.5(2)

Table 6 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3)

Atom	*x*	*y*	*z*	U(eq)
H004	6396.22	5265.3	2883.06	64
H00A	7774.11	5146.25	1300.34	67
H00B	9928.09	4356.22	1791.12	67
H00C	9243.43	6753.59	392.75	88
H00D	11327.16	6006.57	957.53	88
H00E	10216.14	7773.88	911.43	88
H00F	9613.27	9161.12	1986.25	69

H00G	8303.44	10500.62	2625.43	69
H00H	10547.11	7461.45	2809.11	93
H00I	11238.6	5686.14	2882.8	93
H00J	9223.32	6669.31	3409.19	93
H00K	4426.31	4308.94	3580.8	79
H00L	4630.68	11182.86	2728.6	77
H00M	3536.58	10235.59	2209.95	77
H00N	9127.53	11530.08	1152.18	84
H00O	8222.89	10553.83	546.96	84
H00P	9608.61	1577.76	4858.19	89
H00Q	2972.79	12540.39	1299.33	86
H00R	4231.56	11183.54	662.34	86
H00S	2555.79	3440.95	4725.62	93
H00T	5821.44	12966.74	503.02	92
H00U	5908.24	13032.59	1650.69	92
H00V	4213.91	1632.06	5930.2	95
H00W	7736.38	752.33	6015.37	113

6.2 List of publications

1) "*Palladium (II)-catalyzed ortho-arylation of N-benzylpiperidines*", P. W. Tan, M. Haughey, D. J. Dixon, *Chem. Commun*. **2015**, *51*, 4406.
2) "*Expeditious and Divergent Total Syntheses of Aspidosperma Alkaloids Exploiting Iridium(I)-Catalyzed Generation of Reactive Enamine Intermediates*", P. W. Tan, J. Seayad, D. J. Dixon, *Angew. Chem. Int. Ed*. **2016**, *55*, 13436.
3) *"Thioamide Directed Co(III) Catalyzed Selective Amidation of C(sp^3)-H Bonds",* P. W. Tan, A. M. Mak, M. B. Sullivan, D. J. Dixon, J. Seayad, *Angew. Chem. Int. Ed*. **2017**, *56*, 16550.

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